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TOPIC HIGHLIGHT

WJC 6th Anniversary Special Issues (1): Hypertension

High-density lipoprotein and atherosclerosis: Roles of lipid transporters

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Abstract

Various previous studies have found a negative correlation between the risk of cardiovascular events and serum high-density lipoprotein (HDL) cholesterol levels. The reverse cholesterol transport, a pathway of cholesterol from peripheral tissue to liver which has several potent antiatherogenic properties. For instance, the particles of HDL mediate to transport cholesterol from cells in arterial tissues, particularly from atherosclerotic plaques, to the liver. Both ATP-binding cassette transporters (ABC) A1 and ABCG1 are membrane cholesterol transporters and have been implicated in mediating cholesterol effluxes from cells in the presence of HDL and apolipoprotein A-I, a major protein constituent of HDL. Previous studies demonstrated that ABCA1 and ABCG1 or the interaction between ABCA1 and ABCG1 exerted antiatherosclerotic effects. As a therapeutic approach for increasing HDL cholesterol levels, much focus has been placed on increasing HDL cholesterol levels as well as enhancing HDL biochemical functions. HDL therapies that use injections of reconstituted HDL, apoA-I mimetics, or full-length apoA-I have shown dramatic effectiveness. In particular, a novel apoA-I mimetic peptide, Fukuoka University ApoA-I Mimetic Peptide, effectively removes cholesterol *via* specific ABCA1 and other transporters, such as ABCG1, and has an antiatherosclerotic effect by enhancing the biological functions of HDL without changing circulating HDL cholesterol levels. Thus, HDL-targeting therapy has significant atheroprotective potential, as it uses lipid transporter-targeting agents, and may prove to be a therapeutic tool for atherosclerotic cardiovascular diseases.

Key words: ATP-binding cassette transporter; ATP-binding cassette A1; ATP-binding cassette G1; Apolipoprotein A-I; High-density lipoprotein; High-density lipoprotein therapy; apoA-I mimetic peptide; Reconstitutedf high-density lipoprotein

Core tip: The reverse cholesterol transport pathway played with high-density lipoprotein (HDL) has several potential antiatherogenic properties. Both ATP-binding cassette (ABC) A1 and ABCG1 are lipid transporters and have been involved in mediating cholesterol effluxes from cells in the presence of HDL or apoA-I, and they exerted antiatherosclerotic effects. As a therapeutic approach for increasing HDL cholesterol levels, much focus has been placed on increasing not only HDL cholesterol levels, but also HDL-biological functions. Reconstituted HDL and apoA-I mimetics have significant atheroprotective potential, as it uses lipid transporter-targeting agents, and may prove to be a novel therapeutic tool for atherosclerotic cardiovascular diseases.

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INTRODUCTION

High-density lipoprotein (HDL) cholesterol is widely

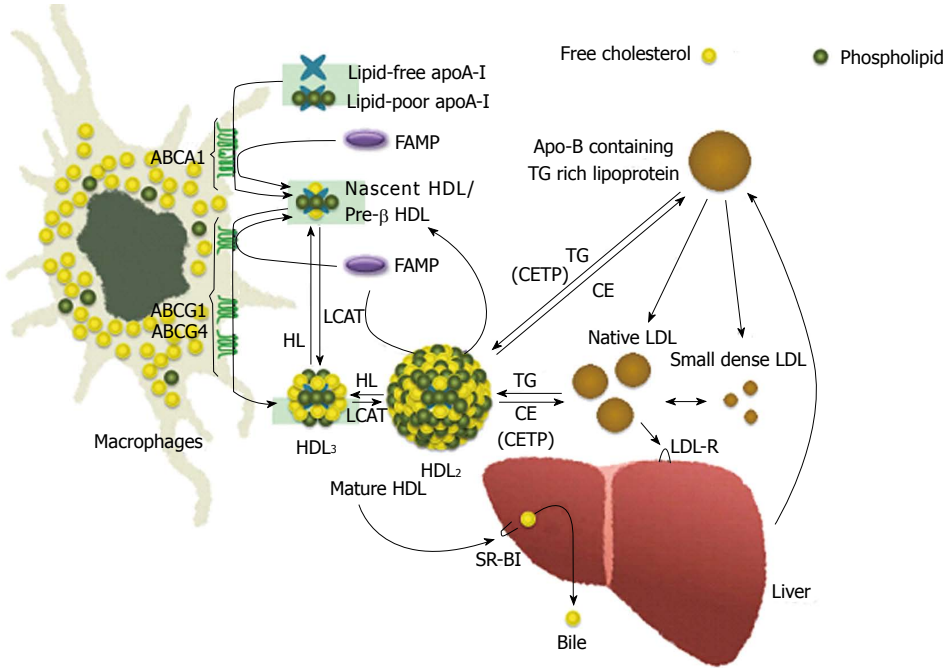

Figure 1 Illustration of high-density lipoprotein metabolism and suggested function of fukuoka university ApoA-I mimetic peptide in high-density lipoprotein metabolism. ABC: ATP-binding cassette transporter; TG: Triglyceride; CE: Cholesteryl ester; CETP: Cholesteryl ester transfer protein; HL: Hepatic lipase; apo: Apolipoprotein; HDL: High-density lipoprotein; FAMP: Fukuoka university ApoA- I mimetic peptide; CETP: CE transfer protein; SR-BI: Scavenger receptor BI; LDL: Llow-density lipoprotein; LCAT: Lecithin cholesterol acyltransferase; LDL-R: Low-density lipoprotein receptor; SR-BI: Scavenger receptor class B, type I ; FAMP: Fukuoka University ApoA- I mimetic peptide.

known as "good cholesterol", because various previous studies have found a negative correlation between the risk of cardiovascular events and serum HDL cholesterol levels[1]. However, this is still controversial whether the association is the cause or just only an ensuing symptom of a general atherosclerotic damage. HDL has several potential for antiatherogenic properties, for instance, cholesterol is transported from peripheral tissues such as the cells in the arterial walls to the liver by HDL particles, where it is used for a composition of lipoproteins and a synthesis of bile acids, steroid hormones, or fat-soluble vitamins[1]. Whereas, low-HDL cholesterolemia is often observed as a characterized component of metabolic syndrome, such as in people who are overweight or obese, those with glucose intolerance or have obvious diabetes, those with hypertriglyceridemia, and those with high blood pressure, each of which conditions contribute to the cause of atherosclerosis[2].

METABOLISM AND THE FUNCTIONS OF HDL

Although HDL is a lipoprotein when isolated by ultracentrifugation has a density in the range of 1.063-1.21 g/mL (HDL_2, 1.063 < d < 1.125 g/mL; HDL_3, 1.125 < d < 1.21 g/mL), HDL composes a heterogeneous group of particles that differ in density, size, composition of apolipoprotein (apo) or lipid, and electrophoretic mobility[3]. It is possible to separate HDL into two major subfractions on the basis of electro-mobility by electrophoresis; the major subfraction has the same mobility as alpha HDL, whereas the other subfractions migrate similar to pre-beta HDL, in addition the majority of HDL particles in human plasma are alpha HDL, and pre-beta HDL represents only 2%-14% of all apoA-I[4,5] (Figure 1).

HDL metabolism has the complicated mechanisms in association with several HDL-related genes such as various enzymes and protein, lipids, receptors, or transporters and its synthesis involves a complex pathway. The underlying genetic deficiency in many cases of primary low-HDL cholesterolemia are not clearly understood, however mutations in three pivotal genes as apoA-I, lecithin: cholesterol acyltransferase, and ATP-binding cassette transporter (ABC) A1, are associated with reducing serum HDL cholesterol levels, furthermore some of these genes' mutations are also closely correlated with an increased risk of premature atherosclerosis and coronary artery disease (CAD)[6].

TANGIER DISEASE, A FAMILIAL HDL DEFICIENCY

Tangier disease (TD) is the most severe form of HDL deficiency, which was first described by Fredrickson *et al*[7]. The biological hallmarks of TD patients' plasma are a defect of HDL cholesterol, reduced low-density lipoprotein (LDL) cholesterol levels, and moderate increased triglyceride. The plasma apoA-I concentration in TD is markedly decreased to approximately 1%-3% of normal. TD is a very rare autosomal recessive disorder which is characterized by the almost absence serum apoA-I and HDL cholesterol levels. Furthermore, cholesteryl ester (CE) accumulates in many macrophage enriched tissues, such

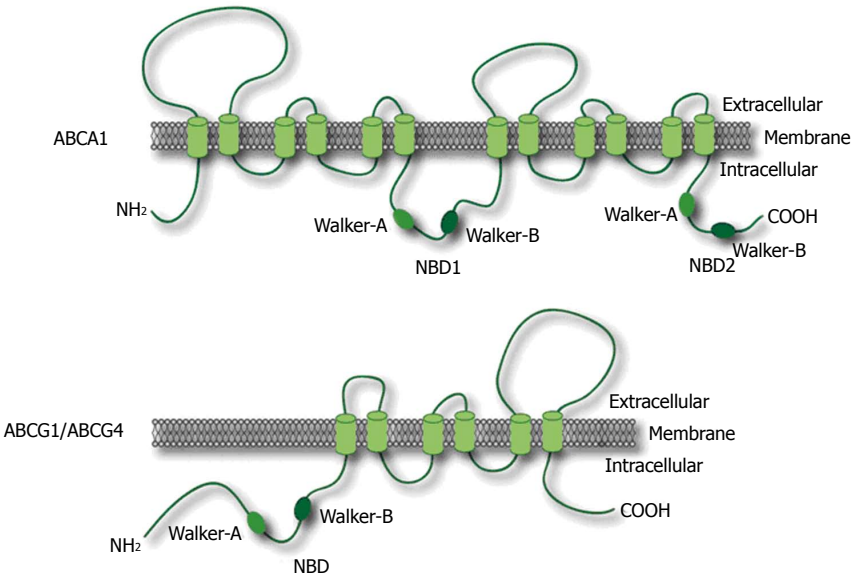

Figure 2 Secondary structures of the ATP-binding cassette transporter A1, ATP-binding cassette G1 and ATP-binding cassette G4 transporters. The ATP-binding cassette transporters (ABC)A1 transporter comprises 2201 amino acids with two transmembrane domains comprising two nucleotide binding domains (NBD-1 and -2) and six transmembrane helices, which contain two conserved peptide motifs, Walker-A and -B. ABCA1 is characterized as two large extracellular loops and N-terminus oriented towards the cytosol. Both ABCG1 and ABCG4 proteins have one transmembrane domain comprising six transmembrane helices and one NBD that contains two conserved peptide motifs, Walker-A and Walker-B.

as tonsils, spleen, liver, lymph nodes, peripheral nerves, thymus, and also arterial walls. Clinical symptoms among homozygotes patients include hepatosplenomegaly, hyperplastic orange-yellow tonsils, corneal opacification, and premature CAD and atheosclerosis in a half of cases as well as relapsing peripheral neuropathy due to CE deposition in macrophages and Schwann cells[7-9].

In 1999, a cause of TD was found in a defect of the ABCA1 (formerly *ABC1*) gene[1,10,11] that is located on chromosome 9q31. This gene comprises 50 exons that span a region of approximately 149 kb[12,13]. ABCA1 has been identified as an important gene for regulating cellular cholesterol homeostasis and serum HDL cholesterol levels, which is defect in patients with TD. *ABCA1* gene mutations cause gene dose-dependent decreases in serum HDL cholesterol levels and a decreased capacity of skin fibroblasts and monocyte-derived macrophages releasing cholesterol in the presence of extracellular apolipoproteins in TD patients and their heterozygous relatives[1,10,11,14,15].

A transmembrane protein, ABC transporter facilitates to carry out the specific substrates across cell membranes in an ATP-dependent manner. ABCA1 is a member of the ABC transporter superfamily comprised 48 human transporters, and the superfamily is divided into seven subfamilies, including from half- to full-transporters, designated ABCA-ABCG. These transporters are integral membrane proteins carrying out various substrates, including lipids, ions, peptides, amino acids, carbohydrates, vitamins, glucuronides, glutathione conjugates, and xenobiotics[16,17]. ABCA1 is expressed in various organs in human, particularly the highest expression levels are existed in the placenta, liver, lung, adrenal glands, and fetal tissues[18].

ABC transporter superfamilies are defined by the presence of similar nucleotide binding domains (NBD) to interact with ATP. These domains have two conserved peptide motifs, Walker-A and Walker-B, which are found in many proteins that utilize ATP[16,19] (Figure 2).

ABC TRANSPORTER ROLES IN HDL METABOLISM

ABCA1 transporter functions and their relationships with HDL metabolism

ABCA1 proteins transport phospholipids (PLs) and cholesterol from the membranous inner leaflet to the outer leaflet, subsequently lipid-poor or lipid-free apoA-I takes up this transported cholesterol and PLs by ABCA1 to form nascent HDL[20]. ABCA1 is localized at the plasma membrane and intracellular compartments, where it can potentially facilitate lipid transport to either cell surface-bound[21] or internalized apolipoproteins[22].

HDL metabolism is composed of at least three different steps. As the first step, lipid-free or lipid-poor apoA-I removes free cholesterol from peripheral cells through ABCA1 transporter to form nascent-HDL. Second, nascent-HDL has a further lipidation, thereafter it grows to mature-HDL. Third, mature-HDL interacts with other apoB containing lipoproteins, such as intermediate density lipoprotein (IDL) and very-low-density lipoprotein (VLDL). Thus, ABCA1 is indispensable for the nascent-HDL formation, in addition it is also an important and essential molecule for the initial step of the reverse cholesterol transport (RCT).

Cultured blood monocyte-derived (mod)-macrophages from a healthy subject showed an approximately 125% increase in cholesterol efflux mediated lipid-free apoA-I, whereas it did not respond to apoA-I mediated efflux in macrophages from TD patients[23]. Although a lipid-free apoA-I showed an increase the cholesterol efflux mediated by in cultured mod-macrophages from healthy persons, the apoA-I did not elevate cholesterol efflux in mod-macrophages from TD patients. These results indicated that ABCA1 is a key molecule for apoA-I-specific cholesterol efflux pathway, but not basal efflux in macrophages.

Since ABCA1 plays an important role in mediat-

ing cholesterol and PL effluxes by lipid-free apoA-I, it is involved in a formation of discoidal HDL precursor, furthermore ABCA1 poorly interacts with HDL2 and HDL3. Patients with TD have extremely low levels of HDL cholesterol and they cannot compose nascent HDL particles due to a genetic defect in *ABCA1* gene.

Disrupting the ABCA1 in mice resulted in HDL deficiency and impaired cholesterol transport similar to TD[24,25]. ABCA1 overexpression resulted in increased apoA-I-mediated cholesterol efflux in transgenic mice[26,27]. These results indicate that ABCA1 is an important gene in regulating circulating HDL cholesterol levels and cellular cholesterol homeostasis.

ABCG1 transporter functions and their relationships to HDL metabolism

ABCG1, formerly ABC8 is also a member of the ABC transporter family which has been mapped on chromosome 21q22.3[19,28-32]. ABCG1 is one of half-transporter that contains only one NBD and a transmembrane domain, in contrast to ABCA1[19,31] (Figure 2). Thus, ABCG1 may require a dimeric partner to become active with ABCG1 or ABCG4.

Although ABCA1 promotes cholesterol efflux to lipid-poor or lipid-free apoA-I, it only modestly induces lipid efflux of smaller particles, such as HDL_3, and does not promote a cholesterol efflux of the larger HDL_2 fraction[33,34]. It has been also shown by Wang *et al*[35] that ABCG1 and ABCG4 contributed to HDL_2- and HDL_3-mediated cholesterol effluxes and had an important function related to HDL lipidation[35-37].

Administering a high-cholesterol, high-fat diet to ABCG1 knock-out mice resulted in a large amount of lipid accumulation in macrophages, whereas overexpression of human *ABCG1* gene was able to protect a dietary fat-induced lipid accumulation in murine model[38]. Moreover, It was shown by Mauldin *et al*[39] that reduced function of ABCG1 facilitated foam cell formation in diabetes mice[39]. Transplanting bone marrow from ABCG1-deficient ($ABCG1^{-/-}$) mice into LDL receptor-deficient mice, a model of familial hypercholesterolemia, produced contrasting effects on the formation of atherosclerotic lesion[40-42]. In contrast to these report, decreased lesion size and formation were observed in the absence of macrophages from ABCG1-deficient mice[41,42], and whole body ABCG1 expression protected against the development of early atherosclerotic plaque[43]. However, it remains unclear that the physiological roles of ABCG1 and its contribution to atherosclerotic progression in humans. In addition, ABC transporters such as ABCG1 and ABCG4, but not ABCA1, are not only responsible for passive and nonspecific efflux pathway but also mature HDL-mediated cholesterol efflux, which are spherical and transport almost all HDL cholesterol[35,37].

ROLES OF ABCG5 AND ABCG8 TRANSPORTER

ABCG5 and ABCG8 are half-transporters as well as ABCG1 that function together as a heterodimer, and mutations in either of these genes can cause sitosterolemia which is a rare autosomal, recessively inherited disorder, characterized by premature atherosclerosis and xanthomas[44-47]. These transporters mediate the sterols efflux including cholesterol and plant sterols from enterocytes return into the intestinal lumen and their excretion into the bile[44,48]. Accordingly, they protect the lipid accumulation in the body and augment RCT system. In animal model, *ABCG5* and *ABCG8* deficient mice have been shown to reduce a secretion of cholesterol in the bile and elevate sterol absorption[49], on the other hand *ABCG5* and *ABCG8* genes-overexpressed mice promotes cholesterol secretion in the bile, decreases cholesterol absorption from diet, and increases neutral sterol excretion in the feces[50]. Liver X receptor (LXR) agonists promote the cholesterol efflux by the upregulation of ABCA1 and ABCG1, and also stimulate ABCG5 and ABCG8 which accelerate direct HDL transport of intestine into the lumen, thus these genes also play an important role in the RCT system and their enhancement by LXR agonists prevent an atherosclerotic development[51].

MECHANISMS OF *ABCA1* AND *ABCG1* GENE REGULATION

ABCA1 gene expression and cellular efflux of cholesterol are enhanced by cholesterol[15,18], oxysterols[52], retinoids[53], and cAMP analogs[15,54]. The *ABCA1* gene promoter has been analyzed[13,52]. Both oxysterols and retinoids are ligands for the nuclear transcription factor, LXRα/β and retinoid X receptor-alpha (RXRα), respectively, which have been identified as an enhancer of *ABCA1* gene expression[52,53,55,56]. It is present in dimeric form of LXR and RXR as active transcriptional heterodimers that preferentially bind to responsive elements in the ABCA1 gene promoter[13,57]. LXRα/β and RXRα bind to the specific responsive element, called direct repeat 4 (DR4) element within the ABCA1 promoter, which is characterized by two direct hexameric repeats separated by four nucleotides, thereafter they are activated by oxysterols and retinoids[58,59]. ABCA1 transcription are activated to bind either one or both ligands. Treatment with either a ligand of LXRα/β or RXRα enhances cellular ABCA1 expression, furthermore their combination treatment has a marked synergistic effect[60].

Since peroxisome proliferator activating receptor (PPAR)-α and -γ agonists such as fibrates and thiazolidine derivative (TZD) upregulate LXR mRNA expression, the activation of PPARs indirectly enhances a transcription activity of ABCA1 *via* LXR in cultured cells. In contrast, it is already known the zinc finger protein ZNF202 transcription factor as a major transcriptional repressor for ABCA1. In addition to the factor ZNF202, unsaturated fatty acids, but not saturated one, drastically suppress ABCA1-mediated cholesterol effluxes from macrophages by which they antagonize the binding of specific agonist, oxysterol to LXR[61,62]. Moreover, various transcription factors, such as upstream stimulatory factor (USF)1, USF2, Fra2, and Sp3, also have

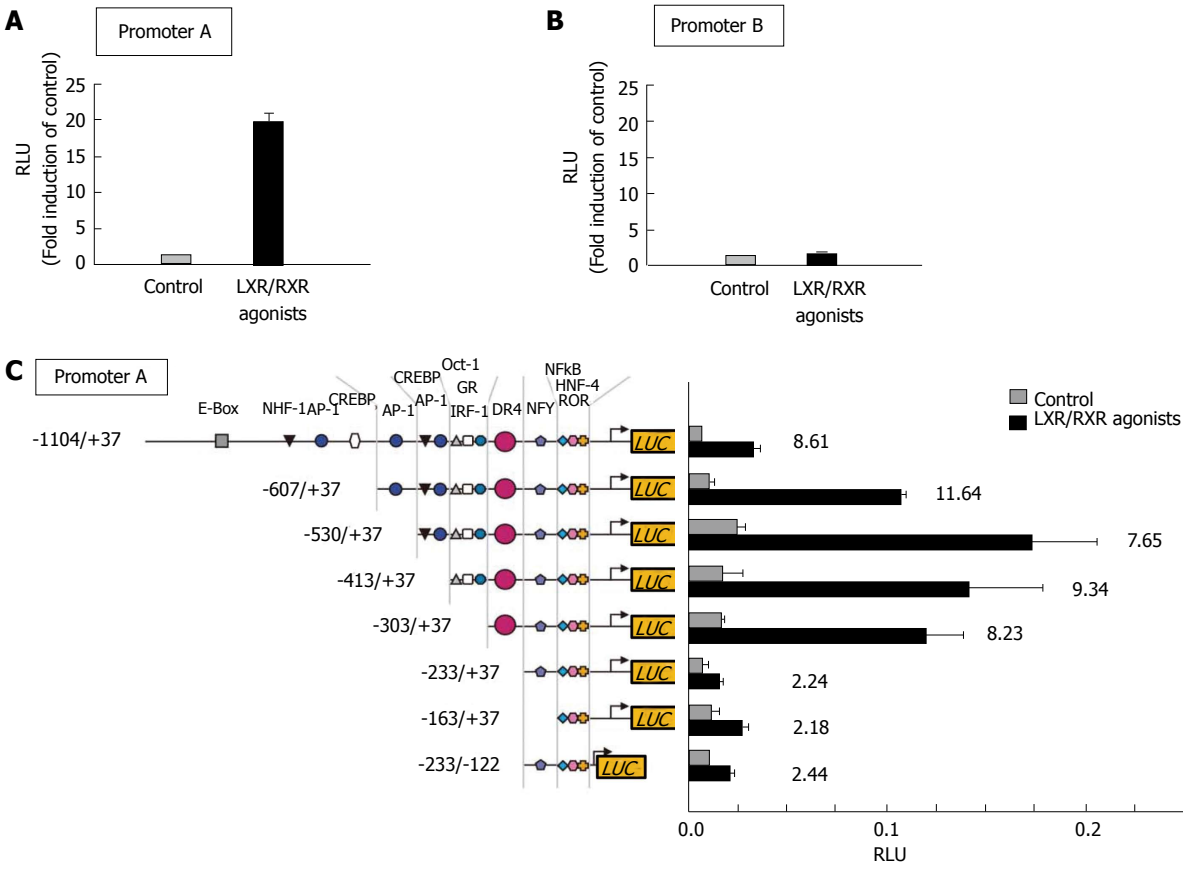

Figure 3 Response of liver X receptor and retinoid X receptor agonists to human ATP-binding G1 promoter activities in RAW264 cells. A: Human wild-type ATP-binding cassette transporter G1 (ABCG1) promoter-A located upstream of exon 1; B: Human wild-type ABCG1 promoter-B located upstream of exon 5; C: ABCG1 promoter (promoter-A; upstream of exon 1) vectors that contain a truncated 5'-region of the *ABCG1* gene. After transfection, cells were incubated with or without agonists of LXR [22(R)-hydroxycholesterol, 10 μmol/L] and RXR (9-cis-retinoic acid, 10 μmol/L). Results are expressed as mean ± SD. Graphs modified from the paper by Uehara *et al*[62]. LXR: Liver X receptor; RXR: Retinoid X receptor; RLU: Relative luciferase units .

the potential to repress the ABCA1 transcription[63].

The *ABCG1* gene has a promoter upstream of exon 1 and another intron promoter, which encodes several transcripts[64-66]. Our previous study demonstrated that LXR activation drastically increased the ABCG1 promoter activity (Promoter-A) located upstream of exon 1 as well as the *ABCA1* gene (Figure 3A). On the other hand, the activity of ABCG1 promoter-B located within intron 4 was not changed by an activation of LXR (Figure 3B)[62]. These results indicate that the gene transcription of exon 5 and subsequent exons might be also regulated, at least in part, by the ABCG1 promoter-A.

Electrophoretic mobility shift assay was done to confirm these findings, and it showed the existence of DNA-binding nuclear receptors on extracted ABCG1 promoter-A having DR4 element. As would be expected from these finding, only the ABCG1 promoter-A contained a DR4 element, but not promoter-B, which is required for binding to LXRα/RXR. In fact, a promoter response to ligands of LXR/RXR was totally abolished in the mutated ABCG1 promoter lacked an active DR4 element[62] (Figure 3C).

ABCG1 SINGLE NUCLEOTIDE POLYMORPHISMS

It remains unclear whether ABCG1 itself contributes to circulating lipid levels, such as HDL cholesterol and arterial plaque regression in humans. There have been only five reports on ABCG1 polymorphisms. Our previous study was the first regarding an ABCG1 polymorphism, which appeared to be a potent functional ABCG1 polymorphism located in the promoter region[67-71]. The ABCG1 promoter -257T>G polymorphism, rs1378577, -394 T/G from the transcription start site (NM_207627.1: c. -394T>G), -134 T/G from exon 1 (NM_207627.1) is a single nucleotide mutation (SNP) on the ABCG1 promoter region upstream of exon 1, which was reported to be a functional promoter with an LXR-responsive element[62,67].

To investigate whether this promoter polymorphism influenced gene transcriptional activity, in vitro luciferase reporter gene assays were performed after transient transfection in cultured cells. In these experiments, the amount of luciferase activity was 25.7% higher in T allelic sequence containing construct than that in G allelic one on ABCG1 promoter-A; these responses were significantly different (Figure 4A). ABCG1 promoter activity induced by LXR and RXR agonists increased by 4.6-fold, and the amount of luciferase produced by the construct containing the T allelic sequence was 30.9% higher than that produced by the construct containing the G allele, which was also significantly different as well as in the absence of LXR/RXR agonists (Figure 4B). The transcription activity

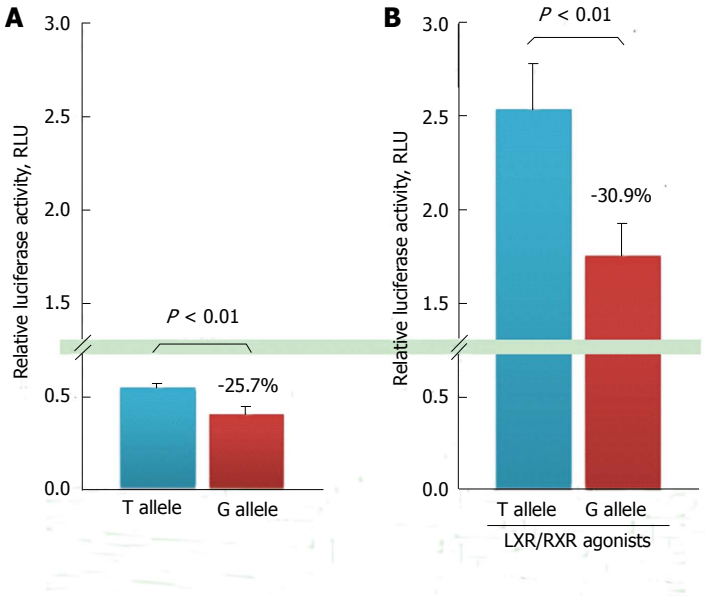

Figure 4 ***In vitro*** **promoter activity assay for ATP-binding G1 promoter-A.** ATP-binding cassette transporter G1 (ABCG1) promoter construct with a −257T/G mutation, −394 T/G from the transcription start site (NM_207627.1: c.-394T > G) on ABCG1 promoter-A, which is reported to be a functional promoter with an LXR-responsive element. A: ABCG1 transcription activity on a construct that contains the T or G allelic sequence; B: ABCG1 transcription activity induced by 5 μmol/L of T0901317 (T0) and 9-cis-retinoic acid (9cisRA) on constructs that contain the T or G allelic sequence. Results are expressed as mean ± SD. Graphs are modified from the paper by Furuyama *et al*[67]. ABC: ATP-binding cassette; RXR: Retinoid X receptor; LXR: Liver X receptor.

in the T allelic sequence was significantly higher than that in the G allelic sequence on ABCG1 promoter-A.

Furthermore, the ABCG1 promoter showed increased activity *via* stimulation by LXR and RXR, and a similar genotype-dependent effect on ABCG1 gene transcription under these conditions was identified. These results suggest that the ABCG1 promoter polymorphism might be an isolated regulating factor for *ABCG1* gene transcription activity, independent of LXR and RXR.

We genotyped 109 Japanese male CAD patients for the ABCG1 promoter SNP. This polymorphism was associated with CAD severity in Japanese men, but not with changes in lipid levels under fasting conditions in a case control study. Logistic regression analysis showed that there was an interaction between the ABCG1 promoter genotype and CAD severity.

Genotype frequencies were grouped on the basis of whether patients had multi- or single-vessel CAD. The adjusted relative risk associated with the G allele (assuming an additive effect) in a matched-pair analysis was 2.1 for multi-vessel CAD compared with single-vessel CAD and 3.5 for the G/G and T/G genotypes compared with T/T (assuming a dominant effect of the G allele)[67]. These results were consistent with the proposition that the variations for *ABCG1* gene might make a contribution to interindividual variability in susceptibility or severity of atherosclerotic changes.

ABCG1 expression levels in atherosclerotic tissues might be lower among those with the G allele and may be associated with a mechanism for an increased incidence of atherosclerosis in these individuals. These results were similar to a previous study by Baldán *et al*[72] of transgenic mice in whom the *ABCG1* gene was deleted[73]. Furthermore, a recent study regarding ABCG1 as a candidate gene with possible important antiatherogenic properties also illustrates the current interest in this transporter.

HDL-TARGETING THERAPY FOR ATHEROSCLEROSIS

Inhibiting scavenger receptor BI (SR-BI), CE transfer protein (CETP) or PL transfer protein, and an activating ABCA1 or apoA-I elevate HDL cholesterol levels. However, it is uncertain whether the effects of these interventions on atherosclerosis are consistence with the results of studies with animal models and inborn human HDL metabolism errors. Although it has not found a such small molecule which strongly promotes apoA-I production, one possible candidate molecule is LXR agonist which increase HDL cholesterol levels *via* upregulation of ABCA1 and ABCG1 expressions. Unfortunately, previous study has shown that concurrent with an activation of RCT, the agonist induces hypertriglycemia consequent on increasing hepatic VLDL production.

As a therapeutic approach for increasing HDL levels, much research has focused both increasing HDL cholesterol levels and on enhancing HDL biochemical functions. HDL therapies that used injections of reconstituted HDL, apoA-I mimetics, or full-length apoA-I are remarkably effective[74,75]. Nissen *et al*[75] showed that in humans, intravenous administation of ETC-216, an apoA-I-Milano complexed with phospholipids, produced a significant regression of coronary atherosclerotic plaques as determined by intravascular ultrasound (IVUS). After infusing ETC-216, regression of coronary atherosclerosis was accompanied by reverse remodeling of the external elastic membrane and with no changes in luminal dimensions as assessed by IVUS analyses[76].

Reconstituted HDL (rHDL), a complex of apoA-I or apoA-I mimetics with PL, must be shaped as disc, and it may be a suitable administration in patients with atherosclerotic plaque and TD. ABCA1 plays an important role for apoA-I-mediated cholesterol efflux in macrophages, and thereby is involved in discoidal HDL precursor formation. Mature HDL particles shaped spherical induce cholesterol effluxes by other transporters such as ABCG1 and ABCG4, rather than ABCA1[35]. We previously established a discoidal rHDL, which was a complex of human serum-derived full length of apoA-I with PL, 1-palmitoyl-2-oleoylphosphatidylcholine (POPC)[77]. Interestingly, the apoA-I complex with a PL, a POPC/apoA-I disc, could take up cholesterol from macrophages in both nor-

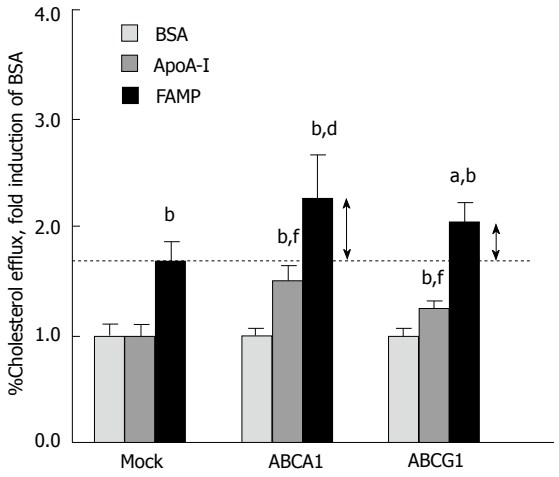

Figure 5 Fukuoka University apoA-Ⅰ mimetic peptide effects on cellular cholesterol effluxes in cells that express ATP-binding A1 and ATP-binding G1. COS-7 cells were transiently transfected with an empty vector (mock) or with human ATP-binding cassette transporter A1 (ABCA1) and ATP-binding cassette transporter G1 (ABCG1) cDNAs. Cholesterol efflux was determined after incubation with apoA-Ⅰ or FAMP. Results are expressed as mean ± SD. $^{a}P < 0.05$ *vs* FAMP in mock; $^{b}P < 0.01$ *vs* BSA; $^{d}P < 0.01$ *vs* FAMP in mock; $^{f}P < 0.01$ *vs* apoA-Ⅰ in mock. Graph modified from the paper by Uehara *et al*[82]. FAMP: Fukuoka University ApoA-Ⅰ mimetic peptide; BSA: bovine serum albumin; apoA-Ⅰ: apolipoprotein A-Ⅰ; FAMP: Fukuoka University ApoA-Ⅰ Mimetic Peptide..

mal subjects and TD patients.

Although studies on the use of apoA-I mimetic peptides (*e.g.*, 4F and L37pA) are underway[78-80], none of these agents are currently available for clinical use. To develop a physiological HDL-generating apoA-I mimetic peptide that functions with ABCA1 transporter, different candidate peptides were synthesized by focusing on the amino acid sequence alignments of human apoA-I interactions with ABCA1. We recently established a novel short apoA-I mimetic peptide that comprised 24 amino acids and without phospholipids Fukuoka University ApoA-I Mimetic Peptide (FAMP), which retained the amphipathic helical structure of the 243-amino acid apoA-I and the ability to associate with lipids[81]. This was shown to enhance HDL function and suppress aortic plaque formation in apoE-knockout mice that were fed a high-fat diet. FAMP markedly increased pre-beta HDL formation as well as increased the overall cholesterol effluxes from peripheral tissues[82].

In contrast to apoA-I, FAMP-mediated cholesterol effluxes were not completely abolished under ABCA1-inactivated conditions, such as in cells treated with probucol, an ABCA1 antagonist, and Tangier macrophages. These results suggested that FAMP functioned in removing cholesterol through both the ABCA1 pathway and another specific pathway that must be dependent on ABCG1 transporters (Figure 1). In support of this, COS-7 cells that were transiently transfected with the *ABCA1* and *ABCG1* genes had significantly increased FAMP-mediated effluxes compared with mock transfection (Figure 5).

Injections of HDL apo-A-I mimetics, apoA-I-Milano, and full-length apoA-I are effective both *in vitro* and *in vivo*. However, it remains unclear whether apoA-I or its mimetics actually enter atherosclerotic plaque lesions and remove cholesterol. ApoA-I may generate nascent, new HDL and reverse the macrophage foam cell phenotype.

We developed a novel PET tracer that was functionalized with DOTA and labeled with ^{68}Ga to specifically image the status of atherosclerotic plaques. Atherosclerotic plaques and aortic atherosclerotic plaques show high uptake of this tracer, and this novel tracer provides for impressive *in vivo* imaging of an aortic plaque using PET/CT[83]. HDL-targeting therapy, including FAMP, may have tremendous atheroprotective potential and prove to be a new therapeutic tool for atherosclerotic cardiovascular disease. While most research has focused on the therapeutic use of HDL, an apoA-I mimetic peptide may also contribute to the development of a tool for plaque diagnosis.

CONCLUSION

The RCT pathway has several potential antiatherogenic properties. Both ABCA1 and ABCG1 are lipid transporters on plasma membrane that have been contributed in mediating effluxes of cholesterol and PLs from cells in the presence of lipid-poor or lipid-free apoA-I and HDL. As a therapeutic approach for increasing HDL levels, much research has focused both on increasing HDL cholesterol levels and on enhancing HDL biochemical functions. HDL therapies with reconstituted HDL, apoA-I mimetics, or full-length apoA-I am dramatically effective. In particular, a novel apoA-I mimetic peptide, FAMP, effectively removes cholesterol *via* specific ABCA1 and other transporters, such as ABCG1. FAMP has an antiatherosclerotic effect by enhancing biological HDL functions without changing circulating HDL cholesterol levels. These HDL-targeting therapies have significant atheroprotective potential, as they are lipid transporter-targeting agents. Thus, HDL-targeting therapy may prove to be a therapeutic tool for atherosclerotic cardiovascular diseases.

REFERENCES

1 **von Eckardstein A**, Nofer JR, Assmann G. High density lipoproteins and arteriosclerosis. Role of cholesterol efflux and reverse cholesterol transport. *Arterioscler Thromb Vasc Biol* 2001; **21**: 13-27 [PMID: 11145929 DOI: 10.1161/01.ATV.21.1.13]

2 **Després JP**, Marette A. Relation of components of insulin resistance syndrome to coronary disease risk. *Curr Opin Lipidol* 1994; **5**: 274-289 [PMID: 7981959 DOI: 10.1097/00041433-199408000-00006]

3 **Havel RJ**, Eder HA, Bragdon JH. The distribution and chemical composition of ultracentrifugally separated lipoproteins in human serum. *J Clin Invest* 1955; **34**: 1345-1353 [PMID: 13252080 DOI: 10.1172/JCI103182]

4 **Kunitake ST**, La Sala KJ, Kane JP. Apolipoprotein A-I-containing lipoproteins with pre-beta electrophoretic mobility. *J Lipid Res* 1985; **26**: 549-555 [PMID: 3926924]

5 **Ishida BY**, Frolich J, Fielding CJ. Prebeta-migrating high density lipoprotein: quantitation in normal and hyperlipidemic plasma by solid phase radioimmunoassay following

electrophoretic transfer. *J Lipid Res* 1987; **28**: 778-786 [PMID: 3114402]
6 **Miller M**, Rhyne J, Hamlette S, Birnbaum J, Rodriguez A. Genetics of HDL regulation in humans. *Curr Opin Lipidol* 2003; **14**: 273-279 [PMID: 12840658 DOI: 10.1097/01.mol.0000073506.41685.d2]
7 **Fredrickson DS**, Altrocchi PH, Avioli LV, Goodman DS and Goodman HC. Tangier disease combined clinical staff conference at the National Institutes of Health. *Ann Intern Med* 1961; **55**: 1016-1031 [DOI: 10.7326/0003-4819-55-6-1016]
8 **Assman G,** von Eckardstein A and Brewer HBJ. Familial high density lipoprotein deficiency: Tangier disease. The metabolic and Molecular Basis of Inherited Disease.7th ed. C. R. Scriver, A. L. Beaudet, W. S. Sly and D. Valle, editor. New York: McGraw-Hill, 1995: 2053-2072
9 **Hobbs HH**, Rader DJ. ABC1: connecting yellow tonsils, neuropathy, and very low HDL. *J Clin Invest* 1999; **104**: 1015-1017 [PMID: 10525038 DOI: 10.1172/JCI8509]
10 **Brooks-Wilson A**, Marcil M, Clee SM, Zhang LH, Roomp K, van Dam M, Yu L, Brewer C, Collins JA, Molhuizen HO, Loubser O, Ouelette BF, Fichter K, Ashbourne-Excoffon KJ, Sensen CW, Scherer S, Mott S, Denis M, Martindale D, Frohlich J, Morgan K, Koop B, Pimstone S, Kastelein JJ, Hayden MR and et al. Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency. *Nat Genet* 1999; **22**: 336-345 [DOI: 10.1038/11905]
11 **Rust S**, Rosier M, Funke H, Real J, Amoura Z, Piette JC, Deleuze JF, Brewer HB, Duverger N, Denèfle P, Assmann G. Tangier disease is caused by mutations in the gene encoding ATP-binding cassette transporter 1. *Nat Genet* 1999; **22**: 352-355 [PMID: 10431238 DOI: 10.1038/11921]
12 **Remaley AT**, Rust S, Rosier M, Knapper C, Naudin L, Broccardo C, Peterson KM, Koch C, Arnould I, Prades C, Duverger N, Funke H, Assman G, Dinger M, Dean M, Chimini G, Santamarina Fojo S, Fredrickson DS, Denefle P and Brewer HB, Jr. Human ATP-binding cassette transporter 1 (ABC1): genomic organization and identification of the genetic defect in the original Tangier disease kindred. *Proc Natl Acad Sci USA* 1999; **96**: 12685-12690 [DOI: 10.1073/pnas.96.22.12685]
13 **Santamarina-Fojo S**, Peterson K, Knapper C, Qiu Y, Freeman L, Cheng JF, Osorio J, Remaley A, Yang XP, Haudenschild C, Prades C, Chimini G, Blackmon E, Francois T, Duverger N, Rubin EM, Rosier M, Denèfle P, Fredrickson DS, Brewer HB. Complete genomic sequence of the human ABCA1 gene: analysis of the human and mouse ATP-binding cassette A promoter. *Proc Natl Acad Sci USA* 2000; **97**: 7987-7992 [PMID: 10884428 DOI: 10.1073/pnas.97.14.7987]
14 **Bodzioch M**, Orsó E, Klucken J, Langmann T, Böttcher A, Diederich W, Drobnik W, Barlage S, Büchler C, Porsch-Ozcürümez M, Kaminski WE, Hahmann HW, Oette K, Rothe G, Aslanidis C, Lackner KJ, Schmitz G. The gene encoding ATP-binding cassette transporter 1 is mutated in Tangier disease. *Nat Genet* 1999; **22**: 347-351 [PMID: 10431237 DOI: 10.1038/11914]
15 **Lawn RM**, Wade DP, Garvin MR, Wang X, Schwartz K, Porter JG, Seilhamer JJ, Vaughan AM, Oram JF. The Tangier disease gene product ABC1 controls the cellular apolipoprotein-mediated lipid removal pathway. *J Clin Invest* 1999; **104**: R25-R31 [PMID: 10525055 DOI: 10.1172/JCI8119]
16 **Klein I**, Sarkadi B, Váradi A. An inventory of the human ABC proteins. *Biochim Biophys Acta* 1999; **1461**: 237-262 [PMID: 10581359 DOI: 10.1016/S0005-2736(99)00161-3]
17 **Dean M**, Annilo T. Evolution of the ATP-binding cassette (ABC) transporter superfamily in vertebrates. *Annu Rev Genomics Hum Genet* 2005; **6**: 123-142 [PMID: 16124856 DOI: 10.1146/annurev.genom.6.080604.162122]
18 **Langmann T**, Klucken J, Reil M, Liebisch G, Luciani MF, Chimini G, Kaminski WE and Schmitz G. Molecular cloning of the human ATP-binding cassette transporter 1 (hABC1): evidence for sterol-dependent regulation in macrophages. *Biochem-Biophys-Res-Commun* 1999; **257**: 29-33 [DOI: 10.1006/bbrc.1999.0406]
19 **Walker JE**, Saraste M, Runswick MJ, Gay NJ. Distantly related sequences in the alpha- and beta-subunits of ATP synthase, myosin, kinases and other ATP-requiring enzymes and a common nucleotide binding fold. *EMBO J* 1982; **1**: 945-951 [PMID: 6329717]
20 **Oram JF**, Lawn RM. ABCA1. The gatekeeper for eliminating excess tissue cholesterol. *J Lipid Res* 2001; **42**: 1173-1179 [PMID: 11483617]
21 **Neufeld EB**, Remaley AT, Demosky SJ, Stonik JA, Cooney AM, Comly M, Dwyer NK, Zhang M, Blanchette-Mackie J, Santamarina-Fojo S, Brewer HB. Cellular localization and trafficking of the human ABCA1 transporter. *J Biol Chem* 2001; **276**: 27584-27590 [PMID: 11349133 DOI: 10.1074/jbc.M103264200]
22 **von Eckardstein A**, Rohrer L. Transendothelial lipoprotein transport and regulation of endothelial permeability and integrity by lipoproteins. *Curr Opin Lipidol* 2009; **20**: 197-205 [PMID: 19395962 DOI: 10.1097/MOL.0b013e32832afd63]
23 **Uehara Y**, Tsuboi Y, Zhang B, Miura S, Baba Y, Higuchi MA, Yamada T, Rye KA, Saku K. POPC/apoA-I discs as a potent lipoprotein modulator in Tangier disease. *Atherosclerosis* 2008; **197**: 283-289 [PMID: 17560579 DOI: 10.1016/j.atherosclerosis.2007.04.025]
24 **Orsó E**, Broccardo C, Kaminski WE, Böttcher A, Liebisch G, Drobnik W, Götz A, Chambenoit O, Diederich W, Langmann T, Spruss T, Luciani MF, Rothe G, Lackner KJ, Chimini G, Schmitz G. Transport of lipids from golgi to plasma membrane is defective in tangier disease patients and Abc1-deficient mice. *Nat Genet* 2000; **24**: 192-196 [PMID: 10655069 DOI: 10.1038/72869]
25 **McNeish J**, Aiello RJ, Guyot D, Turi T, Gabel C, Aldinger C, Hoppe KL, Roach ML, Royer LJ, de Wet J, Broccardo C, Chimini G, Francone OL. High density lipoprotein deficiency and foam cell accumulation in mice with targeted disruption of ATP-binding cassette transporter-1. *Proc Natl Acad Sci USA* 2000; **97**: 4245-4250 [PMID: 10760292 DOI: 10.1073/pnas.97.8.4245]
26 **Vaisman BL**, Lambert G, Amar M, Joyce C, Ito T, Shamburek RD, Cain WJ, Fruchart-Najib J, Neufeld ED, Remaley AT, Brewer HB, Santamarina-Fojo S. ABCA1 overexpression leads to hyperalphalipoproteinemia and increased biliary cholesterol excretion in transgenic mice. *J Clin Invest* 2001; **108**: 303-309 [PMID: 11457883 DOI: 10.1172/JCI200112517]
27 **Singaraja RR**, Bocher V, James ER, Clee SM, Zhang LH, Leavitt BR, Tan B, Brooks-Wilson A, Kwok A, Bissada N, Yang YZ, Liu G, Tafuri SR, Fievet C, Wellington CL, Staels B, Hayden MR. Human ABCA1 BAC transgenic mice show increased high density lipoprotein cholesterol and ApoAI-dependent efflux stimulated by an internal promoter containing liver X receptor response elements in intron 1. *J Biol Chem* 2001; **276**: 33969-33979 [PMID: 11423537 DOI: 10.1074/jbc.M102503200]
28 **Croop JM**, Tiller GE, Fletcher JA, Lux ML, Raab E, Goldenson D, Son D, Arciniegas S, Wu RL. Isolation and characterization of a mammalian homolog of the Drosophila white gene. *Gene* 1997; **185**: 77-85 [PMID: 9034316 DOI: 10.1016/S0378-1119(96)00633-6]
29 **Chen H**, Rossier C, Lalioti MD, Lynn A, Chakravarti A, Perrin G, Antonarakis SE. Cloning of the cDNA for a human homologue of the Drosophila white gene and mapping to chromosome 21q22.3. *Am J Hum Genet* 1996; **59**: 66-75 [PMID: 8659545]
30 **Savary S**, Denizot F, Luciani M, Mattei M, Chimini G. Molecular cloning of a mammalian ABC transporter homologous

to Drosophila white gene. *Mamm Genome* 1996; **7**: 673-676 [PMID: 8703120 DOI: 10.1007/s003359900203]
31 **Dean M**, Rzhetsky A, Allikmets R. The human ATP-binding cassette (ABC) transporter superfamily. *Genome Res* 2001; **11**: 1156-1166 [PMID: 11435397 DOI: 10.1101/gr.GR-1649R]
32 **Klucken J**, Buchler C, Orso E, Kaminski WE, Porsch-Ozcurumez M, Liebisch G, Kapinsky M, Diederich W, Drobnik W, Dean M, Allikmets R and Schmitz G. ABCG1 (ABC8), the human homolog of the Drosophila white gene, is a regulator of macrophage cholesterol and phospholipid transport. *Proc Natl Acad Sci USA* 2000; **97**: 817-822 [DOI: 10.1073/pnas.97.2.817]
33 **Francis GA**, Knopp RH, Oram JF. Defective removal of cellular cholesterol and phospholipids by apolipoprotein A-I in Tangier Disease. *J Clin Invest* 1995; **96**: 78-87 [PMID: 7615839 DOI: 10.1172/JCI118082]
34 **Wang N**, Silver DL, Costet P, Tall AR. Specific binding of ApoA-I, enhanced cholesterol efflux, and altered plasma membrane morphology in cells expressing ABC1. *J Biol Chem* 2000; **275**: 33053-33058 [PMID: 0010918065 DOI: 10.1074/jbc.M005438200]
35 **Wang N**, Lan D, Chen W, Matsuura F, Tall AR. ATP-binding cassette transporters G1 and G4 mediate cellular cholesterol efflux to high-density lipoproteins. *Proc Natl Acad Sci USA* 2004; **101**: 9774-9779 [PMID: 15210959 DOI: 10.1073/pnas.0403506101]
36 **Smith JD**. Insight into ABCG1-mediated cholesterol efflux. *Arterioscler Thromb Vasc Biol* 2006; **26**: 1198-1200 [PMID: 16709952 DOI: 10.1161/01.ATV.0000221217.86465.66]
37 **Uehara Y**, Yamada T, Baba Y, Miura S, Abe S, Kitajima K, Higuchi MA, Iwamoto T, Saku K. ATP-binding cassette transporter G4 is highly expressed in microglia in Alzheimer's brain. *Brain Res* 2008; **1217**: 239-246 [PMID: 18508037]
38 **Kennedy MA**, Barrera GC, Nakamura K, Baldán A, Tarr P, Fishbein MC, Frank J, Francone OL, Edwards PA. ABCG1 has a critical role in mediating cholesterol efflux to HDL and preventing cellular lipid accumulation. *Cell Metab* 2005; **1**: 121-131 [PMID: 16054053 DOI: 10.1016/j.cmet.2005.01.002]
39 **Mauldin JP**, Srinivasan S, Mulya A, Gebre A, Parks JS, Daugherty A, Hedrick CC. Reduction in ABCG1 in Type 2 diabetic mice increases macrophage foam cell formation. *J Biol Chem* 2006; **281**: 21216-21224 [PMID: 16723355 DOI: 10.1074/jbc.M510952200]
40 **Out R**, Hoekstra M, Hildebrand RB, Kruit JK, Meurs I, Li Z, Kuipers F, Van Berkel TJ, Van Eck M. Macrophage ABCG1 deletion disrupts lipid homeostasis in alveolar macrophages and moderately influences atherosclerotic lesion development in LDL receptor-deficient mice. *Arterioscler Thromb Vasc Biol* 2006; **26**: 2295-2300 [PMID: 16857950 DOI: 10.1161/01.ATV.0000237629.29842.4c]
41 **Baldán A**, Pei L, Lee R, Tarr P, Tangirala RK, Weinstein MM, Frank J, Li AC, Tontonoz P, Edwards PA. Impaired development of atherosclerosis in hyperlipidemic Ldlr-/- and ApoE-/- mice transplanted with Abcg1-/- bone marrow. *Arterioscler Thromb Vasc Biol* 2006; **26**: 2301-2307 [PMID: 16888235 DOI: 10.1161/01.ATV.0000240051.22944.dc]
42 **Ranalletta M**, Wang N, Han S, Yvan-Charvet L, Welch C, Tall AR. Decreased atherosclerosis in low-density lipoprotein receptor knockout mice transplanted with Abcg1-/- bone marrow. *Arterioscler Thromb Vasc Biol* 2006; **26**: 2308-2315 [PMID: 16917103 DOI: 10.1161/01.ATV.0000242275.92915.43]
43 **Out R**, Hoekstra M, Meurs I, de Vos P, Kuiper J, Van Eck M, Van Berkel TJ. Total body ABCG1 expression protects against early atherosclerotic lesion development in mice. *Arterioscler Thromb Vasc Biol* 2007; **27**: 594-599 [PMID: 17204665 DOI: 10.1161/01.ATV.0000257136.24308.0c]
44 **Graf GA**, Yu L, Li WP, Gerard R, Tuma PL, Cohen JC, Hobbs HH. ABCG5 and ABCG8 are obligate heterodimers for protein trafficking and biliary cholesterol excretion. *J Biol Chem* 2003; **278**: 48275-48282 [PMID: 14504269 DOI: 10.1074/jbc.M310223200]
45 **Patel SB**, Salen G, Hidaka H, Kwiterovich PO, Stalenhoef AF, Miettinen TA, Grundy SM, Lee MH, Rubenstein JS, Polymeropoulos MH, Brownstein MJ. Mapping a gene involved in regulating dietary cholesterol absorption. The sitosterolemia locus is found at chromosome 2p21. *J Clin Invest* 1998; **102**: 1041-1044 [PMID: 9727073 DOI: 10.1172/JCI3963]
46 **Berge KE**, Tian H, Graf GA, Yu L, Grishin NV, Schultz J, Kwiterovich P, Shan B, Barnes R, Hobbs HH. Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. *Science* 2000; **290**: 1771-1775 [PMID: 11099417 DOI: 10.1126/science.290.5497.1771]
47 **Lee MH**, Lu K, Hazard S, Yu H, Shulenin S, Hidaka H, Kojima H, Allikmets R, Sakuma N, Pegoraro R, Srivastava AK, Salen G, Dean M, Patel SB. Identification of a gene, ABCG5, important in the regulation of dietary cholesterol absorption. *Nat Genet* 2001; **27**: 79-83 [PMID: 11138003 DOI: 10.1038/83799]
48 **Oram JF**, Vaughan AM. ATP-Binding cassette cholesterol transporters and cardiovascular disease. *Circ Res* 2006; **99**: 1031-1043 [PMID: 17095732]
49 **Yu L**, Hammer RE, Li-Hawkins J, Von Bergmann K, Lutjohann D, Cohen JC, Hobbs HH. Disruption of Abcg5 and Abcg8 in mice reveals their crucial role in biliary cholesterol secretion. *Proc Natl Acad Sci USA* 2002; **99**: 16237-16242 [PMID: 12444248 DOI: 10.1073/pnas.252582399]
50 **Yu L**, Li-Hawkins J, Hammer RE, Berge KE, Horton JD, Cohen JC, Hobbs HH. Overexpression of ABCG5 and ABCG8 promotes biliary cholesterol secretion and reduces fractional absorption of dietary cholesterol. *J Clin Invest* 2002; **110**: 671-680 [PMID: 12208868 DOI: 10.1172/JCI16001]
51 **Calpe-Berdiel L**, Rotllan N, Fiévet C, Roig R, Blanco-Vaca F, Escolà-Gil JC. Liver X receptor-mediated activation of reverse cholesterol transport from macrophages to feces in vivo requires ABCG5/G8. *J Lipid Res* 2008; **49**: 1904-1911 [PMID: 18509196 DOI: 10.1194/jlr.M700470-JLR200]
52 **Costet P**, Luo Y, Wang N, Tall AR. Sterol-dependent transactivation of the ABC1 promoter by the liver X receptor/retinoid X receptor. *J Biol Chem* 2000; **275**: 28240-28245 [PMID: 10858438]
53 **Repa JJ**, Turley SD, Lobaccaro JA, Medina J, Li L, Lustig K, Shan B, Heyman RA, Dietschy JM, Mangelsdorf DJ. Regulation of absorption and ABC1-mediated efflux of cholesterol by RXR heterodimers. *Science* 2000; **289**: 1524-1529 [PMID: 10968783 DOI: 10.1126/science.289.5484.1524]
54 **Bortnick AE**, Rothblat GH, Stoudt G, Hoppe KL, Royer LJ, McNeish J, Francone OL. The correlation of ATP-binding cassette 1 mRNA levels with cholesterol efflux from various cell lines. *J Biol Chem* 2000; **275**: 28634-28640 [PMID: 10893411 DOI: 10.1074/jbc.M003407200]
55 **Oram JF**, Lawn RM, Garvin MR, Wade DP. ABCA1 is the cAMP-inducible apolipoprotein receptor that mediates cholesterol secretion from macrophages. *J Biol Chem* 2000; **275**: 34508-34511 [PMID: 10918070 DOI: 10.1074/jbc.M006738200]
56 **Venkateswaran A**, Laffitte BA, Joseph SB, Mak PA, Wilpitz DC, Edwards PA, Tontonoz P. Control of cellular cholesterol efflux by the nuclear oxysterol receptor LXR alpha. *Proc Natl Acad Sci USA* 2000; **97**: 12097-12102 [PMID: 11035776 DOI: 10.1073/pnas.200367697]
57 **Wang N**, Silver DL, Thiele C, Tall AR. ATP-binding cassette transporter A1 (ABCA1) functions as a cholesterol efflux regulatory protein. *J Biol Chem* 2001; **276**: 23742-23747 [PMID: 11309399 DOI: 10.1074/jbc.M102348200]
58 **Willy PJ**, Umesono K, Ong ES, Evans RM, Heyman RA, Mangelsdorf DJ. LXR, a nuclear receptor that defines a distinct retinoid response pathway. *Genes Dev* 1995; **9**: 1033-1045 [PMID: 7744246 DOI: 10.1101/gad.9.9.1033]
59 **Bungert S**, Molday LL, Molday RS. Membrane topology of the ATP binding cassette transporter ABCR and its relationship to ABC1 and related ABCA transporters: identifica-

tion of N-linked glycosylation sites. *J Biol Chem* 2001; **276**: 23539-23546 [PMID: 11320094 DOI: 10.1074/jbc.M101902200]
60 **Schwartz K**, Lawn RM, Wade DP. ABC1 gene expression and ApoA-I-mediated cholesterol efflux are regulated by LXR. *Biochem Biophys Res Commun* 2000; **274**: 794-802 [PMID: 10924356 DOI: 10.1006/bbrc.2000.3243]
61 **Uehara Y**, Engel T, Li Z, Goepfert C, Rust S, Zhou X, Langer C, Schachtrup C, Wiekowski J, Lorkowski S, Assmann G, von Eckardstein A. Polyunsaturated fatty acids and acetoacetate downregulate the expression of the ATP-binding cassette transporter A1. *Diabetes* 2002; **51**: 2922-2928 [PMID: 12351428 DOI: 10.2337/diabetes.51.10.2922]
62 **Uehara Y**, Miura S, von Eckardstein A, Abe S, Fujii A, Matsuo Y, Rust S, Lorkowski S, Assmann G, Yamada T, Saku K. Unsaturated fatty acids suppress the expression of the ATP-binding cassette transporter G1 (ABCG1) and ABCA1 genes via an LXR/RXR responsive element. *Atherosclerosis* 2007; **191**: 11-21 [PMID: 16730733 DOI: 10.1016/j.atherosclerosis.2006.04.018]
63 **Yang XP**, Freeman LA, Knapper CL, Amar MJ, Remaley A, Brewer HB, Santamarina-Fojo S. The E-box motif in the proximal ABCA1 promoter mediates transcriptional repression of the ABCA1 gene. *J Lipid Res* 2002; **43**: 297-306 [PMID: 11861672]
64 **Lorkowski S**, Rust S, Engel T, Jung E, Tegelkamp K, Galinski EA, Assmann G, Cullen P. Genomic sequence and structure of the human ABCG1 (ABC8) gene. *Biochem Biophys Res Commun* 2001; **280**: 121-131 [PMID: 11162488 DOI: 10.1006/bbrc.2000.4089]
65 **Langmann T**, Porsch-Ozcürümez M, Unkelbach U, Klucken J, Schmitz G. Genomic organization and characterization of the promoter of the human ATP-binding cassette transporter-G1 (ABCG1) gene. *Biochim Biophys Acta* 2000; **1494**: 175-180 [PMID: 11072082 DOI: 10.1016/S0167-4781(00)00215-3]
66 **Kennedy MA**, Venkateswaran A, Tarr PT, Xenarios I, Kudoh J, Shimizu N, Edwards PA. Characterization of the human ABCG1 gene: liver X receptor activates an internal promoter that produces a novel transcript encoding an alternative form of the protein. *J Biol Chem* 2001; **276**: 39438-39447 [PMID: 11500512 DOI: 10.1074/jbc.M105863200]
67 **Furuyama S**, Uehara Y, Zhang B, Baba Y, Abe S, Iwamoto T, Miura S, Saku K. Genotypic Effect of ABCG1 gene promoter -257T& gt; G polymorphism on coronary artery disease severity in Japanese men. *J Atheroscler Thromb* 2009; **16**: 194-200 [PMID: 19556716]
68 **Xu Y**, Wang W, Zhang L, Qi LP, Li LY, Chen LF, Fang Q, Dang AM, Yan XW. A polymorphism in the ABCG1 promoter is functionally associated with coronary artery disease in a Chinese Han population. *Atherosclerosis* 2011; **219**: 648-654 [PMID: 21722899 DOI: 10.1016/j.atherosclerosis.2011.05.043]
69 **Di Martino MT**, Arbitrio M, Leone E, Guzzi PH, Rotundo MS, Ciliberto D, Tomaino V, Fabiani F, Talarico D, Sperlongano P, Doldo P, Cannataro M, Caraglia M, Tassone P, Tagliaferri P. Single nucleotide polymorphisms of ABCC5 and ABCG1 transporter genes correlate to irinotecan-associated gastrointestinal toxicity in colorectal cancer patients: a DMET microarray profiling study. *Cancer Biol Ther* 2011; **12**: 780-787 [PMID: 21892003 DOI: 10.4161/cbt.12.9.17781]
70 **Abellán R**, Mansego ML, Martínez-Hervás S, Morcillo S, Pineda-Alonso M, Carmena R, Real JT, Redon J, Rojo-Martínez G, Martín-Escudero JC, Chaves FJ. Dietary polyunsaturated fatty acids may increase plasma LDL-cholesterol and plasma cholesterol concentrations in carriers of an ABCG1 gene single nucleotide polymorphism: study in two Spanish populations. *Atherosclerosis* 2011; **219**: 900-906 [PMID: 21978921 DOI: 10.1016/j.atherosclerosis.2011.09.018]
71 **Olivier M**, Tanck MW, Out R, Villard EF, Lammers B, Bouchareychas L, Frisdal E, Superville A, Van Berkel T, Kastelein JJ, Eck MV, Jukema JW, Chapman MJ, Dallinga-Thie GM, Guerin M, Le Goff W. Human ATP-binding cassette G1 controls macrophage lipoprotein lipase bioavailability and promotes foam cell formation. *Arterioscler Thromb Vasc Biol* 2012; **32**: 2223-2231 [PMID: 22772754]
72 **Baldán A**, Tarr P, Vales CS, Frank J, Shimotake TK, Hawgood S, Edwards PA. Deletion of the transmembrane transporter ABCG1 results in progressive pulmonary lipidosis. *J Biol Chem* 2006; **281**: 29401-29410 [PMID: 16887795 DOI: 10.1074/jbc.M606597200]
73 **Rohrer L**, Ohnsorg PM, Lehner M, Landolt F, Rinninger F, von Eckardstein A. High-density lipoprotein transport through aortic endothelial cells involves scavenger receptor BI and ATP-binding cassette transporter G1. *Circ Res* 2009; **104**: 1142-1150 [PMID: 19372466 DOI: 10.1161/CIRCRESAHA.108.190587]
74 **Iwata A**, Miura S, Zhang B, Imaizumi S, Uehara Y, Shiomi M, Saku K. Antiatherogenic effects of newly developed apolipoprotein A-I mimetic peptide/phospholipid complexes against aortic plaque burden in Watanabe-heritable hyperlipidemic rabbits. *Atherosclerosis* 2011; **218**: 300-307 [PMID: 21696737 DOI: 10.1016/j.atherosclerosis.2011.05.029]
75 **Nissen SE**, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, Eaton GM, Lauer MA, Sheldon WS, Grines CL, Halpern S, Crowe T, Blankenship JC, Kerensky R. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA* 2003; **290**: 2292-2300 [PMID: 14600188 DOI: 10.1001/jama.290.17.2292]
76 **Nicholls SJ**, Tuzcu EM, Sipahi I, Schoenhagen P, Crowe T, Kapadia S, Nissen SE. Relationship between atheroma regression and change in lumen size after infusion of apolipoprotein A-I Milano. *J Am Coll Cardiol* 2006; **47**: 992-997 [PMID: 16516083 DOI: 10.1016/j.jacc.2005.11.040]
77 **Rye KA**, Hime NJ, Barter PJ. Evidence that cholesteryl ester transfer protein-mediated reductions in reconstituted high density lipoprotein size involve particle fusion. *J Biol Chem* 1997; **272**: 3953-3960 [PMID: 9020099 DOI: 10.1074/jbc.272.7.3953]
78 **Navab M**, Anantharamaiah GM, Hama S, Garber DW, Chaddha M, Hough G, Lallone R, Fogelman AM. Oral administration of an Apo A-I mimetic Peptide synthesized from D-amino acids dramatically reduces atherosclerosis in mice independent of plasma cholesterol. *Circulation* 2002; **105**: 290-292 [PMID: 11804981 DOI: 10.1161/hc0302.103711]
79 **Li X**, Chyu KY, Faria Neto JR, Yano J, Nathwani N, Ferreira C, Dimayuga PC, Cercek B, Kaul S, Shah PK. Differential effects of apolipoprotein A-I-mimetic peptide on evolving and established atherosclerosis in apolipoprotein E-null mice. *Circulation* 2004; **110**: 1701-1705 [PMID: 15353488 DOI: 10.1161/01.CIR.0000142857.79401.69]
80 **Remaley AT**, Thomas F, Stonik JA, Demosky SJ, Bark SE, Neufeld EB, Bocharov AV, Vishnyakova TG, Patterson AP, Eggerman TL, Santamarina-Fojo S, Brewer HB. Synthetic amphipathic helical peptides promote lipid efflux from cells by an ABCA1-dependent and an ABCA1-independent pathway. *J Lipid Res* 2003; **44**: 828-836 [PMID: 12562845 DOI: 10.1194/jlr.M200475-JLR200]
81 **Uehara Y**, Ando S, Oniki K, Abe S, Yahiro E, Tanigawa H, Miura SI and Saku K. FAMP, a novel apoA-I mimetic peptide promotes HDL via ABCA1-dependent cholesterol efflux. *Atheroscl Suppl* 2010; **11**: 3-3
82 **Uehara Y**, Ando S, Yahiro E, Oniki K, Ayaori M, Abe S, Kawachi E, Zhang B, Shioi S, Tanigawa H, Imaizumi S, Miura S, Saku K. FAMP, a novel apoA-I mimetic peptide, suppresses aortic plaque formation through promotion of biological HDL function in ApoE-deficient mice. *J Am Heart Assoc* 2013; **2**: e000048 [PMID: 23709562 DOI: 10.1161/JAHA.113.000048]

83 **Kawachi E**, Uehara Y, Hasegawa K, Yahiro E, Ando S, Wada Y, Yano T, Nishikawa H, Shiomi M, Miura S, Watanabe Y, Saku K. Novel molecular imaging of atherosclerosis with gallium-68-labeled apolipoprotein A-I mimetic peptide and positron emission tomography. *Circ J* 2013; **77**: 1482-1489 [PMID: 23459406 DOI: 10.1253/circj.CJ-12-0736]

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TOPIC HIGHLIGHT

WJC 6th Anniversary Special Issues (2): Coronary artery disease

Contribution of cardiovascular magnetic resonance in the evaluation of coronary arteries

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Abstract

Cardiovascular magnetic resonance (CMR) allows the nonradiating assessment of coronary arteries; to achieve better image quality cardiorespiratory artefacts should be corrected. Coronary MRA (CMRA) at the moment is indicated only for the detection of abnormal coronary origin, coronary artery ectasia and/or aneurysms (class Ⅰ indication) and coronary bypass grafts (class Ⅱ indication). CMRA utilisation for coronary artery disease is not yet part of clinical routine. However, the lack of radiation is of special value for the coronary artery evaluation in children and women. CMRA can assess the proximal part of coronary arteries in almost all cases. The best results have been observed in the evaluation of the left anterior descending and the right coronary artery, while the left circumflex, which is located far away from the coil elements, is frequently imaged with reduced quality, compared to the other two. Different studies detected an increase in wall thickness of the coronaries in patients with type Ⅰ diabetes and abnormal renal function. Additionally, the non-contrast enhanced T1-weighed images detected the presence of thrombus in acute myocardial infarction. New techniques using delayed gadolinium enhanced imaging promise the direct visualization of inflamed plaques in the coronary arteries. The major advantage of CMR is the potential of an integrated protocol offering assessment of coronary artery anatomy, cardiac function, inflammation and stress perfusion-fibrosis in the same study, providing an individualized clinical profile of patients with heart disease.

Key words: Coronary angiography; Coronary venous system; Gadolinium; Magnetic resonance imaging

Core tip: Cardiovascular magnetic resonance (CMR) allows the non-radiating assessment of coronary arteries. At the moment it is indicated only to detection of abnormal coronary artery origin, ectasia and/or aneurysms (class Ⅰ indication) and coronary artery bypass grafts (class Ⅱ indication). The utilisation of coronary MRA (CMRA) for coronary artery disease diagnosis is not at the moment part of clinical routine. However, due to lack of radiation is particularly useful for children and women. A combined CMR protocol, including CMRA and stress perfusion-fibrosis evaluation may offer a non-invasive assessment of cardiovascular profile in high risk patients.

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INTRODUCTION

Coronary artery disease (CAD) with its sequelae including myocardial infarction and heart failure, is the main cause of increased mortality in our days[1,2]. The usual way for CAD assessment is the use of invasive coronary angiography; however, the high incidence of CAD and

the queries of invasive assessment necessitate the use of a noninvasive evaluation of coronaries[3,4].

Cardiovascular magnetic resonance (CMR) can provide a combined approach including coronary arteries, cardiac function and stress myocardial perfusion-fibrosis evaluation. Coronary magnetic resonance angiography (CMRA) has been already used for assessment of coronary anatomy and vessels' wall, providing useful information in CAD[5-7].

In this review we provide an update of clinical applications of CMRA, discussing the current limitations and the challenges for future applications.

INDICATIONS FOR CMRA

The clinical indications of CMRA are at the moment limited only to the detection of abnormal origin of coronary arteries, coronary ectasia and/or aneurysms (class I indication) and coronary bypass grafts (CABG) evaluation (class II indication). The routine application of CMRA for diagnosis of CAD is not at the moment part of clinical practice[8,9].

CORONARY VESSELS ABNORMALITIES AND ANEURYSMS (CLASS I INDICATION)

CMRA assesses precisely the abnormal coronary arteries and the location and dimensions of coronary aneurysms. The larger caliber and the proximal location of the coronary artery aneurysms (CAA) facilitate their imaging. The most important benefit of CMRA is the absence of ionizing radiation, which is of special clinical value for children and women[8,10]. Clinical entities, characterized by ectatic or aneurysmatic coronaries, include Kawasaki disease, autoimmune vasculitis and coronary artery ectasia[11,12].

KAWASAKI DISEASE AND OTHER AUTOIMMUNE VASCULITIS

In Kawasaki disease, CMR can diagnose lesions both in acute and chronic phase. During the acute phase, a complete evaluation of the coronary anatomy, left and right ventricular function, myocardial inflammation and myocardial fibrosis either due to inflammatory process or due to myocardial infarction is essential.

The presence of CAA needs serial evaluation for patients' risk stratification. Although transthoracic echocardiography is usually sufficient in young children, the visualization of the coronary arteries becomes progressively more difficult as children grow up. According to previous publications, coronary magnetic resonance, using navigator techniques, has an excellent correlation with X-ray coronary angiography using both Pearson coefficient and Bland-Altman analysis and can be used as a reliable alternative for KD patients[13,14]. Recently, the application of free-breathing techniques in children with KD using the whole-heart approach detected successfully not only the abnormalities of coronary lumen, but also the abnormally thickened vessel wall and improved risk stratification and monitoring of therapy[15]. In parallel with coronary assessment, during the same examination, an evaluation of function and wall motion of both ventricles can be also performed using the standard SSFP sequence[16]. However, only anatomic evaluation is not sufficient to successfully risk stratify KD patients. Previous studies in patients with atherosclerotic coronary artery disease proved that maybe a severe anatomic lesion could not provoke severe myocardial ischemia and in contrary, a marginal coronary lesion can induce significant myocardial ischemia[17]. Magnetic resonance (MR) first-pass myocardial perfusion imaging during hyperaemia, due to the vasodilating agent adenosine, demonstrates a high diagnostic performance of MR perfusion imaging for the detection of anatomically defined coronary artery stenoses[18].

Other autoimmune vasculitis that can potentially develop coronary aneurysms include polyarteritis nodosa, microscopic polyangiitis and Wegener granulomatosis[19]. In these diseases the application of coronary MRA with simultaneous assessment of myocardial oedema-fibrosis may reveal disease activity and pathophysiology of heart lesion noninvasively and without radiation[20].

CORONARY ARTERY ECTASIA

Coronary artery ectasia (CAE) represents a form of atherosclerosis, detected in 3%-8% of subjects during X-ray coronary angiography. Sluggish blood flow is produced within the ectatic segments, leading to chest pain in effort and myocardial infarction, independently of the significance of coexisting stenosis. CAE is the dilatation of an artery 1.5 times greater than the normal coronary artery and is assessed in 5% of angiographic and in 0.22%-1.4% of autopsy cases[21-24]. It may involve the entire vessel or be localized in a specific part of the vessel. If it involves the entire vessel, it is called "ectasia". It is due to atherosclerosis in > 50% of cases. Ectasia coexists with coronary artery disease in the majority of patients. Only 10%-20% of CAE coexist with systemic diseases[25,26], such as scleroderma[27,28], Ehlers-Danlos syndrome[29], different types of antineutrophil cytoplasmic antibody (ANCA)-related vasculitis[19] (Figure 1A), syphilitic aortitis[30] and Kawasaki disease[14] (Figure 1B). In some patients, CAE has a congenital origin[31]. The differentiation between congenital and acquired coronary aneurysms is rather difficult. Acquired CAE should also be differentiated from aneurysms due to different coronary procedures.

The correct follow up of ectatic vessels demands repeated angiograms and CMRA offers an excellent alternative for the evaluation of the initial part of left main, left anterior descending and right coronary arteries[32]. CMRA has been already proved a valuable clinical tool for diagnosis of abnormal coronary origin, and is in some cases superior to X-ray coronary angiography; however, it is still under investigation for the assessment of the CAD[32]. Our group proved that CMRA is equal

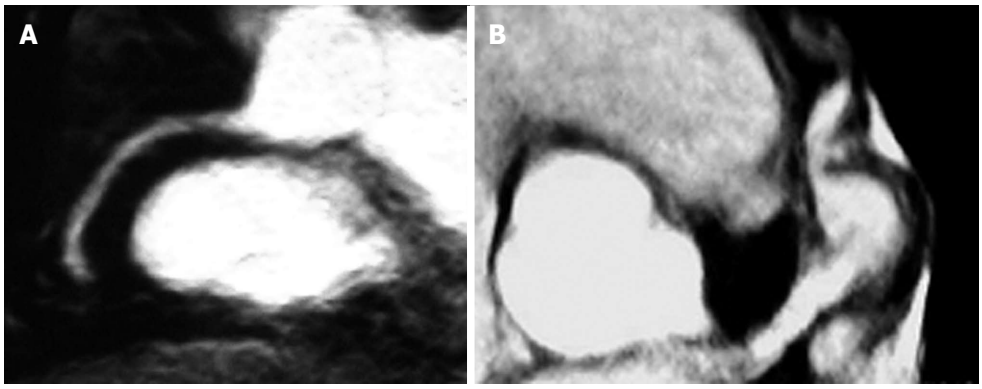

Figure 1 Magnetic resonance angiography. A: Ectatic coronaries in a patient with polyarteritis nodosa, assessed by MRA; B: Aneurysmatic coronaries in a patient with Kawasaki disease, assessed by MRA. MRA: Magnetic resonance angiography.

to quantitative coronary angiography for evaluation of ecstatic/aneurysmatic disease. Furthermore, it is a non-invasive, nonradiating technique[4]. Compared with CT, CMRA does not need use of a contrast agent. CMRA can also give additional data about, vessels' blood flow and stress perfusion-fibrosis pattern[33].

CORONARY BYPASS-GRAFTS (CLASS II INDICATION)

Bypass grafts can be assessed very well by coronary MRA, because they are relatively immobile and have larger diameter compared to coronary arteries. Different imaging ways have been already used, including spin echo[34-37] and gradient echo techniques. The application of contrast agents for better imaging of the blood signal[38,39]. increased the sensitivity to 95%.

However, metallic clips in grafts constitute the commonest limitation of coronary bypass MRA. Coronary MRA can be used at some special centers to detect lesions in bypass grafts[8].

CORONARY MAGNETIC RESONANCE ANGIOGRAPHY FOR ASSESSMENT OF CAD

Coronary MRA assesses the initial part of the coronary arteries in almost 100% of patients, with excellent results acquired for the left anterior descending (LAD) and the right coronary artery (RCA); the left circumflex (LCX), due to its peculiar way, is at a increased distance from the cardiac coil, and therefore its visualization is of inferior quality. According top revious studies, the imaged length for LAD is 50 mm, for RCA is 80 mm and for LCX is 40 mm[40-47]. An excellent agreement between the proximal parts of coronary arteries measured by MRA and by invasive angiography was assessed by previous studies[48].

Unfortunately, the resolution of CMRA remains lower compared with invasive coronary angiography and does not allow the evaluation of stenosis in small coronary arteries. This is the reason of the low specificity documented in a recent international multicenter study[4]; however, CMRA was shown to have a high sensitivity (92%) for the detection of CAD and its diagnostic performance was ameliorated. In a subanalysis of left main or three vessel disease, a sensitivity of 100% and a negative predictive value of 100% was documented. These findings were also supported by smaller single-center studies[40,49-57].

Recently, a meta-analysis compared coronary MRA and multi-slice computed tomography (CT) for assessment of significant CAD[34]. CT was more accurate than MRA and therefore CT was suggested as the preferred non-invasive alternative to X-ray coronary angiography. However, the superiority of CMRA is that it can offer more data about the patient, including cardiac anatomy, function, inflammation, stress perfusion and fibrosis evaluation.

Recently, a multicenter study showed that whole-heart CMRA at 1.5 T can detect significant CAD with high sensitivity (88%) and moderate specificity (72%). Additionally, a negative predictive value (NPV) of 88% indicates that this technique can effectively be used to exclude the presence of significant CAD[58]. We should mention that this NPV reported by this trial is identical to the NPV of the CORE-64 CTA multicenter study[59]. Proving the value of CMRA to rule out CAD in patients with low pre-test probability (< 20%)[60].

Finally, in a direct comparison between CMRA and CTA no significant difference was proved for the detection of CAD between 3 T MR and 64-slice CTA[61]. A comparison between coronary MRA, CTA and invasive coronary angiography (CA) is shown in Table 1.

CORONARY VESSEL WALL ASSESSMENT

The initial CMR images of the coronary vessel wall were taken using fast spin echo techniques[62,63]. A double inversion recovery preparation was used to take black-blood images improving the contrast between blood and vessel wall[64]. Recently, the double inversion recovery prepulse has been combined with fast gradient echo[65], spiral[66]

Table 1 Comparison between invasive coronary coronary angiography, CTA and magnetic resonance angiography

	CA	CTA	MRA
Noninvasive	No	Yes	Yes
Radiation	Yes	Yes	No
Nephrotoxicity	Yes	Yes	No
Accuracy	+++	++	+
Negative predictive value	+++	+++	++
Cost	High	High	High
Calcium detection	±	+	-
Anomalous coronaries	+++	+++	+++
Ectasia/aneurysm	+++	+++	+++
Graft assessment	+++	+++	+++
CAD evaluation	+++	++	+
Plaque evaluation	+++	±	±

CA: Coronary angiography; MRA: Magnetic resonance angiography; CAD: Coronary artery disease; CTA: Computed tomography coronary angiography.

and radial acquisitions[67].

Various studies documented the capability of vessel wall imaging to detect remodeling of coronary arteries in CAD and increased vessel wall thickness in type I diabetes with abnormal renal function[68,69]. It was also documented by Jansen *et al*[70] that non-contrast enhanced T1-weighed MR visualized thrombus in acute myocardial infarction.

Recently, new techniques using delayed gadolinium enhancement facilitated the direct assessment of inflamed plaques in the coronary arteries. Clinically used contrast agents showed non-specific uptake in plaques of patients with chronic angina[71]. Acute coronary syndromes[72] and systemic lupus erythematosus[73]. The contrast enhancement by CMR, assessed in patients with stable angina, was associated with calcified or mixed plaques on MSCT, while in ACS it was transient, probably due to inflammatory process.

New contrast agents have been already used in animals and their accumulation in blood was associated with increased endothelial permeability and/or increased neovascularization[74]. Additionally, increased accumulation of iron-oxide particles (USPIO) was indicative of increased endothelial permeability and vessel wall inflammation, due to intraplaque macrophages[75,76].

Such molecules have been used as targets for new molecular contrast agents that allowed the assessment of inflammatory indexes, such as intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1) or matrix metalloproteinase (MMP)[77,78]. Furthrmore, thrombi labeling using a fibrin-specific contrast agent[79,80] and evaluation of extracellular matrix remodelling, using targeting elastin is a new promising molecular imaging technique[81,82] for early detection of plaque vulnerability[83].

CONCLUSION

CMR is a non-invasive, non-radiating technique for evaluation of coronary arteries and coronary wall. Its major advantage is the potential of a combined protocol, including coronary arteries, cardiac anatomy, function, inflammation and stress perfusion-fibrosis in the same study in CAD and/or heart failure.

CMRA current indications include: (1) assessment of abnormal coronary arteries, coronary ectasia and/or aneurysm (class I indication); and (2) coronary bypass grafts (class II indication). In the future, it may be used to exclude CAD in selected patients. However, further improvements are needed to support its use for routine assessment of high risk populations.

REFERENCES

1 **Ford ES**, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med* 2007; **356**: 2388-2398 [PMID: 17554120 DOI: 10.1056/NEJMsa053935]

2 **Roger VL**, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. *Circulation* 2011; **123**: e18-e209 [PMID: 21160056 DOI: 10.1161/CIR.0b013e3182009701]

3 **Patel MR**, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010; **362**: 886-895 [PMID: 20220183 DOI: 10.1056/NEJMoa0907272]

4 **Kim WY**, Danias PG, Stuber M, Flamm SD, Plein S, Nagel E, Langerak SE, Weber OM, Pedersen EM, Schmidt M, Botnar RM, Manning WJ. Coronary magnetic resonance angiography for the detection of coronary stenoses. *N Engl J Med* 2001; **345**: 1863-1869 [PMID: 11756576 DOI: 10.1056/NEJMoa010866]

5 **Spuentrup E**, Botnar RM. Coronary magnetic resonance imaging: visualization of the vessel lumen and the vessel wall and molecular imaging of arteriothrombosis. *Eur Radiol* 2006; **16**: 1-14 [PMID: 16132919 DOI: 10.1007/s00330-005-2886-7]

6 **Chiribiri A**, Kelle S, Götze S, Kriatselis C, Thouet T, Tangcharoen T, Paetsch I, Schnackenburg B, Fleck E, Nagel E. Visualization of the cardiac venous system using cardiac magnetic resonance. *Am J Cardiol* 2008; **101**: 407-412 [PMID: 18237610 DOI: 10.1016/j.amjcard.2007.08.049]

7 **Chiribiri A**, Kelle S, Köhler U, Tops LF, Schnackenburg B, Bonamini R, Bax JJ, Fleck E, Nagel E. Magnetic resonance cardiac vein imaging: relation to mitral valve annulus and left circumflex coronary artery. *JACC Cardiovasc Imaging* 2008; **1**: 729-738 [PMID: 19356509 DOI: 10.1016/j.jcmg.2008.06.009]

8 **Hundley WG**, Bluemke DA, Finn JP, Flamm SD, Fogel MA, Friedrich MG, Ho VB, Jerosch-Herold M, Kramer CM, Manning WJ, Patel M, Pohost GM, Stillman AE, White RD, Woodard PK. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *J Am Coll Cardiol* 2010; **55**: 2614-2662 [PMID: 20513610 DOI: 10.1016/j.jacc.2009.11.011]

9 **Chiribiri A**, Ishida M, Nagel E, Botnar RM. Coronary imaging with cardiovascular magnetic resonance: Current state of the art. *Prog Cardiovasc Dis* 2011; **54**: 240-252 [DOI: 10.1016/

j.pcad.2011.09.002]
10 **Chiribiri A**, Ishida M, Nagel E, Botnar RM. Coronary imaging with cardiovascular magnetic resonance: current state of the art. *Prog Cardiovasc Dis* 2011; **54**: 240-252 [PMID: 22014491 DOI: 10.1016/j.ijcard.2008.05.075]
11 **Mavrogeni S**, Papadopoulos G, Hussain T, Chiribiri A, Botnar R, Greil GF. The emerging role of cardiovascular magnetic resonance in the evaluation of Kawasaki disease. *Int J Cardiovasc Imaging* 2013; **29**: 1787-1798 [PMID: 23949280 DOI: 10.1007/s10554-013-0276-9]
12 **Mavrogeni S**. Coronary artery ectasia: from diagnosis to treatment. *Hellenic J Cardiol* 2010; **51**: 158-163 [PMID: 20378518]
13 **Mavrogeni S**, Papadopoulos G, Douskou M, Kaklis S, Seimenis I, Baras P, Nikolaidou P, Bakoula C, Karanasios E, Manginas A, Cokkinos DV. Magnetic resonance angiography is equivalent to X-ray coronary angiography for the evaluation of coronary arteries in Kawasaki disease. *J Am Coll Cardiol* 2004; **43**: 649-652 [PMID: 14975477 DOI: 10.1016/j.jacc.2003.08.052]
14 **Greil GF**, Stuber M, Botnar RM, Kissinger KV, Geva T, Newburger JW, Manning WJ, Powell AJ. Coronary magnetic resonance angiography in adolescents and young adults with kawasaki disease. *Circulation* 2002; **105**: 908-911 [PMID: 11864916 DOI: 10.1161/hc0802.105563]
15 **Greil GF**, Seeger A, Miller S, Claussen CD, Hofbeck M, Botnar RM, Sieverding L. Coronary magnetic resonance angiography and vessel wall imaging in children with Kawasaki disease. *Pediatr Radiol* 2007; **37**: 666-673 [PMID: 17541574 DOI: 10.1007/s00247-007-0498-x]
16 **Mavrogeni S**, Papadopoulos G, Douskou M, Kaklis S, Seimenis I, Varlamis G, Karanasios E, Krikos X, Giannoulia A, Cokkinos DV. Magnetic resonance angiography, function and viability evaluation in patients with Kawasaki disease. *J Cardiovasc Magn Reson* 2006; **8**: 493-498 [PMID: 16758550 DOI: 10.1080/10976640600604773]
17 **Doesch C**, Seeger A, Doering J, Herdeg C, Burgstahler C, Claussen CD, Gawaz M, Miller S, May AE. Risk stratification by adenosine stress cardiac magnetic resonance in patients with coronary artery stenoses of intermediate angiographic severity. *JACC Cardiovasc Imaging* 2009; **2**: 424-433 [PMID: 19580724 DOI: 10.1016/j.jcmg.2008.11.017]
18 **Giang TH**, Nanz D, Coulden R, Friedrich M, Graves M, Al-Saadi N, Lüscher TF, von Schulthess GK, Schwitter J. Detection of coronary artery disease by magnetic resonance myocardial perfusion imaging with various contrast medium doses: first European multi-centre experience. *Eur Heart J* 2004; **25**: 1657-1665 [PMID: 15351166 DOI: 10.1016/j.ehj.2004.06.037]
19 **Mavrogeni S**, Manoussakis MN, Karagiorga TC, Douskou M, Panagiotakos D, Bournia V, Cokkinos DV, Moutsopoulos HM. Detection of coronary artery lesions and myocardial necrosis by magnetic resonance in systemic necrotizing vasculitides. *Arthritis Rheum* 2009; **61**: 1121-1129 [PMID: 19644909 DOI: 10.1002/art.24695]
20 **Mavrogeni S**, Sfikakis PP, Gialafos E, Bratis K, Karabela G, Stavropoulos E, Spiliotis G, Sfendouraki E, Panopoulos S, Bournia V, Kolovou G, Kitas GD. Cardiac tissue characterization and the diagnostic value of cardiovascular magnetic resonance in systemic connective tissue diseases. *Arthritis Care Res* (Hoboken) 2014; **66**: 104-112 [PMID: 24106233 DOI: 10.1002/acr.22181]
21 **Hartnell GG**, Parnell BM, Pridie RB. Coronary artery ectasia. Its prevalence and clinical significance in 4993 patients. *Br Heart J* 1985; **54**: 392-395 [PMID: 4052280 DOI: 10.1136/hrt.54.4.392]
22 **Markis JE**, Joffe CD, Cohn PF, Feen DJ, Herman MV, Gorlin R. Clinical significance of coronary arterial ectasia. *Am J Cardiol* 1976; **37**: 217-222 [PMID: 1108631 DOI: 10.1016/0002-9149(76)90315-5]
23 **Oliveros RA**, Falsetti HL, Carroll RJ, Heinle RA, Ryan GF. Atherosclerotic coronary artery aneurysm. Report of five cases and review of literature. *Arch Intern Med* 1974; **134**: 1072-1076 [PMID: 4215378 DOI: 10.1001/archinte.1974.00320240106014]
24 **Swaye PS**, Fisher LD, Litwin P, Vignola PA, Judkins MP, Kemp HG, Mudd JG, Gosselin AJ. Aneurysmal coronary artery disease. *Circulation* 1983; **67**: 134-138 [PMID: 6847792 DOI: 10.1161/01.CIR.67.1.134]
25 **Falsetti HL**, Carrol RJ. Coronary artery aneurysm. A review of the literature with a report of 11 new cases. *Chest* 1976; **69**: 630-636 [PMID: 1083790 DOI: 10.1378/chest.69.5.630]
26 **Befeler B**, Aranda MJ, Embi A, Mullin FL, El-Sherif N, Lazzara R. Coronary artery aneurysms: study of the etiology, clinical course and effect on left ventricular function and prognosis. *Am J Med* 1977; **62**: 597-607 [PMID: 300567 DOI: 10.1016/0002-9343(77)90423-5]
27 **Chaithiraphan S**, Goldberg E, O'Reilly M, Jootar P. Multiple aneurysms of coronary artery in sclerodermal heart disease. *Angiology* 1973; **24**: 86-93 [PMID: 4693051 DOI: 10.1177/000331977302400204]
28 **Tarek el-G**, Yasser AE, Gheita T. Coronary angiographic findings in asymptomatic systemic sclerosis. *Clin Rheumatol* 2006; **25**: 487-490 [PMID: 16440131 DOI: 10.1007/s10067-005-0073-5]
29 **Imahori S**, Bannerman RM, Graf CJ, Brennan JC. Ehlers-Danlos syndrome with multiple arterial lesions. *Am J Med* 1969; **47**: 967-977 [PMID: 5362873 DOI: 10.1016/0002-9343(69)90210-1]
30 **Davidson A**, Eshaghpour E, Young N, Mintz GS. Late thrombosis of a coronary artery mycotic aneurysm. *Am Heart J* 1991; **121**: 1549-1550 [PMID: 2017990 DOI: 10.1016/0002-8703(91)90168-H]
31 **Cohen P**, O'Gara PT. Coronary artery aneurysms: a review of the natural history, pathophysiology, and management. *Cardiol Rev* 2008; **16**: 301-304 [PMID: 18923233 DOI: 10.1097/CRD.0b013e3181852659]
32 **Bluemke DA**, Achenbach S, Budoff M, Gerber TC, Gersh B, Hillis LD, Hundley WG, Manning WJ, Printz BF, Stuber M, Woodard PK. Noninvasive coronary artery imaging: magnetic resonance angiography and multidetector computed tomography angiography: a scientific statement from the american heart association committee on cardiovascular imaging and intervention of the council on cardiovascular radiology and intervention, and the councils on clinical cardiology and cardiovascular disease in the young. *Circulation* 2008; **118**: 586-606 [PMID: 18586979 DOI: 10.1161/CIRCULATIONAHA.108.189695]
33 **Mavrogeni SI**, Manginas A, Papadakis E, Foussas S, Douskou M, Baras P, Seimenis I, Cokkinos DV. Correlation between magnetic resonance angiography (MRA) and quantitative coronary angiography (QCA) in ectatic coronary vessels. *J Cardiovasc Magn Reson* 2004; **6**: 17-23 [PMID: 15054925 DOI: 10.1081/JCMR-120027801]
34 **Galjee MA**, van Rossum AC, Doesburg T, van Eenige MJ, Visser CA. Value of magnetic resonance imaging in assessing patency and function of coronary artery bypass grafts. An angiographically controlled study. *Circulation* 1996; **93**: 660-666 [PMID: 8640993 DOI: 10.1161/01.CIR.93.4.660]
35 **Jenkins JP**, Love HG, Foster CJ, Isherwood I, Rowlands DJ. Detection of coronary artery bypass graft patency as assessed by magnetic resonance imaging. *Br J Radiol* 1988; **61**: 2-4 [PMID: 3258170 DOI: 10.1259/0007-1285-61-721-2]
36 **Rubinstein RI**, Askenase AD, Thickman D, Feldman MS, Agarwal JB, Helfant RH. Magnetic resonance imaging to evaluate patency of aortocoronary bypass grafts. *Circulation* 1987; **76**: 786-791 [PMID: 3498558 DOI: 10.1161/01.CIR.76.4.786]
37 **White RD**, Caputo GR, Mark AS, Modin GW, Higgins CB. Coronary artery bypass graft patency: noninvasive evalua-

tion with MR imaging. *Radiology* 1987; **164**: 681-686 [PMID: 3497409 DOI: 10.1148/radiology.164.3.3497409]
38 **Vrachliotis TG**, Bis KG, Aliabadi D, Shetty AN, Safian R, Simonetti O. Contrast-enhanced breath-hold MR angiography for evaluating patency of coronary artery bypass grafts. *AJR Am J Roentgenol* 1997; **168**: 1073-1080 [PMID: 9124118 DOI: 10.2214/ajr.168.4.9124118]
39 **Wintersperger BJ**, von Smekal A, Engelmann MG, Knez A, Penzkofer HV, Laub G, Reiser M. [Contrast media enhanced magnetic resonance angiography for determining patency of a coronary bypass. A comparison with coronary angiography]. *Rofo* 1997; **167**: 572-578 [PMID: 9465951 DOI: 10.1055/s-2007-1015585]
40 **Botnar RM**, Stuber M, Danias PG, Kissinger KV, Manning WJ. Improved coronary artery definition with T2-weighted, free-breathing, three-dimensional coronary MRA. *Circulation* 1999; **99**: 3139-3148 [PMID: 10377077 DOI: 10.1161/01.CIR.99.24.3139]
41 **Hofman MB**, Paschal CB, Li D, Haacke EM, van Rossum AC, Sprenger M. MRI of coronary arteries: 2D breath-hold vs 3D respiratory-gated acquisition. *J Comput Assist Tomogr* 1995; **19**: 56-62 [PMID: 7822549 DOI: 10.1097/00004728-199501000-00011]
42 **Lobbes MB**, Miserus RJ, Heeneman S, Passos VL, Mutsaers PH, Debernardi N, Misselwitz B, Post M, Daemen MJ, van Engelshoven JM, Leiner T, Kooi ME. Atherosclerosis: contrast-enhanced MR imaging of vessel wall in rabbit model--comparison of gadofosveset and gadopentetate dimeglumine. *Radiology* 2009; **250**: 682-691 [PMID: 19244042 DOI: 10.1148/radiol.2503080875]
43 **Manning WJ**, Li W, Boyle NG, Edelman RR. Fat-suppressed breath-hold magnetic resonance coronary angiography. *Circulation* 1993; **87**: 94-104 [PMID: 8419029 DOI: 10.1161/01.CIR.87.1.94]
44 **Paschal CB**, Haacke EM, Adler LP. Three-dimensional MR imaging of the coronary arteries: preliminary clinical experience. *J Magn Reson Imaging* 1993; **3**: 491-500 [PMID: 8324308 DOI: 10.1002/jmri.1880030311]
45 **Post JC**, van Rossum AC, Hofman MB, Valk J, Visser CA. Three-dimensional respiratory-gated MR angiography of coronary arteries: comparison with conventional coronary angiography. *AJR Am J Roentgenol* 1996; **166**: 1399-1404 [PMID: 8633453 DOI: 10.2214/ajr.166.6.8633453]
46 **Stuber M**, Botnar RM, Danias PG, Sodickson DK, Kissinger KV, Van Cauteren M, De Becker J, Manning WJ. Double-oblique free-breathing high resolution three-dimensional coronary magnetic resonance angiography. *J Am Coll Cardiol* 1999; **34**: 524-531 [PMID: 10440168 DOI: 10.1016/S0735-1097(99)00223-5]
47 **Scheidegger MB**, Müller R, Boesiger P. Magnetic resonance angiography: methods and its applications to the coronary arteries. *Technol Health Care* 1994; **2**: 255-265 [PMID: 7842310]
48 **Bogaert J**, Kuzo R, Dymarkowski S, Beckers R, Piessens J, Rademakers FE. Coronary artery imaging with real-time navigator three-dimensional turbo-field-echo MR coronary angiography: initial experience. *Radiology* 2003; **226**: 707-716 [PMID: 12601209 DOI: 10.1148/radiol.2263011750]
49 **Dewey M**, Teige F, Schnapauff D, Laule M, Borges AC, Rutsch W, Hamm B, Taupitz M. Combination of free-breathing and breathhold steady-state free precession magnetic resonance angiography for detection of coronary artery stenoses. *J Magn Reson Imaging* 2006; **23**: 674-681 [PMID: 16568418 DOI: 10.1002/jmri.20568]
50 **Jahnke C**, Paetsch I, Nehrke K, Schnackenburg B, Gebker R, Fleck E, Nagel E. Rapid and complete coronary arterial tree visualization with magnetic resonance imaging: feasibility and diagnostic performance. *Eur Heart J* 2005; **26**: 2313-2319 [PMID: 15987709 DOI: 10.1093/eurheartj/ehi391]
51 **Jahnke C**, Paetsch I, Schnackenburg B, Bornstedt A, Gebker R, Fleck E, Nagel E. Coronary MR angiography with steady-state free precession: individually adapted breath-hold technique versus free-breathing technique. *Radiology* 2004; **232**: 669-676 [PMID: 15284430 DOI: 10.1148/radiol.2323031225]
52 **Maintz D**, Aepfelbacher FC, Kissinger KV, Botnar RM, Danias PG, Heindel W, Manning WJ, Stuber M. Coronary MR angiography: comparison of quantitative and qualitative data from four techniques. *AJR Am J Roentgenol* 2004; **182**: 515-521 [PMID: 14736693 DOI: 10.2214/ajr.182.2.1820515]
53 **Manning WJ**, Li W, Edelman RR. A preliminary report comparing magnetic resonance coronary angiography with conventional angiography. *N Engl J Med* 1993; **328**: 828-832 [PMID: 8285929 DOI: 10.1056/NEJM199303253281202]
54 **Ozgun M**, Hoffmeier A, Kouwenhoven M, Botnar RM, Stuber M, Scheld HH, Manning WJ, Heindel W, Maintz D. Comparison of 3D segmented gradient-echo and steady-state free precession coronary MRI sequences in patients with coronary artery disease. *AJR Am J Roentgenol* 2005; **185**: 103-109 [PMID: 15972408 DOI: 10.2214/ajr.185.1.01850103]
55 **Sakuma H**, Ichikawa Y, Chino S, Hirano T, Makino K, Takeda K. Detection of coronary artery stenosis with whole-heart coronary magnetic resonance angiography. *J Am Coll Cardiol* 2006; **48**: 1946-1950 [PMID: 17112982 DOI: 10.1016/j.jacc.2006.07.055]
56 **Sakuma H**, Ichikawa Y, Suzawa N, Hirano T, Makino K, Koyama N, Van Cauteren M, Takeda K. Assessment of coronary arteries with total study time of less than 30 minutes by using whole-heart coronary MR angiography. *Radiology* 2005; **237**: 316-321 [PMID: 16126921 DOI: 10.1148/radiol.2371040830]
57 **Schuetz GM**, Zacharopoulou NM, Schlattmann P, Dewey M. Meta-analysis: noninvasive coronary angiography using computed tomography versus magnetic resonance imaging. *Ann Intern Med* 2010; **152**: 167-177 [PMID: 20124233 DOI: 10.7326/0003-4819-152-3-201002020-00008]
58 **Kato S**, Kitagawa K, Ishida N, Ishida M, Nagata M, Ichikawa Y, Katahira K, Matsumoto Y, Seo K, Ochiai R, Kobayashi Y, Sakuma H. Assessment of coronary artery disease using magnetic resonance coronary angiography: a national multicenter trial. *J Am Coll Cardiol* 2010; **56**: 983-991 [PMID: 20828652 DOI: 10.1016/j.jacc.2010.01.071]
59 **Miller JM**, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, Paul N, Clouse ME, Shapiro EP, Hoe J, Lardo AC, Bush DE, de Roos A, Cox C, Brinker J, Lima JA. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008; **359**: 2324-2336 [PMID: 19038879 DOI: 10.1056/NEJMoa0806576]
60 **Nagel E**. Magnetic resonance coronary angiography: the condemned live longer. *J Am Coll Cardiol* 2010; **56**: 992-994 [PMID: 20828653 DOI: 10.1016/j.jacc.2010.02.069]
61 **Hamdan A**, Asbach P, Wellnhofer E, Klein C, Gebker R, Kelle S, Kilian H, Huppertz A, Fleck E. A prospective study for comparison of MR and CT imaging for detection of coronary artery stenosis. *JACC Cardiovasc Imaging* 2011; **4**: 50-61 [PMID: 21232704 DOI: 10.1016/j.jcmg.2010.10.007]
62 **Botnar RM**, Stuber M, Kissinger KV, Kim WY, Spuentrup E, Manning WJ. Noninvasive coronary vessel wall and plaque imaging with magnetic resonance imaging. *Circulation* 2000; **102**: 2582-2587 [PMID: 11085960 DOI: 10.1161/01.CIR.102.21.2582]
63 **Fayad ZA**, Fuster V, Fallon JT, Jayasundera T, Worthley SG, Helft G, Aguinaldo JG, Badimon JJ, Sharma SK. Noninvasive in vivo human coronary artery lumen and wall imaging using black-blood magnetic resonance imaging. *Circulation* 2000; **102**: 506-510 [PMID: 10920061 DOI: 10.1161/01.CIR.102.5.506]
64 **Edelman RR**, Chien D, Kim D. Fast selective black blood MR imaging. *Radiology* 1991; **181**: 655-660 [PMID: 1947077 DOI: 10.1148/radiology.181.3.1947077]
65 **Botnar RM**, Stuber M, Lamerichs R, Smink J, Fischer SE, Harvey P, Manning WJ. Initial experiences with in vivo right coronary artery human MR vessel wall imaging at 3 tesla.

J Cardiovasc Magn Reson 2003; **5**: 589-594 [PMID: 14664136 DOI: 10.1081/JCMR-120025232]
66 **Botnar RM**, Kim WY, Börnert P, Stuber M, Spuentrup E, Manning WJ. 3D coronary vessel wall imaging utilizing a local inversion technique with spiral image acquisition. *Magn Reson Med* 2001; **46**: 848-854 [PMID: 11675634 DOI: 10.1002/mrm.1268]
67 **Katoh M**, Spuentrup E, Buecker A, Schaeffter T, Stuber M, Günther RW, Botnar RM. MRI of coronary vessel walls using radial k-space sampling and steady-state free precession imaging. *AJR Am J Roentgenol* 2006; **186**: S401-S406 [PMID: 16714616 DOI: 10.2214/AJR.04.1864]
68 **Kim WY**, Stuber M, Börnert P, Kissinger KV, Manning WJ, Botnar RM. Three-dimensional black-blood cardiac magnetic resonance coronary vessel wall imaging detects positive arterial remodeling in patients with nonsignificant coronary artery disease. *Circulation* 2002; **106**: 296-299 [PMID: 12119242 DOI: 10.1161/01.CIR.0000025629.85631.1E]
69 **Kim WY**, Astrup AS, Stuber M, Tarnow L, Falk E, Botnar RM, Simonsen C, Pietraszek L, Hansen PR, Manning WJ, Andersen NT, Parving HH. Subclinical coronary and aortic atherosclerosis detected by magnetic resonance imaging in type 1 diabetes with and without diabetic nephropathy. *Circulation* 2007; **115**: 228-235 [PMID: 17190865 DOI: 10.1161/CIRCULATIONAHA.106.633339]
70 **Jansen CH**, Perera D, Makowski MR, Wiethoff AJ, Phinikaridou A, Razavi RM, Marber MS, Greil GF, Nagel E, Maintz D, Redwood S, Botnar RM. Detection of intracoronary thrombus by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation* 2011; **124**: 416-424 [PMID: 21747055 DOI: 10.1161/CIRCULATIONAHA.110.965442]
71 **Yeon SB**, Sabir A, Clouse M, Martinezclark PO, Peters DC, Hauser TH, Gibson CM, Nezafat R, Maintz D, Manning WJ, Botnar RM. Delayed-enhancement cardiovascular magnetic resonance coronary artery wall imaging: comparison with multislice computed tomography and quantitative coronary angiography. *J Am Coll Cardiol* 2007; **50**: 441-447 [PMID: 17662397 DOI: 10.1016/j.jacc.2007.03.052]
72 **Ibrahim T**, Makowski MR, Jankauskas A, Maintz D, Karch M, Schachoff S, Manning WJ, Schömig A, Schwaiger M, Botnar RM. Serial contrast-enhanced cardiac magnetic resonance imaging demonstrates regression of hyperenhancement within the coronary artery wall in patients after acute myocardial infarction. *JACC Cardiovasc Imaging* 2009; **2**: 580-588 [PMID: 19442944 DOI: 10.1016/j.jcmg.2008.12.029]
73 **Puntmann VO**, D'Cruz D, Taylor PC, Hussain T, Indermuhle A, Butzbach B, Botnar R, Nagel E. Contrast enhancement imaging in coronary arteries in SLE. *JACC Cardiovasc Imaging* 2012; **5**: 962-964 [PMID: 22974810 DOI: 10.1016/j.jcmg.2012.03.017]
74 **Phinikaridou A**, Andia ME, Protti A, Indermuehle A, Shah A, Smith A, Warley A, Botnar RM. Noninvasive magnetic resonance imaging evaluation of endothelial permeability in murine atherosclerosis using an albumin-binding contrast agent. *Circulation* 2012; **126**: 707-719 [PMID: 22753191 DOI: 10.1161/CIRCULATIONAHA.112.092098]
75 **Kooi ME**, Cappendijk VC, Cleutjens KB, Kessels AG, Kitslaar PJ, Borgers M, Frederik PM, Daemen MJ, van Engelshoven JM. Accumulation of ultrasmall superparamagnetic particles of iron oxide in human atherosclerotic plaques can be detected by in vivo magnetic resonance imaging. *Circulation* 2003; **107**: 2453-2458 [PMID: 12719280 DOI: 10.1161/01.CIR.0000068315.98705.CC]
76 **Tang TY**, Howarth SP, Miller SR, Graves MJ, Patterson AJ, U-King-Im JM, Li ZY, Walsh SR, Brown AP, Kirkpatrick PJ, Warburton EA, Hayes PD, Varty K, Boyle JR, Gaunt ME, Zalewski A, Gillard JH. The ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) Study. Evaluation using ultrasmall superparamagnetic iron oxide-enhanced magnetic resonance imaging in carotid disease. *J Am Coll Cardiol* 2009; **53**: 2039-2050 [PMID: 19477353 DOI: 10.1016/j.jacc.2009.03.018]
77 **Nahrendorf M**, Jaffer FA, Kelly KA, Sosnovik DE, Aikawa E, Libby P, Weissleder R. Noninvasive vascular cell adhesion molecule-1 imaging identifies inflammatory activation of cells in atherosclerosis. *Circulation* 2006; **114**: 1504-1511 [PMID: 17000904 DOI: 10.1161/CIRCULATIONAHA.106.646380]
78 **Nahrendorf M**, Keliher E, Panizzi P, Zhang H, Hembrador S, Figueiredo JL, Aikawa E, Kelly K, Libby P, Weissleder R. 18F-4V for PET-CT imaging of VCAM-1 expression in atherosclerosis. *JACC Cardiovasc Imaging* 2009; **2**: 1213-1222 [PMID: 19833312 DOI: 10.1016/j.jcmg.2009.04.016]
79 **Botnar RM**, Buecker A, Wiethoff AJ, Parsons EC, Katoh M, Katsimaglis G, Weisskoff RM, Lauffer RB, Graham PB, Gunther RW, Manning WJ, Spuentrup E. In vivo magnetic resonance imaging of coronary thrombosis using a fibrin-binding molecular magnetic resonance contrast agent. *Circulation* 2004; **110**: 1463-1466 [PMID: 15238457 DOI: 10.1161/01.CIR.0000134960.31304.87]
80 **Botnar RM**, Perez AS, Witte S, Wiethoff AJ, Laredo J, Hamilton J, Quist W, Parsons EC, Vaidya A, Kolodziej A, Barrett JA, Graham PB, Weisskoff RM, Manning WJ, Johnstone MT. In vivo molecular imaging of acute and subacute thrombosis using a fibrin-binding magnetic resonance imaging contrast agent. *Circulation* 2004; **109**: 2023-2029 [PMID: 15066940 DOI: 10.1161/01.CIR.0000127034.50006.C0]
81 **Makowski MR**, Wiethoff AJ, Blume U, Cuello F, Warley A, Jansen CH, Nagel E, Razavi R, Onthank DC, Cesati RR, Marber MS, Schaeffter T, Smith A, Robinson SP, Botnar RM. Assessment of atherosclerotic plaque burden with an elastin-specific magnetic resonance contrast agent. *Nat Med* 2011; **17**: 383-388 [PMID: 21336283 DOI: 10.1038/nm.2310]
82 **von Bary C**, Makowski M, Preissel A, Keithahn A, Warley A, Spuentrup E, Buecker A, Lazewatsky J, Cesati R, Onthank D, Schickl N, Schachoff S, Hausleiter J, Schömig A, Schwaiger M, Robinson S, Botnar R. MRI of coronary wall remodeling in a swine model of coronary injury using an elastin-binding contrast agent. *Circ Cardiovasc Imaging* 2011; **4**: 147-155 [PMID: 21378029 DOI: 10.1161/CIRCIMAGING.109.895607]
83 **Chiribiri A**, Botnar RM, Nagel E. Magnetic resonance coronary angiography: where are we today? *Curr Cardiol Rep* 2013; **15**: 328 [PMID: 23307168 DOI: 10.1007/s11886-012-0328-0]

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TOPIC HIGHLIGHT

WJC 6th Anniversary Special Issues (5): Myocardial infarction

ST-segment elevation: Distinguishing ST elevation myocardial infarction from ST elevation secondary to nonischemic etiologies

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Abstract

The benefits of early perfusion in ST elevation myocardial infarctions (STEMI) are established; however, early perfusion of non-ST elevation myocardial infarctions has not been shown to be beneficial. In addition, ST elevation (STE) caused by conditions other than acute ischemia is common. Non-ischemic STE may be confused as STEMI, but can also mask STEMI on electrocardiogram (ECG). As a result, activating the primary percutaneous coronary intervention (pPCI) protocol often depends on determining which ST elevation patterns reflect transmural infarction due to acute coronary artery thrombosis. Coordination of interpreting the ECG in its clinical context and appropriately activating the pPCI protocol has proved a difficult task in borderline cases. But its importance cannot be ignored, as reflected in the 2013 American College of Cardiology Foundation/American Heart Association guidelines concerning the treatment of ST elevation myocardial infarction. Multiples strategies have been tested and studied, and are currently being further perfected. No matter the strategy, at the heart of delivering the best care lies rapid and accurate interpretation of the ECG. Here, we present the different patterns of non-ischemic STE and methods of distinguishing between them. In writing this paper, we hope for quicker and better stratification of patients with STE on ECG, which will lead to be better outcomes.

Key words: Diagnosis; Electrocardiogram; Reperfusion therapy; ST segment elevation; Myocardial infarction

Core tip: At times, distinguishing between myocardial infarction with ST elevation (STEMI) from non-ischemic causes of elevation of the ST segment is difficult, especially in patients with atypical presenting symptoms. Understanding common patterns of ST elevation that are not caused by ischemia is crucial for rapid and accurate diagnosis. However, patients with baseline non-ischemic ST elevation (for example, early repolarization or repolarization changes caused by hypertrophy of the left ventricule) may develop acute myocardial infarction (true STEMI or non-ST elevation myocardial infarction with baseline ST elevation). Here we describe common patterns of non-ischemic ST elevation.

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INTRODUCTION

Today, the electrocardiogram (ECG) is the most com-

monly used diagnostic tool for recognizing and triaging of patients with symptoms suggestive of myocardial infarction (MI). Per the "Third Universal Definition of Myocardial Infarction" document, the ECG should be acquired and interpreted within 10 min of presentation[1]. Additionally, serial ECGs every 15 to 30 min should be performed in patients with ongoing symptoms in whom the initial ECG is not diagnostic of ST elevation MI (STEMI)[1].

ST elevation (STE) is considered to reflect acute transmural ischemia caused by an occlusion of an epicardial coronary artery by a blood clot. Therefore, it is recommended that patients with suspected acute STEMI and without contraindications should be subjected as soon as possible to therapy intended to recanalize the occluded artery by either primary percutaneous coronary intervention (pPCI) or fibrinolysis. In contrast, the guidelines recommend initial conservative therapy for patients with suspected MI without STE, as active ongoing ischemia may not be present and earlier studies have not shown a benefit for reperfusion therapy in patients without STE[2].

As per the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, ST elevation myocardial infarction is a clinical syndrome that compromizes typical symptoms of acute ischemia of the heart muscle in conjunction with elevation of the ST segment and increased blood levels of biomarkers that indicate necrosis of the cardiac muscle. By these guidelines, pPCI is recommended for those with symptoms indicative of ischemia of the heart muscle that began 12 h or less before medical encounter who have elevation of the ST segment[3]. Although the innovation of cardiac troponin (cTn) assays specific to the myocardium is changing the overall diagnosis of MI, the decision to proceed with angiography or give thrombolytics is made based on STE on the ECG and is usually reached before troponins are detectable in the blood. Further, the elderly, patients of female gender, and diabetic patients frequently present with symptoms that are not typical, further emphasizing the role of the presenting ECG for diagnosis and triage of such individuals[4-6].

In most of individuals without prior cardiac disease, the ST segment is at the level of the preceding P-R segment and/or the following T-P segment (so called isoelectric). Deviation of the ST-segment (elevation or depression compared to the isoelectric line) can be a sign of ischemia of the heart muscle. However, deviations of the ST segment relative to the isoelectric line due to nonischemic etiologies are often seen. Elevation of the ST segment due to non-ischemic etiologies was reported up to 15% in the general population. One study[7] found that 91% of 6014 men who served in the United State Air Force, between 16 and 58 years of age, without any apparent cardiac disease had elevation of the ST segment of 0.1 to 0.3 mV in more than one of the precordial leads (most commonly seen in lead V2). Another study suggested that elevation of the ST segment above 0.1 mV in one or more leads (V1 to V4) in 529 men without apparent cardiac disease could be found in 93% among those who were between 17 and 24 years of age. As age progresses, the prevalence of elevation of the ST segment declined[8]. Thus, most men have elevation of the ST segment greater than 0.1 mV in the precordial leads. Therefore, elevation of the ST segment should be regarded as a normal finding and is often termed "male pattern". On the other hand, only fifth of patients of female gender have elevation of the ST segment above 0.1 mV, and this percentage is not influenced by the age of the female patients[9]. These thresholds are discussed in the "Third Universal Definition of Myocardial Infarction" document[1].

Different cutoffs for the amount of STE are causing confusion. The cutoffs for abnormal elevation of the ST segment, per the "Third Universal Definition of Myocardial Infarction" document for leads V2-V3, are elevation of the ST segment at the J-point of above 0.2 mV in men 40 years of age or older, 0.25 mV or above in men below 40 years of age, and 0.15 mV or above in women and/or 0.1 mV or above in all other leads in patients without hypertrophy of the left ventricule or block of the left bundle branch[1]. These criteria are based on the 2% extreme outside of the mean calculated from a population of 1321 Caucasians from the city of Glasgow and the region of Strathclyde in Scotland[9]. The 2013 ACCF/AHA STEMI guidelines have simplified these recommendations. In these guidelines STE at the J point in 2 contiguous leads or more of 0.2 mV or more in males or 0.15 mV or more in women in leads V2-V3 and/or of 0.1 mV or more in all other leads is the threshold[3]. Considering the ethnic homogeneity and the decreasing STE magnitude with age, these cutoffs should appreciated in this context[9]. It is unclear whether the same thresholds for STE can be used in populations of different ethnicity, as higher magnitude of STE was reported in Nigerian healthy men[10]. It is plausible that if the thresholds, endorsed by the "Third Universal Definition of Myocardial Infarction" document are used, the reported incidence of anterior STEMI would decrease, especially in men younger than 40 years of age. Moreover, currently there are no guidelines as to what are considered "normal" STE for patients whose ECG shows criteria for hypertrophy of the left ventricular, left bundle branch block or other forms of advanced intraventricular conduction defects.

As abovementioned, many patients presenting with typical symptoms have elevation of the ST segment due to non-ischemic etiologies (NISTE)[3-6]. Physicians must use all tools at their disposable to reach accurate diagnosis and reduce the risk of false activation of the pPCI protocol or exposure to thrombolytic therapy from one hand, while not missing cases of true STEMI. There are patterns of NISTE that are frequent and typical and can be easily recognized and distinguished from ST elevation myocardia infarction. Yet, there are individuals with pre-existing ST elevation secondary to non-ischemic etiologies (*e.g.*, hypertrophy of the left ventricle or "early repolarization") that can develop superimposed acute MI (ST elevation myocardial infarction or non-STEMI (NSTEMI)); therefore, presence of benign patterns of NISTE does not always rule out acute coronary syndrome (ACS)

Table 1 Common patterns of nonischemic ST elevation

ST elevation secondary to LVH
ST elevation secondary to conduction defect (such as left bundle branch block and non-specific intracardiac conduction delay)
Early repolarization pattern (notched J-point typically in anterolateral leads)
Normal variant of ST elevation (ST elevation mostly in leads V2-V3)
Concave ST elevation
Spontaneously reperfused STEMI
Aneurysm/old myocardial infarction
Pericarditis/myocarditis
Wolf-Parkinson-White syndrome (pre-excitation)
Brugada pattern
Takotsubo (apical ballooning) syndrome
Hyperkalemia
Hypercalcemia

LVH: Left ventricular hypertrophy; STEMI: ST elevation myocardial infarctions.

and even STEMI.

The differential diagnosis of elevation of the ST segment is wide, including conditions with secondary ischemia of the myocardium (for example, dissection of the aortic wall), pre-existing elevation of the ST segment without acute ischemia, and instances with new elevation of the ST segment with chest pain but without evidence of ischemia of the heart muscle (for example, myocarditis or pericarditis, pulmonary embolus, electrolyte imbalance, rate-related repolarization changes, *etc.*). Obviously, with the current emphasis on diagnosing and triaging acute ST elevation myocardial infarction rapidly, the probability of over-diagnosing ST elevation myocardial infarction and false activation of the pPCI protocols or administration of fibrinolytic therapy may increase.

Failure to identify NISTE has its costs. It may delay treatment for the original medical condition (*i.e.*, aortic dissection, pulmonary embolus, peptic disease, *etc.*) and may expose the patient to unnecessary irradiation and exposure to contrast agents, in addition to increased health care costs and exhaustion of the catheterization laboratory personnel.

False-positive activation of the catheterization laboratory (no culprit lesion) have been reported in 9% to 14% of the patients[11,12]. More importantly, inappropriate activation rate, where the cardiologist did not perform an emergent coronary angiogram, is varied from 5% to 23%[12], largely depending on the training of the activator (paramedic or ED physician).

In this paper, we describe different patterns of STE and their underlying causes. We intend to provide insight into pathological *vs* non-pathological STE (Table 1). A better understanding of STE will lead to faster and the more appropriate treatment, lower false-positive and inappropriate activation of urgent reperfusion protocols (fibrinolytic therapy or pPCI), ensuring the best patient outcomes.

"CONVEX" *VS* "CONCAVE" PATTERNS OF STE

As mentioned above, the ST segment is normally isoelectric. ST elevation with convex or straight pattern is traditionally considered as indicative of STEMI in contrast to a concave pattern, which is typically considered to be secondary to nonischemic etiologies. The 2004 ACCF/AHA guidelines supported this belief[13]; however, this recommendation has been omitted from the current 2013 ACCF/AHA guidelines[1].

Wang *et al*[14] also emphasized the importance of the concave tracing in establishing the male pattern, left bundle branch block (LBBB), and LVH forms of STE over STEMI. However, concavity verses convexity must be analyzed carefully and should not be relied on as the sole criteria for distinguishing NISTE from STEMI. Brady *et al*[15] reported 77% sensitivity, 97% specificity, 94% positive predictive value, and 88% negative predictive value for a non-concave STE morphology in acute MI diagnosis. Given the use of ECG for screening, such suboptimal sensitivity would yield poor patient outcomes. Figure 1 depicts an ECG of a man with acute anterior wall ST elevation myocardial infarction presenting with concave form of ST elevation in the precordial leads. Angiography of the coronary arteries revealed total occlusion of the left anterior descending coronary artery (LAD) and the STE resolved after pPCI.

EARLY REPOLARIZATION

The "early repolarization" pattern is usually found 1% to 5% of the population. Most commonly found in young, athletic, black males[16,17]. In the past, early repolarization pattern of NISTE was considered a benign pattern[17]. More recently, however, early repolarization pattern has been associated with cardiac arrhythmia and sudden cardiac mortality, mainly if there is 0.2 mV or more elevation of the ST segment. Nevertheless, this pattern is not caused by acute ischemia mandating emergent reperfusion therapy. The typical pattern appears as no S wave in V_3; 1-4 mm concave elevation of the ST-segment in leads V2-V5 (most prominent in V3) and sometimes the inferior leads; and notching of the downstroke of the R waves ("J" wave), most distinct in lead V5 and V6[16-18]. However, other authors have used different definitions. Figure 2 is an example of early repolarization pattern.

In many cases of "early repolarization", elevation of the ST segment is not lasting and decreases or disappears when the heart rate increases or if the patient hyperventilates. Therefore, significant changes in the magnitude of ST elevation are not necessarily diagnostic for acute myocardial ischemia. At times, concomitant inversion of the T-waves may be present in the precordial leads, which are due to "juvenile T wave pattern" in younger subjects. These changes could be mistaken for acute myocardial ischemia[16].

Hypothermia may cause prominent J-point notch (Osborne waves)[19] that must be distinguished from "early repolarization" pattern. Hypothermia frequently causes slow heart rate and muscle shiver. Osborne waves with elevation of the ST segment are occasionally seen in patients with severe hypercalcemia or disorders of the central nervous system. Low body temperature usually

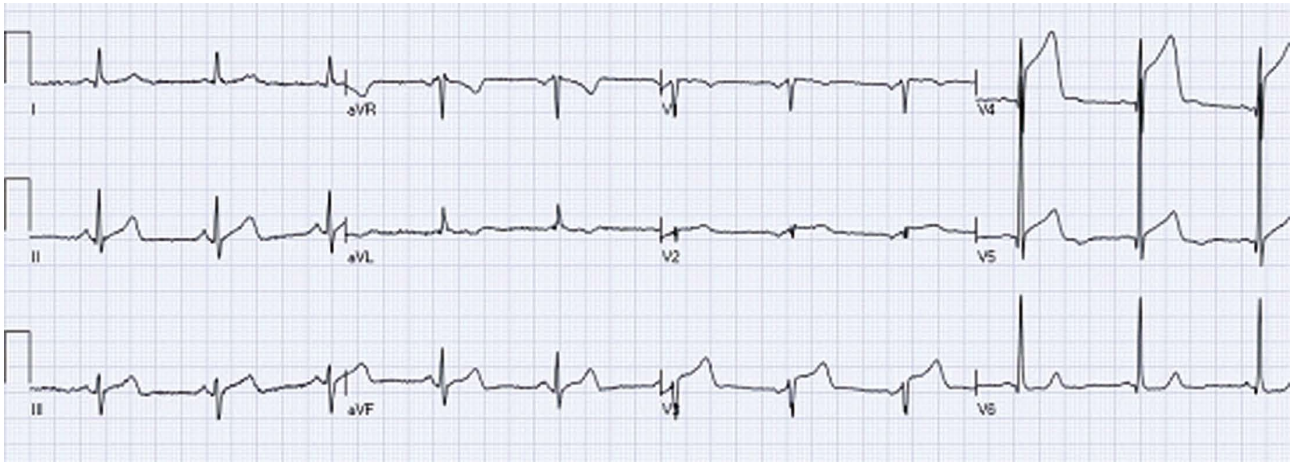

Figure 1 A patient with acute anterior wall ST elevation myocardial infarctions with concave form of ST elevation in the precordial leads (V3-V5). Coronary angiography revealed mid left anterior descending occlusion and primary percutaneous coronary intervention was performed.

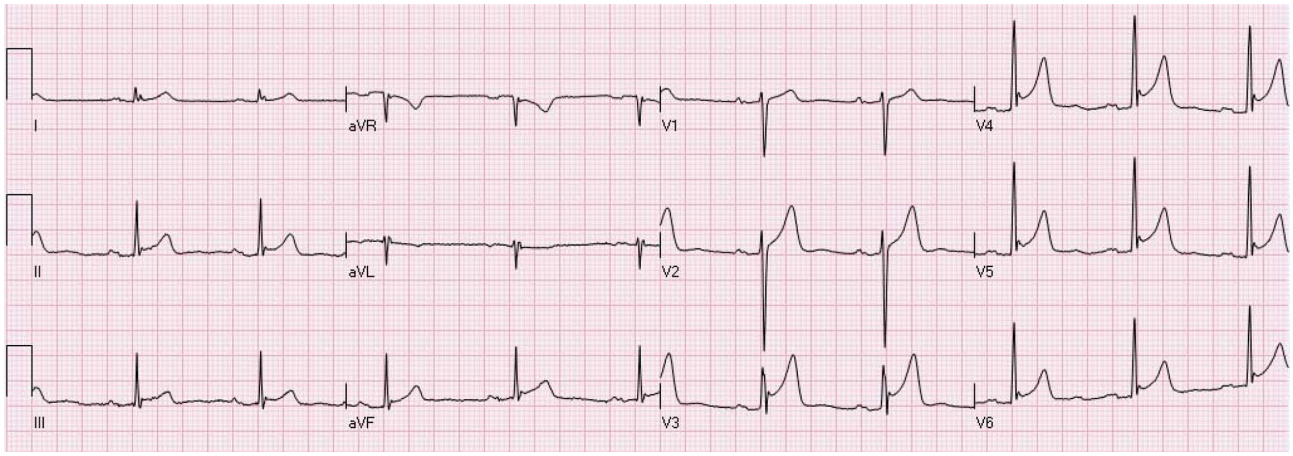

Figure 2 An example of ST elevation due to "early repolarization". ST elevation with notched J waves is seen in the inferior and anterolateral leads.

causes prolongation of the QT interval. On the other hand, hypercalcemia usually induces shortening of the QT interval[20]. Hyperkalemia can also cause elevation of the ST segment. In addition, hyperkalemia often presents with QRS widening and changes can be seen in the P waves and the PR segments. Another entity that can be mistaken for notching of the J-point (so called "epsilon waves") is typically observed in "Arrhythmogenic Right Ventricular Dysplasia". In arrhythmogenic right ventricular dysplasia, however, epsilon waves are commonly present in the precordial leads V1-V3[21].

A "NORMAL-VARIANT" PATTERN OF NISTE

A "normal-variant" ST elevation typically presents as elevation of the ST segments mainly in the precordial leads V1 to V3 (Figure 3)[14]. It is typically seen in young persons, mainly in Hispanic or African American males. QRS criteria for left ventricular hypertrophy are not met and concomitant depression of the ST segments and T waves changes in the lateral leads are not seen. There are investigators who do not make the difference between a "normal variant" pattern and "early repolarization" pattern, grouping them together under the "early repolarization" umbrella. It should be remembered that "early repolarization" and "normal variant" patterns are frequently present in the same patients.

ELEVATION OF THE ST SEGMENTS DUE TO HYPERTROPHY OF THE LEFT VENTRICLE

Just as the QRS complex amplitude may increase by a more massive left ventricle, changes in the ST segments can be amplified[22]. NISTE due to hypertrophy of the left ventricle (LVH) is usually seen in leads V1-V3. Typically, there are QRS amplitude criteria for hypertrophy of the left ventricle and associated depression of the ST segments in the leads facing the lateral wall (V5-V6 and I and aVL) (Figure 4). Frequently elevation of the ST segment is seen in lead aVR. It is crucial not to misdiagnose this pattern as the pattern thought to represent left main

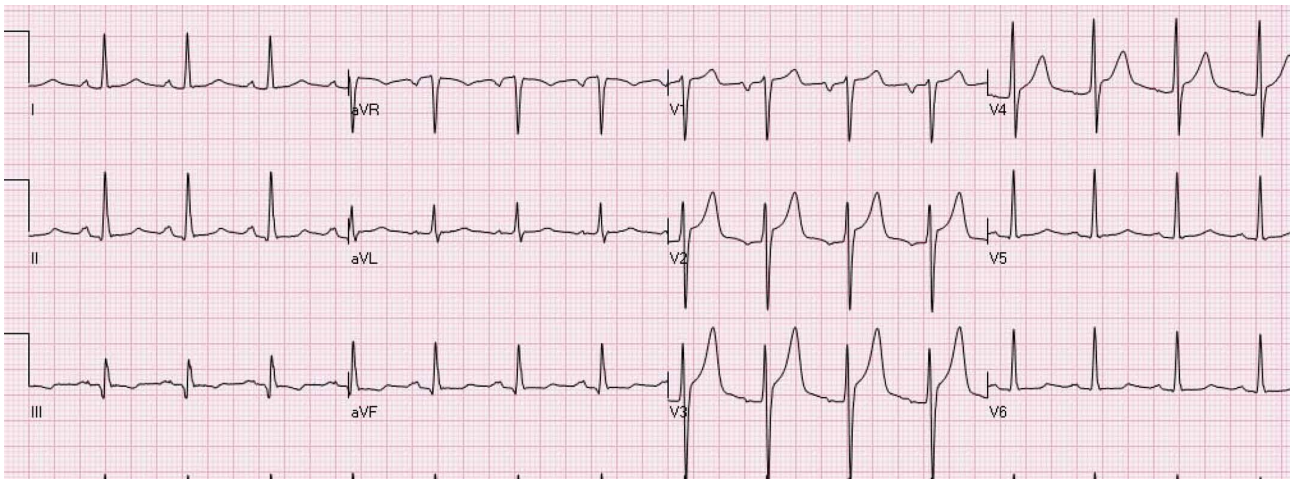

Figure 3 An electrocardiogram of a young male with a "normal variant" concave pattern of ST elevation in leads V2-V4.

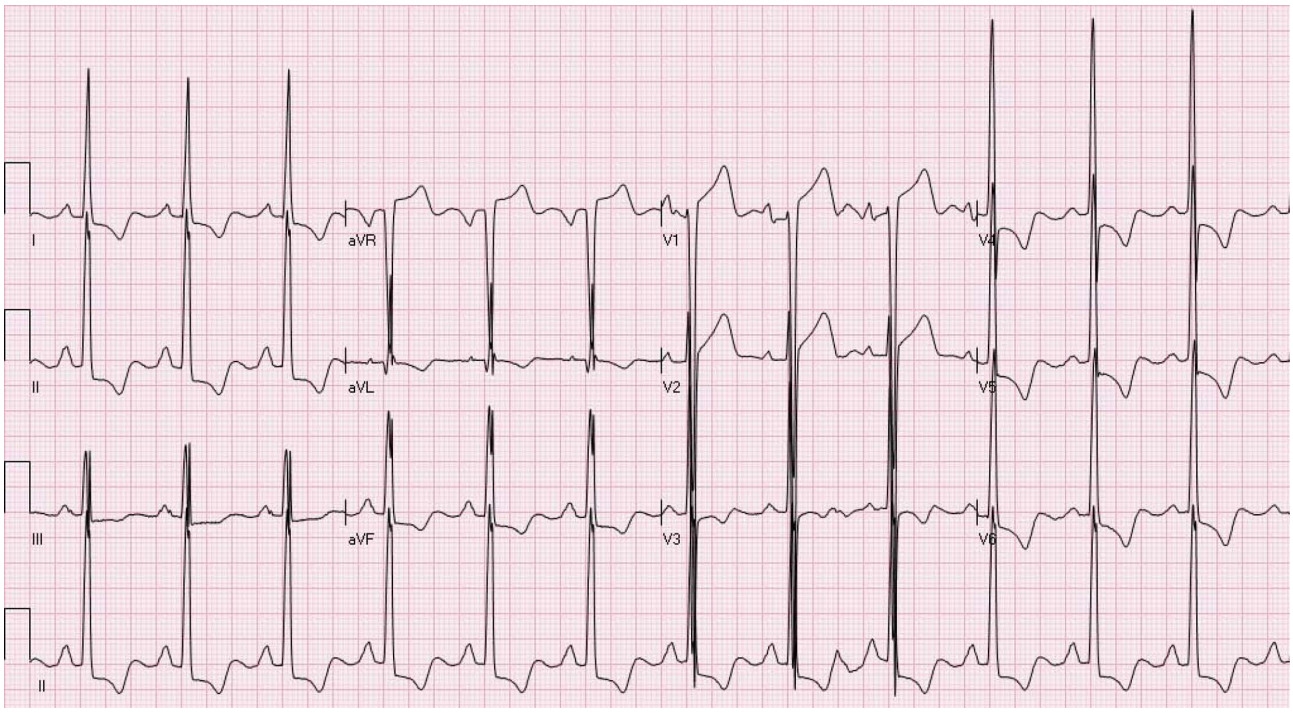

Figure 4 An electrocardiogram showing typical pattern of ST elevation due to hypertrophy of the left ventricular with secondary repolarization changes. There is ST elevation in leads V1-V2 and ST depression with T wave inversion in the inferolateral leads.

induced- or circumferential- subendocardial ischemia (elevation of the ST segments in leads V1 and aVR with accompanying depression of the ST segments in the inferior as well as the anterolateral leads). Per the Third Global MI Task Force consensus paper[1], the cutoffs for the absolute amplitude of the ST segment elevation do not apply for patients with hypertrophy of the left ventricle. Yet; hypertension is an established risk factor for atherosclerotic heart disease, including acute MI. It should be remembered, however, that at times hypertrophy of the left ventricle may present with atypical configurations of ST elevation (Figure 5). Furthermore, frequently patients are presenting with more than one pattern of NISTE (LVH + early repolarization or nonspecific intraventricular conduction delay [IVCD] + LVH and even STEMI on top of ST segment deviations induced by LVH).

ACUTE PERICARDITIS

STE may be seen in the acute or first stage of pericarditis, which occurs in the first few days and may last up to weeks. In most cases, diffuse STE is seen in all the ECG leads, except in leads aVR and V1, that typically have reciprocal depression of the ST segments (Figure 6). This pattern is often associated with PR depression in all ECG leads, except leads V1 and aVR, which occasionally depict reciprocal PR elevation[23]. Focal pericarditis (for example, after acute myocardial infarction or heart surgery), how-

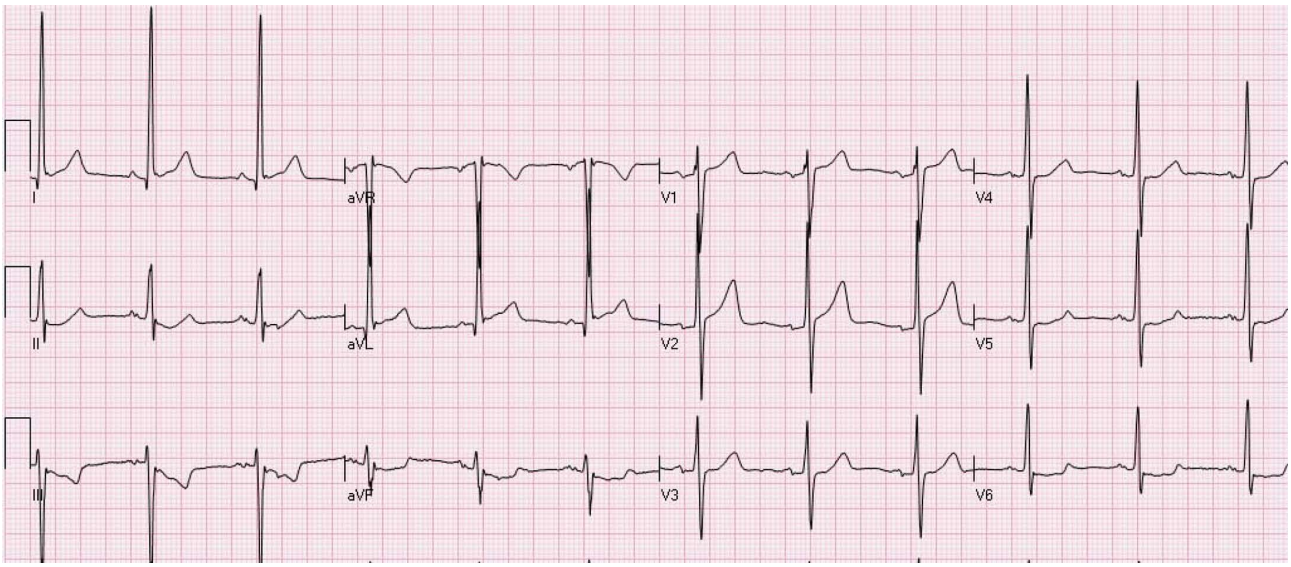

Figure 5 An electrocardiogram of a patient with atypical form of ST elevation secondary to left ventricular hypertrophy. ST elevation is present in leads I, aVL, V1-V2. Mild ST depression is present in the inferior leads and V5-V6.

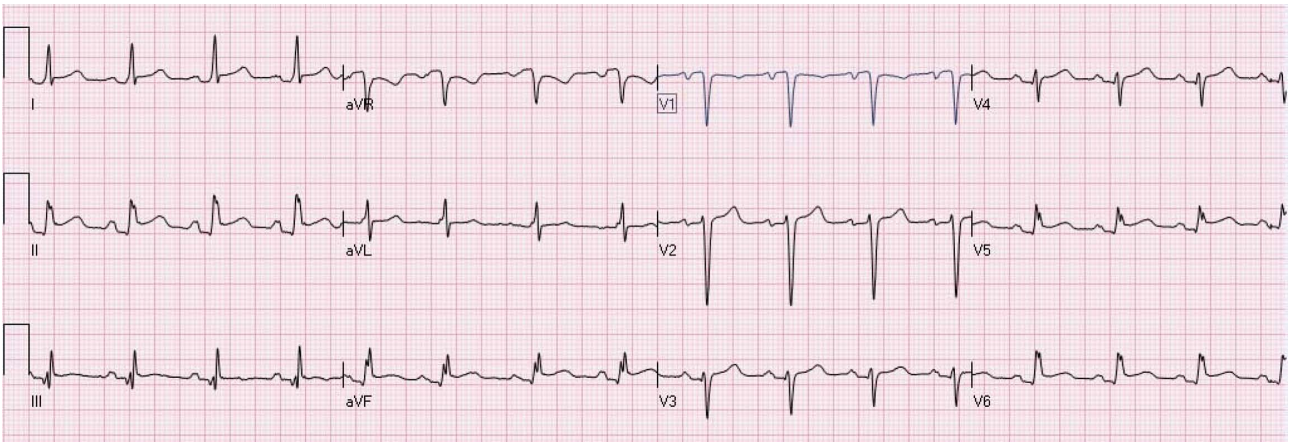

Figure 6 Diffuse ST elevation secondary to acute pericarditis. There is typical depression of the PR segment (seen mainly in leads Ⅱ and aVF. There is ST elevation in the inferolateral leads with ST depression in lead aVR.

ever, may induce more regional and non-typical forms of STE, which at times could be associated with depression of the ST segments in leads other than V1 and aVR . These atypical patterns could be mistaken for STEMI.

STE SECONDARY TO LEFT BUNDLE BRANCH BLOCK

LBBB typically causes marked ST changes (Figure 7), making it difficult to recognize STEMI when the LBBB pattern is present.

New or presumably new LBBB was regarded in the past as an STEMI equivalent[13]. However, the majority of cases with LBBB at the time of presentation, are "not known to be old", simply because an ECG prior to the index presentation is not available for comparison. Presumably new LBBB and even new LBBB at presentation occurs infrequently, is interfering with the analysis of the ECG, and according to the current STEMI guidelines are not considered diagnostic of acute myocardial infarction without the presence of typical clinical symptoms[3].

Only 1% to 9% of patients suspected of an acute myocardial infarction have LBBB (new or old) on their ECG[24]. Of the patients with LBBB on whom the STEMI protocol was initiated, 39% had a final diagnosis of true ACS, 36% had cardiac diagnoses other than ACS (hypertensive emergency, acute heart failure, atrial fibrillation, complete heart block, severe aortic stenosis, *etc.*) and 25% had non-cardiac chest pain[25,26].

LBBB pattern inherently has a masking feature that hides STEMIs. ST deviation typically is directed opposite to the direction of the QRS complex. Acute STEMI, on the other hand, typically presents with ST segment deviations that are concordant with the QRS complex deflections. As patients with LBBB typically show negative QRS complexes in leads V1- V3 (deep S waves), they typically have elevations of the ST segment in the precordial leads V1-V3.

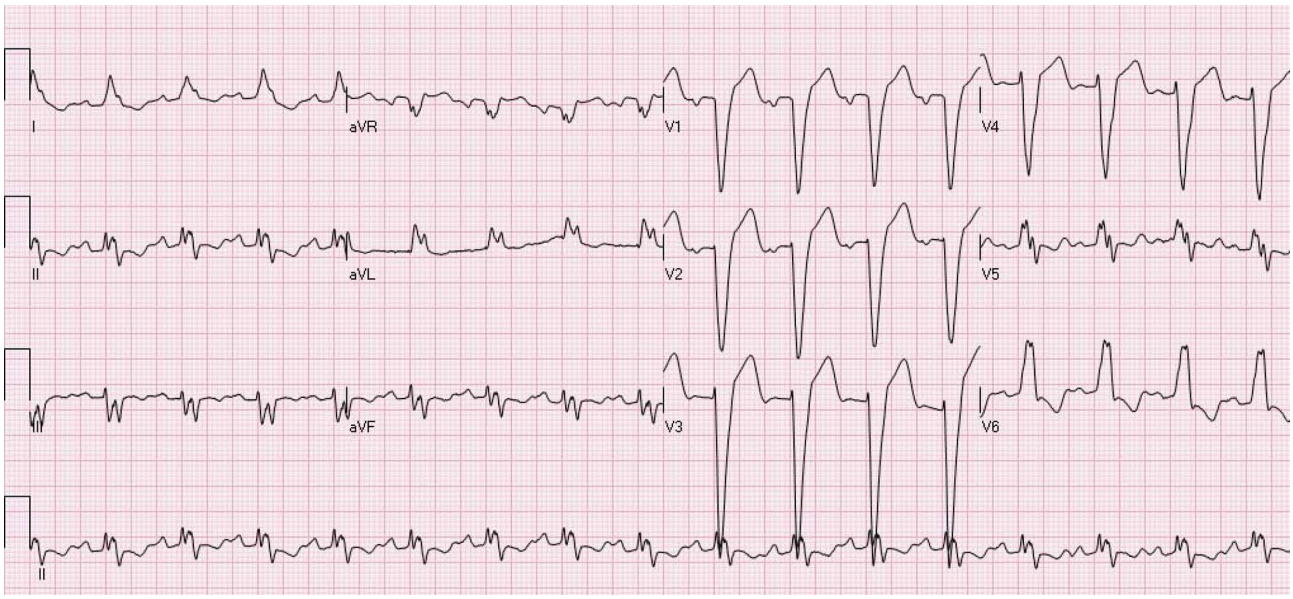

Figure 7 ST elevation secondary to left bundle branch block. The ST segment vector is directed opposite to the QRS vector. STE is present in the leads with negative QRS deflection (mainly leads V1-V3). There is typical ST depression in the leads with positive QRS deflection (the inferolateral leads).

This pattern must not be confused with anterior STEMI.

Criteria for recognizing STEMI in patients with LBBB were published by Sgarbossa and colleagues: (1) STE more than 0.1 MV that is concordant with the vector of the QRS complex; (2) ST depression of more than 0.1 mV in lead V1, V2, or V3; and (3) STE of more than 0.5 mV that is directed opposite to the QRS direction[27,28]. Patients are given a point for each of the above criteria and can be stratified on the likelihood of having STEMI based on their Sgarbossa score.

These criteria have been validated in multiple studies[24]. These criteria are reported to have high specificity; however, their sensitivity for identifying acute myocardial infarction in patients presenting with LBBB is low[24,29]. In a recent meta-analysis, a three point Sgarbossa criteria score ($\geqslant$ 0.1 mV of concordant STE or $\geqslant$ 0.1 mV ST depression in leads V1 to V3) had a sensitivity of 20% and specificity of 98%. If the third original criterion of discordant STE $\geqslant$ 0.5 mV in leads is added, the reported sensitivity is ranging between 20% and 79% and specificity between 61% and 100%[29].

Smith and colleagues[30] suggest replacing the third criteria of > 5mm absolute deviation in leads with discordant QRS complex with an ST/S ratio $\leqslant$ -0.25. Doing so increased the sensitivity from 67% to 91%, but the specificity remained unchanged at 90%. This modified Sgarbossa criteria needs to be validated with further studies[30].

The absolute magnitude of the deviation of the ST segments in patients with LBBB is influence by the degree of aberrancy and could change secondary to changes in the QRS axis, duration or heart rate. In addition, the absolute magnitude of deviation of the ST segment could change between different ECGs secondary to different electrode placement; this is often observed in the anterolateral precordial leads (V4-V6) in patients showing axis deviation to the left.

There is no data as to the thresholds of ST segment deviation in cases with incomplete LBBB (iLBBB; QRS duration of < 120 msec). Especially, it is unclear what are the cutoff values of "normal" STE in the precordial leads V1-V3 in cases with iLBBB.

STE SECONDARY TO OTHER INTRAVENTRICULAR CONDUCTION DELAYS

Patients with nonspecific intraventricular conduction delay may also diplay ST changes secondary to repolarization abnormalities (Figure 8). The pattern and magnitude of ST segment elevation or depression in such patients is highly variable, and the right diagnosis of STEMI can often be made only with comparison the index ECG and previous tracings or following changes over time in followup ECGs. Once more, the absolute magnitude of ST deviation can change as the degree of conduction delay changes (QRS width and axis) and may also depend on the heart rate.

Right bundle branch block (RBBB) is considered not to affect the interpretation of ST elevation or depression. Tachycardia, however, may cause depression of the ST segments in the right precordial leads (V1-V3) in patients with RBBB. These dynamic changes in the ST segments are often mistakenly diagnosed as true inferolateral (posterior) STEMI equivalent.

Pre-excitation (Wolf-Parkinson-White pattern) is occasionally associated with NISTE that are secondary repolarization alterations. The absolute magnitude of ST segment deviation is highly affected by the degree of pre-excitation.

BRUGADA SYNDROME

The Brugada pattern includes a pattern resembling RBBB

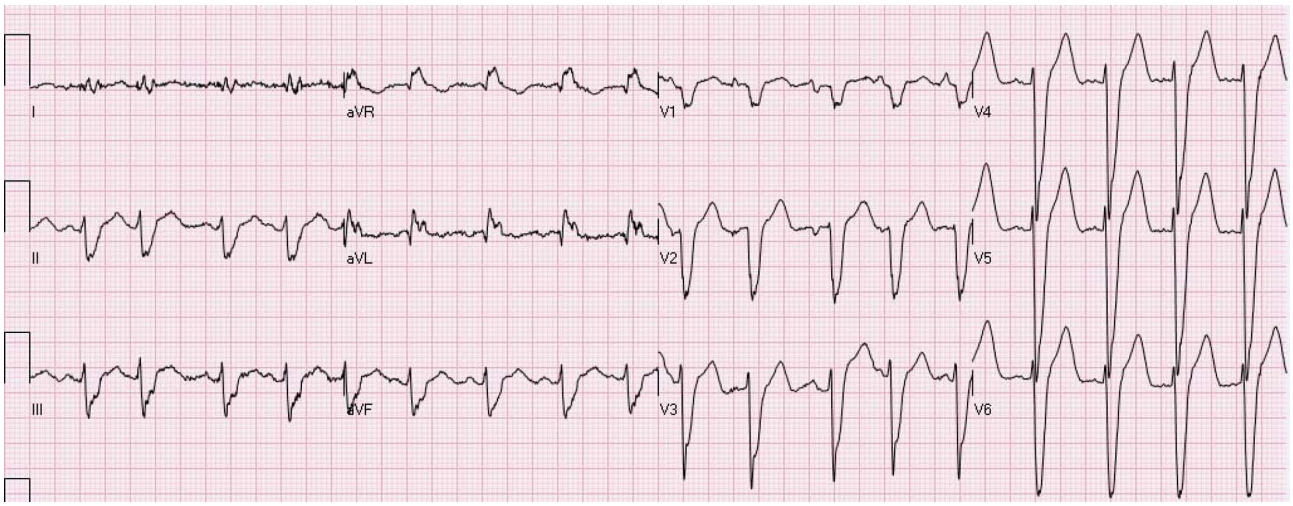

Figure 8 A patient with intraventricular conduction delay. There is mild elevation of the ST segment in the inferior leads and marked ST elevation in V2-V6. The patient is known to have non-ischemic dilated cardiomyopathy and this is his chronic electrocardiogram pattern.

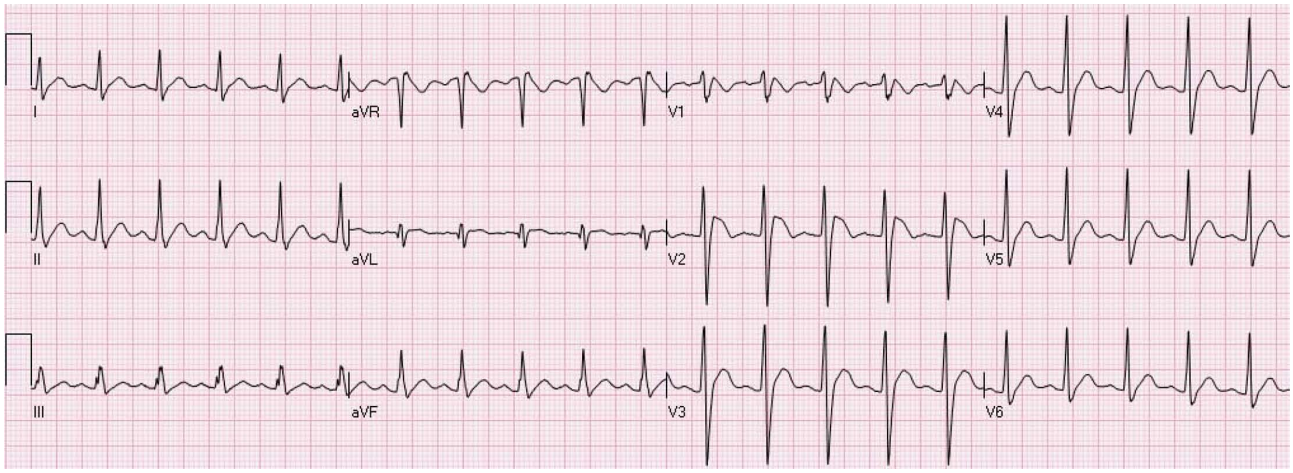

Figure 9 A patient showing a Brugada pattern with RsR', elevation of the ST segment and negative T waves in leads V1-V2.

with elevation of the ST segment in the precordial leads (V1-V2)[31,32]. The Brugada syndrome is linked to an increased risk of ventricular arrhythmia and sudden cardiac death. Type 1 Brugada pattern is defined by a coved elevation of the ST segment smore than 0.2 mV, associated T wave inversion in more than one of the right precordial leads (V1-V3. This pattern can be seen spontaneously or only after the administration of a sodium channel blocker. The diagnosis of Brugada syndrome depends on the presence of ECG Brugada pattern in a patient with documented history of ventricular fibrillation or polymorphic ventricular tachycardia, or a history of sudden cardiac death in family members that are younger than 45 years, comparable ECG configuration in relatives, unexplained syncope, ability to induce of ventricular tachycardia with programmed electrical stimulation, or agonal respiration at night time[33]. Type 2 Brugada pattern typically presents with a saddleback pattern of STE of more than 0.2 mV that attenuates in the middle and distal partof the ST segment with a positive or biphasic T waves in the precordial leads V1 to V3. Type 3 Brugada pattern shows a saddleback or coved pattern of elevation of the ST segment (less than 0.1 mV). Type 2 and 3 Brugada patterns should not be used to diagnose the Brugada syndrome and are not associated with increased risk of ventricular arrhythmia and sudden death. The ECG changes associated with the Brugada syndrome fluctuate with time, with diverse patterns and magnitude of elevation of the ST segments seen on different ECG tracings[33]. Figure 9 is an example of type 1 Brugada pattern.

TAKOTSUBO SYNDROME (APICAL BALLOONING SYNDROME)

Takotsubo syndrome is seen mainly in females after menopause. Typically, the syndrome follows acute physiologic or emotional stress. The subjects frequently experience chest pain or dyspnea. The presenting ECG typically shows elevation of the ST segment in the majority (up to 81.6%) of the patients. STE is typically seen in the precordial leads. In addition, abnormalities of the T waves (64.3%) and Q waves (31.8%) can be detected. Takot-

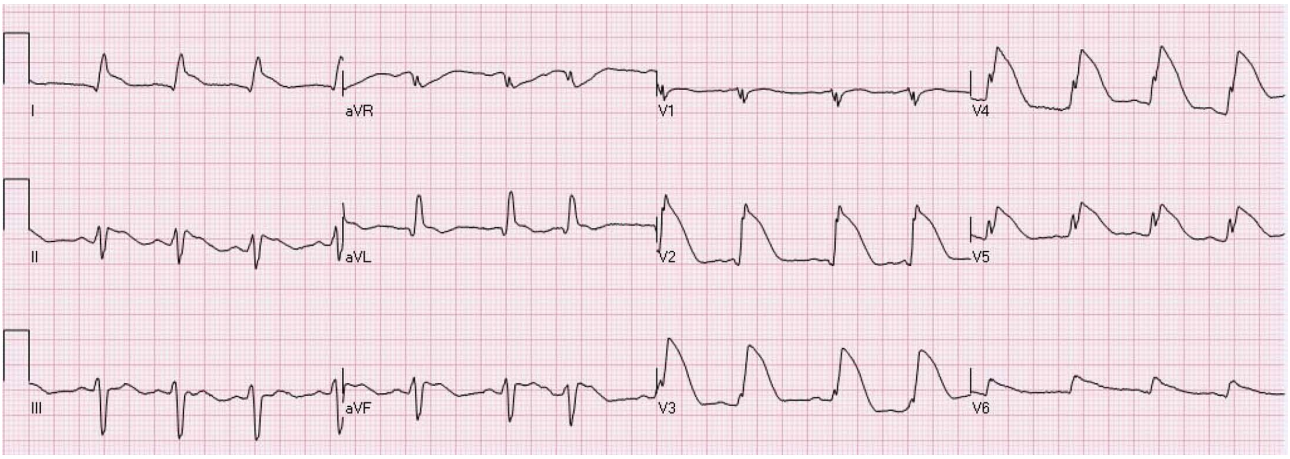

Figure 10 An elderly female patient with ST elevation secondary to Takotsubo. Angiography of the coronary arteries did not demonstrate significant coronary artery narrowings.

subo syndrome is typically associated with mild elevation of the cardiac markers (up to 86.2% of the patients)[34].

In the acute phase, the ECG of Takotsubo patients classically show marked depression of the ST segment in lead aVR, no or minimal elevation of the ST segment in lead V1 and concomitant diffuse STE in the other ECG leads (Figure 10)[35].

Frequently, the initial ECG pattern is mistaken for anterior STEMI (especially the type caused by distal occlusion of a wrapping long LAD that results in concomitant STE in both the inferior and precordial leads). Echocardiogram may show regional wall motion abnormalities that are confined to the apex. This pattern is not typical of the common type of anterior STEMI, but may be seen in patients with apical occlusion of a wrapping LAD. It was suggested that the ECGs of patients with Takotsubo have more marked depression of the ST segment in lead aVR in conjunction with less elevation of the ST segment in the precordial lead V1 relative to the ECGs of patients with typical acute anterior STEMI[36].

Because of the variations in presentation, Takotsubo's may be confused for other STE causes as well. Since many patients present with PR depression, Takotsubo cardiomyopathy often resembles acute pericarditis on EKG[35].

Acute stroke (particularly subarachnoid hemorrhage)[37,38] and pheochromocytoma[39,40] occasionally present with ECG and regional wall motion dysfunction findings that are indistinguishable from Takotsubo cardiomyopathy.

SPONTANEOUSLY REPERFUSED STEMI

The current STEMI guidelines advocate that subjects presenting with symptoms suggestive of ACS within the 12 h before presentation who have elevation of the ST segment in 2 or more adjacent ECG leads should undergo reperfusion therapy as soon as possible[3]. However, a significant percentage of patients probably have (partial) decrease in the severity of symptoms by the time of arrival to the hospital, more often after receiving chewable aspirin on route to the hospital. In many patients with spontaneous reperfusion the ECG depicts (incomplete) decline in STE with concomitant inversion of the last part of the T waves, as shown in Figure 11. This entity is not recognized by the current guidelines and there are no recommendations whether coronary angiography and revascularization can be delayed in patients with clinical suspicion of "spontaneous reperfusion" if they present within 12 h of onset of symptoms and still have some degree of STE. On the other hand, urgent pPCI is not recommended to asymptomatic patients who are hemodynamically stable despite having STE, if they present > 12 h of onset of symptoms[3].

LEFT VENTRICULAR ANEURYSM

Left ventricular aneurysm may result in persistent elevation of the ST segment after a previous MI. Freuqntly, the ECG may be very similar to that of acute STEMI. In fact, STE secondary to aneurysm may be the most frequently misinterpreted pattern in patients presenting to the emergency room with pain in their chest or dyspnea[41]. In Brady and colleagues' study, where 11 hypothetical patients and accompanying EKGs were presented to 458 Emergency room physicians, left ventricular aneurysm was misdiagnosed 72% of the time, making it the most commonly misinterpreted STE pattern[42]. Diagnosis is extremely difficult when previous ECGs are unavailable for comparison. Typically, the ECGs of patients with left ventricular aneurysm depict abnormal Q waves in the ECG leads showing elevation of the ST segment. Figure 12 is an example of persistent STE due to aneurysm in a patient three months after acute MI.

MIXED PATTERNS

In a large number of patients the ECG may show more than one pattern of elevation of the ST segments that makes the precise distinction between NISTE and STEMI extremely hard. At times patients with preexisting benign pattern of NISTE may present with chest pain secondary to NSTEMI. This is termed "pseudo"-STEMI

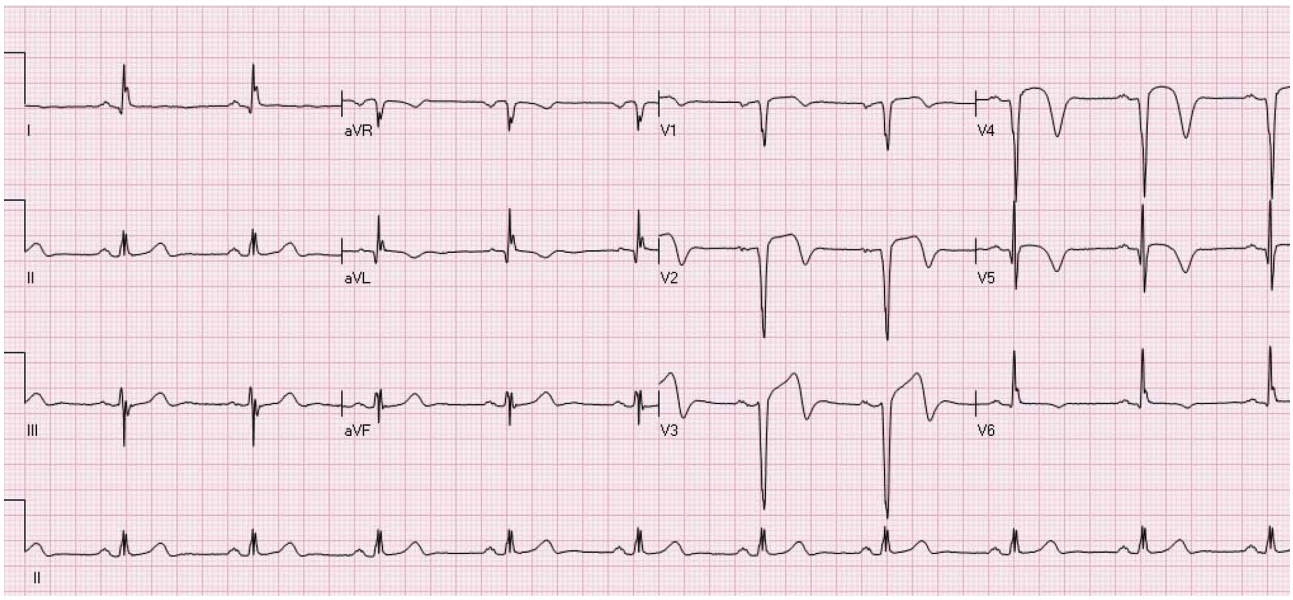

Figure 11 A patient with ST elevation associated with inversion of the terminal portion of the T waves in leads aVL, V1-V5 due to recent anterior ST elevation myocardial infarction. On presentation symptoms have already subsided.

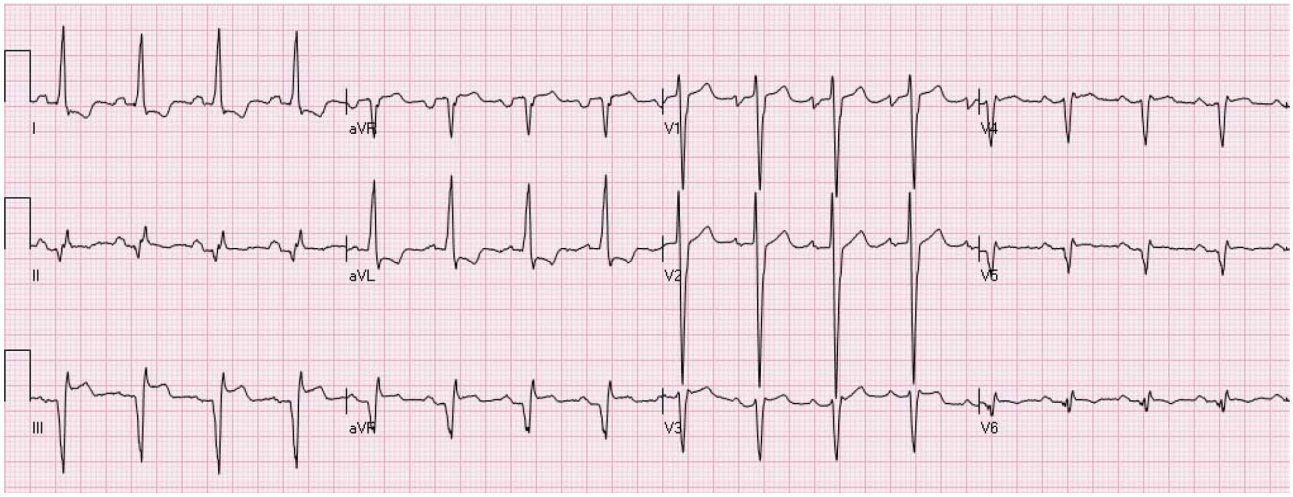

Figure 12 A patient with ST elevation secondary to aneurysm. There are Q waves in the inferior leads + V5-V6 and tall R waves in V1-V2, secondary to old inferolateral ST elevation myocardial infarctions. There is elevation of the ST segments in the inferior leads associated with reciprocal ST depression in leads I and aVL. The electrocardiogram (ECG) is compatible with both acute evolving inferior ST elevation myocardial infarctions or aneurysm. Comparison to previous ECG showed that this pattern is chronic and compatible with aneurysm.

and frequently is mistaken for true STEMI. Some forms of NISTE could show wide variations in the magnitude and extent of STE (for example, the Brugada syndrome or early repolarization). These changes over time; however, differ from the typical pattern of ECG evolution after STEMI.

CONCLUSION

The physician receiving the patient with symptoms compatible with STEMI at the first encounter should make reperfusion decisions as soon as possible after interpreting the initial ECG[1,3]. This goal was set up because the benefits of reperfusion therapy decline rapidly as the duration of ischemia is prolonged. Rapid interpretation of the ECG is crucial to shorten door-to-balloon time[43]. In an attempt to shorten the time to reperfusion, new approaches are currently being tested[44].

One of the more successful strategies is pre-hospital activation of the coronary catheterization laboratory by emergency medical services. Systems have been established in which in addition to interpreting the transmitted ECG, the interpreting physician can directly communicate with the emergency medical system (EMS) team or even the patient *via* a mobile phone[44]. The pre-hospital activation strategy is associated with a door to balloon time reduction of 15.4 min[44]. In the systems used in the United States, on the other hand, the electrogradiographer does not have the advantage of a face-to-face history taking and physical examination of the patient. In addition, even

if previous ECGs are stored in the (electronic) medical records, as a result of privacy issues, ECGs are transmitted without any identifier details, including names. Hence, the interpreter is not able to compare the transmitted ECG with preceding ECGs, even if they are readily available. Diercks and colleagues have shown an improvement in mortality for patients in whom pre-hospital activation system was used (6.7%), *vs* in patients without prehospital activation (9.5%)[45]. Although such approach might increase the sensitivity of detecting STE, the specificity and false activation remains a problem. The reported false-positive rate ranges from 5.6% to 25%[43,46-48]. These data suggest there is significant room for improvement.

To evaluate the capability of experienced experts in ECG reading to differentiate between STEMI to NISTE, 15 experienced ECG readers analyzed 116 ECGs showing elevation of the ST segments. The readers were asked whether the catheterization laboratory should be activated for possible STEMI if patients had symptoms suggestive of ACS[49]. In this set of ECGs, only 7% had adjudicated STEMI and 8 more patients had elevation of the heart muscle markers without clinical indication of STEMI. The number of cases for which acute reperfusion therapy was suggested by each of the ECG experts ranged between 7.8% to 33%. There were wide differences in sensitivity [50% to 100%, (average 75%)] and specificity [73% to 97%, (average 85%)] of the individual readers[49]. This study suggested that there is a need for refining the criteria for differentiating between NISTE and STEMI in different population setting and that the available criteria for diagnosing STEMI should be refined and standardized in order to maximize the accuracy of ECG interpretation.

REFERENCES

1 **Thygesen K**, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S. Third universal definition of myocardial infarction. *Circulation* 2012; **126**: 2020-2035 [PMID: 22923432 DOI: 10.1161/CIR.0b013e31826e1058]

2 Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet* 1994; **343**: 311-322 [PMID: 7905143]

3 **O'Gara PT**, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **61**: e78-140 [PMID: 23256914 DOI: 10.1016/j.jacc.2012.11.019]

4 **Canto JG**, Shlipak MG, Rogers WJ, Malmgren JA, Frederick PD, Lambrew CT, Ornato JP, Barron HV, Kiefe CI. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. *JAMA* 2000; **283**: 3223-3229 [PMID: 10866870]

5 **Deedwania PC**, Carbajal EV. Silent myocardial ischemia. A clinical perspective. *Arch Intern Med* 1991; **151**: 2373-2382 [PMID: 1746993]

6 **Kyker KA**, Limacher MC. Gender differences in the presentation and symptoms of coronary artery disease. *Curr Womens Health Rep* 2002; **2**: 115-119 [PMID: 12116600]

7 **Hiss RG**, Lamb LE, Allen MF. Electrocardiographic findings in 67,375 asymptomatic subjects. X. Normal values. *Am J Cardiol* 1960; **6**: 200-231 [PMID: 13855921]

8 **Surawicz B**, Parikh SR. Prevalence of male and female patterns of early ventricular repolarization in the normal ECG of males and females from childhood to old age. *J Am Coll Cardiol* 2002; **40**: 1870-1876 [PMID: 12446073]

9 **Macfarlane PW**. Age, sex, and the ST amplitude in health and disease. *J Electrocardiol* 2001; **34** Suppl: 235-241 [PMID: 11781962]

10 **Katibi I**, Clark EN, Devine B, Lloyd SM, Macfarlane PW. Normal limits of the electrocardiogram in Nigerians. *J Electrocardiol* 2013; **46**: 289-295 [PMID: 23702151 DOI: 10.1016/j.jelectrocard.2013.04.002]

11 **Larson DM**, Menssen KM, Sharkey SW, Duval S, Schwartz RS, Harris J, Meland JT, Unger BT, Henry TD. "False-positive" cardiac catheterization laboratory activation among patients with suspected ST-segment elevation myocardial infarction. *JAMA* 2007; **298**: 2754-2760 [PMID: 18165668 DOI: 10.1001/jama.298.23.2754]

12 **Rokos IC**, French WJ, Mattu A, Nichol G, Farkouh ME, Reiffel J, Stone GW. Appropriate cardiac cath lab activation: optimizing electrocardiogram interpretation and clinical decision-making for acute ST-elevation myocardial infarction. *Am Heart J* 2010; **160**: 995-1003, 1003.e1-8 [PMID: 21146650 DOI: 10.1016/j.ahj.2010.08.011]

13 **Antman EM**, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DI, Sloan MA, Smith SC. ACC/AHA Guidelines for the Management of Patients With ST-elevation Myocardial Infarction. *J Am Coll Cardiol* 2004; **44**: E1-211

14 **Wang K**, Asinger RW, Marriott HJ. ST-segment elevation in conditions other than acute myocardial infarction. *N Engl J Med* 2003; **349**: 2128-2135 [PMID: 14645641]

15 **Brady WJ**, Syverud SA, Beagle C, Perron AD, Ullman EA, Holstege C, Riviello RJ, Ripley A, Ghaemmaghami CA. Electrocardiographic ST-segment elevation: the diagnosis of acute myocardial infarction by morphologic analysis of the ST segment. *Acad Emerg Med* 2001; **8**: 961-967 [PMID: 11581081]

16 **Klatsky AL**, Oehm R, Cooper RA, Udaltsova N, Armstrong MA. The early repolarization normal variant electrocardiogram: correlates and consequences. *Am J Med* 2003; **115**: 171-177 [PMID: 12935822]

17 **Tikkanen JT**, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med* 2009; **361**: 2529-2537 [PMID: 19917913 DOI: 10.1056/NEJMoa0907589]

18 **Macfarlane PW**, Clark EN, Heng JS. J wave patterns--morphology, prevalence and nomenclature. *J Electrocardiol* 2013;

46: 505-509 [PMID: 24075127 DOI: 10.1016/j.jelectrocard.2013.08.013]
19 **Spodick DH**. Hypothermia with J (Osborne) waves. *Am Heart Hosp J* 2006; **4**: 156 [PMID: 16687964]
20 **Nishi SP**, Barbagelata NA, Atar S, Birnbaum Y, Tuero E. Hypercalcemia-induced ST-segment elevation mimicking acute myocardial infarction. *J Electrocardiol* 2006; **39**: 298-300 [PMID: 16777515]
21 **Nasir K**, Bomma C, Tandri H, Roguin A, Dalal D, Prakasa K, Tichnell C, James C, Spevak PJ, Marcus F, Calkins H. Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria. *Circulation* 2004; **110**: 1527-1534 [PMID: 15381658]
22 **Estes EH**, Jackson KP. The electrocardiogram in left ventricular hypertrophy: past and future. *J Electrocardiol* 2009; **42**: 589-592 [PMID: 19643433 DOI: 10.1016/j.jelectrocard.2009.06.016]
23 **Punja M**, Mark DG, McCoy JV, Javan R, Pines JM, Brady W. Electrocardiographic manifestations of cardiac infectious-inflammatory disorders. *Am J Emerg Med* 2010; **28**: 364-377 [PMID: 20223398 DOI: 10.1016/j.ajem.2008.12.017]
24 **Cai Q**, Mehta N, Sgarbossa EB, Pinski SL, Wagner GS, Califf RM, Barbagelata A. The left bundle-branch block puzzle in the 2013 ST-elevation myocardial infarction guideline: from falsely declaring emergency to denying reperfusion in a high-risk population. Are the Sgarbossa Criteria ready for prime time? *Am Heart J* 2013; **166**: 409-413 [PMID: 24016487 DOI: 10.1016/j.ahj.2013.03.032]
25 **Jain S**, Ting HT, Bell M, Bjerke CM, Lennon RJ, Gersh BJ, Rihal CS, Prasad A. Utility of left bundle branch block as a diagnostic criterion for acute myocardial infarction. *Am J Cardiol* 2011; **107**: 1111-1116 [PMID: 21296327 DOI: 10.1016/j.amjcard.2010.12.007]
26 **Mehta N**, Huang HD, Bandeali S, Wilson JM, Birnbaum Y. Prevalence of acute myocardial infarction in patients with presumably new left bundle-branch block. *J Electrocardiol* 2012; **45**: 361-367 [PMID: 22575807 DOI: 10.1016/j.jelectrocard.2012.04.006]
27 **Sgarbossa EB**. Value of the ECG in suspected acute myocardial infarction with left bundle branch block. *J Electrocardiol* 2000; **33** Suppl: 87-92 [PMID: 11265742]
28 **Sgarbossa EB**, Pinski SL, Barbagelata A, Underwood DA, Gates KB, Topol EJ, Califf RM, Wagner GS. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle-branch block. GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) Investigators. *N Engl J Med* 1996; **334**: 481-487 [PMID: 8559200]
29 **Tabas JA**, Rodriguez RM, Seligman HK, Goldschlager NF. Electrocardiographic criteria for detecting acute myocardial infarction in patients with left bundle branch block: a meta-analysis. *Ann Emerg Med* 2008; **52**: 329-336.e1 [PMID: 18342992]
30 **Smith SW**, Dodd KW, Henry TD, Dvorak DM, Pearce LA. Diagnosis of ST-elevation myocardial infarction in the presence of left bundle branch block with the ST-elevation to S-wave ratio in a modified Sgarbossa rule. *Ann Emerg Med* 2012; **60**: 766-776 [PMID: 22939607 DOI: 10.1016/j.annemergmed.2012.07.119]
31 **Antzelevitch C**, Nof E. Brugada syndrome: recent advances and controversies. *Curr Cardiol Rep* 2008; **10**: 376-383 [PMID: 18715534]
32 **Brugada P**, Brugada R, Brugada J. The Brugada syndrome. *Curr Cardiol Rep* 2000; **2**: 507-514 [PMID: 11060577]
33 **Antzelevitch C**, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, LeMarec H, Nademanee K, Perez Riera AR, Shimizu W, Schulze-Bahr E, Tan H, Wilde A. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 2005; **111**: 659-670 [PMID: 15655131]
34 **Gianni M**, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. *Eur Heart J* 2006; **27**: 1523-1529 [PMID: 16720686]
35 **Zhong-qun Z**, Chong-quan W, Sclarovsky S, Nikus KC, Chao-rong H, Shan M. ST-segment deviation pattern of takotsubo cardiomyopathy similar to acute pericarditis: diffuse ST-segment elevation. *J Electrocardiol* 2012; **46**: 84-89 [PMID: 23276390 DOI: 10.1016/j.jelectrocard.2012.11.013]
36 **Kosuge M**, Ebina T, Hibi K, Morita S, Okuda J, Iwahashi N, Tsukahara K, Nakachi T, Kiyokuni M, Ishikawa T, Umemura S, Kimura K. Simple and accurate electrocardiographic criteria to differentiate takotsubo cardiomyopathy from anterior acute myocardial infarction. *J Am Coll Cardiol* 2010; **55**: 2514-2516 [PMID: 20510222 DOI: 10.1016/j.jacc.2009.12.059]
37 **Rahimi AR**, Katayama M, Mills J. Cerebral hemorrhage: precipitating event for a tako-tsubo-like cardiomyopathy? *Clin Cardiol* 2008; **31**: 275-280 [PMID: 18431739 DOI: 10.1002/clc.20165]
38 **Santana-Cabrera L**, Rodríguez Escot C, Medina Gil JM, Pérez Ortiz C. Takotsubo cardiomyopathy associated with acute subarachnoid hemorrhage. *J Emerg Med* 2012; **42**: 586-587 [PMID: 20933359 DOI: 10.1016/j.jemermed.2010.06.032]
39 **Lassnig E**, Weber T, Auer J, Nömeyer R, Eber B. Pheochromocytoma crisis presenting with shock and tako-tsubo-like cardiomyopathy. *Int J Cardiol* 2009; **134**: e138-e140 [PMID: 18579235 DOI: 10.1016/j.ijcard.2008.03.012]
40 **Takizawa M**, Kobayakawa N, Uozumi H, Yonemura S, Kodama T, Fukusima K, Takeuchi H, Kaneko Y, Kaneko T, Fujita K, Honma Y, Aoyagi T. A case of transient left ventricular ballooning with pheochromocytoma, supporting pathogenetic role of catecholamines in stress-induced cardiomyopathy or takotsubo cardiomyopathy. *Int J Cardiol* 2007; **114**: e15-e17 [PMID: 17052786]
41 **Engel J**, Brady WJ, Mattu A, Perron AD. Electrocardiographic ST segment elevation: left ventricular aneurysm. *Am J Emerg Med* 2002; **20**: 238-242 [PMID: 11992347]
42 **Brady WJ**, Perron AD, Chan T. Electrocardiographic ST-segment elevation: correct identification of acute myocardial infarction (AMI) and non-AMI syndromes by emergency physicians. *Acad Emerg Med* 2001; **8**: 349-360 [PMID: 11282670]
43 **Camp-Rogers T**, Kurz MC, Brady WJ. Hospital-based strategies contributing to percutaneous coronary intervention time reduction in the patient with ST-segment elevation myocardiaI infarction: a review of the "system-of-care" approach. *Am J Emerg Med* 2012; **30**: 491-498 [PMID: 21514087 DOI: 10.1016/j.ajem.2011.02.011]
44 **Bradley EH**, Herrin J, Wang Y, Barton BA, Webster TR, Mattera JA, Roumanis SA, Curtis JP, Nallamothu BK, Magid DJ, McNamara RL, Parkosewich J, Loeb JM, Krumholz HM. Strategies for reducing the door-to-balloon time in acute myocardial infarction. *N Engl J Med* 2006; **355**: 2308-2320 [PMID: 17101617]
45 **Diercks DB**, Kontos MC, Chen AY, Pollack CV, Wiviott SD, Rumsfeld JS, Magid DJ, Gibler WB, Cannon CP, Peterson ED, Roe MT. Utilization and impact of pre-hospital electrocardiograms for patients with acute ST-segment elevation myocardial infarction: data from the NCDR (National Cardiovascular Data Registry) ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry. *J Am Coll Cardiol* 2009; **53**: 161-166 [PMID: 19130984 DOI: 10.1016/j.jacc.2008.09.030]
46 **Adams GL**, Campbell PT, Adams JM, Strauss DG, Wall K, Patterson J, Shuping KB, Maynard C, Young D, Corey C, Thompson A, Lee BA, Wagner GS. Effectiveness of prehospital wireless transmission of electrocardiograms to a cardiologist via hand-held device for patients with acute myocardial infarction (from the Timely Intervention in Myocardial

Emergency, NorthEast Experience [TIME-NE]). *Am J Cardiol* 2006; **98**: 1160-1164 [PMID: 17056318]

47 **Campbell PT**, Patterson J, Cromer D, Wall K, Adams GL, Albano A, Corey C, Fox P, Gardner J, Hawthorne B, Lipton J, Sejersten M, Thompson A, Thompson A, Wilfong S, Maynard C, Wagner G. Prehospital triage of acute myocardial infarction: wireless transmission of electrocardiograms to the on-call cardiologist via a handheld computer. *J Electrocardiol* 2005; **38**: 300-309 [PMID: 16216601]

48 **Sadeghi HM**, Grines CL, Chandra HR, Mehran R, Fahy M, Cox DA, Garcia E, Tcheng JE, Griffin JJ, Stuckey TD, Lansky AJ, O'Neill WW, Stone GW. Magnitude and impact of treatment delays on weeknights and weekends in patients undergoing primary angioplasty for acute myocardial infarction (the cadillac trial). *Am J Cardiol* 2004; **94**: 637-640, A9 [PMID: 15342297]

49 **Jayroe JB**, Spodick DH, Nikus K, Madias J, Fiol M, De Luna AB, Goldwasser D, Clemmensen P, Fu Y, Gorgels AP, Sclarovsky S, Kligfield PD, Wagner GS, Maynard C, Birnbaum Y. Differentiating ST elevation myocardial infarction and nonischemic causes of ST elevation by analyzing the presenting electrocardiogram. *Am J Cardiol* 2009; **103**: 301-306 [PMID: 19166679 DOI: 10.1016/j.amjcard.2008.09.082]

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REVIEW

Non-interventional management of resistant hypertension

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Abstract

Hypertension is one of the most popular fields of research in modern medicine due to its high prevalence and its major impact on cardiovascular risk and consequently on global health. Indeed, about one third of individuals worldwide has hypertension and is under increased long-term risk of myocardial infarction, stroke or cardiovascular death. On the other hand, resistant hypertension, the "uncontrollable" part of arterial hypertension despite appropriate therapy, comprises a much greater menace since long-standing, high levels of blood pressure along with concomitant debilitating entities such as chronic kidney disease and diabetes mellitus create a prominent high cardiovascular risk milieu. However, despite the alarming consequences, resistant hypertension and its effective management still have not received proper scientific attention. Aspects like the exact prevalence and prognosis are yet to be clarified. In an effort to manage patients with resistant hypertension appropriately, clinical doctors are still racking their brains in order to find the best therapeutic algorithm and surmount the substantial difficulties in controlling this clinical entity. This review aims to shed light on the effective management of resistant hypertension and provide practical recommendations for clinicians dealing with such patients.

Key words: Resistant hypertension; Antihypertensive drugs; Adherence; White coat hypertension; Secondary hypertension

Core tip: Patients with resistant hypertension are exposed to high cardiovascular risk and proper medical management continues to puzzle clinicians. The appropriate management of resistant hypertension is still elusive. This review provides practical recommendations for the management of resistant hypertension, aiming to help primary care physicians. It also highlights that the therapeutic scheme should always match the patient's profile in terms of safety, tolerability and effectiveness.

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INTRODUCTION

Despite impressive advances in the area of therapeutics, cardiovascular disease (CVD) continues to be the leading cause of death, even in the 21st century[1,2]. Among causative factors, hypertension carries the greatest risk for cardiovascular (CV) mortality and morbidity. With a prevalence of around 30% worldwide, individuals with high blood pressure have a five times greater risk of suffering

a debilitating stroke, whereas 50% of hypertensives will suffer from ischemic heart disease and around 7.0 million people will die each year[1,2]. Surprisingly, a considerable number of individuals with arterial hypertension remain undertreated or uncontrolled despite a combination of at least three antihypertensive drugs (including a diuretic), thus meeting the classical criteria of resistant hypertension (RH). Furthermore, since hypertension begets hypertension and hypertension worsens vascular disease and vice versa, it is reasonable to consider RH a vascular emergency. In fact, prior to the advent of pharmacological therapy, these are the patients that would progress to an accelerated and malignant hypertension phase with dire consequences.

DEFINITION-PREVALENCE

According to the seventh report of the Joint National Committee 7 (JNC7), RH is defined as the lack of control of blood pressure (BP) or BP above the therapeutic goal despite the use of three antihypertensive drugs, including a diuretic, at optimal doses[3]. BP controlled with more than three antihypertensive medications is also included in the most recent definition of the American Heart Association (AHA)[4]. A more recent definition comes from the latest guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and European Society of Cardiology (ESC). According to the authors, RH is defined as arterial hypertension above the therapeutic goal of systolic blood pressure (SBP) (140 mmHg) and diastolic blood pressure (DBP) (90 mmHg), and resistant to treatment despite the implementation of appropriate lifestyle measures and a combination therapy of three antihypertensive drugs, including a diuretic, at adequate doses[5]. With recent publicity surrounding RH, more and more studies indicate increasing frequency, but true prevalence remains largely unknown. Data from relatively small studies published so far indicate ranging prevalence from 5% in the general population to 50% in nephrology clinics[6-8]. However, more recent data from the United States and Spain suggest a prevalence of resistant hypertension of approximately 10%[9-10]. Yet, even these data are questionable due to methodological limitations[11].

PROGNOSIS

Similarly to prevalence, the prognosis of patients with RH remains an area widely understudied. It is well established that arterial hypertension and CV risk are a very tight dual complex and that CV morbidity and mortality is directly related to BP levels[12]. It thus seems rational to assume that patients with RH presenting with long-standing, uncontrolled, high BP might be at a much higher CV risk[13]. This assumption is further supported by the fact that most patients with RH have many other CV risk factors, such as chronic kidney disease (CKD), obstructive sleep apnea (OSA), diabetes or left ventricular hypertrophy (LVH)[4,8]. Although rationally sound, only small clinical studies and observational cohorts have tried to give a more concrete element to this relationship, demonstrating up to a six fold higher CV risk for patients with RH[14-20]. Therefore, ESH and ESC guidelines incorporated RH as a condition associated with a high risk of CV and renal events[5].

The most significant information in this field comes from two recent studies. In a large retrospective observational study of more than 200000 patients and a median follow-up of 3.8 years, it was found that CV event rates were almost 50% higher in patients with RH compared to those without RH[21]. Although very important, this large study suffers from the inherent drawbacks of retrospective analysis of data stored in large databases. A more accurate estimation of RH-associated CV morbidity comes from a meticulous study of almost 2000 hypertensive patients with a mean follow-up of 3.9 years[22]. It was found that RH was associated with a 2.2-fold increased risk of CV morbidity compared to control patients without RH. However, the accurate risk while being uncontrolled and the exact benefit from efficiently controlling RH are yet to be found.

MANAGEMENT

Given the relatively high prevalence of RH and the presumably high CV risk of this condition, proper management of the affected individuals should be promptly established. In general, the ideal approach of a patient with RH should focus on two goals, with the primary being identification, careful evaluation and, if possible, reversal of contributing factors, followed by an effective individualized drug regimen.

After ensuring that treatment resistance is not due to improper office BP measurement, especially in elderly patients, the astute physician has to exclude other causes of "pseudo-resistance". The possibility of secondary hypertension should be examined, probably evaluating target-organ damage (TOD). Practical recommendations for a step-by-step approach are presented in detail.

WHITE COAT HYPERTENSION

White coat hypertension is a commonly encountered factor that must always be ruled out. Several small studies pointed towards an increased prevalence of white coat hypertension among patients with RH[15,16,23] and a large study of more than 8000 patients with apparent RH unveiled the magnitude of the white coat effect[10]. Using ambulatory BP monitoring, it was found that only 62.5% of patients with office RH actually had true RH, while the remaining 37.5% had white coat hypertension[10]. Apart from ambulatory BP monitoring, white coat hypertension may be excluded with the use of home BP measurements as well. In a large 20 year study of more than 2300 patients with office RH, white coat hypertension was identified in approximately 30% of study participants, mainly through home BP monitoring[24].

Adherence to therapy

Poor adherence to prescribed medication is a major problem in the cardiovascular field. A population study of about half a million patients in Italy revealed that 33% discontinued antihypertensive drugs within 6 mo of treatment initiation and the discontinuation rate reached 50% at 5 years post-treatment[25], with obvious detrimental consequences. Indeed, continuation of antihypertensive drugs is associated with a 37% reduction of CV events in hypertensive patients[26]. Moreover, the CV risk is 25% lower in patients with high compliance compared to those with low compliance with antihypertensive agents[26]. The problem of persistence with antihypertensive therapy in patients with RH was recently highlighted in a small study from Germany. Among 108 patients with true resistant hypertension, it was found that more than half of them were non-adherent to therapy; more impressively, among non-adherent patients, 30% were completely non-adherent and 56% were taking less than half of the prescribed drugs[27]. Although the study was small, it was well-designed and used state-of-the-art toxicological methods to assess antihypertensive drug levels, indicating that poor treatment adherence is actually exaggerated in patients with apparent RH and is a major problem. Another just published study of 339 patients with RH assessing serum levels of antihypertensive drugs confirmed the findings of the previous study since 47% of patients were non-compliant to therapy (either completely or partially)[28].

Clinical inertia

Clinical or physician inertia in the hypertension field can be defined as the failure of treating physicians to initiate, intensify or change therapy when BP values are above the therapeutic goal. It has long been recognized that physicians are often reluctant to appropriately manage high blood pressure levels and do not start, intensify or switch antihypertensive therapy in about one third of occasions[29,30], reaching 50% in patients with comorbidities[31,32]. Clinical inertia seems to play a major role in RH. In a recent study of more than 3500 patients with diagnosed RH, treatment intensification (dose increase or drug addition) occurred in only 21.6% of visits with elevated BP[33].

The observation that treatment intensification occurs in only one of five clinical visits is shocking and deserves to be examined in-depth, to be highlighted and appropriately addressed. First, it seems to reflect everyday clinical practice since the vast majority (99.5%) of clinical visits in the latter study was performed in primary care (family practice, internal medicine and obstetrics/gynecology). However, the big surprise comes from another finding of this study and regards diuretic use: instead of intensifying diuretic use by dose increment, the study reported that diuretic use was actually reduced by 15% at one year after the diagnosis of RH. Another finding of this study confirms the importance of increasing treatment intensity: treatment intensification was associated with a 64% increase in BP control at 1 year post-RH diagnosis.

Drugs inducing hypertension

A long list of drugs (either prescribed or over-the-counter) and exogenous agents result in BP elevation and consequently either induce hypertension or contribute to resistance in drug therapy. Drug-induced hypertension is common and among the main causes of treatment resistance[34]. The most frequent agents associated with drug-induced BP elevation are without any doubt non-steroidal anti-inflammatory drugs which are widely prescribed for a variety of conditions and are also available over-the-counter[35-37]. Other common causes include oral contraceptives, hormone replacement therapy, and sympathomimetics[38-40]. Special attention needs to be drawn to drugs that are not commonly used but are essential for the treatment of specific conditions: erythropoietin for the treatment of CKD-associated anemia and myelodysplastic syndromes, cyclosporine and tacrolimus for organ transplantation, mineralocorticoids for adrenal insufficiency, glucocorticoids for a wide variety of conditions, and some newer anti-neoplastic drugs (VEGF-inhibitors and tyrosine-kinase inhibitors)[41-43]. Finally, illicit drugs and herbal supplements must not be forgotten as causes of treatment resistance in hypertensive patients[44,45].

Some points regarding drug-induced BP elevation need to be highlighted. First is the heterogeneity of BP response to the above mentioned agents. Some patients experience excessive BP elevation while other patients exhibit little if any BP elevation. Then, the necessity of the administered drugs inducing BP elevation dictates management: (1) when the drug is not essential it can be withdrawn; (2) when the drug is essential and replacement with another less susceptible drug or dose reduction seems possible it can be tried; and (3) when the drug is essential and cannot be replaced or down-titrated then the best solution seems to be to treat the elevated BP with the more appropriate antihypertensive drugs for each condition. Last, but most important, is the identification of drug-induced BP elevation. Despite its high frequency and the easiness of its recognition, treating physicians often miss the opportunity of recognizing iatrogenic hypertension, a common identifiable cause of treatment resistance.

Secondary hypertension

Secondary forms of hypertension are not rare and are frequently associated with treatment resistance unless the etiological factor is removed. The list for secondary hypertension is long and includes a wide variety of conditions[46]; however, a detailed presentation of these causes is outside the scope of the current review. Special attention should be given to the most common causes of secondary hypertension: primary hyperaldosteronism, renal parenchymal disease, renovascular disease and obstructive sleep apnea[34]. For example, in a large study of more than 2000 patients with RH, primary hyperaldosteronism was identified in approximately 11% of study participants[24].

The astute physician, however, needs to know all the forms of secondary hypertension, recognize their pre-

senting symptoms, be familiar with the tests required to establish or rule out their diagnosis, and effectively treat these conditions. It has to be noted that a lot of experience is required to raise suspicion and unveil secondary forms of hypertension because there is a two-edged sword: either miss the diagnosis of a secondary form of resistant hypertension or perform several unnecessary tests without an obvious reason and with a tremendous cost. It therefore seems rational to recommend referral to a specialized center when the suspicion of a secondary form is raised by primary care physicians[5].

Target organ damage

The recent 2013 guidelines for the management of arterial hypertension recommend the recognition of TOD in patients with arterial hypertension[5]. The reason for this recommendation lies mainly in a more complete and accurate estimation of CV risk and the subsequent reclassification of patients with low or intermediate risk to a higher risk level, as well as the specific treatment of the various forms of TOD with appropriate antihypertensive drugs. TOD is common in patients with RH and more frequently recognized compared to patients without RH. Indeed, left ventricular hypertrophy, arterial stiffness, microalbuminuria, diastolic dysfunction and chronic kidney disease are more common in patients with RH than in control patients[47-51]. The association between RH and TOD represents a "chicken-egg" question: is it the RH that results in TOD or is hypertension more difficult to control in patients with TOD? Although available data does not allow for definite conclusions, it seems that this association is bi-directional and both types of association occur in patients with RH.

Although we do not wish to dispute the importance of identifying TOD, we believe that it is of marginal clinical significance in patients with RH. Our belief is mainly for two reasons: (1) patients with RH are already at very high CV risk, due not only to hypertension but to the frequent existence of comorbidities as well; and (2) more importantly, patients with RH are already being aggressively treated with the majority of available means of the antihypertensive therapeutic armamentarium and the recognition of TOD is not likely to alter the therapeutic regime. Therefore, the quest for TOD in patients with RH seems to be currently of little if any clinical significance.

NON-PHARMACOLOGICAL APPROACH

Lifestyle factors (obesity, excessive salt intake, physical inactivity, smoking, increased alcohol consumption) contribute significantly to the multifactorial etiology of treatment resistance and are prominent therapeutic targets during assessment of patients with RH[4,8]. Thus, common lifestyle modifications such as dietary weight loss, salt restriction, increased physical activity, smoking cessation and moderation of alcohol intake are recommended and should be always incorporated in the therapeutic plan of individuals with RH[4,8]. However, the evidence behind these recommendations is not always strong and often relies on potential benefits and the lack of harm.

Several lines of evidence from epidemiological longitudinal studies and randomized clinical trials indicate that hypertension is more difficult to control in obese patients and requires more antihypertensive drugs[52-55]. In a recent report from NHANES, obesity was identified as a strong and independent predictor of apparent treatment-resistant hypertension[56]. Obesity-induced treatment resistance might be mediated by sympathetic activation, volume expansion, aldosterone excess and obstructive sleep apnea[57-59]. Although the benefits of weight loss on BP are not questioned, the impact of weight reduction (through lifestyle modification, pharmacological agents or bariatric surgery) on BP in patients with RH is poorly studied and needs to be confirmed by properly designed studies. Likewise, smoking cessation and alcohol moderation have not been adequately studied in RH, despite the undisputable benefits of these changes in lifestyle factors.

The paramount importance of salt restriction in patients with RH was recently highlighted. A small, randomized, cross-over study of 12 patients with RH evaluated the effects of a low and high sodium diet on BP[60]. It was found that a low sodium diet was associated with a substantial reduction of office systolic and diastolic BP by 22.7 and 9.1 mmHg, respectively. Of major importance, a similar reduction in ambulatory BP was observed as well (20.1/9.8 mmHg), both during the day and night, despite the fact that ambulatory BP reduction tends to be significantly lower than office BP reduction[61].

Fitness and increased exercise capacity are associated with significant morbidity and mortality benefits in patients with hypertension, prehypertension and high normal blood pressure, even in elderly patients[62-66]. The significance of regular exercise in patients with RH was recently demonstrated. A randomized study of 50 patients with RH assessed the effects of a treadmill exercise program for 8 to 12 wk[67]. It was found that regular aerobic exercise is associated with a significant reduction in ambulatory BP by 6/3 mmHg. Another small study of 16 patients with RH points towards significant benefits of heated water-based exercise[68] but further studies are needed to confirm these preliminary findings.

DRUG TREATMENT

After all contributing factors have been carefully assessed and effectively managed, treatment of true RH, whether pharmacological or not, relies on inhibiting the pathophysiological pathways resulting in BP elevation. Activation of the renin-angiotensin system (RAS), sympathetic nervous system (SNS) overactivity and intravascular volume expansion are the three cardinal pharmacological targets in the therapeutic algorithm of an individual with RH[4,8,13,34]. The means to achieve these targets cover a broad spectrum of agents, including diuretics, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta blockers (BBs), alpha blockers, centrally acting drugs

and other potent vasodilating agents. The most prescribed drug categories among patients with RH are RAS inhibitors (ACEi and ARBs), diuretics, CCBs and BBs. A recent report of more than 140000 patients with RH included in the large Medstat database revealed that 96.2% of patients were on RAS inhibitors, 93.2% on diuretics, 83.6% on CCBs, and 80% on BBs[69]. Chronotherapeutics might also play a role and bedtime administration of one drug or one dose might be beneficial in terms of both BP control and outcomes[70,71]; however, more solid evidence is needed before the wide generalization of this approach.

We propose a therapeutic approach of a step-by-step addition of antihypertensive drug classes in patients with RH. This approach is based on the pathophysiology of RH, the properties of antihypertensive drugs, the safety profile and the efficacy of each class of agents in RH. It has to be noted, however, that available data in RH is scarce and limited with the vast majority of antihypertensive drugs. Therefore, the proposed approach is more scientifically sound than evidence-based. Prospective studies are needed to evaluate the efficacy, safety and utility of this approach.

Triple therapy

In general terms, combining available agents is the cornerstone of treatment of RH. The challenge, however, rests upon constructing a regime that will be both effective, in terms of blocking the majority of the implicated pathophysiological pathways, and individualized, according to the patient's profile, lifestyle, comorbidities or even financial limitations. Moreover, the optimal combination should be well tolerated by the patient, with minimal adverse events to ensure long-term adherence to therapy.

Taking into account the above considerations, a triple combination of an ACEI or ARB along with a diuretic and a CCB seems to be a reasonable regime when approaching a patient with RH for the first time. This combination is scientifically sound, widely used in everyday clinical practice, and should be applied in high doses as the first therapeutic step in patients with true RH after all forms of "pseudo-resistance" have been excluded. This combination might be applied in terms of switching previous therapy or of treatment intensification in patients already using this combination in lower doses. The proposed triple combination has several advantages in terms of efficacy, safety profile, adherence to therapy and financial costs.

In terms of efficacy, this combination seems very attractive. Inhibition of the RAS system with an ACEI or an ARB is a very useful tool to subdue high BP, especially in patients with concomitant CKD, heart failure, myocardial infarction, diabetes mellitus and most forms of TOD[5]. Combining a RAS inhibitor with a CCB or a diuretic is a very popular and scientifically sound choice, especially for black people and the elderly in whom CCBs and diuretics are of particular value[3]. Several studies have demonstrated the CV benefit of prescribing these two combinations and, as a matter of fact, many fixed-dose combinations have been on the market for several years[72].

In terms of safety, RAS inhibitors are known to attenuate the most common adverse events of the other two classes: peripheral edema induced by calcium antagonists and hypokalemia induced by diuretics[5,72]. In terms of persistence in therapy and cost, dual fixed combinations (RAS inhibitors plus thiazides or calcium antagonists) have been available for many years on the market and physicians are already familiar with their use. Using fixed combinations increases adherence to antihypertensive therapy[73]. Moreover, fixed combinations are usually cheaper than the administration of each drug separately and since drugs comprising these combinations are already off-patent, fixed combinations are preferred from the financial point of view. Triple fixed combinations were recently introduced in the market and are likely to improve patients' adherence to therapy with obvious health and financial benefits[74].

In clinical practice, it is not unusual to see patients referred for RH who are actually receiving inappropriate combinations or low doses of appropriate combinations. This clinical observation provides the basis for the first step of the proposed therapeutic approach. The combination of ACEi with ARBs provides a very good example of inappropriate or non-preferred combinations. This combination was very popular during the last decade despite its moderate efficacy on BP reduction compared to other combinations, mainly due to expectations for potential benefits on target organ protection, especially cardioprotection and nephroprotection. The dual inhibition of the renin-angiotensin system suffered a lethal kick by the ONTARGET study, in which the combination did not confer any additional benefits compared to RAS monotherapy and was associated with more adverse events[75]. More recently, two other studies seem to have put the final nail in the coffin. The NEPHRON-D study found no benefit in patients with CKD[76] and the ALTITUDE study reported similar results for the combination with direct renin inhibitors[77]. Therefore, guidelines for the management of arterial hypertension strongly recommend avoiding dual RAS inhibition. Everyday clinical practice, however, is cruel. Among 140000 patients with RH included in a large database, 15.6% were treated with ACEi plus ARBs[69].

Overall, we believe that a triple combination of RAS-inhibitors, CCBs and diuretics in high doses should be tried in all patients with true resistant hypertension before other drugs are added. Certainly, exceptions apply for this combination as well, such as patients that are intolerant of one or more drugs included in this combination, especially in high doses, since it is known that high doses of CCBs and diuretics are associated with an increased prevalence of peripheral edema and hypokalemia, respectively. Furthermore, CCBs are relatively contraindicated in patients with chronic heart failure and it is better to substitute with beta blockers. Similarly, BB should be pre-

ferred in patients with RH and symptomatic CAD.

Thiazide diuretics

Among the antihypertensive agents available in our quiver, emphasis should be given to diuretics. This is due to the fact that volume expansion seems to be the most implicating pathophysiological cause of RH. In fact, several lines of evidence have demonstrated that over 60% of patients could gain better BP control with proper diuretic therapy. Thus, adding a diuretic, increasing the dosage of the existing one or even changing the prescribed diuretic should be the mainstay of any treatment modification[4,8,13,34].

More specifically, hydrochlorothiazide should be used at adequate doses of up to 50 mg/d, assuming a satisfactory renal function with an estimated glomerular filtration rate (eGFR) > 40-50 mL/min per 1.73 m^2. Chlorthalidone has proved to be similarly or more effective; however, it is not widely prescribed due to its limited availability in fixed dose combinations. Whenever renal insufficiency is present, as defined by levels of eGFR < 40 mL/min per 1.73 m^2, loop diuretics should take their place in the therapeutic regime. Due to their relatively short duration of action, furosemide or bumetanide should be given twice or even thrice daily, whereas torsemide with its longer half-life can be given only once per day.

During the last five years, a vivid discussion has taken place regarding the comparison of hydrochlorothiazide with chlorthalidone[78,79]. Chlorthalidone is long-acting, almost twice as potent as hydrochlorothiazide at the same dose, and has a better 24 h antihypertensive profile[80,81]. In addition, chlorthalidone was used in the ALLHAT study and proved to be equal to other antihypertensive drugs[82], while hydrochlorothiazide and bendrofluazide were used in the ACCOMPLISH and the ASCOT trials respectively and proved to be inferior to comparison therapy[83,84]. Moreover, an indirect comparison of chlorthalidone with hydrochlorothiazide in the MRFIT study pointed towards the superiority of chlorthalidone[85]. However, further studies are needed in this field and specifically in patients with RH before definite conclusions can be drawn.

Mineralocorticoid inhibitors

Activation of the RAS and consequently aldosterone production is a very common phenomenon in RH and a principal therapeutic target[86,87]. Aldosterone excess can be efficiently blocked by mineralocorticoid receptor antagonists (spironolactone and eplerenone). Several small clinical studies during the last decade proved the efficacy of spironolactone in reducing BP in patients with RH by approximately 20/10 mmHg for systolic and diastolic BP respectively[88-93]. This unprecedented BP reduction in patients with RH seems to be independent of baseline aldosterone levels and more pronounced in specific populations such as obese people and those with obstructive sleep apnea. The beneficial effects of spironolactone were confirmed in the ASCOT study, in which spironolactone was used as fourth line therapy in 1411 patients of both treatment arms (diuretic + BBs *vs* ACEi + CCBs) following the addition of doxazosin (an alpha-blocker). Indeed, BP was reduced by 21.9/9.5 mmHg with spironolactone in this study[94]. Of note, patients in the first arm of the study were by definition RH as BP remained uncontrolled despite the use of 3 antihypertensive drugs, including a diuretic.

The enthusiasm for spironolactone use was somehow dampened by the findings of two recent studies. The ASPIRANT study, a double-blind, randomized, placebo-controlled study evaluated the effects of spironolactone in 117 patients with RH[95]. It was found that daytime ambulatory BP reduction with spironolactone was only 5.4/1.0 mmHg. In another, randomized, double-blind, placebo-controlled study of 119 diabetic patients with RH, the average ambulatory daytime BP reduction was 8.9/3.7 mmHg[96].

Another significant concern regards the risk of hyperkalemia and renal function deterioration. Patients with RH are already on RAS inhibition and CKD is frequently encountered in such patients, thus increasing the risk of hyperkalemia. Therefore, extreme caution is required, especially at treatment initiation, on renal function and potassium levels. Although a specific algorithm for RH has not been yet proposed, the recommendations of AHA regarding spironolactone use in patients with heart failure seem prudent and might apply for patients with RH as well[97]. In case of gynecomastia with spironolactone, usually seen at doses above 25 mg/d, eplerenone, a more selective agent, is well tolerated and effective[98]. It has to be noted, however, that larger doses of eplerenone are usually required for the same antihypertensive effect and the significantly higher cost of eplerenone limits its use in RH.

Other antihypertensive drugs

Treatment guidelines recommend maximizing diuretic therapy, either by using chlorthalidone or by adding mineralocorticoid antagonists or both as needed. Are these recommendations implemented in primary care? The truth in everyday clinical practice is once again cruel. Among more than 5 million hypertensive patients included in the Medstat database, 140000 were using four or more antihypertensive drugs, fulfilling the criteria of RH. The rates of chlorthalidone and mineralocorticoid antagonist use were disappointingly low: 3% for chlorthalidone and 5.9% for aldosterone antagonists[69].

However, even in cases where chlorthalidone or spironolactone are used, a considerable proportion of individuals with RH still have uncontrolled BP. These patients will need a fifth medication with the rationale of implementing an agent with a different mechanism of action compared to the already used regime. Blockade of SNS hyperactivity could be a solution to this therapeutic dilemma. BBs are particularly effective when concomitant coronary artery disease or congestive heart failure exists. Another reasonable approach would be to combine a BB along with an alpha blocker such as doxazosin, as data has shown that it is possible to achieve a more potent an-

tihypertensive effect.

Even then, a handful of patients will still resist antihypertensive treatment, thus rendering the evaluation of the role of centrally acting antihypertensive agents (clonidine, moxonidine, methyldopa) or potent vasodilators (hydralazine, minoxidil) as the next step. Although significantly effective in lowering BP, the increased incidence of side effects, their poor tolerability and the lack of concrete data make the implementation of these agents always with caution[3]. Finally, limited data support the antihypertensive action of a non-dihydropyridine CCB complementary to a dihydropyridine one[99]; however, data is limited and requires confirmation in patients with RH.

Failure of drug therapy

After all pathophysiological pathways have been blocked and most appropriate pharmaceutical efforts and combinations have been made, it is evident that a reasonable number of patients will still retain remarkably high levels of BP. Rendering our whole medical armamentarium ineffective or poorly tolerated, this group of patients are undoubtedly the permanent headache of clinicians working in primary care. Advanced help should be sought and these patients should be referred to a hypertension specialist as new and more efficacious treatments, mostly in the interventional sector, come into sight[100-110].

CONCLUSION

Whereas arterial hypertension comprises one of the most extensively studied entities in the medical literature and while a huge collection of antihypertensive agents is available in our therapeutic armamentarium, surprisingly, a considerable number of patients do not achieve optimal BP control. In fact, individuals with RH continue to be exposed to high CV risk and proper medical management continues to puzzle clinicians. In any case, a proper initial approach should include detailed evaluation, exclusion and correction of other contributing factors, along with confirmation of true resistant hypertension. Consequently, an appropriate drug regime should be sought, based on blocking the mechanisms involved in the pathophysiology of RH. At the same time, the therapeutic scheme should always match the patient's profile in terms of safety, tolerability and effectiveness. Until new drug regimens are available, newer techniques of interventional management will keep the promise to radically transform our therapeutic approach towards RH.

REFERENCES

1 **Kearney PM**, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; **365**: 217-223 [PMID: 15652604 DOI: 10.1016/S0140-6736(05)17741-1]

2 **Go AS**, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation* 2014; **129**: e28-e292 [PMID: 24352519 DOI: 10.1161/01.cir.0000441139.02102.80]

3 **Chobanian AV**, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560-2572 [PMID: 12748199 DOI: 10.1001/jama.289.19.2560]

4 **Calhoun DA**, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, Ferdinand K, Giles TD, Falkner B, Carey RM. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation* 2008; **117**: e510-e526 [PMID: 18574054 DOI: 10.1161/CIRCULATIONAHA.108.189141]

5 **ESH/ESC Task Force for the Management of Arterial Hypertension.** 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. *J Hypertens* 2013; **31**: 1925-1938 [PMID: 24107724 DOI: 10.1097/HJH.0b013e328364ca4c]

6 **Alderman MH**, Budner N, Cohen H, Lamport B, Ooi WL. Prevalence of drug resistanpertension. *Hypertension* 1988; **11**: II71-II75 [PMID: 3350596 DOI: 10.1161/01.HYP.11.3_Pt_2.II71]

7 **Kaplan NM**. Resistant hypertension. *J Hypertens* 2005; **23**: 1441-1444 [PMID: 16003165]

8 **Sarafidis PA**, Bakris GL. Resistant hypertension: an overview of evaluation and treatment. *J Am Coll Cardiol* 2008; **52**: 1749-1757 [PMID: 19022154 DOI: 10.1016/j.jacc.2008.08.036]

9 **Persell SD**. Prevalence of resistant hypertension in the United States, 2003-2008. *Hypertension* 2011; **57**: 1076-1080 [PMID: 21502568 DOI: 10.1161/HYPERTENSIONAHA.111.170308]

10 **de la Sierra A**, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, Oliveras A, Ruilope LM. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. *Hypertension* 2011; **57**: 898-902 [PMID: 21444835 DOI: 10.1161/HYPERTENSIONAHA.110.168948]

11 **Anyfanti P**, Gavriilaki E, Douma S. Evaluating the true prevalence of resistant hypertension. *Hypertension* 2011; **58**: e23; author reply e24-e25 [PMID: 21825223 DOI: 10.1161/HYPERTENSIONAHA.111.178111]

12 **Lewington S**, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903-1913 [PMID: 12493255 DOI: 10.1016/S0140-6736(02)11911-8]

13 **Doumas M**, Papademetriou V, Douma S, Faselis C, Tsioufis K, Gkaliagkousi E, Petidis K, Zamboulis C. Benefits from treatment and control of patients with resistant hypertension. *Int J Hypertens* 2010; **2011**: 318549 [PMID: 21234402 DOI: 10.4061/2011/318549]

14 **Salles GF**, Cardoso CR, Muxfeldt ES. Prognostic influence of office and ambulatory blood pressures in resistant hypertension. *Arch Intern Med* 2008; **168**: 2340-2346 [PMID: 19029499 DOI: 10.1001/archinte.168.21.2340]

15 **Pierdomenico SD**, Lapenna D, Bucci A, Di Tommaso R, Di Mascio R, Manente BM, Caldarella MP, Neri M, Cuccurullo F, Mezzetti A. Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension. *Am J Hypertens* 2005; **18**: 1422-1428 [PMID: 16280275 DOI: 10.1016/j.amjhyper.2005.05.014]

16 **Redon J**, Campos C, Narciso ML, Rodicio JL, Pascual JM, Ruilope LM. Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: a prospective study. *Hypertension* 1998; **31**: 712-718 [PMID: 9461245 DOI: 10.1161/01.HYP.31.2.712]

17 **Isaksson H**, Ostergren J. Prognosis in therapy-resistant hypertension. *J Intern Med* 1994; **236**: 643-649 [PMID: 7989899 DOI: 10.1111/j.1365-2796.1994.tb00857.x]

18 **Magnanini MM**, Nogueira Ada R, Carvalho MS, Bloch KV. Ambulatory blood pressure monitoring and cardiovascular risk in resistant hypertensive women. *Arq Bras Cardiol* 2009; **92**: 448-53, 467-472, 484-489 [PMID: 19629313]

19 **Perry HM**, Miller JP, Fornoff JR, Baty JD, Sambhi MP, Rutan G, Moskowitz DW, Carmody SE. Early predictors of 15-year end-stage renal disease in hypertensive patients. *Hypertension* 1995; **25**: 587-594 [PMID: 7721402 DOI: 10.1161/01.HYP.25.4.587]

20 **Benetos A**, Thomas F, Bean K, Gautier S, Smulyan H, Guize L. Prognostic value of systolic and diastolic blood pressure in treated hypertensive men: clarification. *Arch Intern Med* 2003; **163**: 121 [PMID: 12523931 DOI: 10.1001/archinte.163.1.121]

21 **Daugherty SL**, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, O'Connor PJ, Selby JV, Ho PM. Incidence and prognosis of resistant hypertension in hypertensive patients. *Circulation* 2012; **125**: 1635-1642 [PMID: 22379110]

22 **Tsioufis C**, Kasiakogias A, Kordalis A, Dimitriadis K, Thomopoulos C, Tsiachris D, Vasileiou P, Doumas M, Makris T, Papademetriou V, Kallikazaros I, Bakris G, Stefanadis C. Dynamic resistant hypertension patterns as predictors of cardiovascular morbidity: a 4-year prospective study. *J Hypertens* 2014; **32**: 415-422 [PMID: 24241057 DOI: 10.1097/HJH.0000000000000023]

23 **Brown MA**, Buddle ML, Martin A. Is resistant hypertension really resistant? *Am J Hypertens* 2001; **14**: 1263-1269 [PMID: 11775136 DOI: 10.1016/S0895-7061(01)02193-8]

24 **Douma S**, Petidis K, Doumas M, Papaefthimiou P, Triantafyllou A, Kartali N, Papadopoulos N, Vogiatzis K, Zamboulis C. Prevalence of primary hyperaldosteronism in resistant hypertension: a retrospective observational study. *Lancet* 2008; **371**: 1921-1926 [PMID: 18539224 DOI: 10.1016/S0140-6736(08)60834-X]

25 **Corrao G**, Zambon A, Parodi A, Poluzzi E, Baldi I, Merlino L, Cesana G, Mancia G. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. *J Hypertens* 2008; **26**: 819-824 [PMID: 18327094 DOI: 10.1097/HJH.0b013e3282f4edd7]

26 **Corrao G**, Parodi A, Nicotra F, Zambon A, Merlino L, Cesana G, Mancia G. Better compliance to antihypertensive medications reduces cardiovascular risk. *J Hypertens* 2011; **29**: 610-618 [PMID: 21157368 DOI: 10.1097/HJH.0b013e328342ca97]

27 **Jung O**, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, Toennes SW. Resistant hypertension? Assessment of adherence by toxicological urine analysis. *J Hypertens* 2013; **31**: 766-774 [PMID: 23337469 DOI: 10.1097/HJH.0b013e32835e2286]

28 **Strauch B**, Petrák O, Zelinka T, Rosa J, Somlóová Z, Indra T, Chytil L, Marešová V, Kurcová I, Holaj R, Wichterle D, Widimský J. Precise assessment of noncompliance with the antihypertensive therapy in patients with resistant hypertension using toxicological serum analysis. *J Hypertens* 2013; **31**: 2455-2461 [PMID: 24220593 DOI: 10.1097/HJH.0b013e3283652c61]

29 **Berlowitz DR**, Ash AS, Hickey EC, Friedman RH, Glickman M, Kader B, Moskowitz MA. Inadequate management of blood pressure in a hypertensive population. *N Engl J Med* 1998; **339**: 1957-1963 [PMID: 9869666 DOI: 10.1056/NEJM199812313392701]

30 **Moser M**, Franklin SS. Hypertension management: results of a new national survey for the hypertension education foundation: Harris interactive. *J Clin Hypertens* (Greenwich) 2007; **9**: 316-323 [PMID: 17485966 DOI: 10.1111/j.1524-6175.2007.07152.x]

31 **Kerr EA**, Zikmund-Fisher BJ, Klamerus ML, Subramanian U, Hogan MM, Hofer TP. The role of clinical uncertainty in treatment decisions for diabetic patients with uncontrolled blood pressure. *Ann Intern Med* 2008; **148**: 717-727 [PMID: 18490685 DOI: 10.7326/0003-4819-148-10-200805200-00004]

32 **Turner BJ**, Hollenbeak CS, Weiner M, Ten Have T, Tang SS. Effect of unrelated comorbid conditions on hypertension management. *Ann Intern Med* 2008; **148**: 578-586 [PMID: 18413619 DOI: 10.7326/0003-4819-148-8-200804150-00002]

33 **Daugherty SL**, Powers JD, Magid DJ, Masoudi FA, Margolis KL, O'Connor PJ, Schmittdiel JA, Ho PM. The association between medication adherence and treatment intensification with blood pressure control in resistant hypertension. *Hypertension* 2012; **60**: 303-309 [DOI: 10.1161/CIRCULATIONAHA.111.068064]

34 **Faselis C**, Doumas M, Papademetriou V. Common secondary causes of resistant hypertension and rational for treatment. *Int J Hypertens* 2011; **2011**: 236239 [PMID: 21423678 DOI: 10.4061/2011/236239]

35 **Kurth T**, Hennekens CH, Stürmer T, Sesso HD, Glynn RJ, Buring JE, Gaziano JM. Analgesic use and risk of subsequent hypertension in apparently healthy men. *Arch Intern Med* 2005; **165**: 1903-1909 [PMID: 16157836 DOI: 10.1001/archinte.165.16.1903]

36 **Aw TJ**, Haas SJ, Liew D, Krum H. Meta-analysis of cyclooxygenase-2 inhibitors and their effects on blood pressure. *Arch Intern Med* 2005; **165**: 490-496 [PMID: 15710786 DOI: 10.1001/archinte.165.5.ioi50013]

37 **Johnson AG**, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. *Ann Intern Med* 1994; **121**: 289-300 [PMID: 8037411 DOI: 10.7326/0003-4819-121-4-199408150-00011]

38 **Lubianca JN**, Faccin CS, Fuchs FD. Oral contraceptives: a risk factor for uncontrolled blood pressure among hypertensive women. *Contraception* 2003; **67**: 19-24 [PMID: 12521653]

39 **Rosenthal T**, Oparil S. Oral contraceptives, hormones replacement therapy, and hypertension. In: Lip G, Hall J eds. Comprehensive hypertension. New York: Elsevier/Mosby, 2007

40 **Salerno SM**, Jackson JL, Berbano EP. Effect of oral pseudoephedrine on blood pressure and heart rate: a meta-analysis. *Arch Intern Med* 2005; **165**: 1686-1694 [PMID: 16087815 DOI: 10.1001/archinte.165.15.1686]

41 **Sica DA**. Angiogenesis inhibitors and hypertension: an emerging issue. *J Clin Oncol* 2006; **24**: 1329-1331 [PMID: 16446321]

42 **Zhu X**, Stergiopoulos K, Wu S. Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: systematic review and meta-analysis. *Acta Oncol* 2009; **48**: 9-17 [PMID: 18752081 DOI: 10.1080/02841860802314720]

43 **Gampenrieder SP**, Romeder F, Muß C, Pircher M, Ressler S, Rinnerthaler G, Bartsch R, Sattlberger C, Mlineritsch B, Greil R. Hypertension as a predictive marker for bevacizumab in metastatic breast cancer: results from a retrospective matched-pair analysis. *Anticancer Res* 2014; **34**: 227-233 [PMID: 24403467]

44 **Akkina SK**, Ricardo AC, Patel A, Das A, Bazzano LA, Brecklin C, Fischer MJ, Lash JP. Illicit drug use, hypertension, and chronic kidney disease in the US adult population. *Transl Res* 2012; **160**: 391-398 [PMID: 22735028 DOI: 10.1016/j.trsl.2012.05.008]

45 **Ernst E**. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava. *Ann Intern Med* 2002; **136**: 42-53 [PMID: 11777363 DOI: 10.7326/0003-4819-136-1-200201010-00010]

46 **Rimoldi SF**, Scherrer U, Messerli FH. Secondary arterial hypertension: when, who, and how to screen? *Eur Heart J* 2014; **35**: 1245-1254 [PMID: 24366917 DOI: 10.1093/eurheartj/eht534]

47 **Cuspidi C**, Vaccarella A, Negri F, Sala C. Resistant hypertension and left ventricular hypertrophy: an overview. *J Am Soc Hypertens* 2010; **4**: 319-324 [PMID: 21130978 DOI: 10.1016/j.jash.2010.10.003]

48 **Pabuccu T**, Baris N, Ozpelit E, Akdeniz B, Guneri S. The relationship between resistant hypertension and arterial stiffness. *Clin Exp Hypertens* 2012; **34**: 57-62 [PMID: 21967027 DOI: 10.3109/10641963.2011.618203]

49 **Quinaglia T**, Martins LC, Figueiredo VN, Santos RC, Yugar-Toledo JC, Martin JF, Demacq C, Pimenta E, Calhoun DA, Moreno H. Non-dipping pattern relates to endothelial dysfunction in patients with uncontrolled resistant hypertension. *J Hum Hypertens* 2011; **25**: 656-664 [PMID: 21544090 DOI: 10.1038/jhh.2011.43]

50 **Oliveras A**, Armario P, Martell-Clarós N, Ruilope LM, de la Sierra A. Urinary albumin excretion is associated with nocturnal systolic blood pressure in resistant hypertensives. *Hypertension* 2011; **57**: 556-560 [PMID: 21220713 DOI: 10.1161/HYPERTENSIONAHA.110.165563]

51 **Raff U**, Schmidt BM, Schwab J, Schwarz TK, Achenbach S, Bär I, Schmieder RE. Renal resistive index in addition to low-grade albuminuria complements screening for target organ damage in therapy-resistant hypertension. *J Hypertens* 2010; **28**: 608-614 [PMID: 20090556 DOI: 10.1097/HJH.0b013e32833487b8]

52 **Molenaar EA**, Hwang SJ, Vasan RS, Grobbee DE, Meigs JB, D'Agostino RB, Levy D, Fox CS. Burden and rates of treatment and control of cardiovascular disease risk factors in obesity: the Framingham Heart Study. *Diabetes Care* 2008; **31**: 1367-1372 [PMID: 18375414 DOI: 10.2337/dc07-2413]

53 **Bhan V**, Yan RT, Leiter LA, Fitchett DH, Langer A, Lonn E, Tan M, Silagy S, Goodman SG, Yan AT. Relation between obesity and the attainment of optimal blood pressure and lipid targets in high vascular risk outpatients. *Am J Cardiol* 2010; **106**: 1270-1276 [PMID: 21029823 DOI: 10.1016/j.amjcard.2010.06.055]

54 **Lloyd-Jones DM**, Evans JC, Larson MG, O'Donnell CJ, Roccella EJ, Levy D. Differential control of systolic and diastolic blood pressure : factors associated with lack of blood pressure control in the community. *Hypertension* 2000; **36**: 594-599 [PMID: 11040241 DOI: 10.1161/01.HYP.36.4.594]

55 **Cushman WC**, Ford CE, Cutler JA, Margolis KL, Davis BR, Grimm RH, Black HR, Hamilton BP, Holland J, Nwachuku C, Papademetriou V, Probstfield J, Wright JT, Alderman MH, Weiss RJ, Piller L, Bettencourt J, Walsh SM. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *J Clin Hypertens* (Greenwich) 2002; **4**: 393-404 [PMID: 12461301 DOI: 10.1111/j.1524-6175.2002.02045.x]

56 **Egan BM**, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. *Circulation* 2011; **124**: 1046-1058 [PMID: 21824920 DOI: 10.1161/CIRCULATIONAHA.111.030189]

57 **Lambert GW**, Straznicky NE, Lambert EA, Dixon JB, Schlaich MP. Sympathetic nervous activation in obesity and the metabolic syndrome--causes, consequences and therapeutic implications. *Pharmacol Ther* 2010; **126**: 159-172 [PMID: 20171982 DOI: 10.1016/j.pharmthera.2010.02.002]

58 **Logan AG**, Perlikowski SM, Mente A, Tisler A, Tkacova R, Niroumand M, Leung RS, Bradley TD. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *J Hypertens* 2001; **19**: 2271-2277 [PMID: 11725173 DOI: 10.1097/00004872-200112000-00022]

59 **Goodfriend TL**, Calhoun DA. Resistant hypertension, obesity, sleep apnea, and aldosterone: theory and therapy. *Hypertension* 2004; **43**: 518-524 [PMID: 14732721 DOI: 10.1161/01.HYP.0000116223.97436.e5]

60 **Pimenta E**, Gaddam KK, Oparil S, Aban I, Husain S, Dell'Italia LJ, Calhoun DA. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. *Hypertension* 2009; **54**: 475-481 [PMID: 19620517 DOI: 10.1161/HYPERTENSIONAHA.109.131235]

61 **Doumas M**, Anyfanti P, Bakris G. Should ambulatory blood pressure monitoring be mandatory for future studies in resistant hypertension: a perspective. *J Hypertens* 2012; **30**: 874-876 [PMID: 22495128 DOI: 10.1097/HJH.0b013e328352c3c7]

62 **Kokkinos P**, Manolis A, Pittaras A, Doumas M, Giannelou A, Panagiotakos DB, Faselis C, Narayan P, Singh S, Myers J. Exercise capacity and mortality in hypertensive men with and without additional risk factors. *Hypertension* 2009; **53**: 494-499 [PMID: 19171789 DOI: 10.1161/HYPERTENSIONAHA.108.127027]

63 **Faselis C**, Doumas M, Kokkinos JP, Panagiotakos D, Kheirbek R, Sheriff HM, Hare K, Papademetriou V, Fletcher R, Kokkinos P. Exercise capacity and progression from prehypertension to hypertension. *Hypertension* 2012; **60**: 333-338 [PMID: 22753224 DOI: 10.1161/HYPERTENSIONAHA.112.196493]

64 **Kokkinos P**, Doumas M, Myers J, Faselis C, Manolis A, Pittaras A, Kokkinos JP, Papademetriou V, Singh S, Fletcher RD. A graded association of exercise capacity and all-cause mortality in males with high-normal blood pressure. *Blood Press* 2009; **18**: 261-267 [PMID: 19919397 DOI: 10.3109/08037050903272859]

65 **Kokkinos P**, Myers J, Doumas M, Faselis C, Manolis A, Pittaras A, Kokkinos JP, Singh S, Fletcher RD. Exercise capacity and all-cause mortality in prehypertensive men. *Am J Hypertens* 2009; **22**: 735-741 [DOI: 10.1161/CIRCULATIONAHA.110.938852]

66 **Kokkinos P**, Myers J, Faselis C, Panagiotakos DB, Doumas M, Pittaras A, Manolis A, Kokkinos JP, Karasik P, Greenberg M, Papademetriou V, Fletcher R. Exercise capacity and mortality in older men: a 20-year follow-up study. *Circulation* 2010; **122**: 790-797

67 **Dimeo F**, Pagonas N, Seibert F, Arndt R, Zidek W, Westhoff TH. Aerobic exercise reduces blood pressure in resistant hypertension. *Hypertension* 2012; **60**: 653-658 [PMID: 22802220 DOI: 10.1161/HYPERTENSIONAHA.112.197780]

68 **Guimarães GV**, Cruz LG, Tavares AC, Dorea EL, Fernandes-Silva MM, Bocchi EA. Effects of short-term heated water-based exercise training on systemic blood pressure in patients with resistant hypertension: a pilot study. *Blood Press Monit* 2013; **18**: 342-345 [PMID: 24192849 DOI: 10.1097/MBP.0000000000000000]

69 **Hanselin MR**, Saseen JJ, Allen RR, Marrs JC, Nair KV. Description of antihypertensive use in patients with resistant hypertension prescribed four or more agents. *Hypertension* 2011; **58**: 1008-1013 [PMID: 22042809 DOI: 10.1161/HYPERTENSIONAHA.111.180497]

70 **Hermida RC**, Ayala DE, Calvo C, López JE, Mojón A, Fontao MJ, Soler R, Fernández JR. Effects of time of day of treatment on ambulatory blood pressure pattern of patients with resistant hypertension. *Hypertension* 2005; **46**: 1053-1059 [PMID: 16087787 DOI: 10.1161/01.HYP.0000172757.96281.bf]

71 **Hermida RC**, Ayala DE, Fernández JR, Calvo C. Chronotherapy improves blood pressure control and reverts the nondipper pattern in patients with resistant hypertension. *Hypertension* 2008; **51**: 69-76 [PMID: 17968001 DOI: 10.1161/HYPERTENSIONAHA.107.096933]

72 **Gradman AH**, Basile JN, Carter BL, Bakris GL. Combination therapy in hypertension. *J Clin Hypertens* (Greenwich) 2011; **13**: 146-154 [PMID: 21366845 DOI: 10.1111/j.1751-7176.2010.00397.x]

73 **Bangalore S**, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med* 2007; **120**: 713-719 [PMID: 17679131 DOI: 10.1016/j.amjmed.2006.08.033]

74 **Calhoun DA**, Lacourcière Y, Chiang YT, Glazer RD. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized clinical trial. *Hypertension* 2009; **54**: 32-39 [PMID: 19470877 DOI: 10.1161/HYPERTENSIONAHA.109.131300]

75 **Dunkler D**, Dehghan M, Teo KK, Heinze G, Gao P, Kohl M, Clase CM, Mann JF, Yusuf S, Oberbauer R. Diet and kidney disease in high-risk individuals with type 2 diabetes mellitus. *JAMA Intern Med* 2013; **173**: 1682-1692 [PMID: 23939297]

76 **Fried LF**, Emanuele N, Zhang JH, Brophy M, Conner TA, Duckworth W, Leehey DJ, McCullough PA, O'Connor T, Palevsky PM, Reilly RF, Seliger SL, Warren SR, Watnick S, Peduzzi P, Guarino P. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013; **369**: 1892-1903 [PMID: 24206457 DOI: 10.1056/NEJMoa1303154]

77 **Parving HH**, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, Chaturvedi N, Persson F, Desai AS, Nicolaides M, Richard A, Xiang Z, Brunel P, Pfeffer MA. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012; **367**: 2204-2213 [PMID: 23121378]

78 **Khosla N**, Chua DY, Elliott WJ, Bakris GL. Are chlorthalidone and hydrochlorothiazide equivalent blood-pressure-lowering medications? *J Clin Hypertens* (Greenwich) 2005; **7**: 354-356 [PMID: 16088299 DOI: 10.1111/j.1524-6175.2005.04451.x]

79 **Psaty BM**, Lumley T, Furberg CD. Meta-analysis of health outcomes of chlorthalidone-based vs nonchlorthalidone-based low-dose diuretic therapies. *JAMA* 2004; **292**: 43-44 [PMID: 15238589 DOI: 10.1001/jama.292.1.43-c]

80 **Ernst ME**, Carter BL, Goerdt CJ, Steffensmeier JJ, Phillips BB, Zimmerman MB, Bergus GR. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension* 2006; **47**: 352-358 [PMID: 16432050 DOI: 10.1161/01.HYP.0000203309.07140.d3]

81 **Ernst ME**, Carter BL, Zheng S, Grimm RH. Meta-analysis of dose-response characteristics of hydrochlorothiazide and chlorthalidone: effects on systolic blood pressure and potassium. *Am J Hypertens* 2010; **23**: 440-446 [PMID: 20111008 DOI: 10.1038/ajh.2010.1]

82 **ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group,** The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288**: 2981-2997 [PMID: 12479763 DOI: 10.1001/jama.288.23.2981]

83 **Jamerson K**, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, Velazquez EJ. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008; **359**: 2417-2428 [PMID: 19052124 DOI: 10.1056/NEJMoa0806182]

84 **Dahlöf B**, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366**: 895-906 [PMID: 16154016 DOI: 10.1016/S0140-6736(05)67185-1]

85 **Dorsch MP**, Gillespie BW, Erickson SR, Bleske BE, Weder AB. Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. *Hypertension* 2011; **57**: 689-694 [PMID: 21383313 DOI: 10.1161/HYPERTENSIONAHA.110.161505]

86 **Nishizaka MK**, Calhoun DA. The role of aldosterone antagonists in the management of resistant hypertension. *Curr Hypertens Rep* 2005; **7**: 343-347 [PMID: 16157075 DOI: 10.1007/s11906-005-0067-3]

87 **George J**, Struthers AD. Evaluation of the aldosterone-blocking agent eplerenone in hypertension and heart failure. *Expert Opin Pharmacother* 2007; **8**: 3053-3059 [PMID: 18001264 DOI: 10.1517/14656566.8.17.3053]

88 **Nishizaka MK**, Zaman MA, Calhoun DA. Efficacy of low-dose spironolactone in subjects with resistant hypertension. *Am J Hypertens* 2003; **16**: 925-930 [PMID: 14573330 DOI: 10.1016/S0895-7061(03)01032-X]

89 **Sharabi Y**, Adler E, Shamis A, Nussinovitch N, Markovitz A, Grossman E. Efficacy of add-on aldosterone receptor blocker in uncontrolled hypertension. *Am J Hypertens* 2006; **19**: 750-755 [PMID: 16814132 DOI: 10.1016/j.amjhyper.2005.11.016]

90 **Mahmud A**, Mahgoub M, Hall M, Feely J. Does aldosterone-to-renin ratio predict the antihypertensive effect of the aldosterone antagonist spironolactone? *Am J Hypertens* 2005; **18**: 1631-1635 [PMID: 16364838 DOI: 10.1016/j.amjhyper.2005.06.010]

91 **Lane DA**, Shah S, Beevers DG. Low-dose spironolactone in the management of resistant hypertension: a surveillance study. *J Hypertens* 2007; **25**: 891-894 [PMID: 17351384 DOI: 10.1097/HJH.0b013e328014954d]

92 **Ouzan J**, Pérault C, Lincoff AM, Carré E, Mertes M. The role of spironolactone in the treatment of patients with refractory hypertension. *Am J Hypertens* 2002; **15**: 333-339 [PMID: 11991219 DOI: 10.1016/S0895-7061(01)02342-1]

93 **de Souza F**, Muxfeldt E, Fiszman R, Salles G. Efficacy of spironolactone therapy in patients with true resistant hypertension. *Hypertension* 2010; **55**: 147-152 [PMID: 19858405]

94 **Chapman N**, Dobson J, Wilson S, Dahlöf B, Sever PS, Wedel H, Poulter NR; Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Effect of spironolactone on BP in subjects with resistant hypertension. *Hypertension* 2007; **49**: 839–845 [DOI: 10.1161/01.HYP.0000259805.18468.8c]

95 **Václavík J**, Sedlák R, Plachy M, Navrátil K, Plásek J, Jarkovsky J, Václavík T, Husár R, Kociánová E, Táborsky M. Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomized, double-blind, placebo-controlled trial. *Hypertension* 2011; **57**: 1069-1075 [PMID: 21536989 DOI: 10.1161/HYPERTENSIONAHA.111.169961]

96 **Oxlund CS**, Henriksen JE, Tarnow L, Schousboe K, Gram J, Jacobsen IA. Low dose spironolactone reduces blood pressure in patients with resistant hypertension and type 2 diabetes mellitus: a double blind randomized clinical trial. *J Hypertens* 2013; **31**: 2094-2102 [PMID: 24107738 DOI: 10.1097/HJH.0b013e3283638b1a]

97 **Hunt SA**, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005; **112**: e154-e235 [PMID: 16160202]

98 **Calhoun DA**, White WB. Effectiveness of the selective aldosterone blocker, eplerenone, in patients with resistant hypertension. *J Am Soc Hypertens* 2008; **2**: 462-468 [PMID: 20409927 DOI: 10.1016/j.jash.2008.05.005]

99 **Saseen JJ**, Carter BL, Brown TE, Elliott WJ, Black HR. Comparison of nifedipine alone and with diltiazem or verapamil in hypertension. *Hypertension* 1996; **28**: 109-114 [PMID:

8675249]
100 **Krum H**, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K, Kapelak B, Walton A, Sievert H, Thambar S, Abraham WT, Esler M. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; **373**: 1275-1281 [PMID: 19332353 DOI: 10.1016/S0140-6736(09)60566-3]
101 **Esler MD**, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010; **376**: 1903-1909 [PMID: 21093036 DOI: 10.1016/S0140-6736(10)62039-9]
102 **Doumas M**, Faselis C, Papademetriou V. Renal sympathetic denervation and systemic hypertension. *Am J Cardiol* 2010; **105**: 570-576 [PMID: 20152255 DOI: 10.1016/j.amjcard.2009.10.027]
103 **Doumas M**, Douma S. Renal sympathetic denervation: the jury is still out. *Lancet* 2010; **376**: 1878-1880 [PMID: 21093037 DOI: 10.1016/S0140-6736(10)62111-3]
104 **Worthley SG**, Tsioufis CP, Worthley MI, Sinhal A, Chew DP, Meredith IT, Malaiapan Y, Papademetriou V. Safety and efficacy of a multi-electrode renal sympathetic denervation system in resistant hypertension: the EnligHTN I trial. *Eur Heart J* 2013; **34**: 2132-2140 [PMID: 23782649]
105 **Doumas M**, Faselis C, Papademetriou V. Renal sympathetic denervation in hypertension. *Curr Opin Nephrol Hypertens* 2011; **20**: 647-653 [PMID: 21885968 DOI: 10.1097/MNH.0b013e32834b620c]
106 **Doumas M**, Douma S. Interventional management of resistant hypertension. *Lancet* 2009; **373**: 1228-1230 [PMID: 19332354 DOI: 10.1016/S0140-6736(09)60624-3]
107 **Papademetriou V**, Doumas M, Anyfanti P, Faselis C, Kokkinos P, Tsioufis K. Renal nerve ablation for hypertensive patients with chronic kidney disease. *Curr Vasc Pharmacol* 2013; **11**: In press
108 **Scheffers IJ**, Kroon AA, Schmidli J, Jordan J, Tordoir JJ, Mohaupt MG, Luft FC, Haller H, Menne J, Engeli S, Ceral J, Eckert S, Erglis A, Narkiewicz K, Philipp T, de Leeuw PW. Novel baroreflex activation therapy in resistant hypertension: results of a European multi-center feasibility study. *J Am Coll Cardiol* 2010; **56**: 1254-1258 [PMID: 20883933 DOI: 10.1016/j.jacc.2010.03.089]
109 **Doumas M**, Guo D, Papademetriou V. Carotid baroreceptor stimulation as a therapeutic target in hypertension and other cardiovascular conditions. *Expert Opin Ther Targets* 2009; **13**: 413-425 [PMID: 19335064 DOI: 10.1517/14728220902780185]
110 **Doumas M**, Faselis C, Tsioufis C, Papademetriou V. Carotid baroreceptor activation for the treatment of resistant hypertension and heart failure. *Curr Hypertens Rep* 2012; **14**: 238-246 [PMID: 22457242 DOI: 10.1007/s11906-012-0258-7]

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REVIEW

Mitochondria-targeted agents: Future perspectives of mitochondrial pharmaceutics in cardiovascular diseases

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Abstract

Mitochondria are one of the major sites for the generation of reactive oxygen species (ROS) as an undesirable side product of oxidative energy metabolism. Damaged mitochondria can augment the generation of ROS. Dysfunction of mitochondria increase the risk for a large number of human diseases, including cardiovascular diseases (CVDs). Heart failure (HF) following ischemic heart disease, infantile cardiomyopathy and cardiac hypertrophy associated with left ventricular dilations are some of the CVDs in which the role of mitochondrial oxidative stress has been reported. Advances in mitochondrial research during the last decade focused on the preservation of its function in the myocardium, which is vital for the cellular energy production. Experimental and clinical trials have been conducted using mitochondria-targeted molecules like: MnSOD mimetics, such as EUK-8, EUK-134 and MitoSOD; choline esters of glutathione and *N*-acetyl-L-cysteine; triphenylphosphonium ligated vitamin E, lipoic acid, plastoquinone and mitoCoQ$_{10}$; and Szeto-Schiller (SS)- peptides (SS-02 and SS-31). Although many results are inconclusive, some of the findings, especially on CoQ$_{10}$, are worthwhile. This review summarizes the role of mitochondria-targeted delivery of agents and their consequences in the control of HF.

Key words: Cardiovascular diseases; Oxidative stress; Antioxidant; Electron transport chain; Mitochondrial medicine; Heart failure

Core tip: Dysfunction of mitochondria increases the risk for a large number of human diseases, including cardiovascular diseases. Heart failure (HF) following ischemic heart disease, infantile cardiomyopathy and cardiac hypertrophy associated with left ventricular dilations are some of the cardiovascular diseases in which the role of mitochondrial oxidative stress has been reported. Recent reports on chronic HF followed by ischemic heart disease suggested a reduced supply of energy necessary for the contractile function of cardiomyocytes. Since mitochondrial damages are central to the pathophysiology of HF, various approaches are used to target compounds at mitochondria alone or adjunct to standard therapies.

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INTRODUCTION

Although substantial improvements were made in the treatment of cardiovascular events during the last decade, cardiovascular disease (CVD), such as atherosclerosis,

ischemic heart disease (IHD), heart failure (HF), stroke and hypertension, still remain one of the major challenges to humans. HF is a leading cause of morbidity and mortality in industrialized countries. It is also a growing public health problem, mainly because of the aging of population and an increase in prevalence in the elderly. In developing countries, around 2% of adults suffer from HF; the prevalence is found to be increased to approximately 6%-10% over the age of 65[1]. The mechanisms of HF are complex and multifactorial. Common causes of HF include myocardial infarction (MI) and other forms of IHD, valvular heart disease and different types of cardiomyopathies. A study of healthy adults in the United States reported that IHD increases the risk factors of HF by approximately 62%[2]. No curative treatment is currently available for HF. The existing therapies for HF are able to relieve symptoms but are unable to reverse molecular changes that occur in the cardiomyocytes. A reduced supply of energy necessary for the contractile function of cardiomyocytes can explain the chronic HF followed by IHD[3]. This may probably be due to the increased production of oxygen radicals with or without preserving the antioxidant status in the cardiomyocytes[4].

The primary factor that initiates the dysfunction of mitochondria has been proposed to be the defects in oxidative phosphorylation (OXPHOS) which can further enhance the production of reactive oxygen species (ROS) and eventually destroy the mtDNA[5]. Since slowly dividing/postmitotic cardiac myocytes are highly dependent on energy from OXPHOS, the cardiac myocardium will be affected, especially when the proportion of the damaged mitochondria is considerably high, as evidenced in HF[3]. Hence, challenging mitochondrial dysfunction remains one of the main streams of mitochondrial research that is primarily focussed on alleviating the organ damage associated with CVD. In spite of experimental evidence to support the role of mitochondria-mediated antioxidant therapy to alleviate the ROS-mediated injury in CVD, clinical studies are fragmentary. Many antioxidant molecules are designed and evaluated in clinical and experimental trials to stop the deterioration of mitochondrial function but only a few achieve success. Hence, mitochondrial-targeted antioxidant therapy for CVDs is a controversial field and warrants further research. It is worth knowing the scope for mitochondrially-mediated interventions in the conventional therapeutic regimen in order to render complete protection for early stages of CVD to result in protection for HF. This review discusses the mitochondria-targeted delivery of agents to alleviate the decline of myocardial function in CVD.

FORMATION AND DAMAGE INDUCED BY REACTIVE OXYGEN SPECIES IN THE MITOCHONDRIA OF CARDIOMYOCYTES

Mitochondria play a key role in cardiac energy balance. Energy for cardiomyocytes is solely met from mitochondrial OXPHOS. Moreover, mitochondria are involved

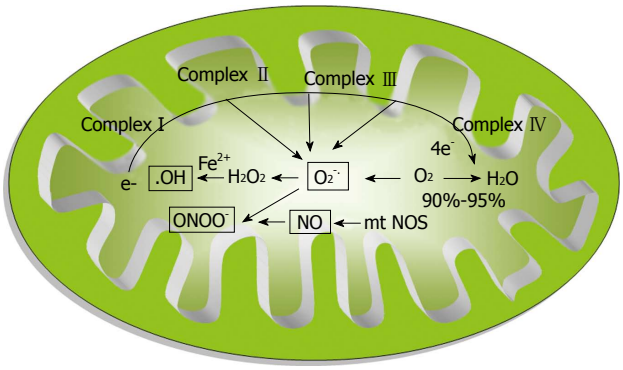

Figure 1 Formation of various reactive oxygen species in mitochondria. HO·: Hydroxyl radical; O_2^{-}: Super oxide anion radical; $ONOO^{-}$: Peroxynitrite; mtNOS: Mitochondrial-specific nitric oxide synthase; NO: Nitric oxide.

in maintaining the fine regulatory balance between Ca^{2+} concentration and production of ROS and nitric oxide (NO). The majority of cellular oxygen (O_2) that enters into mitochondria is reduced to water in the mitochondrial respiratory chain, whereas a fraction of all O_2 consumed can be converted to potentially cytotoxic ROS, such as superoxide anion radical (O_2^{-}), indicating that the mitochondrion itself is the source of ROS[6]. Any factor that affects the flow of electrons (e-) in the electron transport chain (ETC) can result in the leakage of e- to O_2, leading to the formation of O_2^{-}. The O_2^{-} is a primary radical that could produce other ROS, such as hydrogen peroxide (H_2O_2) and hydroxyl radicals (·OH), in the failing myocardium. The ·OH is generated by the reduction of H_2O_2 in the presence of endogenous iron and copper by means of the Fenton reaction. Copper and iron are found to be mobilized following myocardial ischemia. Chevion *et al*[7] reported a 8 to 9-fold higher level of copper and iron in the first coronary flow fraction of reperfusion after 35 min of ischemia compared to the pre-ischemic value in isolated rat heart. This was further supported by the obervation of Reddy *et al*[8] that early treatment with deferoxamine, a potent iron chelator, limits the injury related to myocardial ischemia/reperfusion in dogs, probably due to the lesser availability of iron for the Fenton reaction. The production of various ROS in the mitochondrion is given in Figure 1.

The drugs being used in clinical practice, such as statins (decreases ubiquinone), aspirin and valproic acid (sequesters of CoA), doxorubicin and daunorubicin (releases ROS), and acetaminophen (decreases reduced glutathione), will affect mitochondrial energy production and may play a critical role in the development of cardiomyopathy[6]. Physiologically, increased demand of the organ can favor the generation of free radicals. Sudheesh *et al*[9] recently reported that isoproterenol-induced acute MI in rat affected the respiratory chain complexes I -IV, mediated through an increase in the ROS level in the cardiomyocytes. Furthermore, the declined antioxidant status in the mitochondria during aging can also provoke mitochondrial dysfunction in cardiomyocytes[10]. Hypercholesterolemia can also affect mitochondrial functions by declining the mitochondrial membrane potential mediated through

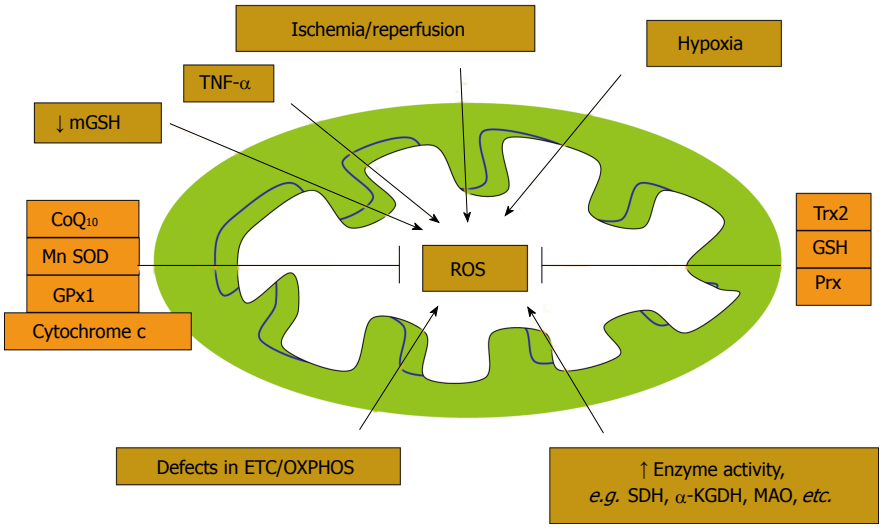

Figure 2 Factors that form and attenuate (antioxidants) reactive oxygen species in mitochondria. SDH: Succinate dehydrogenase; αKGDH: Alpha ketoglutarate dehydrogenase; MAO: Monoamine oxidase; Trx: Thioredoxins; Prx: Peroxiredoxin; OXPHOS: Oxidative phosphorylations; TNF-α: Tumor necrosis factor-alpha; GSH: Reduced glutathione; MnSOD: Manganese containing superoxide dismutase; GPx1: Glutathione peroxidase; CoQ_{10}: Co-enzyme Q_{10}.

the generation of ROS and activation of mitochondrial apoptotic pathway[11].

Evidence shows that cytokines, such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-6, are important pathological factors in inflammatory responses during the pathological progression of myocardial ischemia/reperfusion and hypertrophy. They are released during chronic inflammation, either in endothelial cells or cardiomyocytes, and inhibit the electron transport through the complex I and complex Ⅲ-ubiquinone cycle, facilitating the generation of ROS[12]. Elevated activities of certain mitochondrial enzymes are also directly correlated with the excess production of ROS (Figure 2). The generated ROS is known to induce oxidation of low-density lipoproteins (LDL) in the coronary sinus of patients with dilated cardiomyopathy[13]. The oxidized LDL is abrogated by binding to the lectin-like oxidized LDL scavenger receptor-1 (LOX-1) on the arterial wall[14]. Activation of LOX-1 has been related to many pathophysiological events that lead to IHD.

The generated ROS under oxidative stress may contribute to potential mitochondrial damage that induces endothelial dysfunction and promotes leukocyte adhesion, inflammation, thrombosis and smooth muscle cell proliferation[15]. Among the damage induced by generated ROS at the cellular level, mtDNA remains the major target (Figure 3). mtDNA contains about 16.5 kb of circular double-stranded DNA to encode 13 protein components of the ETC. Mitochondrial function is controlled by the mtDNA, as well as factors that regulate mtDNA transcription and/or replication. A large part of the O_2^- that is formed inside the mitochondria cannot pass through the membrane and hence affect the DNA. Since 1988 when the first mutation in mtDNA was established, more than 400 mutations have been identified. The mutations described are either typically 50% to 60% for single, large-scale deletions or 80% to 90% for point mutations in patients with mitochondrial myopathy and encephalomyopathy[16]. In general, the majority of pathogenic point mutations are maternally transmitted, whereas large-scale deletions of mtDNA are mostly sporadic. More than 10 different types of deletions have been identified in the mtDNA among these; the 4977-bp deletion is the most prevalent in skeletal muscle, whereas the 7436-bp deletion was detected in the heart of human subjects in their late thirties, with no apparent sex difference[17]. However, the clinical severity of the disease is usually correlated with the presence of > 80% of the mutated mtDNA in the target tissues[18]. Furthermore, at the same level, large-scale deletions cause much more severe pathologies than point mutations. The patterns of distribution of the mutated mtDNA and the energy demand of the target tissues are two important factors that determine the pathological outcome of the mutation. HF is frequently associated with qualitative and quantitative defects in mtDNA and is found to increase with the age of human subjects. Recent evidence has suggested that mitochondria have enzymes to proofread mtDNA and fix mutations that may occur due to free radicals[19].

Often, the damaged mtDNA is degraded by autophagy, whereas mtDNA that escapes the process of autophagy, as observed in atherosclerosis, can induce a potent inflammatory response. Ding *et al*[14] demonstrated that the damaged mitochondria induced by ox-LDL can result in the expression of toll-like receptor-9 (TLR-9) on the cell membrane. TLR-9 senses the unmethylated CpG motifs in damaged mt DNA and induces inflammation which is mediated through the pro-inflammatory cytokines. Ding *et al*[14] also demonstrated an intense autophagy, TLR-9 expression and inflammatory signals in the aorta of LDL receptor knockout mice when fed with a high cholesterol diet. Use of LOX-1 antibody or the ROS inhibitor apocynin attenuated ox-LDL-mediated autophagy, mtDNA damage and TLR-9 expression.

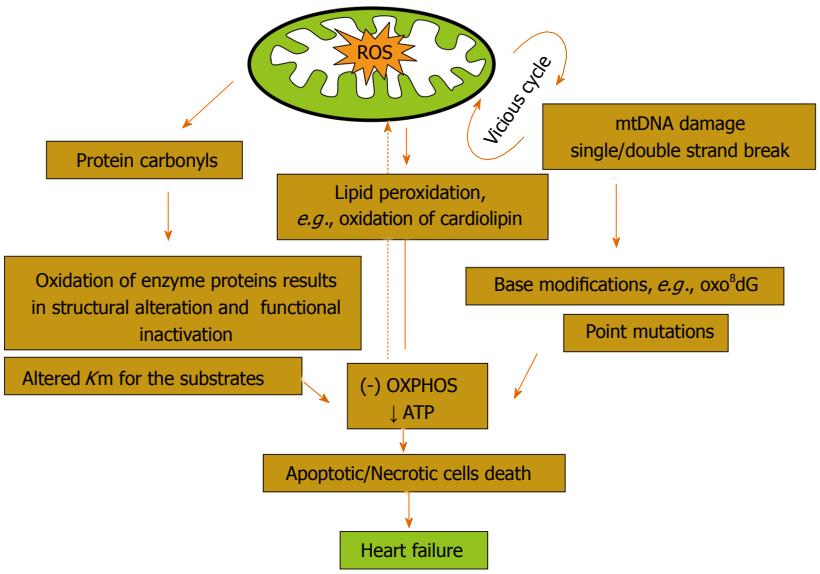

Figure 3 Damage induced by reactive oxygen species in mitochondria. OXPHOS: Oxidative phosphorylations; ROS: Reactive oxygen species.

Experiments using siRNA to DNase Ⅱ suggested that the DNase Ⅱ digested mtDNA and protected the tissue from inflammation.

In addition to the mtDNA mutations, damage to protein and lipid molecules in the mitochondrial membrane can contribute to the declined OXPHOS. Cardiolipin, an essential phospholipid present in the inner membrane of mitochondria that serves as a cofactor for a number of critical mitochondrial transport proteins and retains cytochrome c at the inner mitochondrial membrane through the electrostatic interaction, declines during the oxidative damage. Peroxidation of cardiolipin and its release into the cytosol can execute apoptotic cell death[20]. Amino acids, such as lysine, arginine, glutamic acid, histidine, proline and threonine present in the protein, favor the formation of protein carbonyl or nitration of the tyrosine residues, either by direct oxidation or by the binding of aldehydes that formed from the peroxidation of lipids. Mitochondrial aconitase and adenine nucleotide translocase are highly sensitive to O_2^-[21]. ROS-derived lipid hydroperoxide can also initiate the strand breaks and base modifications in mt DNA. Many cardiotoxic stimuli can lead to ROS generation, Ca^{2+} overload of the mitochondrial matrix, and opening of a large, nonspecific channel in the inner mitochondrial membrane, such as permeability transition pore (PTP), finally alter the mitochondrial permeability transition (MPT). Ca^{2+} overload to the mitochondrial matrix can further enhance the generation of ROS. Although the exact mechanism of ROS production is debatable, the effect is probably mediated through Ca^{2+} mediated inhibition on the complex Ⅰ[22], Ⅲ[23] and Ⅳ[23] of ETC (Figure 4). Ca^{2+} can stimulate the TCA cycle dehydrogenases to increase the production of reduced substrate for OXPHOS[24] and further increase the rate of respiration as well. Ca^{2+} can also activate mitochondrial nitric oxide synthase to produce NO which in turn inhibits the complex Ⅳ[25]. The simultaneous generation of NO with O_2^- favors the formation of peroxynitrite, one of the major agents to induce conformational change in many proteins[26]. MPT dissipates the proton electrochemical potential gradients, depletion of ATP and swelling, as well as rupture of the mitochondria that leads to the release of pro-apoptotic proteins into the cytosol and eventually results in death of cardiomyocytes. Evidence indicates that the activity of complex Ⅱ is not affected as it is entirely encoded by nuclear DNA, whereas complex Ⅳ activity (cytochrome C oxidase), along with complex Ⅰ, partially encoded by mtDNA genes, are frequently reduced in patients with mtDNA or tRNA mutations[19]. Mt tRNA gene mutations can also variably affect the activity of respiratory chain complexes.

ANTIOXIDANTS AND PROTECTION OF MITOCHONDRIA IN THE CARDIOMYOCYTES

Mitochondrial oxidative stress resulting from an imbalance between the generation of ROS and the existing mitochondrial antioxidant mechanisms has been described in the pathogenesis of CVDs, including HF[27]. HF followed by MI can be initiated with the mitochondrial damage and dysfunction that can be ascribed to: (1) increased lipid peroxidation; (2) reduced mitochondrial gene replication, mtDNA copy number and mitochondrial gene transcription; and (3) reduced OXPHOS due to low respiratory chain complex enzyme activities (Figure 5). Therefore, preservation of mitochondrial function is essential. Therapies that are designed to interfere with mitochondrial oxidative stress could be beneficial.

Various molecules are involved in the mitochondrial protection for the myocardium. Among them, tumor necrosis factor receptor-associated protein 1 (TRAP1), a member of the mitochondrial heat-shock family of proteins (70 kDa), has a central role. Overexpressed TRAP1 in the ischemia-like condition preserves ATP levels and

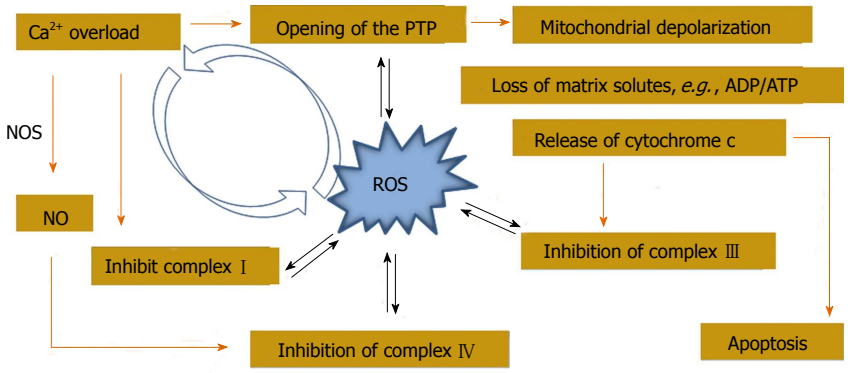

Figure 4 Crosstalk between mitochondrial Ca^{2+} handling and reactive oxygen species generation. PTP: Permeability transition pore; NOS: Nitric oxide synthase; ADP: Adenosine diphosphate; ATP: Adenosine triphosphate.

cell viability during oxygen-glucose deprivation. The protective effects of TRAP1 against oxidative stress-induced cell death can be ascribed to translocation of cytosolic serine/threonine protein kinase, PTEN-induced putative kinase 1, to mitochondria and phosphorylation of TRAP1 that will prevent the release of cytochrome c and thus preserves MPT. TRAP1 expression is found to be elevated in the cardiomyocytes during hypoxia. However, the excess production of ROS in reperfusion/ischemic injury can inhibit the TRAP1 mediated protection that eventually results in the death of cardiomyocytes[28]. Hence, the role of enzymatic and non-enzymatic antioxidants in the mitochondria has been inevitable to protect the mitochondrial damage. Various mitochondrial antioxidants are useful in alleviating the oxidative stress and are depicted in Figure 2.

The first line of defense against ROS-mediated cardiac injury comprises several antioxidant enzymes, including Mn-superoxide dismutase (MnSOD) and glutathione peroxidase (mtGPx). Among these, mtGPx is an essential enzyme that performs several vital functions. Experimental studies reported the declined cardiac mitochondrial antioxidants, such as activity of Mn-SOD, mtGPx and level of reduced glutathione (GSH) in the myocardium of the aged as well as MI-induced rats[10]. Besides, the activities of the respiratory chain complexes I -IV and Krebs cycle dehydrogenases also declined[9]. Several dietary supplements, including the mitochondrial cofactor and antioxidant lipoic acid (LA), can increase the endogenous antioxidants as well as mitochondrial bioenergetics[6]. Overexpression of the genes for peroxiredoxin-3, a mitochondrial antioxidant, or mitochondrial transcription factor A (TFAM) could ameliorate the decline in mtDNA copy number in failing hearts[28]. Overexpression of TFAM may protect mtDNA from damage by direct binding and stabilizing of mtDNA. Similarly, overexpression of mtGPx inhibit the development of left ventricular remodeling and failure after MI[29].

Co-enzyme Q10 (CoQ_{10}) and L-carnitine can be considered to be a safe adjunct to standard therapies in CVD[30]. CoQ_{10} is an endogenous compound found in the inner mitochondrial membrane that is essential for electron transport in the ETC and thus for the production of ATP. In addition to its role in bioenergetics, CoQ_{10} is demonstrated to be an inhibitor of thrombus formation and able to reduce ROS in mitochondria. Both pre-clinical and clinical studies have shown moderately beneficial effects of CoQ_{10} in reducing blood pressure, blood glucose and myocardial damage[31]. Besides the application of CoQ_{10} in CVD, its use against the adverse effect of drugs, mainly statins, in the intervention of CVD has recently attracted attention. Nevertheless, the antioxidant property of statins[32,33] can block the endogenous biosynthesis of CoQ_{10} required for the ETC, resulting in cardiomyopathy and muscle pain[34]. CoQ_{10} supplementation (100 mg/d) for 30 d has been found to decrease the muscle pain associated with statin treatment[35]. In another study, fifty consecutive new patients discontinued 28 mo of statin therapy due to side effects and began CoQ_{10} supplementation at an average of 240 mg/d[36] and were followed for an average of 22 mo (84% for more than 12 mo). The prevalence of fatigue from 84% on the initial visit decreased to 16%, the rate of myalgia from 64% to 6%, dyspnea from 58% to 12%, memory loss from 8% to 4% and peripheral neuropathy from 10% to 2%. Moreover, statin-induced cardiomyopathy was found to be reversed with the combination of statin discontinuation and supplementation with CoQ_{10}.

L-carnitine therapy in HF patients (2 g/d, orally) showed improved survival[37]. A recent study in patients with mild diastolic HF treated with L-carnitine (1.5 g/d, *p.o* for 3 mo) showed improvement in diastolic function[38]. Therapy with L-carnitine 9 g/d, intravenously for 5 d followed by 6 g/d orally for 12 mo along with the standard medical therapy may limit the adverse effects of acute MI on the heart muscle[39,40]. Tolerance to exercise was significantly improved in patients with higher left ventricular ejection fraction volume (greater than 30%) when treated with the propionyl-L-carnitine adjunct to appropriate medical therapy[41].

Carvedilol, both the beta blocker (β1, β2) and alpha blocker (α1), is indicated in the management of congestive HF. It is used as an adjunct to conventional treatments with its effect probably mediated through the potent antioxidant and anti-apoptotic activities[42]. The Japanese Diastolic Heart Failure Study has recently suggested the beneficial effects of standard dose prescriptions of carvedilol (> 7.5 mg/d) in HF without affecting

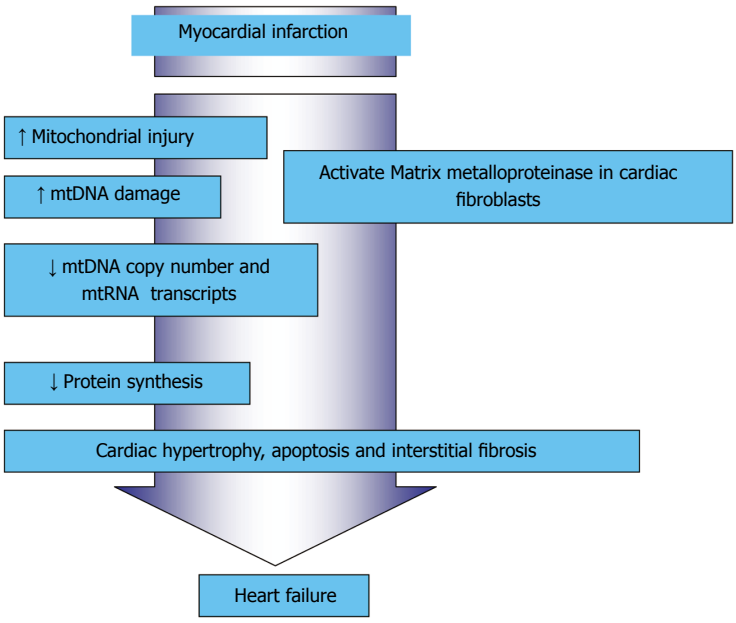

Figure 5 Myocardial infarction-induced mitochondrial damage and dysfunction that resulted in heart failure.

the ejection fraction[43]. An ACE inhibitor, captopril, was also shown to increase the mitochondrial content in the hearts of dogs following coronary ligation[44], suggesting that some of its beneficial effects may be due to the stimulation of mitochondrial biogenesis[45]. However, many extensive clinical trials using conventional antioxidants such as Vitamin E or Vitamin C yielded disappointing results[46,47]. According to Murphy and Smith[48], a possible explanation for this may be that the antioxidants are distributed widely in the body with only a small fraction being taken up by mitochondria. Therefore, targeting biologically active molecules to mitochondria will open up avenues for manipulating mitochondrial functions.

FUTURE PERSPECTIVES OF MITOCHONDRIAL PHARMACEUTICS IN CARDIOVASCULAR DISEASES

The increase of mitochondrial concentrations of antioxidant drugs by selective targeting mitochondria should be a practical approach for a wide range of human diseases. Mitochondria-targeted antioxidants have been developed as pharmaceuticals and have been shown to be safe and effective in phase Ⅱ clinical trials. Various antioxidant molecules targeting mitochondria in cardiomyocytes are given in Table 1. In general, attempts to achieve cell protection using antioxidants have been successfully undertaken with two free radical scavengers, such as 4-hydroxy-2,2,6,6-tetramethylpiperidin-N-oxide and Salen-Mn(Ⅲ) complex of o-vanillin (EUK-134). Inorganic MnSOD mimetics, such as EUK-8 and EUK-134, possess antioxidant properties of both MnSOD and catalase and have been successfully synthesized and partially tested in terms of their antioxidant and anti-apoptotic properties that appear to be effective in the heart[49]. The mitochondrial-targeted version of vitamin E protected mitochondria from oxidative damage induced by iron/ascorbate far more effectively than vitamin E itself[50].

The GSH pool in mitochondria, approximately 15% of total cellular GSH, is found to be reduced during oxidative stress. Choline esters of GSH and *N*-acetyl-L-cysteine were prepared as mitochondria-targeted antioxidants[51]. However, *in vivo* data are not available to support their efficacy. Recently, many trials have been conducted in which cationic molecules are targeted using the negative membrane potential of the inner membrane as a promising approach in this field. Triphenylphosphonium (TPP) cation is one among such molecules that are conjugated to a range of antioxidants. Antioxidants ligated with TPP, such as vitamin E[50], LA[52], plastoquinone[53] and mitochondrial CoQ_{10} (MitoQ)[54], have been experimentally confirmed to be effective in ameliorating mitochondrial oxidative stress in CVD. TPP, like pentaaza macrocyclic Mn(Ⅱ) superoxide dismutase (SOD) mimetic, MitoSOD, is found to be very effective in selectively protecting mitochondria from damage[55].

Adlam *et al*[54] reported that the myocardium of the rat administered with MitoQ can render protection against heart dysfunction, tissue damage and mitochondrial dysfunction induced from ischemia-reperfusion injury. It can be given either as *iv* or orally without toxicity. Graham *et al*[56] showed that MitoQ protects the development of hypertension, improves endothelial functions and reduces cardiac hypertrophy in young hypertensive rats. MitoQ is also a promising, novel strategy for preserving vascular endothelial function with advancing age and can prevent age-related CVD in mice[57]. However, MitoQ was not useful in protecting oxidative damage to cardiolipin, accumulation of protein carbonyls, activity of mitochondrial respiratory complexes, mtDNA copy number, or damage to mtDNA[58-60].

Another critical molecule in this field is a synthetic peptide called Szeto-Schiller (SS) - peptides, synthesized from basic and aromatic amino acids. SS-peptides comprised four alternating aromatic/basic D-amino acids in

Table 1 Mitochondria-targeted antioxidants

Sl no.	Antioxidants
1	4-hydroxy-2,2,6,6-tetramethylpiperidin-N-oxide (TEMPOL)
2	Salen-Mn(III) complex of o-vanillin (EUK-8, EUK-134)
3	Choline esters of glutathione and N-acetyl-l-cysteine
4	Triphenylphosphonium ligated vitamin E, lipoic acid, plastoquinone, Mito SOD and Mito CoQ_{10}
5	SS-peptides (SS-02 and SS-31)

SS: Szeto-Schiller.

the first or second position with three positive charges at physiological pH. SS-02 and SS-31 were shown to be protective against cardiac ischemia-reperfusion injury when administered on reperfusion by *iv*, *ip* or subcutaneously[61]. Pre-ischemic intraperitoneal administration of these peptides to rats significantly reduced infarct size[62]. SS-02 has more efficacy as the free radical scavenger than SS-31. The uptake into tissues or metabolism of these peptides has not yet been thoroughly reported. However, studies with isolated mitochondria showed that despite the cationic nature, these peptides were found to predominantly target the IMM rather than the mitochondrial matrix[63]. SS-31 is currently in clinical trials for ischemia-reperfusion injury and protects mitochondrial cristae by interacting with cardiolipin on the IMM. SS peptides scavenge H_2O_2 and peroxynitrite inhibits lipid peroxidation. They can also inhibit the decline of MPT and cytochrome c release, thus preventing oxidant-induced cell death[64]. Although the delivery of antioxidants may protect mitochondria from oxidative stress caused by a variety of insults, the area of mitochondria-specific delivery of drugs is still in its infancy. Among the molecules studied in CVD, clinical trials on CoQ_{10} have found that it can be considered a safe adjunct to conventional therapies in CVD. Despite the beneficial effect of CoQ_{10}, given alone or in addition to conventional therapies in hypertension and in HF, less extensive evidence in IHD has been found[65]. The present findings demonstrate that mitochondrial damage plays a prominent role in HF following MI and further research into the role of mitochondria-targeted agents to prevent the HF is compulsory.

CONCLUSION

Mitochondrial dysfunction plays a key role in the pathogenesis of ischemia and reperfusion injury and cardiomyopathy. Mutations in mt DNA and abnormalities in mitochondrial function are associated with common forms of cardiac diseases. Despite the promising mitochondria-targeted drugs that are emerging from the laboratory, very few have successfully completed clinical trials. Antioxidants ligated with TPP, such as vitamin E, lipoic acid, plastoquinone, MnSOD and mitochondrial CoQ_{10}, have been experimentally determined as effective in ameliorating the mitochondrial oxidative stress associated with CVD. Among the molecules targeting mitochondria, MitoQ provides a novel approach to attenuate oxidative damage with the potential to become a new therapeutic intervention in humans. However, there are insufficient data from well designed randomized trials to issue a general recommendation for people to take antioxidant supplements in order to prevent heart disease. Since mitochondrial damage is central to the pathophysiology of HF, various approaches used to target antioxidant compounds at mitochondria should be explored in the development for the treatment of HF. A great deal of future research will be needed before mitochondria-directed therapies are made available for the prevention and treatment of CVD.

REFERENCES

1 **McMurray JJ**, Pfeffer MA. Heart failure. *Lancet* 2005; **365**: 1877-1889 [DOI: 10.1016/S0140-6736(05)66621-4]
2 **He J**, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Arch Intern Med* 2001; **161**: 996-1002 [PMID: 11295963 DOI: 10.1001/archinte.161.7.996]
3 **Bayeva M**, Gheorghiade M, Ardehali H. Mitochondria as a therapeutic target in heart failure. *J Am Coll Cardiol* 2013; **61**: 599-610 [PMID: 23219298 DOI: 10.1016/j.jacc.2012.08.1021]
4 **Ballinger SW**. Mitochondrial dysfunction in cardiovascular disease. *Free Radic Biol Med* 2005; **38**: 1278-1295 [PMID: 15855047 DOI: 10.1016/j.freeradbiomed.2005.02.014]
5 **Liu Y**, Fiskum G, Schubert D. Generation of reactive oxygen species by the mitochondrial electron transport chain. *J Neurochem* 2002; **80**: 780-787 [PMID: 11948241 DOI: 10.1046/j.0022-3042.2002.00744.x]
6 **Fosslien E**. Review: Mitochondrial medicine--cardiomyopathy caused by defective oxidative phosphorylation. *Ann Clin Lab Sci* 2003; **33**: 371-395 [PMID: 14584751]
7 **Chevion M**, Jiang Y, Har-El R, Berenshtein E, Uretzky G, Kitrossky N. Copper and iron are mobilized following myocardial ischemia: possible predictive criteria for tissue injury. *Proc Natl Acad Sci USA* 1993; **90**: 1102-1106 [PMID: 8430081 DOI: 10.1073/pnas.90.3.1102]
8 **Reddy BR**, Kloner RA, Przyklenk K. Early treatment with deferoxamine limits myocardial ischemic/reperfusion injury. *Free Radic Biol Med* 1989; **7**: 45-52 [DOI: 10.1016/0891-5849(89)90099-3]
9 **Sudheesh NP**, Ajith TA, Janardhanan KK. Ganoderma lucidum ameliorate mitochondrial damage in isoproterenol-induced myocardial infarction in rats by enhancing the activities of TCA cycle enzymes and respiratory chain complexes. *Int J Cardiol* 2013; **165**: 117-125 [PMID: 21864918 DOI: 10.1016/j.ijcard.2011.07.103]
10 **Sudheesh NP**, Ajith TA, Janardhanan KK, Krishnan CV. Effect of POLY-MVA, a palladium alpha-lipoic acid complex formulation against declined mitochondrial antioxidant status in the myocardium of aged rats. *Food Chem Toxicol* 2010; **48**: 1858-1862 [PMID: 20412826 DOI: 10.1016/j.fct.2010.04.022]
11 **McCommis KS**, McGee AM, Laughlin MH, Bowles DK, Baines CP. Hypercholesterolemia increases mitochondrial oxidative stress and enhances the MPT response in the porcine myocardium: beneficial effects of chronic exercise. *Am J Physiol Regul Integr Comp Physiol* 2011; **301**: R1250-R1258 [PMID: 21865543 DOI: 10.1152/ajpregu.00841.2010]
12 **Marín-García J**, Goldenthal MJ, Moe GW. Abnormal cardiac and skeletal muscle mitochondrial function in pacing-induced cardiac failure. *Cardiovasc Res* 2001; **52:** 103-10 [DOI: 10.1016/S0008-6363(01)00368-6]
13 **Tsutsui T**, Tsutamoto T, Wada A, Maeda K, Mabuchi N,

Hayashi M, Ohnishi M, Kinoshita M. Plasma oxidized low-density lipoprotein as a prognostic predictor in patients with chronic congestive heart failure. *J Am Coll Cardiol* 2002; **39**: 957-62 [DOI: 10.1016/S0735-1097(02)01721-7]
14 **Ding Z**, Liu S, Wang X, Khaidakov M, Dai Y, Mehta JL. Oxidant stress in mitochondrial DNA damage, autophagy and inflammation in atherosclerosis. *Sci Rep* 2013; **3**: 1077 [PMID: 23326634 DOI: 10.1038/srep01077]
15 **Davidson SM**. Endothelial mitochondria and heart disease. *Cardiovasc Res* 2010; **88**: 58-66 [PMID: 20558442 DOI: 10.1093/cvr/cvq195]
16 **Holt IJ**, Harding AE, Morgan-Hughes JA. Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies. *Nature* 1988; **331**: 717-719 [PMID: 2830540 DOI: 10.1038/331717a0]
17 **Wei YH**. Mitochondrial DNA alterations as ageing-associated molecular events. *Mutat Res* 1992; **275**: 145-55 [DOI: 10.1016/0921-8734(92)90019-L]
18 **Wei YH**. Mitochondrial DNA mutations and oxidative damage in aging and diseases: an emerging paradigm of gerontology and medicine. *Proc Natl Sci Counc Repub China B* 1998; **22**: 55-67 [PMID: 9615468]
19 **Arbustini E,** Diegoli M, Fasani R, Grasso M, Morbini P, Banchieri N, Bellini O, Dal Bello B, Pilotto A, Magrini G, Campana C, Fortina P, Gavazzi A, Narula J, Viganò M. Mitochondrial DNA mutations and mitochondrial abnormalities in dilated cardiomyopathy. *Am J Pathol* 1998; **153:** 1501-10 [DOI: 10.1016/S0002-9440(10)65738-0]
20 **Ott M**, Robertson JD, Gogvadze V, Zhivotovsky B, Orrenius S. Cytochrome c release from mitochondria proceeds by a two-step process. *Proc Natl Acad Sci USA* 2002; **99**: 1259-1263 [PMID: 11818574 DOI: 10.1073/pnas.241655498]
21 **Vasquez-Vivar J**, Kalyanaraman B, Kennedy MC. Mitochondrial aconitase is a source of hydroxyl radical. An electron spin resonance investigation. *J Biol Chem* 2000; **275**: 14064-14069 [PMID: 10799480]
22 **Batandier C**, Leverve X, Fontaine E. Opening of the mitochondrial permeability transition pore induces reactive oxygen species production at the level of the respiratory chain complex I. *J Biol Chem* 2004; **279**: 17197-17204 [PMID: 14963044 DOI: 10.1074/jbc.M310329200]
23 **Grijalba MT**, Vercesi AE, Schreier S. Ca2 -induced increased lipid packing and domain formation in submitochondrial particles. A possible early step in the mechanism of Ca2 -stimulated generation of reactive oxygen species by the respiratory chain. *Biochemistry* 1999; **38**: 13279-13287 [DOI: 10.1021/bi9828674]
24 **Wan B**, LaNoue KF, Cheung JY, Scaduto RC. Regulation of citric acid cycle by calcium. *J Biol Chem* 1989; **264**: 13430-13439 [PMID: 2503501]
25 **Brookes P**, Darley-Usmar VM. Hypothesis: the mitochondrial NO () signaling pathway, and the transduction of nitrosative to oxidative cell signals: an alternative function for cytochrome C oxidase. *Free Radic Biol Med* 2002; **32**: 370–74 [DOI: 10.1016/S0891-5849(01)00805-X]
26 **Brookes PS**, Darley-Usmar VM. Role of calcium and superoxide dismutase in sensitizing mitochondria to peroxynitrite-induced permeability transition. *Am J Physiol Heart Circ Physiol* 2004; **286**: H39-H46 [PMID: 12933349 DOI: 10.1152/ajpheart.00742.2003]
27 **Subramanian S,** Kalyanaraman B, Migrino RQ. Mitochondrially targeted antioxidants for the treatment of cardiovascular diseases. *Recent Pat Cardiovasc Drug Discov* 2010; **5**: 54-65 [DOI: 10.2174/157489010790192601]
28 **Xiang F**, Huang YS, Shi XH, Zhang Q. Mitochondrial chaperone tumour necrosis factor receptor-associated protein 1 protects cardiomyocytes from hypoxic injury by regulating mitochondrial permeability transition pore opening. *FEBS J* 2010; **277**: 1929-1938 [PMID: 20236315 DOI: 10.1111/j.1742-4658.2010.07615.x]
29 **Tsutsui H**, Kinugawa S, Matsushima S. Mitochondrial oxidative stress and dysfunction in myocardial remodelling. *Cardiovasc Res* 2009; **81**: 449-456 [PMID: 18854381 DOI: 10.1093/cvr/cvn280]
30 **Hagen TM**, Moreau R, Suh JH, Visioli F. Mitochondrial decay in the aging rat heart: evidence for improvement by dietary supplementation with acetyl-L-carnitine and/or lipoic acid. *Ann N Y Acad Sci* 2002; **959**: 491-507 [PMID: 11976222 DOI: 10.1111/j.1749-6632.2002.tb02119.x]
31 **Garrido-Maraver J**, Cordero MD, Oropesa-Avila M, Vega AF, de la Mata M, Pavon AD, Alcocer-Gomez E, Calero CP, Paz MV, Alanis M, de Lavera I, Cotan D, Sanchez-Alcazar JA. Clinical applications of coenzyme Q10. *Front Biosci* 2014; **19**: 619-633 [DOI: 10.2741/4231]
32 **Ajith TA**, Divya KR. An in vitro comparative study on the antibacterial and antioxidant activities of atorvastatin and simvastatin. *Pharmaceutical Biol* 2007; **45**: 1-5 [DOI: 10.1080/13880200701574992]
33 **Ajith TA**, Riji T, Anu V. In vitro antioxidant and DNA protective effects of a novel HMG.CoA reductase inhibitor, rosuvastatin. *Clin Exp Physiol Pharmacol* 2008; **35**: 625-29 [DOI: 10.1111/j.1440-1681.2007.04853.x]
34 **Littarru GP**, Langsjoen P. Coenzyme Q10 and statins: biochemical and clinical implications. *Mitochondrion* 2007; **7** Suppl: S168-S174 [PMID: 17482884 DOI: 10.1016/j.mito.2007.03.002]
35 **Caso G**, Kelly P, McNurlan MA, Lawson WE. Effect of coenzyme q10 on myopathic symptoms in patients treated with statins. *Am J Cardiol* 2007; **99**: 1409-1412 [PMID: 17493470 DOI: 10.1016/j.amjcard.2006.12.063]
36 **Langsjoen PH**, Langsjoen JO, Langsjoen AM, Lucas LA. Treatment of statin adverse effects with supplemental Coenzyme Q10 and statin drug discontinuation. *Biofactors* 2005; **25**: 147-152 [DOI: 10.1002/biof.5520250]
37 **Rizos I**. Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration. *Am Heart J* 2000; **139**: S120-S123 [PMID: 10650325 DOI: 10.1067/mhj.2000.103917]
38 **Serati AR**, Motamedi MR, Emami S, Varedi P, Movahed MR. L-carnitine treatment in patients with mild diastolic heart failure is associated with improvement in diastolic function and symptoms. *Cardiology* 2010; **116**: 178-182 [PMID: 20639632 DOI: 10.1159/000318810]
39 **Colonna P**, Iliceto S. Myocardial infarction and left ventricular remodeling: results of the CEDIM trial. Carnitine Ecocardiografia Digitalizzata Infarto Miocardico. *Am Heart J* 2000; **139**: S124-S130 [PMID: 10650326 DOI: 10.1067/mhj.2000.103918]
40 **Tarantini G**, Scrutinio D, Bruzzi P, Boni L, Rizzon P, Iliceto S. Metabolic treatment with L-Carnitine in acute anterior ST segment elevation myocardial infarction. A randomized controlled trial. *Cardiology* 2006; **106**: 215-223 [PMID: 16685128 DOI: 10.1159/000093131]
41 Study on propionyl-L-carnitine in chronic heart failure. *Eur Heart J* 1999; **20**: 70-76 [DOI: 10.1053/euhj.1998.1271]
42 **Cheng J**, Kamiya K, Kodama I. Carvedilol: molecular and cellular basis for its multifaceted therapeutic potential. *Cardiovasc Drug Rev* 2001; **19**: 152-171 [PMID: 11484068]
43 **Yamamoto K**, Origasa H, Suzuki Y, Takahashi T, Shinozaki T, Watanabe T, Sakata Y, Izumi C, Taira K, Hori M. Relation of risk factors with response to carvedilol in heart failure with preserved ejection fraction - A report from the Japanese Diastolic Heart Failure Study (J-DHF). *J Cardiol* 2013; **S0914-5087**: 326-332
44 **Yanagishita T**, Tomita M, Itoh S, Mukae S, Arata H, Ishioka H, Geshi E, Konno N, Katagiri T. Protective effect of captopril on ischemic myocardium. *Jpn Circ J* 1997; **61**: 161-169 [DOI: 10.1253/jcj.61.161]
45 **Sanbe A**, Tanonaka K, Kobayasi R, Takeo S. Effects of long-term therapy with ACE inhibitors, captopril, enalapril and trandolapril, on myocardial energy metabolism

in rats with heart failure following myocardial infarction. *J Mol Cell Cardiol* 1995; **27**: 2209–2222 [DOI: 10.1016/S0022-2828(95)91551-6]
46 **Bjelakovic G**, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database Syst Rev* 2008; **(2)**: CD007176 [PMID: 18425980]
47 **Cochemé HM**, Murphy MP. Can antioxidants be effective therapeutics? *Curr Opin Investig Drugs* 2010; **11**: 426-431 [PMID: 20336590]
48 **Murphy MP**, Smith RA. Targeting antioxidants to mitochondria by conjugation to lipophilic cations. *Annu Rev Pharmacol Toxicol* 2007; **47**: 629-656 [PMID: 17014364 DOI: 10.1146/annurev.pharmtox.47.120505.105110]
49 **Pucheu S**, Boucher F, Sulpice T, Tresallet N, Bonhomme Y, Malfroy B, de Leiris J. EUK-8 a synthetic catalytic scavenger of reactive oxygen species protects isolated iron-overloaded rat heart from functional and structural damage induced by ischemia/reperfusion. *Cardiovasc Drugs Ther* 1996; **10**: 331-339 [PMID: 8877076]
50 **Smith RA**, Porteous CM, Coulter CV, Murphy MP. Selective targeting of an antioxidant to mitochondria. *Eur J Biochem* 1999; **263**: 709-716 [PMID: 10469134 DOI: 10.1046/j.1432-1327.1999.00543.x]
51 **Sheu SS**, Nauduri D, Anders MW. Targeting antioxidants to mitochondria: a new therapeutic direction. *Biochim Biophys Acta* 2006; **1762**: 256-265 [PMID: 16352423 DOI: 10.1016/j.bbadis.2005.10.007]
52 **Brown SE**, Ross MF, Sanjuan-Pla A, Manas AR, Smith RA, Murphy MP. Targeting lipoic acid to mitochondria: synthesis and characterization of a triphenylphosphonium-conjugated alpha-lipoyl derivative. *Free Radic Biol Med* 2007; **42**: 1766-1780 [PMID: 17512456 DOI: 10.1016/j.freeradbiomed.2007.02.033]
53 **Skulachev VP**, Anisimov VN, Antonenko YN, Bakeeva LE, Chernyak BV, Erichev VP, Filenko OF, Kalinina NI, Kapelko VI, Kolosova NG, Kopnin BP, Korshunova GA, Lichinitser MR, Obukhova LA, Pasyukova EG, Pisarenko OI, Roginsky VA, Ruuge EK, Senin II, Severina II, Skulachev MV, Spivak IM, Tashlitsky VN, Tkachuk VA, Vyssokikh MY, Yaguzhinsky LS, Zorov DB. An attempt to prevent senescence: a mitochondrial approach. *Biochim Biophys Acta* 2009; **1787**: 437-461 [PMID: 19159610 DOI: 10.1016/j.bbabio.2008.12.008]
54 **Adlam VJ**, Harrison JC, Porteous CM, James AM, Smith RA, Murphy MP, Sammut IA. Targeting an antioxidant to mitochondria decreases cardiac ischemia-reperfusion injury. *FASEB J* 2005; **19**: 1088-1095 [PMID: 15985532]
55 **Kelso GF**, Maroz A, Cochemé HM, Logan A, Prime TA, Peskin AV, Winterbourn CC, James AM, Ross MF, Brooker S, Porteous CM, Anderson RF, Murphy MP, Smith RA. A mitochondria-targeted macrocyclic Mn(II) superoxide dismutase mimetic. *Chem Biol* 2012; **19**: 1237-1246 [PMID: 23102218 DOI: 10.1016/j.chembiol.2012.08.005]
56 **Graham D**, Huynh NN, Hamilton CA, Beattie E, Smith RA, Cochemé HM, Murphy MP, Dominiczak AF. Mitochondria-targeted antioxidant MitoQ10 improves endothelial function and attenuates cardiac hypertrophy. *Hypertension* 2009; **54**: 322-328 [PMID: 19581509]
57 **Gioscia-Ryan RA**, Larocca TJ, Sindler AL, Zigler MC, Murphy MP, Seals DR. Mitochondria-targeted antioxidant (MitoQ) ameliorates age-related arterial endothelial dysfunction in mice. *J Physiol* 2014; (Accepted Article) [DOI: 10.1113/jphysiol.2013.268680]
58 **Paradies G**, Petrosillo G, Paradies V, Ruggiero FM. Role of cardiolipin peroxidation and Ca2+ in mitochondrial dysfunction and disease. *Cell Calcium* 2009; **45**: 643-650 [PMID: 19368971 DOI: 10.1016/j.ceca.2009.03.012]
59 **Davies SM**, Poljak A, Duncan MW, Smythe GA, Murphy MP. Measurements of protein carbonyls, ortho- and meta-tyrosine and oxidative phosphorylation complex activity in mitochondria from young and old rats. *Free Radic Biol Med* 2001; **31**: 181-190 [DOI: 10.1016/S0891-5849(01)00576-7]
60 **Santos JH**, Meyer JN, Mandavilli BS, Van Houten B. Quantitative PCR-based measurement of nuclear and mitochondrial DNA damage and repair in mammalian cells. *Methods Mol Biol* 2006; **314**: 183-199 [PMID: 16673882 DOI: 10.1385/1-59259-973-7]
61 **Szeto HH**. Mitochondria-targeted cytoprotective peptides for ischemia-reperfusion injury. *Antioxid Redox Signal* 2008; **10**: 601-619 [PMID: 17999629 DOI: 10.1089/ars.2007.1892]
62 **Cho J**, Won K, Wu D, Soong Y, Liu S, Szeto HH, Hong MK. Potent mitochondria-targeted peptides reduce myocardial infarction in rats. *Coron Artery Dis* 2007; **18**: 215-220 [PMID: 17429296 DOI: 10.1097/01.mca.0000236285.71683.b6]
63 **Zhao K**, Zhao G-M, Wu D, Soong Y, Birk AV, Schiller PW, Szeto HH. Cell-permeable Peptide Antioxidants Targeted to Inner Mitochondrial Membrane inhibit Mitochondrial Swelling, Oxidative Cell Death, and Reperfusion Injury. *J Biol Chem* 2004; **279**: 34682-34690 [PMID: 15178689 DOI: 10.1074/jbc.M402999200]
64 **Rocha M,** Hernandez-Mijares A, Garcia-Malpartida K, Bañuls C, Bellod L, Victor VM. Mitochondria-targeted antioxidant peptides. *Curr Pharm Des* 2010; **16:** 3124-31 [DOI: 10.2174/138161210793292519]
65 **Pepe S**, Marasco SF, Haas SJ, Sheeran FL, Krum H, Rosenfeldt FL. Coenzyme Q10 in cardiovascular disease. *Mitochondrion* 2007; **7** Suppl: S154-S167 [PMID: 17485243 DOI: 10.1016/j.mito.2007.02.005]

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MINIREVIEWS

Perioperative clinical variables and long-term survival following vascular surgery

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Abstract

Cardiovascular disease is the leading cause of death in patients with peripheral arterial disease (PAD). Coronary artery disease (CAD) is highly prevalent, and often times coexist, in patients with PAD. The management of patients with PAD that requires a high-risk vascular surgical procedure for intermittent claudication, critical limb ischemia or expanding abdominal aortic aneurysm requires risk stratification with the revised cardiac risk index, optimization of medical therapies, and limited use of cardiac imaging prior to surgery. Preventive revascularization in patients with stable CAD, with the sole intention to mitigate the risk of cardiac complications in the peri-operative period, is not effective and may be associated with significant bleeding and thrombotic risks, in particular if stents are used. A strategy of universal use of cardiac troponins in the perioperative period for active surveillance of myocardial ischemia may be more reasonable and cost-effective than the current standard of care of widespread use of cardiac imaging prior to high-risk surgery. An elevated cardiac troponin after vascular surgery is predictive of long-term mortality risk. Medical therapies such as aspirin and statins are recommended for patients with post-operative myocardial ischemia. Ongoing trials are assessing the role of novel anticoagulants. Additional research is needed to define the role of cardiac imaging and invasive angiography in this population.

Key words: Peripheral arterial disease; Myocardial infarction; Coronary artery disease; Prognosis; Coronary revascularization

Core tip: Patients with advanced peripheral arterial disease who need vascular surgery have a high prevalence of coronary atherosclerosis and are at increased risk of perioperative myocardial infarction. Coronary revascularization prior to the vascular operation is not an effective intervention to mitigate this risk. A strategy of widespread use of cardiac troponins in the perioperative period is recommended to detect perioperative ischemic events associated with a long-term mortality risk. The selective use of medical interventions, cardiac imaging and coronary angiography in this population deserves further study.

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INTRODUCTION

The approach to patients with peripheral arterial disease (PAD) is best appreciated in the broader context of the epidemiology of the disease, risk factors, and surgical and endovascular interventions to improve symptoms, pre-

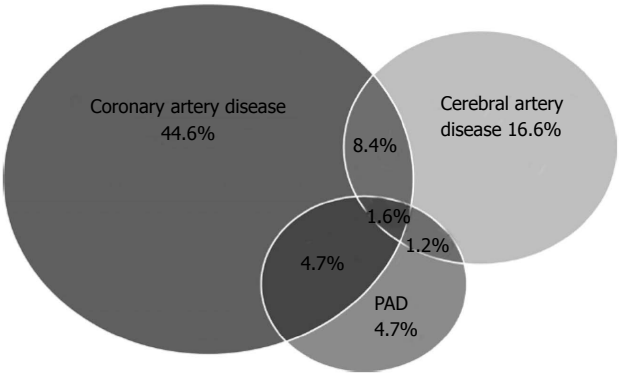


Figure 1 Data from the Reduction of Atherothrombosis for Continued Health registry. Approximately 50% of patients with peripheral arterial disease (PAD) and polyvascular disease have concomitant coronary artery disease. Reproduced with permission from society for vascular surgery.

serve limb viability or prevent aneurismal rupture.

Peripheral arterial disease (PAD) and coronary artery disease (CAD) often coexist in the same patient and share a common risk factor profile, pathophysiology, and array of therapeutic interventions[1-3]. Cardiovascular disease is the leading cause of death in patients with PAD, responsible for about two of every three deaths[4].

Vascular surgery is considered a high-risk operation with one in four patients experiencing a peri-operative myocardial infarction (PMI), which is associated with increased long-term mortality[5,6]. Identifying the clinical variables associated with increased risk of PMI prior to surgery as well as defining the best strategy for surveillance of PMI after high-risk surgery are of critical importance in clinical practice to mitigate risk and improve outcomes.

Definition of PAD

The definition of PAD is based on a resting ankle-brachial index (ABI) of $\leqslant 0.90$[1]. Noticeably, the presence of symptoms is not required to diagnose PAD. For every patient with symptoms of PAD there are 4 with no symptoms as defined by ABI or duplex ultrasonography[7]. Screening for PAD is therefore recommended to detect the disease in individuals with a high pre-test probability. In the PARTNERS (PAD Awareness, Risk, and Treatment: New Resources for Survival) study the prevalence of PAD defined by ABI was 29%[8]. Therefore, current ACC/AHA guidelines recommend screening for PAD in patients aged $\geqslant 70$ or 50-69 years with a risk factor for vascular disease[1]. Intermittent claudication (IC) is the most common presenting symptom of symptomatic PAD. IC is characterized by leg pain (muscular pain) with activity that is relieved by physical rest. Claudication tends to occur one anatomical level below the arterial level of obstruction or occlusion. For example a patient with superficial femoral artery (SFA) occlusion will likely have calf symptoms. The prevalence of IC in the general population is low but increases significantly with age so that in patients aged 60 or older is about 6%[9].

Risk factors for PAD

The risk factors for developing PAD and CAD show significant overlap and include male gender, age, hypertension, hyperlipidemia, renal insufficiency, black race, and more importantly diabetes mellitus (DM) and smoking, both of which have odds ratios (ORs) over 3 for symptomatic PAD[2,10-14]. Likewise, diabetics and smokers have a 3 to 4-fold increase in the risk of developing critical limb ischemia and amputations[2,12].

POLYVASCULAR DISEASE

The prevalence of CAD in patients with PAD depends on the setting and the sensitivity of the method used to identify occult CAD. In the REACH (Reduction of Atherotrombosis for Continued Health) outpatient registry (Figure 1), 50% of patients with PAD and polyvascular disease had coexistent CAD[3]. In a landmark angiographic study of 1000 patients undergoing coronary angiography prior to vascular surgery conducted at the cleveland clinic by Hertzer *et al*[15] only 8% had normal coronary arteries prior to surgery, 2/3 had severe CAD, 10% had inoperable CAD and 18% had moderate CAD.

The annual rate of major adverse cardiovascular events (MACE) (myocardial infarction, stroke, and vascular death) in patients with PAD is 5%-7%[1,2]. Critical limb ischemia (CLI) patients have 20% mortality only in the first year after initial presentation. CAD is responsible for 40%-60% of deaths among patients with PAD while cerebral arterial disease accounts for another 10%-20% of deaths[1,2,4]. The severity of PAD, as quantified by ABI, correlates with the risk of MACE so that for every 0.10 decrease in ABI there is a corresponding 10% increase in MACE[16]. There is a strong association between MACE and ABI $\leqslant 0.60$ in patients with diabetes[16] (Figure 2).

CARDIAC RISK STRATIFICATION PRIOR TO VASCULAR SURGERY

Variables to assess prior to a vascular operation include the type of operation (open *vs* endovascular), the risk of concomitant CAD and the functional status of the patient[17]. Open abdominal aneurismal repair with cross-clamp of the aorta and non-elective operations carry the highest risk of cardiovascular complications[18] in part due to the hemodynamic stress of the surgery, CAD burden, and the acuity of the condition that often hampers the ability to start preoperative interventions to mitigate cardiac risk.

Evaluating the functional status of subjects undergoing vascular surgery is an important step in assessing if a patient can tolerate the hemodynamic stress of a prolonged surgery. If a patient is unable to achieve a metabolic demand of 4-METS, which is a level compatible with routine activities of daily living, the risk of surgical complications increases and additional testing may be warranted. Stress imaging testing, usually with pharma-

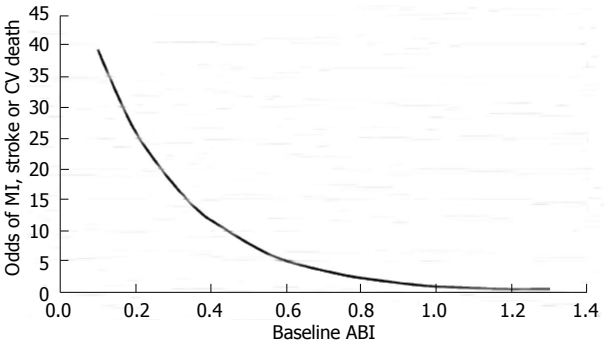


Figure 2 Odds of a major cardiovascular event according to baseline ankle-brachial index in patients with diabetes mellitus. Reproduced with permission from Mehler *et al*[16]. MI: Myocardial infarction; CV: Cardiovascular, ABI: Ankle-brachial index.

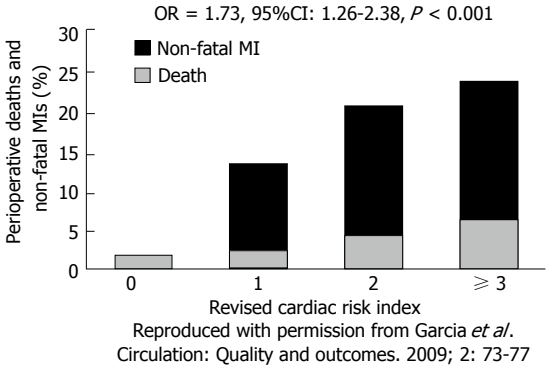


Figure 3 Outcomes at 30 d following vascular surgery according to number of risks as enumerated in the revised cardiac risk index. MI: Myocardial infarction.

cological agents such as adenosine or dobutamine, has been recommended prior to high-risk vascular surgery in patients with functional capacity < 4 METS[17]. The presence of large or multiple ischemic segments or transient ischemic dilatation of the left ventricle may indicate either multivessel or left main CAD. These findings are considered high risk and are associated with an increased risk of perioperative cardiac complications and reduced long-term survival[19]. Coronary angiography is recommended to patients that have high-risk findings on non-invasive imaging, as certain angiographic subsets (*i.e.*, left main CAD) derive a long-term benefit from revascularization[20]. An initial approach that combines clinical and stress-imaging variables is cost-effective[21].

The Revised Cardiac Risk Index (RCRI) is a risk score comprised of six clinical variables (Table 1) that has been validated in a general surgery population as a tool to predict the risk of cardiac adverse events at 30 d[22]. A RCRI ⩾ 3 is associated with > 5% risk of a serious cardiac complication in the postoperative period. However, in vascular surgery the RCRI tends to underestimate the risk of cardiac complications. In the Coronary Artery Revascularization Prophylaxis (CARP) trial a RCRI > 1 was predictive of a 10% risk of MI or death at 30 d in the preoperative revascularization (PR) group and 15% in the medical arm (Figure 3)[23].

Table 1 The Revised Cardiac Risk Index is comprised of 6 clinical variables that receive 1 point if present and 0 if absent

High-risk procedures (*i.e.*, vascular surgery)
History of cerebrovascular disease
History of coronary artery disease
History of congestive heart failure
Creatinine > 2.0 mg%
Diabetes (insulin-dependent)

A score ⩾ 3 predicts a 10% risk of serious cardiac complications after non-cardiac surgery.

PREOPERATIVE CORONARY REVASCULARIZATION

The CARP Trial was a randomized, multisite VA study designed to assess the role of PR in patients with CAD undergoing elective vascular surgery[24]. A total of 510 patients were enrolled and randomized to either PR or no PR prior to elective vascular surgery. Indications for surgery included an expanding AAA in 33% of patients and arterial occlusive disease of the lower limbs in 67%. The index revascularization procedure consisted of percutaneous coronary intervention (PCI) in 59% and coronary artery bypass graft (CABG) surgery in 41% of patients. At 2.7 years, mortality in the PR group was 22% and in the no PR group was 23% (P = 0.92; RR = 0.98, 95%CI: 0.70-1.37) (Figure 4). Similarly, no difference in outcomes was seen within 30-d, mortality was 3.1% in the PR group and 3.4% in the no PR group (P = 0.87) and a MI occurred in 11.6% of the PR group and 14.3% of the no PR group (P = 0.37). The main conclusion of the CARP study is that preoperative coronary artery revascularization prior to vascular surgery does not result in better short- or long-term clinical outcomes in patients with stable CAD.

The pilot Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo (DECREASE) - V study randomized 101 patients with stress-induced ischemia and multivessel or left main CAD to PR or no PR prior to high-risk vascular surgery[25]. At 1-year, the composite of non-fatal myocardial infarction and mortality between groups (49% *vs* 44%, P = 0.48) was no different. Taken together these data do not support a strategy of PR prior to elective vascular surgery in patients with stable CAD.

PERIOPERATIVE MYOCARDIAL INFARCTION

Definition and predictors

The Third Universal Definition of myocardial infarction (MI) proposed by the ESC/ACCF/AHA/WHF task force requires a rise and fall of cardiac biomarkers, preferably troponins, with at least one value above the 99th percentile of the upper reference limit (URL) coupled with a clinical correlate of ischemia such as ischemic

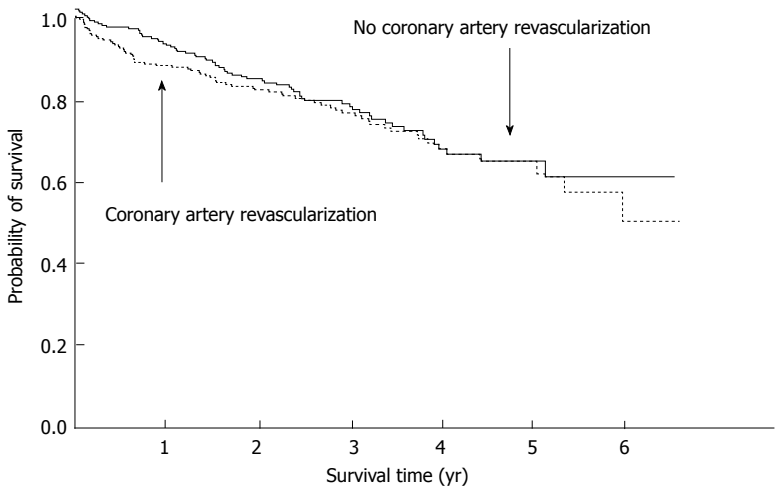
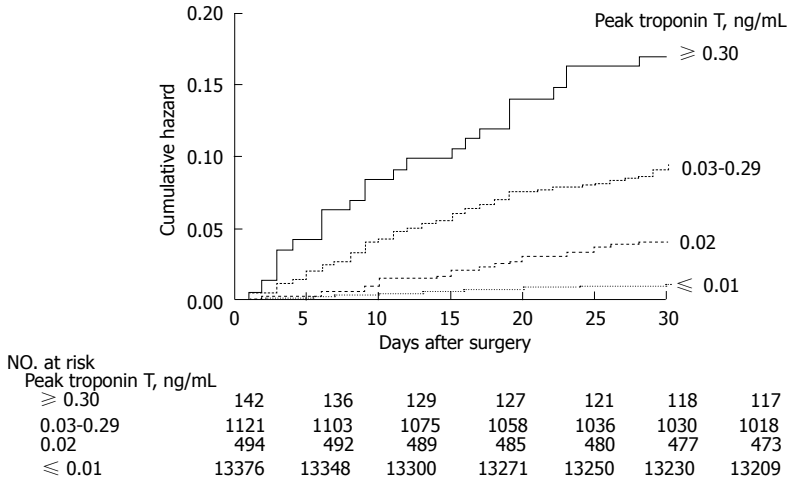


Figure 4 Primary outcome of the coronary artery revascularization prophylaxis trial: Overall survival at 2.7 yr was no different between groups (22 % *vs* 23%).



NO. at risk

Peak troponin T, ng/mL							
⩾ 0.30	142	136	129	127	121	118	117
0.03-0.29	1121	1103	1075	1058	1036	1030	1018
0.02	494	492	489	485	480	477	473
⩽ 0.01	13376	13348	13300	13271	13250	13230	13209

Figure 5 The vascular events in Noncardiac Surgery Patients Cohort Evaluation Study. Peak troponin T values (TnT) of 0.02 ng/mL were associated with increased (4%) risk of death at 30 d relative to TnT levels < 0.01. Reproduced with permission from Devereaux *et al*[28].

symptoms, electrocardiographic ischemic changes, or imaging criteria of new loss of previously viable myocardium[26]. However, owing to the effects of anesthesia, and other factors such as widespread use of narcotics, the vast majority of perioperative ischemic events are clinically silent. In the Perioperative ischemic evaluation (POISE) trial 65% of patients with a perioperative ischemic event did not experience ischemic symptoms[27]. The risk of death at 30 d was 9.7% in patients with a symptomatic MI and 12.5% in patients with an asymptomatic MI. Thus, the universal definition of MI may not be as sensitive in the perioperative period to detect ischemic events that are associated with poor intermediate- and long-term outcomes. An isolated peak cardiac biomarker elevation (preferably troponins) above the 99th URL, with or without a correlate of ischemia, may be the most sensitive tool to detect perioperative ischemic events that are clinically important. In the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) registry[28], a peak postoperative troponin T (TnT) measured within the first 3 d after surgery was the strongest predictor of 30-d mortality and explained 41.8% of the deaths in population attributable risk analysis (Figure 5). A peak TnT of 0.02 ng/mL was associated with a 4% risk of death at 30 d[28].

Preoperative clinical variables that predicted 30-d mortality risk and were retained in the model that included peak TnT values included: age > 65, recent history of high-risk CAD, peripheral arterial disease, history of stroke, chronic obstructive pulmonary disease (COPD), cancer, urgent/emergency surgery, and major general or neurosurgical procedures. Of note, major vascular surgery and diabetes were not predictive of 30-d mortality in the model that included TnT[28].

In a cohort of 377 patients included in the CARP trial in whom cardiac troponin I was measured and analyzed by a core lab after the vascular surgery the proportion of patients with a perioperative myocardial infarction was 26%. Independent predictors of an MI included: age > 70 (OR = 1.84; 95%CI: 1.14-2.98; P = 0.01), abdominal aortic surgery (OR = 1.82; 95%CI: 1.09-3.03; P = 0.02), diabetes (OR = 1.86; 95%CI: 1.11-3.11; P = 0.02), angina (OR = 1.67; 95%CI: 1.03-2.64; P = 0.04), and baseline ST-T wave abnormalities (OR = 1.62; 95%CI: 1.00-2.6; P = 0.05)[29].

Pathophysiology

Clinical, angiographic, and pathological studies have shed light into the mechanisms underlying postoperative ischemic events[30-33]. Most of these events are caused by a mismatch between O_2 supply and demand, usually with severe CAD in the background that is unmasked by

the stress of the surgery. Landesberg *et al*[30] showed that tac ST-segment depression related to rapid heart rates is common in the perioperative period and predictive of long-term mortality. The duration of ST-segment depression and peak catecholamine levels after surgery are associated with infarct size. Chronic total occlusions (CTOs) are common in patients with a perioperative ischemic event or cardiac death (81%) relative to only 29% in patients without ischemic complications after surgery[31]. Two pathological studies reported conflicting data on the incidence of plaque rupture after fatal postoperative MI[32-33]. Dawood *et al*[32] described evidence of plaque rupture in only 7% of patients (42 autopsies). Conversely, a higher incidence of plaque rupture (46%) was described by Cohen *et al*[33]. Differences in timing of the autopsy relative to the time of the MI may account for some of the discrepancies in the data.

Management of perioperative myocardial infarction

Data from randomized clinical trials are lacking to guide therapy in the postoperative period. Small studies have shown that interventions aimed at improving oxygen delivery and minimizing myocardial oxygen consumption are beneficial in this setting[34]. The main goal of therapy is to preserve coronary perfusion pressure during diastole. This is best achieved with judicious utilization of beta-blockers, analgesia, and fluid administration with the intention to avoid tachycardia and hypotension. In the POISE trial for every 10-beats/min increase in heart rate there was a 31% relative increase in the odds of perioperative MI[27]. Current guidelines recommend aggressive blood pressure control in patients with PAD, in particular in patients with diabetes and/or chronic kidney disease (goal < 130/80 mmHg)[35]. In the HOPE (Heart Outcomes Prevention Evaluation) trial ramipril 10 mg was associated with a 22% reduction in cardiovascular events and is currently recommended for high-risk patients, including those with PAD[36].

Statins contribute to plaque stabilization by decreasing circulating levels of inflammatory cytokines and reactive oxygen species while increasing expression of nitric oxide synthase[37]. Additionally, evidence from randomized clinical trials and observational studies support its use in clinical practice. In the DECREASE-Ⅲ study a 53% reduction in CV death and myocardial infarction was seen with high-dose fluvastatin in patients undergoing vascular surgery[38]. In another trial of 100 patients randomly assigned to 20 mg of atorvastatin or placebo prior to vascular surgery, the use of statins was associated with a significant reduction in cardiac events, from 26% to 8% at 6 mo[39]. An observational study of 164 veterans undergoing vascular surgery at our medical center demonstrated that utilization of statin drugs was associated with a reduction in long-term mortality[5]. Guidelines recommend the use of statins in patients with peripheral arterial disease to reduce cardiovascular events[2].

Owing to concerns for bleeding after non-cardiac surgery, the use of medical therapies and interventional strategies commonly used to treat spontaneous MIs such as antiplatelet agents, anticoagulants and invasive coronary angiography are rarely used in this setting and have not been extensively studied in clinical trials. The management of myocardial infarction After NoncArdiac surgery (MANAGE) trial (NCT01661101) will be the first study to randomize patients (n = 3200) with a PMI after noncardiac surgery to dabigatran or placebo. The primary end point is the occurrence of a major vascular complication (vascular mortality, nonfatal MI, nonfatal stroke, and pulmonary embolism). The trial plans to complete enrollment in November 2015.

FUTURE DIRECTIONS

Another strategy for prevention of myocardial ischemia during surgery is ischemic preconditioning, which describes the protection afforded by application of nonlethal episodes of myocardial ischemia prior to the index ischemic event[40,41]. The Cardiac Remote Ischemic Preconditioning Prior to Elective Vascular Surgery (CRIPES, NCT: 01558596) was designed to determine the feasibility and safety of using remote ischemic preconditioning (RIPC) prior to vascular surgery, and to obtain preliminary estimates of its effects on detectable postsurgical increases in cardiac troponin I [42]. A similar strategy of RIPC has been evaluated prior to coronary angioplasty[43] and coronary artery bypass surgery[44] with positive initial results.

CONCLUSION

Patients with PAD in need of elective vascular surgery have a high prevalence of coronary atherosclerosis and are at increased risk of perioperative myocardial infarction. Coronary revascularization prior to the vascular operation is not an effective intervention to mitigate this risk. A strategy of widespread use of cardiac troponins in the perioperative period is recommended to detect perioperative ischemic events associated with a long-term mortality risk. The selective use of medical interventions, cardiac imaging and coronary angiography in this population deserves further study.

REFERENCES

1 **Hirsch AT**, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WR, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor LM, White CJ, White J, White RA, Antman EM, Smith SC, Adams CD, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guide-

lines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *J Am Coll Cardiol* 2006; **47**: 1239-1312 [PMID: 16545667 DOI: 10.1016/j.jacc.2005.10.009]

2 **Norgren L**, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007; **45** Suppl S: S5-S67 [PMID: 17223489]

3 **Bhatt DL**, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, Goto S, Liau CS, Richard AJ, Röther J, Wilson PW. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006; **295**: 180-189 [PMID: 16403930 DOI: 10.1001/jama.295.2.180]

4 **Criqui MH**, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, Browner D. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992; **326**: 381-386 [PMID: 1729621 DOI: 10.1056/NEJM199202063260605]

5 **Marston N**, Brenes J, Garcia S, Kuskowski M, Adabag S, Santilli S, McFalls EO. Peak postoperative troponin levels outperform preoperative cardiac risk indices as predictors of long-term mortality after vascular surgery Troponins and postoperative outcomes. *J Crit Care* 2012; **27**: 66-72 [PMID: 21798697 DOI: 10.1016/j.jcrc.2011.06.004]

6 **McFalls EO**, Ward HB, Moritz TE, Littooy F, Santilli S, Rapp J, Larsen G, Reda DJ. Clinical factors associated with long-term mortality following vascular surgery: outcomes from the Coronary Artery Revascularization Prophylaxis (CARP) Trial. *J Vasc Surg* 2007; **46**: 694-700 [PMID: 17903649 DOI: 10.1016/j.jvs.2007.05.060]

7 **Hiatt WR**, Hoag S, Hamman RF. Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. *Circulation* 1995; **91**: 1472-1479 [PMID: 7867189 DOI: 10.1161/01.CIR.91.5.1472]

8 **Hirsch AT**, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 2001; **286**: 1317-1324 [PMID: 11560536 DOI: 10.1001/jama.286.11.1317]

9 **Fowkes FG**, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1991; **20**: 384-392 [PMID: 1917239 DOI: 10.1093/ije/20.2.384]

10 **Criqui MH**, Vargas V, Denenberg JO, Ho E, Allison M, Langer RD, Gamst A, Bundens WP, Fronek A. Ethnicity and peripheral arterial disease: the San Diego Population Study. *Circulation* 2005; **112**: 2703-2707 [PMID: 16246968 DOI: 10.1161/CIRCULATIONAHA.105.546507]

11 **Selvin E**, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation* 2004; **110**: 738-743 [PMID: 15262830 DOI: 10.1161/01.CIR.0000137913.26087.F0]

12 **Selvin E**, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004; **141**: 421-431 [PMID: 15381515 DOI: 10.7326/0003-4819-141-6-200409210-00007]

13 **Ridker PM**, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA* 2001; **285**: 2481-2485 [PMID: 11368701 DOI: 10.1001/jama.285.19.2481]

14 **Muntner P**, Wildman RP, Reynolds K, Desalvo KB, Chen J, Fonseca V. Relationship between HbA1c level and peripheral arterial disease. *Diabetes Care* 2005; **28**: 1981-1987 [PMID: 16043742 DOI: 10.2337/diacare.28.8.1981]

15 **Hertzer NR**, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WF, Graor RA, Dewolfe VG, Maljovec LC. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg* 1984; **199**: 223-233 [PMID: 6696538 DOI: 10.1097/00000658-198402000-00016]

16 **Mehler PS**, Coll JR, Estacio R, Esler A, Schrier RW, Hiatt WR. Intensive blood pressure control reduces the risk of cardiovascular events in patients with peripheral arterial disease and type 2 diabetes. *Circulation* 2003; **107**: 753-756 [PMID: 12578880 DOI: 10.1161/01.CIR.0000049640.46039.52]

17 **Fleisher LA**, Beckman JA, Brown KA, Calkins H, Chaikof EL, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF, Smith SC, Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol* 2007; **50**: 1707-1732 [PMID: 17950159 DOI: 10.1016/j.jacc.2007.09.003]

18 **McFalls EO**, Ward HB, Moritz TE, Apple FS, Goldman S, Pierpont G, Larsen GC, Hattler B, Shunk K, Littooy F, Santilli S, Rapp J, Thottapurathu L, Krupski W, Reda DJ, Henderson WG. Predictors and outcomes of a perioperative myocardial infarction following elective vascular surgery in patients with documented coronary artery disease: results of the CARP trial. *Eur Heart J* 2008; **29**: 394-401 [PMID: 18245121 DOI: 10.1093/eurheartj/ehm620]

19 **Eagle KA**, Brundage BH, Chaitman BR, Ewy GA, Fleisher LA, Hertzer NR, Leppo JA, Ryan T, Schlant RC, Spencer WH, Spittell JA, Twiss RD. Guidelines for perioperative cardiovascular evaluation for noncardiac surgery: an abridged version of the report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Mayo Clin Proc* 1997; **72**: 524-531 [PMID: 9179136 DOI: 10.4065/72.6.524]

20 **Garcia S**, Moritz TE, Ward HB, Pierpont G, Goldman S, Larsen GC, Littooy F, Krupski W, Thottapurathu L, Reda DJ, McFalls EO. Usefulness of revascularization of patients with multivessel coronary artery disease before elective vascular surgery for abdominal aortic and peripheral occlusive disease. *Am J Cardiol* 2008; **102**: 809-813 [PMID: 18805102 DOI: 10.1016/j.amjcard.2008.05.022]

21 **Boersma E**, Poldermans D, Bax JJ, Steyerberg EW, Thomson IR, Banga JD, van De Ven LL, van Urk H, Roelandt JR. Predictors of cardiac events after major vascular surgery: Role of clinical characteristics, dobutamine echocardiography, and beta-blocker therapy. *JAMA* 2001; **285**: 1865-1873 [PMID: 11308400 DOI: 10.1001/jama.285.14.1865]

22 **Lee TH**, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L. Derivation and prospective validation of a simple index for predic-

tion of cardiac risk of major noncardiac surgery. *Circulation* 1999; **100**: 1043-1049 [PMID: 10477528 DOI: 10.1161/01.CIR.100.10.1043]

23 **Garcia S**, Moritz TE, Goldman S, Littooy F, Pierpont G, Larsen GC, Reda DJ, Ward HB, McFalls EO. Perioperative complications after vascular surgery are predicted by the revised cardiac risk index but are not reduced in high-risk subsets with preoperative revascularization. *Circ Cardiovasc Qual Outcomes* 2009; **2**: 73-77 [PMID: 20031818 DOI: 10.1161/CIRCOUTCOMES.108.827683]

24 **McFalls EO**, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, Pierpont G, Santilli S, Rapp J, Hattler B, Shunk K, Jaenicke C, Thottapurathu L, Ellis N, Reda DJ, Henderson WG. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med* 2004; **351**: 2795-2804 [PMID: 15625331 DOI: 10.1056/NEJMoa041905]

25 **Poldermans D**, Schouten O, Vidakovic R, Bax JJ, Thomson IR, Hoeks SE, Feringa HH, Dunkelgrün M, de Jaegere P, Maat A, van Sambeek MR, Kertai MD, Boersma E. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V Pilot Study. *J Am Coll Cardiol* 2007; **49**: 1763-1769 [PMID: 17466225 DOI: 10.1016/j.jacc.2006.11.052]

26 **Thygesen K**, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, Clemmensen PM, Dellborg M, Hod H, Porela P, Underwood R, Bax JJ, Beller GA, Bonow R, Van der Wall EE, Bassand JP, Wijns W, Ferguson TB, Steg PG, Uretsky BF, Williams DO, Armstrong PW, Antman EM, Fox KA, Hamm CW, Ohman EM, Simoons ML, Poole-Wilson PA, Gurfinkel EP, Lopez-Sendon JL, Pais P, Mendis S, Zhu JR, Wallentin LC, Fernández-Avilés F, Fox KM, Parkhomenko AN, Priori SG, Tendera M, Voipio-Pulkki LM, Vahanian A, Camm AJ, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Morais J, Brener S, Harrington R, Morrow D, Lim M, Martinez-Rios MA, Steinhubl S, Levine GN, Gibler WB, Goff D, Tubaro M, Dudek D, Al-Attar N. Universal definition of myocardial infarction. *Circulation* 2007; **116**: 2634-2653 [PMID: 17951284 DOI: 10.1161/CIRCULATIONAHA.107.187397]

27 **Devereaux PJ**, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Rao-Melacini P, Chrolavicius S, Yang H, Macdonald C, Avezum A, Lanthier L, Hu W, Yusuf S. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med* 2011; **154**: 523-528 [PMID: 21502650 DOI: 10.7326/0003-4819-154-8-201104190-00003]

28 **Devereaux PJ**, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, Wang CY, Garutti RI, Jacka MJ, Sigamani A, Srinathan S, Biccard BM, Chow CK, Abraham V, Tiboni M, Pettit S, Szczeklik W, Lurati Buse G, Botto F, Guyatt G, Heels-Ansdell D, Sessler DI, Thorlund K, Garg AX, Mrkobrada M, Thomas S, Rodseth RN, Pearse RM, Thabane L, McQueen MJ, VanHelder T, Bhandari M, Bosch J, Kurz A, Polanczyk C, Malaga G, Nagele P, Le Manach Y, Leuwer M, Yusuf S. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012; **307**: 2295-2304 [PMID: 22706835 DOI: 10.1001/jama.2012.5502]

29 **Devereaux PJ**, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008; **371**: 1839-1847 [PMID: 18479744]

30 **Landesberg G**, Mosseri M, Zahger D, Wolf Y, Perouansky M, Anner H, Drenger B, Hasin Y, Berlatzky Y, Weissman C. Myocardial infarction after vascular surgery: the role of prolonged stress-induced, ST depression-type ischemia. *J Am Coll Cardiol* 2001; **37**: 1839-1845 [PMID: 11401120 DOI: 10.1016/S0735-1097(01)01265-7]

31 **Ellis SG**, Hertzer NR, Young JR, Brener S. Angiographic correlates of cardiac death and myocardial infarction complicating major nonthoracic vascular surgery. *Am J Cardiol* 1996; **77**: 1126-1128 [PMID: 8644673 DOI: 10.1016/S0002-9149(96)00130-0]

32 **Dawood MM**, Gutpa DK, Southern J, Walia A, Atkinson JB, Eagle KA. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. *Int J Cardiol* 1996; **57**: 37-44 [PMID: 8960941 DOI: 10.1016/S0167-5273(96)02769-6]

33 **Cohen MC**, Aretz TH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. *Cardiovasc Pathol* 1999; **8**: 133-139 [PMID: 10722235 DOI: 10.1016/S1054-8807(98)00032-5]

34 **Martinez E**, Kim L, Rosenfeld B, Faraday N, Bass E, Perler B, Williams GN, Dorman T, Pronovost P. Early detection and real-time intervention of postoperative myocardial ischemia: the STOPMI (Study for the Treatment of Perioperative Myocardial Ischemia) Study. Abstract presented at: Association of University Anesthesiologists; May 16-18, 2008; Durham NC

35 **European Society of Hypertension-European Society of Cardiology Guidelines Committee.** 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; **21**: 1011-1053 [PMID: 12777938 DOI: 10.1097/00004872-200306000-00001]

36 **Yusuf S**, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; **342**: 145-153 [PMID: 10639539 DOI: 10.1056/NEJM200001203420301]

37 **Davignon J**. Beneficial cardiovascular pleiotropic effects of statins. *Circulation* 2004; **109**: III39-III43 [PMID: 15198965]

38 **Schouten O**, Boersma E, Hoeks SE, Benner R, van Urk H, van Sambeek MR, Verhagen HJ, Khan NA, Dunkelgrun M, Bax JJ, Poldermans D. Fluvastatin and perioperative events in patients undergoing vascular surgery. *N Engl J Med* 2009; **361**: 980-989 [PMID: 19726772 DOI: 10.1056/NEJMoa0808207]

39 **Durazzo AE**, Machado FS, Ikeoka DT, De Bernoche C, Monachini MC, Puech-Leão P, Caramelli B. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. *J Vasc Surg* 2004; **39**: 967-975; discussion 975-976 [PMID: 15111846]

40 **Przyklenk K**, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation* 1993; **87**: 893-899 [PMID: 7680290 DOI: 10.1161/01.CIR.87.3.893]

41 **Gho BC**, Schoemaker RG, van den Doel MA, Duncker DJ, Verdouw PD. Myocardial protection by brief ischemia in noncardiac tissue. *Circulation* 1996; **94**: 2193-2200 [PMID: 8901671 DOI: 10.1161/01.CIR.94.9.2193]

42 **Garcia S**, Rector TS, Zakharova MY, Magras A, Sandoval Y. Cardiac Remote Ischemic Preconditioning Prior to Elective Major Vascular Surgery (CRIPES): Study Design and Rationale. *J Clin Trials* 2013; **S5**: 002

43 **Hoole SP**, Heck PM, Sharples L, Khan SN, Duehmke R, Densem CG, Clarke SC, Shapiro LM, Schofield PM, O'Sullivan M, Dutka DP. Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent) Study: a prospective, randomized control trial. *Circulation* 2009; **119**: 820-827 [PMID: 19188504 DOI: 10.1161/CIRCULATIONAHA.108.809723]

44 **Hausenloy DJ**, Mwamure PK, Venugopal V, Harris J, Bar-

nard M, Grundy E, Ashley E, Vichare S, Di Salvo C, Kolvekar S, Hayward M, Keogh B, MacAllister RJ, Yellon DM. Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. *Lancet* 2007; **370**: 575-579 [PMID: 17707752 DOI: 10.1016/S0140-6736(07)61296-3]

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MINIREVIEWS

Quantitative assessment of myocardial blush grade in patients with coronary artery disease and in cardiac transplant recipients

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Abstract

Quantitative assessment of myocardial perfusion by myocardial blush grade (MBG) is an angiographic computer-assisted method to assess myocardial tissue-level reperfusion in patients with acute coronary syndromes and microvascular integrity in heart transplant recipients with suspected cardiac allograft vasculopathy. This review describes the ability of quantitative MBG as a simple, fast and cost effective modality for the prompt diagnosis of impaired microvascular integrity during routine cardiac catheterization. Herein, we summarize the existing evidence, its usefulness in the clinical routine, and compare this method to other techniques which can be used for the assessment of myocardial perfusion.

Key words: Quantitative myocardial blush grade; Prognosis; Heart transplantation; Coronary artery disease

Core tip: In this article, we highlight the ability of quantitative myocardial blush grade for the assessment of microvascular integrity in patients with acute coronary syndromes (ACS) and heart transplant (HT) recipients with cardiac allograft vasculopathy (CAV). Using an, in the meanwhile well-established, computational algorithm, a prompt diagnosis can be made in the catheterization lab, which can identify patients with ACS and increased risk for myocardial remodelling and congestive heart failure in the long-term. In addition, this computational algorithm can identify HT recipients with increased risk for CAV and adverse cardiovascular outcomes.

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INTRODUCTION

Impaired myocardial perfusion by either epicardial coronary artery disease (CAD) or small vessel disease is a common challenge in cardiology worldwide. Both CAD and cardiac allograft vasculopathy (CAV) in heart transplant (HT) recipients significantly influence mortality in such patient cohorts. Considering the vast amount of health care costs for post-rehabilitation support after myocardial infarction[1] and HT[2], preventive medical care should primarily focus on the early detection of cardiac pathology and risk stratification of such patients. Quantitative assessment of epicardial and microvascular integrity can aid tailoring pharmacologic therapy of patients identified at high risk for future events, which may ultimately improve clinical outcomes. We therefore

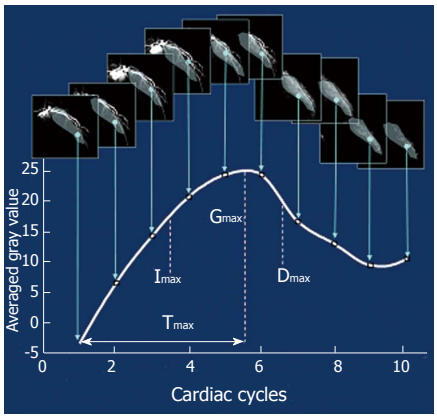

Figure 1 Digital subtraction images of a myocardial region of interest illustrate the temporal distribution of grey level rise and venous washout of contrast agent during a coronary catheter image sequence.

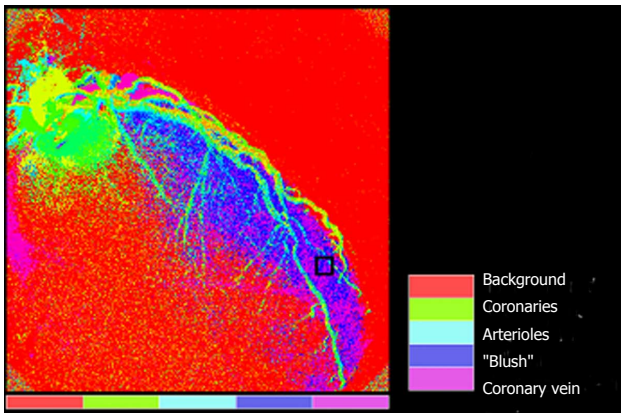

Figure 2 The parametric image shows coloured phases of cardiac perfusion in a combined presentation. The arterial phase is followed by early and late myocardial infusion until the contrast agent arrives in the venous system.

previously developed a computer-assisted program for the analysis of microvascular integrity in patients undergoing cardiac catheterization either during acute myocardial infarction for reperfusion of the infarcted tissue[3,4] or during surveillance coronary angiography in cardiac transplant recipients[5,6]. Furthermore, such measures of perfusion can also be applied in patients undergoing fractional flow reserve analysis (FFR) for the assessment of the functional significance of coronary lesions of moderate severity[7].

METHODOLOGICAL APPROACH WITH OUR MYOCARDIAL BLUSH GRADE ALGORITHM

We previously introduced a computer-based algorithm for the quantification of MBG in patients with first time acute myocardial infarction[3]. This method aimed at the objective assessment of reperfused myocardial tissue and the estimation of infarct size and functional recovery of the myocardium at risk. This method is based on conventional cine angiographic films. In order to achieve maximal quality of the digital subtraction angiography images, the sequence is synchronized with the baseline electrocardiogram (ECG). The spatio-temporal spread of blood, or the so-called MBG, through epicardial vessels and then to the microvasculature and the myocardium, indicated by dye injection, represents a characteristic pattern for the myocardial perfusion. This dynamic temporal pattern is characterized by typical features as the maximal value of MBG intensity and the increase and decrease velocity which correspond to the different phases of flooding in and washout. Regions of interest are positioned in the distal part of each coronary artery in order to measure the plateau of mean grey level pixel intensity (G_{max} which is measured on a standard gray scale of 0 to 255) as well as the time to maximal intensity rise (T_{max} measured in seconds) (Figure 1). The ratio G_{max}/T_{max} is subsequently computed in each coronary vessel. Furthermore, based on the distribution of MBG over time in the epicardial vessels, arterioles and capillaries, parametric quantification can be applied as shown in Figure 2. To allow for quantification of MBG, frames should be recorded long enough in order to allow filling of the coronary veins, and images should be acquired during breath hold in order to avoid artefacts due to movement of the diaphragm. On the basis of 100 different temporal MBG profiles, an algorithm is established which classifies the acquired blush patterns into 4 different grades[8]. An example of a patient with post-interventional high G_{max}/T_{max} and full functional recovery after first acute non-ST-elevation myocardial infarction (NSTEMI) of the left anterior descending is illustrated in Figure 3.

CURRENT EVIDENCE

In a swine model by Boyle *et al*[9], the quantitative myocardial blush grades could be assessed automatically and were closely related to established angiographic parameters of myocardial perfusion.

Our first clinical findings showed that quantitative MBG is applicable for the evaluation of microvascular tissue perfusion in patients with ST-elevation myocardial infarction (STEMI), being highly predictive for functional recovery of the myocardium at risk as assessed by echocardiography[3]. Hereby, multivariate analysis showed that MBG and Troponin T elevation were independent predictors of residual ejection fraction > 50%. Quantitative MBG by G_{max}/T_{max} showed the highest odds ratio and was therefore considered as the most robust variable for the prediction of the primary endpoint.

Furthermore, quantitative MBG was related to infarct transmurality and residual ejection fraction by cardiac magnetic resonance (CMR) in both STEMI and NSTEMI patients. This objective information can be acquired during routine cardiac catheterization, immediately after interventional treatment of the infarct related lesion, and can be used for the immediate risk stratification of pa-

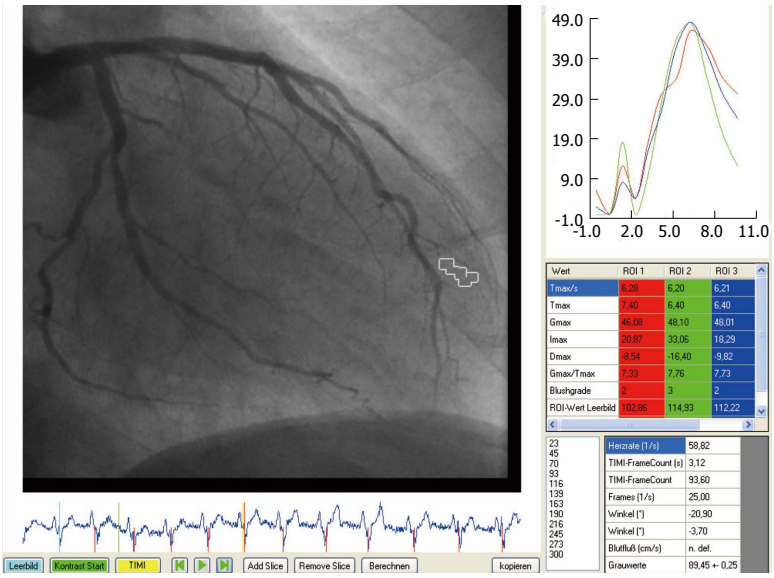

Figure 3 Computer-assisted program illustrating post-interventional high myocardial blush grade after successful left anterior descending revascularization in a non-ST-elevation myocardial infarction patient.

tients with ACS[4]. Hereby, G_{max}/T_{max} was at least as accurate as infarct transmurality for the prediction of residual ejection fraction. Both clearly surpassed the accuracy of visual MBG.

Besides patients with CAD, we also investigated our computer-assisted program on the growing group of HT recipients. For this purpose, transplanted patients who underwent surveillance cardiac catheterization were subsequently analyzed by CMR, to assess myocardial relaxation and perfusion reserve during adenosine stress. Close correlations were observed between G_{max}/T_{max} with perfusion reserve and with mean diastolic strain rates. Visual and quantitative MBG had significantly higher accuracy than stenosis severity on coronary angiograms for the detection of diminished myocardial perfusion. Furthermore, quantitative MBG provided more robust prediction of survival compared to visually estimated blush and to coronary lumen narrowing assessment. Hereby, our findings indicate that quantitative MBG can be performed on coronary angiograms of HT recipients just as well, and may aid the detection of CAV in such individuals with impaired perfusion but with angiographically "normal" coronaries[5].

Impaired myocardial perfusion in transplanted hearts is closely associated with outcomes. In this regard, G_{max}/T_{max} is a simple to acquire and useful surrogate parameter of myocardial perfusion in HT recipients, which can predict cardiac outcomes. G_{max}/T_{max} differentiated between patients with high rate of cardiac events compared to those with higher quantitative MBG, who exhibited much better outcomes during a mean follow-up duration of 2.7 years. In addition, close correlations were observed between MBG and perfusion reserve measured by stress magnetic resonance imaging. Quantification of MBG may therefore be useful for the risk stratification of such patients[6].

Finally, preliminary clinical data indicate that MBG during adenosine infusion can be used to estimate angiographic perfusion reserve and is associated with FFR measures and with the myocardial perfusion reserve, assessed by CMR[7].

COMPARISON TO OTHER INVASIVE AND NON-INVASIVE APPROACHES FOR THE ASSESSMENT OF MYOCARDIAL PERFUSION

So far, different non-invasive and invasive imaging methods have been used for analysis and risk stratification of CAD and CAV patients, as, *e.g.*, myocardial contrast echocardiography (MCE), CMR imaging and angiographic parameters including Thrombolysis in Myocardial Infarction (TIMI) flow grade, TIMI frame count, TIMI myocardial perfusion grade and MBG.

NON-INVASIVE IMAGING COMPARED TO ANGIOGRAPHIC PERFUSION MEASURES

Myocardial contrast echocardiography

Myocardial perfusion and function can be assessed during MCE. This technique provides real-time visualisation of ischemic myocardium in regions of reduced blood flow. Although MCE is a practicable and non-invasive technique, it is limited by observer dependency and technical challenges pending on patients' echogenic windows[10].

CMR imaging

This is the current reference method for the assessment of cardiac anatomy, perfusion and function, viability and if required metabolism, all within a single examination, non-invasively and without ionizing radiation for the patients. Therefore, our studies mostly compare MBG to either CMR derived ejection fraction, remodelling, infarct size and transmurality or perfusion reserve index[4-6,11].

INVASIVE ASSESSMENT OF CARDIAC PERFUSION IN PATIENTS WITH ACS: FROM THE EPICARDIUM TO THE MYOCARDIUM

TIMI flow grades and TIMI frame count

Reperfusion after myocardial infarction or ACS determines clinical outcome[12]. However, clinical and experimental data indicate that stenosis reduction during percutaneous coronary intervention (PCI) is not always associated with adequate myocardial tissue reperfusion, so that patients with TIMI 3 flow grade after PCI may still exhibit impaired microvascular integrity[3,13,14]. Thus, epicardial restoration of coronary blood flow is only prerequisite, but not a guarantee for myocardial recovery[15], the latter being a major predictor of mortality and morbidity in CAD patients.

TIMI myocardial perfusion grade and visual myocardial blush grade

Visually assessed MBG represents a reasonable alternative to TIMI flow grade and TIMI frame count, since it can distinguish between high and low risk constellations. The TIMI myocardial perfusion grade demonstrates a similar method that also considers the dynamic contrast agent washout. Unfortunately, the accuracy of both techniques is limited due to their categorical nature, which is associated with high observer variability, especially with non-expert readers.

Quantitative myocardial blush grade

The "Quantitative Blush Evaluator" (QuBE) from the TAPAS trial, an open-source computer program for quantification of myocardial perfusion, was used on angiograms in patients with acute STEMI[16]. The QuBE score correlated significantly with visual MBG as well as infarct size and microvascular dysfunction assessed by CMR[17]. Nevertheless, it has exclusively been used for STEMI patients so far, and further evaluation in other patient cohorts is warranted.

CONCLUSION

Quantitative assessment of MBG can be performed on coronary angiograms of either CAD or CAV patients. In this regard, G_{max}/T_{max} is a simple and useful surrogate parameter of microvascular integrity, which can (1) estimate clinical outcome in HT recipients with impaired perfusion reserve but without angiographically evident atherosclerosis and (2) infarct transmurality and functional recovery in both STEMI and NSTEMI. These results can be used for tailoring pharmacological treatment and aid early risk stratification in both CAD and CAV patients.

REFERENCES

1 **Stargardt T**, Schreyögg J, Kondofersky I. Measuring the relationship between costs and outcomes: the example of acute myocardial infarction in German hospitals. *Health Econ* 2014; **23**: 653-669 [PMID: 23696223 DOI: 10.1002/hec.2941]

2 **Digiorgi PL**, Reel MS, Thornton B, Burton E, Naka Y, Oz MC. Heart transplant and left ventricular assist device costs. *J Heart Lung Transplant* 2005; **24**: 200-204 [PMID: 15701438 DOI: 10.1016/j.healun.2003.11.397]

3 **Korosoglou G**, Haars A, Michael G, Erbacher M, Hardt S, Giannitsis E, Kurz K, Franz-Josef N, Dickhaus H, Katus HA, Kuecherer H. Quantitative evaluation of myocardial blush to assess tissue level reperfusion in patients with acute ST-elevation myocardial infarction: incremental prognostic value compared with visual assessment. *Am Heart J* 2007; **153**: 612-620 [PMID: 17383301 DOI: 10.1016/j.ahj.2006.12.019]

4 **Riedle N**, Dickhaus H, Erbacher M, Steen H, Andrassy M, Lossnitzer D, Hardt S, Rottbauer W, Zugck C, Giannitsis E, Katus HA, Korosoglou G. Early assessment of infarct size and prediction of functional recovery by quantitative myocardial blush grade in patients with acute coronary syndromes treated according to current guidelines. *Catheter Cardiovasc Interv* 2010; **76**: 502-510 [PMID: 20882653 DOI: 10.1002/ccd.22540]

5 **Korosoglou G**, Riedle N, Erbacher M, Dengler TJ, Zugck C, Rottbauer W, Hardt S, Bekeredjian R, Kristen A, Giannitsis E, Osman NF, Dickhaus H, Katus HA. Quantitative myocardial blush grade for the detection of cardiac allograft vasculopathy. *Am Heart J* 2010; **159**: 643-651.e2 [PMID: 20362724]

6 **Hofmann NP**, Voss A, Dickhaus H, Erbacher M, Doesch A, Ehlermann P, Gitsioudis G, Buss SJ, Giannitsis E, Katus HA, Korosoglou G. Long-term outcome after heart transplantation predicted by quantitative myocardial blush grade in coronary angiography. *Am J Transplant* 2013; **13**: 1491-1502 [PMID: 23617734 DOI: 10.1111/ajt.12223]

7 **Korosoglou G**, Hofmann NP, Erbacher M, Dickhaus H, Bekeredjian R, Neumann FJ, Katus HA, Hardt SE. Quantitative myocardial blush grade reserve during pharmacologic hyperemia is related to fractional flow reserve measures in patients with stable coronary artery disease. *Clin Res Cardiol* 2013; **102** (abstract)

8 **Dickhaus H**, Erbacher M, Kücherer H. Quantification of myocardial perfusion for CAD diagnosis. *Stud Health Technol Inform* 2007; **129**: 1339-1343 [PMID: 17911932]

9 **Boyle AJ**, Schuleri KH, Lienard J, Vaillant R, Chan MY, Zimmet JM, Mazhari R, Centola M, Feigenbaum G, Dib J, Kapur NK, Hare JM, Resar JR. Quantitative automated assessment of myocardial perfusion at cardiac catheterization. *Am J Cardiol* 2008; **102**: 980-987 [PMID: 18929697 DOI: 10.1016/j.amjcard.2008.05.064]

10 **Korosoglou G**, Hansen A, Hoffend J, Gavrilovic G, Wolf D, Zehelein J, Haberkorn U, Kuecherer H. Comparison of real-time myocardial contrast echocardiography for the assessment of myocardial viability with fluorodeoxyglucose-18 positron emission tomography and dobutamine stress echocardiography. *Am J Cardiol* 2004; **94**: 570-576 [PMID: 15342285 DOI: 10.1016/j.amjcard.2004.05.018]

11 **Hofmann NP**, Steuer C, Voss A, Erbel C, Celik S, Doesch A, Ehlermann P, Buss SJ, Giannitsis E, Katus HA, and Korosoglou G. Comprehensive Bio-Imaging using Myocardial Perfusion Reserve Index during Adenosine Cardiac Magnetic Resonance and the High-sensitive Troponin T for the Prognosis of Heart Transplant Recipients. *Am J Transplant* 2014 Oct 7; Epub ahead of print [DOI: 10.1111/ajt.12924]

12 **Cannon CP**. Importance of TIMI 3 flow. *Circulation* 2001; **104**: 624-626 [PMID: 11489764 DOI: 10.1161/01.CIR.104.6.624]

13 **Galiuto L**, DeMaria AN, del Balzo U, May-Newman K, Flaim SF, Wolf PL, Kirchengast M, Iliceto S. Ischemia-reperfusion injury at the microvascular level: treatment by endothelin A-selective antagonist and evaluation by myocardial contrast echocardiography. *Circulation* 2000; **102**: 3111-3116 [PMID: 11120703]

14 **Hansen A**, Kumar A, Wolf D, Frankenbergerova K, Filusch A, Gross ML, Mueller S, Katus H, Kuecherer H. Evaluation of cardioprotective effects of recombinant soluble P-selectin

glycoprotein ligand-immunoglobulin in myocardial ischemia-reperfusion injury by real-time myocardial contrast echocardiography. *J Am Coll Cardiol* 2004; **44**: 887-891 [PMID: 15312876 DOI: 10.1016/j.jacc.2004.05.052]

15 **Ito H**, Okamura A, Iwakura K, Masuyama T, Hori M, Takiuchi S, Negoro S, Nakatsuchi Y, Taniyama Y, Higashino Y, Fujii K, Minamino T. Myocardial perfusion patterns related to thrombolysis in myocardial infarction perfusion grades after coronary angioplasty in patients with acute anterior wall myocardial infarction. *Circulation* 1996; **93**: 1993-1999 [PMID: 8640973 DOI: 10.1161/01.CIR.93.11.1993]

16 **Vogelzang M**, Vlaar PJ, Svilaas T, Amo D, Nijsten MW, Zijlstra F. Computer-assisted myocardial blush quantification after percutaneous coronary angioplasty for acute myocardial infarction: a substudy from the TAPAS trial. *Eur Heart J* 2009; **30**: 594-599 [PMID: 19168868 DOI: 10.1093/eurheartj/ehn542]

17 **Porto I**, Hamilton-Craig C, De Maria GL, Vergallo R, Cautilli G, Galiuto L, Burzotta F, Leone AM, Niccoli G, Natale L, Bonomo L, Crea F. Quantitative Blush Evaluator accurately quantifies microvascular dysfunction in patients with ST-elevation myocardial infarction: comparison with cardiovascular magnetic resonance. *Am Heart J* 2011; **162**: 372-381.e2 [PMID: 21835300]

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OBSERVATIONAL STUDY

Neuroticism personality trait is associated with Quality of Life in patients with Chronic Heart Failure

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Abstract

AIM: To evaluate Quality of life (QoL) in chronic heart failure (CHF) in relation to Neuroticism personality trait and CHF severity.

METHODS: Thirty six consecutive, outpatients with Chronic Heart Failure (6 females and 30 males, mean age: 54 ± 12 years), with a left ventricular ejection fraction ⩽ 45% at optimal medical treatment at the time of inclusion, were asked to answer the Kansas City Cardiomyopathy Questionnaire (KCCQ) for Quality of Life assessment and the NEO Five-Factor Personality Inventory for personality assessment. All patients underwent a symptom limited cardiopulmonary exercise testing on a cycle-ergometer, in order to access CHF severity. A multivariate linear regression analysis using simultaneous entry of predictors was performed to examine which of the CHF variables and of the personality variables were correlated independently to QoL scores in the two summary scales of the KCCQ, namely the Overall Summary Scale and the Clinical Summary Scale.

RESULTS: The Neuroticism personality trait score had a significant inverse correlation with the Clinical Summary Score and Overall Summary Score of the KCCQ (r = -0.621, P < 0.05 and r = -0.543, P < 0.001, respectively). KCCQ summary scales did not show significant correlations with the personality traits of Extraversion, Openness, Conscientiousness and Agreeableness. Multivariate linear regression analysis using simultaneous entry of predictors was also conducted to determine the best linear combination of statistically significant univariate predictors such as Neuroticism, VE/VCO_2 slope and VO_2 peak, for predicting KCCQ Clinical Summary Score. The results show Neuroticism (β = -0.37, P < 0.05), VE/VCO_2 slope (β = -0.31, P < 0.05) and VO_2 peak (β = 0.37, P < 0.05) to be independent predictors of QoL. In multivariate regression analysis Neuroticism (b = -0.37, P < 0.05), the slope of ventilatory equivalent for carbon dioxide output during exercise, (VE/VCO_2 slope) (b = -0.31, P < 0.05) and peak oxygen uptake (VO_2 peak), (b = 0.37, P < 0.05) were independent predictors of QoL (adjusted R2 = 0.64; F = 18.89, P < 0.001).

CONCLUSION: Neuroticism is independently associated with QoL in CHF. QoL in CHF is not only determined by disease severity but also by the Neuroticism personality trait.

Key words: Chronic heart failure; Five-Factor Personality Inventory; Kansas City Cardiomyopathy Questionnaire; Quality of Life

Core tip: Of the patients with chronic heart failure (CHF), those who are experiencing low Quality of Life (QoL) show higher morbidity, hospitalization rates and mortality. There is a link between low QoL, low adherence to pharmaceutical and non-pharmaceutical treatment as well as exercise training rehabilitation, and high anxiety and depression levels. The personality of the patient has been also found to play a role in affecting QoL and therefore prognosis. Taking into account that the personality trait of Neuroticism, has been found to affect QoL in chronically ill individuals, this study explores its possible role in predicting QoL in CHF population in relation to disease severity.

Samartzis L, Dimopoulos S, Manetos C, Agapitou V, Tasoulis A, Tseliou E, Pozios I, Kaldara E, Terrovitis J, Nanas S. Neuroticism personality trait is associated with Quality of life in patients with Chronic Heart Failure. *World J Cardiol* 2014; 6(10): 1113-1121 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i10/1113.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i10.1113

INTRODUCTION

The quantification of patients' Quality of life (QoL) is becoming a useful endpoint in the study of chronic heart failure (CHF), not only as a marker of health care quality, but also as a tool for monitoring patients over time[1,2]. The evaluation of patients' QoL as well as of factors that are pertinent to it are considered as important for the prognosis in CHF, as QoL has been shown to identify patients with more severe syndrome[3-6] and at greater risk for hospitalization or death[7-9]. QoL is closely related to exercise intolerance, and exercise capacity improvement by exercise training in CHF improved QoL and reduced mortality and cardiac events[10,11]. Furthermore, QoL in CHF has been associated with psychological factors such as depression, anxiety and personality. Depressed as well as anxious CHF patients were found to have poor QoL[12], with depression being a strong predictor of QoL even after adjustment with disease severity[13].

However the role of personality in the QoL of CHF has been largely overlooked, as most studies have focused on the role of depression and anxiety as the main psychological determinants. The personality trait that has been most widely studied in CHF population is type-D, which was found to be independently associated with impaired QoL in CHF[14], anxiety and depression[15], and increased mortality[16]. Another well documented personality trait, Neuroticism, has been demonstrated to affect QoL in chronically ill individuals as well as to be correlated with increased levels of anxiety and depression[17-21]. However, there have been only a few reports indicating a possible role of Neuroticism to predict QoL[22] and prognosis in CHF patients[23,24].

Therefore, the personality trait of Neuroticism constitutes an interesting but yet not well explored factor in the relationship between personality and QoL in patients with CHF. The aim of this study is to investigate the role of Neuroticism in QoL in CHF in relation to CHF severity. We hypothesized that Neuroticism affects QoL in patients with stable CHF, independently of the disease severity.

MATERIALS AND METHODS

Study population

The study population consisted of 36 consecutive stable CHF outpatients (6 women and 30 men), with a left ventricular ejection fraction (LVEF) $\leqslant$ 45% at optimal medical treatment at the time of inclusion, who were referred to our laboratory from the Heart Failure Clinic of the Medical School of the University of Athens, during the years 2008-2009, in order to perform a symptom-limited cardiopulmonary exercise test (CPET), as a part of heart failure evaluation.

Patients were excluded from the study if there was any contraindication for a CPET according to the American Thoracic Society/American College of Chest Physicians Statement on CPET[25] and if there was a history of moderate to severe chronic obstructive pulmonary disease or cancer disease or other systemic inflammatory chronic illness. Patients enrolled in the study had no history of a known psychiatric disorder or psychiatric/psychological treatment. Patients who were on psychotropic medication or who received any form of psychotherapy treatment were excluded of the study. None of the patients had a history of psychiatric hospitalization in the past. Baseline demographic data and clinical characteristics of all patients are presented in Table 1. Informed consent was obtained from all patients, as approved by the Human Study Committee of our Institution.

Design of the study

All patients underwent an incremental symptom-limited CPET, and the day of exercise testing they were administered a questionnaire consisted of a self-rating psychometric tests battery to complete in their home. Data collection was obtained from patients' questionnaire responses and analyzed by an expert clinician to psychiatric disorders.

Cardiopulmonary exercise testing

All patients performed a symptom-limited CPET on an electro-magnetically braked cycle ergometer (Ergoline 800; Sensor Medics, Anaheim, California, United States). The work rate increment was estimated by using Hansen *et al*[26]'s equation in order to attain test duration of 8-12 min. Measurements were recorded for 2 min at rest, for 3 min of unloaded pedaling before exercise, during exercise and for recovering period. Oxygen saturation was measured continuously by pulse oximetry, heart rate and

Table 1 Demographic data and clinical characteristics in all chronic heart failure patients (n = 36)

Age, yr	54 ± 12
Gender, (M/F)	30/6
BMI, kg/m²	28.3 ± 4.9
NYHA class Ⅰ/Ⅱ/Ⅲ	(10/20/6)
LVEF	33% ± 10%
CHF Etiology	
Non-ischemic	18 (50%)
Ischemic	18 (50%)
Medical treatment	
ACE inhibitors	88%
β-blockers	85%
Diuretics	85%
Spironolactone	52%
Amiodarone	35%
Digitalis	11%
Nitrates	20%
Antiplatelets	44%
Anticoagulants	23%

Continuous variables values are presented as means ± SD. BMI: Body mass index; NYHA: New York Heart Association; LVEF: Left ventricle ejection fraction; ACE: Angiotensin-converting enzyme; CHF: Chronic heart failure.

rhythm were monitored by a MAX1, 12-lead ECG System (Marquette), arterial pressure was measured every 2 min with a mercury sphygmomanometer. Oxygen uptake (VO_2), carbon dioxide output (VCO_2) and ventilation (VE) were measured breath-by-breath. All patients were verbally encouraged to exercise to exhaustion, as defined by intolerable leg fatigue or dyspnea.

Cardiopulmonary measurements

The gas exchange measurements served to calculate VO_2 at peak exercise (VO_2 peak, mL/kg per minute), anaerobic threshold (AT, mL/kg per minute), and VE/VCO_2 slope between exercise onset and AT. The peak values for VO_2, VCO_2, and VE were calculated as the average of measurements made during the 20-s period before exercise was terminated. AT was determined using the V-slope technique[27], and the result was confirmed graphically from a plot of ventilatory equivalent for oxygen (VE/VO_2) and carbon dioxide (VE/VCO_2) against time. The ventilatory response to exercise was calculated as the slope by linear regression of VE *vs* VCO_2 from the beginning of exercise to AT, where the relationship is linear, calculated as in previous study[28].

Personality measurements

Personality traits were assessed with the widely used NEO-Five Factor Inventory (NEO-FFI, Greek version), which is a 60-item self-report questionnaire based on the five factor model of personality. The NEO-FFI[29] is a shortened version of the NEO-PI-R (Costa and McCrae 1992). Patients rate each item on a five-point Likert-like scale. Each item-score ranges on a scale from strongly disagree (0) to strongly agree (4). The instrument is designed to measure each of the well-established five factors of personality: Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness. The Five Factor Model of personality[29,30] is a personality concept that includes behavioral, emotional as well as cognitive personality patterns.

Neuroticism reflects distress-proneness, negative emotions and chronic emotional maladjustment, stress reactivity and instability. Extraversion refers to positive mood, sociability, need for stimulation, vigor, quantity and intensity of preferred interpersonal interactions as well as activity level and capacity for enjoyment. Openness refers to openness to experience as well as active seeking and appreciation of experiences for their own sake, and also involves entailing interest in novel ideas, aesthetic and intellectual sensibility. Agreeableness is an interpersonal factor reflecting altruism, trust, amicability, and also refers to the kind of interactions a person prefers along a continuum from compassion to antagonism. Conscientiousness involves organization, persistence, control, reliability, diligence, and also assesses the degree of achievement-orientated behavior and motivation in goal-directed behavior.

Quality of life measurements

As a measurement of QoL in CHF patients the Greek version of the Kansas City Cardiomyopathy Questionnaire was used. The KCCQ is a 23-item, disease specific questionnaire that quantifies the domains of health status that are symptoms (frequency, severity, change over time), physical limitations, a heart failure specific assessment of their quality of life and self-efficacy domain that is a measure of patients' knowledge of how to best manage their disease. The psychometric properties of the KCCQ have been well documented[3].

The use of the KCCQ in outpatient clinical practice can both quantify patients' health status and provide insight into their prognosis[8]. QoL identifies CHF patients at risk for hospitalization or death, as a low KCCQ score is an independent predictor of poor prognosis in patients with CHF[7]. Studies have been shown that cross-sectional variations[7,8] as well as changes in serial health status assessments[9] in KCCQ scores are prognostic indicators of subsequent mortality as well as hospitalizations due to CHF.

Statistical analysis

All continuous variables are expressed as mean ± SD. A P value of 0.05 or lower was considered as statistically significant. All variables were tested for normal distribution. Pearson's coefficient was used to assess correlations between the study variables. A multivariate linear regression analysis using simultaneous entry of predictors was performed to examine which variables were correlated independently to QoL scores in the two summary scales of the KCCQ that are the overall summary scale (OSS) and the clinical summary scale (CSS). The Statistical Package for the Social Sciences (SPSS Statistics 17.0) software was used to analyze the data.

Table 2 Psychometric and cardiopulmonary exercise testing measurements in all chronic heart failure patients (n = 36)

KPLS	85 ± 14
KSSS	64 ± 21
KSFS	86 ± 16
KSBS	80 ± 19
KTSS	82 ± 17
KSES	67 ± 27
KQOLS	57 ± 24
KSLS	75 ± 26
KOSS	75 ± 17
KCSS	85 ± 14
Neuroticism	16 ± 5
Extraversion	29 ± 8
Openness	25 ± 5
Agreeableness	26 ± 6
Conscientiousness	30 ± 5
VO_2 peak, mL/kg per minute	15.9 ± 4.4
WRp, Watt	99 ± 41
VE/VCO_2 slope	35 ± 7
AT, mL/kg per minute	9.7 ± 2.4

KCCQ: Kansas City Cardiomyopathy Questionnaire; KPLS: Kansas Physical Limitation Score; KSSS: Kansas Symptom Stability Score; KSFS: Kansas Symptom Frequency Score; KSBS: Kansas Symptom Burden Score; KTSS: Kansas Total Symptom Score; KSES: Kansas Self-Efficacy Score; KQOLS: Kansas Quality of Life Score; KSLS: Kansas Social Limitation Score; KOSS: Kansas Overall Summary Score; KCSS: Kansas Clinical Summary Score; VO_2 peak: Peak oxygen uptake; WRp: Peak work rate; VE/VCO_2 slope: The slope of ventilatory equivalent for carbon dioxide output during exercise; AT: Anaerobic threshold.

RESULTS

Psychometric and cardiopulmonary exercise testing measurements are presented in Table 2.

Correlation analysis

The correlations between KCCQ QoL measurements and NEO-FFI personality parameters, by means of Pearson's coefficients showed a strong relationship between QoL and Neuroticism (Table 3 and Figure 1). KCCQ summary scales did not show significant correlations with the personality traits of Extraversion, Openness, Conscientiousness and Agreeableness (Table 3). QoL as measured by the OSS and CSS subscales of the KCCQ, had also a significant correlation with CHF severity (Figures 2 and 3) as expressed by VE/VCO_2 slope (r = -0.59, $P < 0.001$ and $r = -0.55$, $P < 0.001$, respectively) and VO_2 peak ($r = 0.56$, $P < 0.001$ and $r = 0.65$, $P < 0.001$, respectively).

Model of predictors of Quality of life

A univariate linear regression was performed to examine which variables were significantly correlated to QoL scales, including age, Body Mass Index, Personality traits, VE/VCO_2 slope and VO_2 peak.

Multivariate linear regression analysis using simultaneous entry of predictors was conducted to determine the best linear combination of statistically significant univariate predictors such as Neuroticism, VE/VCO_2 slope and VO_2 peak, for predicting KCCQ Overall Summary Score.

Table 3 Pearson's Simple Correlations between Kansas City Cardiomyopathy Questionnaire Quality of Life and NEO Five-Factor Inventory personality parameters

	Neuroticism	Extraversion	Openness	Agreeableness	Conscientiousness
KPLS	-0.53[b]	-0.01	0.31	-0.15	-0.03
KSSS	-0.30	-0.02	-0.06	-0.17	-0.15
KSFS	-0.54[b]	-0.31	-0.09	-0.41	-0.24
KSBS	-0.57[b]	-0.27	-0.15	-0.27	-0.37
KTSS	-0.61[b]	-0.29	-0.09	-0.35	-0.32
KSES	0.00	-0.14	-0.24	-0.28	-0.42
KQOLS	-0.38[a]	-0.13	-0.02	-0.26	-0.31
KSLS	-0.39[a]	-0.12	0.13	0.02	0.10
KOSS	-0.54[b]	0.05	0.08	-0.19	-0.07
KCSS	-0.62[b]	-0.08	0.10	-0.28	-0.10

The statistical significance was set at P value < 0.05. [a]$P < 0.05$; [b]$P < 0.01$. KCCQ: Kansas City Cardiomyopathy Questionnaire; KPLS: Kansas Physical Limitation Score; KSSS: Kansas Symptom Stability Score; KSFS: Kansas Symptom Frequency Score; KSBS: Kansas Symptom Burden Score; KTSS: Kansas Total Symptom Score; KSES: Kansas Self-Efficacy Score; KQOLS: Kansas Quality of Life Score; KSLS: Kansas Social Limitation Score; KOSS: Kansas Overall Summary Score; KCSS: Kansas Clinical Summary Score; NEO-FFI: NEO Five-Factor Inventory.

The results show that Neuroticism ($\beta = 0.32$, $P < 0.05$), VE/VCO_2 slope ($\beta = 0.41$, $P < 0.05$) are independent predictors of QoL (adjusted $R^2 = 0.51$, F = 13.33, $P < 0.001$), with VO_2 peak showing a trend (Table 4).

Multivariate linear regression analysis using simultaneous entry of predictors was also conducted to determine the best linear combination of statistically significant univariate predictors such as Neuroticism, VE/VCO_2 slope and VO_2 peak, for predicting KCCQ Clinical Summary Score. The results show Neuroticism ($\beta = -0.37$, $P < 0.05$), VE/VCO_2 slope ($\beta = -0.31$, $P < 0.05$) and VO_2 peak ($\beta = 0.37$, $P < 0.05$) to be independent predictors of QoL (Table 4). Even after accounting for CHF etiology, no changes emerged concerning the predictors in the two models described above.

DISCUSSION

This study provides confirming evidence for the hypothesis that personality factors affect QoL in CHF. More specifically, in our study the personality trait of Neuroticism is associated with QoL independently of the CHF severity. To our knowledge this study is the first to show that the personality trait of Neuroticism, estimated by the NEO-FFI, affects QoL, in CHF patients after adjustment for disease severity evaluated by a symptom-limited cardiopulmonary exercise test.

Previous researchers have reported that Neuroticism, estimated by the Eysenk Personality Inventory, can predict the mental health component of the generic QoL, after adjustment for disease severity (assessed by the 6-min walk distance)[22]. A positive correlation between Neuroticism and depression was also found by the same research group in CHF patients[24]. In a prospective cohort study, Murberg *et al*[23] using the Eysenk Personality Questionnaire have shown that Neuroticism, predicts mortality

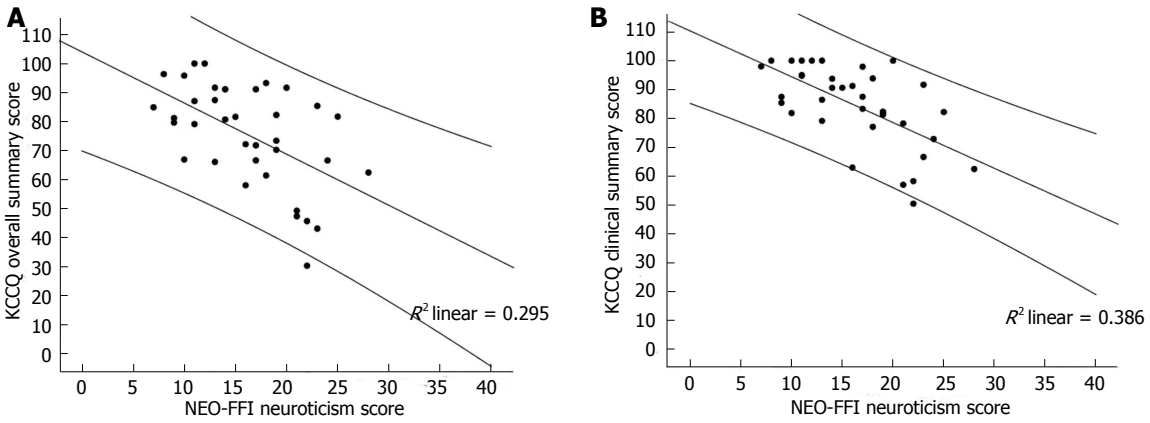

Figure 1 Scattergrams of correlation of Quality of Life subscales (Kansas City Cardiomyopathy Questionnaire Overall Summary Score, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score) with NEO- Five-Factor Inventory Neuroticism personality trait (A and B, respectively).

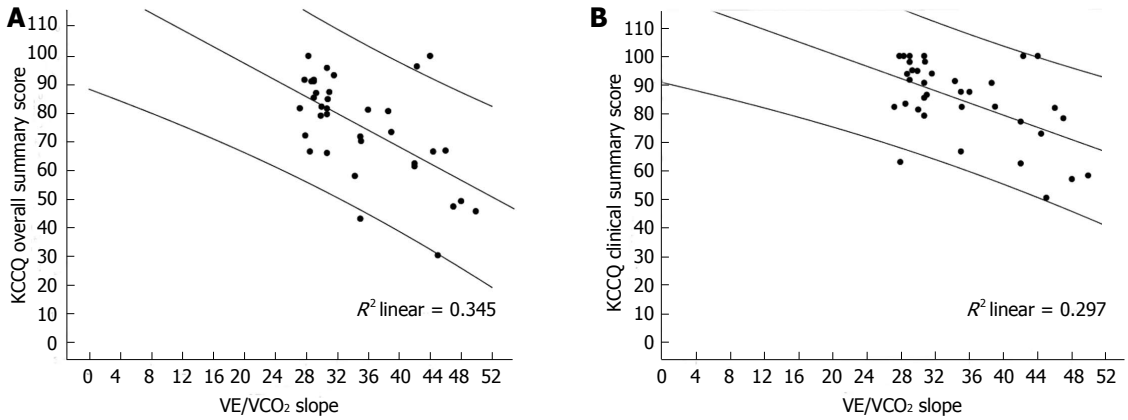

Figure 2 Scattergrams of correlations of Quality of Life (Kansas City Cardiomyopathy Questionnaire Overall Summary Score, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score) with VE/VCO2 slope (A and B, respectively).

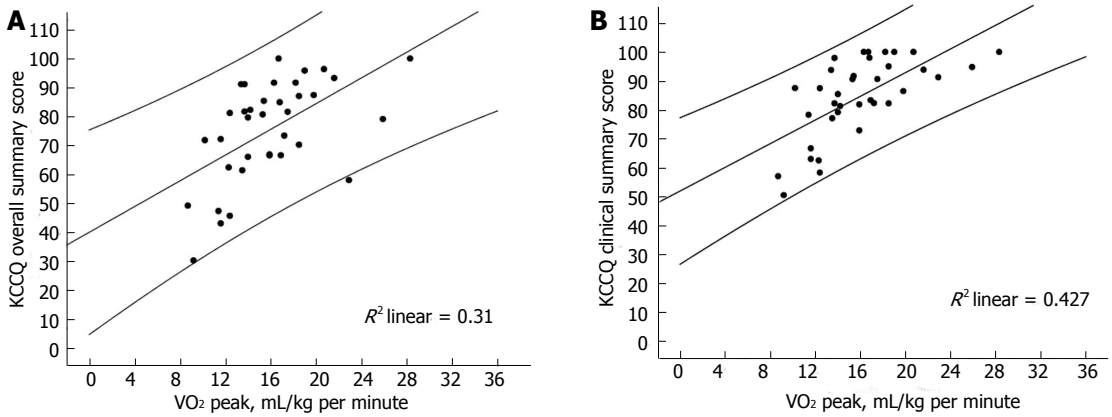

Figure 3 Scattergrams of correlation of Quality of Life (Kansas City Cardiomyopathy Questionnaire Overall Summary Score, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score) with VO2 peak (A and B, respectively).

in CHF independently of the disease severity (assessed by the pro-ANP biochemical prognostic marker). In our study, the Neuroticism trait emerged as an independent predictor of QoL in CHF patients, even after adjustment for the most robust prognostic indicators of mortality, namely cardiopulmonary exercise, stress test parameters, confirming previous reports. Furthermore, CHF patients enrolled at the present study were receiving modern optimal medical treatment including beta-blockers, ACE-inhibitors, aldosterone antagonists.

Recently, other studies have examined the relationship between personality and QoL and demonstrated that type D personality is independently associated with impaired health status in CHF[14,31]. Previous data have also supported the finding that the relationship between personality type-D and CHF is not confounded by dis-

Table 4 Multiple linear regression analyses of predictors of Quality of Life

Variables	KCCQ summary scales							
	KCCQ Overall Summary Score adjusted R^2 = 0.51; F = 13.33, P < 0.001				KCCQ Clinical Summary Score adjusted R^2 = 0.64; F = 18.89, P < 0.001			
	B	SE	beta	Sig.	B	SE	beta	Sig.
Neuroticism	-1.02	0.43	-0.32	P < 0.05	-0.95	0.31	-0.37	P < 0.05
VE/VCO_2 slope	-1.01	0.32	-0.41	P < 0.05	-0.6	0.23	-0.31	P < 0.05
VO_2 peak	1.04	0.55	0.26	NS	1.16	0.39	0.37	P < 0.05

KCCQ: Kansas City Cardiomyopathy Questionnaire; VE/VCO_2 slope: The slope of ventilatory equivalent for carbon dioxide output during exercise; VO_2 peak: Peak oxygen uptake.

ease severity, assessed by BNP measurements[32]. In the present study we have shown that the personality trait of Neuroticism, affects independently QoL in CHF patients. The relationship between type-D personality and Neuroticism has been previously studied and a positive relationship was found between them in both subscales of the type-D evaluation tool DS14, namely the Negative Affectivity and Social Inhibition[33]. Other psychological factors such as depression and anxiety have also been associated with decreased QoL in CHF patients[12].

Our data have shown that CHF patients who score high on the Neuroticism scale have low QoL independently of the severity of the CHF as expressed by VE/VCO_2 slope and VO_2 peak, strong predictors of mortality[28]. Because of the cross-sectional design of the study, the results are by definition bidirectional. Nevertheless it could plausibly be assumed that the direction of the relationship is rather from Neuroticism to impaired QoL, as personality traits are usually formed before the age of 30 and tend to remain stable through the rest of adulthood[34-37]. As supported by epidemiological data, CHF usually occurs mainly after the age of 30, increasing incidence with aging[38,39]. Thus it can be inferred that the development of Neuroticism personality trait precedes the development and progress of CHF.

Chronic stress pattern and autonomic dysregulation might explain the relationship between Neuroticism and QoL found in our data. The personality trait of Neuroticism is correlated to chronic anxiety[40]. Neuroticism leads to a dysfunctional pattern of stress management as well as a pattern of frequent experience of negative feelings in everyday life, and that means vulnerability to common psychological stressors. This chronic inadequate stress management predisposes to autonomic nervous dysfunction[41] and cardiovascular dysregulation[42,43]. The relationship between chronic stress and cardiovascular dysfunction is also well known in animals[44]. A recent study has shown that type-D personality is correlated to impaired heart rate recovery[45], an index of parasympathetic abnormality. This index is related to psychological distress and QoL and is a strong independent predictor of mortality[46] and poor QoL[47] in CHF patients. It could be assumed that this autonomic nervous system dysregulation is a possible mechanism that might mediate the relationship between Neuroticism and decreased health status in CHF patients. Future studies are needed to evaluate the possible association of Neuroticism with autonomic nervous system impairment in CHF patients.

Our study supports the hypothesis that a more holistic approach is preferable, when evaluating a patient with chronic heart failure, a finding of significant clinical importance. A low KCCQ score is an independent predictor of poor prognosis in outpatients with CHF[7-9] and according to the findings of present study, this is not only related to disease severity but also predicted by a high NEO-FFI Neuroticism score. Patients scoring high in the Neuroticism personality trait have lower QoL independently of CHF severity, therefore, Neuroticism may constitute a prognostic factor for these patients. The knowledge of the severity of the Neuroticism trait could also affect the treatment options, as it can help with the identification of patients that probably need additional psychological or psychiatric care to cope with their heart disease.

Certain limitations of the study should be taken into account during result interpretation. This study is cross-sectional, therefore not designed to prove causality. Intervention studies targeting Neuroticism with prospective design are needed for clarifying the direction of the relationships between Neuroticism, CHF severity and QoL, in terms of their predictive value for clinical outcome. No structured clinical interview was used as a screening tool for psychopathology in this non-psychiatric setting sample of ambulatory patients of the outpatient Heart Failure Clinic. Due to the small number of female patients in our sample, it was not possible to perform gender-specific analysis and/or between-gender comparisons. Duration of disease variables was not included in the analysis, but disease severity estimation was based only on current measurements *via* the CPET and the psychometric evaluation. Although duration of diagnosis it is not theoretically possible to affect personality traits of the patients, it might affect QoL. Due to the small sample size it was not possible to control for anxiety and depression levels. Larger sample size and sophisticated statistical methods could help to further highlight the association between Neuroticism, CHF severity and QoL. A prospective study of exercise rehabilitation program effects could lead to better exploration of the role of Neuroticism to QoL and disease severity. The role of Neuroticism in other chronic illnesses beyond CHF should be also investigated in future studies.

In conclusion, Neuroticism personality trait predicts independently QoL in CHF patients after adjustment for CHF severity. Notwithstanding the limitations of a small study, we propose that a more flexible approach to CHF diagnosis, which includes personality dimensions along with a description of CHF symptoms, may result in a more inclusive and useful diagnostic scheme for treating people with chronic heart failure. Taking into account the relationship between Neuroticism and QoL, personality factors could probably help to explain at least partially some of the mortality risk in CHF patients previously predicted by poor QoL. Psychiatric interventions might possibly be incorporated into the treatment of these patients to improve QoL and possibly prognosis.

COMMENTS

Background

Measuring and exploring factors that affect Quality of life (QoL) is important for chronic heart failure (CHF) patients in order to monitor their treatment course and assessing prognosis, as well as for evaluating treatment interventions' and health services effectiveness. Patients that are experiencing low QoL present higher morbidity, hospitalization rate and mortality. QoL in CHF is related to exercise capacity and adherence to rehabilitation programs and low QoL is related to exercise training intolerance. Of the psychological factors that affect QoL, anxiety and depression levels have been shown to play an important role, but the role of personality traits of the CHF patient hasn't been well understood yet. Taking into account that the personality trait of Neuroticism, has been demonstrated to affect QoL in chronically ill individuals, there is a need for exploration of its possible role as a predictor of QoL in patients with CHF.

Research frontiers

Of the available generic and disease-specific tools for describing dimensions of QoL in CHF, the Kansas City Cardiomyopathy Questionnaire is a self-reported, disease specific questionnaire that is considered reliable and valid for this population. Cardiopulmonary exercise testing has emerged over the years as a very useful modality for assessing variables related to exercise capacity and with CHF severity in this population.

Innovations and breakthroughs

Previous researchers have reported that Neuroticism, estimated by the Eysenk Personality Inventory (EPI), can predict the mental health component of the generic QoL, after adjustment for disease severity assessed by the 6-min walk distance. Also a prospective cohort study using the Eysenk Personality Questionnaire (EPQ), an expanded version of EPI, has shown that Neuroticism predicts mortality in CHF independently of the disease severity assessed by the pro-ANP biochemical prognostic marker. These study provides additional evidence for the hypothesis that personality factors affect QoL in CHF. More specifically, these found that the personality trait of Neuroticism is associated with QoL independently of the CHF severity. To these knowledge this study is the first to show that the personality trait of Neuroticism, estimated by the Five-Factor Personality Inventory, affects QoL, in CHF patients after adjustment for disease severity evaluated by a symptom-limited cardiopulmonary exercise test, the "gold" standard for the assessment of exercise capacity in these patients.

Applications

The results of this study showed that not only disease severity but also the personality characteristic of Neuroticism can affect patients' QoL, therefore worsening prognosis of CHF. The personality of CHF patient has to be taken into account during CHF treatment and rehabilitation programs, and a tailor-made individualized psychosocial intervention by a mental health professional might help improving patients QoL and consequently CHF prognosis.

Terminology

CHF population in this manuscript refers to patients with Chronic Heart Failure, that are currently been stabilized in optimal medical treatment and their left ventricle ejection fraction remains less than 45%. CPET refers to CardioPulmonary Exercise Testing that is used for evaluation of the patient in terms of heart function and exercise capacity. This evaluation is also important for exercise training rehabilitation of the CHF patient.

Peer review

This is a very interesting and novel observational study of the effect of neuroticism on quality of life of a Greek cohort of chronic heart failure patients. The paper reads well overall and reports some novel findings.

REFERENCES

1 **Spertus J**. Selecting end points in clinical trials: What evidence do we really need to evaluate a new treatment? *Am Heart J* 2001; **142**: 745-747 [PMID: 11685157 DOI: 10.1067/mhj.2001.119135]

2 **Normand SL**, Rector TS, Neaton JD, Piña IL, Lazar RM, Proestel SE, Fleischer DJ, Cohn JN, Spertus JA. Clinical and analytical considerations in the study of health status in device trials for heart failure. *J Card Fail* 2005; **11**: 396-403 [PMID: 15948091 DOI: 10.1016/j.cardfail.2005.04.002]

3 **Green CP**, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol* 2000; **35**: 1245-1255 [PMID: 10758967 DOI: 10.1016/S0735-1097(00)00531-3]

4 **Juenger J**, Schellberg D, Kraemer S, Haunstetter A, Zugck C, Herzog W, Haass M. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. *Heart* 2002; **87**: 235-241 [PMID: 11847161 DOI: 10.1136/heart.87.3.235]

5 **Athanasopoulos LV**, Dritsas A, Doll HA, Cokkinos DV. Comparative value of NYHA functional class and quality-of-life questionnaire scores in assessing heart failure. *J Cardiopulm Rehabil Prev* 2010; **30**: 101-105 [PMID: 19952769 DOI: 10.1097/HCR.0b013e3181be7e47]

6 **Athanasopoulos LV**, Dritsas A, Doll HA, Cokkinos DV. Explanation of the variance in quality of life and activity capacity of patients with heart failure by laboratory data. *Eur J Cardiovasc Prev Rehabil* 2010; **17**: 375-379 [PMID: 19940776 DOI: 10.1097/HJR.0b013e328333e962]

7 **Heidenreich PA**, Spertus JA, Jones PG, Weintraub WS, Rumsfeld JS, Rathore SS, Peterson ED, Masoudi FA, Krumholz HM, Havranek EP, Conard MW, Williams RE. Health status identifies heart failure outpatients at risk for hospitalization or death. *J Am Coll Cardiol* 2006; **47**: 752-756 [PMID: 16487840 DOI: 10.1016/j.jacc.2005.11.021]

8 **Soto GE**, Jones P, Weintraub WS, Krumholz HM, Spertus JA. Prognostic value of health status in patients with heart failure after acute myocardial infarction. *Circulation* 2004; **110**: 546-551 [PMID: 15262843 DOI: 10.1161/01.CIR.0000136991.85540.A9]

9 **Kosiborod M**, Soto GE, Jones PG, Krumholz HM, Weintraub WS, Deedwania P, Spertus JA. Identifying heart failure patients at high risk for near-term cardiovascular events with serial health status assessments. *Circulation* 2007; **115**: 1975-1981 [PMID: 17420346 DOI: 10.1161/CIRCULATIONAHA.106.670901]

10 **Flynn KE**, Piña IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, Fine LJ, Howlett JG, Keteyian SJ, Kitzman DW, Kraus WE, Miller NH, Schulman KA, Spertus JA, O'Connor CM, Weinfurt KP. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009; **301**: 1451-1459 [PMID: 19351942 DOI: 10.1001/jama.2009.457]

11 **O'Connor CM**, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009; **301**: 1439-1450 [PMID: 19351941 DOI: 10.1001/jama.2009.454]

12 **Chung ML**, Moser DK, Lennie TA, Rayens MK. The effects of depressive symptoms and anxiety on quality of life in patients with heart failure and their spouses: testing dyadic

dynamics using Actor-Partner Interdependence Model. *J Psychosom Res* 2009; **67**: 29-35 [PMID: 19539816 DOI: 10.1016/j.jpsychores.2009.01.009]
13 **Faller H**, Steinbüchel T, Störk S, Schowalter M, Ertl G, Angermann CE. Impact of depression on quality of life assessment in heart failure. *Int J Cardiol* 2010; **142**: 133-137 [PMID: 19162345 DOI: 10.1016/j.ijcard.2008.12.093]
14 **Schiffer AA**, Pedersen SS, Widdershoven JW, Hendriks EH, Winter JB, Denollet J. The distressed (type D) personality is independently associated with impaired health status and increased depressive symptoms in chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2005; **12**: 341-346 [PMID: 16079641 DOI: 10.1097/01.hjr.0000173107.76109.6c]
15 **Spindler H**, Kruse C, Zwisler AD, Pedersen SS. Increased anxiety and depression in Danish cardiac patients with a type D personality: cross-validation of the Type D Scale (DS14). *Int J Behav Med* 2009; **16**: 98-107 [PMID: 19322662 DOI: 10.1007/s12529-009-9037-5]
16 **Schiffer AA**, Smith OR, Pedersen SS, Widdershoven JW, Denollet J. Type D personality and cardiac mortality in patients with chronic heart failure. *Int J Cardiol* 2010; **142**: 230-235 [PMID: 19162343 DOI: 10.1016/j.ijcard.2008.12.090]
17 **Jerant A**, Chapman BP, Franks P. Personality and EQ-5D scores among individuals with chronic conditions. *Qual Life Res* 2008; **17**: 1195-1204 [PMID: 18839336 DOI: 10.1007/s11136-008-9401-y]
18 **Chapman BP**, Duberstein PR, Sörensen S, Lyness JM. Personality and perceived health in older adults: the five factor model in primary care. *J Gerontol B Psychol Sci Soc Sci* 2006; **61**: P362-P365 [PMID: 17114306]
19 **Duberstein PR**, Sörensen S, Lyness JM, King DA, Conwell Y, Seidlitz L, Caine ED. Personality is associated with perceived health and functional status in older primary care patients. *Psychol Aging* 2003; **18**: 25-37 [PMID: 12641310 DOI: 10.1037/0882-7974.18.1.25]
20 **Gilhooly M**, Hanlon P, Cullen B, Macdonald S, Whyte B. Successful ageing in an area of deprivation: part 2--a quantitative exploration of the role of personality and beliefs in good health in old age. *Public Health* 2007; **121**: 814-821 [PMID: 17606277 DOI: 10.1016/j.puhe.2007.03.003]
21 **Goodwin R**, Engstrom G. Personality and the perception of health in the general population. *Psychol Med* 2002; **32**: 325-332 [PMID: 11866326 DOI: 10.1017/S0033291701005104]
22 **Westlake C**, Dracup K, Creaser J, Livingston N, Heywood JT, Huiskes BL, Fonarow G, Hamilton M. Correlates of health-related quality of life in patients with heart failure. *Heart Lung* 2002; **31**: 85-93 [PMID: 11910383 DOI: 10.1067/mhl.2002.122839]
23 **Murberg TA**, Bru E, Svebak S, Tveterås R, Aarsland T. Depressed mood and subjective health symptoms as predictors of mortality in patients with congestive heart failure: a two-years follow-up study. *Int J Psychiatry Med* 1999; **29**: 311-326 [PMID: 10642905 DOI: 10.1016/S0191-8869(00)00067-2]
24 **Westlake C**, Dracup K, Fonarow G, Hamilton M. Depression in patients with heart failure. *J Card Fail* 2005; **11**: 30-35 [PMID: 15704061 DOI: 10.1016/j.cardfail.2004.03.007]
25 **American Thoracic Society; American College of Chest Physicians.** ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003; **167**: 211-277 [PMID: 12524257 DOI: 10.1164/rccm.167.2.211]
26 **Hansen JE**, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis* 1984; **129**: S49-S55 [PMID: 6421218]
27 **Beaver WL**, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* (1985) 1986; **60**: 2020-2027 [PMID: 3087938]
28 **Nanas SN**, Nanas JN, Sakellariou DCh, Dimopoulos SK, Drakos SG, Kapsimalakou SG, Mpatziou CA, Papazachou OG, Dalianis AS, Anastasiou-Nana MI, Roussos C. VE/VCO2 slope is associated with abnormal resting haemodynamics and is a predictor of long-term survival in chronic heart failure. *Eur J Heart Fail* 2006; **8**: 420-427 [PMID: 16310408 DOI: 10.1016/j.ejheart.2005.10.003]
29 **Costa PT**, McCrae RR. Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI) professional manual. Odessa, FL: Psychological Assessment Resources, 1992
30 **Digman J**. Personality Structure: Emergence of the 5-Factor Model. *Annu Rev Psychol* 1990: 417-440 [DOI: 10.1146/annurev.ps.41.020190.002221]
31 **Pedersen SS**, Herrmann-Lingen C, de Jonge P, Scherer M. Type D personality is a predictor of poor emotional quality of life in primary care heart failure patients independent of depressive symptoms and New York Heart Association functional class. *J Behav Med* 2010; **33**: 72-80 [PMID: 19937107 DOI: 10.1007/s10865-009-9236-1]
32 **Pelle AJ**, van den Broek KC, Szabó B, Kupper N. The relationship between type D personality and chronic heart failure is not confounded by disease severity as assessed by BNP. *Int J Cardiol* 2010; **145**: 82-83 [PMID: 19477027 DOI: 10.1016/j.ijcard.2009.05.018]
33 **De Fruyt FDJ**. Type D personality: A Five-Factor Model perspective. *Psychol Health* 2002; **17**: 671-683 [DOI: 10.1080/08870440290025858]
34 **Costa PT**, McCrae RR. Personality in adulthood: a six-year longitudinal study of self-reports and spouse ratings on the NEO Personality Inventory. *J Pers Soc Psychol* 1988; **54**: 853-863 [PMID: 3379583 DOI: 10.1037/0022-3514.54.5.85310.1037/0022-3514.54.5.853]
35 **Terracciano A**, Costa PT, McCrae RR. Personality plasticity after age 30. *Pers Soc Psychol Bull* 2006; **32**: 999-1009 [PMID: 16861305 DOI: 10.1177/0146167206288599]
36 **McCrae RR**, Costa PT, Arenberg D. Constancy of adult personality structure in males: longitudinal, cross-sectional and times-of-measurement analyses. *J Gerontol* 1980; **35**: 877-883 [PMID: 6969272 DOI: 10.1093/geronj/35.6.877]
37 **Costa PT**, McCrae RR, Zonderman AB, Barbano HE, Lebowitz B, Larson DM. Cross-sectional studies of personality in a national sample: 2. Stability in neuroticism, extraversion, and openness. *Psychol Aging* 1986; **1**: 144-149 [PMID: 3267391 DOI: 10.1037/0882-7974.1.2.144]
38 **Cowie MR**, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC, Grobbee DE. The epidemiology of heart failure. *Eur Heart J* 1997; **18**: 208-225 [PMID: 9043837 DOI: 10.1093/oxfordjournals.eurheartj.a015223]
39 **Cowie MR**, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V, Sutton GC. Incidence and aetiology of heart failure; a population-based study. *Eur Heart J* 1999; **20**: 421-428 [PMID: 10213345 DOI: 10.1053/euhj.1998.1280]
40 **Brandes M**, Bienvenu OJ. Personality and anxiety disorders. *Curr Psychiatry Rep* 2006; **8**: 263-269 [PMID: 16879789 DOI: 10.1007/s11920-006-0061-8]
41 **Watkins LL**, Blumenthal JA, Carney RM. Association of anxiety with reduced baroreflex cardiac control in patients after acute myocardial infarction. *Am Heart J* 2002; **143**: 460-466 [PMID: 11868052 DOI: 10.1067/mhj.2002.120404]
42 **Grippo AJ**, Johnson AK. Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. *Stress* 2009; **12**: 1-21 [PMID: 19116888 DOI: 10.1080/10253890802046281]
43 **Lucini D**, Di Fede G, Parati G, Pagani M. Impact of chronic psychosocial stress on autonomic cardiovascular regulation in otherwise healthy subjects. *Hypertension* 2005; **46**: 1201-1206 [PMID: 16203875 DOI: 10.1161/01.HYP.0000185147.32385.4b]
44 **Sgoifo A**, Pozzato C, Costoli T, Manghi M, Stilli D, Ferrari PF, Ceresini G, Musso E. Cardiac autonomic responses to intermittent social conflict in rats. *Physiol Behav* 2001; **73**: 343-349 [PMID: 11438360 DOI: 10.1016/S0031-9384(01)00455-3]

45 **von Känel R**, Barth J, Kohls S, Saner H, Znoj H, Saner G, Schmid JP. Heart rate recovery after exercise in chronic heart failure: role of vital exhaustion and type D personality. *J Cardiol* 2009; **53**: 248-256 [PMID: 19304130 DOI: 10.1016/j.jjcc.2008.11.008]

46 **Nanas S**, Anastasiou-Nana M, Dimopoulos S, Sakellariou D, Alexopoulos G, Kapsimalakou S, Papazoglou P, Tsolakis E, Papazachou O, Roussos C, Nanas J. Early heart rate recovery after exercise predicts mortality in patients with chronic heart failure. *Int J Cardiol* 2006; **110**: 393-400 [PMID: 16371237 DOI: 10.1016/j.ijcard.2005.10.032]

47 **von Känel R**, Saner H, Kohls S, Barth J, Znoj H, Saner G, Schmid JP. Relation of heart rate recovery to psychological distress and quality of life in patients with chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2009; **16**: 645-650 [PMID: 19801939 DOI: 10.1097/HJR.0b013e3283299542]

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CASE REPORT

Aorto-right atrial fistula: Late complication of tricuspid valve infective endocarditis

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Abstract

Abnormal connections between the ascending aorta and the cardiac chambers are rare, especially in the context of right-sided infective endocarditis (IE). Transthoracic echocardiography (TTE) with color-flow Doppler, transesophageal echocardiography (TEE), or both may be required for diagnosis. We present the case of a woman admitted with right-sided heart failure (HF) symptoms. She had a previous history of tricuspid valve IE 30 years ago. TTE and TEE revealed an aorto-right atrium fistula located just under the non-coronary cusp into the right atrium at the level of the previously affected tricuspid valve. The Patient refused surgery and was discharged home on HF medications. She has been stable for the last 3 years. The peculiarity of this case is the late symptomatic presentation of the aorto-atrial fistula and the unusual association to tricuspid valve IE.

Key words: Aorto-cardiac fistula; Infective endocarditis; Tricuspid valve

Core tip: Aorto-cardiac fistulas are rare, usually associated to prosthetic aortic valve infective endocarditis. The median duration of symptoms to echocardiographic detection of fistulization is about one month. We present a case of aorto-atrial fistula at late presentation, 30 years after tricuspid valve infective endocarditis. This article describes the epidemiology, clinical manifestations, pathophysiology, diagnostic modalities, treatment and outcomes of aorto-cardiac fistulas.

Villablanca PA, Sukhal S, Maitas O, Onuegbu A, Muñoz-Peña JM, Joseph A, Requena C, Mohananey D. Aorto-right atrial fistula: Late complication of tricuspid valve infective endocarditis. *World J Cardiol* 2014; 6(10): 1122-1126 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i10/1122.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i10.1122

INTRODUCTION

Aorto-cardiac fistulas (ACF) are a rare complication of infective endocarditis (IE); it is usually a complication of prosthetic aortic valve IE. We report a case of a patient who was found to have an Aorto-right atrial fistula 30 years after his tricuspid valve IE was treated. No similar late complication of tricuspid valve IE has been reported.

CASE REPORT

A 51-year-old woman presented to the emergency department (ED) with worsening decreased exercise tolerance over the past 2 mo. Her past medical history was significant for a previous culture-negative tricuspid valve IE in 1980 that was treated medically with antibiotics, permanent atrial fibrillation, asthma and hypothyroidism. Home medications included aspirin, furosemide, metoprolol and albuterol.

The patient stated that in the last 2 mo she developed worsening shortness of breath, lower extremity edema, chest tightness, palpitations, weakness-fatigue and

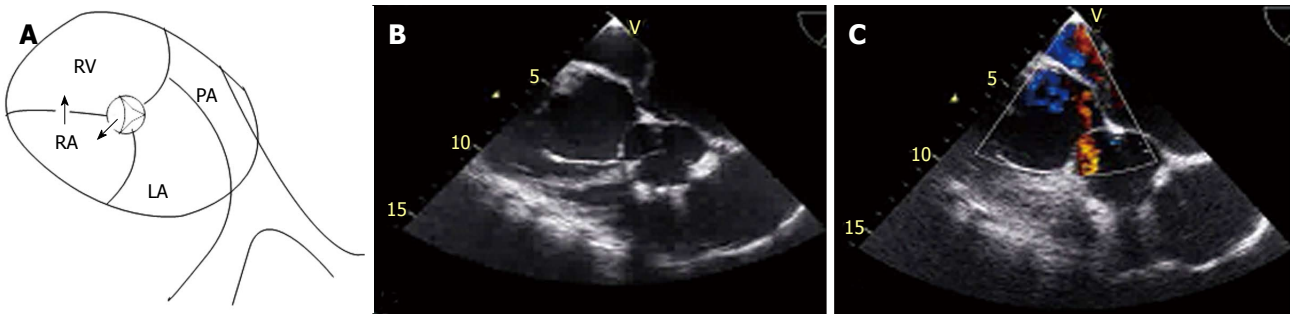

Figure 1 Schematic of abnormal fistula flow and transesophageal doppler imaging. A: Schematic diagram indicating the flow of blood during diastole, as showed by the transesophageal echocardiogram with Doppler; B: Transesophageal 4 chamber view at the level of the aortic valve, with chamber anatomy corresponding to schematic in A; C: Diastolic blood into the RA from the non-coronary cusp of the aorta. RA: Right atrium; RV: Right ventricle; LA: Left atrium; PA: Pulmonary artery.

abdominal discomfort. She denied any inciting events. Within the last two weeks, her New York Heart Association (NYHA) functional class deteriorated from NYHA class I to NYHA class Ⅲ, manifested by shortness of breath on minimal exertion, relieved only by rest. The patient denied orthopnea, paroxysmal nocturnal dyspnea, hemoptysis, chest pain, fevers, chills and weight loss.

On physical examination, her heart rate was 134 beats/min, blood pressure 115/62 mmHg and a temperature of 36 ℃. Cardiac examination revealed a markedly elevated jugular venous pressure of 12 cm, grade 4/6 low frequency pansystolic murmur in the lower left sternal border, irregularly irregular rhythm, hepatojugular reflux and lower extremity edema up to the knees. The rest of the physical examination was normal.

Laboratory work up included BMP, CBC, ESR, CRP, which were unremarkable, except for microcytic anemia of 8.2 g/dL with normal ferritin and a BNP of 1046 pg/dL. The EKG demonstrated atrial fibrillation, right axis deviation and an incomplete right bundle branch block. The chest X-ray was significant for moderate cardiomegaly with right atrial and ventricular enlargement. She was started on diuretics and beta-blockers for heart failure (HF) exacerbation secondary to atrial fibrillation with rapid ventricular response and then transferred to the general medicine floor.

On the next day of admission, a transthoracic echocardiography (TTE) was performed, showing normal left ventricular size and systolic function, severe dilation of the right ventricle with mark hypocontractility, severe tricuspid regurgitation with the anterior leaflet calcified with flail segments from previous IE. There was a diastolic flow into the right atrium from the aorta (non coronary cusp). There was no evidence of aortic insufficiency, outflow tract gradient, or ventricular septal defect. Given our suspicion for aorto-atrial fistula, a transesophageal echocardiogram (TEE) was done, showing a small fistula from just under the non-coronary cusp into the right atrium at the level of the previously affected tricuspid valve (Figure 1). The patient underwent cardiac catheterization, which showed normal coronary arteries and confirmed the echocardiographic findings of an Aorto-right atrial fistula and tricuspid regurgitation.

Cardiac surgery service was consulted for tricuspid valve replacement and repair of the fistula. Patient refused surgery due to religious issues and was discharged home on diuretics, beta-blockers, angiotensin receptor 2 blockers and spironolactone. At 3-year follow up, patient has been stable, with no further exacerbation. Surgery has been offered repeatedly, we explained the risks and benefits of performing the surgery and the good results that can be accomplished with an acceptable morbidity and mortality, yet she only wants to continue with medical management.

DISCUSSION

IE has been associated with a myriad of complications such as HF and stroke[1]. The frequency and type of complications due to IE have changed with advances in diagnosis and therapy. Uncontrolled rare extra-valvular cardiac complications of IE, such as fistulous intra-cardiac connections, which were previously common complications of IE, are infrequent in the antibiotic era. Reported for the first time in 1924 as an incidental finding on autopsy[2], the incidence of ACF has been described in less than 2.2% of cases of native valve IE[3] and 3.3% of prosthetic valve IE[4] in retrospective studies. *Staphylococcus aureus* has been documented as the most common etiology reported on both autopsies and retrospective studies[3-5] with *Streptococcus spp.*, *Enterococcus spp.*, and other bacterial and fungal infections as other documented etiologies[6].

ACF has been documented in a variety of clinical scenarios, most frequently occurring in cases of aortic valve IE, and is more common in prosthetic than native aortic valve. ACF is present in less than 1% of right-sided IE cases, and is usually associated with concomitant native aortic IE[7,8]. There are isolated cases in the English literature that report ACF secondary to native tricuspid valve[9]. It has been described also with blunt trauma[10], stab wound of the chest[11], ruptured aneurysms of the sinus of valsalva (SV)[12], aortic dissection[13], congenital disorder[14], cardiac valve surgery[15], percutaneous cardiac valve implantation[16], heart transplantation[17], and autoimmune vasculitis[18].

The proposed theory to explain the fistulization mechanism between the aorta and the cardiac chamber is through the bacterial invasion and spread of the affected valve into the adjacent tissues and structures, resulting in the formation of a periannular abscess and erosion of the SV. The aortic abscesses involving the SV may rupture internally with erosion of the sinus and subsequent development of aorto-cavitary or aorto-pericardial fistulas[3,5,7,19,20]. Perivalvular abscesses have been reported as the cause of 6%-9% of fistula cases[21,22]. Due to its relative avascularity and infected regurgitation of jet striking subvalvular structures[23], the intervalvular fibrosa is more susceptible to infection[24]. The ACF creates a left to right shunt from any of the three aortic valve sinuses to any of the four cardiac chambers with no preponderance from any specific aortic sinus to a specific cavity, resulting in further hemodynamic deterioration[5,7]. These pathologic communications are highly morbid and lead to hemodynamic instability secondary to the shunt effect[19].

Diagnosing ACF can be challenging, and the clinical presentation will depend on the size of the shunt. Patients with a small ACF may be completely asymptomatic with an associated murmur only[25,26], but the clinical presentation may range from refractory HF[20] to a chest pain syndrome due to acute coronary syndrome and aortic dissection[17,27]. Cardiac auscultation may cause a continuous murmur[28], a thrill[29] or both[25], and can be the key to further pursue this diagnosis with appropriate imaging modalities. The median duration of symptoms to echocardiographic detection of fistulization is about 25 d as reported in a retrospective multi-center study[7]. There are isolated cases reported years after prosthetic valve implantation[15]. A high index of suspicion is required, especially in the background of recent surgery or previous IE.

Although aortography is the gold standard for diagnosis, non-invasive methods such as contrast enhanced CT, MRI, and echocardiography are currently preferred. TTE is the initial test of choice in the routine assessment of patients presenting with HF symptoms or murmurs, and is therefore usually the first image modality that allows us to confirm or suspect the presence of an ACF. However, TEE is superior to TTE for better delineation of function and morphology when intra-cardiac complications, such as ACF, are suspected[30,31]. The high rate of echocardiographic diagnosis is likely due to the high-pressure differences between the aorta and the cardiac chambers, which enables observation of the highly turbulent flow that is easily detectable by color Doppler[7]. Three–dimensional echocardiography has been reported to have the potential to delineate anatomic structures, allowing a greater understanding of the pathological process and also obtaining unconventional views of cardiac structures[32]. It can delineate structures that are otherwise not visible in TEE and TTE, allowing cropping, full-volume data; and slicing in various planes[33,34]. Computed tomography, magnetic resonance imaging, and aortography can allow better description, position, dimension and anatomic conditions of the ACF, and may be required as an important adjunctive tool to confirm the diagnosis and delineate the anatomy before closure[35-38].

Surgery, which is the primary treatment of ACF, may carry severe complications, particularly with critically unstable patients with an increased postoperative mortality after surgical correction[4]. Factors associated with adverse outcomes include staphylococcal infection, urgent or emergency surgery, moderate to severe HF, renal failure, increased age and residual fistula[3,7,19,20,22,39]. With the high postoperative mortality with surgical closure of ACF and with the advancement of endovascular technologies, more emphasis is now placed on percutaneous closure with devices such as an Amplatzer plug[40,41], though it should be avoided in in patients with active infection.

We report a case of a patient who was found to have an Aorto-right atrial fistula 30 years after his tricuspid valve was treated for IE. To our knowledge and after a systematic review of the English literature, no similar late complication of treated IE has been reported.

COMMENTS

Case characteristics

A 51-year-old female with a history of tricuspid valve infective endocarditis presented with shortness of breath.

Clinical diagnosis

Right side heart failure symptoms.

Differential diagnosis

Aorto-cardiac fistula *vs* valvular heart disease *vs* new infective endocarditis.

Laboratory diagnosis

Hb of 8.2 g/dL with normal ferritin and a BNP of 1046 pg/dL; inflammatory markers (erythrocyte sedimentation rate, serum C-reactive protein, blood cell count) were within normal limits.

Imaging diagnosis

Transthoracic and transesophageal echocardiography demonstrated Aorto-right atrial fistula.

Treatment

The patient was medically managed for her heart failure after she refused surgical treatment.

Related reports

Echocardiography images and explanatory figure are provided in the case report.

Experiences and lessons

A high index of suspicion for aorto-cardiac fistula is required, especially in the background of recent surgery or previous infective endocarditis.

Peer review

This is an interesting paper.

REFERENCES

1 **Mansur AJ**, Grinberg M, da Luz PL, Bellotti G. The complications of infective endocarditis. A reappraisal in the 1980s. *Arch Intern Med* 1992; **152**: 2428-2432 [PMID: 1456853]

2 **Boyd L**. A study of four thousand cases of aneurysm of the thoracic aorta. *AM J MED SCI* 1924; **168**: 654-667

3 **Anguera I**, Miro JM, Evangelista A, Cabell CH, San Roman JA, Vilacosta I, Almirante B, Ripoll T, Fariñas MC, Anguita M, Navas E, Gonzalez-Juanatey C, Garcia-Bolao I, Muñoz P, de Alarcon A, Sarria C, Rufi G, Miralles F, Pare C, Fowler VG, Mestres CA, de Lazzari E, Guma JR, Moreno A, Corey GR. Periannular complications in infective endocarditis involving native aortic valves. *Am J Cardiol* 2006; **98**: 1254-1260 [PMID: 17056342 DOI: 10.1016/j.amjcard.2006.06.016]

4 **Anguera I**, Miro JM, San Roman JA, de Alarcon A, Anguita M, Almirante B, Evangelista A, Cabell CH, Vilacosta I, Ripoll

T, Muñoz P, Navas E, Gonzalez-Juanatey C, Sarria C, Garcia-Bolao I, Fariñas MC, Rufi G, Miralles F, Pare C, Fowler VG, Mestres CA, de Lazzari E, Guma JR, del Río A, Corey GR. Periannular complications in infective endocarditis involving prosthetic aortic valves. *Am J Cardiol* 2006; **98**: 1261-1268 [PMID: 17056343 DOI: 10.1016/j.amjcard.2006.05.066]

5 **Arnett EN**, Roberts WC. Valve ring abscess in active infective endocarditis. Frequency, location, and clues to clinical diagnosis from the study of 95 necropsy patients. *Circulation* 1976; **54**: 140-145 [PMID: 1277418]

6 **Williams-Phillips S**. Aorto-cavitary fistula: a complication of infective endocarditis. *West Indian Med J* 2012; **61**: 756-759 [PMID: 23620977]

7 **Anguera I**, Miro JM, Vilacosta I, Almirante B, Anguita M, Muñoz P, Roman JA, de Alarcon A, Ripoll T, Navas E, Gonzalez-Juanatey C, Cabell CH, Sarria C, Garcia-Bolao I, Fariñas MC, Leta R, Rufi G, Miralles F, Pare C, Evangelista A, Fowler VG, Mestres CA, de Lazzari E, Guma JR. Aorto-cavitary fistulous tract formation in infective endocarditis: clinical and echocardiographic features of 76 cases and risk factors for mortality. *Eur Heart J* 2005; **26**: 288-297 [PMID: 15618052 DOI: 10.1093/eurheartj/ehi034]

8 **Yuan SM**. Right-sided infective endocarditis: recent epidemiologic changes. *Int J Clin Exp Med* 2014; **7**: 199-218 [PMID: 24482708]

9 **Akowuah EF**, Casula R, Thanos A, Cooper GJ. Aorto-right atrial fistula associated with native tricuspid valve endocarditis. *J Cardiovasc Surg* (Torino) 2002; **43**: 841-842 [PMID: 12483176]

10 **Muehlschlegel JD**, Alomar-Melero E, Staples ED, Janelle GM. Acute high-output failure from an aortoventricular fistula due to a ruptured sinus of Valsalva aneurysm after blunt chest trauma. *Anesth Analg* 2006; **103**: 1408-1409 [PMID: 17122212 DOI: 10.1213/01.ane.0000242526.04908.2e]

11 **Barbosa FM**, Quiroga JM, Otero AE, Girela GA. Aortic valve regurgitation with aorto-right ventricular fistula following penetrating cardiac injury. *Interact Cardiovasc Thorac Surg* 2011; **13**: 653-654 [PMID: 21908889 DOI: 10.1510/icvts.2011.275297]

12 **Onorato E**, Casilli F, Mbala-Mukendi M, Perlasca E, Santoro F, Bortone F, Arena V. Sudden heart failure due to a ruptured posterior Valsalva sinus aneurysm into the right atrium: feasibility of catheter closure using the Amplatzer duct occluder. *Ital Heart J* 2005; **6**: 603-607 [PMID: 16274025]

13 **Matsuhisa H**, Obo H, Nakagiri K, Mukohara N, Shida T. Aorto-right atrial fistula caused by type A aortic dissection. *Ann Thorac Surg* 2004; **78**: 2173-2175 [PMID: 15561067 DOI: 10.1016/j.athoracsur.2003.08.007]

14 **Pinaud F**, Pezard P, Merheb M, Sibileau E, Baufreton C. Congenital aorto-right ventricular fistula in an adult. *Eur Heart J* 2009; **30**: 2116 [PMID: 19460841 DOI: 10.1093/eurheartj/ehp206]

15 **Roy D**, Saba S, Grinberg I, Zughaib M, Sakwa M, Clancy P, McKendrick G. Aorto-right ventricular fistula: a late complication of aortic valve replacement. *Tex Heart Inst J* 1999; **26**: 140-142 [PMID: 10397439]

16 **Muñoz-García AJ**, Rodríguez-Bailón I, Briales JH, Navarro MJ, García JM, de Teresa-Galván E. Aorto-right ventricular fistula after percutaneous aortic valve implantation of a CoreValve prosthesis. *Tex Heart Inst J* 2011; **38**: 728-729 [PMID: 22199450]

17 **Caruso A**, Iarussi D, Materazzi C, Dialetto G, Covino F, Bossone E, Cotrufo M. Aortic dissection with fistula to right atrium after heart transplantation: diagnosis by transthoracic and transesophageal echocardiography. *Echocardiography* 2000; **17**: 337-340 [PMID: 10979003]

18 **Melua A**, Campbell N, McCluskey D, MacGowan SW. Aorto-atrial fistula without aneurysm formation in Behçet's disease. *Heart* 1998; **80**: 200-201 [PMID: 9813571]

19 **Anguera I**, Quaglio G, Miró JM, Paré C, Azqueta M, Marco F, Mestres CA, Moreno A, Pomar JL, Mezzelani P, Sanz G. Aortocardiac fistulas complicating infective endocarditis. *Am J Cardiol* 2001; **87**: 652-654, A10 [PMID: 11230858]

20 **Archer TP**, Mabee SW, Baker PB, Orsinelli DA, Leier CV. Aorto-left atrial fistula. A reversible cause of acute refractory heart failure. *Chest* 1997; **111**: 828-831 [PMID: 9118732]

21 **San Román JA**, Vilacosta I, Sarriá C, de la Fuente L, Sanz O, Vega JL, Ronderos R, González Pinto A, Jesús Rollán M, Graupner C, Batlle E, Lahulla F, Stoermann W, Portis M, Fernández-Avilés F. Clinical course, microbiologic profile, and diagnosis of periannular complications in prosthetic valve endocarditis. *Am J Cardiol* 1999; **83**: 1075-1079 [PMID: 10190523]

22 **Choussat R**, Thomas D, Isnard R, Michel PL, Iung B, Hanania G, Mathieu P, David M, du Roy de Chaumaray T, De Gevigney G, Le Breton H, Logeais Y, Pierre-Justin E, de Riberolles C, Morvan Y, Bischoff N. Perivalvular abscesses associated with endocarditis; clinical features and prognostic factors of overall survival in a series of 233 cases. Perivalvular Abscesses French Multicentre Study. *Eur Heart J* 1999; **20**: 232-241 [PMID: 10082156]

23 **Chandra S**, Ameta D, Kharwar RB, Goyal M, Kumar D, Dwivedi SK, Saran RK. Three-dimensional echocardiographic delineation of an acquired aorto-left atrial fistula complicating native aortic valve endocarditis - "advantage of three dimensions". *Echocardiography* 2013; **30**: E326-E330 [PMID: 23931072 DOI: 10.1111/echo.12319]

24 **Kim HW**, Chung CH. Mitral-aortic intervalvular fibrosa pseudoaneurysm resulting in the displacement of the left main coronary artery after aortic valve replacement. *J Thorac Cardiovasc Surg* 2010; **139**: e18-e20 [PMID: 19660298 DOI: 10.1016/j.jtcvs.2008.07.045]

25 **Chow WH**, Lee PK, Cheung KL, Mok CK. Two-dimensional and pulsed Doppler echocardiographic diagnosis of an acquired aortic right ventricular fistula. *Clin Cardiol* 1989; **12**: 544-545 [PMID: 2791376]

26 **Lorenz J**, Reddy CV, Khan R, Hoover E, Hsu HK, El-Sherif N. Aortico-right ventricular shunt following aortic valve replacement. *Chest* 1983; **83**: 922-925 [PMID: 6851697]

27 **Amabile N**, Gil JM, Sarran A. Aorto-right ventricular fistula presenting 10 years after aortic surgery as an acute coronary syndrome. *Arch Cardiovasc Dis* 2009; **102**: 153-154 [PMID: 19303583 DOI: 10.1016/j.acvd.2008.08.003]

28 **Cakir C**, Duygu H, Kilicaslan B, Ertas F, Ozen N, Nazli C, Ergene O. Postoperative diagnosis of aorto-right ventricular outflow tract fistula caused by stab wound: a case report. *J Am Soc Echocardiogr* 2007; **20**: 1415.e5-1415.e7 [PMID: 17628398 DOI: 10.1016/j.echo.2007.05.005]

29 **Jackson DH**, Murphy GW, Stewart S, DeWeese JA, Schreiner BF. Delayed appearance of left-to-right shunt following aortic valvular replacement. Report of two cases. *Chest* 1979; **75**: 184-186 [PMID: 421554]

30 **Ananthasubramaniam K**. Clinical and echocardiographic features of aorto-atrial fistulas. *Cardiovasc Ultrasound* 2005; **3**: 1 [PMID: 15655075 DOI: 10.1186/1476-7120-3-1]

31 **Patsouras D**, Argyri O, Siminilakis S, Michalis L, Sideris D. Aortic dissection with aorto-left atrial fistula formation soon after aortic valve replacement: A lethal complication diagnosed by transthoracic and transesophageal echocardiography. *J Am Soc Echocardiogr* 2002; **15**: 1409-1411 [PMID: 12415238]

32 **Maffè S**, Zenone F, Dellavesa P, Paffoni P, Paino AM, Signorotti F, Cucchi L, Pardo NF, Parravicini U. Usefulness of three-dimensional transthoracic echocardiography in particular clinical settings: a case of aorto-cavitary fistula in periprosthetic aortic valve abscess. *Echocardiography* 2012; **29**: E141-E144 [PMID: 22329527 DOI: 10.1111/j.1540-8175.2011.01641.x]

33 **Chan KL**, Liu X, Ascah KJ, Beauchesne LM, Burwash IG. Comparison of real-time 3-dimensional echocardiography

with conventional 2-dimensional echocardiography in the assessment of structural heart disease. *J Am Soc Echocardiogr* 2004; **17**: 976-980 [PMID: 15337963 DOI: 10.1016/j.echo.2004.05.005]

34 **Patel V**, Fountain A, Guglin M, Nanda NC. Three-dimensional transthoracic echocardiography in identification of Aorto-right atrial fistula and aorto-right ventricular fistulas. *Echocardiography* 2010; **27**: E105-E108 [PMID: 20584055 DOI: 10.1111/j.1540-8175.2010.01225.x]

35 **Park H**, Park TH, Lee DY, Ahn J, Baek HK, Kim MH, Kim YD, Park KJ, Wu JS. A case of aortic dissection with fistula from aorta to right ventricle. *Korean Circ J* 2012; **42**: 629-631 [PMID: 23091509 DOI: 10.4070/kcj.2012.42.9.629]

36 **Rajiah P**, Kanne JP. Cardiac MRI: Part 1, cardiovascular shunts. *AJR Am J Roentgenol* 2011; **197**: W603-W620 [PMID: 21940532 DOI: 10.2214/AJR.10.7257]

37 **Dwivedi SK**, Vijay SK, Chandra S, Ahmad N, Saran RK, Singh SK. Giant aorto-right ventricular fistula with single coronary artery. *Circulation* 2012; **125**: e462-e465 [PMID: 22431888 DOI: 10.1161/CIRCULATIONAHA.111.045039]

38 **Siebers C**, Schramm R, Friedmann A, Weig T. Severe cardiogenic shock due to acute onset of an aorto-to-right atrial shunt in a patient with aortic valve endocarditis. *Int J Surg Case Rep* 2014; **5**: 108-110 [PMID: 24463563 DOI: 10.1016/j.ijscr.2013.12.015]

39 **Ellis SG**, Goldstein J, Popp RL. Detection of endocarditis-associated perivalvular abscesses by two-dimensional echocardiography. *J Am Coll Cardiol* 1985; **5**: 647-653 [PMID: 3973262]

40 **Lu TL**, Beregi JP, Rey C, Midulla M, Lions C. Percutaneous closure of an aorto-right ventricular fistula with an Amplatzer plug. *J Vasc Interv Radiol* 2011; **22**: 100-101 [PMID: 21195903 DOI: 10.1016/j.jvir.2010.09.019]

41 **Lebreiro AM**, Silva JC. Transcatheter closure of an iatrogenic aorto-right ventricular fistula. *Catheter Cardiovasc Interv* 2012; **79**: 448-452 [PMID: 21735529 DOI: 10.1002/ccd.23222]

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CASE REPORT

Electrical storm in systemic sclerosis: Inside the electroanatomic substrate

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Abstract

We report the case of a 63-year-old woman affected by a severe form of systemic scleroderma with pulmonary involvement (interstitial fibrosis diagnosed by biopsy and moderate pulmonary hypertension) and cardiac involvement (paroxysmal atrial fibrillation, right atrial flutter treated by catheter ablation, ventricular tachyarrhythmias, previous dual chamber implantable cardioverter defibrillator implant). Because of recurrent electrical storms refractory to *iv* antiarrhythmic drugs the patient was referred to our institution to undergo catheter ablation. During electrophysiological procedure a 3D shell of cardiac anatomy was created with intracardiac echocardiography pointing out a significant right ventricular dilatation with a complex aneurysmal lesion characterized by thin walls and irregular multiple trabeculae. A substrate-guided strategy of catheter ablation was accomplished leading to a complete electrical isolation of the aneurism and to the abolishment of all abnormal electrical activities. The use of advanced strategies of imaging together with electroanatomical mapping added important information to the complex arrhythmogenic substrate and improved efficacy and safety.

Key words: Ventricular tachycardia; Electrical storm; Radiofrequency catheter ablation; Systemic sclerosis

Core tip: We report the case of a 63-year-old woman affected by a severe form of systemic scleroderma with cardiac involvement. Because of recurrent electrical storms the patient underwent catheter ablation. Intracardiac echocardiography pointed out a significant right ventricular dilatation with a complex aneurysmal lesion characterized by thin walls and irregular multiple trabeculae. A substrate-guided strategy of catheter ablation was accomplished leading to a complete electrical isolation of the aneurism. The use of advanced strategies of imaging together with electroanatomical mapping added important information to the complex arrhythmogenic substrate and improved efficacy and safety.

Casella M, Carbucicchio C, Russo E, Pizzamiglio F, Golia P, Conti S, Costa F, Dello Russo A, Tondo C. Electrical storm in systemic sclerosis: Inside the electroanatomic substrate. *World J Cardiol* 2014; 6(10): 1127-1130 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i10/1127.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i10.1127

INTRODUCTION

Systemic sclerosis (SS) is a rare systemic infiltrative dis-

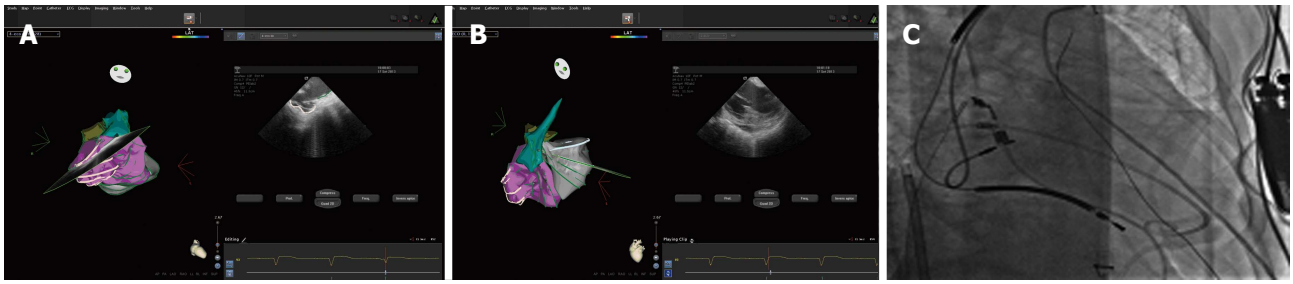

Figure 1 Movies. A: Intracardiac echocardiography (ICE) imaging showing right ventricle (RV) aneurysmal dilatation; B: At ICE, left ventricle was of normal size but with diffuse parietal hypertrophy and a mild pericardial effusion around the mitral valve plane; C: Right ventricular (RV) angiography in right anterior oblique projection.

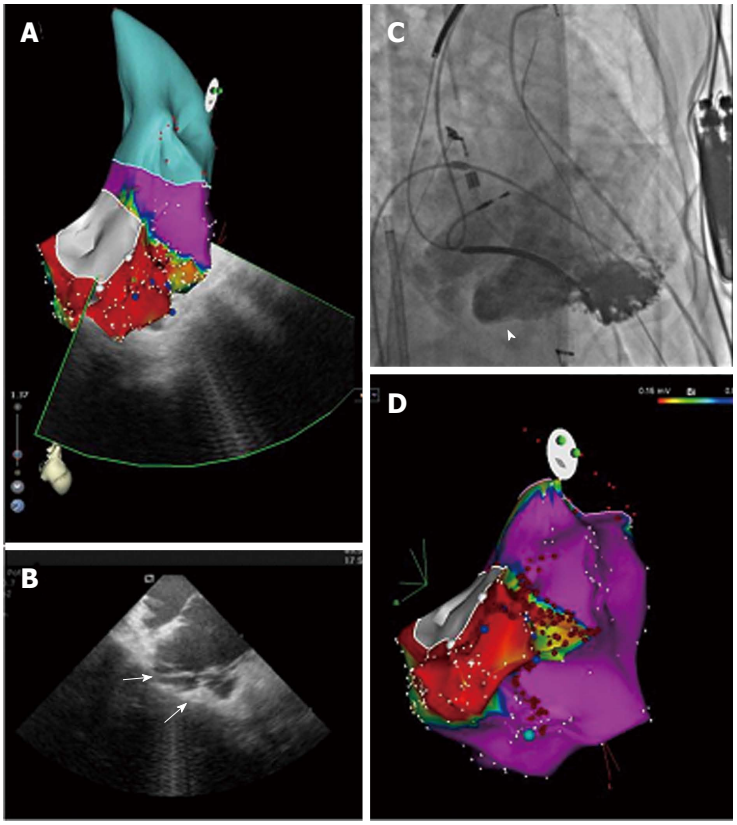

Figure 2 Right ventricle imaging. A: Bipolar voltage map of the right ventricle (RV) in right anterior oblique view. The bipolar potential voltage values were normal in the whole ventricle (purple) except for a wide area (red) around the inferior-lateral portion of tricuspid valve; B: Intracardiac echo fan intersecting the low-voltage area, showing aneurysmal dilatation (arrows) characterized by thin walls and irregular multiple trabeculae; C: RV angiography confirming the presence of the aneurysmal dilatation (head arrow); D: substrate map in right anterior oblique view showing the RF lesion points. CA was guided by substrate map and was performed all along the borders of the aneurysm and extended to the peri-aneurysmal area leading to abolishment of all abnormal electrical activities.

order characterized by a widespread damage to small blood vessels and connective tissue fibrosis resulting in multi-organ involvement. Ventricular tachyarrhythmias (VTs) are frequent clinical manifestation of SS-associated cardiovascular damage and a possible cause of sudden death. Antiarrhythmic therapy is usually limited by concomitant therapy or side effects. In many cases the use of an implantable cardioverter defibrillator (ICD) is mandatory. In this setting catheter ablation (CA) has been proposed as an alternative option but no evidence exists about the characteristics of the arrhythmogenic substrate.

CASE REPORT

A 63-year-old woman affected by a severe form of SS was referred to our institution for management of her VTs. She presented both an advanced pulmonary and cardiac involvement. Since June 2006 she has been suffering from multiple episodes of sustained VT; pharmacological therapy by beta blockers, sotalol or amiodarone was ineffective and limited by side effects (Raynaud's phenomenon and pulmonary interstitial fibrosis) thus the patient underwent a dual chamber ICD implant; on September 2013 the patient developed recurrent electrical storms refractory to *i.v.* antiarrhythmic drugs.

On the second day after admission, CA was performed. First, a 3D shell of cardiac anatomy was created on an electroanatomic mapping system integrated with intracardiac echocardiography (ICE) (Cartosound, Biosense-Webster, United States)[1]. ICE allowed to detect a significant right ventricular (RV) dilatation with a complex lesion characterized by thin walls and irregular multiple trabeculae, expanding from the inferior to the lateral RV wall in perivalvular basal segments (Figure 1A and B) this aneurysmal dilatation was easily identified angiographically, too (Figure 1C, Figure 2).

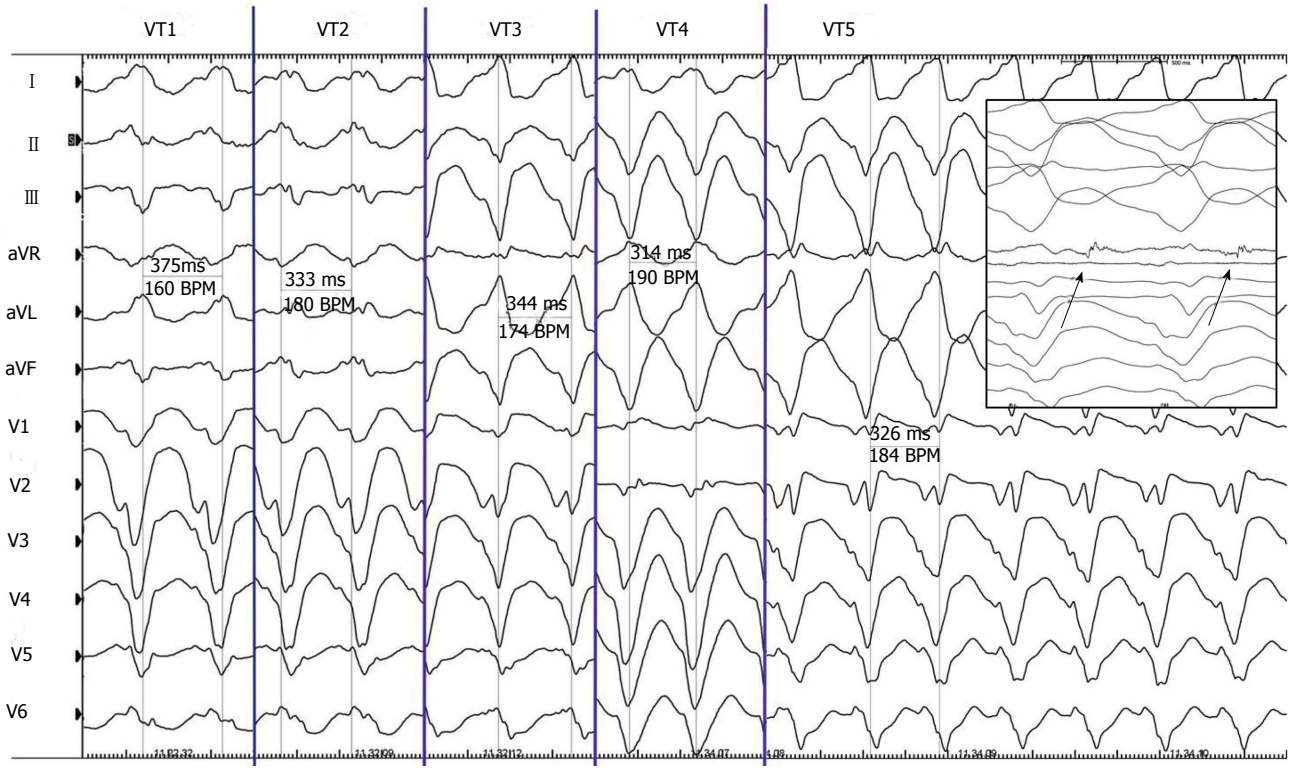

Figure 3 Cycle and QRS morphologies of all the 5 sustained ventricular tachyarrhythmias observed and mapped during the procedure. In the box it is possible to appreciate the mid-diastolic potential (arrows) recorded during ventricular tachyarrhythmias (VT) 5. BPM: Beat per minute.

A complete electroanatomical map (EAM) of the aneurysm was obtained by ICE, showing an area of dense scar surrounded by near-scar tissue with abnormal electrical activities (AEAs) all along the borders of the aneurism. Five VT morphologies spontaneously occurred (Figure 3); only 2 of them were effectively mapped creating an activation map and identifying a mid-diastolic potential, both were terminated by radiofrequency (RF) delivery at the critical isthmus located at the border of the aneurysm. Then a substrate-guided CA was accomplished targeting all AEAs by sequential RF energy pulses (30 up to 40 Watts, SF Thermocool, Biosense-Webster, United States), to achieve the complete electrical isolation of the aneurysm. At the end of the procedure, a complete protocol of programmed electrical stimulation (drive 600 and 400 ms, up to three extrastimuli) from the RV apex was negative. No VT recurrence was observed in a 6 mo follow up period on amiodarone (1 g/wk) therapy.

DISCUSSION

Tachyarrhythmias appear as frequent clinical manifestations of SS-associated cardiovascular damage. Arrhythmias occurrence may be associated with poor outcome and represent 6% of the overall causes of death in the large European League Against Rheumatism Scleroderma Trials and up to 12% in Research (EUSTAR) database[2].

Since different classes of anti-arrhythmics are available and SS patients may have multiple organs involved and take concomitant drugs, the choice of treatment must be personalized to the patient. ICDs have been used effectively in selected patients to prevent sudden cardiac death. There is no specific recommendation in VT treatment in SS patients, and the use of CA has been reported anecdotally[3,4]. We present the first case of SS patient with multiple VT morphologies undergoing successful CA guided by an integrated approach aiming at the electro-anatomical characterization of RV cardiomyopathy. Based on our experience CA should be considered as an adjunctive treatment in patients with sustained, monomorphic VTs refractory to pharmacological therapy. Our experience adds new pieces on the knowledge of the arrhythmic substrate in SS. First of all, CA approach requires an accurate imaging of the RV acquired by both angiography and real time echo (ICE, as in our case, or transoesophageal) to identify the area of interest and to reduce potential risk as RF delivery in very thin tissue[5]. Secondary, a combined high density mapping of the whole scar and peri-scar area allows a substrate-guided abolition of all AEAs leading to a successful procedure.

Malignant VTs may be expression of an advanced form of RV disease in patients with SS and CA may be proposed as a therapeutic option for VT treatment. The combination of advanced strategies of imaging together with EAM should be preferred due to the complex arrythmogenic substrate to improve efficacy and safety.

ACKNOWLEDGMENTS

The authors thank Dr. Viviana Biagioli for editorial assis-

tance.

COMMENTS

Case characteristics

A 63-year-old woman affected by a severe form of systemic sclerosis (SS) with previous dual chamber implantable cardioverter defibrillator implant presented with drug-refractory multiple forms of ventricular tachycardias.

Clinical diagnosis

Identification of aneurismal lesion of the right ventricular (RV) with the critical isthmus from which the five morphologies of ventricular tachyarrhythmias (VTs) arise.

Differential diagnosis

Arrhythmogenic right ventricular dysplasia, myocarditis.

Laboratory diagnosis

Positive Antinuclear Antibodies; metabolic panel and liver function test were within normal limits.

Imaging diagnosis

Intracardiac echocardiography allowed to detect a significant RV dilatation with a complex lesion characterized by thin walls and irregular multiple trabeculae.

Pathological diagnosis

A complete electroanatomical map of the aneurysm showed an area of dense scar surrounded with abnormal electrical activities.

Treatment

Five VTs morphologies were terminated by radiofrequency (RF) delivery at the critical isthmus located at the border of the aneurysm.

Related reports

There is no specific recommendation in VT treatment in SS patients, and the use of CA has been reported anecdotally.

Term explanation

CARTO system is a non fluoroscopic mapping system allowing to accurately determine the location of arrhythmia origin, define cardiac chamber geometry in 3D, delineate areas of anatomic interest.

Experiences and lessons

This is the first case of systemic sclerosis patient with multiple VT morphologies undergoing successful CA guided by an integrated approach aiming at the electro-anatomical characterization of RV cardiomyopathy.

Peer review

This case report describes a case of SS complicated by multiple VTs. This very rare case nicely demonstrates image findings together with important electrophysiologic features in this entity.

REFERENCES

1 **Dello Russo A**, Casella M, Pelargonio G, Bonelli F, Santangeli P, Fassini G, Riva S, Carbucicchio C, Giraldi F, De Iuliis P, Bartoletti S, Pintus F, Di Biase L, Pepi M, Natale A, Fiorentini C, Tondo C. Intracardiac echocardiography in electrophysiology. *Minerva Cardioangiol* 2010; **58**: 333-342 [PMID: 20485239]

2 **Tyndall AJ**, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE, Bancel DF, Allanore Y, Müller-Ladner U, Distler O, Iannone F, Pellerito R, Pileckyte M, Miniati I, Ananieva L, Gurman AB, Damjanov N, Mueller A, Valentini G, Riemekasten G, Tikly M, Hummers L, Henriques MJ, Caramaschi P, Scheja A, Rozman B, Ton E, Kumánovics G, Coleiro B, Feierl E, Szucs G, Von Mühlen CA, Riccieri V, Novak S, Chizzolini C, Kotulska A, Denton C, Coelho PC, Kötter I, Simsek I, de la Pena Lefebvre PG, Hachulla E, Seibold JR, Rednic S, Stork J, Morovic-Vergles J, Walker UA. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis* 2010; **69**: 1809-1815 [DOI: 10.1136/ard.2009.114264]

3 **Chung HH**, Kim JB, Hong SH, Lee HJ, Joung B, Lee MH. Radiofrequency Catheter Ablation of Hemodynamically Unstable Ventricular Tachycardia Associated with Systemic Sclerosis. *J Korean Med Sci* 2012; **27**: 215-221 [DOI: 10.3346/jkms.2012.27.2.215]

4 **Lacroix D**, Brigadeau F, Marquié C, Klug D. Electroanatomic mapping and ablation of ventricular tachycardia associated with systemic sclerosis. *Europace* 2004; **6**: 336-342 [PMID: 15172658]

5 **Khouzam RN**, D'Cruz IA, Arroyo M, Minderman D. Systemic scleroderma with moderate to severe mitral regurgitation: unusual three-dimensional echocardiographic features. *Can J Cardiol* 2008; **24**: 152 [PMID: 18273492]

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CASE REPORT

Anaphylactic cardiovascular collapse during hemodialysis: Kounis syndrome in the dialysis room

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Core tip: This is the first report of Kounis syndrome occurring in the dialysis room in a patient using a new dialysis machine. The apparatus components acting as allergens are incriminated since subsequent hemodialysis sessions with the apparatus used before the anaphylactic reaction were without any sequelae. Materials such as polyurethane, polyamide, polycarbonate, silicon rubber and polypropylene acting as allergens might prove risky in sensitive patients during hemodialysis. Atopic patients should be always interrogated about allergies and patch testing concerning the apparatus components should be performed in such patients.

Mazarakis A, Bardousis K, Almpanis G, Mazaraki I, Ouzounis A, Kounis NG. Anaphylactic cardiovascular collapse during hemodialysis: Kounis syndrome in the dialysis room. *World J Cardiol* 2014; 6(10): 1131-1134 Available from: URL: http://www.wjgnet.com/1949-8462/full/v6/i10/1131.htm DOI: http://dx.doi.org/10.4330/wjc.v6.i10.1131

Abstract

Kounis syndrome seems to be not a rare disease but a rarely diagnosed disorder. Multiple causes can join forces and trigger the development of this syndrome. We report the first case of Kounis syndrome manifesting as myocardial infarction with cardiovascular collapse that occurred in the dialysis room following an allergic reaction. The dialysis apparatus material of polyurethane, polyamide, polycarbonate, silicon rubber and polypropylene were incriminated causes. Physicians should be aware of the causality and existence of this disorder in order to achieve early and correct diagnosis and apply the appropriate therapeutic measures.

Key words: Anaphylactic shock; Dialysis room; Dialysis apparatus; Kounis syndrome; Mast cell degranulation

INTRODUCTION

Kounis syndrome is hypersensitivity-associated acute coronary syndrome manifesting as acute myocardial infarction, coronary spasm or even stent thrombosis[1]. It is caused by numerous drugs, materials, mertals, environmental exposures and conditions associated with mast cell activation. During mast cell activation the released mediators can induce either coronary artery spasm which can progress to acute myocardial infarction or atheromatous plaque erosion or rupture culminating to coronary thrombosis. Kounis syndrome is ubiquitous disease affecting patients of any age, from 2-year-old to octagenarians, involving numerous and continuously increasing causes, with broadening clinical manifestations[2,3]. The following report concerns of a patient who developed

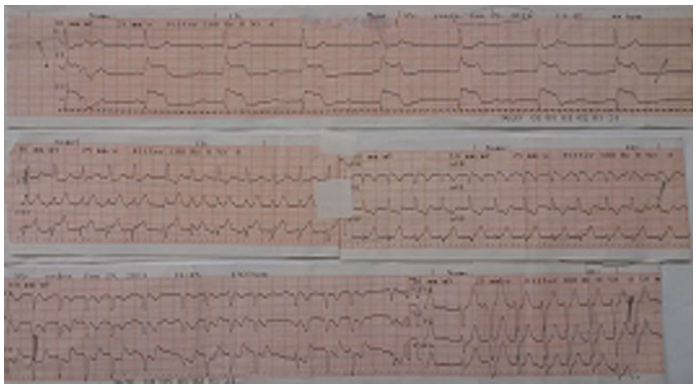

Figure 1 Electrocardiogram showing complete heart block and ST elevation in the inferior leads during anaphylaxis followed by rapid atrial fibrillation during antihistamine and adrenaline administration.

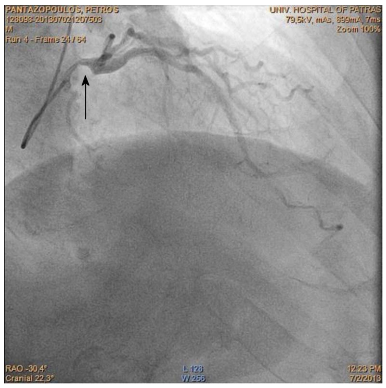

Figure 2 Coronary arteriogram revealing severe left main disease.

this syndrome during hemodialysis. To our knowledge this is the first case of Kounis syndrome occurring in the dialysis room.

CASE REPORT

A 75-year-old diabetic, hypertensive man having history of coronary artery disease with acute myocardial infarction 12 years ago and stent implantation in the left anterior descending coronary artery and undergoing hemodialysis thrice a week for the last 3 years due to diabetic chronic kidney disease, was transferred to the emergency department after an episode of loss of consciousness accompanied by chest discomfort during dialysis.

He was asymptomatic until he had been connected to the hemodialysis machine in the renal unit for his routine dialysis session. The staff of the unit confirmed changing of the hemodialysis apparatus before the current session with an older brand due to unavailability of the previously used machine. The new apparatus consisted of polyamix membrane, potting material made from polyurethane, housing caps made from polycarbonate, protective plugs made from polypropylene and o-ring made from silicon. Five minutes following the connection with the new dialysis apparatus the patient developed an erythematous rash that covered his trunk and complained of feeling "burning" in his face, chest pain, dyspnea, palpitations and suddenly lost consciousness. A severe anaphylactic reaction associated with Kounis syndrome probably due to the new dialyzer- was suspected and immediate cardiopulmonary resuscitation was started with chest compressions, antihistamines, hydrocortisone intravenously and adrenaline intramuscular doses of 0.2-0.5 mg (1:1000). His blood pressure was 60/40 mmHg and the electrocardiogram revealed complete heart block with cardiac rate of 40 beats per minute and 5-7mm ST elevation in leads Ⅱ and Ⅲ, AVF. Within 3 min the patient was alerted but confused. His blood pressure was raised to 85/60 mmHg, electrocardiogram revealed atrial fibrillation with rapid ventricular response 135 beat per minute and ST elevation 1-2 mm in leads Ⅱ, Ⅲ and aVF and ST depression 1 mm in leads Ⅰ, aVL, V1-V3 (Figure 1). He was then transferred to our coronary care unit for further treatment and evaluation.

Upon arrival to the unit the patient was alert, complaining of mild retrosternal chest pain and Killip class Ⅱ dyspnea. His blood pressure was 90/50 mmHg, the heart rate was 120 bpm regular and his temperature was 36.0 C. The oxygen saturation, while breathing in the room air was 93%, the electrocardiogram revealed sinus tachycardia with 122 bpm and minimal 0.5-1 mm ST elevation in leads Ⅱ, Ⅲ and aVF and 1mm horizontal-downsloping ST depression in leads Ⅰ, aVL, V1-V6.

Treatment started with 300 mg clopidogrel and 4000IU of low molecular weight heparin. He was not aspirin naïve because of his previous myocardial infarction, so no oral loading dose of aspirin was administered. Peak high sensitivity troponin Ⅰ levels were 0.350 ng/mL, eosinophils 8%, IgEs were elevated to 170 IU/mL (normal levels < 110 IU/mL) but specific IgEs for the dialysis apparatus were not detected. Transthoracic echocardiographic study showed hypokinesis of basal and mid portions of the infero-posterior wall of the left ventricle with an estimated ejection fraction of 50%. Skin prick tests were not performed on ethical grounds.

The patient remained hemodynamically and electrically stable, asymptomatic and afebrile. Coronary angiography revealed severe stenosis of the left main artery and 70% stenosis of the first segment of right coronary artery and patent previous stent (Figure 2). The patient underwent successful coronary artery bypass surgery. Subsequent hemodialysis sessions with the apparatus used before the anaphylactic reaction were re-started and were without any sequelae.

DISCUSSION

The described patient developed severe anaphylaxis associated with myocardial infarction and cardiovascular collapse in the hemodialysis room soon after changing the dialysis apparatus. He was found to have increased IgEs and eosinophil count suggesting hypersensitivity reaction and was diagnosed as type Ⅱ variant of Kounis syndrome. All 4 components of the used apparatus namely polyamix membrane, potting material made from polyurethane, housing caps made from polycarbonate, protective plugs made from polypropylene and o-ring made from silicon rubber have been incriminated to induce hypersensitivity reactions. Polyamix membrane is made from a polymer blend of polyarylethersulfone, polyvinylpyrrolidone and polyamide all of which are sensitizers[4]. Polyurethane chemicals are produced by the reaction of isocyanates and they may cause allergic contact dermatitis or precipitate asthma attacks[5]. Polycarbonate can induced allergic reactions especially in dental procedures[6]. Polypropylene is able to induce irritant contact dermatitis[7] and silicon rubber has induced hypersensitivity reactions known as "latex-fruit syndrome"[8]. These materials have been incriminated to induce hypersensitivity reactions by activating high and low affinity IgE receptors known as FCγR Ⅰ, FCγRⅡ, FCεR Ⅰ and FCεRⅡ receptors situated on both mast cell and platelet surface[9].

Therefore the described patient was exposed to 5 antigens. Indeed, clinical studies indicate that sensitive patients simultaneously exposed to several allergens can have more symptoms than mono-sensitized individuals[10]. This could be an explanation for the patient's immediate cardiovascular collapse. On the other hand, immunoglobulin E antibodies with different specificities can have additive effects and small, even subthreshold numbers of them can join forces and trigger the cells to release their mediators. This can occur when the patient is simultaneously exposed to the corresponding antigens[11]. The initiation of allergic inflammation takes place when allergens cross-bridge their corresponding, receptor-bound, immunoglobin IgE antibodies on the mast cell or basophil cell surface. These cells degranulate and release their mediators when the critical number of bridged IgE antibodies reaches the order of 2000 out of maximal number of some 500000-1000000 IgE antibodies on the cell surface[12]. A total of approximately 1000 bridges are necessary to induced mast cell degranulation.

Kounis syndrome seems to be not a rare disease but a rarely diagnosed disorder. Multiple and combined causes can trigger the development of this syndrome. Physicians should be aware of its pathophysiology and existence in order to apply predictive, preventive, diagnostic and appropriate therapeutic measures.

COMMENTS

Case characteristics

A 75-year-old diabetic, hypertensive man suffering from coronary artery disease and renal failure developed anaphylactic cardiac collapse soon after been connected with the dialysis apparatus.

Clinical diagnosis

The appearance of erythematous rash that covered his trunk together with feeling "burning" in his face, chest pain, dyspnea, palpitations, sudden loss of consciousness, electrocardiophic changes, increased cardiac enzymes, increased eosinophils and IgEs were suggestive of type Ⅱ variant of hypersensitivity-associated Kounis syndrome.

Differential diagnosis

The differential diagnosis included anaphylactic shock and acute myocardial infarction but their combination is classical with Kounis acute associated with hypersensitity coronary syndrome.

Laboratory diagnosis

Serial electrocardiographic changes of complete heart block, atrial fibrillation, ST segment elevation, increased cardiac enzymes and troponin Ⅰ, increased eosinophils, increased IgEs and hypokinetic basal and mid portions of the infero-posterior wall of the left ventricle were observed.

Imaging diagnosis

Coronary angiography revealed severe stenosis of the left main artery and 70% stenosis of the first segment of right coronary artery but patent previous stent that had been implanted in the left anterior descending artery 12 years previously.

Pathological diagnosis

Neither pathological examination nor skin biopsy for the erythematous rash was thought necessary to be performed.

Treatment

The patient was treated initially with chest compressions, antihistamines, hydrocortisone intravenously and adrenaline intramuscular doses followed by clopidogrel and of low molecular weight heparin and finally underwent successful coronary artery bypass surgery. Subsequent hemodialysis sessions with the apparatus used before the anaphylactic reaction were re-started and were without any sequelae.

Related reports

No related reports are available and this case of Kounis syndrome is the first in the world literature.

Term explanation

This case of Kounis type II variant syndrome is characterized as unique.

Experience and lessons

Kounis syndrome is not a rare disease but a rarely diagnosed disorder caused by multiple and combined causes therefore physicians should be aware of its pathophysiology and existence in order to apply predictive, preventive, diagnostic and appropriate therapeutic measures.

Peer review

This is a very interesting report of the case of Kounis syndrome occuring in the dialysis room.

REFERENCES

1 **Kounis NG**. Coronary hypersensitivity disorder: the Kounis syndrome. *Clin Ther* 2013; **35**: 563-571 [PMID: 23490289 DOI: 10.1016/j.clinthera.2013.02.022]

2 **Parent B**, Wearden P, Kounis NG, Chrysostomou C. Kounis syndrome or allergic coronary vasospasm in a two-year-old. *Congenit Heart Dis* 2011; **6**: 499-503 [PMID: 21418536 DOI: 10.1111/j.1747-0803.2011.00499.x]

3 **Biteker M**, Duran NE, Biteker FS, Civan HA, Kaya H, Gökdeniz T, Yildiz M, Ozkan M. Allergic myocardial infarction in childhood: Kounis syndrome. *Eur J Pediatr* 2010; **169**: 27-29 [PMID: 19277706 DOI: 10.1007/s00431-009-0965-5]

4 **Situm M**, Lugović-Mihić L, Bulat V, Peternel R, Vojniković B, Martinis M, Toth I. Dermatological aspects of contact dermatitis from eyeglass frames and optical materials. *Coll Antropol* 2013; **37** Suppl 1: 19-24 [PMID: 23837217]

5 **Turan H**, Saricaoğlu H, Turan A, Tunali S. Polyurethane toilet seat contact dermatitis. *Pediatr Dermatol* 2011; **28**: 731-732 [PMID: 21575050 DOI: 10.1111/j.1525-1470.2011.01482.x]

6 **Tanoue N**, Nagano K, Matsumura H. Use of a light-polymerized composite removable partial denture base for a patient

hypersensitive to poly(methyl methacrylate), polysulfone, and polycarbonate: a clinical report. *J Prosthet Dent* 2005; **93**: 17-20 [PMID: 15623992 DOI: 10.1016/j.prosdent.2004.09.022]

7 **Patiwael JA**, Wintzen M, Rustemeyer T, Bruynzeel DP. Airborne irritant contact dermatitis due to synthetic fibres from an air-conditioning filter. *Contact Dermatitis* 2005; **52**: 126-129 [PMID: 15811024 DOI: 10.1111/j.0105-1873.2005.00526.x]

8 **Ricci G**, Piccinno V, Calamelli E, Giannetti A, Pession A. Latex-fruit syndrome in Italian children and adolescents with natural rubber latex allergy. *Int J Immunopathol Pharmacol* 2013; **26**: 263-268 [PMID: 23527732]

9 **Kounis NG**, Mazarakis A, Tsigkas G, Giannopoulos S, Goudevenos J. Kounis syndrome: a new twist on an old disease. *Future Cardiol* 2011; **7**: 805-824 [PMID: 22050066 DOI: 10.2217/fca.11.63]

10 **MacGlashan DW**, Bochner BS, Adelman DC, Jardieu PM, Togias A, McKenzie-White J, Sterbinsky SA, Hamilton RG, Lichtenstein LM. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. *J Immunol* 1997; **158**: 1438-1445 [PMID: 9013989]

11 **Nopp A**, Johansson SG, Lundberg M, Oman H. Simultaneous exposure of several allergens has an additive effect on multisensitized basophils. *Allergy* 2006; **61**: 1366-1368 [PMID: 17002715 DOI: 10.1111/j.1398-9995.2006.01211.x]

12 **Wickman M**. When allergies complicate allergies. *Allergy* 2005; **60** Suppl 79: 14-18 [PMID: 15842228 DOI: 10.1111/j.1398-9995.2005.00852.x]

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INSTRUCTIONS TO AUTHORS

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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Author(s) and editor(s)

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Conference paper

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Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee.

Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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