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REVIEW

Endothelial progenitor cells: Exploring the pleiotropic effects of statins

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Abstract

Statins have become a cornerstone of risk modification for ischaemic heart disease patients. A number of studies have shown that they are effective and safe. However studies have observed an early benefit in terms of a reduction in recurrent infarct and or death after a myocardial infarction, prior to any significant change in lipid profile. Therefore, pleiotropic mechanisms, other than lowering lipid profile alone, must account for this effect. One such proposed pleiotropic mechanism is the ability of statins to augment both number and function of endothelial progenitor cells. The ability to augment repair and maintenance of a functioning endothelium may have profound beneficial effect on vascular repair and potentially a positive impact on clinical outcomes in patients with cardiovascular disease. The following literature review will discuss issues surrounding endothelial progenitor cell (EPC) identification, role in vascular repair, factors affecting EPC numbers, the role of statins in current medical practice and their effects on EPC number.

Key words: Statins; Endothelial progenitor cells; Pleiotropic effects; Ischaemic heart disease; Pleiotropic mechanisms

Core tip: Statin therapy is a cornerstone of current management in coronary artery disease. Conventional thinking of stain therapy is for reduction of low-density lipoproteins. However a number of studies have observed an early benefit prior to any significant change in lipid profile. Therefore alternative pleiotropic mechanisms to account for this have been proposed. One such proposed mechanism is the ability of statins to augment both number and function of endothelial progenitor cells (EPCs). The following literature review discusses issues surrounding EPC identification, role in vascular repair, the role of statins in current medical practice and their effects on EPCs.

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INTRODUCTION

The maintenance of endothelial integrity is essential for the preservation of a healthy vasculature[1]. This integrity results from a balance between on-going endothelial damage and the rate of vascular repair. Disruption of endothelial integrity or impairment of endothelial repair mechanisms is a central step in both the initiation and progression of atherosclerosis[2]. Endothelial repair is dependent on undifferentiated cells migrating to sites of vascular injury[3-5] then differentiating into mature endothelial cells[6-13]. These undifferentiated cells are called endothelial progenitor cells (EPCs) have a central role in vascular repair by virtue of their ability to proliferate, migrate to site of vascular injury and then differentiate into mature vascular endothelium[13,14]. EPCs perpetuate this cycle by secreting pro-angiogenic cytokines[15].

Statins form the corner stone of treatment of coronary artery disease. The safety and efficacy of statins in reducing cardiac events by decreasing serum LDL-cholesterol has been well described[16-18]. Recently however studies have shown the early beneficial effect of statins occurs before any significant change in lipid profile. This led to the hypothesis that cardiovascular benefits of statins may occur *via* alternative mechanisms other than reduction of LDL-cholesterol alone[19,20]. One such proposed mechanism is the ability of statins to augment both number and function of EPCs.

The following literature review discusses issues surrounding EPC identification, role in vascular repair, factors affecting EPC numbers, the role of statins in current medical practice and their effects on EPC number.

RESEARCH AND LITERATURE

We performed a review of various studies within the literature available on endothelial progenitor cell and statins. The authors searched various databases (EMBASE, OVID, PubMed) using the keywords: "Endothelial progenitor cells", "statin", "pleiotropic effects". We studied the various publications that we obtained from the search results. Full text manuscripts were obtained. We only included papers in the English language.

EPCS

Cellular identification and staging of differentiation has been made possible by specific surface receptors called epitopes that allow immunophenotyping. This process allows identification of subset of cellular surface molecule termed cluster of differentiation (CD). Cellular subtypes may be defined by the presence or absence of a particular CD molecule. Therefore "CD" may be "+ "or "-" denoting either presence or absence of a particular CD, and is used to describe stem cells rather than fully differentiated cell types. Certain cell types may have variable CD marker expression during maturation for example, and therefore classed as bright (high), mid (mid) or dim (low) denoting intensity of expression[21,22].

Vascular repair had previously been thought to be due to migration and proliferation of fully differentiated endothelial cells, in a process called angiogenesis[23]. Asahara *et al*[24] identified putative cells with cell surface marker $CD34^+$, alternately named kinase insert domain receptor (KDR/VEGFR) markers capable of differentiating into endothelial cells both *in vitro* and *in vivo*[24-26]. Subsequent studies recognised that in fact undifferentiated cells subsequently termed EPCs migrated to sites of neovascularization and then differentiate into endothelial cells[24,26] in a process called vasculogenesis[27]. EPCs are derived from pluripotential stem cells within the bone marrow. These then evolve into mature endothelial cells[24] accounting for only 0.001%-0.0001% of peripheral blood cells in an unstressed state[28]. Circulating EPCs may be isolated from bone marrow or the circulation as mononuclear cells[24,29,30], expressing a variety of endothelial surface markers[31]. However, there currently remains a lack of consensus on phenotypic and functional definition of endothelial precursor cells[32,33].

EPCs are a diverse group of cells of different lineages that have angiogenic potential, but are not always necessarily able to differentiate into functional endothelial cells as would be suggested from their name[32]. EPCs are derived from $CD34^+$ hematopoietic progenitor cells[6,24,29,31], with the subset of EPCs characterized by co-expression of endothelial marker proteins[6,29,31]. Studies have identified 3 markers associated with early functional EPCs including CD133, CD34, and the vascular endothelial growth factor receptor-2 (VEGFR-2) also known as kinase insert domain receptor (KDR, Flk-1 or CD309)[7,31]. Therefore EPCs express markers of both hematopoietic stem cells (CD34 and CD133) and endothelial cells (CD146, vWF, and VEGFR2)[26,28,29,31,34-37]. The presence of certain cell surface markers are depend on the stage of maturations of the EPC. For example the cell surface marker CD133, a 120-kDa trans-membrane polypeptide, is expressed on bone marrow derived hematopoietic stem and progenitor cells in peripheral blood[37]. The expression of CD133 on EPCs declines during maturation within the peripheral circulation. Currently there remains some uncertainty as to when EPCs lose the CD133 surface marker, whether during transmigration from bone marrow to circulation or later whilst in the peripheral blood system[38]. Nevertheless the loss of CD133 represents the transformation into more mature EPCs that are endothelial-like cells[37].

Table 1 Table to show cell markers during development of endothelial progenitor cell

	Endothelial progenitor cells		
	Bone marrow	Circulation	
		Early EPCs	Mature EPCs
$CD133^+$	+	+/-	-
$CD34^+$	+	+	+
$VEGFR2^+$	+	++	+++
$CD31^+$	-	+	+
VE-cadherin	-	+	+
vWF	-	+	+

EPC: Endothelial progenitor cell; VEGFR: Vascular endothelial growth factor receptor.

Whereas the expression of CD34 a cell surface marker found on immature pluripotential stem cells[31] that acts as an adhesion molecule, although the precise function remains unclear, gradually increases as the CD133 decreases as the EPC matures[37]. During the course of maturity EPCs begin to have increased expression of other markers specific to endothelial cells such as VEGFR-2, VE-cadherin, and von Willebrand factor (vWF)[37].

The expression of $CD34^+$, $CD133^+$, and/or $VEGF2^+$ has been used as identifying markers of EPCs in a number of studies[28,32,39-41]. Whereas as other studies advocate the use of $CD133^+$ either alone or in combination with $CD34^+$/VEGFR-2^+ cells for identification of EPCs[31,42]. In contrast, other studies have suggested that $CD133^+$ are haematopoietic cell lines and have not been identified in and therefore unable to form endothelial phenotypic EPCs[7,40,43]. Ingram *et al*[28] proposed that $CD45^-$ cells incorporated "true" circulating EPCs and verified by other studies[28,39,40,43]. Interestingly, $CD34^+$/$VEGFR2^+$ and diminished (dim) CD45 ($CD45^{dim}$) cells have been found to have greater correlation with coronary heart disease severity and response to statin therapy[44,45].

In summary, the maturity of the EPC is marked by the gradual loss of CD133, gradual increased expression of $CD34^+$ and the appearance of CD31, VE-cadherin and vWF cell surface markers (Table 1).

EPCS AND CORONARY ARTERY DISEASE

Endothelial integrity is essential for healthy vasculature, and can be thought of as a balance between continued endothelial damage and the capacity to repair by a pool of EPCs[9,46]. It is now generally accepted that cardiovascular risk correlates with EPC numbers. Highlighting the integral relationship between endothelium and atherosclerosis[47-51], disruption of endothelial integrity by endothelial cell injury has been shown to be a stimulus for the development of atherosclerosis[2], but also as a stimulus for augmentation of EPC number and function[9,52,53]. Continued endothelial damage[54] may lead to an eventual reduction of the number of EPCs. Elevated EPC numbers have been shown to be associated with augmented formation of collaterals in coronary artery disease[55] and restoration of endothelial vasodilator function[9]. A reduction in EPC numbers may lead to deficient endothelial repair and progression of atherosclerosis, with further EPC depletion and perpetuation of atherosclerosis[9,56]. However, it is uncertain whether low numbers of circulating EPCs represents enhanced usage by vascular repair processes, or reduced production by bone marrow.

$CD34^+$ $VEGFR2^+$ EPCs cells have been shown to be reduced in patients with atherosclerotic coronary and peripheral disease[57]. Vasa *et al*[56] found not only reduced numbers, but also impaired function of EPCs in patients with coronary artery disease. Elevated numbers of EPC have been associated with freedom from myocardial infarction, hospitalization, revascularization and cardiovascular death in patients with coronary artery disease[56,58]. Furthermore the predictive value of EPC count has been shown to be independent of traditional cardiovascular risk factors[9,46,59]. In fact, the extent of the reduction in EPC numbers has been associated not only with coronary artery disease burden[60], but also the presence of symptoms[61,62].

Finally, elevated numbers of circulating $CD34^+$/$CD133^+$/VEGFR2 EPCs have been observed after an acute myocardial infarction[42,63]. This may be regarded as a consequence of cardiac ischaemia together with raised inflammatory and haematopoietic cytokines stimulating EPC mobilisation from the bone marrow[64-66]. A similar response is seen following coronary angioplasty[67], and interestingly, the combination of an acute coronary syndrome (ACS) treated by angioplasty provoked an enhanced EPC response[68]. Therefore, EPC may have a central role not only in repairing coronary vessels after plaque rupture, but also after any coronary intervention.

STATIN THERAPY

Statins act by competitively inhibiting 3 hydroxy-3-methylglutaryl Coenzyme A (HMG CoA) reductase, the rate limiting step in the mevalonate pathway producing isoprenoids including cholesterol. The competitive inhibition of HMG CoA reductase induces the expression of LDL receptors within the liver, thereby increasing the catabolism of plasma LDL, with a consequent decrease in LDL-cholesterol levels[69].

The safety and efficacy of statins in reducing cardiac events by decreasing serum LDL-cholesterol has been well described[16-18]. Statin therapy has been shown to reduce death and cardiovascular events in primary prevention of atherosclerosis[70], stable coronary artery disease[16,71-73], ACS[74,75] and secondary prevention[72]. Statins also appear to reduce development of atherosclerotic lesions[76,77] and decrease plaque burden[13,78].

The beneficial effect of intensive statin therapy was studied in a prospective meta-analysis of 90056 patients from 14 randomised trials and found greater

cholesterol reduction was associated with better patient outcomes[19]. The study found that the 5-year incidence of major adverse cardiac events, coronary revascularization and stroke was reduced by one fifth for every millimoles per liter reduction in LDL cholesterol, which was irrespective of the initial lipid profile[19].

Another meta-analysis found aggressive statin therapy was associated with reduced peri-procedural myocardial infarction and a 44% risk reduction in major adverse cardiovascular events at 30-d irrespective of clinical presentation[79]. Moreover, the ARMYDA-RECAPTURE study[80] found reloading of the high dose statin, atorvastatin 80 mg in 383 NSTEMI and stable angina patients on chronic therapy prior to percutaneous coronary intervention (PCI) had a 50% reduction in 30-d major adverse cardiac events in both group with a greater reduction in NSTEMI group[80].

These studies led to the universal adoption of statin therapy in patients with coronary artery disease irrespective of presentation from stable angina to ACSs[81,82].

THE EFFECT OF STATIN THERAPY ON EPCS

Several studies have shown the early beneficial effect of statins occurs before any significant change in lipid profile. This led to the hypothesis that cardiovascular benefits of statins may occur *via* alternative mechanisms other than reduction of LDL-cholesterol alone[19,20]. These potential beneficial effect(s) may represent a potential therapeutic target for ischemic heart disease patients, and therefore is of great interest. There have been a number of mechanisms proposed to account for pleiotropic effects of statin therapy. These include reduction in vascular inflammation[83], reduction of platelet aggregability and thrombus deposition[77,84-86], enhancement of fibrinolysis[87] and increased endothelium derived NO production[88-90]. However the mechanism that has evoked the most interest is the impact of statins on EPCs[70].

Statin therapy has been associated with greater numbers of circulating EPCs by enhancing mobilization, differentiation, increasing longevity, enhance homing to sites of vascular injury with augmentation of re-endothelisation by enhancing expression of adhesion molecules on EPC cell surface membrane[3,70,91-94].

However, the duration of the effect on EPC number by statin therapy continues to remain contentious.

In one study, atorvastatin therapy was shown to significantly increase circulating EPC as soon as 1 wk with plateauing after 3-4 wk with a 3-fold increase of EPCs from baseline in a stable angina population was also observed[70]. Whereas Deschaseaux *et al*[95] investigated whether EPCs could be firstly detected and secondly characterized in patients receiving long-term statin therapy defined as 4 wk. The group found a significantly greater number of $CD34^+$, $CD34^+/CD144^+$ circulating EPC in patients receiving statin therapy compared to statin naïve patients. Interestingly two types of EPCs were detected, early and late EPCs. The early EPCs were found to form elongated cells whereas the late EPC population gave rise to cobblestone-like colonies with strong proliferation capacities seen *in-vitro* cell culture. The numbers of early EPCs were significantly higher in patients not receiving statin therapy whereas late EPCs were significantly higher in patients receiving statin therapy. The study also observed that long term statin therapy specifically maintained late EPCs in circulation with a $CD34^+/CD144^+$ phenotype. Rodent studies have found rosuvastatin resulted in a greater than 3 fold increase in EPC numbers when compared with placebo as long as 10 wk after myocardial infarction[56]. Long-term atorvastatin 10 mg for 12 mo markedly increased EPC number with an associated decrease in oxidative DNA damage[35]. However to the contrary, Hristov *et al*[96] found reduced numbers of circulating EPCs in CHD patients on long-term statin treatment.

Statins appear to have a dose dependant effect on EPC count. A double blinded randomised pilot study found greater number of circulating $CD34^+$ $VEGFR\text{-}2^+$ EPCs after 12 wk of therapy with pravastatin 20 mg when compared to atorvastatin 10 mg[97]. Similarly, in ACS patients' intensive statin therapy with atorvastatin 80 mg after primary or rescue PCI was associated with greater EPC count at 4-mo follow up as compared to 20 mg atorvastatin. The authors found no beneficial effect in an improvement of LV function[98]. Furthermore statin reloading in patients on moderate statin therapy undergoing percutaneous coronary intervention has been shown to increase EPC count[99,100] this correlates with the beneficial effect of statin reloading of high dose statin in patients on chronic therapy[80] mentioned above.

PLEIOTROPIC EFFECTS OF STATIN THERAPY

Several proposed intracellular signaling mechanisms accounting for the pleiotropic effect of statin therapy have been put forward. Figure 1 below summarizes the positive and negative effects on EPC proliferation, mobilisation and longevity but also the effect of statin therapy.

Nitric oxide pathway

The first proposed intracellular signaling mechanisms involves nitric oxide pathway. The endothelium releases nitric oxide (NO), a primary mediator of smooth muscle tone that causes vasodilatation through the activity of endothelial-type nitric oxide synthase (eNOS)[101-104]. NO has an central role in vascular homeostasis with its bioavailability dependent on expression of endothelial eNOS[105], presence of eNOS substrate and or co-factors[106], phosphorylation of eNOS[107,108] or due to excessive depletion of NO such as seen with presence of

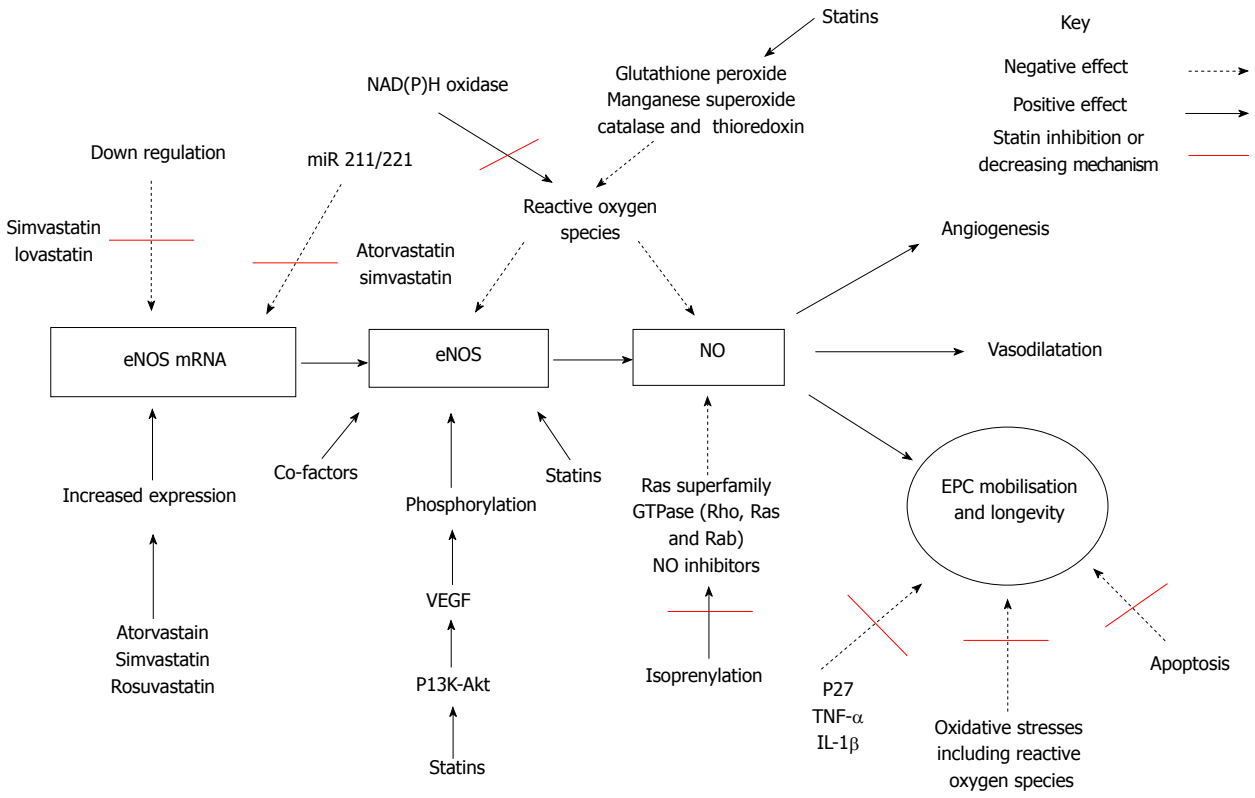

Figure 1 Simplified diagram illustrating the positive and negative effects on endothelial progenitor cell proliferation, mobilisation and longevity together with proposed mechanisms of action of statin therapy. EPC: Endothelial progenitor cell; NO: Nitric oxide; eNOS: Endothelial nitric oxide synthase; VEGF: Vascular endothelial growth factor; mRNA: Messenger ribonucleic acid; TNF: Tumor necrosis factor alpha; IL-1: Interleukin 1; P13k-AKT: Phosphoinositide 3-kinase - protein kinase B pathway; NAD(P)H oxidase: Nicotinamide adenine dinucleotide phosphate-oxidase; miR : Micro non-coding ribonucleic acid.

excessive reactive oxygen species[109]. However the main functions of NO is as a cellular signaling molecule[101], an angiogenic factor involved in stimulation, promotion, and stabilization of new blood vessels together with VEGFs, FGFs, Angiopoietins, PDGF, MCP-1, TGF, various integrins, VE-cadherin[110-113]. Statin therapy has been proposed to both enhance expression and activity of eNOS[114] a prerequisite stage for statin-mediated EPC mobilisation[115]. Statins are known to augment eNOS activity[116-118], increase eNOS expression and restoration of endothelial function[104,119-121]. Statins have also been associated with increased EPC longevity *via* several pathways including inhibition of p27[122], down regulating TNF-α or IL-1β expression[123] and prolonging eNOS expression[122] and finally by increasing eNOS mRNA half-life[124,125]. Kosmidou *et al*[126] found simvastatin and rosuvastatin prolonged expression by increasing 3' polyadenylation of eNOS mRNA. Laufs *et al*[88,124] firstly noted simvastatin and lovastatin reversed the down-regulation of eNOS expression caused by hypoxia and secondly simvastatin reversed down regulation of eNOS expression induced by oxidized LDL[88,124] a recognised cause of atherosclerosis.

miR 221 and miR 222 levels

A second observed pleotropic mechanism of statin therapy has been a decreased level of micro non-coding RNAs called miR 221 and miR 222. These negatively regulate protein expression at post-transcriptional stage[127]. This down regulating effect occurs by targeting 3' untranslated regions resulting in either degradation of target mRNA or impairing translation[128]. Furthermore miR-221 and miR-222 have been observed to regulate proliferation and differentiation of CD34-positive haematopoietic progenitor cells by reducing expression of *c-kit* receptor factor impairs haematopoietic progenitor cell proliferation[129]. Increased miR-221 and or miR-221 expression in EPC down regulates EPC differentiation and mobilisation *via* c-kit and or eNOS pathways in coronary artery disease patients[127]. Atorvastatin has been shown firstly to decrease miR 221 and miR 222, and secondly increase EPC numbers[127]. Cerda *et al*[130] found both atorvastatin and simvastatin increased NO levels and NOS3 mRNA expression, whereas ezetimibe did not. Atorvastatin, simvastatin and ezetimibe have all been shown to down-regulate the expression of miR-221, whereas miR-222 was reduced only after atorvastatin treatment. The magnitude of the reduction of miR-221 and miR-222 after treatment with statins correlated with an increment in NOS3 mRNA levels[130]. The eNOS and miR221/222 are thought likely to be components of the same pathway[131].

The PI3K/Akt/mTOR pathway

The third proposed pleiotrophic mechanism involves the phosphoinositide 3-kinase (PI3K)/protein kinase B

(Akt)/mammalian target of rapamycin (mTOR) signaling pathway plays. The PI3K/Akt/mTOR pathway plays a central role in multiple cellular processes, including cell proliferation, angiogenesis, metabolism, differentiation and longevity[132,133]. PI3K generates phosphatidylinositol 3,4,5-triphosphate (PIP3) an important lipid secondary messenger which in turn plays a central role in several signal transduction pathways[134,135] including activation of the serine/threonine kinases PDKl and Akt. Akt controls protein synthesis and cell growth *via* the phosphorylation of mTOR[136]. The PI3K/Akt pathway has been associated with angiogenesis through the regulation of the NO signaling pathway[137]. The PI3K pathway releases a group of angiogenic factors including VEGF. VEGFR2 has a central role in VEGF-induced angiogenesis[138]. VEGF is required for the migration of endothelial cells and *via* PI3K-Akt dependent manner allows formation of capillary like structures[139]. Studies have shown that NO production may be induced by VEGF and appears to be attenuated by the inhibition of PI3K[140]. This is thought to occur *via* phosphorylation of eNOS at the serine 1177 residue by Akt[107,141], required for the VEGF induced endothelial cell migration[142]. Factors that stimulate the PI3K/Akt protein kinase pathway, including statins, have been shown also to activate eNOS[87,141,143]. In turn, the expression of eNOS appears to be fundamental for mobilization of EPC and any impairment in PI3K/Akt/eNOS/NO signaling pathway may result in decreased EPC number[91,92].

The PI3K/Akt/mTOR intracellular pathway *via* inhibition of the Rho kinase has also been shown to preserves mitochondrial permeability transition pore preventing mitochondrial apoptosis, and therefore death, while conserving cardiomyocyte function[144,145].

These proposed mechanisms may account for difference in the effect of statin therapy in acute or chronic therapy. Statins given during acute ischaemic stress have been shown to firstly potentiate adenosine receptors[146,147] eventually leading to downstream regulation of eNOS and therefore increases NO production. Secondly statins augment activation of the reperfusion injury salvage kinase (RISK) pathway[148]. This results in enhanced activity of the PI3K/Akt/mTOR intracellular signal pathways[149], leading to preservation of mitochondrial function and cardio-protection. Short-term high dose statin therapy have shown an increase in both EPC mobilisation from bone marrow and augmented function[92,150-154].

Whereas chronic statin therapy has been linked to a phenomenon termed pre-ischaemic conditioning, protecting the myocardium against ischaemia[155]. This is believed to be secondary to statin induced NO availability by up regulation of eNOS and stabilisation of eNOS mRNA. Secondly, by increased production of NO and superoxide radicals improves vascular function and reducing vascular inflammation respectively[88,156]. Statins also inhibit isoprenylation of a number of Ras superfamily GTPase including Rho, Ras and Rab[157] NO inhibitors resulting in increased NO bioavailability. Thirdly, by preventing mitochondrial apoptosis and preservation of cardiomyocyte function *via* the up-regulation of the PI3K/Akt/mTOR intracellular signalling pathway by inhibition of Rho kinase[144,145]. However, the RISK pathway has been shown the down regulated with chronic statin therapy[158] and has been shown to become reactivated by statin re-loading[159]. The latter may account for the increase in EPC count in patients on chronic statin therapy reloaded with statin therapy[80,99,100].

Oxidative stresses

Finally, EPC mobilisation and or function may also be affected by oxidative stress[153,160]. Oxidative stresses occur secondary to generation of oxygen free radicals or reactive oxygen species (ROS). Oxidative stress has a central role in cardiovascular disease, and a pivotal role in atherosclerosis[161]. Cellular oxidative stress seen with oxidized low-density lipoprotein (ox-LDL) has a central role in the pathogenesis of atherosclerosis. LDL is oxidised by reactive oxygen species from both circulating cells and cells on vascular walls[162,163]. In essence, LDL oxidation is a result of a chain reaction of free radicals converting polyunsaturated fatty acids into lipid peroxides and as a consequence, formation of active aldehydes[164]. The biochemical reaction forming ox-LDL have been found to cause senescence of EPCs[165]. Whereas high density lipoprotein is regarded as atheroprotective due to some part of its antioxidant properties also has a positive effect on EPC number and function[166]. There are a number of endogenous antioxidants exerting protective effects by scavenging ROS. An indirect way ROS effects EPCs includes ROS reacting with NO forming a potent oxidant[167] with a consequent decrease in NO. Decrease in NO either by excessive oxidation or impaired production reduces EPC mobilisation and/or function[161,168]. Secondly, direct exposure to oxidative stresses or in disease conditions with high oxidative stress, for example diabetes, is associated with induced EPC apoptosis with significant reduction in EPC numbers[168,169], mobilisation, function[170] and reduced ability to migrate and or integrate into vasculature[161,171].

In an attempt to counteract the effects of oxidative stress EPCs produce superoxide dismutase[172]. Interestingly, cardiovascular risk factors have been found to alter and or reduce the EPC antioxidant ability. Healthy volunteers have found to express higher levels of antioxidative enzyme catalases including glutathione peroxidase and manganese superoxide dismutase when comparing patients with cardiovascular disease[173,174]. The underlying pathophysiological mechanism currently remains undetermined. The antioxidant pleiotropic effect of statins may include indirect mechanism increasing NO bioavailability accounting for antioxidant properties contributing to an increase in EPC mobilisation and or function[114,175]. Secondly statin therapy has also been shown to inhibit activation of NAD(P)H oxidase and ROS release[176] but also activate catalase and thioredoxin

ROS scavenging mechanisms[176,177]. Finally, statins appear to have a direct effect by significantly reducing peroxide induced apoptosis of EPCs[169] and decreasing the oxidative damage to DNA in EPCs[178].

G proteins and G protein-coupled receptors

G protein-coupled receptors (GPCR) are comprised of seven trans-membrane domain proteins and are a super family consisting of a large and diverse number of proteins encoded by approximately 5% of human genes[179]. There have been a number of classification systems proposed the most recent "GRAFS" (Glutamate, Rhodopsin, Adhesion, Frizzled/Taste2 and Secretin)[180]. In mammals there are five main families[181]. GPCRs have an integral role in transfer of extracellular stimuli to within the cell by conformational changes in trans-membrane domain structure[182-185]. They regulate physiological responses to a myriad of endogenous ligands including amines, glycoproteins, peptides and lipids. Therefore, not surprisingly that GPCRs have been implicated in regulation of cellular maintenance, differentiation, proliferation and migration of various stem cells[186-189].

GPCRs modulate activity of intracellular signaling *via* G proteins. There are currently four known G protein subfamilies each able to potentiate a number of drown stream effectors triggering a number of signaling pathways[182]. These include activation of Rho associated kinases[190,191], activation or inhibition of cyclic AMP production[192] and PI3Ks and therefore modulate the PI3K/Akt pathway[193,194]. The aforementioned have been implicated in EPC proliferation and function as described above. GPCRs have evoked great interest as a possible target for novel drug therapy[195] as an estimated 50% of all currently prescribed drugs target only a small proportion of GPCRs[196]. They are also becoming increasingly recognised as having a major role in stem cell signaling[197]. The role of GPCR in regulation and function of EPCs and the effect of statin therapy remains yet to be elucidated however current evidence suggests that they may have a pivotal role.

CONCLUSION

EPCs have a pivotal role in the maintenance of vascular integrity. However, factors that influence EPC number, migration and function are now becoming recognised and have potentially a significant role in management of ischaemic heart disease patients. Statins once thought to modify cardiovascular risk only by lowering LDL-cholesterol are now being acknowledged as having alternative mechanisms that appear to have beneficial pleiotropic effects. One such mechanism may be mediated by EPCs. A number of studies have shown positive pleiotropic effect of statins on EPCs, both function and number. There appears to be a complex interaction between statins and EPC that is only now becoming recognised. Despite great progress since Asahara's pioneering work, there remain gaps within our knowledge regarding the pleiotropic effect(s) of statins on EPCs. Further studies are required to elucidate and fully understand any pleiotropic effect and this may guide future beneficial therapeutic interventions.

REFERENCES

1 **Dong C**, Goldschmidt-Clermont PJ. Endothelial progenitor cells: a promising therapeutic alternative for cardiovascular disease. *J Interv Cardiol* 2007; **20**: 93-99 [PMID: 17391216 DOI: 10.1111/j.1540-8183.2007.00251.x]

2 **Ross R**. Atherosclerosis--an inflammatory disease. *N Engl J Med* 1999; **340**: 115-126 [PMID: 9887164 DOI: 10.1056/NEJM199901143400207]

3 **Walter DH**, Rittig K, Bahlmann FH, Kirchmair R, Silver M, Murayama T, Nishimura H, Losordo DW, Asahara T, Isner JM. Statin therapy accelerates reendothelialization: a novel effect involving mobilization and incorporation of bone marrow-derived endothelial progenitor cells. *Circulation* 2002; **105**: 3017-3024 [PMID: 12081997 DOI: 10.1161/01.CIR.0000018166.84319.55]

4 **Griese DP**, Ehsan A, Melo LG, Kong D, Zhang L, Mann MJ, Pratt RE, Mulligan RC, Dzau VJ. Isolation and transplantation of autologous circulating endothelial cells into denuded vessels and prosthetic grafts: implications for cell-based vascular therapy. *Circulation* 2003; **108**: 2710-2715 [PMID: 14597586 DOI: 10.1161/01.CIR.0000096490.16596.A6]

5 **Fujiyama S**, Amano K, Uehira K, Yoshida M, Nishiwaki Y, Nozawa Y, Jin D, Takai S, Miyazaki M, Egashira K, Imada T, Iwasaka T, Matsubara H. Bone marrow monocyte lineage cells adhere on injured endothelium in a monocyte chemoattractant protein-1-dependent manner and accelerate reendothelialization as endothelial progenitor cells. *Circ Res* 2003; **93**: 980-989 [PMID: 14525810 DOI: 10.1161/01.RES.0000099245.08637.CE]

6 **Bhattacharya V**, McSweeney PA, Shi Q, Bruno B, Ishida A, Nash R, Storb RF, Sauvage LR, Hammond WP, Wu MH. Enhanced endothelialization and microvessel formation in polyester grafts seeded with CD34(+) bone marrow cells. *Blood* 2000; **95**: 581-585 [PMID: 10627466]

7 **Gehling UM**, Ergün S, Schumacher U, Wagener C, Pantel K, Otte M, Schuch G, Schafhausen P, Mende T, Kilic N, Kluge K, Schäfer B, Hossfeld DK, Fiedler W. In vitro differentiation of endothelial cells from AC133-positive progenitor cells. *Blood* 2000; **95**: 3106-3112 [PMID: 10807776]

8 **Hu Y**, Davison F, Zhang Z, Xu Q. Endothelial replacement and angiogenesis in arteriosclerotic lesions of allografts are contributed by circulating progenitor cells. *Circulation* 2003; **108**: 3122-3127 [PMID: 14656919 DOI: 10.1161/01.CIR.0000105722.96112.67]

9 **Hill JM**, Zalos G, Halcox JP, Schenke WH, Waclawiw MA, Quyyumi AA, Finkel T. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. *N Engl J Med* 2003; **348**: 593-600 [PMID: 12584367 DOI: 10.1056/NEJMoa022287]

10 **Takahashi T**, Kalka C, Masuda H, Chen D, Silver M, Kearney M, Magner M, Isner JM, Asahara T. Ischemia- and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization. *Nat Med* 1999; **5**: 434-438 [PMID: 10202935 DOI: 10.1038/7434]

11 **Carmeliet P**. Angiogenesis in health and disease. *Nat Med* 2003; **9**: 653-660 [PMID: 12778163 DOI: 10.1038/nm0603-653]

12 **Urbich C**, Heeschen C, Aicher A, Dernbach E, Zeiher AM, Dimmeler S. Relevance of monocytic features for neovascularization capacity of circulating endothelial progenitor cells. *Circulation* 2003; **108**: 2511-2516 [PMID: 14581410 DOI: 10.1161/01.CIR.0000096483.29777.50]

13 **Nissen SE**, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart JC, Tardif JC, Schoenhagen P, Crowe T, Cain V, Wolski K, Goormastic M, Tuzcu EM. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 2006; **295**: 1556-1565 [PMID: 16533939 DOI: 10.1001/jama.295.13.jpc60002]

14 **Rafii S**, Lyden D. Therapeutic stem and progenitor cell transplantation for organ vascularization and regeneration. *Nat Med* 2003; **9**: 702-712 [PMID: 12778169 DOI: 10.1038/nm0603-702]

15 **Mukai N**, Akahori T, Komaki M, Li Q, Kanayasu-Toyoda T, Ishii-Watabe A, Kobayashi A, Yamaguchi T, Abe M, Amagasa T, Morita I. A comparison of the tube forming potentials of early and late endothelial progenitor cells. *Exp Cell Res* 2008; **314**: 430-440 [PMID: 18083163 DOI: 10.1016/j.yexcr.2007.11.016]

16 Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344**: 1383-1389 [PMID: 7968073]

17 **Shepherd J**, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995; **333**: 1301-1307 [PMID: 7566020 DOI: 10.1056/NEJM199511163332001]

18 **Pedersen TR**, Berg K, Cook TJ, Faergeman O, Haghfelt T, Kjekshus J, Miettinen T, Musliner TA, Olsson AG, Pyörälä K, Thorgeirsson G, Tobert JA, Wedel H, Wilhelmsen L. Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 1996; **156**: 2085-2092 [PMID: 8862101 DOI: 10.1001/archinte.1996.00440170097011]

19 **Baigent C**, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005; **366**: 1267-1278 [PMID: 16214597 DOI: 10.1016/S0140-6736(05)67394-1]

20 Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). *Circulation* 1998; **97**: 1440-1445 [PMID: 9576423 DOI: 10.1161/01.CIR.97.15.1440]

21 **Chan JK**, Ng CS, Hui PK. A simple guide to the terminology and application of leucocyte monoclonal antibodies. *Histopathology* 1988; **12**: 461-480 [PMID: 3294157 DOI: 10.1111/j.1365-2559.1988.tb01967.x]

22 **Ho IC**, Tai TS, Pai SY. GATA3 and the T-cell lineage: essential functions before and after T-helper-2-cell differentiation. *Nat Rev Immunol* 2009; **9**: 125-135 [PMID: 19151747 DOI: 10.1038/nri2476]

23 **Folkman J**. Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat Med* 1995; **1**: 27-31 [PMID: 7584949 DOI: 10.1038/nm0195-27]

24 **Asahara T**, Murohara T, Sullivan A, Silver M, van der Zee R, Li T, Witzenbichler B, Schatteman G, Isner JM. Isolation of putative progenitor endothelial cells for angiogenesis. *Science* 1997; **275**: 964-967 [PMID: 9020076 DOI: 10.1126/science.275.5302.964]

25 **Stump MM**, Jordan GL, Debakey ME, Halpert B. Endothelium grown from circulating blood on isolated intravascular dacron hub. *Am J Pathol* 1963; **43**: 361-367 [PMID: 14057632]

26 **Asahara T**, Masuda H, Takahashi T, Kalka C, Pastore C, Silver M, Kearne M, Magner M, Isner JM. Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization. *Circ Res* 1999; **85**: 221-228 [PMID: 10436164 DOI: 10.1161/01.RES.85.3.221]

27 **Risau W**. Mechanisms of angiogenesis. *Nature* 1997; **386**: 671-674 [PMID: 9109485 DOI: 10.1038/386671a0]

28 **Ingram DA**, Caplice NM, Yoder MC. Unresolved questions, changing definitions, and novel paradigms for defining endothelial progenitor cells. *Blood* 2005; **106**: 1525-1531 [PMID: 15905185 DOI: 10.1182/blood-2005-04-1509]

29 **Shi Q**, Rafii S, Wu MH, Wijelath ES, Yu C, Ishida A, Fujita Y, Kothari S, Mohle R, Sauvage LR, Moore MA, Storb RF, Hammond WP. Evidence for circulating bone marrow-derived endothelial cells. *Blood* 1998; **92**: 362-367 [PMID: 9657732]

30 **Lin Y**, Weisdorf DJ, Solovey A, Hebbel RP. Origins of circulating endothelial cells and endothelial outgrowth from blood. *J Clin Invest* 2000; **105**: 71-77 [PMID: 10619863 DOI: 10.1172/JCI8071]

31 **Peichev M**, Naiyer AJ, Pereira D, Zhu Z, Lane WJ, Williams M, Oz MC, Hicklin DJ, Witte L, Moore MA, Rafii S. Expression of VEGFR-2 and AC133 by circulating human CD34(+) cells identifies a population of functional endothelial precursors. *Blood* 2000; **95**: 952-958 [PMID: 10648408]

32 **Hirschi KK**, Ingram DA, Yoder MC. Assessing identity, phenotype, and fate of endothelial progenitor cells. *Arterioscler Thromb Vasc Biol* 2008; **28**: 1584-1595 [PMID: 18669889 DOI: 10.1161/ATVBAHA.107.155960]

33 **Fadini GP**, Losordo D, Dimmeler S. Critical reevaluation of endothelial progenitor cell phenotypes for therapeutic and diagnostic use. *Circ Res* 2012; **110**: 624-637 [PMID: 22343557 DOI: 10.1161/CIRCRESAHA.111.243386]

34 **Fadini GP**, Baesso I, Albiero M, Sartore S, Agostini C, Avogaro A. Technical notes on endothelial progenitor cells: ways to escape from the knowledge plateau. *Atherosclerosis* 2008; **197**: 496-503 [PMID: 18249408 DOI: 10.1016/j.atherosclerosis.2007.12.039]

35 **Hristov M**, Erl W, Weber PC. Endothelial progenitor cells: mobilization, differentiation, and homing. *Arterioscler Thromb Vasc Biol* 2003; **23**: 1185-1189 [PMID: 12714439 DOI: 10.1161/01.ATV.0000073832.49290.B5]

36 **Urbich C**, Dimmeler S. Endothelial progenitor cells: characterization and role in vascular biology. *Circ Res* 2004; **95**: 343-353 [PMID: 15321944 DOI: 10.1161/01.RES.0000137877.89448.78]

37 **Yin AH**, Miraglia S, Zanjani ED, Almeida-Porada G, Ogawa M, Leary AG, Olweus J, Kearney J, Buck DW. AC133, a novel marker for human hematopoietic stem and progenitor cells. *Blood* 1997; **90**: 5002-5012 [PMID: 9389720]

38 **Quirici N**, Soligo D, Caneva L, Servida F, Bossolasco P, Deliliers GL. Differentiation and expansion of endothelial cells from human bone marrow CD133(+) cells. *Br J Haematol* 2001; **115**: 186-194 [PMID: 11722432 DOI: 10.1046/j.1365-2141.2001.03077.x]

39 **Bertolini F**, Shaked Y, Mancuso P, Kerbel RS. The multifaceted circulating endothelial cell in cancer: towards marker and target identification. *Nat Rev Cancer* 2006; **6**: 835-845 [PMID: 17036040 DOI: 10.1038/nrc1971]

40 **Timmermans F**, Van Hauwermeiren F, De Smedt M, Raedt R, Plasschaert F, De Buyzere ML, Gillebert TC, Plum J, Vandekerckhove B. Endothelial outgrowth cells are not derived from CD133+ cells or CD45+ hematopoietic precursors. *Arterioscler Thromb Vasc Biol* 2007; **27**: 1572-1579 [PMID: 17495235 DOI: 10.1161/ATVBAHA.107.144972]

41 **Friedrich EB**, Walenta K, Scharlau J, Nickenig G, Werner N. CD34-/CD133+/VEGFR-2+ endothelial progenitor cell subpopulation with potent vasoregenerative capacities. *Circ Res* 2006; **98**: e20-e25 [PMID: 16439688 DOI: 10.1161/01.RES.0000205765.28940.93]

42 **Gill M**, Dias S, Hattori K, Rivera ML, Hicklin D, Witte L, Girardi L, Yurt R, Himel H, Rafii S. Vascular trauma induces rapid but transient mobilization of VEGFR2(+)AC133(+) endothelial precursor cells. *Circ Res* 2001; **88**: 167-174 [PMID: 11157668 DOI: 10.1161/01.RES.88.2.167]

43 **Case J**, Mead LE, Bessler WK, Prater D, White HA, Saadatzadeh MR, Bhavsar JR, Yoder MC, Haneline LS, Ingram DA. Human CD34+AC133+VEGFR-2+ cells are not endothelial progenitor cells but distinct, primitive hematopoietic progenitors. *Exp Hematol* 2007; **35**: 1109-1118 [PMID: 17588480 DOI: 10.1016/j.exphem.2007.04.002]

44 **Schmidt-Lucke C**, Fichtlscherer S, Aicher A, Tschöpe C, Schultheiss HP, Zeiher AM, Dimmeler S. Quantification of circulating endothelial progenitor cells using the modified ISHAGE protocol. *PLoS One* 2010; **5**: e13790 [PMID: 21072182 DOI: 10.1371/journal.pone.0013790]

45 **Farace F**, Gross-Goupil M, Tournay E, Taylor M, Vimond N, Jacques N, Billiot F, Mauguen A, Hill C, Escudier B. Levels of circulating CD 45(dim)CD34(+)VEGFR2(+) progenitor cells correlate with outcome in metastatic renal cell carcinoma patients treated with tyrosine kinase inhibitors. *Br J Cancer* 2011; **104**: 1144-1150 [PMID: 21386843 DOI: 10.1038/bjc.2011.72]

46 **Schmidt-Lucke C**, Rössig L, Fichtlscherer S, Vasa M, Britten M, Kämper U, Dimmeler S, Zeiher AM. Reduced number of circulating endothelial progenitor cells predicts future cardiovascular events:

proof of concept for the clinical importance of endogenous vascular repair. *Circulation* 2005; **111**: 2981-2987 [PMID: 15927972 DOI: 10.1161/CIRCULATIONAHA.104.504340]

47 **Padfield GJ**, Newby DE, Mills NL. Understanding the role of endothelial progenitor cells in percutaneous coronary intervention. *J Am Coll Cardiol* 2010; **55**: 1553-1565 [PMID: 20378071 DOI: 10.1016/j.jacc.2009.10.070]

48 **Schächinger V**, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000; **101**: 1899-1906 [PMID: 10779454 DOI: 10.1161/01.CIR.101.16.1899]

49 **Suwaidi JA**, Hamasaki S, Higano ST, Nishimura RA, Holmes DR, Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation* 2000; **101**: 948-954 [PMID: 10704159 DOI: 10.1161/01.CIR.101.9.948]

50 **Halcox JP**, Schenke WH, Zalos G, Mincemoyer R, Prasad A, Waclawiw MA, Nour KR, Quyyumi AA. Prognostic value of coronary vascular endothelial dysfunction. *Circulation* 2002; **106**: 653-658 [PMID: 12163423 DOI: 10.1161/01.CIR.0000025404.78001.D8]

51 **Gokce N**, Keaney JF, Hunter LM, Watkins MT, Menzoian JO, Vita JA. Risk stratification for postoperative cardiovascular events via noninvasive assessment of endothelial function: a prospective study. *Circulation* 2002; **105**: 1567-1572 [PMID: 11927524 DOI: 10.1161/01.CIR.0000012543.55874.47]

52 **Rouhl RP**, van Oostenbrugge RJ, Damoiseaux J, Tervaert JW, Lodder J. Endothelial progenitor cell research in stroke: a potential shift in pathophysiological and therapeutical concepts. *Stroke* 2008; **39**: 2158-2165 [PMID: 18451350 DOI: 10.1161/STROKEAHA.107.507251]

53 **Sen S**, McDonald SP, Coates PT, Bonder CS. Endothelial progenitor cells: novel biomarker and promising cell therapy for cardiovascular disease. *Clin Sci* (Lond) 2011; **120**: 263-283 [PMID: 21143202 DOI: 10.1042/CS20100429]

54 **Dimmeler S**, Vasa-Nicotera M. Aging of progenitor cells: limitation for regenerative capacity? *J Am Coll Cardiol* 2003; **42**: 2081-2082 [PMID: 14680730 DOI: 10.1016/j.jacc.2003.09.016]

55 **Lambiase PD**, Edwards RJ, Anthopoulos P, Rahman S, Meng YG, Bucknall CA, Redwood SR, Pearson JD, Marber MS. Circulating humoral factors and endothelial progenitor cells in patients with differing coronary collateral support. *Circulation* 2004; **109**: 2986-2992 [PMID: 15184289 DOI: 10.1161/01.CIR.0000130639.97284.EC]

56 **Vasa M**, Fichtlscherer S, Aicher A, Adler K, Urbich C, Martin H, Zeiher AM, Dimmeler S. Number and migratory activity of circulating endothelial progenitor cells inversely correlate with risk factors for coronary artery disease. *Circ Res* 2001; **89**: E1-E7 [PMID: 11440984 DOI: 10.1161/hh1301.093953]

57 **Chironi G**, Walch L, Pernollet MG, Gariepy J, Levenson J, Rendu F, Simon A. Decreased number of circulating CD34+KDR+ cells in asymptomatic subjects with preclinical atherosclerosis. *Atherosclerosis* 2007; **191**: 115-120 [PMID: 16620831 DOI: 10.1016/j.atherosclerosis.2006.02.041]

58 **Werner N**, Wassmann S, Ahlers P, Schiegl T, Kosiol S, Link A, Walenta K, Nickenig G. Endothelial progenitor cells correlate with endothelial function in patients with coronary artery disease. *Basic Res Cardiol* 2007; **102**: 565-571 [PMID: 17932708 DOI: 10.1007/s00395-007-0680-1]

59 **Werner N**, Kosiol S, Schiegl T, Ahlers P, Walenta K, Link A, Böhm M, Nickenig G. Circulating endothelial progenitor cells and cardiovascular outcomes. *N Engl J Med* 2005; **353**: 999-1007 [PMID: 16148285 DOI: 10.1056/NEJMoa043814]

60 **Kunz GA**, Liang G, Cuculi F, Gregg D, Vata KC, Shaw LK, Goldschmidt-Clermont PJ, Dong C, Taylor DA, Peterson ED. Circulating endothelial progenitor cells predict coronary artery disease severity. *Am Heart J* 2006; **152**: 190-195 [PMID: 16824855 DOI: 10.1016/j.ahj.2006.02.001]

61 **Gaspardone A**, Menghini F, Mazzuca V, Skossyreva O, Barbato G, de Fabritiis P. Progenitor cell mobilisation in patients with acute and chronic coronary artery disease. *Heart* 2006; **92**: 253-254 [PMID: 16415195 DOI: 10.1136/hrt.2004.058636]

62 **Güven H**, Shepherd RM, Bach RG, Capoccia BJ, Link DC. The number of endothelial progenitor cell colonies in the blood is increased in patients with angiographically significant coronary artery disease. *J Am Coll Cardiol* 2006; **48**: 1579-1587 [PMID: 17045891 DOI: 10.1016/j.jacc.2006.04.101]

63 **Shintani S**, Murohara T, Ikeda H, Ueno T, Honma T, Katoh A, Sasaki K, Shimada T, Oike Y, Imaizumi T. Mobilization of endothelial progenitor cells in patients with acute myocardial infarction. *Circulation* 2001; **103**: 2776-2779 [PMID: 11401930 DOI: 10.1161/hc2301.092122]

64 **Wojakowski W**, Tendera M, Michałowska A, Majka M, Kucia M, Maślankiewicz K, Wyderka R, Ochała A, Ratajczak MZ. Mobilization of CD34/CXCR4+, CD34/CD117+, c-met+ stem cells, and mononuclear cells expressing early cardiac, muscle, and endothelial markers into peripheral blood in patients with acute myocardial infarction. *Circulation* 2004; **110**: 3213-3220 [PMID: 15533859 DOI: 10.1161/01.CIR.0000147609.39780.02]

65 **Massa M**, Rosti V, Ferrario M, Campanelli R, Ramajoli I, Rosso R, De Ferrari GM, Ferlini M, Goffredo L, Bertoletti A, Klersy C, Pecci A, Moratti R, Tavazzi L. Increased circulating hematopoietic and endothelial progenitor cells in the early phase of acute myocardial infarction. *Blood* 2005; **105**: 199-206 [PMID: 15345590 DOI: 10.1182/blood-2004-05-1831]

66 **Leone AM**, Rutella S, Bonanno G, Abbate A, Rebuzzi AG, Giovannini S, Lombardi M, Galiuto L, Liuzzo G, Andreotti F, Lanza GA, Contemi AM, Leone G, Crea F. Mobilization of bone marrow-derived stem cells after myocardial infarction and left ventricular function. *Eur Heart J* 2005; **26**: 1196-1204 [PMID: 15734770 DOI: 10.1093/eurheartj/ehi164]

67 **Banerjee S**, Brilakis E, Zhang S, Roesle M, Lindsey J, Philips B, Blewett CG, Terada LS. Endothelial progenitor cell mobilization after percutaneous coronary intervention. *Atherosclerosis* 2006; **189**: 70-75 [PMID: 16806234 DOI: 10.1016/j.atherosclerosis.2006.04.026]

68 **Laufs U**, Liao JK. Targeting Rho in cardiovascular disease. *Circ Res* 2000; **87**: 526-528 [PMID: 11009552 DOI: 10.1161/01.RES.87.7.526]

69 **Istvan ES**. Structural mechanism for statin inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase. *Am Heart J* 2002; **144**: S27-S32 [PMID: 12486413 DOI: 10.1067/mhj.2002.130300]

70 **Vasa M**, Fichtlscherer S, Adler K, Aicher A, Martin H, Zeiher AM, Dimmeler S. Increase in circulating endothelial progenitor cells by statin therapy in patients with stable coronary artery disease. *Circulation* 2001; **103**: 2885-2890 [PMID: 11413075 DOI: 10.1161/hc2401.092816]

71 Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 1998; **339**: 1349-1357 [PMID: 9841303 DOI: 10.1056/NEJM199811053391902]

72 **Sacks FM**, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996; **335**: 1001-1009 [PMID: 8801446 DOI: 10.1056/NEJM199610033351401]

73 **LaRosa JC**, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; **352**: 1425-1435 [PMID: 15755765 DOI: 10.1056/NEJMoa050461]

74 **Ridker PM**, Morrow DA, Rose LM, Rifai N, Cannon CP, Braunwald E. Relative efficacy of atorvastatin 80 mg and pravastatin 40 mg in achieving the dual goals of low-density lipoprotein cholesterol & lt; 70 mg/dl and C-reactive protein & lt; 2 mg/l: an analysis of the PROVE-IT TIMI-22 trial. *J Am Coll Cardiol* 2005; **45**: 1644-1648 [PMID: 15893181 DOI: 10.1016/j.jacc.2005.02.080]

75 **Schwartz GG**, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T. Effects of atorvastatin on early recurrent ischemic events in acute coronary

syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001; **285**: 1711-1718 [PMID: 11277825 DOI: 10.1001/jama.285.13.1711]

76 **Maron DJ**, Fazio S, Linton MF. Current perspectives on statins. *Circulation* 2000; **101**: 207-213 [PMID: 10637210 DOI: 10.1161/01.CIR.101.2.207]

77 **Lacoste L**, Lam JY, Hung J, Letchacovski G, Solymoss CB, Waters D. Hyperlipidemia and coronary disease. Correction of the increased thrombogenic potential with cholesterol reduction. *Circulation* 1995; **92**: 3172-3177 [PMID: 7586300 DOI: 10.1161/01.CIR.92.11.3172]

78 **Nissen SE**, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, Grines CL, DeMaria AN. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* 2004; **291**: 1071-1080 [PMID: 14996776 DOI: 10.1001/jama.291.9.1071]

79 **Patti G**, Cannon CP, Murphy SA, Mega S, Pasceri V, Briguori C, Colombo A, Yun KH, Jeong MH, Kim JS, Choi D, Bozbas H, Kinoshita M, Fukuda K, Jia XW, Hara H, Cay S, Di Sciascio G. Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: a collaborative patient-level meta-analysis of 13 randomized studies. *Circulation* 2011; **123**: 1622-1632 [PMID: 21464051 DOI: 10.1161/CIRCULATIONAHA.110.002451]

80 **Di Sciascio G**, Patti G, Pasceri V, Gaspardone A, Colonna G, Montinaro A. Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention: results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) Randomized Trial. *J Am Coll Cardiol* 2009; **54**: 558-565 [PMID: 19643320 DOI: 10.1016/j.jacc.2009.05.028]

81 **Amsterdam EA**, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **64**: e139-e228 [PMID: 25260718 DOI: 10.1016/j.jacc.2014.09.017]

82 **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. *Circulation* 2013; **127**: e362-e425 [PMID: 23247304 DOI: 10.1161/CIR.0b013e3182742cf6]

83 **Bustos C**, Hernández-Presa MA, Ortego M, Tuñón J, Ortega L, Pérez F, Díaz C, Hernández G, Egido J. HMG-CoA reductase inhibition by atorvastatin reduces neointimal inflammation in a rabbit model of atherosclerosis. *J Am Coll Cardiol* 1998; **32**: 2057-2064 [PMID: 9857893 DOI: 10.1016/S0735-1097(98)00487-2]

84 **Laufs U**, Gertz K, Huang P, Nickenig G, Böhm M, Dirnagl U, Endres M. Atorvastatin upregulates type III nitric oxide synthase in thrombocytes, decreases platelet activation, and protects from cerebral ischemia in normocholesterolemic mice. *Stroke* 2000; **31**: 2442-2449 [PMID: 11022078 DOI: 10.1161/01.STR.31.10.2442]

85 **Dogra GK**, Watts GF, Chan DC, Stanton K. Statin therapy improves brachial artery vasodilator function in patients with Type 1 diabetes and microalbuminuria. *Diabet Med* 2005; **22**: 239-242 [PMID: 15717868 DOI: 10.1111/j.1464-5491.2004.01382.x]

86 **Dangas G**, Smith DA, Unger AH, Shao JH, Meraj P, Fier C, Cohen AM, Fallon JT, Badimon JJ, Ambrose JA. Pravastatin: an antithrombotic effect independent of the cholesterol-lowering effect. *Thromb Haemost* 2000; **83**: 688-692 [PMID: 10823263]

87 **Dimmeler S**, Aicher A, Vasa M, Mildner-Rihm C, Adler K, Tiemann M, Rütten H, Fichtlscherer S, Martin H, Zeiher AM. HMG-CoA reductase inhibitors (statins) increase endothelial progenitor cells via the PI 3-kinase/Akt pathway. *J Clin Invest* 2001; **108**: 391-397 [PMID: 11489932 DOI: 10.1172/JCI13152]

88 **Laufs U**, La Fata V, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. *Circulation* 1998; **97**: 1129-1135 [PMID: 9537338 DOI: 10.1161/01.CIR.97.12.1129]

89 **Kureishi Y**, Luo Z, Shiojima I, Bialik A, Fulton D, Lefer DJ, Sessa WC, Walsh K. The HMG-CoA reductase inhibitor simvastatin activates the protein kinase Akt and promotes angiogenesis in normocholesterolemic animals. *Nat Med* 2000; **6**: 1004-1010 [PMID: 10973320 DOI: 10.1038/79510]

90 **Laufs U**, Liao JK. Post-transcriptional regulation of endothelial nitric oxide synthase mRNA stability by Rho GTPase. *J Biol Chem* 1998; **273**: 24266-24271 [PMID: 9727051 DOI: 10.1074/jbc.273.37.24266]

91 **Aicher A**, Heeschen C, Mildner-Rihm C, Urbich C, Ihling C, Technau-Ihling K, Zeiher AM, Dimmeler S. Essential role of endothelial nitric oxide synthase for mobilization of stem and progenitor cells. *Nat Med* 2003; **9**: 1370-1376 [PMID: 14556003 DOI: 10.1038/nm948]

92 **Llevadot J**, Murasawa S, Kureishi Y, Uchida S, Masuda H, Kawamoto A, Walsh K, Isner JM, Asahara T. HMG-CoA reductase inhibitor mobilizes bone marrow--derived endothelial progenitor cells. *J Clin Invest* 2001; **108**: 399-405 [PMID: 11489933 DOI: 10.1172/JCI13131]

93 **Bush LR**, Shebuski RJ. In vivo models of arterial thrombosis and thrombolysis. *FASEB J* 1990; **4**: 3087-3098 [PMID: 2210155]

94 **Urbich C**, Dernbach E, Zeiher AM, Dimmeler S. Double-edged role of statins in angiogenesis signaling. *Circ Res* 2002; **90**: 737-744 [PMID: 11934843 DOI: 10.1161/01.RES.0000014081.30867.F8]

95 **Deschaseaux F**, Selmani Z, Falcoz PE, Mersin N, Meneveau N, Penfornis A, Kleinclauss C, Chocron S, Etievent JP, Tiberghien P, Kantelip JP, Davani S. Two types of circulating endothelial progenitor cells in patients receiving long term therapy by HMG-CoA reductase inhibitors. *Eur J Pharmacol* 2007; **562**: 111-118 [PMID: 17320859 DOI: 10.1016/j.ejphar.2007.01.045]

96 **Hristov M**, Fach C, Becker C, Heussen N, Liehn EA, Blindt R, Hanrath P, Weber C. Reduced numbers of circulating endothelial progenitor cells in patients with coronary artery disease associated with long-term statin treatment. *Atherosclerosis* 2007; **192**: 413-420 [PMID: 16837000 DOI: 10.1016/j.atherosclerosis.2006.05.031]

97 **Lin LY**, Huang CC, Chen JS, Wu TC, Leu HB, Huang PH, Chang TT, Lin SJ, Chen JW. Effects of pitavastatin versus atorvastatin on the peripheral endothelial progenitor cells and vascular endothelial growth factor in high-risk patients: a pilot prospective, double-blind, randomized study. *Cardiovasc Diabetol* 2014; **13**: 111 [PMID: 25027585 DOI: 10.1186/s12933-014-0111-1]

98 **Leone AM**, Rutella S, Giannico MB, Perfetti M, Zaccone V, Brugaletta S, Garramone B, Niccoli G, Porto I, Liuzzo G, Biasucci LM, Bellesi S, Galiuto L, Leone G, Rebuzzi AG, Crea F. Effect of intensive vs standard statin therapy on endothelial progenitor cells and left ventricular function in patients with acute myocardial infarction: Statins for regeneration after acute myocardial infarction and PCI (STRAP) trial. *Int J Cardiol* 2008; **130**: 457-462 [PMID: 18667247 DOI: 10.1016/j.ijcard.2008.05.036]

99 **Ye H**, He F, Fei X, Lou Y, Wang S, Yang R, Hu Y, Chen X. High-dose atorvastatin reloading before percutaneous coronary intervention increased circulating endothelial progenitor cells and reduced inflammatory cytokine expression during the perioperative period. *J Cardiovasc Pharmacol Ther* 2014; **19**: 290-295 [PMID: 24346155 DOI: 10.1177/1074248413513500]

100 **Ricottini EMR**, Patti G. Benefit of atorvastatin reload on endothelial progenitor cells in patients on chronic statin treatment undergoing PCI. *J Am Coll Cardiol* 2013; **61**: 10 [DOI: 10.1016/S0735-1097(13)61635-6]

101 **Knowles RG**, Moncada S. Nitric oxide synthases in mammals. *Biochem J* 1994; **298** (Pt 2): 249-258 [PMID: 7510950 DOI:

10.1042/bj2980249]
102 **Moncada S**, Higgs A. The L-arginine-nitric oxide pathway. *N Engl J Med* 1993; **329**: 2002-2012 [PMID: 7504210 DOI: 10.1056/NEJM199312303292706]
103 **Sessa WC**. The nitric oxide synthase family of proteins. *J Vasc Res* 1994; **31**: 131-143 [PMID: 7511942 DOI: 10.1159/000159039]
104 **Moncada S**, Palmer RM, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. *Pharmacol Rev* 1991; **43**: 109-142 [PMID: 1852778]
105 **Wilcox JN**, Subramanian RR, Sundell CL, Tracey WR, Pollock JS, Harrison DG, Marsden PA. Expression of multiple isoforms of nitric oxide synthase in normal and atherosclerotic vessels. *Arterioscler Thromb Vasc Biol* 1997; **17**: 2479-2488 [PMID: 9409218 DOI: 10.1161/01.ATV.17.11.2479]
106 **Stuehr DJ**, Griffith OW. Mammalian nitric oxide synthases. *Adv Enzymol Relat Areas Mol Biol* 1992; **65**: 287-346 [PMID: 1373932 DOI: 10.1002/9780470123119.ch8]
107 **Dimmeler S**, Fleming I, Fisslthaler B, Hermann C, Busse R, Zeiher AM. Activation of nitric oxide synthase in endothelial cells by Akt-dependent phosphorylation. *Nature* 1999; **399**: 601-605 [PMID: 10376603 DOI: 10.1038/21224]
108 **Fleming I**, Fisslthaler B, Dimmeler S, Kemp BE, Busse R. Phosphorylation of Thr(495) regulates Ca(2+)/calmodulin-dependent endothelial nitric oxide synthase activity. *Circ Res* 2001; **88**: E68-E75 [PMID: 11397791 DOI: 10.1161/hh1101.092677]
109 **Rubanyi GM**, Vanhoutte PM. Superoxide anions and hyperoxia inactivate endothelium-derived relaxing factor. *Am J Physiol* 1986; **250**: H822-H827 [PMID: 3010744]
110 **Carmeliet P**. Mechanisms of angiogenesis and arteriogenesis. *Nat Med* 2000; **6**: 389-395 [PMID: 10742145 DOI: 10.1038/74651]
111 **Carmeliet P**, Jain RK. Angiogenesis in cancer and other diseases. *Nature* 2000; **407**: 249-257 [PMID: 11001068 DOI: 10.1038/35025220]
112 **Semenza GL**. Vasculogenesis, angiogenesis, and arteriogenesis: mechanisms of blood vessel formation and remodeling. *J Cell Biochem* 2007; **102**: 840-847 [PMID: 17891779 DOI: 10.1002/jcb.21523]
113 **Wahlberg E**. Angiogenesis and arteriogenesis in limb ischemia. *J Vasc Surg* 2003; **38**: 198-203 [PMID: 12844115 DOI: 10.1016/S0741-5214(03)00151-4]
114 **Landmesser U**, Engberding N, Bahlmann FH, Schaefer A, Wiencke A, Heineke A, Spiekermann S, Hilfiker-Kleiner D, Templin C, Kotlarz D, Mueller M, Fuchs M, Hornig B, Haller H, Drexler H. Statin-induced improvement of endothelial progenitor cell mobilization, myocardial neovascularization, left ventricular function, and survival after experimental myocardial infarction requires endothelial nitric oxide synthase. *Circulation* 2004; **110**: 1933-1939 [PMID: 15466656 DOI: 10.1161/01.CIR.0000143232.67642.7A]
115 **Matsuno H**, Takei M, Hayashi H, Nakajima K, Ishisaki A, Kozawa O. Simvastatin enhances the regeneration of endothelial cells via VEGF secretion in injured arteries. *J Cardiovasc Pharmacol* 2004; **43**: 333-340 [PMID: 15076215 DOI: 10.1097/00005344-200403000-00002]
116 **Liao JK**, Shin WS, Lee WY, Clark SL. Oxidized low-density lipoprotein decreases the expression of endothelial nitric oxide synthase. *J Biol Chem* 1995; **270**: 319-324 [PMID: 7529227 DOI: 10.1074/jbc.270.1.319]
117 **Liao JK**, Clark SL. Regulation of G-protein alpha i2 subunit expression by oxidized low-density lipoprotein. *J Clin Invest* 1995; **95**: 1457-1463 [PMID: 7706449 DOI: 10.1172/JCI117816]
118 **Tamai O**, Matsuoka H, Itabe H, Wada Y, Kohno K, Imaizumi T. Single LDL apheresis improves endothelium-dependent vasodilatation in hypercholesterolemic humans. *Circulation* 1997; **95**: 76-82 [PMID: 8994420 DOI: 10.1161/01.CIR.95.1.76]
119 **López-Farré A**, Caramelo C, Esteban A, Alberola ML, Millás I, Montón M, Casado S. Effects of aspirin on platelet-neutrophil interactions. Role of nitric oxide and endothelin-1. *Circulation* 1995; **91**: 2080-2088 [PMID: 7895367 DOI: 10.1161/01.CIR.91.7.2080]
120 **Latini R**, Bianchi M, Correale E, Dinarello CA, Fantuzzi G, Fresco C, Maggioni AP, Mengozzi M, Romano S, Shapiro L. Cytokines in acute myocardial infarction: selective increase in circulating tumor necrosis factor, its soluble receptor, and interleukin-1 receptor antagonist. *J Cardiovasc Pharmacol* 1994; **23**: 1-6 [PMID: 7511719 DOI: 10.1097/00005344-199401000-00001]
121 **Ma XL**, Weyrich AS, Lefer DJ, Lefer AM. Diminished basal nitric oxide release after myocardial ischemia and reperfusion promotes neutrophil adherence to coronary endothelium. *Circ Res* 1993; **72**: 403-412 [PMID: 8418991 DOI: 10.1161/01.RES.72.2.403]
122 **Assmus B**, Urbich C, Aicher A, Hofmann WK, Haendeler J, Rössig L, Spyridopoulos I, Zeiher AM, Dimmeler S. HMG-CoA reductase inhibitors reduce senescence and increase proliferation of endothelial progenitor cells via regulation of cell cycle regulatory genes. *Circ Res* 2003; **92**: 1049-1055 [PMID: 12676819 DOI: 10.1161/01.RES.0000070067.64040.7C]
123 **Kusuyama T**, Omura T, Nishiya D, Enomoto S, Matsumoto R, Murata T, Takeuchi K, Yoshikawa J, Yoshiyama M. The effects of HMG-CoA reductase inhibitor on vascular progenitor cells. *J Pharmacol Sci* 2006; **101**: 344-349 [PMID: 16891763 DOI: 10.1254/jphs.FP0060102]
124 **Laufs U**, Fata VL, Liao JK. Inhibition of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase blocks hypoxia-mediated down-regulation of endothelial nitric oxide synthase. *J Biol Chem* 1997; **272**: 31725-31729 [PMID: 9395516 DOI: 10.1074/jbc.272.50.31725]
125 **Davis ME**, Cai H, McCann L, Fukai T, Harrison DG. Role of c-Src in regulation of endothelial nitric oxide synthase expression during exercise training. *Am J Physiol Heart Circ Physiol* 2003; **284**: H1449-H1453 [PMID: 12595302 DOI: 10.1152/ajpheart.00918.2002]
126 **Kosmidou I**, Moore JP, Weber M, Searles CD. Statin treatment and 3' polyadenylation of eNOS mRNA. *Arterioscler Thromb Vasc Biol* 2007; **27**: 2642-2649 [PMID: 17916773 DOI: 10.1161/ATVBAHA.107.154492]
127 **Minami Y**, Satoh M, Maesawa C, Takahashi Y, Tabuchi T, Itoh T, Nakamura M. Effect of atorvastatin on microRNA 221 / 222 expression in endothelial progenitor cells obtained from patients with coronary artery disease. *Eur J Clin Invest* 2009; **39**: 359-367 [PMID: 19371267 DOI: 10.1111/j.1365-2362.2009.02110.x]
128 **Petersen CP**, Bordeleau ME, Pelletier J, Sharp PA. Short RNAs repress translation after initiation in mammalian cells. *Mol Cell* 2006; **21**: 533-542 [PMID: 16483934 DOI: 10.1016/j.molcel.2006.01.031]
129 **Felli N**, Fontana L, Pelosi E, Botta R, Bonci D, Facchiano F, Liuzzi F, Lulli V, Morsilli O, Santoro S, Valtieri M, Calin GA, Liu CG, Sorrentino A, Croce CM, Peschle C. MicroRNAs 221 and 222 inhibit normal erythropoiesis and erythroleukemic cell growth via kit receptor down-modulation. *Proc Natl Acad Sci U S A* 2005; **102**: 18081-18086 [PMID: 16330772 DOI: 10.1073/pnas.0506216102]
130 **Cerda A**, Fajardo CM, Basso RG, Hirata MH, Hirata RD. Role of microRNAs 221/222 on statin induced nitric oxide release in human endothelial cells. *Arq Bras Cardiol* 2015; **104**: 195-201 [PMID: 25517390 DOI: 10.5935/abc.20140192]
131 **Kuehbacher A**, Urbich C, Dimmeler S. Targeting microRNA expression to regulate angiogenesis. *Trends Pharmacol Sci* 2008; **29**: 12-15 [PMID: 18068232 DOI: 10.1016/j.tips.2007.10.014]
132 **Bader AG**, Kang S, Zhao L, Vogt PK. Oncogenic PI3K deregulates transcription and translation. *Nat Rev Cancer* 2005; **5**: 921-929 [PMID: 16341083 DOI: 10.1038/nrc1753]
133 **Dimmeler S**, Zeiher AM. Akt takes center stage in angiogenesis signaling. *Circ Res* 2000; **86**: 4-5 [PMID: 10625297 DOI: 10.1161/01.RES.86.1.4]
134 **Whitman M**, Downes CP, Keeler M, Keller T, Cantley L. Type I phosphatidylinositol kinase makes a novel inositol phospholipid, phosphatidylinositol-3-phosphate. *Nature* 1988; **332**: 644-646 [PMID: 2833705 DOI: 10.1038/332644a0]
135 **Toker A**, Cantley LC. Signalling through the lipid products of phosphoinositide-3-OH kinase. *Nature* 1997; **387**: 673-676 [PMID: 9192891 DOI: 10.1038/42648]
136 **Karar J**, Maity A. PI3K/AKT/mTOR Pathway in Angiogenesis. *Front Mol Neurosci* 2011; **4**: 51 [PMID: 22144946 DOI: 10.3389/fnmol.2011.00051]

137 **Kawasaki K**, Smith RS, Hsieh CM, Sun J, Chao J, Liao JK. Activation of the phosphatidylinositol 3-kinase/protein kinase Akt pathway mediates nitric oxide-induced endothelial cell migration and angiogenesis. *Mol Cell Biol* 2003; **23**: 5726-5737 [PMID: 12897144 DOI: 10.1128/MCB.23.16.5726-5737.2003]

138 **Ellis LM**, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. *Nat Rev Cancer* 2008; **8**: 579-591 [PMID: 18596824 DOI: 10.1038/nrc2403]

139 **Morales-Ruiz M**, Fulton D, Sowa G, Languino LR, Fujio Y, Walsh K, Sessa WC. Vascular endothelial growth factor-stimulated actin reorganization and migration of endothelial cells is regulated via the serine/threonine kinase Akt. *Circ Res* 2000; **86**: 892-896 [PMID: 10785512 DOI: 10.1161/01.RES.86.8.892]

140 **Papapetropoulos A**, García-Cardeña G, Madri JA, Sessa WC. Nitric oxide production contributes to the angiogenic properties of vascular endothelial growth factor in human endothelial cells. *J Clin Invest* 1997; **100**: 3131-3139 [PMID: 9399960 DOI: 10.1172/JCI119868]

141 **Fulton D**, Gratton JP, McCabe TJ, Fontana J, Fujio Y, Walsh K, Franke TF, Papapetropoulos A, Sessa WC. Regulation of endothelium-derived nitric oxide production by the protein kinase Akt. *Nature* 1999; **399**: 597-601 [PMID: 10376602 DOI: 10.1038/21218]

142 **Dimmeler S**, Dernbach E, Zeiher AM. Phosphorylation of the endothelial nitric oxide synthase at ser-1177 is required for VEGF-induced endothelial cell migration. *FEBS Lett* 2000; **477**: 258-262 [PMID: 10908731 DOI: 10.1016/S0014-5793(00)01657-4]

143 **Bahlmann FH**, De Groot K, Spandau JM, Landry AL, Hertel B, Duckert T, Boehm SM, Menne J, Haller H, Fliser D. Erythropoietin regulates endothelial progenitor cells. *Blood* 2004; **103**: 921-926 [PMID: 14525788 DOI: 10.1182/blood-2003-04-1284]

144 **Rikitake Y**, Liao JK. Rho GTPases, statins, and nitric oxide. *Circ Res* 2005; **97**: 1232-1235 [PMID: 16339495 DOI: 10.1161/01.RES.0000196564.18314.23]

145 **Lemoine S**, Zhu L, Legallois D, Massetti M, Manrique A, Hanouz JL. Atorvastatin-induced cardioprotection of human myocardium is mediated by the inhibition of mitochondrial permeability transition pore opening via tumor necrosis factor-α and Janus kinase/signal transducers and activators of transcription pathway. *Anesthesiology* 2013; **118**: 1373-1384 [PMID: 23416384 DOI: 10.1097/ALN.0b013e31828a7039]

146 **Sanada S**, Asanuma H, Minamino T, Node K, Takashima S, Okuda H, Shinozaki Y, Ogai A, Fujita M, Hirata A, Kim J, Asano Y, Mori H, Tomoike H, Kitamura S, Hori M, Kitakaze M. Optimal windows of statin use for immediate infarct limitation: 5'-nucleotidase as another downstream molecule of phosphatidylinositol 3-kinase. *Circulation* 2004; **110**: 2143-2149 [PMID: 15451788 DOI: 10.1161/01.CIR.0000143830.59419.73]

147 **Solenkova NV**, Solodushko V, Cohen MV, Downey JM. Endogenous adenosine protects preconditioned heart during early minutes of reperfusion by activating Akt. *Am J Physiol Heart Circ Physiol* 2006; **290**: H441-H449 [PMID: 16155103 DOI: 10.1152/ajpheart.00589.2005]

148 **Hausenloy DJ**, Yellon DM. New directions for protecting the heart against ischaemia-reperfusion injury: targeting the Reperfusion Injury Salvage Kinase (RISK)-pathway. *Cardiovasc Res* 2004; **61**: 448-460 [PMID: 14962476 DOI: 10.1016/j.cardiores.2003.09.024]

149 **Efthymiou CA**, Mocanu MM, Yellon DM. Atorvastatin and myocardial reperfusion injury: new pleiotropic effect implicating multiple prosurvival signaling. *J Cardiovasc Pharmacol* 2005; **45**: 247-252 [PMID: 15725950 DOI: 10.1097/01.fjc.0000154376.82445.06]

150 **Hibbert B**, Ma X, Pourdjabbar A, Simard T, Rayner K, Sun J, Chen YX, Filion L, O'Brien ER. Pre-procedural atorvastatin mobilizes endothelial progenitor cells: clues to the salutary effects of statins on healing of stented human arteries. *PLoS One* 2011; **6**: e16413 [PMID: 21283543 DOI: 10.1371/journal.pone.0016413]

151 **Baran Ç**, Durdu S, Dalva K, Zaim Ç, Dogan A, Ocakoglu G, Gürman G, Arslan Ö, Akar AR. Effects of preoperative short term use of atorvastatin on endothelial progenitor cells after coronary surgery: a randomized, controlled trial. *Stem Cell Rev* 2012; **8**: 963-971 [PMID: 22076751 DOI: 10.1007/s12015-011-9321-z]

152 **Schmidt-Lucke C**, Fichtlscherer S, Rössig L, Kämper U, Dimmeler S. Improvement of endothelial damage and regeneration indexes in patients with coronary artery disease after 4 weeks of statin therapy. *Atherosclerosis* 2010; **211**: 249-254 [PMID: 20211468 DOI: 10.1016/j.atherosclerosis.2010.02.007]

153 **Tousoulis D**, Andreou I, Tsiatas M, Miliou A, Tentolouris C, Siasos G, Papageorgiou N, Papadimitriou CA, Dimopoulos MA, Stefanadis C. Effects of rosuvastatin and allopurinol on circulating endothelial progenitor cells in patients with congestive heart failure: the impact of inflammatory process and oxidative stress. *Atherosclerosis* 2011; **214**: 151-157 [PMID: 21122851 DOI: 10.1016/j.atherosclerosis.2010.11.002]

154 **Jialal I**, Devaraj S, Singh U, Huet BA. Decreased number and impaired functionality of endothelial progenitor cells in subjects with metabolic syndrome: implications for increased cardiovascular risk. *Atherosclerosis* 2010; **211**: 297-302 [PMID: 20171637 DOI: 10.1016/j.atherosclerosis.2010.01.036]

155 **Cohen MV**, Yang XM, Downey JM. Nitric oxide is a preconditioning mimetic and cardioprotectant and is the basis of many available infarct-sparing strategies. *Cardiovasc Res* 2006; **70**: 231-239 [PMID: 16376869 DOI: 10.1016/j.cardiores.2005.10.021]

156 **Scalia R**, Gooszen ME, Jones SP, Hoffmeyer M, Rimmer DM, Trocha SD, Huang PL, Smith MB, Lefer AM, Lefer DJ. Simvastatin exerts both anti-inflammatory and cardioprotective effects in apolipoprotein E-deficient mice. *Circulation* 2001; **103**: 2598-2603 [PMID: 11382730 DOI: 10.1161/01.CIR.103.21.2598]

157 **Wassmann S**, Laufs U, Müller K, Konkol C, Ahlbory K, Bäumer AT, Linz W, Böhm M, Nickenig G. Cellular antioxidant effects of atorvastatin in vitro and in vivo. *Arterioscler Thromb Vasc Biol* 2002; **22**: 300-305 [PMID: 11834532 DOI: 10.1161/hq0202.104081]

158 **Mensah K**, Mocanu MM, Yellon DM. Failure to protect the myocardium against ischemia/reperfusion injury after chronic atorvastatin treatment is recaptured by acute atorvastatin treatment: a potential role for phosphatase and tensin homolog deleted on chromosome ten? *J Am Coll Cardiol* 2005; **45**: 1287-1291 [PMID: 15837263 DOI: 10.1016/j.jacc.2005.01.021]

159 **Mihos CG**, Pineda AM, Santana O. Cardiovascular effects of statins, beyond lipid-lowering properties. *Pharmacol Res* 2014; **88**: 12-19 [PMID: 24631782 DOI: 10.1016/j.phrs.2014.02.009]

160 **Tousoulis D**, Andreou I, Antoniades C, Tentolouris C, Stefanadis C. Role of inflammation and oxidative stress in endothelial progenitor cell function and mobilization: therapeutic implications for cardiovascular diseases. *Atherosclerosis* 2008; **201**: 236-247 [PMID: 18599065 DOI: 10.1016/j.atherosclerosis.2008.05.034]

161 **Yao EH**, Yu Y, Fukuda N. Oxidative stress on progenitor and stem cells in cardiovascular diseases. *Curr Pharm Biotechnol* 2006; **7**: 101-108 [PMID: 16724944 DOI: 10.2174/138920106776597685]

162 **Morel DW**, DiCorleto PE, Chisolm GM. Endothelial and smooth muscle cells alter low density lipoprotein in vitro by free radical oxidation. *Arteriosclerosis* 1984; **4**: 357-364 [PMID: 6466193 DOI: 10.1161/01.ATV.4.4.357]

163 **Lamb DJ**, Wilkins GM, Leake DS. The oxidative modification of low density lipoprotein by human lymphocytes. *Atherosclerosis* 1992; **92**: 187-192 [PMID: 1632847 DOI: 10.1016/0021-9150(92)90277-N]

164 **Lim S**, Barter P. Antioxidant effects of statins in the management of cardiometabolic disorders. *J Atheroscler Thromb* 2014; **21**: 997-1010 [PMID: 25132378 DOI: 10.5551/jat.24398]

165 **Carracedo J**, Merino A, Briceño C, Soriano S, Buendía P, Calleros L, Rodriguez M, Martín-Malo A, Aljama P, Ramírez R. Carbamylated low-density lipoprotein induces oxidative stress and accelerated senescence in human endothelial progenitor cells. *FASEB J* 2011; **25**: 1314-1322 [PMID: 21228221 DOI: 10.1096/fj.10-173377]

166 **Tso C**, Martinic G, Fan WH, Rogers C, Rye KA, Barter PJ. High-density lipoproteins enhance progenitor-mediated endothelium repair in mice. *Arterioscler Thromb Vasc Biol* 2006; **26**: 1144-1149 [PMID: 16528007 DOI: 10.1161/01.ATV.0000216600.37436.cf]

167 **Griendling KK**, FitzGerald GA. Oxidative stress and cardiovascular injury: Part II: animal and human studies. *Circulation* 2003; **108**: 2034-2040 [PMID: 14581381 DOI: 10.1161/01.CIR.0000093661.90582.c4]

168 **Thum T**, Fraccarollo D, Schultheiss M, Froese S, Galuppo P, Widder JD, Tsikas D, Ertl G, Bauersachs J. Endothelial nitric oxide synthase uncoupling impairs endothelial progenitor cell mobilization and function in diabetes. *Diabetes* 2007; **56**: 666-674 [PMID: 17327434 DOI: 10.2337/db06-0699]

169 **Urbich C**, Knau A, Fichtlscherer S, Walter DH, Brühl T, Potente M, Hofmann WK, de Vos S, Zeiher AM, Dimmeler S. FOXO-dependent expression of the proapoptotic protein Bim: pivotal role for apoptosis signaling in endothelial progenitor cells. *FASEB J* 2005; **19**: 974-976 [PMID: 15824087 DOI: 10.1096/fj.04-2727fje]

170 **Fleissner F**, Thum T. Critical role of the nitric oxide/reactive oxygen species balance in endothelial progenitor dysfunction. *Antioxid Redox Signal* 2011; **15**: 933-948 [PMID: 20712407 DOI: 10.1089/ars.2010.3502]

171 **Tepper OM**, Galiano RD, Capla JM, Kalka C, Gagne PJ, Jacobowitz GR, Levine JP, Gurtner GC. Human endothelial progenitor cells from type II diabetics exhibit impaired proliferation, adhesion, and incorporation into vascular structures. *Circulation* 2002; **106**: 2781-2786 [PMID: 12451003 DOI: 10.1161/01.CIR.0000039526.42991.93]

172 **Tao J**, Yang Z, Wang JM, Wang LC, Luo CF, Tang AL, Dong YG, Ma H. Shear stress increases Cu/Zn SOD activity and mRNA expression in human endothelial progenitor cells. *J Hum Hypertens* 2007; **21**: 353-358 [PMID: 17287843 DOI: 10.1038/sj.jhh.1002147]

173 **He T**, Peterson TE, Holmuhamedov EL, Terzic A, Caplice NM, Oberley LW, Katusic ZS. Human endothelial progenitor cells tolerate oxidative stress due to intrinsically high expression of manganese superoxide dismutase. *Arterioscler Thromb Vasc Biol* 2004; **24**: 2021-2027 [PMID: 15319267 DOI: 10.1161/01.ATV.0000142810.27849.8f]

174 **Dernbach E**, Urbich C, Brandes RP, Hofmann WK, Zeiher AM, Dimmeler S. Antioxidative stress-associated genes in circulating progenitor cells: evidence for enhanced resistance against oxidative stress. *Blood* 2004; **104**: 3591-3597 [PMID: 15161665 DOI: 10.1182/blood-2003-12-4103]

175 **Endres M**. Statins: potential new indications in inflammatory conditions. *Atheroscler Suppl* 2006; **7**: 31-35 [PMID: 16503422 DOI: 10.1016/j.atherosclerosissup.2006.01.005]

176 **Bauer SM**, Goldstein LJ, Bauer RJ, Chen H, Putt M, Velazquez OC. The bone marrow-derived endothelial progenitor cell response is impaired in delayed wound healing from ischemia. *J Vasc Surg* 2006; **43**: 134-141 [PMID: 16414400 DOI: 10.1016/j.jvs.2005.08.038]

177 **Masuda H**, Kalka C, Takahashi T, Yoshida M, Wada M, Kobori M, Itoh R, Iwaguro H, Eguchi M, Iwami Y, Tanaka R, Nakagawa Y, Sugimoto A, Ninomiya S, Hayashi S, Kato S, Asahara T. Estrogen-mediated endothelial progenitor cell biology and kinetics for physiological postnatal vasculogenesis. *Circ Res* 2007; **101**: 598-606 [PMID: 17656679 DOI: 10.1161/CIRCRESAHA.106.144006]

178 **Ii M**, Nishimura H, Iwakura A, Wecker A, Eaton E, Asahara T, Losordo DW. Endothelial progenitor cells are rapidly recruited to myocardium and mediate protective effect of ischemic preconditioning via "imported" nitric oxide synthase activity. *Circulation* 2005; **111**: 1114-1120 [PMID: 15723985 DOI: 10.1161/01.CIR.0000157144.24888.7E]

179 **Zhang Y**, Devries ME, Skolnick J. Structure modeling of all identified G protein-coupled receptors in the human genome. *PLoS Comput Biol* 2006; **2**: e13 [PMID: 16485037 DOI: 10.1371/journal.pcbi.0020013]

180 **Bjarnadóttir TK**, Gloriam DE, Hellstrand SH, Kristiansson H, Fredriksson R, Schiöth HB. Comprehensive repertoire and phylogenetic analysis of the G protein-coupled receptors in human and mouse. *Genomics* 2006; **88**: 263-273 [PMID: 16753280 DOI: 10.1016/j.ygeno.2006.04.001]

181 **Schöneberg T**, Hofreiter M, Schulz A, Römpler H. Learning from the past: evolution of GPCR functions. *Trends Pharmacol Sci* 2007; **28**: 117-121 [PMID: 17280721 DOI: 10.1016/j.tips.2007.01.001]

182 **Pierce KL**, Premont RT, Lefkowitz RJ. Seven-transmembrane receptors. *Nat Rev Mol Cell Biol* 2002; **3**: 639-650 [PMID: 12209124 DOI: 10.1038/nrm908]

183 **Perez DM**. The evolutionarily triumphant G-protein-coupled receptor. *Mol Pharmacol* 2003; **63**: 1202-1205 [PMID: 12761327 DOI: 10.1124/mol.63.6.1202]

184 **Rosenbaum DM**, Rasmussen SG, Kobilka BK. The structure and function of G-protein-coupled receptors. *Nature* 2009; **459**: 356-363 [PMID: 19458711 DOI: 10.1038/nature08144]

185 **Venkatakrishnan AJ**, Deupi X, Lebon G, Tate CG, Schertler GF, Babu MM. Molecular signatures of G-protein-coupled receptors. *Nature* 2013; **494**: 185-194 [PMID: 23407534 DOI: 10.1038/nature11896]

186 **Callihan P**, Mumaw J, Machacek DW, Stice SL, Hooks SB. Regulation of stem cell pluripotency and differentiation by G protein coupled receptors. *Pharmacol Ther* 2011; **129**: 290-306 [PMID: 21073897 DOI: 10.1016/j.pharmthera.2010.10.007]

187 **Kobayashi NR**, Hawes SM, Crook JM, Pébay A. G-protein coupled receptors in stem cell self-renewal and differentiation. *Stem Cell Rev* 2010; **6**: 351-366 [PMID: 20625855 DOI: 10.1007/s12015-010-9167-9]

188 **Nature Reviews Drug Discovery GPCR Questionnaire Participants.** The state of GPCR research in 2004. *Nat Rev Drug Discov* 2004; **3**: 575, 577-626 [PMID: 15272499 DOI: 10.1038/nrd1458]

189 **Jacoby E**, Bouhelal R, Gerspacher M, Seuwen K. The 7 TM G-protein-coupled receptor target family. *ChemMedChem* 2006; **1**: 761-782 [PMID: 16902930 DOI: 10.1002/cmdc.200600134]

190 **Kozasa T**, Jiang X, Hart MJ, Sternweis PM, Singer WD, Gilman AG, Bollag G, Sternweis PC. p115 RhoGEF, a GTPase activating protein for Galpha12 and Galpha13. *Science* 1998; **280**: 2109-2111 [PMID: 9641915 DOI: 10.1126/science.280.5372.2109]

191 **Noma K**, Oyama N, Liao JK. Physiological role of ROCKs in the cardiovascular system. *Am J Physiol Cell Physiol* 2006; **290**: C661-C668 [PMID: 16469861 DOI: 10.1152/ajpcell.00459.2005]

192 **Taussig R**, Iñiguez-Lluhi JA, Gilman AG. Inhibition of adenylyl cyclase by Gi alpha. *Science* 1993; **261**: 218-221 [PMID: 8327893 DOI: 10.1126/science.8327893]

193 **Morello F**, Perino A, Hirsch E. Phosphoinositide 3-kinase signalling in the vascular system. *Cardiovasc Res* 2009; **82**: 261-271 [PMID: 19038971 DOI: 10.1093/cvr/cvn325]

194 **Gilman AG**. G proteins: transducers of receptor-generated signals. *Annu Rev Biochem* 1987; **56**: 615-649 [PMID: 3113327 DOI: 10.1146/annurev.bi.56.070187.003151]

195 **Ghanemi A**. Targeting G protein coupled receptor-related pathways as emerging molecular therapies. *Saudi Pharm J* 2015; **23**: 115-129 [PMID: 25972730 DOI: 10.1016/j.jsps.2013.07.007]

196 **Lin SH**, Civelli O. Orphan G protein-coupled receptors: targets for new therapeutic interventions. *Ann Med* 2004; **36**: 204-214 [PMID: 15181976 DOI: 10.1080/07853890310024668]

197 **Lynch JR**, Wang JY. G Protein-Coupled Receptor Signaling in Stem Cells and Cancer. *Int J Mol Sci* 2016; **17**: [PMID: 27187360 DOI: 10.3390/ijms17050707]

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REVIEW

Vitamin D and acute myocardial infarction

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Abstract

Vitamin D deficiency is a prevalent condition, cutting across all ethnicities and among all age groups, and occurring in about 30%-50% of the population. Besides vitamin D established role in calcium homeostasis, its deficiency is emerging as a new risk factor for coronary artery disease. Notably, clinical investigations have suggested that there is an association between hypovitaminosis D and acute myocardial infarction (AMI). Not only has it been linked to incident AMI, but also to increased morbidity and mortality in this clinical setting. Moreover, vitamin D deficiency seems to predispose to recurrent adverse cardiovascular events, as it is associated with post-infarction complications and cardiac remodeling in patients with AMI. Several mechanisms underlying the association between vitamin D and AMI risk can be involved. Despite these observational and mechanistic data, interventional trials with supplementation of vitamin D are controversial. In this review, we will discuss the evidence on the association between vitamin D deficiency and AMI, in terms of prevalence and prognostic impact, and the possible mechanisms mediating it. Further research in this direction is warranted and it is likely to open up new avenues for reducing the risk of AMI.

Key words: Vitamin D; Acute myocardial infarction; Incidence; Prognosis

Core tip: Vitamin D deficiency is a prevalent condition and it is emerging as a new risk factor for coronary artery disease. Notably, hypovitaminosis D has been reported to be common in patients with acute myocardial infarction, and preliminary studies indicate a possible association with short-term and long-term morbidity and mortality. Although these observational initial proofs, interventional trials with supplementation of vitamin D have yielded controversial results. We herein discuss the current evidence suggesting an association between acute myocardial infarction and vitamin D deficiency, in terms of prevalence and prognostic impact, and the possible underlying mechanisms.

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INTRODUCTION

Cardiovascular disease, and specifically acute myocardial infarction (AMI), is the main cause of morbidity and mortality in western countries, despite current preventive and therapeutic strategies[1,2].

Besides the traditional, most recognized risk factors for AMI development, new risk factors are emerging with potential relevant therapeutic implications. Among them, hypovitaminosis D has been the focus of recent interest. It is well known that vitamin D insufficiency, or deficiency, is highly prevalent in the general population[3-7]. Traditionally, the most characterized consequences of vitamin D depletion have involved bone metabolism and calcium homeostasis[8]. However, its close association with major cardiovascular risk factors, such as diabetes, hypertension, and chronic kidney disease, and the detection of nuclear vitamin D receptors (VDR) on vascular endothelial cells and cardiomyocytes have paved the way to studies investigating the intriguing link between hypovitaminosis D and cardiac disease[9-11].

Deficiency of vitamin D was shown to be common in AMI, and preliminary studies indicate a possible association with their short-term and long-term prognosis[12-14]. Indeed, vitamin D deficiency seems to predispose to in-hospital and recurrent adverse cardiac events, since it is associated with the number of affected coronary arteries, AMI complications, and cardiac remodeling in patients with AMI[12-14].

In this review, we provide an overview on the currently available evidence supporting the relationship between hypovitaminosis D and AMI, its prognostic relevance, and the possible underlying mechanisms. Finally, we will try to identify challenges and future investigative perspectives in this field.

Vitamin D metabolism

There are two major forms of vitamin D: Vitamin D2, which is contained in plants and fortified foods, and vitamin D3, which is obtained from aliments or through the conversion of dehydrocholesterol in the skin[11,15]. Of note, the cutaneous synthesis of vitamin D3 from sunlight exposure is the main source of vitamin D in humans. Vitamin D undergoes hydroxylation in the liver to 25-hydroxyvitamin D - its main circulating form in the blood - and then in the kidney to 1,25-dihydroxyvitamin D. The 1,25(OH) vitamin D3 reaches the nucleus where, by binding to its receptors, it regulates the transcription and function of more than 200 genes[16,17]. The VDR, which are expressed in enterocytes, osteoblasts, parathyroid glands, distal renal tubule cells, regulate calcium homeostasis and bone metabolism. Recent investigations have also demonstrated their presence on endothelial cells, lymphocytes, macrophages, smooth vascular muscle cells, beta-pancreatic cells and cardiomyocytes, through which vitamin D3 mediates cardiovascular effects[18-20].

Table 1 Most relevant risk factors for vitamin D deficiency

Age
Increased distance from the equator
Winter season
Darkly pigmented skin
Institutionalized/housebound
Sunscreens and cover-up clothing
Air pollution
Smoking
Obesity
Physical inactivity
Malabsorption
Chronic kidney disease
Liver disease
Drugs (glucocorticoids, antirejection medications, human immunodeficiency virus medications, antiepileptic drugs, *etc.*)

There is no consensus on how to define vitamin D deficiency, and this introduces significant difficulties in conducting epidemiological studies in this field[21-24]. The most widely accepted definition for normal vitamin D serum levels, according to the United States Endocrine Society guideline recommendations, is $\geqslant$ 30 ng/mL. Vitamin D insufficiency is characterized by levels of 21-29 ng/mL, while its deficiency by levels $\leqslant$ 20 ng/mL[25]. Vitamin D deficiency is the most common nutritional deficiency worldwide in both children and adults[26]. In the United States and Europe, > 40% of the adult population has low vitamin D levels[26]. The Third National Health and Examination Survey (NHANES Ⅲ) reports a high prevalence of vitamin D deficiency and its rapid increase, going from 55% in the period 1988-1994 to 77% in the years 2001-2004[27,28]. The main causes of vitamin D deficiency are listed in Table 1.

Rationale for the link between vitamin D and AMI

A growing amount of data has highlighted the potential link between vitamin D and cardiovascular disease. Firstly, VDR have been found in the myocardium, as well as in vascular cells[18,29,30]. Secondly, epidemiological studies demonstrated that the incidence of coronary artery disease, diabetes, hypertension, and hypovitaminosis D, increase in proportion to distance from the equator[31]. Cardiac death and prevalence of vitamin D deficiency have also been reported to be at their highest during periods of decreased sunlight exposure (*i.e.,* winter months)[32]. Thirdly, new evidence suggests that vitamin D deficiency has a role in the development of different cardiovascular risk factors, in particular hypertension[33,34], metabolic syndrome[35], and diabetes mellitus[36-38]. Finally, patients with conditions known to be associated with vitamin D deficiency, such as chronic kidney disease and primary hyperparathyroidism, die more frequently from cardiovascular causes than from those related to their underlying disease[39].

Taken together, these findings strongly support the

notion that vitamin D is involved in cardiac risk factor development, finally leading to an increased burden in coronary artery disease and to a worse short-term and long-term outcome in AMI patients.

Clinical studies on vitamin D in AMI

An initial Danish report in 1978 examined vitamin D levels in 75 patients with stable angina, in 53 patients with AMI, and in 409 healthy subjects, and it found that vitamin D levels were significantly lower in patients with angina or AMI than in controls[40]. In 1990, a case control study showed that AMI patients had lower vitamin D levels than controls, and this difference was more pronounced in the winter-spring period[41]. Of note, the relative risk of AMI decreased across increasing quartiles of vitamin D, suggesting an inverse correlation between vitamin D levels and AMI risk[41]. These figures have also been confirmed in more contemporary cohorts. Among 1739 Framingham Offspring Study healthy participants, the rates of major cardiovascular events were 50% and 80% higher in those with vitamin D insufficiency and deficiency, respectively[42]. In particular, subjects with no history of coronary artery disease and vitamin D levels < 10 ng/mL experienced a hazard ratio of 1.8 for developing a first cardiovascular event during a 5-year follow-up compared with subjects with levels > 15 ng/mL[43]. Finally, in 18225 men in the Health Professionals Follow-up Study, low vitamin D levels were associated with a higher risk of AMI, even after controlling for other cardiovascular risk factors and, at 10-year follow-up, subjects with normal vitamin D levels (> 30 ng/mL) had approximately half the risk of AMI[43]. These findings have been recently confirmed in a large meta-analysis that showed an adjusted pooled relative risk of 1.52 for total cardiovascular events when comparing the lowest to the highest categories of baseline circulating vitamin D concentration[44]. Thus, there is growing evidence suggesting that vitamin D deficiency represents a novel risk factor for AMI.

In agreement with these epidemiological data, prospective reports have found a high prevalence of vitamin D deficiency in patients hospitalized with AMI. A multicenter study performed in 239 acute coronary syndrome patients showed that 96% of them had vitamin D levels < 30 ng/mL at hospital presentation[45]. In line with this, Ng *et al*[13] demonstrated that 74% of AMI patients had low vitamin D levels and, of note, 36% of them had a severe deficiency. Correia *et al*[46] reported a median serum concentration of vitamin D of 18.5 ng/mL in a cohort of 206 AMI patients (7% with STEMI), and a severe deficiency in 10% of the sample analyzed. Similar findings were also observed by De Metrio *et al*[12] and Aleksova *et al*[14], who reported a prevalence of hypovitaminosis D in AMI patients of 89% and 68%, respectively.

Low vitamin D levels seem to be not only a prevalent independent risk factor for AMI, but also to be associated with a worse outcome when it occurs (Table 2). Correia *et al*[46] provided the first evidence of the potential independent association between severe deficiency of vitamin D and in-hospital mortality in patients with acute coronary syndromes. Indeed, patients with vitamin D levels < 10 ng/mL had a 24% in-hospital cardiovascular mortality rate, significantly higher than that observed in the remaining patients (4.9%, with a relative risk 4.3). A possible association between hypovitaminosis D and higher in-hospital mortality was also reported by Khalili *et al*[47] in 139 STEMI patients. However, the study was underpowered to show statistically significant difference in in-hospital mortality between patients with normal and low vitamin D[48]. More robust data have been provided on the long-term clinical implications of low vitamin D levels in AMI. Thus far, the largest study assessing vitamin D and prognosis in 1259 acute coronary syndrome patients is that by Ng *et al*[13]. In their study, the lowest vitamin D quartile (< 7.3 ng/mL) was associated with long-term major adverse cardiovascular events. Notably, the association was predominantly with re-hospitalization for acute decompensated heart failure or for successive acute coronary syndrome[13]. In agreement with these findings, in our cohort of AMI patients, the lowest quartile of vitamin D was a strong predictor of 1-year mortality (Figure 1)[12]. Of note, vitamin D deficiency was again a borderline independent predictor of in-hospital mortality, possibly due to the relatively low in-hospital mortality rate of our population, and it was associated with the highest risk of several in-hospital major adverse cardiac events. Interestingly, the lowest vitamin D quartile was associated with a higher incidence of bleeding requiring transfusion, although similar baseline hemoglobin values[12]. This is a crucial issue in the setting of AMI, as potent antithrombotic therapy is the mainstay of treatment, and bleeding and transfusions have a detrimental role on outcomes. We also found an association between the lowest vitamin D quartile and acute respiratory insufficiency rate[12]. The higher occurrence of these threatening complications might have contributed to the higher in-hospital mortality risk found in AMI patients and low vitamin D levels.

The causal relationship between vitamin D status and outcomes in AMI remains to be elucidated. Indeed, in more than 3000 patients undergoing coronary angiography, a significant association between hypovitaminosis D and lower left ventricular function was shown[49]. Of note, in this report, vitamin D deficiency was associated with deaths due to heart failure and with sudden cardiac deaths[50]. This highlights the possible relevance of vitamin D contribution to several aspects of AMI, such as acute ventricular dysfunction, heart failure progression, post-AMI ventricular remodeling, inflammation, thrombotic/bleeding balance and arrhythmias, which should be more deeply investigated through well-designed studies. Taking together, these considerations, along with older age, higher incidence of well-known cardiovascular risk factors, and lower rate of

Table 2 Main prospective studies on serum vitamin D levels in patients with acute myocardial infarction

Ref.	Study population (*n*)	Definitions of vitamin D levels (ng/mL)	Prevalence	End points considered	Major findings
Lee *et al*[45]	NSTEMI STEMI (*n* = 219)	Normal > 30 insufficiency 21-29 deficiency < 20	4% were normal 75% were insufficient 21% were deficient	Prevalence and vitamin D correlates	Vitamin D deficiency was more commonly observed in non-Caucasian patients, in diabetics patients, and in those with a higher body mass index
Khalili *et al*[47]	STEMI (*n* = 139)	Deficiency < 30	73% were deficient	In-hospital mortality correlation with MMP-9 levels at 72 h	Inverse correlation between vitamin D and MMP-9 levels
Correia *et al*[46]	UA NSTEMI STEMI (*n* = 206)	Severe deficiency < 10	10% were severely deficient	In-hospital mortality long-term mortality (mean FU 635 d)	A significant higher incidence of in-hospital and long-term mortality in patients with severe vitamin D deficiency
Ng *et al*[13]	NSTEMI STEMI (*n* = 1259)	Deficiency < 20	74% were deficient	long-term incidence of mortality and MACE (median FU 550 d)	A significant higher incidence of MACE in patients with deficient vitamin D levels
De Metrio *et al*[12]	NSTEMI STEMI (*n* = 814)	Normal > 30 Insufficiency 21-29 Deficiency < 20	11% were normal 19% were insufficient 70% were deficient	In-hospital mortality and in-hospital MACE 1-yr mortality and 1-yr re-admission for acute coronary syndrome and acute decompensated heart failure	A higher incidence of in-hospital mortality, mechanical ventilation, and major bleeding in patients with the lowest quartile of vitamin D levels A significant higher incidence of 1-yr mortality and re-hospitalization for acute decompensated heart failure in patients with the lowest quartile of vitamin D levels
Aleksova *et al*[14]	NSTEMI STEMI (*n* = 478)	Sufficient > 30 Insufficiency 21-30 Deficiency ⩽ 20	10% were sufficient 22% were insufficient 68% were deficient	Independent predictors of vitamin D deficiency	Older age, female gender, higher body mass index, autumn/winter sampling, and lower GFR predicted vitamin D deficiency

HR: Hazard ratio; FU: Follow-up; GFR: Glomerular filtration rate; MACE: Major adverse cardiac event; MMP-9: Matrix metalloproteinase-9; NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; UA: Unstable angina.

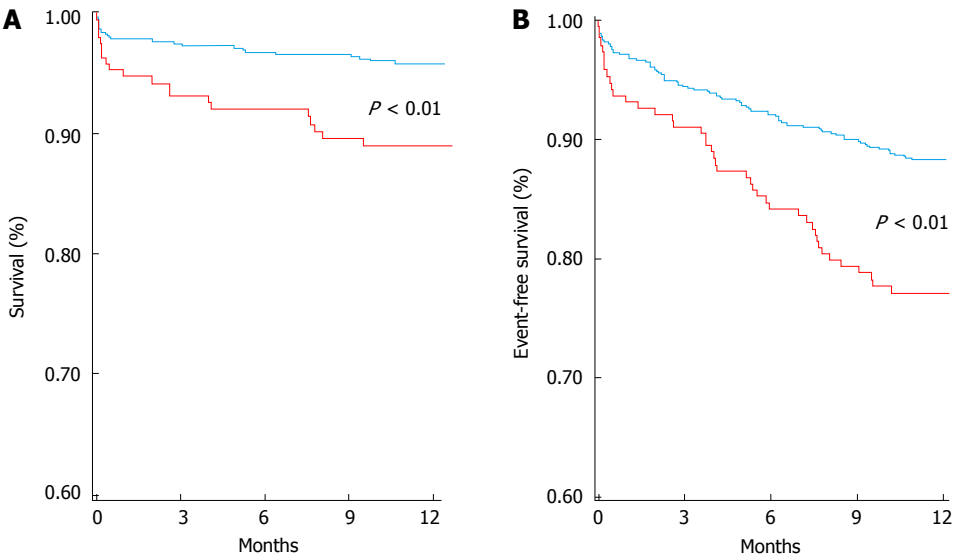

Figure 1 Kaplan-Meier curve analysis stratified according to vitamin D levels. The lowest quartile (red line) *vs* the other three quartiles pooled together (blue line) for 1-year mortality (A), and for the combined end point[1] (B), in the whole study population. *P* value by Log rank test. Reproduced from De Metrio *et al*[12]. [1]Combined end point: death, major bleeding (requiring blood transfusion), acute pulmonary edema, cardiogenic shock, clinically significant tachyarrhythmias and bradyarrhythmias, and acute kidney injury.

reperfusion strategy, might explain the worse outcome of AMI patients presenting with low vitamin D levels (Figure 2). A similar prognostic relevance has also been reported in critically ill patients, in whom a low vitamin D status was significantly associated with disease severity and mortality[50-52].

Potential therapeutic implications

Although many studies suggest a higher cardiovascular risk associated with low vitamin D levels, the data

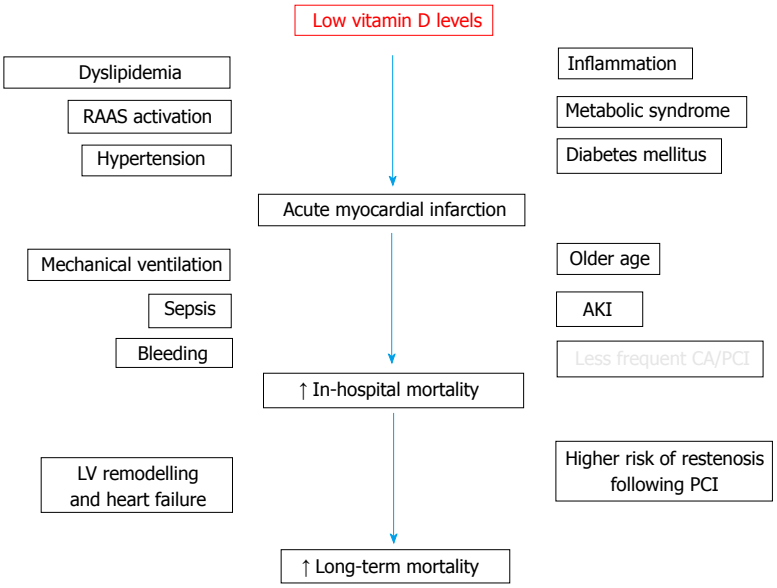

Figure 2 Potential factors impacting on acute myocardial infarction occurrence and outcome associated with low vitamin D levels. AKI: Acute kidney injury; CA/PCI: Coronary angiography/percutaneous coronary intervention; LV: Left ventricular; RAAS: Renin-angiotensin-aldosterone system.

regarding vitamin D supplementation are more sparse and controversial, in terms of primary prevention[53-57]. The potential benefit of vitamin D administration in the early phase of AMI has not been investigated yet. From a clinical point of view, vitamin D levels can be rapidly determined by blood testing and treated by supplementation. It has been demonstrated that a single oral ultra-high dose of vitamin D is able to restore normal levels in 2 d in critically ill patients, with no adverse effects, potentially providing an easy-to-administer dosing regimen for intervention trials in acute cardiovascular settings[58]. Although this evidence was not focused on AMI patients, it may pave the way for new investigations based on the use of a high oral loading dose regimen of vitamin D for restoration of adequate levels within few days. Notably, a dose-response association with cardiovascular risk and mortality has been demonstrated by Wang *et al*[44], and this was particularly true when short-term outcomes were considered.

Data on vitamin D supplementation in the setting of secondary prevention of AMI are also lacking. Yet, it has been recently demonstrated that high-dose vitamin D supplementation for 1-year in patients with chronic heart failure due to left ventricular systolic dysfunction and vitamin D deficiency, on contemporary optimal medical therapy, resulted in a significant improvement in left ventricular structure and function[59]. Of note, in almost 60% of these patients, the etiology was ischemic heart disease, suggesting a possible beneficial effect on post-AMI ventricular dysfunction[59].

Some studies have also proposed a possible association between low vitamin D and increased levels of cholesterol and of inflammatory markers, in particular C-reactive protein, in the setting of AMI[12,46]. Interestingly, 1-year atorvastatin treatment in patients with AMI determined a marked decrease in cholesterol and an unexpected increase in vitamin D levels, reinforcing the interplay among inflammation, low vitamin D and dyslipidemia[60,61].

Future perspectives and conclusions

Thus far, evidences in this field have been mainly driven by observational cohort studies, and these data are hypothesis-generating. Therefore, whether vitamin D is a risk factor or marker in this clinical setting cannot be inferred from the current literature. Larger studies are needed in order to shed lights on this issue. Because of their health status, frail patients with a high cardiovascular risk burden may spend mostly of their time indoors, which leads to low levels of vitamin D. This is also supported by the fact that such a similar observation has been found in patients with cancer, multiple sclerosis, and psychiatric diseases, potentially supporting the notion that hypovitaminosis D may be simply a marker of health[62]. However, even when adjusted for major confounders, vitamin D status still remains an independent risk factor, as it is significantly linked to incident AMI, worse short-term outcome, and recurrent major adverse cardiovascular events.

Whether vitamin D supplementation can counteract this increased risk in AMI patients is still an unanswered question, which should be investigated in large, well-designed, adequately powered interventional trials.

REFERENCES

1 **GBD 2013 Mortality and Causes of Death Collaborators**. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; **385**: 117-171 [PMID: 25530442 DOI: 10.1016/S0140-6736(14)61682-2]

2 **Nichols M**, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. *Eur Heart J* 2014; **35**: 2950-2959 [PMID: 25139896 DOI: 10.1093/eurheartj/ehu299]

3 **Alkerwi A**, Sauvageot N, Gilson G, Stranges S. Prevalence and Correlates of Vitamin D Deficiency and Insufficiency in Luxembourg Adults: Evidence from the Observation of Cardiovascular Risk Factors (ORISCAV-LUX) Study. *Nutrients* 2015; **7**: 6780-6796 [PMID:

26287235 DOI: 10.3390/nu7085308]
4 **Holick MF**. The vitamin D deficiency pandemic: a forgotten hormone important for health. *Public Health Reviews* 2010; **32**: 267-283
5 **Vandevijvere S**, Amsalkhir S, Van Oyen H, Moreno-Reyes R. High prevalence of vitamin D deficiency in pregnant women: a national cross-sectional survey. *PLoS One* 2012; **7**: e43868 [PMID: 22937114 DOI: 10.1371/journal.pone.0043868]
6 **Lips P**. Vitamin D status and nutrition in Europe and Asia. *J Steroid Biochem Mol Biol* 2007; **103**: 620-625 [PMID: 17287117 DOI: 10.1016/j.jsbmb.2006.12.076]
7 **Harinarayan CV**. Prevalence of vitamin D insufficiency in postmenopausal south Indian women. *Osteoporos Int* 2005; **16**: 397-402 [PMID: 15776219 DOI: 10.1007/s00198-004-1703-5]
8 **Bouillon R**, Suda T. Vitamin D: calcium and bone homeostasis during evolution. *Bonekey Rep* 2014; **3**: 480 [PMID: 24466411 DOI: 10.1038/bonekey.2013.214]
9 **Duplancic D**, Cesarik M, Poljak NK, Radman M, Kovacic V, Radic J, Rogosic V. The influence of selective vitamin D receptor activator paricalcitol on cardiovascular system and cardiorenal protection. *Clin Interv Aging* 2013; **8**: 149-156 [PMID: 23430986 DOI: 10.2147/CIA.S38349]
10 **Gouni-Berthold I**, Krone W, Berthold HK. Vitamin D and cardiovascular disease. *Curr Vasc Pharmacol* 2009; **7**: 414-422 [PMID: 19601865 DOI: 10.2174/157016109788340686]
11 **Dusso AS**, Brown AJ, Slatopolsky E. Vitamin D. *Am J Physiol Renal Physiol* 2005; **289**: F8-28 [PMID: 15951480 DOI: 10.1152/ajprenal.00336.2004]
12 **De Metrio M**, Milazzo V, Rubino M, Cabiati A, Moltrasio M, Marana I, Campodonico J, Cosentino N, Veglia F, Bonomi A, Camera M, Tremoli E, Marenzi G. Vitamin D plasma levels and in-hospital and 1-year outcomes in acute coronary syndromes: a prospective study. *Medicine* (Baltimore) 2015; **94**: e857 [PMID: 25984675 DOI: 10.1097/MD.0000000000000857]
13 **Ng LL**, Sandhu JK, Squire IB, Davies JE, Jones DJ. Vitamin D and prognosis in acute myocardial infarction. *Int J Cardiol* 2013; **168**: 2341-2346 [PMID: 23415169 DOI: 10.1016/j.ijcard.2013.01.030]
14 **Aleksova A**, Belfiore R, Carriere C, Kassem S, La Carrubba S, Barbati G, Sinagra G. Vitamin D Deficiency in Patients with Acute Myocardial Infarction: An Italian Single-Center Study. *Int J Vitam Nutr Res* 2015; **85**: 23-30 [PMID: 26780274 DOI: 10.1024/0300-9831/a000220]
15 **Calvo MS**, Whiting SJ, Barton CN. Vitamin D intake: a global perspective of current status. *J Nutr* 2005; **135**: 310-316 [PMID: 15671233]
16 **Rosen CJ**. Clinical practice. Vitamin D insufficiency. *N Engl J Med* 2011; **364**: 248-254 [PMID: 21247315 DOI: 10.1056/NEJMcp1009570]
17 **Holick MF**. Vitamin D deficiency. *N Engl J Med* 2007; **357**: 266-281 [PMID: 17634462 DOI: 10.1056/NEJMra070553]
18 **Somjen D**, Weisman Y, Kohen F, Gayer B, Limor R, Sharon O, Jaccard N, Knoll E, Stern N. 25-hydroxyvitamin D3-1alpha-hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. *Circulation* 2005; **111**: 1666-1671 [PMID: 15795327 DOI: 10.1161/01.CIR.0000160353.27927.70]
19 **Zhou C**, Lu F, Cao K, Xu D, Goltzman D, Miao D. Calcium-independent and 1,25(OH)2D3-dependent regulation of the renin-angiotensin system in 1alpha-hydroxylase knockout mice. *Kidney Int* 2008; **74**: 170-179 [PMID: 18385669 DOI: 10.1038/ki.2008.101]
20 **Adams JS**, Hewison M. Extrarenal expression of the 25-hydroxyvitamin D-1-hydroxylase. *Arch Biochem Biophys* 2012; **523**: 95-102 [PMID: 22446158 DOI: 10.1016/j.abb.2012.02.016]
21 IOM (Institute of Medicine) Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: The National Academies Press, 2011 [DOI: 10.17226/13050]
22 **SACN (Scientific Advisory Committee on Nutrition).** Update on vitamin D. Position statement. London: The Stationary Office, 2007
23 **Thacher TD**, Clarke BL. Vitamin D insufficiency. *Mayo Clin Proc* 2011; **86**: 50-60 [PMID: 21193656 DOI: 10.4065/mcp.2010.0567]
24 **Hilger J**, Friedel A, Herr R, Rausch T, Roos F, Wahl DA, Pierroz DD, Weber P, Hoffmann K. A systematic review of vitamin D status in populations worldwide. *Br J Nutr* 2014; **111**: 23-45 [PMID: 23930771 DOI: 10.1017/S0007114513001840]
25 **Holick MF**, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011; **96**: 1911-1930 [PMID: 21646368 DOI: 10.1210/jc.2011-0385]
26 **Hossein-nezhad A**, Holick MF. Vitamin D for health: a global perspective. *Mayo Clin Proc* 2013; **88**: 720-755 [PMID: 23790560 DOI: 10.1016/j.mayocp.2013.05.011]
27 **Kendrick J**, Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey. *Atherosclerosis* 2009; **205**: 255-260 [PMID: 19091317 DOI: 10.1016/j.atherosclerosis.2008.10.033]
28 **Kim DH**, Sabour S, Sagar UN, Adams S, Whellan DJ. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). *Am J Cardiol* 2008; **102**: 1540-1544 [PMID: 19026311 DOI: 10.1016/j.amjcard.2008.06.067]
29 **Yao T**, Ying X, Zhao Y, Yuan A, He Q, Tong H, Ding S, Liu J, Peng X, Gao E, Pu J, He B. Vitamin D receptor activation protects against myocardial reperfusion injury through inhibition of apoptosis and modulation of autophagy. *Antioxid Redox Signal* 2015; **22**: 633-650 [PMID: 25365634 DOI: 10.1089/ars.2014.5887]
30 **Kawashima H**. Receptor for 1,25-dihydroxyvitamin D in a vascular smooth muscle cell line derived from rat aorta. *Biochem Biophys Res Commun* 1987; **146**: 1-6 [PMID: 3038100 DOI: 10.1016/0006-291X(87)90681-4]
31 **Fabsitz R**, Feinleib M. Geographic patterns in county mortality rates from cardiovascular diseases. *Am J Epidemiol* 1980; **111**: 315-328 [PMID: 7361756]
32 **Zipes DP**. Warning: the short days of winter may be hazardous to your health. *Circulation* 1999; **100**: 1590-1592 [PMID: 10517728]
33 **Forman JP**, Giovannucci E, Holmes MD, Bischoff-Ferrari HA, Tworoger SS, Willett WC, Curhan GC. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension* 2007; **49**: 1063-1069 [PMID: 17372031 DOI: 10.1161/HYPERTENSIONAHA.107.087288]
34 **Forman JP**, Curhan GC, Taylor EN. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension among young women. *Hypertension* 2008; **52**: 828-832 [PMID: 18838623 DOI: 10.1161/HYPERTENSIONAHA.108.117630]
35 **Hyppönen E**, Boucher BJ, Berry DJ, Power C. 25-hydroxyvitamin D, IGF-1, and metabolic syndrome at 45 years of age: a cross-sectional study in the 1958 British Birth Cohort. *Diabetes* 2008; **57**: 298-305 [PMID: 18003755 DOI: 10.2337/db07-1122]
36 **Scragg R**, Sowers M, Bell C. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. *Diabetes Care* 2004; **27**: 2813-2818 [PMID: 15562190]
37 **Chonchol M**, Scragg R. 25-Hydroxyvitamin D, insulin resistance, and kidney function in the Third National Health and Nutrition Examination Survey. *Kidney Int* 2007; **71**: 134-139 [PMID: 17082756 DOI: 10.1038/sj.ki.5002002]
38 **Mattila C**, Knekt P, Männistö S, Rissanen H, Laaksonen MA, Montonen J, Reunanen A. Serum 25-hydroxyvitamin D concentration and subsequent risk of type 2 diabetes. *Diabetes Care* 2007; **30**: 2569-2570 [PMID: 17626891 DOI: 10.2337/dc07-0292]
39 **Go AS**, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351**: 1296-1305 [PMID: 15385656 DOI: 10.1056/NEJMoa041031]
40 **Lund B**, Badskjaer J, Lund B, Soerensen OH. Vitamin D and ischaemic heart disease. *Horm Metab Res* 1978; **10**: 553-556 [PMID: 744575 DOI: 10.1055/s-0028-1093390]
41 **Scragg R**, Jackson R, Holdaway IM, Lim T, Beaglehole R. Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D3 levels: a community-based study. *Int J Epidemiol* 1990; **19**: 559-563

[PMID: 2262248]
42 **Wang TJ**, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, Benjamin EJ, D'Agostino RB, Wolf M, Vasan RS. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008; **117**: 503-511 [PMID: 18180395 DOI: 10.1161/CIRCULATIONAHA.107.706127]
43 **Giovannucci E**, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med* 2008; **168**: 1174-1180 [PMID: 18541825 DOI: 10.1001/archinte.168.11.1174]
44 **Wang L**, Song Y, Manson JE, Pilz S, März W, Michaëlsson K, Lundqvist A, Jassal SK, Barrett-Connor E, Zhang C, Eaton CB, May HT, Anderson JL, Sesso HD. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. *Circ Cardiovasc Qual Outcomes* 2012; **5**: 819-829 [PMID: 23149428 DOI: 10.1161/CIRCOUTCOMES.112.967604]
45 **Lee JH**, Gadi R, Spertus JA, Tang F, O'Keefe JH. Prevalence of vitamin D deficiency in patients with acute myocardial infarction. *Am J Cardiol* 2011; **107**: 1636-1638 [PMID: 21439530 DOI: 10.1016/j.amjcard.2011.01.048]
46 **Correia LC**, Sodré F, Garcia G, Sabino M, Brito M, Kalil F, Barreto B, Lima JC, Noya-Rabelo MM. Relation of severe deficiency of vitamin D to cardiovascular mortality during acute coronary syndromes. *Am J Cardiol* 2013; **111**: 324-327 [PMID: 23174181 DOI: 10.1016/j.amjcard.2012.10.006]
47 **Khalili H**, Talasaz AH, Salarifar M. Serum vitamin D concentration status and its correlation with early biomarkers of remodeling following acute myocardial infarction. *Clin Res Cardiol* 2012; **101**: 321-327 [PMID: 22159952 DOI: 10.1007/s00392-011-0394-0]
48 **De Metrio M**, Milazzo V, Marenzi G. Serum vitamin D concentration status and its correlation with early biomarkers of remodeling following acute myocardial infarction. *Clin Res Cardiol* 2012; **101**: 771-772 [PMID: 22527093 DOI: 10.1007/s00392-012-0457-x]
49 **Pilz S**, März W, Wellnitz B, Seelhorst U, Fahrleitner-Pammer A, Dimai HP, Boehm BO, Dobnig H. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. *J Clin Endocrinol Metab* 2008; **93**: 3927-3935 [PMID: 18682515 DOI: 10.1210/jc.2008-0784]
50 **Perron RM**, Lee P. Efficacy of high-dose vitamin D supplementation in the critically ill patients. *Inflamm Allergy Drug Targets* 2013; **12**: 273-281 [PMID: 23782210 DOI: 10.2174/18715281113129990047]
51 **Braun AB**, Litonjua AA, Moromizato T, Gibbons FK, Giovannucci E, Christopher KB. Association of low serum 25-hydroxyvitamin D levels and acute kidney injury in the critically ill. *Crit Care Med* 2012; **40**: 3170-3179 [PMID: 22975885 DOI: 10.1097/CCM.0b013e318260c928]
52 **Moromizato T**, Litonjua AA, Braun AB, Gibbons FK, Giovannucci E, Christopher KB. Association of low serum 25-hydroxyvitamin D levels and sepsis in the critically ill. *Crit Care Med* 2014; **42**: 97-107 [PMID: 23982028 DOI: 10.1097/CCM.0b013e31829eb7af]
53 **Autier P**, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007; **167**: 1730-1737 [PMID: 17846391 DOI: 10.1001/archinte.167.16.1730]
54 **Wang L**, Manson JE, Song Y, Sesso HD. Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events. *Ann Intern Med* 2010; **152**: 315-323 [PMID: 20194238 DOI: 10.7326/0003-4819-152-5-201003020-00010]
55 **Avenell A**, MacLennan GS, Jenkinson DJ, McPherson GC, McDonald AM, Pant PR, Grant AM, Campbell MK, Anderson FH, Cooper C, Francis RM, Gillespie WJ, Robinson CM, Torgerson DJ, Wallace WA. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). *J Clin Endocrinol Metab* 2012; **97**: 614-622 [PMID: 22112804 DOI: 10.1210/jc.2011-1309]
56 **Hsia J**, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, Heckbert SR, Johnson KC, Manson JE, Sidney S, Trevisan M. Calcium/vitamin D supplementation and cardiovascular events. *Circulation* 2007; **115**: 846-854 [PMID: 17309935 DOI: 10.1161/CIRCULATIONAHA.106.673491]
57 **Trivedi DP**, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 2003; **326**: 469 [PMID: 12609940 DOI: 10.1136/bmj.326.7387.469]
58 **Amrein K**, Sourij H, Wagner G, Holl A, Pieber TR, Smolle KH, Stojakovic T, Schnedl C, Dobnig H. Short-term effects of high-dose oral vitamin D3 in critically ill vitamin D deficient patients: a randomized, double-blind, placebo-controlled pilot study. *Crit Care* 2011; **15**: R104 [PMID: 21443793 DOI: 10.1186/cc10120]
59 **Witte KK**, Byrom R, Gierula J, Paton MF, Jamil HA, Lowry JE, Gillott RG, Barnes SA, Chumun H, Kearney LC, Greenwood JP, Plein S, Law GR, Pavitt S, Barth JH, Cubbon RM, Kearney MT. Effects of Vitamin D on Cardiac Function in Patients With Chronic HF: The VINDICATE Study. *J Am Coll Cardiol* 2016; **67**: 2593-2603 [PMID: 27058906 DOI: 10.1016/j.jacc.2016.03.508]
60 **Pérez-Castrillón JL**, Vega G, Abad L, Sanz A, Chaves J, Hernandez G, Dueñas A. Effects of Atorvastatin on vitamin D levels in patients with acute ischemic heart disease. *Am J Cardiol* 2007; **99**: 903-905 [PMID: 17398180 DOI: 10.1016/j.amjcard.2006.11.036]
61 **Walter DH**, Fichtlscherer S, Britten MB, Rosin P, Auch-Schwelk W, Schächinger V, Zeiher AM. Statin therapy, inflammation and recurrent coronary events in patients following coronary stent implantation. *J Am Coll Cardiol* 2001; **38**: 2006-2012 [PMID: 11738308]
62 **Eren E**, Ellidag HY, Yılmaz A, Aydın Ö, Yılmaz N. No association between vitamin D levels and inflammation markers in patients with acute coronary syndrome. *Adv Med Sci* 2015; **60**: 89-93 [PMID: 25615956 DOI: 10.1016/j.advms.2014.12.003]

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Ambulatory pulmonary artery pressure monitoring in advanced heart failure patients

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Abstract

Heart failure (HF) is an emerging epidemic associate with significant morbidity, mortality, and health care expenditure. Although there were major advances in pharmacologic and device based therapies for the management of HF, mortality of this condition remains high. Accurate monitoring of HF patients for exacerbations is very important to reduce recurrent hospitalizations and its associated complications. With the failure of clinical signs, tele-monitoring, and laboratory bio-markers to function as early markers of HF exacerbations, more sophisticated techniques were sought to accurately predict the circulatory status in HF patients in order to execute timely pharmacological intervention to reduce frequent hospitalizations. CardioMEMS™ (St. Jude Medical, Inc., Saint Paul, Minnesota) is an implantable, wireless pulmonary arterial pressure (PAP) monitoring system which transmits the patient's continuous PAPs to the treating health care provider in the ambulatory setting. PAP-guided medical therapy modification has been shown to significantly reduce HF-related hospitalization and overall mortality. In advanced stages of HF, wireless access to hemodynamic information correlated with earlier left ventricular assist device implantation and shorter time to heart transplantation.

Key words: CardioMEMS; Heart failure; Remote heart failure monitoring; Pulmonary arterial pressure monitoring; Left ventricular assist device

Core tip: Traditional heart failure monitoring methods have failed to accurately and timely identify worsening heart failure. Remote pulmonary artery pressure monitoring *via* CardioMEMS™ heart failure system identified heart failure exacerbations earlier and more accurately than clinical signs, and timely medical

interventions resulted in reduced hospitalizations and mortality. Remote pulmonary artery pressure monitoring appears to have positive clinical implications in patients with mechanical circulatory support.

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INTRODUCTION

Heart failure (HF) is a chronic debilitating condition which impairs the ability of the heart to effectively pump the blood to the body to meet its metabolic requirements. HF is an emerging epidemic with an estimated prevalence of 5.8 million in the United States, and over 23 million worldwide[1]. Within the United States, the incidence of HF exceeds 650000 each year with an estimated annual financial burden of around 30.7 billion dollars[2,3]. Although there were major advances in pharmacologic and device based therapies for the management of HF which improved the overall survival over time, mortality of this condition remains high. The estimated survival after the diagnosis of HF is 50% at 5 years and 10% at 10 years[1]. Hospitalization for acute decompensated HF serves as a poor prognostic indicator with an approximate 30% and 50% readmission rates at 1-mo and 6-mo, respectively[1,3]. With improved survival of patients after acute myocardial infarction, a growing elderly population, and frequent hospitalizations in the HF population owing to acute exacerbations, HF continuous to be one of the leading causes of morbidity, mortality, and health care expenditures in the United States and worldwide.

Around 150000-250000 Americans suffer from advanced stage HF[4]. Although cardiac transplantation is the gold standard treatment in such patients, limited organ availability restricts the number of heart transplants to around 2500 per year (https://www.unos.org/data/transplant-trends/#transplants_by_organ). More than 4000 patients are currently on the waiting list for a cardiac transplant (www.unos.org/data/transplant-trends/#waitlists_by_organ), a number which is expected to increase significantly because of the increasing number of patients living with advanced HF and an increasing elderly population. Left ventricle assist device (LVAD) has emerged as a life-saving option for these patients as either bridge to transplant, bridge to decision, bridge to recovery or as destination therapy. Around 15000 HF patients across the world are currently supported with LVADs[5]. LVAD serves as destination therapy in more than 45% of the patients living with the device[5].

PREVIOUSLY TESTED METHODS FOR MONITORING HF PATIENTS

Identification of physical manifestations such as weight gain, extremity edema, fatigue, shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, jugular venous distention, third heart sounds, and rales, *etc*. have poor to moderate sensitivities and are often late manifestations of worsening HF, thereby, relying on these markers have limited impact on reducing HF hospitalizations[6]. Also, such efforts largely employ patient self-management strategies, including diuretic dose adjustments based on clinical worsening, and are unsuccessful in patients with poor self-care skills and compliance[6]. Two large trials which investigated the benefits of tele-monitoring in HF population failed to show any significant decrease in the all-cause mortality and HF hospitalizations in the tele-monitored group[6]. A smart-phone based electrocardiographic monitoring of HF has been recently proposed, but there is not much data exploring this idea[7].

Lainchbury *et al*[8] compared N-terminal pro-B-type natriuretic (NT-proBNP) guided titration of medical therapy in HF patients with intensive clinical management and with usual care in a randomized sample of 564 patients. There was a reduction in the 3-year mortality in the NT-proBNP-guided group compared to the clinically-guided group (30.9%; $P = 0.048$) and to those with usual care (31.3%; $P = 0.021$). These benefits were selectively seen in patients $\leqslant$ 75 years of age. However, there was no statistically significant difference in the overall hospitalizations for HF and the secondary outcomes among all the groups[8]. Another study monitored plasma B-type natriuretic peptide (BNP) levels in up to 558 chronic stable HF patients in an ambulatory setting to predict imminent decompensation[9]. The study showed that both symptomatic and asymptomatic HF patients had a wide range of plasma BNP levels. Interestingly, 21% of symptomatic decompensated HF patients had BNP levels below the diagnostic threshold of < 100 pg/mL[9].

REMOTE HEMODYNAMIC MONITORING IN HF PATIENTS

With the failure of reliable clinical symptoms/signs, tele-monitoring, and laboratory bio-markers to help reduce the hospitalizations, and health care expenditure in the HF population, more sophisticated techniques were sought to accurately predict the circulatory status in HF patients in order to execute timely pharmacological intervention to prevent the primary onus of this disease, *i.e.*, hospitalizations. Echocardiography is being used as a monitoring system in the hospitalized and ambulatory population, but it is associated with significant costs, less accuracy, and observer variability. Traditionally, in hospitalized HF patients, right heart catheterization

(RHC) provides invaluable information regarding the volume status and filling pressures which can form the basis of successful medical management. However, RHC is not routinely recommended to aid in the management of hospitalized decompensated HF patients owing to its invasive nature and associated risks. We had no such accurate monitoring systems in the ambulatory setting until scientific advances led to the development of implantable hemodynamic monitors (IHMs) which provided hemodynamic information comparable to the information obtained from a RHC[10]. The idea of IHM based monitoring and necessary interventions in HF patients was innovative and exiting.

Earlier trials of implantable hemodynamic monitoring in HF patients did not show significant clinical benefit or were unable to adequately assess clinical efficacy. The COMPASS-HF (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) trial using Chronicle (Medtronic Inc., Minneapolis, Minnesota) to estimate right ventricular pressures and guide medical therapy, did not show a significant reduction in HF-related events when compared to the control group[11]. The Reducing Decompensation Events Utilizing Intracardiac Pressures in Patients With Chronic Heart Failure (REDUCEhf) study employed a device combining IHM and implantable cardioverter-defibrillator technology to measure right ventricular pressures and guide medical therapy[12]. The REDUCEhf study was unable to test clinical efficacy end points adequately and findings from this study did not show a difference in the rate of HF-equivalents when medical therapy was guided based on the information obtained from the IHM[12].

The Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients (HOMEOSTASIS) trial is a small study of 40 patients in which the benefit of physician-directed patient self-management of left atrial pressures as measured with the implantable HeartPOD (St. Jude Medical Inc, Minneapolis, Minnesota) was investigated[13]. Left atrial pressure guided medical therapy was associated with an improved event-free survival (death or hospitalization for acute decompensated HF), reduced mean daily left atrial pressures, improved New York Heart Association (NYHA) functional class, improved left ventricular ejection fraction, increased doses of neuro-hormonal antagonists, and reduced diuretic doses[13]. Encouraging results from this smaller study formed the basis of the larger and currently ongoing LAPTOP-HF trial which will investigate the role of implantable left atrial pressure monitoring in conjunction with a new HF treatment paradigm across the spectrum of HF patients[14].

CARDIOMEMS™ AND REMOTE PULMONARY ARTERIAL PRESSURE MONITORING

CardioMEMS™ (St. Jude Medical, Inc., Saint Paul, Minnesota) is a wireless pulmonary arterial (PA) pressure monitoring system. It measures PA pressures from a battery free capacitive electromechanical sensor which is permanently implanted with a delivery system in the distal pulmonary artery with a RHC *via* transvenous access. An electronic system transmits the generated data to a secure network where it is readily available for interpretation by the treating clinician. Verdejo *et al*[15] showed that wireless PA pressure monitoring using the CardioMEMS sensor correlated with Swan-Ganz catheter and echocardiographic PA pressure measurements. The outcomes of remote management of HF patients guided by wireless PA pressure monitoring was investigated in the landmark CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class Ⅲ Heart Failure Patients) trial[16].

The CHAMPION trial is a randomized, controlled, multi-center, single-blind trial in which 550 NYHA class Ⅲ HF patients were implanted with the wireless CardioMEMS HF pressure sensor system[16]. Physicians had access to the PA pressures of the patients in the treatment group only, in which medications were adjusted based on the generated data. The control group received traditional HF management. The primary efficacy endpoint was the rate of HF-related hospitalizations at 6 mo. In comparison to the control group, there was a remarkable 28% reduction in HF-related hospitalizations at 6 mo, and 37% at 15 mo in the treatment group (Hazard ratio 0.63, $P < 0.0001$)[17]. There were no pressure sensor failures and 98.6% of the study population was free from device-related or system-related complications[17]. A sub-analysis of the original trial in HF with preserved ejection fraction (HFpEF) patients showed that there was a 50% reduction ($P < 0.0001$) in HF-related hospitalizations at 17 mo in the treatment group[18]. These landmark findings led to the Food and Drug Administration approval of the CardioMEMS™ HF system for ambulatory hemodynamic monitoring in NYHA class Ⅲ HF with reduced ejection fraction (HFrEF) and HFpEF patients, who are on optimal medical therapy, and had a HF hospitalization in the previous year[19]. In the 2016 European society of Cardiology guidelines, CardioMEMS received a Class Ⅱb recommendation for directed therapy management and monitoring tool in HF patients[20].

Numerous sub-analyses supported the encouraging results obtained from the original CHAMPION trial. The reduced HF-related hospitalization rate was postulated to be from physician controlled effective changes in diuretic dosing in the treatment group ($P < 0.0001$ for more frequent diuretic dose changes in treatment group compared to control)[21]. Wireless PA pressure-guided HF management was superior to clinical signs-guided management with a 67% relative risk reduction ($P = 0.0007$) in HF hospitalizations when diuretic doses were adjusted based on PA pressure alone *vs* clinical signs alone[22]. At 6 mo, the target group experienced a higher frequency of medication adjustments with significant increases in the doses of diuretics, vasodilators, and

neuro-hormonal antagonists with preserved renal function despite intensification of diuretic therapy[23]. Remote PA pressure-guided treatment resulted in similar reductions in HF hospitalization in HFrEF patients with and without a cardiac resynchronization therapy (CRT) device, suggesting that HF management guided by PA pressures may provide additive benefits to CRT[24].

Wireless PA-pressure monitoring on top of guideline-directed medical therapy and CRT or ICD, had an additive effect in improving HF hospitalizations and mortality[25]. There were significant reductions in all-cause hospitalization ($P < 0.0032$), and in the number of deaths or all-cause hospitalization in the treatment group ($P = 0.0017$)[26]. Interestingly, it was observed that measurement of PA pressures using RHC alone may result in under-diagnosing pulmonary hypertension related to HF. Of the 217 patients who did not meet criteria for pulmonary hypertension during implantation RHC, 49% met criteria for pulmonary hypertension based in the first week IHM data[27]. Alam *et al*[28] compared 34 HF patients who had an implanted CardioMEMS HF system with 32 HF patients without an IHM, and reported a three-fold improvement in the Kansas City Cardiomyopathy Questionnaire scores ($P < 0.001$) and increased 6-min walk distance ($P < 0.001$) in the CardioMEMS group. These findings represent improved quality of life and exercise capacity. Results from the CHAMPION trial and subsequent sub-analysis confirmed that early and appropriate medical interventions following early detection of elevated PA pressures resulted in a significant reduction of HF-related hospitalizations, readmission rates and mortality.

There is an increasing trend in the number of HF patients living with LVADs and an increasing use of LVAD as destination therapy for advanced HF patients. Feldman *et al*[29] conducted a sub-analysis of the CHAMPION trial to determine the validity of remote PA pressure directed therapy on optimization of medications, pump parameters, and timing of heart transplantation in patients receiving a LVAD. Of the 27 patients who received an LVAD, 15 patients were assigned to the treatment group where their medical therapy was modified based on PA pressures and 12 patients in the control group received standard care. The data obtained from CardioMEMS HF system led to significantly more medication changes in the treatment arm ($P = 0.025$). Wireless access to hemodynamic information correlated with earlier LVAD implantation ($P = 0.001$) and shorter time to transplantation ($P = 0.001$) in the treatment arm[29].

Over the last few decades, efforts have been directed at reducing recurrent hospitalizations for worsening HF in this patient population. A variety of markers varying from clinical symptoms and signs to laboratory testing have been investigated to identify acute decompensated HF early enough to prevent hospitalizations, subsequent morbidity, and health care expenditure. Daily weight monitoring is a cornerstone for managing HF patients. It has been shown that increases in body weight begin at least 1 week before a HF hospitalization[30]. However, less than a half of the HF patients including those recently discharged after a hospitalization for HF exacerbation check their weight on a daily basis[31]. Daily electronic body weight transmission to a HF clinic in patients with severe HF who had a recent HF hospitalization did not show any benefit in reducing HF re-hospitalization or death[32].

CONCLUSION

HF continues to be a major public health problem with a significant financial burden. As more and more people are living with HF, it is important have a simple, reliable, and valid monitoring system to aid in the early identification and appropriate management of worsening HF in the ambulatory setting. IHM is an innovative and exciting monitoring system for HF management. CardioMEMS has steered HF research into a new direction which will serve as the gateway to future therapies and innovations in the management of chronic HF patients. Also with increasing number of people living with LVADs and LVAD being used as destination therapy in a large percentage of the LVAD population, CardioMEMS will be a promising monitoring system to better manage HF as well as the LVAD device in this population. However, given the small number of participants involved in many of the available trials, large multicenter randomized clinical trials are needed to make valid recommendations in an effort to lower mortality and improve quality of life in the chronically sick HF population. Wireless left atrial pressure-guided and PA pressure-guided management of HF can have a substantial positive effect on reducing the financial burden of HF and improving the overall morbidity and mortality in this population.

REFERENCES

1 **Roger VL**. Epidemiology of heart failure. *Circ Res* 2013; **113**: 646-659 [PMID: 23989710 DOI: 10.1161/CIRCRESAHA.113.300268]

2 **Mozaffarian D**, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation* 2016; **133**: e38-360 [PMID: 26673558 DOI: 10.1161/CIR.0000000000000350]

3 **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **62**: e147-e239 [PMID: 23747642 DOI: 10.1016/j.jacc.2013.05.019]

4 **Miller LW**, Guglin M. Patient selection for ventricular assist devices: a moving target. *J Am Coll Cardiol* 2013; **61**: 1209-1221 [PMID: 23290542 DOI: 10.1016/j.jacc.2012.08.1029]

5 **Kirklin JK**, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, Miller MA, Baldwin JT, Young JB. Seventh INTERMACS annual report: 15,000 patients and counting. *J Heart Lung Transplant* 2015; **34**: 1495-1504 [PMID: 26520247 DOI: 10.1016/j.healun.2015.10.003]

6 **Lampert BC**, Emani S. Remote hemodynamic monitoring for ambulatory left ventricular assist device patients. *J Thorac Dis* 2015; **7**: 2165-2171 [PMID: 26793337 DOI: 10.3978/j.issn.2072-1439.2015.10.45]

7 **Madias JE**. A proposal for monitoring patients with heart failure via "smart phone technology"-based electrocardiograms. *J Electrocardiol* 2016; **49**: 699-706 [PMID: 27334627 DOI: 10.1016/j.jelectrocard.2016.06.001]

8 **Lainchbury JG**, Troughton RW, Strangman KM, Frampton CM, Pilbrow A, Yandle TG, Hamid AK, Nicholls MG, Richards AM. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. *J Am Coll Cardiol* 2009; **55**: 53-60 [PMID: 20117364 DOI: 10.1016/j.jacc.2009.02.095]

9 **Tang WH**, Girod JP, Lee MJ, Starling RC, Young JB, Van Lente F, Francis GS. Plasma B-type natriuretic peptide levels in ambulatory patients with established chronic symptomatic systolic heart failure. *Circulation* 2003; **108**: 2964-2966 [PMID: 14662703 DOI: 10.1161/01.CIR.0000106903.98196.B6]

10 **Merchant FM**, Dec GW, Singh JP. Implantable sensors for heart failure. *Circ Arrhythm Electrophysiol* 2010; **3**: 657-667 [PMID: 21156777 DOI: 10.1161/CIRCEP.110.95950]

11 **Bourge RC**, Abraham WT, Adamson PB, Aaron MF, Aranda JM, Magalski A, Zile MR, Smith AL, Smart FW, O'Shaughnessy MA, Jessup ML, Sparks B, Naftel DL, Stevenson LW. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure: the COMPASS-HF study. *J Am Coll Cardiol* 2008; **51**: 1073-1079 [PMID: 18342224 DOI: 10.1016/j.jacc.2007.10.061]

12 **Adamson PB**, Gold MR, Bennett T, Bourge RC, Stevenson LW, Trupp R, Stromberg K, Wilkoff BL, Costanzo MR, Luby A, Aranda JM, Heywood JT, Baldwin HA, Aaron M, Smith A, Zile M. Continuous hemodynamic monitoring in patients with mild to moderate heart failure: results of The Reducing Decompensation Events Utilizing Intracardiac Pressures in Patients With Chronic Heart Failure (REDUCEhf) trial. *Congest Heart Fail* 2011; **17**: 248-254 [PMID: 21906250 DOI: 10.1111/j.1751-7133.2011.00247.x]

13 **Ritzema J**, Troughton R, Melton I, Crozier I, Doughty R, Krum H, Walton A, Adamson P, Kar S, Shah PK, Richards M, Eigler NL, Whiting JS, Haas GJ, Heywood JT, Frampton CM, Abraham WT. Physician-directed patient self-management of left atrial pressure in advanced chronic heart failure. *Circulation* 2010; **121**: 1086-1095 [PMID: 20176990 DOI: 10.1161/CIRCULATIONAHA.108.800490]

14 **Maurer MS**, Adamson PB, Costanzo MR, Eigler N, Gilbert J, Gold MR, Klapholz M, Saxon LA, Singh JP, Troughton R, Abraham WT. Rationale and Design of the Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy Study (LAPTOP-HF). *J Card Fail* 2015; **21**: 479-488 [PMID: 25921522 DOI: 10.1016/j.cardfail.2015.04.012]

15 **Verdejo HE**, Castro PF, Concepción R, Ferrada MA, Alfaro MA, Alcaíno ME, Deck CC, Bourge RC. Comparison of a radiofrequency-based wireless pressure sensor to swan-ganz catheter and echocardiography for ambulatory assessment of pulmonary artery pressure in heart failure. *J Am Coll Cardiol* 2007; **50**: 2375-2382 [PMID: 18154961 DOI: 10.1016/j.jacc.2007.06.061]

16 **Adamson PB**, Abraham WT, Aaron M, Aranda JM, Bourge RC, Smith A, Stevenson LW, Bauman JG, Yadav JS. CHAMPION trial rationale and design: the long-term safety and clinical efficacy of a wireless pulmonary artery pressure monitoring system. *J Card Fail* 2011; **17**: 3-10 [PMID: 21187258 DOI: 10.1016/j.cardfail.2010.08.002]

17 **Abraham WT**, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 2011; **377**: 658-666 [PMID: 21315441 DOI: 10.1016/S0140-6736(11)60101-3]

18 **Adamson PB**, Abraham WT, Bourge RC, Costanzo MR, Hasan A, Yadav C, Henderson J, Cowart P, Stevenson LW. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. *Circ Heart Fail* 2014; **7**: 935-944 [PMID: 25286913 DOI: 10.1161/CIRCHEARTFAILURE.113.001229]

19 **US Food and Drug Administration Center for Devices and Radiological Health**. CardioMEMSTM HF System approval letter. [accessed 2014 Jul 2]. Available from: URL: http//www.accessdata.fda.gov/cdrh_docs/pdf10/P100045a.pdf

20 **Ponikowski P**, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; **18**: 891-975 [PMID: 27207191 DOI: 10.1002/ejhf.592]

21 **Costanzo MR**, Adamson PB, AbrahamWT, Jeffries B, Neville S, Cowart P. Diuretic use guided by a wireless implanted pulmonary artery pressure monitoring system in NYHA class III heart failure patients: Observations from the CHAMPION trial. *Circulation* 2012; **126**: A19396

22 **Goldberg LR**, Desai AS, Costanzo MR, Stevenson LW, Adamson PB, Heywood JT, Abraham WT. Pressure for action: implantable pulmonary artery pressure sensor measurements alone beat clinical signs to guide prevention of heart failure hospitalizations, Boston: 2015. Available from: URL: http//www.abstractsonline.com/pp8/#!/3647/presentation/13016

23 **Costanzo MR**, Stevenson LW, Adamson PB, Desai AS, Heywood JT, Bourge RC, Bauman J, Abraham WT. Interventions Linked to Decreased Heart Failure Hospitalizations During Ambulatory Pulmonary Artery Pressure Monitoring. *JACC Heart Fail* 2016; **4**: 333-344 [PMID: 26874388 DOI: 10.1016/j.jchf.2015.11.011]

24 **Weiner S**, Abraham WT, Adamson PB, Neville S, Henderson, J. Effect of CRT on heart failure related hospitalizations in patients with reduced EF utilizing remote pulmonary artery pressures in the CHAMPION trial. *Heart Rhythm* 2011; **8**: S437

25 **Abraham WT**, Adamson PB, Stevenson LW, Costanzo MR, Bourge RC, Bauman J, Yadav J. Pulmonary artery pressure management in heart failure patients with cardiac resynchronization therapy or implantable cardioverter defibrillator devices significantly reduces heart failure hospitalizations and mortality above and beyond background guide-directed medical therapy, Boston: 2015. Available from: URL: http//www.abstractsonline.com/pp8/#!/3647/presentation/12502

26 **Adamson PB**, Abraham WT, Stevenson L, Neville S, Cowart P, Yadav J. Benefits of pulmonary artery pressure monitoring extend to reduction of all-cause rehospitalizations. *Amer Colle Cardiol* 2014; **63**: A746 [DOI: 10.1016/S0735-1097(14)60746-4]

27 **Raina A**, Abraham WT, Adamson PB, Bauman J, Benza RL. Limitations of right heart catheterization in the diagnosis and risk stratification of patients with pulmonary hypertension related to left heart disease: insights from a wireless pulmonary artery pressure monitoring system. *J Heart Lung Transplant* 2015; **34**: 438-447 [PMID: 25813770 DOI: 10.1016/j.healun.2015.01.983]

28 **Alam A**, Jermyn R, Joseph M, Patel S, Jorde U, Saeed O. Improved quality of life scores and exercise capacity with remote pulmonary artery pressure monitoring in patients with chronic heart failure, Chicago: 2016. Available from: URL: http//www.abstractsonline.com/pp8/#!/3874/presentation/43252

29 **Feldman D**, Naka Y, Cabuay B, Yakayama H, Bauman J, Cowart P, Corcoran K. A wireless hemodynamic pressure sensor before and after ventricular assist device placement: A sub-study of the CHAMPION trial. *J Heart Lung Transplant* 2011; **30**: S86 [DOI: 10.1016/j.healun.2011.01.248]

30 **Chaudhry SI**, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. *Circulation* 2007; **116**: 1549-1554 [PMID: 17846286 DOI: 10.1161/CIRCULATIONAHA.107.690768]
31 **Bui AL**, Fonarow GC. Home monitoring for heart failure management. *J Am Coll Cardiol* 2012; **59**: 97-104 [PMID: 22222071 DOI: 10.1016/j.jacc.2011.09.044]
32 **Lyngå P**, Persson H, Hägg-Martinell A, Hägglund E, Hagerman I, Langius-Eklöf A, Rosenqvist M. Weight monitoring in patients with severe heart failure (WISH). A randomized controlled trial. *Eur J Heart Fail* 2012; **14**: 438-444 [PMID: 22371525 DOI: 10.1093/eurjhf/hfs023]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Does heart rate variability correlate with long-term prognosis in myocardial infarction patients treated by early revascularization?

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Informed consent statement: All participants had been fully informed on the procedures they were undergoing and a written consent was obtained from them.

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Abstract

AIM

To assess the prevalence of depressed heart rate variability (HRV) after an acute myocardial infarction (MI), and to evaluate its prognostic significance in the present era of immediate reperfusion.

METHODS

Time-domain HRV (obtained from 24-h Holter recordings) was assessed in 326 patients (63.5 ± 12.1 years old; 80% males), two weeks after a complicated MI treated by early reperfusion: 208 ST-elevation myocardial infarction (STEMI) patients (in which reperfusion was

successfully obtained within 6 h of symptoms in 94% of cases) and 118 non-ST-elevation myocardial infarction (NSTEMI) patients (percutaneous coronary intervention was performed within 24 h and successful in 73% of cases). Follow-up of the patients was performed *via* telephone interviews a median of 25 mo after the index event (95%CI of the mean 23.3-28.0). Primary end-point was occurrence of all-cause or cardiac death; secondary end-point was occurrence of major clinical events (MCE, defined as mortality or readmission for new MI, new revascularization, episodes of heart failure or stroke). Possible correlations between HRV parameters (mainly the standard deviation of all normal RR intervals, SDNN), clinical features (age, sex, type of MI, history of diabetes, left ventricle ejection fraction), angiographic characteristics (number of coronary arteries with critical stenoses, success and completeness of revascularization) and long-term outcomes were analysed.

RESULTS

Markedly depressed HRV parameters were present in a relatively small percentage of patients: SDNN < 70 ms was found in 16% and SDNN < 50 ms in 4% of cases. No significant differences were present between STEMI and NSTEMI cases as regards to their distribution among quartiles of SDNN (χ^2 =1.536, P = 0.674). Female sex and history of diabetes maintained a significant correlation with lower values of SDNN at multivariate Cox regression analysis (respectively: P = 0.008 and P = 0.008), while no correlation was found between depressed SDNN and history of previous MI (P = 0.999) or number of diseased coronary arteries (P = 0.428) or unsuccessful percutaneous coronary intervention (PCI) (P = 0.691). Patients with left ventricle ejection fraction (LVEF) < 40% presented more often SDNN values in the lowest quartile (P < 0.001). After > 2 years from infarction, a total of 10 patients (3.1%) were lost to follow-up. Overall incidence of MCE at follow-up was similar between STEMI and NSTEMI (P = 0.141), although all-cause and cardiac mortality were higher among NSTEMI cases (respectively: 14% *vs* 2%, P = 0.001; and 10% *vs* 1.5%, P = 0.001). The Kaplan-Meier survival curves for all-cause mortality and for cardiac deaths did not reveal significant differences between patients with SDNN in the lowest quartile and other quartiles of SDNN (respectively: P = 0.137 and P = 0.527). Also the MCE-free survival curves were similar between the group of patients with SDNN in the lowest quartile *vs* the patients of the other SDNN quartiles (P = 0.540), with no difference for STEMI (P = 0.180) or NSTEMI patients (P = 0.541). By the contrary, events-free survival was worse if patients presented with LVEF < 40% (P = 0.001).

CONCLUSION

In our group of patients with a recent complicated MI, abnormal autonomic parameters have been found with a prevalence that was similar for STEMI and NSTEMI cases, and substantially unchanged in comparison to what reported in the pre-primary-PCI era. Long-term outcomes did not correlate with level of depression of HRV parameters recorded in the subacute phase of the disease, both in STEMI and in NSTEMI patients. These results support lack of prognostic significance of traditional HRV parameters when immediate coronary reperfusion is utilised.

Key words: Heart rate variability; Autonomic nervous system; Primary percutaneous coronary intervention; Myocardial infarction; ST-elevation myocardial infarction; Non-ST-elevation myocardial infarction; Left ventricle ejection fraction; Long-term prognosis

Core tip: Depressed heart rate variability (HRV) is usually considered a negative long-term prognostic factor after an acute myocardial infarction (MI). Anyway, most of the supporting research was conducted before the era of immediate reperfusion by percutaneous coronary intervention. In our study, in MI patients treated by early reperfusion abnormal values of HRV are present in a low percentage of cases. Low HRV does not correlate with long term-prognosis, both in ST-elevation and non-ST-elevation MI patients. Abnormal HRV seems to have lost prognostic significance in the present era of primary percutaneous revascularization.

Compostella L, Lakusic N, Compostella C, Truong LVS, Iliceto S, Bellotto F. Does heart rate variability correlate with long-term prognosis in myocardial infarction patients treated by early revascularization? *World J Cardiol* 2017; 9(1): 27-38 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i1/27.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i1.27

INTRODUCTION

The first clinical evidence that one measure of heart rate variability (HRV), the standard deviation of all normal RR intervals (SDNN), was a powerful predictor of cardiac mortality after an acute myocardial infarction (AMI) was given by the wide longitudinal study by Kleiger *et al*[1] in 1987. Since then, marked abnormalities of various parameters of HRV, indicating profound derangement of the cardiac autonomic system, have been often described after AMI and have been confirmed to be reliable predictors of poor long-term prognosis[2,3]. The large multicentre ATRAMI study conducted in 1998 demonstrated that 15% of AMI patients observed during the first 4 week of the acute event, presented a SDNN < 70 ms, and that among the group with depressed SDNN long-term mortality was 5 times higher than in the patients with better preserved HRV parameters[4]. These results confirmed the findings of previous studies, such as the GISSI-2 study that used similar evaluation parameters[5]. Other studies used various and different methods to assess HRV (time and frequency domain

measures, discriminant analysis, fractal and other non-linear HRV analysis, with both short-term and long-term evaluations) and observed AMI patients at variable periods of time after the index event; they reported a wide range of prevalence of reduced HRV parameters (ranging from 7% to 34%)[6,7], and different incidence of long-term mortality (ranging from 0% to 45%)[8-10]. Despite this, the cited studies mainly confirmed that abnormal HRV holds a negative predictive value on both short and long-term prognosis, with HRV parameters holding high specificity, but poor sensitivity[11].

A limitation of the reported studies is that the majority of them did not provide data of how patients with ST-elevation myocardial infarction (STEMI) behave separately from non-ST-elevation myocardial infarction (NSTEMI) patients. Furthermore, the majority of studies on HRV in patients with a recent AMI have been conducted in an era prior to that of immediate reperfusion by percutaneous coronary intervention (PCI). Among 21 papers analyzed in the recent review by Brateanu *et al*[10], patients had been treated by primary PCI only in 5 studies and in widely variable percentages (ranging from 18% up to 95% of cases)[6,12]; so, little information is currently available on prevalence and prognostic significance of depressed HRV in present day AMI patients.

Aims of this study were to assess the prevalence of severely decreased HRV in patients during the subacute phase of a STEMI treated by primary PCI, and to evaluate if HRV maintains a prognostic value in the current era of immediate percutaneous reperfusion, comparing results with those of NSTEMI cases.

MATERIALS AND METHODS

Design of the study

We retrospectively reviewed the clinical files of 326 consecutive patients which were part of a larger study on the effects of cardiac rehabilitation (CR) after AMI. All had suffered a complicated AMI (208 STEMI, 118 NSTEMI) and had been admitted to our CR unit for a period of residential, exercise-based rehabilitation, a median of 13.5 d (95%CI of the mean 15.2-17.3) after the index event. All patients had undergone coronary angiography on initial admission to the Intensive Coronary Care Unit, within 24 h from beginning of AMI symptoms: 194 (94%) STEMI underwent successful PCI of the culprit coronary artery within 6 h of symptoms[13], while only a small percentage of them (14 cases, 6%) could not be revascularized due to unfavourable coronary anatomy and had to be placed on medical therapy; NSTEMI patients underwent coronary angiography within 24 h[14], with successful PCI in 86 cases (73%) and medical therapy in the remaining 32 cases. Of the primary-PCI STEMI patients, 67 (32%) had also been immediately treated on non-culprit coronary lesions; 42 (36%) NSTEMI patients were similarly also immediately treated on non-culprit coronary lesions. Eight (4%) STEMI and 4 (3%) NSTEMI patients received further elective percutaneous revascularization during the initial stay in the Cardiology Department. Overall, at the time of transferral to the CR unit, 121 (58%) STEMI patients and 54 (46%) NSTEMI patients had a complete revascularization, while 87 STEMI and 64 NSTEMI patients were still incompletely revascularized.

Patients were selected for referral to our CR program if they suffered a complicated AMI (cardiogenic shock or pulmonary edema, episode of cardiac arrest, complex ventricular arrhythmias), or if they had incomplete revascularization (because of unfavorable coronary anatomy or technical failure)[15]. Low risk patients were referred as out-patients to a CR program in a different centre and excluded from this study.

Echo- or cardiac MRI- documented intracavitary thrombosis, extreme thinning or intra-myocardial bleeding and/or suspected rupture of the ventricular wall were other exclusion criteria from referral to the CR program.

The following clinical variables were recorded for each patient: Age, gender, body mass index, cardiovascular risk factors, site of infarction, culprit coronary artery vessel, number of diseased coronary artery vessels (defined as presence of diameter stenosis > 50%), history of previous PCI or coronary or valvular surgery, presence of ancillary diseases (renal failure, thyroid dysfunction, known diabetes or abnormal glucose metabolism, pulmonary diseases, history or presence of neoplastic diseases, carotid and peripheral vascular disease) and previous and concurrent drug therapy. During their hospitalisation in CR, all patients without previous diagnosis of diabetes underwent an oral glucose tolerance test to identify subclinical abnormal glucose metabolism. Left ventricular ejection fraction (LVEF) was measured before discharge by 2-D echocardiography, following the Simpson method.

Holter monitoring

On the day of admittance to CR, all patients underwent 24-h ECG Holter recording, using 3-channel digital recorders (Lifecard CF, Del Mar Reynolds, Irvine, CA, United States), monitoring chest leads CM5, CM3 and modified aVF. Recordings were analyzed using a commercial Holter device system (Del Mar-Reynolds Impresario Holter Analysis System, vers. 2.8.0024; Time-domain HRV Analyzer, vers. 1.0.8.4, CENTUM and Del Mar Reynolds Medical Inc., Irvine, CA, United States; sampling rate of 128 Hz).

After cleansing of arrhythmias and artefacts, the usual time domain HRV variables were assessed including: Standard deviation of all normal-to-normal (NN) intervals (SDNN), standard deviation of all 5-min mean NN intervals (SDANN), root mean square of successive differences (RMSSD), and mean of the standard deviations of all RR intervals of all 5-min segments in the 24 h (SDNN-i). For the purposes of

this study, the main variable that was considered in the correlations with other clinical parameters was the SDNN, as it is usually considered a measure of total variance in heart rate; it is also the variable most widely used in previous studies[10] and more strongly associated with mortality compared to other variables[1]. SDNN parameters were analyzed for the entire 24 h period; analysis of day and night hours was also done separately. "Day" was defined as the time period between 06:00 and 22:59 and "night" as the period between 23:00 and 05:59.

Patients with atrial fibrillation, or rhythm disturbances that could interfere with accurate HRV analysis (*e.g.*, frequent ectopic beats, rhythm induced by pacemaker) were excluded from the study, as were patients with inadequate/inaccurate recordings.

End points and follow-up

The primary outcome measure was the occurrence of cardiac death; the secondary end-point was occurrence of major clinical events (MCE), defined as death (all-cause mortality, cardiac mortality) or readmission for a new AMI, new revascularization, episodes of heart failure or stroke. At the time of follow-up, the clinical status of the patients was assessed by telephonic interviews, performed either by a doctor or a trained team nurse. In case of clinical events, detailed information was obtained from the patient or his/her relatives. Outcomes were analyzed by intention to treat.

Statistical analysis

Continuous variables were expressed as a mean ± standard deviation (SD) and compared using an unpaired *t* test; otherwise, variables were expressed with median and interquartile range (IQR) and compared using a Wilcoxon-Mann-Withney test. Categorical variables were expressed as frequencies and percentages and were compared between groups by a χ^2 test. The relationships between continuous variables were evaluated by Pearson's correlation coefficient. A Cox regression multivariate analysis was also performed to determine the influence of different factors on HRV parameters, including in the multivariable model only variables with a *P* value $\leqslant$ 0.1 at univariate analysis. HRV variables were initially analyzed as continuous variables; subsequently, HRV variables that showed a significant association with other factors at multivariate analysis were dichotomized and analyzed according to the lowest quartile value. Kaplan-Meier estimates of the distribution of times from baseline to death were computed, and Mantel-Cox Log-Rank analysis was performed to compare the survival curves between the groups. All reported probability values are two-tailed and the significance level was set at 0.05. Statistical analyses were performed using SPSS 18 software package (SPSS Inc, Chicago, IL, United States).

Statement

During CR hospitalization, all participants had been fully informed on the procedures they were undergoing; a written consent was obtained from all patients before performance of the medical procedures. The routine diagnostic examinations and follow-up protocol for CR were applied; no special tests or treatments were performed. The research was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. This study is part of a larger follow-up study on patients admitted to CR; approval of the Provincial Ethics Committee (Provincial Health Directorate, Belluno, Italy) was obtained for the main research.

RESULTS

General findings and HRV parameters

Main patients' characteristics are presented in Table 1, together with the medical therapy prescribed at the time of discharge from hospital. Patients with NSTEMI were older than those with STEMI, and presented more often history of hypertension, previous MI and coronary revascularization procedures, and clinical signs of metabolic syndrome. Patients with NSTEMI had greater number of critical coronary stenoses, revascularization was more often incomplete, and such patients presented more often with symptoms of heart failure on initial admission to the coronary care unit.

In the same Table 1, time-domain HRV parameters are also reported. In spite of the above described clinical differences, all main HRV parameters did not show significant differences between STEMI and NSTEMI patients, except for mean heart rate that was lower in NSTEMI cases.

In a total of 52 patients (16% of the whole group; 16% of STEMI and 15% of NSTEMI: χ^2 = 0.067, *P* = 0.796), SDNN was < 70 ms, and in 13 (4% of the whole group; STEMI 5.3%, NSTEMI 1.7%: χ^2 = 2.539, *P* = 0.111) it was < 50 ms. When subdivided into 4 quartiles according to the value of SDNN, the 81 patients in the lowest quartile presented a mean SDNN of 63.7 ± 11.8 ms (*vs* a mean of 119.4 ± 35.0 ms of the other quartiles; *P* < 0.001). Patients with STEMI or NSTEMI were equally distributed between quartiles of SDNN (χ^2 = 1.536, *P* = 0.674).

On average, SDNN was higher during night hours than during day-time (*P* < 0.001), although in 109 patients the day-night variation was insignificant or negative; patients with STEMI or NSTEMI behaved in the same way as regards day *vs* night SDNN.

Female patients presented on average lower values of SDNN than male patients (97.1 ± 42.2 ms *vs* 107.9 ± 38.1 ms; *P* = 0.046), and in 24 out of 65 cases they presented SDNN values in the lower quartile (females 37% *vs* males 17%; χ^2 = 6.723, *P* = 0.010).

SDNN values in the lower quartile were present more frequently in patients older than 65 years (χ^2 = 4.478, *P* = 0.034), as well as in patients with known diabetes (χ^2 = 10.859, *P* = 0.001) but not in patients with abnormal glucose metabolism detected during the rehabilitation period (χ^2 = 0.762, *P* = 0.383). Patients

Table 1 Main data of patients, reported for the whole group and for patients with ST-elevation myocardial infarction and non-ST-elevation myocardial infarction

	All patients (*n* = 326)	STEMI (*n* = 208)	NSTEMI (*n* = 118)	*P*[1]	*P*[2]
Age, yr	63.5 ± 12.1	61.3 ± 12.5	67.4 ± 10.4	< 0.001	
Male, *n* (%)	261 (80)	171 (82)	90 (76)		0.197
History and cardiovascular risk factors					
Known diabetes, *n* (%)	82 (25)	45 (22)	37 (31)		0.055
Abnormal glucose metabolism, *n* (%)	106 (32)	68 (33)	38 (32)		0.733
Hypertension, *n* (%)	238 (73)	134 (64)	104 (88)		< 0.001
Smoking habit, *n* (%)	106 (32)	81 (39)	25 (21)		0.001
Family history, *n* (%)	179 (55)	111 (53)	68 (58)		0.367
Previous CABG, *n* (%)	26 (8)	7 (3)	19 (16)		< 0.001
Previous PCI, *n* (%)	43 (13)	13 (6)	30 (25)		< 0.001
Previous AMI, *n* (%)	60 (18)	21 (10)	39 (33)		< 0.001
Previous stroke, *n* (%)	11 (3)	5 (2)	6 (5)		0.193
Total cholesterol (under treatment), mg/dL	124.3 ± 26.0	123.4 ± 26.3	125.8 ± 25.5	0.424	
Metabolic syndrome, *n* (%)	204 (62)	124 (60)	80 (68)		0.011
BMI	27.2 ± 4.3	26.9 ± 3.7	27.9 ± 5.2	0.090	
AMI characteristics					
Anterior, *n* (%)	171 (52)	138 (66)	33 (28)		< 0.001
Inferior, *n* (%)	86 (26)	66 (32)	20 (17)		0.003
Other, *n* (%)	69 (21)	4 (2)	65 (55)		< 0.001
Coronary vessels with critical lesions, *n*	2.05 ± 0.85	1.94 ± 0.84	2.25 ± 0.85	0.002	
1-vessel disease, *n* (%)	105 (32)	75 (36)	30 (26)		0.014
2-vessels disease, *n* (%)	97 (30)	68 (33)	29 (25)		
3-vessels disease, *n* (%)	124 (38)	66 (31)	58 (49)		
Coronary arteries treated by PCI, *n*	1.29 ± 0.82	1.34 ± 0.72	1.20 ± 0.97	0.141	
Incomplete revascularization, *n* (%)	151 (46)	87 (42)	64 (54)		0.031
Left ventricle ejection fraction, %	47.2 ± 10.3	47.8 ± 9.2	46.4 ± 12.0	0.222	
Patients with LVEF < 40%, *n* (%)	85 (26)	43 (21)	41 (35)		0.006
Patient with heart failure at initial admission, *n* (%)	37 (11)	15 (7)	22 (19)		0.002
Time before Holter, d	16.2 ± 9.6	15.6 ± 9.5	17.4 ± 9.8	0.117	
Therapy at time of discharge from hospital (number of cases, %)					
Aspirin	314 (96)	202 (97)	112 (95)		0.469
Clopidogrel	302 (93)	192 (92)	110 (93)		0.458
Warfarin	38 (12)	22 (11)	16 (14)		0.399
β-blocker	290 (89)	189 (91)	101 (86)		0.198
Ca-antagonist	38 (12)	18 (9)	20 (17)		0.022
ACE-inhibitor	264 (81)	180 (86)	84 (71)		0.001
AT-II-antagonist	43 (13)	16 (8)	27 (23)		< 0.001
Statin	314 (96)	201 (97)	113 (96)		0.893
Diuretic(s)	140 (43)	75 (36)	65 (55)		0.001
HRV parameters					
Mean heart rate, bpm	68.1 ± 10.0	69.1 ± 10.1	66.2 ± 9.7	0.016	
pNN50	10.1 ± 12.0	9.5 ± 10.5	11.1 ± 14.3	0.245	
Triangular Index	18.6 ± 29.9	19.6 ± 44.4	17.0 ± 26.6	0.567	
SDNN, ms	105.7 ± 39.1	105.7 ± 39.2	105.7 ± 39.2	0.990	
SDNN day, ms	95.8 ± 35.4	95.2 ± 33.9	96.8 ± 37.9	0.688	
SDNN night, ms	103.5 ± 41.0	102.8 ± 41.6	104.8 ± 40.1	0.671	
RMSSD, ms	45.0 ± 37.7	42.2 ± 30.6	49.9 ± 47.4	0.079	
SDANN, ms	92.1 ± 33.1	93.5 ± 35.1	89.7 ± 29.4	0.331	
SDNN-i, ms	41.4 ± 22.5	40.7 ± 18.9	42.6 ± 27.7	0.444	

[1]Level of significance from unpaired *t* tests for STEMI and NSTEMI patients; [2]Level of significance from χ^2 tests for STEMI and NSTEMI patients. ms: Milliseconds; STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction; CABG: Coronary artery by-pass graft; PCI: Percutaneous coronary intervention; AMI: Acute myocardial infarction; BMI: Body mass index; LVEF: Left ventricle ejection fraction; ACE: Angiotensin converting enzyme; AT-II: Angiotensin II receptor type 2; HRV: Heart rate variability; SDNN: Standard deviation of all normal-to-normal intervals; RMSSD: Root mean square of successive differences between normal-to-normal intervals.

with known diabetes presented also absence of the day/night variation of SDNN (SDNN day: 85.2 ± 32.2 ms in diabetic patients *vs* 99.5 ± 35.7 ms in non-diabetics, $P = 0.002$; SDNN night: 85.3 ± 31.0 ms in diabetic patients *vs* 109.8 ± 42.2 ms in non-diabetic patients, $P < 0.001$; SDNN day *vs* night: $P = 0.975$ in diabetic *vs* $P < 0.001$ in non-diabetic patients).

Patients with history of previous MI, or previous CABG or previous PCI were equally distributed among quartiles of SDNN (respectively: $\chi^2 = 0.017$, $P = 0.999$; $\chi^2 = 1.306$, $P = 0.728$; $\chi^2 = 1.729$, $P = 0.631$).

No correlation was found between number of diseased coronary arteries and quartiles of SDNN (whole group: ρ -0.044, $P = 0.428$; STEMI: ρ 0.001, $P = 0.985$;

NSTEMI: ρ -0.120, *P* = 0.199). Patients with complete or incomplete coronary revascularization did not differ as regards distribution among quartile of SDNN (χ^2 = 0.059, *P* = 0.807).

Similarly, no correlation was found between quartile of SDNN and successful *vs* unsuccessful primary PCI (whole group: χ^2 = 0.158, *P* = 0.691; STEMI: χ^2 = 0.031, *P* = 0.861; NSTEMI: χ^2 = 0.684, *P* = 0.408). Overall, patients with unsuccessful primary PCI presented markedly reduced variation of SDNN values between day and night (SDNN day 94.7 ± 39.3 ms; SDNN night 102.9 ± 37.9 ms; *P* = 0.092); by the contrary, such variations persisted in patients with successful primary PCI (SDNN day 96.2 ± 34.6 ms; SDNN night 103.9 ± 41.5 ms; *P* < 0.001).

In the whole group of patients, a linear correlation was found between LVEF and the values of some HRV parameters (SDNN: ρ 0.168, *P* = 0.002; SDANN: ρ 0.225, *P* < 0.001), but not with other HRV parameters such as RMSSD, SDNN Index, Triangular Index and pNN50. Patients with lower LVEF (< 40%) presented more often values of SDNN in the lowest quartile (χ^2 = 12.668; *P* < 0.001). Mean heart rate during the 24 h of Holter recording was lower in patients with higher LVEF (ρ -0.310, *P* < 0.001).

The 37 patients that presented symptoms of heart failure during the acute phase of AMI showed SDNN values in the lower quartile more often than the remaining patients (χ^2 = 7.884; *P* = 0.005), with SDNN < 70 ms in 32% of cases (*vs* 14% of the patients without initial symptoms of heart failure; χ^2 = 8.457; *P* = 0.004).

At multivariate Cox regression analysis, a significant correlation with the lowest quartile of SDNN was maintained only by female sex, history of diabetes mellitus and LVEF < 40% (respectively: β = -0.143, *P* = 0.008; β = 0.146, *P* = 0.008; β = -0.179, *P* =0.001).

Clinical features and outcome

Ten (3.1%) patients were lost to follow up, which occurred a median of 25.0 mo after the index event (95%CI of the mean: 23.3-28.0).

Of the 316 patients which could be interviewed, MCE occurred in 56 (17.2%) of which 20 deaths (6.3%; 14 cardiac deaths), 9 cases of new non fatal AMI (3.0%), 5 patients with stroke (1.6%) and 17 cases of successful elective revascularization (5.4%: 4 CABG, 13 elective PCI); 21 (6.6%) patients had one or more hospital readmissions for heart failure.

No significant difference in overall incidence of MCE at follow-up was evident between cases with STEMI *vs* NSTEMI (χ^2 = 2.166, *P* = 0.141), although all-cause mortality was higher among NSTEMI patients (14% *vs* 2%; χ^2 = 17.863, *P* < 0.001) as well as cardiac mortality (10% *vs* 1.5%; χ^2 = 11.471, *P* = 0.001). Only after one and a half year of follow-up, the Kaplan-Meier MCE-free survival curves begin to diverge, with NSTEMI patients presenting worse outcomes (Mantel-Cox Log-Rank: χ^2 = 5.525, *P* = 0.019); Figure 1A.

Patients with a 3-vessel disease and those who received an incomplete revascularization had a greater incidence of MCE during the period of follow-up (respectively: χ^2 = 14.369, *P* = 0.006; and χ^2 = 6.987, *P* = 0.008). A significant correlation was evident between all-cause deaths or cardiovascular deaths and number of diseased vessels (respectively: χ^2 = 19.218, *P* = 0.001; and χ^2 = 13.077, *P* = 0.011). Incomplete revascularization showed a correlation with all-cause deaths (χ^2 = 4.732, *P* = 0.030) but not with cardiac deaths (χ^2 = 1.859, *P* = 0.173) at follow-up.

The 234 patients that maintained a better preserved myocardial function, as suggested by LVEF > 40%, had lower number of MCE (32) and cardiovascular deaths (3) in the follow-up, than patients with more compromised LVEF, that suffered 24 MCEs and 11 cardiovascular deaths among 82 patients (for MCE: χ^2 = 10.126, *P* = 0.001, and OR = 0.383, 95%CI: 0.209-0.701; for cardiovascular deaths: χ^2 = 21.110, *P* < 0.001, and OR = 0.084, 95%CI: 0.023-0.309).

At multivariate Cox regression analysis, the variables that showed predictive value for MCE were presence of a three-vessel disease (β = 0.062, *P* = 0.013), elective PCI (β = 0.250, *P* = 0.021), known diabetes mellitus (β = 0.124, *P* = 0.013) and LVEF < 40% (β = -0.114, *P* = 0.017), while no significant correlation was found with age, sex, number of vessels treated by PCI (β = -0.032, *P* = 0.229), history of incomplete revascularization, STEMI *vs* NSTEMI (β = -0.002, *P* = 0.970), site of infarction or presence of signs of heart failure during initial admission.

In Figure 1B, the Kaplan-Meier events-free survival curves are presented for patients stratified according to LVEF ⩽ 40% *vs* LVEF > 40%; the Mantel-Cox Log-Rank demonstrated statistically significant differences between the curves (χ^2 = 10.896, *P* = 0.001).

HRV and outcome

Even in the subgroup in the lower quartile of SDNN, no difference was found in incidence of MCE (14/76 cases) in comparison with other subgroups (42/240 cases), (χ^2 = 0.034, *P* = 0.855); this finding was similar for STEMI and NSTEMI patients (respectively: 10 MCE among 52 STEMI patients with lower quartile of SDNN *vs* 21/150 of the other quartiles, χ^2 = 0.813, *P* = 0.367; and 4 MCE among 24 NSTEMI patients with lower quartile of SDNN *vs* 21/90 of the other quartiles, χ^2 = 0.492, *P* = 0.483).

Patients with negative day-night variations of SDNN presented long-term events similar to patients with positive SDNN day-night variations (χ^2 = 2.107, *P* = 0.147).

The Kaplan-Meier MCE-free survival curves were similar between the group of patients with SDNN in the lowest quartile *vs* the patients of the other SDNN quartiles (Log-Rank χ^2 = 0.376, *P* = 0.540; Figure 2A), with no difference for STEMI (Log-Rank χ^2 = 1.801, *P* =

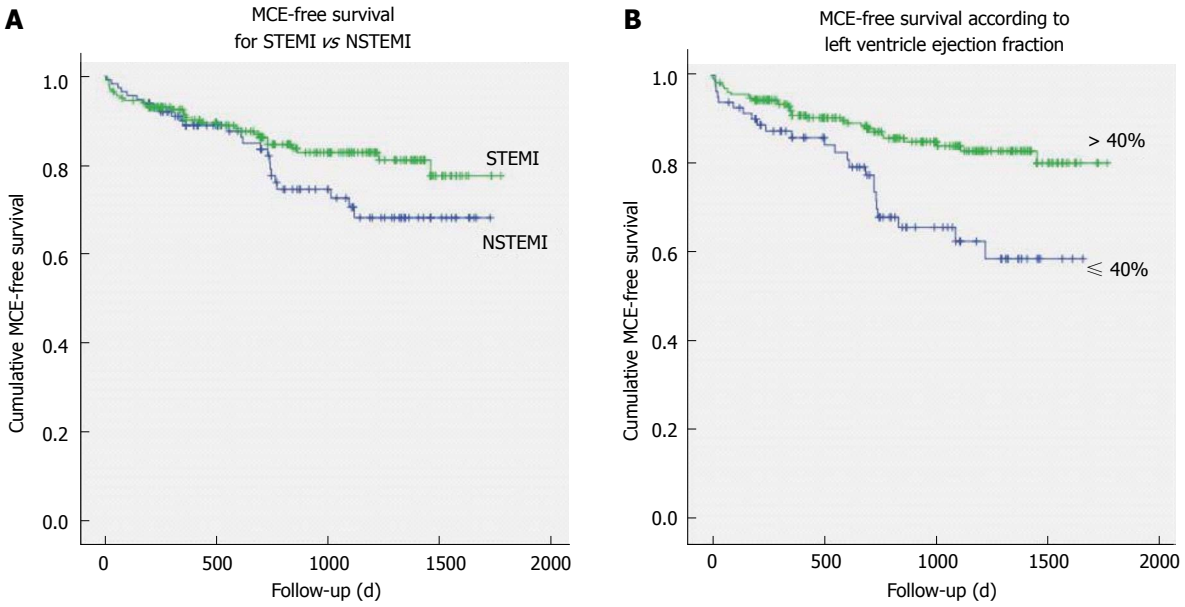

Figure 1 Kaplan-Meier major clinical events-free survival curves for: Patients with recent ST-elevation myocardial infarction *vs* patients with recent non-ST-elevation myocardial infarction (A), patients with preserved left ventricle ejection fraction (> 40%) *vs* patients with depressed left ventricle ejection fraction (⩽ 40%) (B). STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction; MCE: Major clinical events.

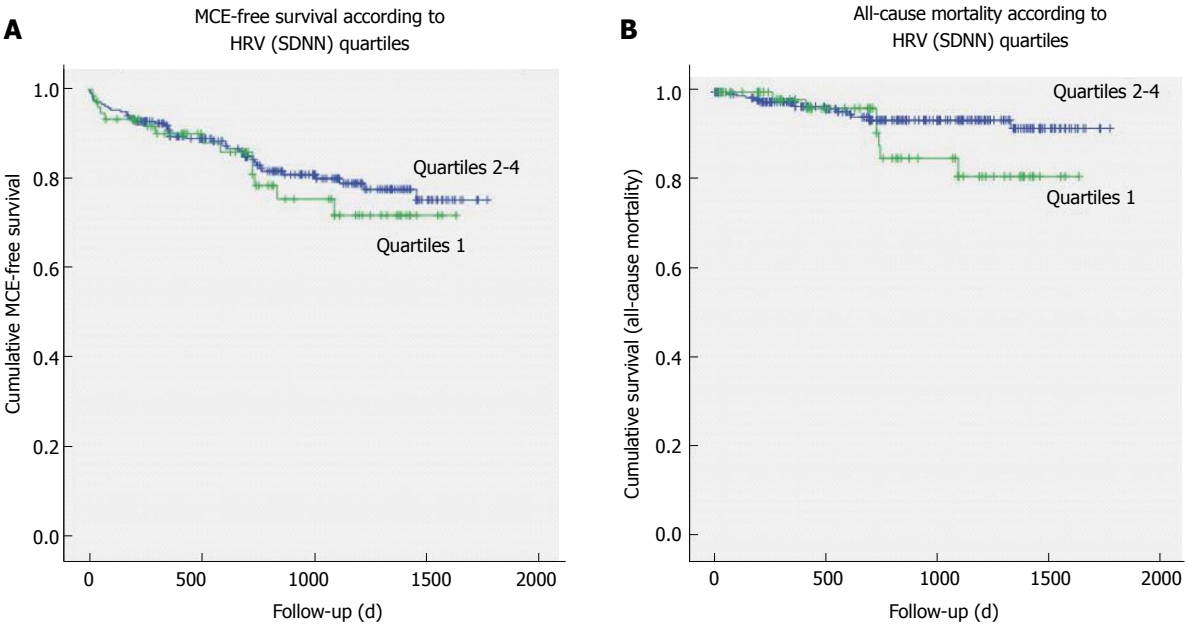

Figure 2 Kaplan-Meier survival curves for patients with lowest quartile of standard deviation of all normal-to-normal intervals *vs* patients in the other standard deviation of all normal-to-normal intervals quartiles: Major clinical events-free survival curves (A), all-cause mortality curves (B). HRV: Heart rate variability; SDNN: Standard deviation of all normal-to-normal intervals; MCE: Major clinical events.

0.180) or NSTEMI patients (Log-Rank χ^2 = 0.373, P = 0.541). In particular, no correlation was found between quartile of SDNN and recurrence of MI during the follow-up period (χ^2 = 0.489, P = 0.484).

As regards to death for all causes, 7 out of 20 deaths occurred among patients with lowest quartile of SDNN (χ^2 = 1.401, P = 0.236); analyzing the whole group of AMI patients, the Kaplan-Meier survival curves for all-cause mortality (Figure 2B) and for cardiac deaths did not evidence significant differences between patients with SDNN in the lowest quartile and other quartiles of SDNN (Mantel-Cox log rank, respectively: χ^2 = 2.207, P = 0.137; and χ^2 = 0.399, P = 0.527). After separating STEMI from NSTEMI patients, different survival curves have been observed only for all-cause mortality (Figure 3), but not for cardiac mortality: STEMI patients with SDNN in the lowest quartile presented 3 out of 4 all-cause deaths (Mantel-Cox log rank χ^2 = 6.591, P = 0.010) and 2 out of 3 cardiac deaths (Log-Rank χ^2 = 3.685, P = 0.055), while among NSTEMI patients no

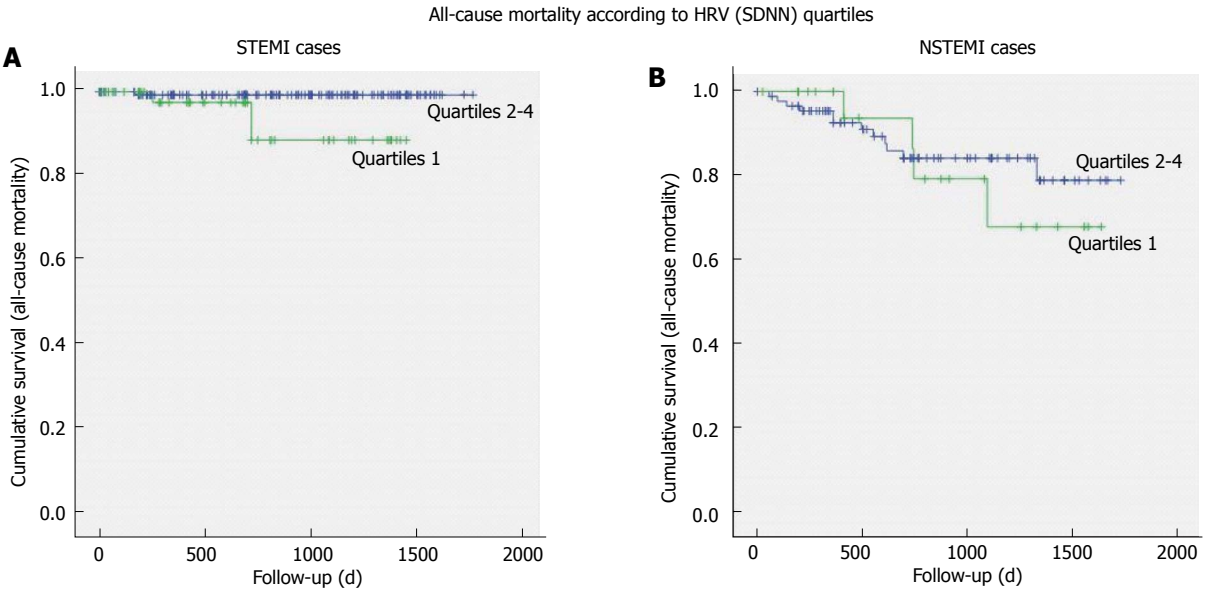

Figure 3 Kaplan-Meier all-cause mortality curves for ST-elevation myocardial infarction patients (A) and non-ST-elevation myocardial infarction patients (B) divided between cases with lowest quartile of standard deviation of all normal-to-normal intervals *vs* cases in the other standard deviation of all normal-to-normal intervals quartiles. HRV: Heart rate variability; SDNN: Standard deviation of all normal-to-normal intervals; STEMI: ST-elevation myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction.

difference in the survival curves was observed between patients with SDNN in the lowest quartile *vs* the other quartiles (all-cause mortality: Log-Rank χ^2 = 0.195, *P* = 0.659; cardiac deaths: Log rank χ^2 = 0.040, *P* = 0.842).

Analysis of the long term outcomes of patients with low values of RMSSD gave similar results as those described for low SDNN values: Kaplan-Meier events free survival did not differ between patients with RSDNN in lowest quartile *vs* the other quartiles, both for incidence of MCE (χ^2 = 0.849, *P* = 0.357) and all-cause or cardiac mortality (respectively: χ^2 = 0.060, *P* = 0.806; and χ^2 = 0.245, *P* = 0.621).

Patients lost to follow-up

Patients' main clinical parameters (age, sex, time from STEMI to CR, site of infarction, number of diseased vessels, fasting glucose, HbA1c, haemoglobin level at admission, LVEF) and HRV values (SDNN, RMSSD, SDNNi, SDANN) have been compared between the 10 cases lost to follow-up and the 314 patients that completed the study. Patients lost to follow-up presented more elevated average values of HbA1c (7.2% ± 2.0% *vs* 6.4% ± 1.1%; *P* = 0.022) but not of fasting glucose (109.5 ± 37.9 mg/dL *vs* 95.2 ± 22.5 mg/dL; *P* = 0.085) at admission. All the other clinical and HRV parameters were not significantly different in comparison to followed-up patients.

DISCUSSION

In studied patients with STEMI, treatment by primary PCI did not demonstrate a clear effect in reduction of the prevalence of marked depression of HRV in comparison to what was reported in studies performed in the pre-primary-PCI era: The prevalence of 16% of STEMI patients with SDNN < 70 ms at 2 wk from the acute event is the same as that recorded in the GISSI-2 and the ATRAMI studies, in which patients had been treated conservatively or by thrombolysis[4,5]. It is however much lower than that reported by Wiliński *et al*[7] in patients treated by primary PCI (21% in patients < 65 years old and 34% in those ⩾ 65 years old), as well as in other smaller dimension studies in which patients had also been treated by primary PCI[9,16]. When considering the subgroup of patients with even more depressed HRV (using the cut-off of SDNN < 50 ms, as in the pivotal study by Kleiger *et al*[1]), the prevalence of this abnormal parameter was lower in our STEMI patients (5% in our study *vs* 15% in Kleiger's study), being somehow similar to that observed also by Erdogan *et al*[6] (7%) in patients treated by immediate revascularization. A number of other studies investigating HRV in the post-acute phase of MI have been conducted in the last 15 years. In such studies the percentage of patients treated by primary PCI varied between 18% and 70%, so that their results about the effects of early revascularization on HRV parameters are not easily comparable between them and with our ones[11,12,17-19].

Even if the percentage of patients with markedly depressed SDNN was not clearly reduced by the immediate reperfusion strategy, the overall derangement of HRV parameters in our cases was limited, in spite of our study population being constituted by patients that suffered a complicated AMI: On average, mean HRV values were only slightly lower than those reported in literature for healthy persons of the same age group[20]. In fact, in previous studies, it has been observed that

autonomic function is better preserved in patients treated by primary PCI, in comparison to patients who receive fibrinolysis or are treated conservatively[21]. It must also be added that all our patients were under treatment with ACE-inhibitors and beta-blockers, drugs that may impact on HRV in post-infarction patients[22-25].

Patients with NSTEMI did not show significant differences in the analyzed HRV parameters in comparison to STEMI patients, even though they presented various factors that may have lead to more depressed HRV (older age, greater prevalence of previous AMI, multiple risk factors, heart failure complicating the initial phase of AMI, often a 3-vessel disease and incomplete revascularization). To the best of our knowledge, before the present study no information was available in the literature regarding HRV in NSTEMI patients, when considered separately.

In 13 follow-up studies conducted between 1987 and 1999 where HRV was analyzed in AMI patients not treated with immediate PCI reperfusion, the reported incidence of long-term mortality ranged widely between 3.4% and 45% of study cases; from the data provided in the papers mortality can be estimated on average to be around 10%[1,4,5,8,26-34]. Almost all these studies included both STEMI and NSTEMI patients. More recently, only STEMI patients have been analysed, following treatment by primary PCI: Their long-term mortality rate was reported to be substantially lower than in the pre-primary-PCI era, being possible to calculate it on average around 5% of cases[6,9,16].

In spite of our patients having experienced various kinds of major complications during the initial phase of MI, in STEMI cases both the overall mortality and cardiac mortality at long-term follow-up were rather low, and significantly lower than the long-term mortality of NSTEMI patients. The timely reperfusion strategy, with consequent reduction of infarct size and salvage of more heart muscle, as well as the multiple pharmacological therapy used, may have contributed to the better long-term survival of our STEMI patients[35]; the period of intensive and comprehensive exercise-based cardiac rehabilitation followed by our patients may also have contributed to their better prognosis[36].

Low values of SDNN (lowest quartile) recorded at two weeks from the index event did not possess a predictive value for cardiac mortality in our STEMI patients, or in NSTEMI patients, or in the group of MI patients considered as a whole. In the pivotal study by Kleiger *et al*[1], the finding of a markedly depressed SDNN was a predictor of long-term mortality more than 5 times higher than in patients with preserved SDNN; identical results have been confirmed in the ATRAMI study[4], and substantially similar outcomes have also been reported in other studies performed in the pre-primary-PCI era[5,29,30], as well as in studies that included low percentage of PCI-treated patients[17].

Among primary-PCI treated patients, Erdogan *et al*[6] found that SDNN was lower in non-survivors than in survivors after a mean follow-up of 4.3 ± 3 years, but this HRV parameter predicted only 1 in 24 cardiac deaths, indicating that the predictive value of a depressed SDNN is low. Our results indicate that the limited derangement of HRV parameters and the low long-term mortality recorded among our patients do not allow to identify if a markedly depressed HRV (as estimated by low SDNN) could still be considered an indicator of poor survival in patients treated by primary PCI.

In the attempt to identify possible differences in secondary outcomes linked to different levels of HRV derangement among AMI patients treated by primary PCI, we studied the long-term incidence of Major Clinical Events, which is a composite parameter that has recently been used in other studies[9,16]. Other than mortality (cardiovascular and all-cause deaths), it includes also non-fatal events, such as new AMI, new coronary revascularization, episodes of heart failure, episodes of stroke.

Amongst our cases, patients with more depressed SDNN did not show any significant difference of MCE-free outcomes in comparison to patients with preserved parameters, after a median follow-up period of 25 mo (a period that is in range with most of the previous studies)[10]. This is quite a different finding in comparison to other recent small scale studies, that confirmed that abnormal HRV retains some (although low) negative predictive value on long-term prognosis also in primary-PCI treated AMI patients[9,16].

Almost all our patients had been submitted to revascularization of the coronary culprit lesion during the initial phases of their AMI, and a substantial percentage of them had also received revascularization of other critically stenosed coronary arteries, before transferral to CR and recording of 24-h Holter. These facts, together with the pharmacological treatment with beta-blockers and ACE-inhibitors or AT-Ⅱ-antagonists in use at the time of Holter recording, could have reduced both the autonomic derangement during the subacute phase of the MI and the risk of adverse events in the long-term follow-up.

Limitations of the study

Criteria of exclusion from this study included presence of atrial fibrillation or flutter, a rhythm induced by the pacemaker, or inadequate Holter recordings. Although such patients may have had significant autonomic dysfunction, HRV could not be measured in them. Consequently it is not known if a depressed HRV could have had any long-term impact on their prognosis.

The degrees of autonomic derangement presented by our patients, that may have been conditioned by the kind of complications suffered during the initial phase of their disease, may possibly not be generalized to the other complicated or uncomplicated STEMI patients.

HRV was performed only in time domain; no analysis was available in the frequency domain. However, it is

already known that time-domain HRV indices measured over a 24-h period are well correlated with frequency domain indices in coronary artery disease patients[34]. Among time-domain parameters, SDNN was identified as having the same high predictive value as the frequency-domain LF amplitude in post-AMI patients[16].

Conclusions

In conclusion, in our group of patients with a recent complicated MI, abnormal autonomic parameters (evidenced by low HRV) have been found with a prevalence that was similar for STEMI and NSTEMI cases, and substantially unchanged in comparison to what reported in the pre-primary-PCI era.

Long-term outcomes in PCI-treated STEMI patients were more favorable than in old cohorts of patients. They did not correlate with the level of depression of HRV parameters recorded in the subacute phase of the disease, both in STEMI and in NSTEMI patients. Traditional HRV parameters seem to have lost their prognostic significance in the present era of immediate coronary reperfusion.

COMMENTS

Background

After an acute myocardial infarction (AMI), overactivation of the sympathetic component and relative suppression of the parasympathetic component of the autonomic nervous system occur, leading to a marked imbalance of cardiac autonomic regulation. Such sympatho-vagal imbalance is usually considered to be linked to increased short and long-term mortality. Clinically, cardiac autonomic modulation can be evaluated observing the fluctuations of instantaneous heart rate (intervals between normal RR complexes) during variable periods of time (often 24 h). The most simple and widely used parameter for evaluation of heart rate variability (HRV) is the SDNN (standard deviation of all normal RR intervals), that gives an overall estimate of cardiac autonomic control. In the last 30 years, various studies confirmed that depressed values of SDNN indicate poor prognosis after an AMI. Unfortunately, most of these studies on the prognostic value of depressed HRV in post-AMI patients have been conducted before the primary-PCI era: So, their results may not be easily applied to present day patients, in which early reperfusion (that may lead to salvage of cardiac muscle and preservation of better heart function), multiple pharmacological therapies and cardiac rehabilitation may impact on autonomic balance, quality of life and long-term survival.

Research frontiers

A few small-scale studies have been conducted so far on AMI patients treated by primary PCI, investigating if depressed HRV maintains a correlation with long-term prognosis. Such studies did not reach clear conclusions. With the present work, the authors aimed at contributing and clarifying if parameters of HRV (in particular SDNN) could still be considered reliable prognostic indicators in primary-PCI-treated AMI patients.

Innovations and breakthroughs

While in the past depressed HRV had been identified as a reliable marker of poor prognosis after an AMI, this paper demonstrates that nowadays in AMI patients treated by early revascularization HRV has lost its prognostic significance. In addition, the paper is the first to report HRV parameters separately for patients with ST-elevation and Non-ST-elevation myocardial infarction.

Applications

The evaluation of simple HRV parameters does not seem to hold any more prognostic significance in AMI patients treated by early revascularization. Further studies are needed in these patients to identify reliable long-term prognostic indicators.

Terminology

HRV refers to the evaluation of the oscillations in the intervals between consecutive heart beats. They are determined by cyclic variations of sympathetic and parasympathetic autonomic influences on cardiac pace-maker cells, modulated by central and peripheral mechanisms (respiratory and vasomotor centres, fluctuations in arterial pressure, humoral factors). After an AMI, HRV usually presents various degrees of depression, linked to a marked increase of the sympathetic activity (probably due to abnormal geometry of the beating heart and consequent distortion of autonomic nervous endings). The most simple method of evaluating HRV is by statistical analysis of the time intervals between consecutive normal RR beats ("time domain" method); the standard deviation of these intervals (SDNN) has been used in our study. SDNN reflects all the cyclic components responsible for variability in the period of recording; for this reason, it has been used in various studies for assessment of risk after AMI.

Peer-review

The authros analysed the potential prognosis of HRV in patients treated with primary PCI.

REFERENCES

1 **Kleiger RE**, Miller JP, Bigger JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987; **59**: 256-262 [PMID: 3812275 DOI: 10.1016/0002-9149(87)90795-8]

2 Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J* 1996; **17**: 354-381 [PMID: 8737210]

3 **Buccelletti E**, Gilardi E, Scaini E, Galiuto L, Persiani R, Biondi A, Basile F, Silveri NG. Heart rate variability and myocardial infarction: systematic literature review and metanalysis. *Eur Rev Med Pharmacol Sci* 2009; **13**: 299-307 [PMID: 19694345]

4 **La Rovere MT**, Bigger JT, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 1998; **351**: 478-484 [PMID: 9482439 DOI: 10.1016/S0140-6736(97)11144-8]

5 **Zuanetti G**, Neilson JM, Latini R, Santoro E, Maggioni AP, Ewing DJ. Prognostic significance of heart rate variability in post-myocardial infarction patients in the fibrinolytic era. The GISSI-2 results. Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico. *Circulation* 1996; **94**: 432-436 [PMID: 8759085 DOI: 10.116/01.CIR.94.3.432]

6 **Erdogan A**, Coch M, Bilgin M, Parahuleva M, Tillmanns H, Waldecker B, Soydan N. Prognostic value of heart rate variability after acute myocardial infarction in the era of immediate reperfusion. *Herzschrittmacherther Elektrophysiol* 2008; **19**: 161-168 [PMID: 19214416 DOI: 10.1007/s00399-008-0024-3]

7 **Wiliński J**, Sondej T, Kusiak A, Wiliński B, Kameczura T, Bacior B, Czarnecka D. Heart rate variability in the course of ST--segment elevation myocardial infarction treated with primary percutaneous transluminal coronary angioplasty in elderly and younger patients. *Przegl Lek* 2014; **71**: 61-65 [PMID: 25016777]

8 **Mäkikallio TH**, Høiber S, Køber L, Torp-Pedersen C, Peng CK, Goldberger AL, Huikuri HV. Fractal analysis of heart rate dynamics as a predictor of mortality in patients with depressed left ventricular function after acute myocardial infarction. TRACE Investigators. TRAndolapril Cardiac Evaluation. *Am J Cardiol* 1999; **83**: 836-839 [PMID: 10190395 DOI: 10.1016/S0002-9149(98)01076-5]

9 **Larosa C**, Sgueglia GA, Sestito A, Infusino F, Niccoli G, Lamendola P, Mariani L, Santangeli P, Lombardo A, Crea F, Lanza GA. Predictors of impaired heart rate variability and clinical outcome in patients with acute myocardial infarction treated by primary angioplasty. *J*

Cardiovasc Med (Hagerstown) 2008; **9**: 76-80 [PMID: 18268424 DOI: 10.2459/JCM.0b013e3280c56d56]

10 **Brateanu A**. Heart rate variability after myocardial infarction: what we know and what we still need to find out. *Curr Med Res Opin* 2015; **31**: 1855-1860 [PMID: 26313812 DOI: 10.1185/03007995.2015.1086992]

11 **Huikuri HV**, Raatikainen MJ, Moerch-Joergensen R, Hartikainen J, Virtanen V, Boland J, Anttonen O, Hoest N, Boersma LV, Platou ES, Messier MD, Bloch-Thomsen PE. Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular function after an acute myocardial infarction. *Eur Heart J* 2009; **30**: 689-698 [PMID: 19155249 DOI: 10.1093/eurheartj/ehn537]

12 **Stein PK**, Domitrovich PP, Huikuri HV, Kleiger RE. Traditional and nonlinear heart rate variability are each independently associated with mortality after myocardial infarction. *J Cardiovasc Electrophysiol* 2005; **16**: 13-20 [PMID: 15673380 DOI: 10.1046/j.1540-8167.2005.04358.x]

13 **Steg PG**, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; **33**: 2569-2619 [PMID: 22922416 DOI: 10.1093/eurheartj7ehs215]

14 **Roffi M**, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol Ç, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016; **37**: 267-315 [PMID: 26320110 DOI: 10.1093/eurheartj/ehv320]

15 **Greco C**, Cacciatore G, Gulizia M, Martinelli L, Oliva F, Olivari Z, Seccareccia F, Temporelli PL, Urbinati S. [Selection criteria for referral to cardiac rehabilitation centers]. *Monaldi Arch Chest Dis* 2011; **76**: 1-12 [PMID: 21751732 DOI: 10.4081/monaldi.2011.200]

16 **Coviello I**, Pinnacchio G, Laurito M, Stazi A, Battipaglia I, Barone L, Mollo R, Russo G, Villano A, Sestito A, Lanza GA, Crea F. Prognostic role of heart rate variability in patients with ST-segment elevation acute myocardial infarction treated by primary angioplasty. *Cardiology* 2013; **124**: 63-70 [PMID: 23328532 DOI: 10.1159/000345779]

17 **Tapanainen JM**, Thomsen PE, Køber L, Torp-Pedersen C, Mäkikallio TH, Still AM, Lindgren KS, Huikuri HV. Fractal analysis of heart rate variability and mortality after an acute myocardial infarction. *Am J Cardiol* 2002; **90**: 347-352 [PMID: 12161220 DOI: 10.1016/S0002-9149(02)02488-8]

18 **Mäkikallio TH**, Barthel P, Schneider R, Bauer A, Tapanainen JM, Tulppo MP, Schmidt G, Huikuri HV. Prediction of sudden cardiac death after acute myocardial infarction: role of Holter monitoring in the modern treatment era. *Eur Heart J* 2005; **26**: 762-769 [PMID: 15778204 DOI: 10.1093/eurheartj/ehj188]

19 **Perkiömäki JS**, Jokinen V, Tapanainen J, Airaksinen KE, Huikuri HV. Autonomic markers as predictors of nonfatal acute coronary events after myocardial infarction. *Ann Noninvasive Electrocardiol* 2008; **13**: 120-129 [PMID: 18426437 DOI: 10.1111/j.1542-474X.2008.00211.x]

20 **Umetani K**, Singer DH, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. *J Am Coll Cardiol* 1998; **31**: 593-601 [PMID: 9502641 DOI: 10.1016/S0735-1097(97)00554-8]

21 **Lakusic N**, Smalcelj A, Mahovic D, Puljevic D, Lovric-Bencic M. Heart rate variability differences in post-myocardial infarction patients based on initial treatment during acute phase of disease. *Int J Cardiol* 2008; **126**: 437-438 [PMID: 17477989 DOI: 10.1016/j.ijcard.2007.02.048]

22 **Kontopoulos AG**, Athyros VG, Papageorgiou AA, Skeberis VM, Basayiannis EC, Boudoulas H. Effect of angiotensin-converting enzyme inhibitors on the power spectrum of heart rate variability in post-myocardial infarction patients. *Coron Artery Dis* 1997; **8**: 517-524 [PMID: 9431480]

23 **Lurje L**, Wennerblom B, Tygesen H, Karlsson T, Hjalmarson A. Heart rate variability after acute myocardial infarction in patients treated with atenolol and metoprolol. *Int J Cardiol* 1997; **60**: 157-164 [PMID: 9226286 DOI: 10.1016/S0167-5273(97)00104-6]

24 **Stein PK**, Domitrovich PP, Kleiger RE, Schechtman KB, Rottman JN. Clinical and demographic determinants of heart rate variability in patients post myocardial infarction: insights from the cardiac arrhythmia suppression trial (CAST). *Clin Cardiol* 2000; **23**: 187-194 [PMID: 10761807 DOI: 10.1002/clc.4960230311]

25 **Lampert R**, Ickovics JR, Viscoli CJ, Horwitz RI, Lee FA. Effects of propranolol on recovery of heart rate variability following acute myocardial infarction and relation to outcome in the Beta-Blocker Heart Attack Trial. *Am J Cardiol* 2003; **91**: 137-142 [PMID: 12521623 DOI: 10.1016/S0002-9149(02)03098-9]

26 **Odemuyiwa O**, Malik M, Farrell T, Bashir Y, Poloniecki J, Camm J. Comparison of the predictive characteristics of heart rate variability index and left ventricular ejection fraction for all-cause mortality, arrhythmic events and sudden death after acute myocardial infarction. *Am J Cardiol* 1991; **68**: 434-439 [PMID: 1872267 DOI: 10.1016/0002-9149(91)90774-F]

27 **Odemuyiwa O**, Poloniecki J, Malik M, Farrell T, Xia R, Staunton A, Kulakowski P, Ward D, Camm J. Temporal influences on the prediction of postinfarction mortality by heart rate variability: a comparison with the left ventricular ejection fraction. *Br Heart J* 1994; **71**: 521-527 [PMID: 8043330 DOI: 10.1136/hrt.71.6.521]

28 **Vaishnav S**, Stevenson R, Marchant B, Lagi K, Ranjadayalan K, Timmis AD. Relation between heart rate variability early after acute myocardial infarction and long-term mortality. *Am J Cardiol* 1994; **73**: 653-657 [PMID: 8166060 DOI: 10.1016/0002-9149(94)90928-8]

29 **Bigger JT**, Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. *Circulation* 1993; **88**: 927-934 [PMID: 8353919 DOI: 10.1161/01.CIR.88.3.927]

30 **Copie X**, Hnatkova K, Staunton A, Fei L, Camm AJ, Malik M. Predictive power of increased heart rate versus depressed left ventricular ejection fraction and heart rate variability for risk stratification after myocardial infarction. Results of a two-year follow-up study. *J Am Coll Cardiol* 1996; **27**: 270-276 [PMID: 8557893 DOI: 10.1016/0735-1097(95)00454-8]

31 **Fei L**, Copie X, Malik M, Camm AJ. Short- and long-term assessment of heart rate variability for risk stratification after acute myocardial infarction. *Am J Cardiol* 1996; **77**: 681-684 [PMID: 8651116 DOI: 10.1016/S0002-9149(97)89199-0]

32 **Touboul P**, Andre-Fouët X, Leizorovicz A, Itti R, Lopez M, Sayegh Y, Milon H, Kirkorian G. Risk stratification after myocardial infarction. A reappraisal in the era of thrombolysis. The Groupe d' Etude du Pronostic de l'Infarctus du Myocarde (GREPI). *Eur Heart J* 1997; **18**: 99-107 [PMID: 9049521]

33 **Voss A**, Hnatkova K, Wessel N, Kurths J, Sander A, Schirdewan A, Camm AJ, Malik M. Multiparametric analysis of heart rate variability used for risk stratification among survivors of acute myocardial infarction. *Pacing Clin Electrophysiol* 1998; **21**: 186-192 [PMID: 9474670 DOI: 10.11/j.1540-8159.1998.tb01086.x]

34 **Bigger JT**, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Correlations among time and frequency domain measures of heart period variability two weeks after acute myocardial infarction. *Am J Cardiol* 1992; **69**: 891-898 [PMID: 1550018]

35 **Ndrepepa G**. Improving myocardial injury, infarct size, and myocardial salvage in the era of primary PCI for STEMI. *Coron*

Artery Dis 2015; **26**: 341-355 [PMID: 25715338 DOI: 10.1097/MCA.0000000000000220]

36 **Dunlay SM**, Pack QR, Thomas RJ, Killian JM, Roger VL. Participation in cardiac rehabilitation, readmissions, and death after acute myocardial infarction. *Am J Med* 2014; **127**: 538-546 [PMID: 24556195 DOI: 10.1016/j.amjmed.2014.02.008]

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ORIGINAL ARTICLE

Observational Study

One-year outcome of percutaneous mitral valve repair in patients with severe symptomatic mitral valve regurgitation

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Author contributions: Gotzmann M was the guarantor and designed the study; Gotzmann M, Sprenger I, Ewers A and Bösche L participated in the acquisition, analysis, and interpretation of the data; Gotzmann M drafted the initial manuscript; Mügge A and Bösche L critically revised the article for important intellectual content.

Institutional review board statement: The study was reviewed and approved by the Ruhr-University Bochum Institutional Review Board.

Informed consent statement: All patients provided oral and written informed consent with respect to the intervention. However, due to the retrospective nature of the study, there was no written consent of patients prior to study enrolment. The study was approved by the Ruhr-University Bochum Institutional Review Board. All patient data were anonymized.

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Abstract

AIM

To investigate one-year outcomes after percutaneous mitral valve repair with MitraClip® in patients with severe mitral regurgitation (MR).

METHODS

Our study investigated consecutive patients with symptomatic severe MR who underwent MitraClip® implantation at the University Hospital Bergmannsheil from 2012 to 2014. The primary study end-point was all-cause mortality. Secondary end-points were degree of MR and functional status after percutaneous mitral valve repair.

RESULTS

The study population consisted of 46 consecutive patients (mean logistic EuroSCORE 32% ± 21%). The degree of MR decreased significantly (severe MR before MitraClip® 100% *vs* after MitraClip® 13%; $P < 0.001$), and the NYHA functional classes improved (NYHA III/IV before MitraClip® 98% *vs* after MitraClip® 35%; $P < 0.001$). The mortality rates 30 d and one year after percutaneous mitral valve repair were 4.3% and 19.5%,

respectively. During the follow-up of 473 ± 274 d, 11 patients died (90% due to cardiovascular death). A pre-procedural plasma B-type natriuretic peptide level > 817 pg/mL was associated with all-cause mortality (hazard ratio, 6.074; 95%CI: 1.257-29.239; P = 0.012).

CONCLUSION

Percutaneous mitral valve repair with MitraClip® has positive effects on hemodynamics and symptoms. Despite the study patients' multiple comorbidities and extremely high operative risk, one-year outcomes after MitraClip® are favorable. Elevated B-type natriuretic peptide levels indicate poorer mid-term survival.

Key words: Severe mitral regurgitation; Percutaneous mitral valve repair; MitraClip®; One-year outcome

Core tip: Percutaneous mitral valve repair with the MitraClip® device has positive effects on hemodynamics and symptoms. Despite the multiple comorbidities and extremely high operative risk of the study patients, mid-term outcomes after MitraClip® implantation are favorable. Elevated B-type natriuretic peptide (> 817 pg/mL) levels are indicative of poorer long-term survival.

Gotzmann M, Sprenger I, Ewers A, Mügge A, Bösche L. One-year outcome of percutaneous mitral valve repair in patients with severe symptomatic mitral valve regurgitation. *World J Cardiol* 2017; 9(1): 39-46 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i1/39.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i1.39

INTRODUCTION

Severe mitral regurgitation (MR) is a common valvular heart disease that has an unfavorable prognosis[1]. When possible, mitral valve repair is considered the optimal surgical treatment[1].

In the last few years, percutaneous mitral valve repair has developed into an alternative technique for patients with severe MR, with more than 20000 procedures worldwide[2,3]. However, the Everest II study is the only randomized trial that has compared percutaneous repair with heart surgery, and it mainly included patients with degenerative MR who did not have an elevated operative risk[2]. By contrast, the current European Society of Cardiology guidelines recommend applying MitraClip® only in symptomatic high-risk patients with severe functional MR (level of evidence IIb)[1].

In recent years, some registry studies[4-6] and several smaller studies[7-11] concerning MitraClip® have been published. However, relatively little is known about the long-term results of percutaneous mitral valve repair. Therefore, the aim of this study was to assess the one-year outcome after percutaneous mitral valve repair with MitraClip®.

MATERIALS AND METHODS

We performed a retrospective study to evaluate the effects of percutaneous mitral valve repair using MitraClip® (Abbott Vascular, Menlo Park, California, United States) on symptoms, hemodynamics and outcomes. The primary study endpoint was all-cause mortality. The secondary endpoints were functional status and degree of MR after percutaneous mitral valve repair.

This study included consecutive patients with symptomatic severe MR who underwent MitraClip® implantation from May 2012 to December 2014 at the University Hospital Bergmannsheil. The risk of mitral valve surgery was estimated using the logistic EuroSCORE I[12] and the logistic EuroSCORE II[13]. All patient cases were discussed by the cardiology team. The decision to perform percutaneous mitral valve repair was based on: (1) a high EuroSCORE I (> 20%); and (2) serious comorbidities with a considerable risk for heart surgery [for example, porcelain aorta, left ventricular ejection fraction (LVEF) < 30%, previous chest radiation and severe chronic obstructive pulmonary disease]. The contraindications were active endocarditis, intracardiac thrombus, limited life expectancy (< 1 year) and unsuitable mitral valve morphology, according to the EVEREST criteria[2].

Written informed consent was given by all patients to receive percutaneous mitral valve repair with the MitraClip®. The study was reviewed and approved by the Ruhr-University Bochum Institutional Review Board.

Pre-procedural investigations

The pre-procedural examinations of study patients comprised an anamnesis, assessment of functional capacity (NYHA class), laboratory measurements, transthoracic and transesophageal echocardiography and coronary angiography. The diagnosis of coronary artery disease was made in patients with a coronary artery stenosis > 50% in the pre-procedural coronary angiography, previous myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention.

We measured plasma B-type natriuretic peptide levels on the same day as clinical and echocardiographical examinations. By using a chemiluminescent immunoassay kit (Biosite Triage, San Diego, CA, United States) we analyzed the levels of plasma B-type natriuretic peptide.

All patients underwent transthoracic and transesophageal echocardiography (Vivid 7 or Vivid 9, General Electrics, Horton, Norway) according to the guidelines of the American Society of Echocardiography[14]. Using the modified Devereux formula left ventricular myocardial mass was calculated. The Simpson method (using 4- and 2-chamber views) was applied to measure LVEF[14].

According to the American Society of Echocardiography, MR and tricuspid regurgitation was graded as mild, moderate or severe[15]. In addition, MR was classified as degenerative, functional or mixed[15]. According to the current recommendations, systolic pulmonary pressure and tricuspid annular plane systolic excursion were measured[16].

Percutaneous mitral valve repair

Percutaneous mitral valve repair with the MitraClip® device was executed under general anesthesia without hemodynamic support using a femoral vein. The transseptal puncture and positioning of the device were performed under transesophageal echocardiography and fluoroscopic guidance. After positioning a clip, the remaining MR and mean transmitral gradient were assessed. If the reduction in MR was unsatisfactory, a second clip was positioned. A maximum mean transmitral gradient of 5 mmHg was accepted. Before and after implantation, left atrial pressure was measured invasively. The procedure and MitraClip® system have been previously described in detail[2,3].

Patients were treated with aspirin for 6 mo and with clopidogrel for 30 d[2]. When clinically indicated (mainly due to atrial fibrillation), patients also received oral anticoagulation.

Postprocedural investigations

The procedural and in-hospital difficulties were reported according to current recommendations[17]. Within 48 h after the MitraClip® procedure, a transthoracic echocardiography was performed.

Follow-up examinations of all surviving study patients were conducted 3 ± 2 mo after the MitraClip® implantation and comprised an assessment of functional capacity (NYHA class) and a transthoracic echocardiography. Any changes in MR, left atrial volume and diameter and left ventricular geometry and function were documented. The follow-up of patients was at least 12 mo and death, myocardial infarction, stroke and hospitalization due to heart failure were documented. During routine ambulatory visits follow-up information was obtained. In case of patients' death, we contacted their physicians to get information about reasons of death.

Statistical analysis

Numerical values were expressed as mean ± SD. For the comparison of continuous variables we used unpaired *t* tests or Mann-Whitney *U* test, where appropriate. In order to compare categorical variables we performed χ^2 analysis. To examine continuous variables before and after MitraClip® implantation, we applied paired Student's *t* test (for normally distributed variables) or Wilcoxon test (for non-normally distributed variables). For categorical variables, we used McNemar's test to measure changes before and after MitraClip® implantation. Univariate Cox proportional hazards model was performed to assess predictors of all-cause death. For this, all the parameters in Tables 1 and 2 were included in the analysis.

In order to determine cut-off values for plasma B-type natriuretic peptide (BNP), receiver operating characteristic (ROC) curves were performed. The Kaplan-Meier method was used for analysis of all-cause mortality. A comparison of survival between different groups of patients was assumed with log-rank tests. A P value < 0.05 was considered to be statistically significant. All probability values reported were two-sided. A statistical review of the study was performed by a biomedical statistician. The analyses were done using SPSS software (version 20.0; SPSS Inc., Chicago, IL, United States).

RESULTS

A total of 48 consecutive patients with native MR who underwent percutaneous mitral valve repair with the MitraClip® device were enrolled between May 2012 and December 2014. During the procedures, no patients died and no cases of stroke or myocardial infarction occurred. In one patient, positioning of the MitraClip® was not possible, and the procedure was thus abandoned. In another patient, leaflet detachment occurred after implantation of the clip. One day after the unsuccessful procedure, this patient received surgical mitral valve repair. Therefore, these two patients were not included in the analysis. The final study cohort consisted of 46 patients. Clip embolization, acute conversion to open surgery, pericardial tamponade, need for resuscitation, need for dialysis, respiratory failure and major bleeding did not occur after MitraClip® implantation.

Study cohort and procedure

The mean age of the study patients (21 women, 25 men) was 76.5 ± 9.4 years, and the mean logistic EuroSCORE Ⅰ was 32% ± 21%. Plasma BNP was measured in 36 of the 46 patients. The baseline characteristics of the patients are provided in Table 1.

The mean procedure time was 143 ± 34 min (door-to-door time, including general anesthesia). One clip was implanted in 31 patients (67%), and two clips were implanted in 15 patients (33%). Immediately after the percutaneous mitral valve repair, transesophageal echocardiography revealed remaining severe MR in 2 patients (4%). There were no cases of post-procedural mitral stenosis (the transmitral gradient was ≤ 5 mmHg in all patients). The invasive hemodynamic measurements demonstrated a significant decrease in mean left atrial pressure (left atrial pressure before procedure 27 ± 10 mmHg *vs* left atrial pressure after procedure 23 ± 10 mmHg, P = 0.018).

Clinical follow-up

The mean duration of hospitalization after MitraClip® procedure was 11 ± 8 d. Within 30 d after the MitraClip® implantation, 2 patients suffered from death due to heart failure. Follow-up examinations were done in

Table 1 Clinical characteristics, laboratory values and echocardiography results

	Total (n = 46)	Survivors (n = 35)	Non-survivors (n = 11)	P value
Age (yr)	76.5 ± 9.4	76.4 ± 9.5	76.9 ± 9.6	0.871
Women, n (%)	21 (46)	16 (46)	5 (45)	0.988
Body mass index (kg/m²)	26.8 ± 4.3	26.8 ± 4.5	26.6 ± 3.7	0.928
NYHA class				0.818
NYHA class II, n (%)	1 (2)	1 (3)	0 (0)	
NYHA class III, n (%)	27 (59)	20 (57)	7 (64)	
NYHA class IV, n (%)	18 (39)	14 (40)	4 (36)	
Hypertension, n (%)	31 (69)	23 (66)	8 (80)	0.389
Diabetes mellitus, n (%)	21 (47)	17 (49)	4 (40)	0.632
Coronary artery disease, n (%)	27 (60)	22 (63)	5 (50)	0.464
Previous coronary artery bypass grafting, n (%)	15 (34)	12 (35)	3 (30)	0.756
Previous heart valve surgery, n (%)	6 (13)	5 (14)	1 (10)	0.725
Previous stroke, n (%)	5 (11)	5 (14)	0 (0)	0.205
Atrial fibrillation/flutter, n (%)	33 (73)	25 (71)	8 (80)	0.589
Implanted PM/ICD/CRT-device, n (%)	15 (34)	9 (26)	6 (60)	0.067
Chronic obstructive pulmonary disease, n (%)	14 (31)	12 (34)	2 (20)	0.389
Peripheral artery disease, n (%)	6 (13)	4 (11)	2 (18)	0.482
Logistic EuroSCORE I (%)	31.8 ± 21.1	32.1 ± 21.4	30.9 ± 21.2	0.870
Logistic EuroSCORE II (%)	11.9 ± 9.5	12.0 ± 9.5	11.6 ± 9.98	0.885
Laboratory parameters				
Creatinine (mg/dL)	1.4 ± 0.5	1.4 ± 0.5	1.28 ± 0.39	0.476
Hemoglobin (g/dL)	12.1 ± 1.7	12.3 ± 1.6	11.4 ± 2.0	0.256
Plasma BNP (pg/mL) (n = 36)	1022 ± 897	793 ± 611	1710 ± 1264	0.006
Echocardiography				
Mitral regurgitation etiology				
Organic, n (%)	17 (37)	14 (40)	3 (27)	0.446
Functional, n (%)	21 (46)	16 (46)	5 (45)	0.988
Mixed, n (%)	8 (17)	5 (14)	3 (27)	0.322
Left atrial diameter (mm)	51 ± 6	51 ± 6	50 ± 5	0.793
Left atrial volume (mL)	115 ± 43	110 ± 42	134 ± 45	0.118
LV end-diastolic diameter (mm)	55 ± 10	55 ± 10	57 ± 10	0.498
LV end-systolic diameter (mm)	42 ± 12	41 ± 11	45 ± 12	0.313
LV end-diastolic volume (mL)	159 ± 70	152 ± 62	181 ± 93	0.258
LV end-systolic volume (mL)	96 ± 63	88 ± 55	121 ± 82	0.151
LV ejection fraction (%)	42 ± 14	44 ± 14	37 ± 14	0.203
MAPSE (mm)	12 ± 3	13 ± 3	11 ± 3	0.163
TAPSE (mm)	17 ± 5	17 ± 4	18 ± 6	0.527
Tricuspid regurgitation (moderate/severe), n (%)	31 (67)	21 (60)	10 (91)	0.070
sPAP (mmHg)	44 ± 12	44 ± 12	43 ± 14	0.844

NYHA: New York Heart Association; PM/ICD/CRT: Pacemaker, implantable cardioverter defibrillator, Cardiac Resynchronization Therapy; BNP: B-type natriuretic peptide; LV: Left ventricular; sPAP: Systolic pulmonary artery pressure.

the remaining 44 patients (the mean follow-up was 95 d after the percutaneous mitral valve repair).

Prior to the procedure, 98% of our study population was considered NYHA functional class Ⅲ or Ⅳ. After the percutaneous mitral valve repairs, the NYHA functional classes and degree of MR improved significantly (both P < 0.001) (Figure 1). Additionally, the left atrial diameter, left atrial volume and systolic pulmonary artery pressure decreased. By contrast, the left ventricular dimensions and LVEF remained unchanged (Table 2). In our study, there were no differences in clinical course after mitral valve repair between patients with organic and with functional MR.

Mortality and morbidity

The all-cause mortality rate 30 d after percutaneous mitral valve repair was 4.3% (n = 2), and this rate increased to 19.5% (n = 9) at one year. In the first year after the MitraClip® implantation, no cases of myocardial infarction occurred, but 2 patients suffered from ischemic stroke. One of these patients had atrial fibrillation and received aspirin and coumarin at the time of stroke. This patient died within the first year. The other patient was in sinus rhythm and received monotherapy with aspirin. Hospitalization due to heart failure occurred in 16 patients (35% of study patients), and of these patients, 7 died within the first year after MitraClip® implantation.

During the follow-up of 473 ± 274 d, the primary endpoint (all-cause mortality) was attained in 11 patients (24%). Reasons for death included heart failure (n = 7), myocardial infarction (n = 1), unknown causes (n = 2) and malignancy (n = 1). Kaplan-Meier curves were created for the analysis of all-cause mortality (Figure 2A).

Predictors of outcome

In the univariate Cox analysis, only plasma BNP was

Table 2 New York Heart Association class and hemodynamics before and after MitraClip implantation (*n* = 44)

	Before MitraClip	After MitraClip	*P* value
NYHA class III and IV, *n* (%)	43 (98)	16 (35)	< 0.001
Mitral regurgitation (severe)	44 (100)	6 (14)	< 0.001
Left atrial diameter (mm)	50 ± 6	49 ± 7	0.039
Left atrial volume (mL)	114 ± 43	102 ± 42	0.008
LV end-diastolic diameter (mm)	55 ± 10	54 ± 11	0.308
LV end-systolic diameter (mm)	42 ± 12	41 ± 12	0.367
LV end-diastolic volume (mL)	158 ± 69	159 ± 75	0.866
LV end-systolic volume (mL)	95 ± 63	95 ± 61	0.993
LV ejection fraction (%)	42 ± 15	44 ± 13	0.216
Severe tricuspid regurgitation, *n* (%)	12 (27)	9 (20)	0.763
sPAP (mmHg)	44 ± 13	27 ± 10	0.027

LV: Left ventricular; sPAP: Systolic pulmonary artery pressure.

significantly associated to the primary study endpoint. Patients who died after percutaneous mitral valve repair had significantly higher pre-procedural BNP levels compared to patients who survived (Table 1). The ability of BNP to predict all cause-mortality was assessed using ROC curve analysis. Using a cut-off point of BNP > 817 pg/mL, the sensitivity was 78% and the specificity was 70% [area under the ROC curve (AUC) = 0.778, (95%CI: 0.621-0.936; $P < 0.001$)]. A pre-procedural plasma BNP level > 817 pg/mL was associated with all-cause mortality (HR = 6.074; 95%CI: 1.257-29.239; $P = 0.012$) (Figure 2B).

DISCUSSION

The main result of this study was an improvement in hemodynamics (Figure 1A and Table 2) and symptoms (Figure 1B) in patients with severe symptomatic MR after receiving percutaneous mitral valve repair with the MitraClip® system. However, the relatively high one-year mortality rate (19.5%) observed in the present study must be mentioned (Figure 2A). Preexisting co-morbidities of these selected patients who had a very high mean logistic EuroSCORE I of 31.8% (Table 1) is the most likely explanation. Several previous studies reported comparable mortality rates after MitraClip® implantation[3-11].

Additionally, our study suggests that pre-procedural plasma BNP is an independent predictor of all-cause mortality after percutaneous mitral valve repair (Figure 2B).

Symptoms and hemodynamics

Since the first description of percutaneous mitral valve repair with the MitraClip® device, this technique has now widely used. Today, it is a recognized treatment for high-risk patients with severe and symptomatic MR[1].

Several studies demonstrate symptomatic benefits of percutaneous mitral valve repair in terms of changes in NYHA functional class[3-11,18,19]. Vakil *et al*[18] found that three-quarters of patients were in NYHA class I or II after MitraClip® implantation. Our study confirmed a significant enhancement in NYHA class after MitraClip® implantation (Figure 1B and Table 2).

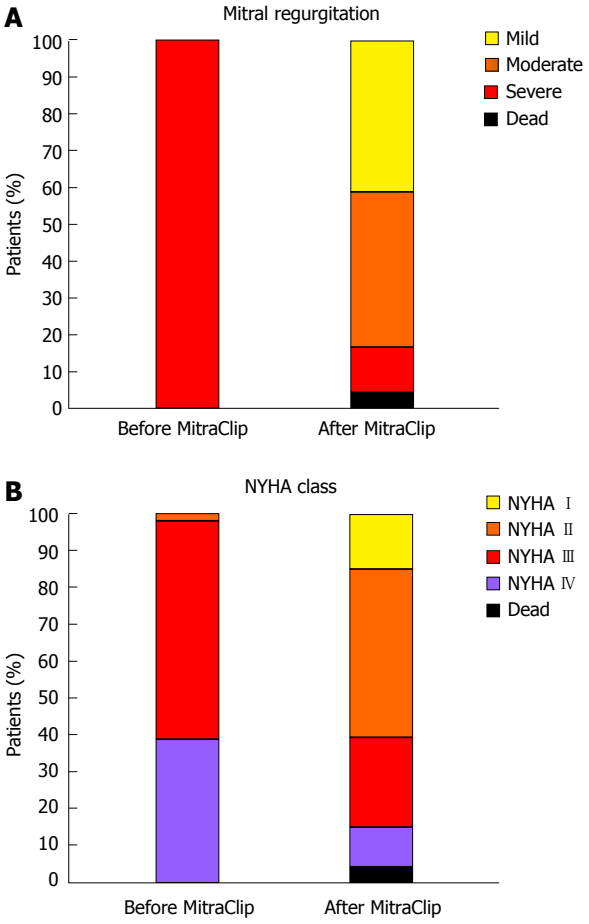

Figure 1 Changes in mitral regurgitation and New York Heart Association functional class. A: Degree of mitral regurgitation before and after percutaneous mitral valve repair with the MitraClip® system in all study patients (*n* = 46); B: NYHA functional classes before and after percutaneous mitral valve repair with the MitraClip® system in all study patients (*n* = 46). NYHA: New York Heart Association functional class.

Other than the fact that percutaneous mitral valve repair is beneficial for treating the symptoms of valvular heart failure, some studies have additionally demonstrated favorable effects of repair on reverse cardiac remodeling[2,8,10,19].

Taramasso *et al*[19] revealed an enhancement in LVEF after MitraClip® implantation in patients with heart failure. By contrast, Feldman *et al*[2] reported a reduction in left ventricular volumes and LVEF after MitraClip®. These different findings may be explained by the fact that patients with functional and degenerative MR have different types of reverse remodeling. In patients with degenerative MR, end-systolic volume remains stable, whereas left ventricular end-diastolic volume decreases. In contrast, in patients with functional MR, a significant decrease in left ventricular end-diastolic and end-systolic volume is observed[20]. Therefore, LVEF decreases slightly in degenerative MR[2] and remains constant or increased in functional MR[19,20].

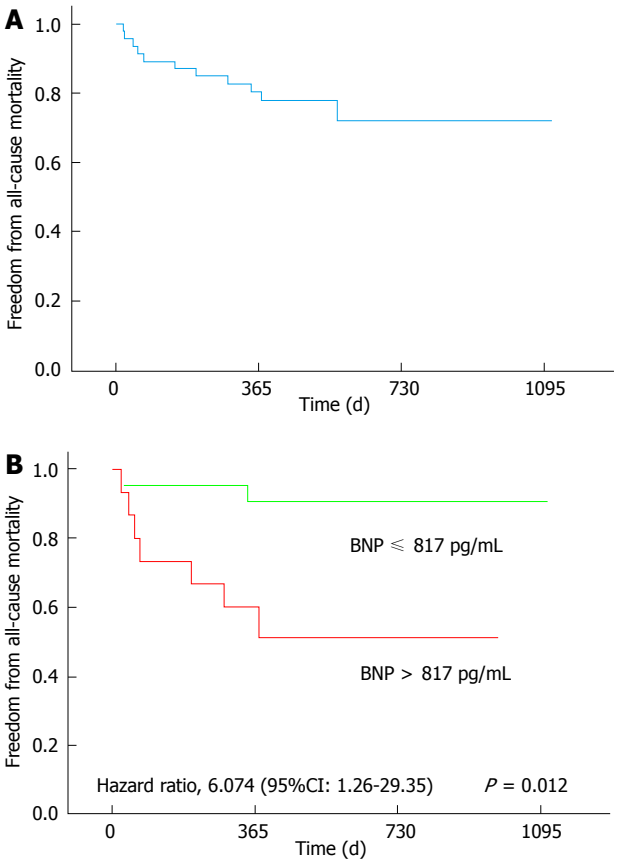

Figure 2 All-cause mortality and B-type natriuretic peptide. A: Kaplan-Meier estimates of freedom from all-cause mortality; B: Kaplan-Meier estimates of freedom from all-cause mortality according to low pre-procedural BNP levels (BNP ⩽ 817 pg/mL) and high pre-procedural BNP levels (BNP > 817 pg/mL). BNP: B-type natriuretic peptide.

In our study, the proportion of patients with functional and degenerative MR was approximately equal (Table 1). There were no differences in clinical course after mitral valve repair between patients with organic and functional MR. Potentially due to the relatively small number of patients, we observed that the LVEF, the left ventricular end-systolic and end-diastolic volumes remained nearly constant (Table 2).

Our study demonstrated a clear reduction in the severity of MR (Figure 1A), a reduction in left atrial volume and size and a decline in systolic pulmonary artery pressure (Table 2).

30-d and one-year outcomes

The all-cause mortality rate 30 d after percutaneous mitral valve repair was 4.3%, and this rate was 19.5% at one year. During the follow-up of 473 ± 274 d, 11 patients (24%) died. Cardiovascular mortality accounted for the majority of the deaths at follow-up (90%). Patients' various cardiac and non-cardiac diseases may explain the relatively high long-term mortality. Similar one-year mortality rates have been reported in several other studies[3-11]. However, it should be emphasized that the patients in our study had an extremely high operative risk (mean logistic EuroSCORE Ⅰ > 31%). Thus, the risk profile of our patient cohort was less favorable than those of most other studies[3-11]. Our study suggests that even patients with an extremely high operative risk can be successfully treated with the MitraClip® system.

BNP and outcome

Plasma BNP levels have a prognostic impact in patients undergoing surgical mitral surgery[21]. In patients undergoing percutaneous mitral valve repair with the MitraClip® device, Taramasso *et al*[19] found that pre-procedural pro-BNP levels (pro-BNP level ⩾ 1600 pg/mL) were an independent predictor of mortality. Furthermore, Neuss *et al*[22] demonstrated that among patients with end-stage heart failure and NT-proBNP values > 10000 pg/mL, the mortality rate was extremely high, despite a successful percutaneous mitral valve repair with MitraClip®. Our results are in line with these studies. Although pre-procedural measurements of plasma BNP were performed in only 36 of the 46 patients, we found that BNP levels > 817 pg/mL were related with a considerably higher long-term mortality rate (Figure 2B). Notably, plasma BNP was the only independent predictor of long-term mortality. On the other hand, our study suggests that patients with plasma BNP levels ⩽ 817 pg/mL have favorable long-term results after MitraClip® implantation (Figure 2B).

Limitations

The main limitation of our study is the relatively small number of patients and the fact that this study was conducted only at one center. However, the percutaneous repair of the mitral valve is a relatively new technique. There are still few long-term results of MitraClip® implantation. Another important limitation is the absence of a control group in our study. A comparison with conservatively treated patients, or patients undergoing heart surgery would give a more rigorous investigation of the effects of percutaneous mitral valve repair. As our study examined relatively few patients, the associations found in this paper must still be considered preliminary.

COMMENTS

Background

Mitral regurgitation (MR) is the most common heart valve disease and the second most common reason for heart valve surgery. When feasible, mitral valve repair is considered the optimal surgical treatment. However, a considerable portion of patients with severe MR cannot receive surgical treatment because of their co-morbidities and high surgical risks. In the last few years, percutaneous mitral valve repair has become an alternative technique for patients with severe MR.

Research frontiers

In the last few years, percutaneous mitral valve repair has become an alternative technique for patients with severe MR, with more than 20000 procedures worldwide. However, the Everest Ⅱ study is the only randomized trial that has compared percutaneous repair with heart surgery, and it mainly included patients with degenerative MR and without an elevated operative risk. By contrast, the

current European Society of Cardiology guidelines recommend applying the MitraClip® only in symptomatic high-risk patients with severe functional MR (level of evidence IIb). In recent years, some registry studies and several smaller studies concerning MitraClip® have been published. However, relatively little is known about the mid- and long-term results of percutaneous mitral valve repair.

Innovations and breakthroughs

The aim of the present study was to assess the mid-term outcomes after percutaneous mitral valve repair with MitraClip®. The study demonstrates that percutaneous mitral valve repair with MitraClip® had positive effects on hemodynamics and symptoms. Despite the multiple comorbidities and extremely high operative risk of the study patients, the mid-term outcome after MitraClip® was favorable. Elevated BNP levels were indicative of a poorer long-term survival.

Applications

The data in this study suggest that patients with an extremely high risk can also be successfully treated with the MitraClip® system. In addition, pre-procedural plasma BNP levels > 817 pg/mL were associated with significantly higher long-term mortality. On the other hand, the study suggests that patients with plasma BNP levels ≤ 817 pg/mL had favorable long-term results after MitraClip®.

Terminology

MR is a valvular heart disease that is characterized by an abnormal systolic blood flow into the left atrium and a volume overload of the left ventricle. The reasons for this condition include defects of the valve (usually referred to as degenerative mitral valve regurgitation) or heart failure with dilatation of the ventricle (usually called functional mitral valve regurgitation). Mitral valve repair is the standard therapy. Percutaneous mitral valve repair has emerged as an alternative technique.

Peer-review

Good article, well written, interesting for the reader, with a useful "take home message".

REFERENCES

1 **Vahanian A**, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012; **33**: 2451-2496 [PMID: 22922415 DOI: 10.1093/eurheartj/ehs109]

2 **Feldman T**, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engeron E, Loghin C, Trento A, Skipper ER, Fudge T, Letsou GV, Massaro JM, Mauri L. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011; **364**: 1395-1406 [PMID: 21463154 DOI: 10.1056/NEJMoa1009355]

3 **Glower DD**, Kar S, Trento A, Lim DS, Bajwa T, Quesada R, Whitlow PL, Rinaldi MJ, Grayburn P, Mack MJ, Mauri L, McCarthy PM, Feldman T. Percutaneous mitral valve repair for mitral regurgitation in high-risk patients: results of the EVEREST II study. *J Am Coll Cardiol* 2014; **64**: 172-181 [PMID: 25011722 DOI: 10.1016/j.jacc.2013.12.062]

4 **Maisano F**, Franzen O, Baldus S, Schäfer U, Hausleiter J, Butter C, Ussia GP, Sievert H, Richardt G, Widder JD, Moccetti T, Schillinger W. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. *J Am Coll Cardiol* 2013; **62**: 1052-1061 [PMID: 23747789 DOI: 10.1016/j.jacc.2013.02.094]

5 **Nickenig G**, Estevez-Loureiro R, Franzen O, Tamburino C, Vanderheyden M, Lüscher TF, Moat N, Price S, Dall'Ara G, Winter R, Corti R, Grasso C, Snow TM, Jeger R, Blankenberg S, Settergren M, Tiroch K, Balzer J, Petronio AS, Büttner HJ, Ettori F, Sievert H, Fiorino MG, Claeys M, Ussia GP, Baumgartner H, Scandura S, Alamgir F, Keshavarzi F, Colombo A, Maisano F, Ebelt H, Aruta P, Lubos E, Plicht B, Schueler R, Pighi M, Di Mario C. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 Pilot European Sentinel Registry. *J Am Coll Cardiol* 2014; **64**: 875-884 [PMID: 25169171 DOI: 10.1016/j.jacc.2014.06.1166]

6 **Puls M**, Lubos E, Boekstegers P, von Bardeleben RS, Ouarrak T, Butter C, Zuern CS, Bekeredjian R, Sievert H, Nickenig G, Eggebrecht H, Senges J, Schillinger W. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry. *Eur Heart J* 2016; **37**: 703-712 [PMID: 26614824 DOI: 10.1093/eurheartj/ehv627]

7 **Capodanno D**, Adamo M, Barbanti M, Giannini C, Laudisa ML, Cannata S, Curello S, Immè S, Maffeo D, Bedogni F, Petronio AS, Ettori F, Tamburino C, Grasso C. Predictors of clinical outcomes after edge-to-edge percutaneous mitral valve repair. *Am Heart J* 2015; **170**: 187-195 [PMID: 26093881 DOI: 10.1016/j.ahj.2015.04.010]

8 **Boerlage-vanDijk K**, Wiegerinck EM, Araki M, Meregalli PG, Bindraban NR, Koch KT, Vis MM, Piek JJ, Tijssen JG, Bouma BJ, Baan J. Predictors of outcome in patients undergoing MitraClip implantation: An aid to improve patient selection. *Int J Cardiol* 2015; **189**: 238-243 [PMID: 25897916 DOI: 10.1016/j.ijcard.2015.01.045]

9 **Triantafyllis AS**, Kortlandt F, Bakker AL, Swaans MJ, Eefting FD, van der Heyden JA, Post MC, Rensing BW. Long-term survival and preprocedural predictors of mortality in high surgical risk patients undergoing percutaneous mitral valve repair. *Catheter Cardiovasc Interv* 2016; **87**: 467-475 [PMID: 26268819 DOI: 10.1002/ccd.26137]

10 **Lesevic H**, Sonne C, Braun D, Orban M, Pache J, Kastrati A, Schömig A, Mehilli J, Barthel P, Ott I, Sack G, Massberg S, Hausleiter J. Acute and Midterm Outcome After MitraClip Therapy in Patients With Severe Mitral Regurgitation and Left Ventricular Dysfunction. *Am J Cardiol* 2015; **116**: 749-756 [PMID: 26160468 DOI: 10.1016/j.amjcard.2015.05.048]

11 **Velazquez EJ**, Samad Z, Al-Khalidi HR, Sangli C, Grayburn PA, Massaro JM, Stevens SR, Feldman TE, Krucoff MW. The MitraClip and survival in patients with mitral regurgitation at high risk for surgery: A propensity-matched comparison. *Am Heart J* 2015; **170**: 1050-1059.e3 [PMID: 26542516 DOI: 10.1016/j.ahj.2015.08.004]

12 **Roques F**, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, Cortina J, David M, Faichney A, Gabrielle F, Gams E, Harjula A, Jones MT, Pintor PP, Salamon R, Thulin L. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg* 1999; **15**: 816-822; discussion 822-823 [PMID: 10431864]

13 **Nashef SA**, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. EuroSCORE II. *Eur J Cardiothorac Surg* 2012; **41**: 734-744; discussion 744-745 [PMID: 22378855 DOI: 10.1093/ejcts/ezs043]

14 **Lang RM**, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18**: 1440-1463 [PMID: 16376782]

15 **Zoghbi WA**, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003; **16**: 777-802 [PMID: 12835667]

16 **Rudski LG**, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*

2010; **23**: 685-713; quiz 786-788 [PMID: 20620859 DOI: 10.1016/j.echo.2010.05.010]

17 **Kappetein AP**, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J* 2012; **33**: 2403-2418 [PMID: 23026477 DOI: 10.1093/eurheartj/ehs255]

18 **Vakil K**, Roukoz H, Sarraf M, Krishnan B, Reisman M, Levy WC, Adabag S. Safety and efficacy of the MitraClip® system for severe mitral regurgitation: a systematic review. *Catheter Cardiovasc Interv* 2014; **84**: 129-136 [PMID: 24323764 DOI: 10.1002/ccd.25347]

19 **Taramasso M**, Maisano F, Latib A, Denti P, Buzzatti N, Cioni M, La Canna G, Colombo A, Alfieri O. Clinical outcomes of MitraClip for the treatment of functional mitral regurgitation. *EuroIntervention* 2014; **10**: 746-752 [PMID: 24469474 DOI: 10.4244/EIJV10I6A128]

20 **Grayburn PA**, Foster E, Sangli C, Weissman NJ, Massaro J, Glower DG, Feldman T, Mauri L. Relationship between the magnitude of reduction in mitral regurgitation severity and left ventricular and left atrial reverse remodeling after MitraClip therapy. *Circulation* 2013; **128**: 1667-1674 [PMID: 24014834 DOI: 10.1161/CIRCULATIONAHA.112.001039]

21 **Hwang IC**, Kim YJ, Kim KH, Lee SP, Kim HK, Sohn DW, Oh BH, Park YB. Prognostic value of B-type natriuretic peptide in patients with chronic mitral regurgitation undergoing surgery: mid-term follow-up results. *Eur J Cardiothorac Surg* 2013; **43**: e1-e6 [PMID: 22997191 DOI: 10.1093/ejcts/ezs513]

22 **Neuss M**, Schau T, Schoepp M, Seifert M, Hölschermann F, Meyhöfer J, Butter C. Patient selection criteria and midterm clinical outcome for MitraClip therapy in patients with severe mitral regurgitation and severe congestive heart failure. *Eur J Heart Fail* 2013; **15**: 786-795 [PMID: 23325017 DOI: 10.1093/eurjhf/hfs214]

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ORIGINAL ARTICLE

Observational Study

How far cardio metabolic and psychological factors affect salt sensitivity in normotensive adult population?

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Abstract

AIM

To evaluate the prevalence of salt sensitivity and the impact of cardiometabolic and psychological characteristics on salt sensitivity in normotensive population.

METHODS

Of all participants, anthropometric measurements and fasting venous blood samples were collected, and study questionnaires were completed. Salt Sensitivity was defined based on the difference in mean arterial pressure with infusion of 2 L of normal saline followed by a low sodium diet and administration of three doses

of oral furosemide the day after.

RESULTS

Of 131 participants, 56 (42.7%) were diagnosed with salt sensitivity. Crude and age and sex adjusted regression analysis showed that low-density lipoprotein cholesterol and depression were positively associated with salt sensitivity (OR = 1.02, 95%CI: 1.01-1.04 and OR = 1.15, 95%CI: 1.00-1.34, respectively).

CONCLUSION

The high prevalence of salt sensitivity and its significant relation with prevalent risk factors necessitates considering its reduction actions at the population level and the need for further research.

Key words: Salt sensitivity; Cardiovascular disease risk factors

Core tip: Mean blood pressure can be reduced following a decrease in sodium intake in both hypertensive and normotensive individuals. Normotensive individuals with salt sensitivity trait are more likely to develop hypertension and other health problems. A relatively high prevalence of salt sensitivity has been indicated among Iranian adults. Low-density lipoprotein cholesterol was found to have strong positive association with salt sensitivity. Depressive individuals were more salt sensitive.

Sadeghi M, Roohafza H, Pourmoghaddas M, Behnamfar O, Pourmoghaddas Z, Heidari E, Mahjoor Z, Mousavi M, Bahonar A, Sarrafzadegan N. How far cardio metabolic and psychological factors affect salt sensitivity in normotensive adult population? *World J Cardiol* 2017; 9(1): 47-54 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i1/47.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i1.47

INTRODUCTION

Hypertension is a prevalent well-documented risk factor for cardiovascular disease and premature mortality and therefore is an important public health issue[1]. Essential hypertension is a common disorder in areas with average daily sodium intake of over 100 meq/d (2.3 g sodium), however, is rarely seen with average daily sodium intake of less than 50 meq/d (1.2 g sodium)[2,3].

It has been demonstrated in multiple studies that mean blood pressure (BP) can be reduced following a decrease in sodium intake in both hypertensive and normotensive individuals[4,5]. Based on these reports, a minimum level of dietary sodium independent of other risk factors is required for development of hypertension[6,7].

There is an important clinical benefit to identify and target individuals who are more sensitive to alterations in dietary sodium intake by implementing dietary sodium reduction interventions. BP variations in response to changes in dietary sodium intake are known as Salt Sensitivity. This responsiveness of BP, however, may vary significantly from individual to individual[8,9]. Normotensive individuals with this trait of salt sensitivity are said to be more likely to develop hypertension and other health problems including Cardiovascular, Respiratory, and renal disorders independent of hypertension later in life[10,11].

Although incompletely understood, multiple mechanisms for sodium sensitivity have been demonstrated, from impaired renal sodium excretion, abnormalities in signaling and vascular tone, to the role of genetics in sodium regulation[12,13].

In spite of the fact that the protocols and methods of salt sensitivity definition vary in different studies, there is a general accordance in the main observations. Salt sensitivity appears to be a reproducible phenomenon with different measurement techniques[14].

Salt sensitivity is a practical clinical concept in spite of all the difficulties in measurement and identifying the sensitive individuals. This fact that is evident by positive outcomes of the recommended dietary approaches for the prevention and treatment of hypertension (HTN) (DASH diet)[15] There are certain traits and disorders that are markedly associated with salt sensitivity including African American ethnicity, obesity, chronic kidney disease, and cardiovascular risk factors[9,16].

Previous studies conducted in the Eastern Mediterranean region (EMR) demonstrate a substantially high incidence rate of almost all cardiovascular diseases particularly HTN and increased rate of mortality even in treated subjects[17-20]. These findings along with the increasing trend of salt intake at the population level[21], beside the lack of evidence of salt sensitivity of BP in Iran and in the region, highlight the importance of conducting this study. Therefore, we aimed to evaluate the prevalence of salt sensitivity in a normotensive Iranian adult population and to investigate the impact of cardiometabolic risk factors and psychological characteristics, on salt sensitivity.

MATERIALS AND METHODS

Participants and studied variables

The study was conducted by the hypertension research center affiliated to Cardiovascular Research Institute (a WHO collaborating center in the EMR) from July to October 2014. In order to find potential volunteers from community, we used a wide range of materials from flyers and brochures to posters. A total of 140 healthy participants volunteered to take part in this cross-sectional study. Eligibility requirements included willingness to participate in the study, age 18 years and older, normal BP defined as systolic BP below 140 mmHg and diastolic BP below 90 mmHg based on 3 screening visits of 1 wk apart. The exclusion criteria was

history of hypertension; history of special diet including low salt diets; history of taking antihypertensive medications and diuretics for any reason, oral contraceptives and nonsteroidal anti-inflammatory drugs; any history of myocardial infarction, heart failure, cerebrovascular accidents and renal failure. Written informed consents were obtained from each participant and the study protocol was approved by the ethical committee of Cardiovascular Research Institute.

A questionnaire was used at the baseline observation by trained staff to collect information on demographic characteristics as well as family history of hypertension, coronary artery disease, and lifestyle habits including regular physical activity, dietary pattern and smoking status. The Hospital Anxiety and Depression Scale questionnaire was also used to determine the score of anxiety and depression. This scale consists of seven items for anxiety and seven items for depression, with scores ranging from 0 to 21. The higher scores demonstrate more intensity in anxiety or depression level. Scores higher than 7, in both domains indicate that participants are likely to be depressed or suffer from anxiety[22,23].

Anthropometric measurements of weight, height, waist and hip circumferences were obtained during baseline examination with the individual in minimal clothing. The WHO STEPS Surveillance Manual (The WHO STEP wise Approach to Chronic Disease Risk Factor Surveillance) was used for measuring waist and hip circumference[24]. Body mass index (BMI) was calculated as weight (in kilograms) over height squared (in meters).

Venous blood samples after fasting for at least 8 h were taken for measurement of fasting blood sugar (FBS), serum blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), sodium (Na), potassium (K) levels, and lipid profile including low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), and total cholesterol (TC). Plasma measurements were assessed using commercially available kits (Parsazmoun). BP was measured by trained staff for each participant using an automated mercury sphygmomanometer with the individual in sitting position and 5 min of rest. All the participants were asked to avoid consumption of alcohol, tea, or coffee, physical exercise or smoking for at least one hour prior to admission. Mean arterial pressure (MAP) was calculated as [(2 × diastolic) + systolic]/3 and reported for each measurement.

We considered the following definitions for cardiovascular risk factors: Current smoking of at least one cigarette per day; lack of regular physical activity (less than 30 min a day, five days a week); raised blood glucose (FBS > 126 mg/dL); elevated blood cholesterol [TC > 200 mg/dL, TG > 150 mg/dL, LDL > 130 mg/dL, HDL below 40 mg/dL (male) and less than 50 mg/dL (female)]; and being overweight or obese (BMI > 25 kg/m^2, waist circumference > 92 cm in males and > 88 cm in females)[25].

Study design

The study was conducted in two days. On the first day of the study, individuals were admitted at 8 AM and were put on a low calorie and low sodium diet (10 mmol/d). At this time, venous blood samples were obtained, anthropometric measurements were calculated, and the questionnaires were filled out from participants by trained staff. Two hours after the admission, three measurements of BP were obtained with five minutes intervals and the mean of them was recorded as the baseline BP.

After obtaining the baseline BP, 2 L of normal saline was administered intravenously over 4 h (500 mL/h). Two hours after normal saline infusion, BP was obtained and post-saline MAP was calculated. Then participants were discharged and were asked to return back to the clinic the next morning.

To ensure compliance to the study protocol, individuals were required to eat pre-packaged foods that were prepared according to the protocol including low-carbohydrate, low-fat, and low-sodium diet (10 mmol/d) and were instructed to avoid any foods that were not provided by the study staff. Participants were also followed up over the night by telephone to evaluate any potential side effects and to ensure their adherence to the study dietary protocol.

On the following day, participants were admitted again at 8 AM and BPs were obtained. Sodium and volume depletion was then induced by a low sodium diet (10 mmol/d) and administration of three doses of oral furosemide (40 mg each dose, at 10 AM, 2 PM and 6 PM). Two hours after completion of the last dose of furosemide, BP was measured according to the study protocol. The MAP after sodium and volume depletion was compared with the post-saline MAP.

Individuals who demonstrated a decrease in MAP $\geqslant$ 10 mmHg were defined as "salt sensitive". Those with MAP decrease < 10 mmHg were categorized as "salt insensitive" including both the salt resistant (ΔMAP < 6 mmHg) and intermediate (ΔMAP 6-10 mmHg) with respect to sodium sensitivity.

Statistical analysis

All data were analyzed by SPSS, version 15 (SPSS Inc, Chicago, IL, United States). Respectively, a *P* value $\leqslant$ 0.05 and *P* value $\leqslant$ 0.1 were considered as statistically and marginally significant for all analyses. Student's *t* test for continuous variables and χ^2 test for discrete variables were used. Man-Whitney test was applied where appropriate. Multiple Logistic Regression model was carried out to examine the association between demographic, anthropometric, psychological characteristics and laboratory studies of those with the salt sensitivity. Odds ratios (ORs) were reported with the corresponding 95%CI. Repeated measure ANOVA was used for comparing the means of systolic BP in different times.

The dependent variable was salt sensitivity. Inde-

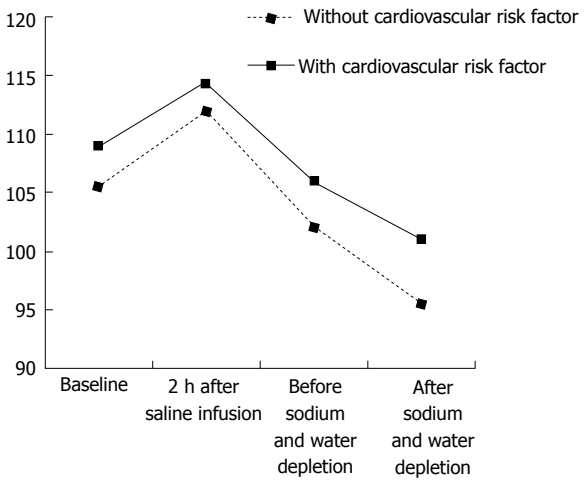

Figure 1 Means of systolic blood pressure mmHg (vertical axes), measurements at: (1) baseline; (2) 2 h after saline infusion; (3) before sodium and water depletion; and (4) after sodium and water depletion (horizontal axes), among individuals without or with at least one cardiovascular risk factor.

pendent variables included demographic, anthropometric, psychosocial characteristics, laboratory studies, and cardiovascular risk factors of those adjusted based on age and sex. The statistical methods of the study were reviewed by biomedical statistician.

RESULTS

Of the total of 140 participants, 9 who failed to adhere to dietary protocol or did not complete the intervention were excluded from the study. Among the 131 individuals included in the study, 56 participants (42.7%) were diagnosed with salt sensitivity while 75 (57.3%) participants including 52 (39.7%) salt resistant and 23 (17.6%) intermediate were determined as salt insensitive group. Of participants, hundred were male and 31 were female, with a mean age of 25.70 ± 5.71. Significant differences were not statistically detected in the age or sex distribution between both groups.

Table 1 shows the baseline demographic, psychological and anthropometric characteristics of participants as well as laboratory evaluations. Lipid profile tests revealed that LDL cholesterol level was significantly higher in Salt Sensitive group compared with Salt Insensitive one (P = 0.038). In the Salt Sensitive group, BMI, FBS, BUN, and Cr levels were higher than those in the Salt Insensitive group with a marginally significant difference (P = 0.057, 0.072, 0.077, 0.067, respectively). There wasn't any significant difference in the Depression or Anxiety Score between two groups.

Table 2 shows the Crude, and age and sex-adjusted logistic regression analysis with salt sensitivity as an outcome. As shown in Table 2, with adjusted logistic regression analysis, LDL along with Depression were found to be the only two variables of significance (OR = 1.02, 95%CI: 1.01-1.04 and OR = 1.15, 95%CI: 1.00-1.34, respectively). At last, multiple logistic regression model with variables including, WC, Depression, FBS, LDL, Cr, age and sex was performed. Finding showed that there were not statistically difference between the result of multiple logistic regression model and age and sex adjusted logistic regression analysis and depression and LDL was still significant.

Means of systolic and diastolic BP measurements in participants without any cardiovascular risk factor compared with those with at least one risk factor at the baseline observation, 2 h after saline infusion, and before and after sodium and water depletion is shown in Figure 1. It has been founded that there is significant difference between baseline, 2 h after saline infusion and before and after sodium and water depletion (F = 102.02, $P \leqslant 0.001$). No significant interaction was observed between groups and times. (F = 0.99, P = 0.39).

DISCUSSION

As a whole, 131 normotensive individuals properly completed the study protocol and were included in the study analysis. This study showed a relatively high prevalence of salt sensitivity among Iranian adults as well as significant and positive association between the level of LDL cholesterol and salt sensitivity. Based on age and sex adjusted logistic regression analysis, LDL cholesterol and depression were found to have strong positive association with salt sensitivity.

Multiple studies conducted in the EMR have shown high incidence rate of hypertension and its low control level in the region[18-20]. This factor along with high average intake of sodium in the Iranian diet[21] highlight the importance of integrating salt sensitivity in risk assessment and management of hypertension in the region.

The heterogeneity and susceptibility of individual BP response to Sodium intake is the basis for development of salt sensitivity and appears to be a common, normally distributed biological concept in populations[10,26]. The salt sensitivity definition and categorizing individuals to salt sensitive or insensitive is arbitrary and several methods exist to measure salt sensitivity. It can be defined as BP variations in response to a change in dietary salt or as the difference in MAP with infusion of normal saline followed by a low sodium diet and loop diuretic administration the day after[15,16]. Our protocol, with salt loading and depletion, allowed us to maximize the follow-up and adherence to the protocol with a more practical and controllable intervention. Despite the differences in the measurement or definition methods, there has been accordance in several findings[26,27].

Overall, 42.7% of participants in our study were diagnosed with salt sensitivity. Even though relatively high, it is still in line with previous reports. The salt sensitivity has been observed in 25%-50% of normotensives and 40%-75% of hypertensive patients

Table 1 Baseline demographic, cardiometabolic and psychological characteristics of participants with respect to salt sensitivity

Variable	Salt insensitive *n* = 75	Salt sensitive *n* = 56	*P* value
Sex (male) (%)	55 (73.3)	45 (80.4)	0.349[1]
Age (yr) (mean ± SD)	25.23 ± 4.68	26.36 ± 6.91	0.272[2]
Family history of HTN (y/*n*) (%)	22 (29.3)	16 (28.6)	0.995[1]
Family history of CAD (y/*n*) (%)	7 (9.3)	6 (10.7)	0.770[1]
Regular physical activity (y/*n*) (%)	30 (40.0)	19 (33.9)	0.522[1]
Current smoker (y/*n*) (%)	12 (16.0)	8 (14.3)	0.865[1]
Weight (kg) (mean ± SD)	68.21 ± 13.05	71.16 ± 12.33	0.193[2]
Body mass index (kg/m^2) (mean ± SD)	22.75 ± 2.71	23.71 ± 2.93	0.057[2]
Waist circumference (cm) (mean ± SD)	81.54 ± 8.96	82.86 ± 8.41	0.404[2]
Hip circumference (cm) (mean ± SD)	96.97 ± 5.90	97.38 ± 5.77	0.698[2]
Waist to hip ratio (mean ± SD)	0.83 ± 0.06	0.84 ± 0.05	0.346[2]
Waist to height ratio (mean ± SD)	0.47 ± 0.04	0.48 ± 0.49	0.382[2]
Fasting blood sugar (mg/dL) (mean ± SD)	79.71 ± 6.16	82.64 ± 10.74	0.072[2]
Total cholesterol (mg/dL) (mean ± SD)	156.54 ± 28.70	164.66 ± 26.64	0.109[2]
High-density lipoprotein cholesterol (mg/dL) (mean ± SD)	46.23 ± 11.90	44.09 ± 12.23	0.327[2]
Low-density lipoprotein cholesterol (mg/dL) (mean ± SD)	82.56 ± 21.27	90.05 ± 17.49	0.038[2]
Triglyceride (mg/dL) (mean ± SD)	136.75 ± 97.26	145.32 ± 75.93	0.594[2]
Uric acid (mg/dL) (mean ± SD)	6.91 ± 6.57	6.42 ± 1.56	0.597[2]
Sodium (mg/dL) (mean ± SD)	140.30 ± 2.42	140.46 ± 2.39	0.699[2]
Potassium (mg/dL) (mean ± SD)	4.38 ± 0.53	4.34 ± 0.34	0.662[2]
Blood urea nitrogen (mg/dL) (mean ± SD)	12.56 ± 3.72	13.73 ± 3.63	0.077[2]
Creatinine (mg/dL) (mean ± SD)	0.92 ± 0.12	0.96 ± 0.10	0.067[2]
Depression score (mean ± SD)	4.00 ± 2.66	3.25 ± 2.15	0.095[3]
Anxiety score (mean ± SD)	3.73 ± 3.18	3.08 ± 3.25	0.161[3]

[1]*P* value obtained from χ^2; [2]*P* value obtained from t-test; [3]*P* value obtained from Man-Whitney. HTN: Hypertension; CAD: Coronary artery disease.

Table 2 Crude, age and sex-adjusted logistic regression analysis with salt sensitivity as an outcome

Variable	Crude OR (95%CI)	*P* value	Adjusted OR (95%CI)	*P* value
Total cholesterol (mg/dL)	1.01 (1.00-1.02)	0.11	1.01 (1.00-1.03)	0.12
Triglyceride (mg/dL)	1.01 (1.00-1.01)	0.59	1.00 (1.00-1.01)	0.87
High-density lipoprotein cholesterol (mg/dL)	0.99 (0.96-1.02)	0.33	0.99 (0.96-1.02)	0.45
Low-density lipoprotein cholesterol (mg/dL)	1.02 (1.01-1.04)	0.04	1.02 (1.01-1.04)	0.04
Fasting blood sugar (mg/dL)	1.04 (1.00-1.09)	0.06	1.04 (0.99-1.09)	0.14
Sodium (mg/dL)	1.06 (0.97-1.04)	0.35	1.03(0.98-1.05)	0.37
Potassium (mg/dL)	1.05 (0.99-1.07)	0.51	1.06(0.98-1.06)	0.41
Body mass index (kg/m^2)	1.14 (1.00-1.28)	0.06	1.12 (0.97-1.28)	0.13
Waist circumference (cm)	1.02 (0.98-1.06)	0.40	1.02 (0.97-1.06)	0.49
Waist to hip ratio	1.19 (0.83-1.69)	0.34	1.16 (0.76-1.79)	0.48
Regular physical activity (y/*n*)	0.79 (0.38-1.64)	0.52	0.85 (0.39-1.82)	0.66
Smoking (y/*n*)	1.07 (0.95-1.15)	0.40	1.08 (0.97-1.25)	0.47
Depression (y/*n*)	1.14 (0.98-1.32)	0.06	1.15 (1.00-1.34)	0.04
Family history of HTN (y/*n*)	1.19 (0.37-3.85)	0.77	1.28 (0.35-4.76)	0.70

HTN: Hypertension.

depending on the measurement techniques and geographic variation of studies in different ethnic populations[4,5,28].

Several mechanisms for sodium sensitivity have been demonstrated[29]. Impaired renal sodium excretion with resultant sodium retention that leads to volume expansion has been suggested as one of the underlying mechanism[30-32]. Abnormalities in signaling and vascular tone in response to sodium intake are another possible process[13,14]. Multiple genes are shown to be associated with sodium regulation and salt sensitivity[33,34]. This genetic predisposition is thought to be responsible for several relations seen in the salt sensitive group.

The strong, positive association of LDL cholesterol level with salt sensitivity presented in Table 2 can be interpreted by the role of genetic predisposition. In a study by Hoffmann *et al*[35], the endothelial nitric oxide synthase (*ENOS*) gene polymorphism was shown to be associated with higher levels of LDL cholesterol and reduced levels of nitric oxide (NO) production that can be responsible for the increased BP sensitivity to salt. Several previous studies have also revealed that the alpha-adducin gene polymorphisms may increase the LDL cholesterol levels and are probably responsible for salt sensitivity of BP[33,36,37].

In the present study, depression was found to

be a potential predictive variable for salt sensitivity. The mechanism by which depression is related to salt sensitivity is not clearly understood and further studies are required. However, this association can be explained by the role of stress as a predisposing factor to depression in susceptibility of BP to salt. Previous studies have demonstrated the contribution of the stress and sympathetic nervous system to salt sensitivity[10,38,39]. One mechanism might be the impaired stress-induced renin-angiotensin-aldosterone system regulation[40].

Depression and elevated LDL cholesterol level are reported to be highly prevalent among the Iranian population[41]. The fact that makes the importance of these two factors in salt sensitivity was even more significant among Iranian population.

Our findings showed that in the crude model, BMI, FBS, BUN and Cr levels were related to salt sensitivity with a marginally significant difference. The association between BMI and salt sensitivity has been noted in previous studies[39,42]. This relation may be explained by the higher sodium renal tubular reabsorption in obese individuals or due to drinking more soft drinks while eating salty products. Multiple previous studies have identified strong association between the plasma glucose level as a metabolic risk factor with salt sensitivity of BP independent of BMI, physical activity and hypertension[43]. Reduced renal function, which can be monitored with the level of BUN and Cr, has been also shown in previous observations to be associated with salt sensitivity[31].

The prevalence of salt sensitivity is increased among older individuals with a family history of hypertension[11,29], however, our results failed to show an association between higher age or positive family history of HTN and salt sensitivity. Multiple Factors such as including only normotensive participants, and relatively small sample size of the study can be considered as the reason for these inconclusive observations or differences found in our study compared to others.

The limitations of our study include relatively small sample size, the measurement method used for defining salt sensitivity, and exclusion of hypertensive individuals from the study. Even though all these factors were intentionally incorporated into the study design to enhance the practicality, feasibility and efficacy of the study, they ought to be considered as the limitations of the study.

According to our knowledge, this study is the first to investigate and report the prevalence and characteristics of salt sensitivity in our country and the EMR. The important clinical and public health implications of our study necessitate the need for more studies with larger sample size and to consider hypertensive patients too.

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COMMENTS

Background

Blood pressure (BP) can be reduced following a decrease in sodium intake in both hypertensive and normotensive individuals. There is an important clinical benefit to identify and target individuals who are more sensitive to alterations in dietary sodium intake by implementing dietary sodium reduction interventions. Normotensive individuals more likely develop hypertension and other health problems including cardiovascular, respiratory, and renal disorders independent of hypertension later in life.

Research frontiers

Increasing trend of salt intake at the population level beside the lack of evidence of salt sensitivity of BP in Iran and in the region, highlight the importance of conducting this study.

Innovations and breakthroughs

This study evaluates the prevalence of salt sensitivity in a normotensive Iranian adult population and to investigate the impact of cardiometabolic risk factors and psychological characteristics, on salt sensitivity. According to our knowledge, this study is the first to investigate and report the prevalence and characteristics of salt sensitivity in our country and the Eastern Mediterranean Region.

Applications

Salt sensitivity is a practical clinical concept in spite of all the difficulties in measurement and identifying the sensitive individuals.

Terminology

Salt sensitivity is a measure of how your BP responds to salt intake. People are either salt-sensitive or salt-resistant. Salt sensitive individuals are more likely to have high BP than those who are resistant to salt; Normotensive having or denoting a normal BP.

Peer-review

This is an interesting manuscript about the relations of salt sensitivity to cardiometabolic risk factors and psychological characteristics.

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 **Adrogué HJ**, Madias NE. Sodium and potassium in the pathogenesis of hypertension. *N Engl J Med* 2007; **356**: 1966-1978 [PMID: 17494929 DOI: 10.1056/NEJMra064486]

3 **Elliott P**, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, Marmot M. Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. Intersalt Cooperative Research Group. *BMJ* 1996; **312**: 1249-1253 [PMID: 8634612 DOI: 10.1136/bmj.312.7041.1249]

4 **Whelton PK**, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C, Winston MC, Karimbakas J. Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. *JAMA* 2002; **288**: 1882-1888 [PMID: 12377087 DOI: 10.1001/jama.288.15.1882]

5 **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]

6 **Strazzullo P**, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ* 2009; **339**: b4567 [PMID: 19934192 DOI: 10.1136/bmj.b4567]

7 **Aburto NJ**, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. Effect of lower sodium intake on health: systematic review and meta-analyses. *BMJ* 2013; **346**: f1326 [PMID: 23558163 DOI: 10.1136/bmj.f1326]

8 **Weinberger MH**. Salt sensitivity of blood pressure in humans. *Hypertension* 1996; **27**: 481-490 [PMID: 8613190 DOI: 10.1161/01.HYP.27.3.481]

9 **Obarzanek E**, Proschan MA, Vollmer WM, Moore TJ, Sacks FM, Appel LJ, Svetkey LP, Most-Windhauser MM, Cutler JA. Individual blood pressure responses to changes in salt intake: results from the DASH-Sodium trial. *Hypertension* 2003; **42**: 459-467 [PMID: 12953018 DOI: 10.1161/01.HYP.0000091267.39066.72]

10 **Barba G**, Galletti F, Cappuccio FP, Siani A, Venezia A, Versiero M, Della Valle E, Sorrentino P, Tarantino G, Farinaro E, Strazzullo P. Incidence of hypertension in individuals with different blood pressure salt-sensitivity: results of a 15-year follow-up study. *J Hypertens* 2007; **25**: 1465-1471 [PMID: 17563570 DOI: 10.1097/HJH.0b013e3281139ebd]

11 **Frisoli TM**, Schmieder RE, Grodzicki T, Messerli FH. Salt and hypertension: is salt dietary reduction worth the effort? *Am J Med* 2012; **125**: 433-439 [PMID: 22482843 DOI: 10.1016/j.amjmed.2011.10.023]

12 **Kotchen TA**, Cowley AW, Frohlich ED. Salt in health and disease--a delicate balance. *N Engl J Med* 2013; **368**: 2531-2532 [PMID: 23802533 DOI: 10.1056/NEJMc1305326]

13 **Schmidlin O**, Forman A, Leone A, Sebastian A, Morris RC. Salt sensitivity in blacks: evidence that the initial pressor effect of NaCl involves inhibition of vasodilatation by asymmetrical dimethylarginine. *Hypertension* 2011; **58**: 380-385 [PMID: 21788605 DOI: 10.1161/HYPERTENSIONAHA.111.170175]

14 **Nakagawa K**, Holla VR, Wei Y, Wang WH, Gatica A, Wei S, Mei S, Miller CM, Cha DR, Price E, Zent R, Pozzi A, Breyer MD, Guan Y, Falck JR, Waterman MR, Capdevila JH. Salt-sensitive hypertension is associated with dysfunctional Cyp4a10 gene and kidney epithelial sodium channel. *J Clin Invest* 2006; **116**: 1696-1702 [PMID: 16691295 DOI: 10.1172/JCI27546]

15 **Vollmer WM**, Sacks FM, Ard J, Appel LJ, Bray GA, Simons-Morton DG, Conlin PR, Svetkey LP, Erlinger TP, Moore TJ, Karanja N. Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. *Ann Intern Med* 2001; **135**: 1019-1028 [PMID: 11747380 DOI: 10.7326/0003-4819-135-12-200112180-00005]

16 **Chen J**, Gu D, Huang J, Rao DC, Jaquish CE, Hixson JE, Chen CS, Chen J, Lu F, Hu D, Rice T, Kelly TN, Hamm LL, Whelton PK, He J. Metabolic syndrome and salt sensitivity of blood pressure in non-diabetic people in China: a dietary intervention study. *Lancet* 2009; **373**: 829-835 [PMID: 19223069 DOI: 10.1016/S0140-6736(09)60144-6]

17 **Talaei M**, Sarrafzadegan N, Sadeghi M, Oveisgharan S, Marshall T, Thomas GN, Iranipour R. Incidence of cardiovascular diseases in an Iranian population: the Isfahan Cohort Study. *Arch Iran Med* 2013; **16**: 138-144 [PMID: 23432164]

18 **Talaei M**, Sadeghi M, Mohammadifard N, Shokouh P, Oveisgharan S, Sarrafzadegan N. Incident hypertension and its predictors: the Isfahan Cohort Study. *J Hypertens* 2014; **32**: 30-38 [PMID: 24048009 DOI: 10.1097/HJH.0b013e32836591d4]

19 **Aljefree N**, Ahmed F. Prevalence of Cardiovascular Disease and Associated Risk Factors among Adult Population in the Gulf Region: A Systematic Review. *Advances in Public Health* 2015; **23**

20 **Khosravi A**, Pourmoghaddas M, Kelishadi R, Sabet B, Ansari R, Shirani S. Trends in Blood Pressure Level, Prevalence of Hypertension and its Care in Isfahan. *Iran Red Crescent Med J* 2005; **2006**: 62-68

21 **Khosravi A**, Kelishadi R, Sarrafzadegan N, Boshtam M, Nouri F, Zarfeshani S, Esmaillzadeh A. Impact of a community-based lifestyle intervention program on blood pressure and salt intake of normotensive adult population in a developing country. *J Res Med Sci* 2012; **17**: 235-241 [PMID: 23267374]

22 **Zigmond AS**, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**: 361-370 [PMID: 6880820 DOI: 10.1111/j.1600-0447.1983.tb09716.x]

23 **Montazeri A**, Vahdaninia M, Ebrahimi M, Jarvandi S. The Hospital Anxiety and Depression Scale (HADS): translation and validation study of the Iranian version. *Health Qual Life Outcomes* 2003; **1**: 14 [PMID: 12816545 DOI: 10.1186/1477-7525-1-14]

24 WHO STEPS surveillance manual: the WHO STEPwise approach to chronic disease risk factor surveillance/Noncommunicable Diseases and Mental Health, World Health Organization. Available from: URL: http://www.who.int/iris/handle/10665/43376

25 Global Atlas on Cardiovascular Disease Prevention and Control. Mendis S, Puska P, Norrving B editors. Geneva: World Health Organization (in collaboration with the World Heart Federation and World Stroke Organization), 2011

26 **Kawasaki T**, Delea CS, Bartter FC, Smith H. The effect of high-sodium and low-sodium intakes on blood pressure and other related variables in human subjects with idiopathic hypertension. *Am J Med* 1978; **64**: 193-198 [PMID: 629267 DOI: 10.1016/0002-9343(78)90045-1]

27 **Chiolero A**, Würzner G, Burnier M. Renal determinants of the salt sensitivity of blood pressure. *Nephrol Dial Transplant* 2001; **16**: 452-458 [PMID: 11239015 DOI: 10.1093/ndt/16.3.452]

28 **GenSalt Collaborative Research Group**. GenSalt: rationale, design, methods and baseline characteristics of study participants. *J Hum Hypertens* 2007; **21**: 639-646 [PMID: 17443206 DOI: 10.1038/sj.jhh.1002207]

29 **van Paassen P**, de Zeeuw D, de Jong PE, Navis G. Renin inhibition improves pressure natriuresis in essential hypertension. *J Am Soc Nephrol* 2000; **11**: 1813-1818 [PMID: 11004211]

30 **Aviv A**, Hollenberg NK, Weder AB. Sodium glomerulopathy: tubuloglomerular feedback and renal injury in African Americans. *Kidney Int* 2004; **65**: 361-368 [PMID: 14717906 DOI: 10.1111/j.1523-1755.2004.00389.x]

31 **de Wardener HE**, He FJ, MacGregor GA. Plasma sodium and hypertension. *Kidney Int* 2004; **66**: 2454-2466 [PMID: 15569339 DOI: 10.1111/j.1523-1755.2004.66018.x]

32 **Iwamoto T**, Kita S, Zhang J, Blaustein MP, Arai Y, Yoshida S, Wakimoto K, Komuro I, Katsuragi T. Salt-sensitive hypertension is triggered by Ca2+ entry via Na+/Ca2+ exchanger type-1 in vascular smooth muscle. *Nat Med* 2004; **10**: 1193-1199 [PMID: 15475962 DOI: 10.1038/nm1118]

33 **Beeks E**, Kessels AG, Kroon AA, van der Klauw MM, de Leeuw PW. Genetic predisposition to salt-sensitivity: a systematic review. *J Hypertens* 2004; **22**: 1243-1249 [PMID: 15201536 DOI: 10.1097/01.hjh.0000125443.28861.0d]

34 **Poch E**, González D, Giner V, Bragulat E, Coca A, de La Sierra A. Molecular basis of salt sensitivity in human hypertension. Evaluation of renin-angiotensin-aldosterone system gene polymorphisms. *Hypertension* 2001; **38**: 1204-1209 [PMID: 11711524 DOI: 10.1161/hy1101.099479]

35 **Hoffmann IS**, Tavares-Mordwinkin R, Castejon AM, Alfieri AB, Cubeddu LX. Endothelial nitric oxide synthase polymorphism, nitric oxide production, salt sensitivity and cardiovascular risk factors in Hispanics. *J Hum Hypertens* 2005; **19**: 233-240 [PMID: 15565175 DOI: 10.1038/sj.jhh.1001801]

36 **Castejon AM**, Alfieri AB, Hoffmann IS, Rathinavelu A, Cubeddu LX. Alpha-adducin polymorphism, salt sensitivity, nitric oxide excretion, and cardiovascular risk factors in normotensive Hispanics. *Am J Hypertens* 2003; **16**: 1018-1024 [PMID: 14643575 DOI: 10.1016/j.amjhyper.2003.07.022]

37 **Ramu P**, Umamaheswaran G, Shewade DG, Swaminathan RP, Balachander J, Adithan C. Gly460Trp polymorphism of the ADD1 gene and essential hypertension in an Indian population: A meta-analysis on hypertension risk. *Indian J Hum Genet* 2010; **16**: 8-15 [PMID: 20838486 DOI: 10.4103/0971-6866.64938]

38 **Campese VM**, Romoff MS, Levitan D, Saglikes Y, Friedler RM, Massry SG. Abnormal relationship between sodium intake and

sympathetic nervous system activity in salt-sensitive patients with essential hypertension. *Kidney Int* 1982; **21**: 371-378 [PMID: 7069999 DOI: 10.1038/ki.1982.32]

39 **Strazzullo P**, Barba G, Cappuccio FP, Siani A, Trevisan M, Farinaro E, Pagano E, Barbato A, Iacone R, Galletti F. Altered renal sodium handling in men with abdominal adiposity: a link to hypertension. *J Hypertens* 2001; **19**: 2157-2164 [PMID: 11725158 DOI: 10.1097/00004872-200112000-00007]

40 **Schneider MP**, Klingbeil AU, Schlaich MP, Langenfeld MR, Veelken R, Schmieder RE. Impaired sodium excretion during mental stress in mild essential hypertension. *Hypertension* 2001; **37**: 923-927 [PMID: 11244019 DOI: 10.1161/01.HYP.37.3.923]

41 **Sadeghi M**, Roohafza H, Afshar H, Rajabi F, Ramzani M, Shemirani H, Sarafzadeghan N. Relationship between depression and apolipoproteins A and B: a case-control study. *Clinics* (Sao Paulo) 2011; **66**: 113-117 [PMID: 21437446 DOI: 10.1590/S1807-59322011000100020]

42 **Hall JE**. Mechanisms of abnormal renal sodium handling in obesity hypertension. *Am J Hypertens* 1997; **10**: 49S-55S [PMID: 9160781 DOI: 10.1016/S0895-7061(97)00075-7]

43 **Hoffmann IS**, Cubeddu LX. Increased blood pressure reactivity to dietary salt in patients with the metabolic syndrome. *J Hum Hypertens* 2007; **21**: 438-444 [PMID: 17273153 DOI: 10.1038/sj.jhh.1002153]

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CASE REPORT

Simultaneous ramp right heart catheterization and echocardiography in a ReliantHeart left ventricular assist device

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Abstract

Many clinicians caring for patients with continuous flow left ventricular assist devices (CF-LVAD) use ramp right heart catheterization (RHC) studies to optimize pump speed and also to troubleshoot CF-LVAD malfunction. An investigational device, the ReliantHeart Heart Assist 5 (Houston, TX), provides the added benefit of an ultrasonic flow probe on the outflow graft that directly measures flow through the CF-LVAD. We performed a simultaneous ramp RHC and echocardiogram on a patient who received the above CF-LVAD to optimize pump parameters and investigate elevated flow through the CF-LVAD as measured by the flow probe. We found that the patient's hemodynamics were optimized at their baseline pump speed, and that the measured cardiac output *via* the Fick principle was lower than that measured by the flow probe. Right heart catheterization may be useful to investigate discrepancies between flow measured by a CF-LVAD and a patient's clinical presentation, particularly in investigational devices where little clinical experience exists. More data is needed to elucidate the correlation between the flow measured by an ultrasonic probe and cardiac output as measured by RHC.

Key words: Left ventricular assist devices; Right heart catheterization; Ramp study; Flow estimation

Core tip: Commercially available left ventricular assist

devices estimate flow through the device, but a new investigational device with an ultrasonic flow probe directly measures flow. Despite a reported accuracy in the flow probe's measurement of flow, we found that this value was inaccurate in a patient whose flows were discrepant to the patient's clinical status by performing echocardiography and right heart catheterization. Care should be taken to verify technical advances in mechanical circulatory support, and both imaging and hemodynamic evaluations can help clinicians make more informed decisions.

Banerjee D, Dutt D, Duclos S, Sallam K, Wheeler M, Ha R. Simultaneous ramp right heart catheterization and echocardiography in a ReliantHeart left ventricular assist device. *World J Cardiol* 2017; 9(1): 55-59 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i1/55.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i1.55

INTRODUCTION

To optimize the function of continuous left ventricular assist devices (CF-LVAD) after implantation, we and others[1] routinely use ramp right heart catheterization (RHC) protocols. These studies may provide added data beyond ramp echocardiogram protocols[2], since a ramp RHC can simultaneously measure right and left sided filling pressures (central venous pressure and pulmonary capillary wedge pressure, respectively). While use of echocardiography has proven useful for optimization of HeartMate Ⅱ (Pleasanton, CA) CF-LVAD pump speed, this has not proven helpful for other CF-LVADs[3]. As new CF-LVADs are developed and implanted, ramp RHC studies can be particularly helpful in defining optimal pump speed, since there is little clinical experience to turn to for guidance.

An investigational CF-LVAD, the ReliantHeart Heart Assist 5 (Houston, TX), incorporates an ultrasonic flow probe around the outflow graft that directly measures flow with a high reported accuracy[4]. There is no initial calibration with echo of RHC required, nor is there calibration based on blood viscosity (hematocrit) or patient's heart rhythm.

Here we provide the initial report of a combined ramp RHC and ramp echocardiogram in a patient after ReliantHeart implantation, and provide a comparison of measured flow through the CF-LVAD to cardiac output measured by right heart catheterization.

A 50-year-old man underwent placement of a ReliantHeart LVAD as a bridge to cardiac transplantation at our hospital. In the intensive care unit his flow through the CF-LVAD as measured by the flow probe ranged between 5 and 6 L/min, with cardiac output measured *via* the Fick principle in the 7-8 L/min range, and cardiac output by thermodilution in the 7-8 L/min range as well. The flow through the CF-LVAD as measured by the flow probe increased to a range of 8-9 L/min on post-operative day 8, just prior to transfer out of the intensive care unit. Serum lactate dehydrogenase (LDH) levels were normal, and there were no signs of hemolysis in laboratory studies. The elevated measured flows with concomitant elevation in power consumption to 7-8 W raised a concern for pump malfunction, and we performed simultaneous ramp RHC and ramp echocardiography for further evaluation.

CASE REPORT

The patient was brought to the catheterization laboratory in the post-absorptive state. A Swan-Ganz catheter was placed *via* the right internal jugular vein *via* the Seldinger technique, and two pressure transducers were attached to the catheter to measure central venous pressure and pulmonary capillary wedge pressure simultaneously. We changed the speed by 400 revolutions per minute (rpm) and waited two minutes at each setting before measuring intracardiac pressures and cardiac output (CO) *via* an assumed Fick determination (CO = $VO_{2\ max}$/(oxygen concentration opf arterial blood - oxygen concentration of mixed venous blood). VO_{2max} was assumed at 125 mL O_2/BSA. At each setting, we also performed transthoracic echocardiography, measuring left ventricular end diastolic dimension, septal positioning, frequency of aortic valve opening, and the degree of mitral regurgitation.

Table 1 displays the measured changes in hemodynamic parameters with changes in RPM.

The baseline speed was 9100 RPM. We changed speed by 400 RPM increments to determine the best hemodynamics (normal biventricular filling pressures with normal cardiac output), as well as optimal aortic valve opening (aortic valve opening frequency of at least 1:3 cardiac cycles).

Biventricular filling pressures declined with an increase in pump speed, while cardiac output increased. The "v-wave" in the PCWP tracing was present at lower speeds (Figure 1A), but was reduced at 9100 RPM (Figure 1B). The flow measured through the CF-LVAD was consistently higher than the measured cardiac output by the Fick principle.

Echocardiography revealed that at 8300 RPM the aortic valve opened with every cardiac cycle, at 8700 RPM the valve opened 1:2 cardiac cycles, and the valve remained closed at 9100 RPM. At baseline RPM the left ventricular end diastolic dimension (LVIDd) was 8.0 cm and the interventricular septum (IVS) bowed mildly toward the LV. As pump speed increased, the degree of mitral regurgitation decreased, the LVIDd decreased further to 7.8 cm but the IVS shifted even more toward the LV. At lower speeds the IVS was midline, and at 8300 RPM the LVIDd was 8.3 cm. There was no evidence of aortic insufficiency or intracardiac shunting.

As a result, given acceptable hemodynamics at 8700 RPM and intermittent aortic valve opening with optimal

Table 1 Changes in hemodynamic parameters with changes in speed of the ReliantHeart continuous flow left ventricular assist devices

RPM	RAP (mmHg)	RVP	PAP	PCWP	CO (L/min)	CI (L/min per meters square)	Flow (L/min)	Power (W)
8300	11		44/20/28	15	6.3	2.2	7.3	6.4
8700	10		40/18/25	14	6.4	2.5	7.9	7.1
9100 baseline	7	30/15	33/15/21	10	6.5	2.8	8.4	7.8
9500	6		35/15/22	10	6.7	2.9	8.7	8.6

RPM: Revolutions per minute; RAP: Right atrial pressure; RVP: Right ventricular pressure; PAP: Pulmonary arterial pressure; PCWP: Pulmonary capillary wedge pressure; CO: Cardiac output; CI: Cardiac index.

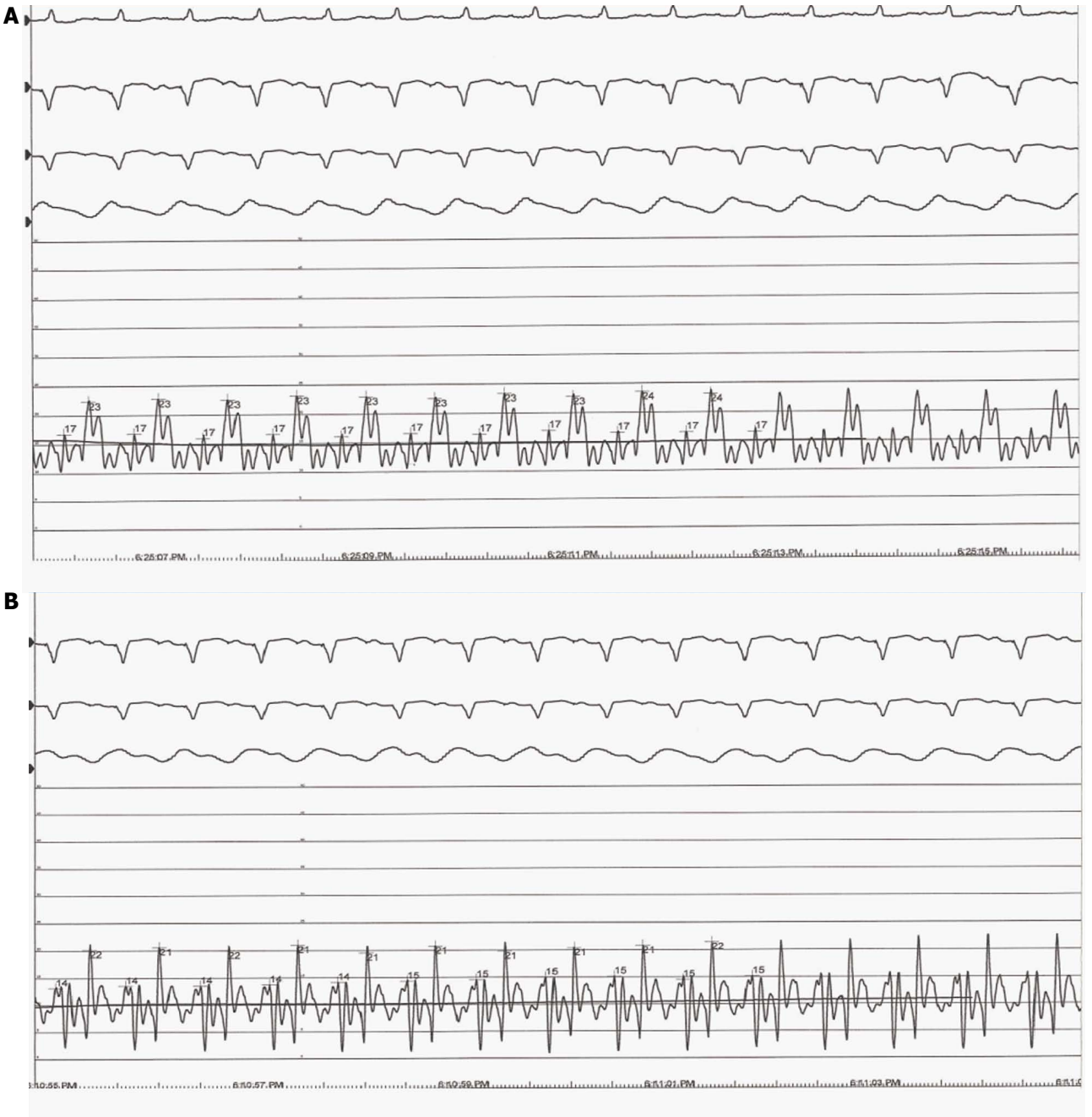

Figure 1 This figure shows the effect of increasing pump speed on the pulmonary capillary wedge pressure tracing. In 8700 RPM (A), the PCWP is measured at 14 mmHg with a pronounced "v" wave. At 9100 RPM (B), the "V-wave" disappears, and the PCWP has decreased to 10 mmHg. Flow and Power refer to flow measured by the LVAD and power consumed by the LVAD, respectively. LVAD: Left ventricular assist devices.

position of the IVS, the speed was changed to 8700 RPM at the conclusion of the study.

DISCUSSION

We here report, to our knowledge, the first combined ramp RHC and ramp echocardiogram procedure in a patient receiving the ReliantHeart investigational CF-LVAD. This study reinforces the importance of incorporating simultaneous hemodynamic and echocardiographic data into defining the optimal pump speed for a patient with a CF-LVAD.

Our group commonly performs both ramp RHC and ramp echocardiography in patients for speed optimization post CF-LVAD placement, in the post-operative setting, as well as annually, and with clinical and laboratory data concerning for possible pump thrombosis. Published results corroborate the finding of our clinical practice. Ramp RHC in particular can demonstrate inadequate unloading of the left ventricle in patients who seem well compensated by clinical examination, or those with significant right ventricular dysfunction.

Ramp RHC can also be used to troubleshoot abnormal CF-LVAD parameters that are discrepant from clinical evaluation. In other CF-LVADs, high pump flows may signify pump thrombus or septic physiology. In this case, because an ultrasonic flow probe measured high flow, we worried the patient could indeed be in high flow state concerning for sepsis, intra-cardiac shunt or aortic regurgitation. On invasive hemodynamic assessment, we found the patient was adequately unloaded by the CF-LVAD (normal filling pressures and cardiac output) at the baseline RPM. After increasing the RPM, the loss of the V-wave on the PCWP tracing, coupled with aortic valve closure by echocardiogram, argued against the presence of a high cardiac output state, as these suggest further unloading by the CF-LVAD.

Interestingly, the flows measured by the flow probe at the time of the study were higher than the total cardiac output, suggesting a degree of inaccuracy in the flow probe measurement. We would have expected the measured flow through the CF-LVAD to be lower than the total cardiac output as measured by the Fick principle, as the total cardiac output should account for both flow through the native heart and flow through the CF-LVAD. That relationship was seen earlier in the patient's hospital course, but was lost by the time the patient left the intensive care unit.

We do not have extensive data detailing the correlation between flow as measured by the ultrasonic flow probe of this investigational device and measured cardiac output *via* the Fick principle. We did note that the device's power consumption also increased after implant to 8 W, although this was within the manufacturer specifications. This is an investigational device, and expected pump parameters still need to be described. In any case, early high pump powers are not necessarily indicative of future adverse events[5], and our patient had stable serum LDH values and no other evidence of pump thrombus.

One potential explanation for the unexpectedly high flows as measured by the flow probe is pressure drift, a slow change in the sensor that can shift its calibration and lead to inaccurate readings[6]. This drift has been seen in implantable left atrial pressure sensors over time. In addition, intraoperative placement of the flow probe is important. If the graft is not contacting the flow probe, then the measured flow may not be accurate. Shift of the flow probe over time could also lead to a shift in measured flow. Clinicians should use corroborative techniques (such as RHC) to confirm abnormal changes in CF-LVAD flows before acting on that data, both for CF-LVADs that estimate flows and those that directly measure flows.

One limitation of our study was the use of an assumed Fick calculation. We felt that was mitigated somewhat by the concomitant thermodilution data in the intensive care unit, which closely correlated with the Fick cardiac output. Simultaneous measurement of Fick and thermodilution cardiac outputs in the catheterization laboratory, as well as the use of metabolic cart to calculate peak oxygen consumption would more directly address this limitation.

In summary, we report here the utility of combined ramp RHC and ramp echocardiography to optimize speed in a patient receiving an investigational CF-LVAD, and troubleshoot abnormal parameters reported by that CF-LVAD. More data is needed to elucidate the correlation between the flow measured by the ultrasonic probe and cardiac output as measured by RHC.

COMMENTS

Case characteristics

A 59-year-old man with a severe nonischemic cardiomyopathy presented with elevated left ventricular assist device flows as measured by an ultrasonic flow probe despite normal clinical status.

Clinical diagnosis

Inaccurate flow estimation by ultrasonic flow probe.

Differential diagnosis

Left ventricular assist devices (LVAD) pump thrombus, LVAD outflow graft malposition, infection.

Laboratory diagnosis

All laboratory studies were within normal limits.

Imaging diagnosis

Echocardiogram revealed normal LVAD function with appropriate decompression of the left ventricle as speed increased.

Related reports

Pressure drift has been noted in other pressure sensors, such as left atrial and pulmonary artery pressure monitors.

Term explanation

Ultrasonic.

Experience and lessons

Ultrasonic flow probes may provide inaccurate measures of flow through left ventricular assist devices, and more data is needed to elucidate the correlation

between the flow measured by the ultrasonic probe and cardiac output as measured by right heart catheterization.

Peer-review

The paper is well written.

REFERENCES

1 **Uriel N**, Sayer G, Addetia K, Fedson S, Kim GH, Rodgers D, Kruse E, Collins K, Adatya S, Sarswat N, Jorde UP, Juricek C, Ota T, Jeevanandam V, Burkhoff D, Lang RM. Hemodynamic Ramp Tests in Patients With Left Ventricular Assist Devices. *JACC Heart Fail* 2016; **4**: 208-217 [PMID: 26746378 DOI: 10.1016/j.jchf.2015.10.001]

2 **Estep JD**, Vivo RP, Krim SR, Cordero-Reyes AM, Elias B, Loebe M, Bruckner BA, Bhimaraj A, Trachtenberg BH, Ashrith G, Torre-Amione G, Nagueh SF. Echocardiographic Evaluation of Hemodynamics in Patients With Systolic Heart Failure Supported by a Continuous-Flow LVAD. *J Am Coll Cardiol* 2014; **64**: 1231-1241 [PMID: 25236515 DOI: 10.1016/j.jacc.2014.06.1188]

3 **Uriel N**, Levin AP, Sayer GT, Mody KP, Thomas SS, Adatya S, Yuzefpolskaya M, Garan AR, Breskin A, Takayama H, Colombo PC, Naka Y, Burkhoff D, Jorde UP. Left Ventricular Decompression During Speed Optimization Ramps in Patients Supported by Continuous-Flow Left Ventricular Assist Devices: Device-Specific Performance Characteristics and Impact on Diagnostic Algorithms. *J Card Fail* 2015; **21**: 785-791 [PMID: 26117282 DOI: 10.1016/j.cardfail.2015.06.010]

4 **Dean DA**, Jia CX, Cabreriza SE, D'Alessandro DA, Dickstein ML, Sardo MJ, Chalik N, Spotnitz HM. Validation study of a new transit time ultrasonic flow probe for continuous great vessel measurements. *ASAIO J* 1996; **42**: M671-M676 [PMID: 8944965]

5 **Salerno CT**, Sundareswaran KS, Schleeter TP, Moanie SL, Farrar DJ, Walsh MN. Early elevations in pump power with the HeartMate II left ventricular assist device do not predict late adverse events. *J Heart Lung Transplant* 2014; **33**: 809-815 [PMID: 24735680 DOI: 10.1016/j.healun.2014.02.024]

6 **Yu L**, Kim BJ, Meng E. Chronically implanted pressure sensors: challenges and state of the field. *Sensors* (Basel) 2014; **14**: 20620-20644 [PMID: 25365461 DOI: 10.3390/s141120620]

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CASE REPORT

Longitudinal deformation of a third generation zotarolimus eluting stent: "The concertina returns!"

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Abstract

In the current case series we describe two cases of longitudinal stent deformation in ostial lesions treated with a new generation zotarolimus eluting stent and review current literature on longitudinal stent deformation. Historically not a common occurrence, longitudinal deformation occurred mainly in Promus Element everolimus eluting stents, which had only two rather than the commonly used 3 links between stent rings. Longitudinal deformation commonly occurs secondary to compression of the proximal edge of the stent by either the guide catheters, or intravascular balloons and imaging catheters. The degree of deformation however, depends on the longitudinal strength and design of the stent.

Key words: Coronary angioplasty; Longitudinal stent deformation; Coronary stents; Procedural complications

Core tip: In the current case series we describe two cases of longitudinal stent deformation in ostial lesions treated with a new generation zotarolimus eluting stent and review current literature on longitudinal stent deformation.

Panoulas VF, Demir OM, Ruparelia N, Malik I. Longitudinal deformation of a third generation zotarolimus eluting stent: "The concertina returns!" *World J Cardiol* 2017; 9(1): 60-64 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i1/60.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i1.60

INTRODUCTION

Over the last decade there has been remarkable progress in coronary stent design and materials. Early generation stents were stainless steel followed by the use of cobalt chromium and platinum chromium alloys, enabling stents to be thinner and more flexible, hence improving deliverability and conformability. In addition, thin stent struts have been associated with improved outcomes in drug eluting stents[1-3]. With the reduction in strut thickness, innovative designs have enabled maintenance of radial strength, however, longitudinal stent strength may have been compromised.

A recently observed complication includes longitudinal stent deformation, defined as the distortion or shortening of a stent in the longitudinal axis following successful stent deployment[4]. Longitudinal stent strength is dependent on the architectural composition - number, orientation, shape, thickness and material of the crest (or ring) and links. For example, the reduction in number of links between cells may enhance deliverability (by allowing more lateral bending) but as a consequence may compromise longitudinal strength. Longitudinal deformation can result in protrusion of struts into lumen. Extensive malapposition of struts may result in disruption of blood flow and increased risk of stent thrombosis[5,6]. In addition, longitudinal deformation of drug eluting stents may result in uneven drug delivery that can result in higher rates of instent restenosis[7].

In the current case series and review we describe two cases of longitudinal deformation with the new Resolute Onyx (Medtronic Inc., United States) zotarolimus eluting stents (ZES) and review the literature on longitudinal deformation. This new generation ZES has a novel design, manufactured from a single strand of core wire (platinum iridium) shaped into a continuous sinusoidal waveform. The strut thickness is 81 μm, rendering it extremely trackable and conformable. Every 4th crown is laser fused to provide uniform longitudinal strength across the length of the stent.

CASE REPORT

Case 1

A 78-year-old male with diabetes mellitus, hypertension, hypercholesterolemia, and chronic renal failure presented with stable angina. Elective coronary angiography demonstrated significant lesions in the ostial and mid segments of a tortuous right coronary artery (RCA) (Figure 1A). The Judkins Right 4 catheter did not provide sufficient support therefore a 3 dimensional (3D) right coronary (Williams) guide catheter was used to intubate the RCA. This provided improved, yet suboptimal support, therefore a buddy wire was used to facilitate the implantation of a ZES (Resolute Onyx 2.75 mm × 38 mm, Medtronic) in the mid segment. Subsequently, the ostial-proximal lesion was pre-dilated, stented with a Resolute Onyx 3.0 mm × 22 mm ZES and post-dilated with a 3.0 mm non-compliant (NC) balloon (Figure 1B). Following stent deployment and removal of the buddy wire, significant longitudinal deformation was noted (Figure 1C), which was treated with non-compliant balloon dilatation and third ZES insertion (Resolute Onyx 3.0 mm × 18 mm) all the way to the ostium (Figure 1D).

Case 2

A 85-year-old male with end stage renal failure and severely impaired left ventricular systolic function presented with rapidly conducted atrial fibrillation and raised troponin (6000, upper normal limits 30) with inferolateral ST depression on electrocardiogram. On coronary angiography, he had severe three-vessel and left main disease. After being turned down for surgery, his proximal tight RCA lesion was stented with a Resolute Onyx 4.5 mm × 12 mm and post-dilated with a 5 mm non-compliant balloon. In view of the heavily calcified ostial/distal left main stem (LMS) and proximal left anterior descending (LAD) disease (Figure 2A) and bursting non-compliant balloons, decision was made to rotablate the lesions first with 1.5 mm burr. Subsequently a 3.0 mm non-compliant balloon was used to pre-dilate all lesions successfully. The proximal LAD was stented with a Resolute Onyx 3.0 mm × 26 mm stent. The whole length of the LMS into the proximal LAD was stented with a 3.5 mm × 34 mm Resolute Onyx covering the LMS ostium (Figure 2B and C). The LMS segment of the stent was post-dilated with a 4.5 mm NC balloon. Immediately after and despite taking care in removing the trapped LCx wire, there was longitudinal deformation of the stent, which no longer covered the LMS ostium (Figure 2D). After ballooning the deformed stent with a 4.5 mm non-compliant balloon the ostium was covered with another 4.0 mm × 8 mm stent and post-dilated with 4.5 mm NC balloon with an excellent final result (Figure 2E).

DISCUSSION

To our knowledge this case series demonstrates the first reported cases of longitudinal deformation in patients treated with the new Resolute Onyx stent platform.

Traditionally, longitudinal strength was not considered standard characteristics for stent performance. However, recent evidence has highlighted possible complications since longitudinal deformation was first reported by Hanratty *et al*[8], describing 3 cases where longitudinal compression of a previously deployed stent resulted in

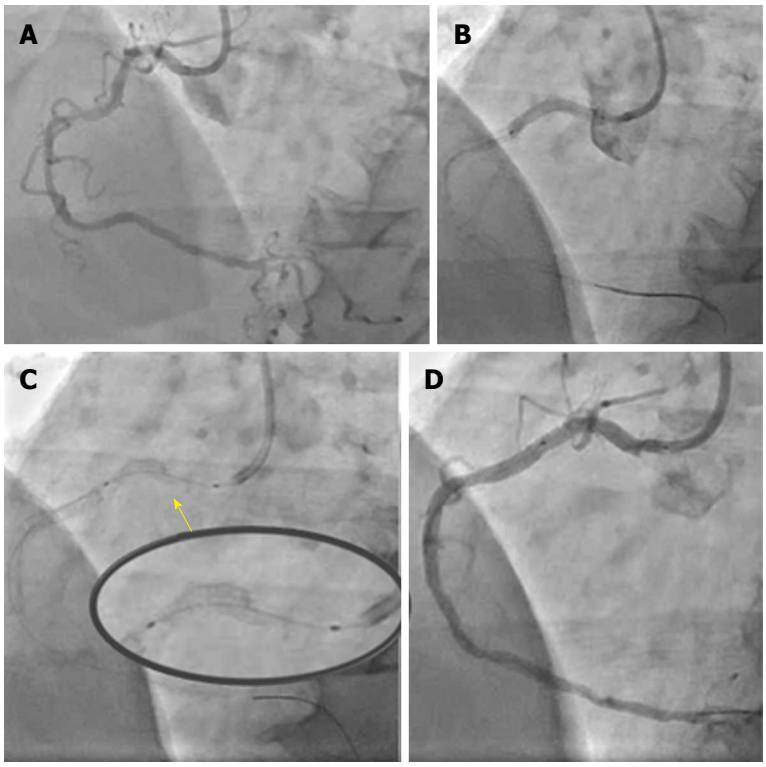

Figure 1 Longitudinal deformation of a stent implanted at the ostium of the right coronary artery. A: Initial angiogram showing severe calcific lesions in proximal and mid right coronary artery; B: Proximal lesion stented all the way to cover the ostium with a Resolute Onyx 3.0 mm × 22 mm stent; C: Longitudinal deformation of proximal stent treated with 3.0 non-compliant balloon and another 3.0 mm × 18 mm Resolute Onyx stent; D: Final angiographic result.

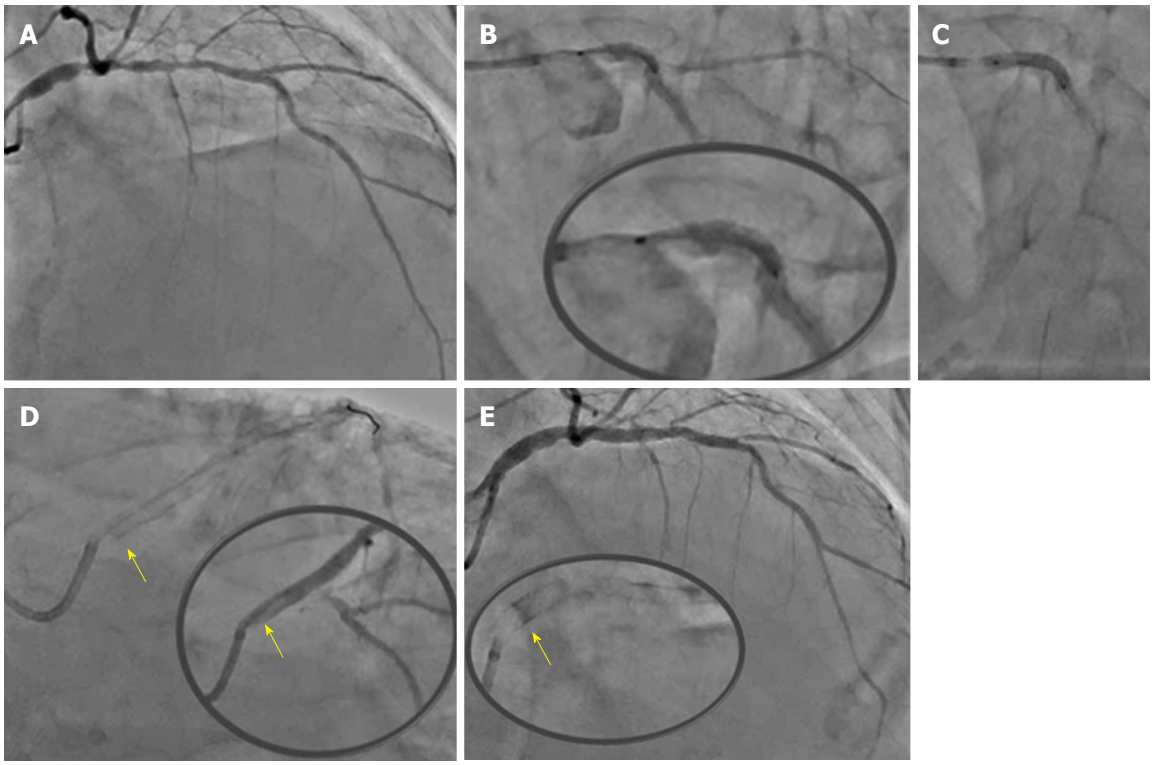

Figure 2 Longitudinal deformation of an ostial left main stem stent. A: Initial angiogram showing significant calcific ostial and distal left main lesions with further significant proximal LAD calcific disease; B: After 1.5 burr rotablation, LMS into proximal LAD was stented with a 3.5 mm × 34 mm Resolute Onyx (B) to 14atm covering the LMS ostium (C). The LMS segment of the stent was post-dilated with a 4.5 NC balloon and the jailed LCx wire removed; D: Longitudinal deformation of the ostial LMS stent (yellow arrow pointing at the proximal deformed edge of the stent); E: Final angiographic result after covering the ostial LMS with a 4.0 mm × 8 mm Resolute Onyx stent. LAD: Left anterior descending; LMS: Left main stem.

Table 1 Design characteristics of commonly used stents

Stents	Xience V	Xience PRIME/ Xience Xpedition	Promus Element	Promus Premier	SYNERGY	Resolute Onyx
Stent platform	Vision: CoCr	Multilink-9: CoCr	PtCr	PtCr	PtCr	PtIr core Co alloy outer
Strut thickness	81 μm	81 μm	81 μm	81 μm	74 μm	81 μm (up to 4.0 mm) 91 μm (4.5 and 5.0 mm)
Connectors	3 links	3 links	2 links	2 links (4 between the 3 proximal hoops)	2 links	Every 4th crown laser fused (in the 2.75, 3.0 mm platforms every 5th crown fused)
Drug eluting Polymer	Everolimus Primer layer PBMA Drug matrix layer A semicrystalline random copolymer: PvDF-HFP	Everolimus Primer layer PBMA Drug matrix layer A semicrystalline random copolymer: PvDF-HFP	Everolimus Primer layer PBMA Drug matrix layer A semicrystalline random copolymer: PvDF-HFP	Everolimus Primer layer PBMA Drug matrix layer A semicrystalline random copolymer: PvDF-HFP	Everolimus Bioabsorbable PLGA	Zotarolimus Biocompatible BioLinx polymer
Manufacturer	Abbott vascular, Santa Clara, CA, United States	Abbott vascular, Santa Clara, CA, United States	Boston Scientific, Natick, MA, United States	Boston Scientific, Natick, MA, United States	Boston Scientific, Natick, MA, United States	Medtronic CardioVascular Ltd, MN, United States

CoCr: Cobalt–chromium; PBMA: Poly(n-butyl methacrylate); PLGA: Poly(d,l-lactide-co-glycolide); PtCr: Platinum–chromium; PtIr: Platinum-iridium; PvDF-HFP: Poly(vinylidene uoride-co-hexa uoropropylene).

stent deformation. Two were identified angiographically and one with the aid of intravascular imagining. It was first documented with the Promus Element (Boston Scientific) stent which was related to guide catheter compression of stents deployed in an ostial location[8]. However, Hanratty *et al*[8] have observed this phenomenon in other drug eluting stents. A retrospective analysis of 4455 interventional cases over a four-year period showed stent deformation occurred in 0.2% of patients affecting 0.097% of stents deployed[7]. In 6 cases, Promus Element was involved, and there was 1 case each involving Endeavor (Medtronic), Biomatrix (Biosensors Interventional Technologies), and TAXUS Liberté (Boston Scientific) stents. The rate of stent deformation varied from 0% in several other stent types to 0.86% in the case of the Promus Element stent. In the same series, there was one case of late stent thrombosis attributable to longitudinal stent deformation[7]. In the DUTCH-PEERS study 906 patients were assigned to receive third generation zotarolimus-eluting stents (Resolute Integrity, Medtronic) and 905 to receive everolimus-eluting stents (Promus Element, Boston Scientific)[9]. Longitudinal stent deformation was seen only in the everolimus-eluting stent group [nine (1.0%) of 905 *vs* 0 of 906, $P = 0.002$; nine of 1591 (0.6%) everolimus-eluting stents implanted became deformed], but was not associated with any adverse events.

Despite drug eluting stents having improved remarkably the safety and efficacy of revascularization procedures, stent design is a continuously developing field that aims to balance numerous performance attributes such as stent flexibility, shortening on expansion, trackability, scaffolding, radiopacity, longitudinal strength, radial strength and recoil. An experimental evaluation of longitudinal strength of four commercially available stent design families demonstrated that a 50 g force resulted in longitudinal compression of 1.25-5.30 mm (4.46%-18.93%, compared with the nominal expanded stent length). The Promus Element stent platform had an average longitudinal compression of 13.20 mm (47.07%), demonstrating marked lower resistance to longitudinal compression (Table 1)[10]. Newer stent platforms with ultrathin struts (down to 60 μm) have shown non-inferiority to established everolimus platforms[11] but their longitudinal strength has yet to be assessed on the bench.

In our series both cases of longitudinal deformation occurred in the hands of very experienced operators implanting the scaffold at an ostial location. Potential reasons behind the deformation could include guide catheter compression of the proximal edge of the ostial stent post removal of jailed wires (case 1 or 2) or aggressive post-dilatation of the stent with a significantly larger NC balloon causing longitudinal shortening (case 2). It is unclear whether laser fusion provides less support compared to traditional links and further evidence is required prior to drawing any conclusions.

In conclusion, longitudinal stent deformation can occur even with new generation ZES and identification is important as, if left untreated, it may associate with a risk of future stent thrombosis, restenosis, and challenges in rewiring and retreating these lesions in the future.

COMMENTS

Case characteristics

The authors presented two cases, one with stable angina and one presenting with a non ST elevation myocardial infarction, requiring treatment of ostial lesions with new generation drug eluting stents.

Treatment

Both cases were treated with the third generation zotarolimus eluting stent

Resolut Onyx, and in both cases longitudinal deformation of the stents was observed. This was managed with further ballooning and stenting.

Experiences and lessons

Longitudinal stent deformation can occur even with new generation ZES and identification is important.

Peer-review

This manuscript reports two cases of longitudinal deformation of a 22-mm and 34-mm third generation zotarolimus eluting stent. The issue brought up by the authors is interesting and the cases well documented.

REFERENCES

1 **Moreno R**, Jimenez-Valero S, Sanchez-Recalde A, Galeote G, Calvo L, Martin-Reyes R, Sabate M, Plaza I, Macaya C, Lopez-Sendon JL. Periprocedural (30-day) risk of myocardial infarction after drug-eluting coronary stent implantation: a meta-analysis comparing cobalt-chromium and stainless steel drug-eluting coronary stents. *EuroIntervention* 2011; **6**: 1003-1010 [PMID: 21330250 DOI: 10.4244/EIJV6I8A173]

2 **Sen H**, Lam MK, Löwik MM, Danse PW, Jessurun GA, van Houwelingen KG, Anthonio RL, Tjon Joe Gin RM, Hautvast RW, Louwerenburg JH, de Man FH, Stoel MG, van der Heijden LC, Linssen GC, IJzerman MJ, Tandjung K, Doggen CJ, von Birgelen C. Clinical Events and Patient-Reported Chest Pain in All-Comers Treated With Resolute Integrity and Promus Element Stents: 2-Year Follow-Up of the DUTCH PEERS (DUrable Polymer-Based STent CHallenge of Promus ElemEnt Versus ReSolute Integrity) Randomized Trial (TWENTE II). *JACC Cardiovasc Interv* 2015; **8**: 889-899 [PMID: 26003019 DOI: 10.1016/j.jcin.2015.01.033]

3 **Maeng M**, Tilsted HH, Jensen LO, Krusell LR, Kaltoft A, Kelbæk H, Villadsen AB, Ravkilde J, Hansen KN, Christiansen EH, Aarøe J, Jensen JS, Kristensen SD, Bøtker HE, Thuesen L, Madsen M, Thayssen P, Sørensen HT, Lassen JF. Differential clinical outcomes after 1 year versus 5 years in a randomised comparison of zotarolimus-eluting and sirolimus-eluting coronary stents (the SORT OUT III study): a multicentre, open-label, randomised superiority trial. *Lancet* 2014; **383**: 2047-2056 [PMID: 24631162 DOI: 10.1016/S0140-6736(14)60405-0]

4 **Kwok OH**. Stent "concertina: " stent design does matter. *J Invasive Cardiol* 2013; **25**: E114-E119 [PMID: 23735364]

5 **Ormiston JA**, Webber B, Ubod B, White J, Webster MW. Stent longitudinal strength assessed using point compression: insights from a second-generation, clinically related bench test. *Circ Cardiovasc Interv* 2014; **7**: 62-69 [PMID: 24368821 DOI: 10.1161/CIRCINTERVENTIONS.113.000621]

6 **Ormiston JA**, Webber B, Webster MW. Stent longitudinal integrity bench insights into a clinical problem. *JACC Cardiovasc Interv* 2011; **4**: 1310-1317 [PMID: 22136972 DOI: 10.1016/j.jcin.2011.11.002]

7 **Williams PD**, Mamas MA, Morgan KP, El-Omar M, Clarke B, Bainbridge A, Fath-Ordoubadi F, Fraser DG. Longitudinal stent deformation: a retrospective analysis of frequency and mechanisms. *EuroIntervention* 2012; **8**: 267-274 [PMID: 22052084 DOI: 10.4244/EIJV8I2A41]

8 **Hanratty CG**, Walsh SJ. Longitudinal compression: a "new" complication with modern coronary stent platforms--time to think beyond deliverability? *EuroIntervention* 2011; **7**: 872-877 [PMID: 21970984 DOI: 10.4244/EIJV7I7A135]

9 **von Birgelen C**, Sen H, Lam MK, Danse PW, Jessurun GA, Hautvast RW, van Houwelingen GK, Schramm AR, Gin RM, Louwerenburg JW, de Man FH, Stoel MG, Löwik MM, Linssen GC, Saïd SA, Nienhuis MB, Verhorst PM, Basalus MW, Doggen CJ, Tandjung K. Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients requiring a percutaneous coronary intervention (DUTCH PEERS): a randomised, single-blind, multicentre, non-inferiority trial. *Lancet* 2014; **383**: 413-423 [PMID: 24183564 DOI: 10.1016/S0140-6736(13)62037-1]

10 **Prabhu S**, Schikorr T, Mahmoud T, Jacobs J, Potgieter A, Simonton C. Engineering assessment of the longitudinal compression behaviour of contemporary coronary stents. *EuroIntervention* 2012; **8**: 275-281 [PMID: 22057097 DOI: 10.4244/EIJV8I2A42]

11 **Pilgrim T**, Heg D, Roffi M, Tüller D, Muller O, Vuilliomenet A, Cook S, Weilenmann D, Kaiser C, Jamshidi P, Fahrni T, Moschovitis A, Noble S, Eberli FR, Wenaweser P, Jüni P, Windecker S. Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial. *Lancet* 2014; **384**: 2111-2122 [PMID: 25189359 DOI: 10.1016/S0140-6736(14)61038-2]

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CASE REPORT

Interventional treatment of the left subclavian in 2 patients with coronary steal syndrome

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Abstract

In patients with history of coronary artery disease angina pectoris is usually attributed to the progression of atherosclerotic lesions. However, in patients with previous coronary artery bypass graft operation (CABG) using internal mammary artery grafts, great vessel disease should also be considered. Herein we present two patients with history of CABG whose symptoms were suspicious for coronary ischemia. During cardiac catheterization reverse blood flow was observed from the left artery disease to the left internal mammary artery (LIMA) graft in both cases. After angioplasty and stent implantation of the left subclavian artery antegrade flow was restored in the LIMA grafts and both patients had complete resolution of symptoms.

Key words: Coronary steal syndrome; Coronary artery bypass graft; Left subclavian artery; Reverse blood flow; Cardiac catheterization

Core tip: Both coronary and peripheral artery diseases are comorbidities with increasing morbidity and mortality. In patients with history of coronary artery disease and previous coronary revascularization, angina pectoris is usually attributed to the progression of atherosclerotic lesions. However, in patients who previously underwent coronary artery bypass graft operation (CABG) using internal mammary artery grafts, subclavian artery disease should also be considered. Herein we present 2 patients who previously underwent CABG with symptoms of myocardial ischemia due to subclavian artery stenosis.

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INTRODUCTION

Coronary and peripheral artery disease (CAD and PAD) are both comorbidities which exhibit a high prevalence and increasing morbidity and mortality in the western world[1]. Especially PAD is estimated to affect over 200 million people worldwide, and around 30% of primary care individuals over 70 years old[2,3]. Patients with symptomatic PAD exhibit a life expectancy of 80% at 5 years of follow-up, whereas 20% of such patients experience non-fatal cardiovascular complications[4,5]. Interestingly, PAD patients have significantly less chance of receiving appropriate risk factor modification (*e.g.*, statin therapy) and antithrombotic treatment compared to patients with CAD[1]. In addition, the prevalence of unrecognised PAD is extremely high (68%) in patients referred for coronary angiography for suspected CAD, especially in individuals with low socioeconomic status[6].

In patients with history of CAD and previous coronary revascularization, angina pectoris is usually attributed to the progression of atherosclerotic lesions. However, in patients who previously underwent coronary artery bypass graft operation (CABG) using internal mammary artery grafts, great vessel disease, for example of the subclavian artery, should also be considered. In this regard, the coronary subclavian steal syndrome is a rare complication after CABG when the left internal mammary artery (LIMA) graft is used. This disease is characterized by retrograde flow from the LIMA graft to the distal post-stenotic part of the subclavian artery during muscle work and increased oxygen and blood demand of the arm in order to maintain adequate perfusion of the left hand. As a result, patients with such a condition may develop typical symptoms of myocardial ischemia despite patency of the grafted vessels.

CASE REPORT

Herein we present a mini series of two patients (Patient A, Patient B) with suspected progress of the known multi-vessel CAD. Both patients had history of previous CABG including a LIMA graft to the left artery disease (LAD). Baseline characteristics of our patients are provided in Table 1.

Patient A was referred to our department for an elective coronary angiography due to typical angina symptoms (CCS class Ⅲ) during exertion since 4 wk. He had a history of multi vessel disease with prior CABG 14 years ago.

The initial coronary angiography revealed a 75% ostial stenosis of the left main coronary artery. Despite the presence of significant left main stenosis, reverse blood flow was observed from the LAD to the LIMA graft. Thus, contrast opacification could be followed up to the insertion of the graft at the subclavian artery (Figure 1). Both the 2 vein grafts to the left circumflex and the right coronary artery were patent. In addition, angiography of the subclavian artery revealed high grade lesions in the subclavian and the origin of the left vertebral artery (Figure 1). Hereby, con-current retrograde flow from the LAD was observed during contrast agent injection.

Due to typical angina and significant left main disease, PCI of left main artery and stent placement (Promus Element 4.0 mm × 20 mm, Boston Scientific) was performed in patient A with a good angiographic result (Figure 2). However, retrograde flow from the LAD to the LIMA graft remained after percutaneous coronary intervention (PCI), and sparse flow was seen in the distal LAD despite successful left main PCI (orange and blue arrows in Figure 2, respectively). After 4 wk the patient was scheduled for PCI of his left subclavian artery due to suspected LIMA steal syndrome. Interestingly, at that time he reported on persistence of CCS class Ⅲ anginal symptoms. Angioplasty could be performed successfully, followed by bifurcation stent

Table 1 Baseline characteristics of our 2 patients: Typical angina symptoms indicate Canadian Cardiovascular Society

	Patient A	Patient B
Sex	Male	Male
Age (yr)	75	78
Cardiovascular risk factors	Arterial hypertension Hyperlipidemia Obesity	Arterial hypertension Hyperlipidemia Previous smoker
CAD	Known 3-vessel-disease	Known 2-vessel disease
CABG	14 yr ago LIMA graft to the LAD Venous grafts to the right coronary (RCA) and the LCX	9 yr ago LIMA graft to the LAD Venous graft to the first marginal branch
Left ventricular function	Mildly impaired	Mildly impaired
PAD history	Previous recanalization of left (2009) and right (2010) superficial femoral artery	Surgical endatherectomy of the left internal carotid artery 2013 High grade lesions in the left vertebral artery and left subclavian artery (accidental finding in a computed tomography performed one year earlier)
Initial symptoms	Typical angina symptoms (CCS III)	Presyncope and atypical angina
Baseline medication	Aspirin ß-blocker Angiotensin converting enzyme inhibitor Statin	Aspirin ß-blocker Angiotensin converting enzyme inhibitor Statin Calcium antagonist Diuretics

LIMA: Left internal mammary artery; LCX: Left circumflex artery; LAD: Left anterior descending; CAD: Coronary artery disease; CABG: Coronary artery bypass graft operation.

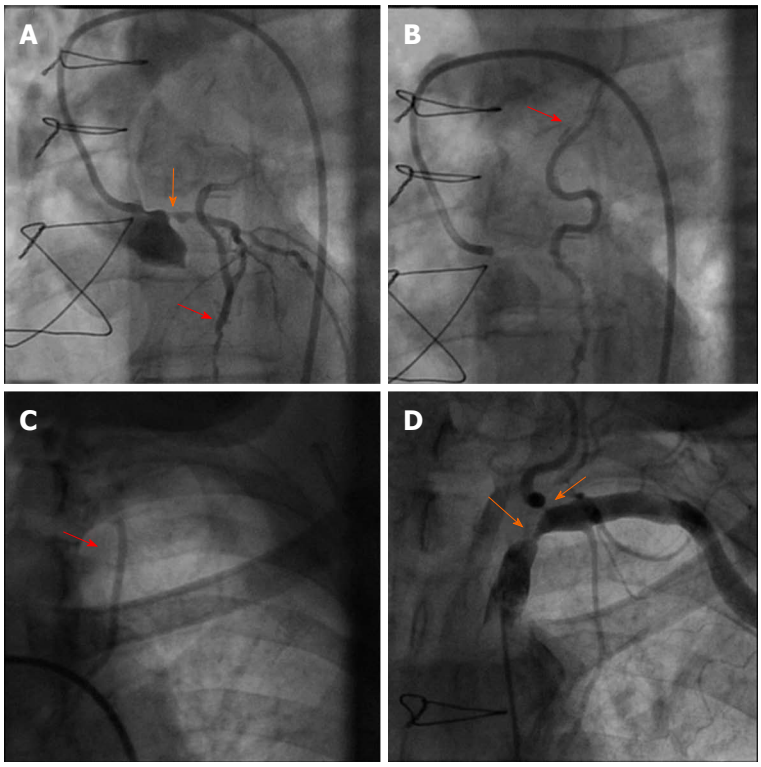

Figure 1 Reverse blood flow was observed from the left artery disease to the left internal mammary artery graft. During coronary angiography (red arrows in A and B) despite 75% stenosis of the left main coronary artery (orange arrow in A), contrast injection could be followed up to the insertion of the graft in the subclavian artery (red arrow in C). Angiography of the subclavian artery revealed high grade lesions in the subclavian and left vertebral artery (orange arrows in D).

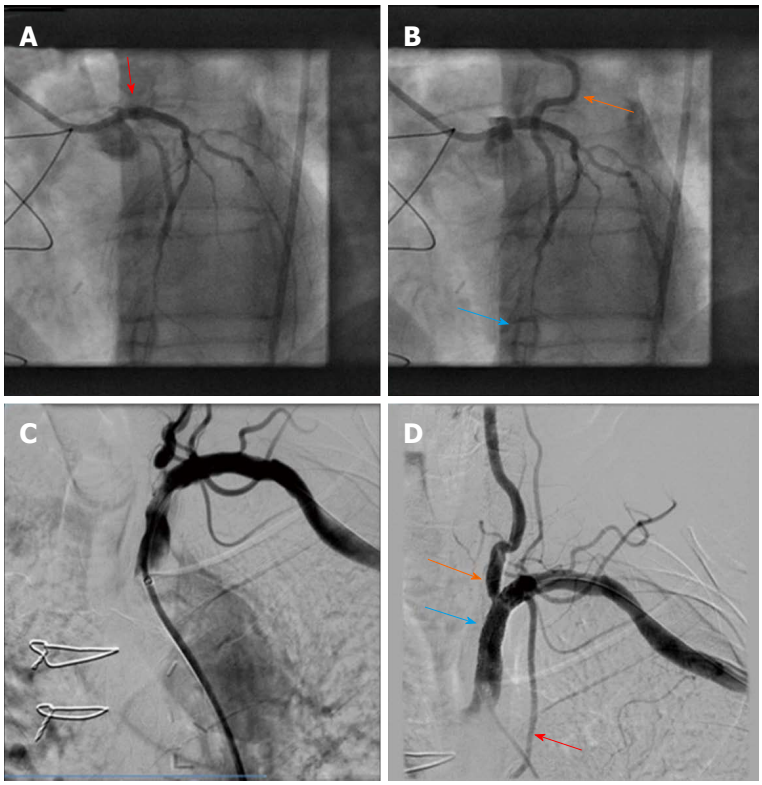

Figure 2 Percutaneous coronary intervention of left main artery and stent placement. It was performed with a good angiographic result (red arrow in A) However, retrograde flow from the left artery disease LAD to the LIMA graft remained after PCI, and sparse flow was seen in the distal LAD (orange and blue arrows in B, respectively). DSA confirmed the presence of high grades stenosis of the left subclavian and vertrebral artery (C). After angioplasty and bifurcation stent implantation a good angiographic result can be appreciated (orange and blue arrows in D) with normal opacification of the LIMA graft (red arrow in D). PCI: Percutaneous coronary intervention; LAD: Left artery disease; LIMA: Left internal mammary artery; DSA: Digital subtraction angiography.

implantation of the stenotic subclavian and vertebral arteries (balloon expandable Visi-Pro 8.0 mm × 27 mm, Covidien for the subclavian and Taxus Element 4.5 mm × 12 mm, Boston Scientific for the vertebral artery) and final kissing balloon inflation. Subsequently, a good angiographic result was observed with restored antegrade flow indicated in the LIMA graft (Figure 2).

For patient B, the initial cause for admission to our hospital was a presyncopal episode and atypical angina. Cardiac catheterization was performed due to the high risk profile of the patient, including known multi-vessel disease and CABG 9 years ago. After selection of a left radial access for coronary angiography and wire insertion into the subclavian artery, we proceeded with selective contrast injection into the LIMA graft to the LAD. Surprisingly, contrast opacification was not possible

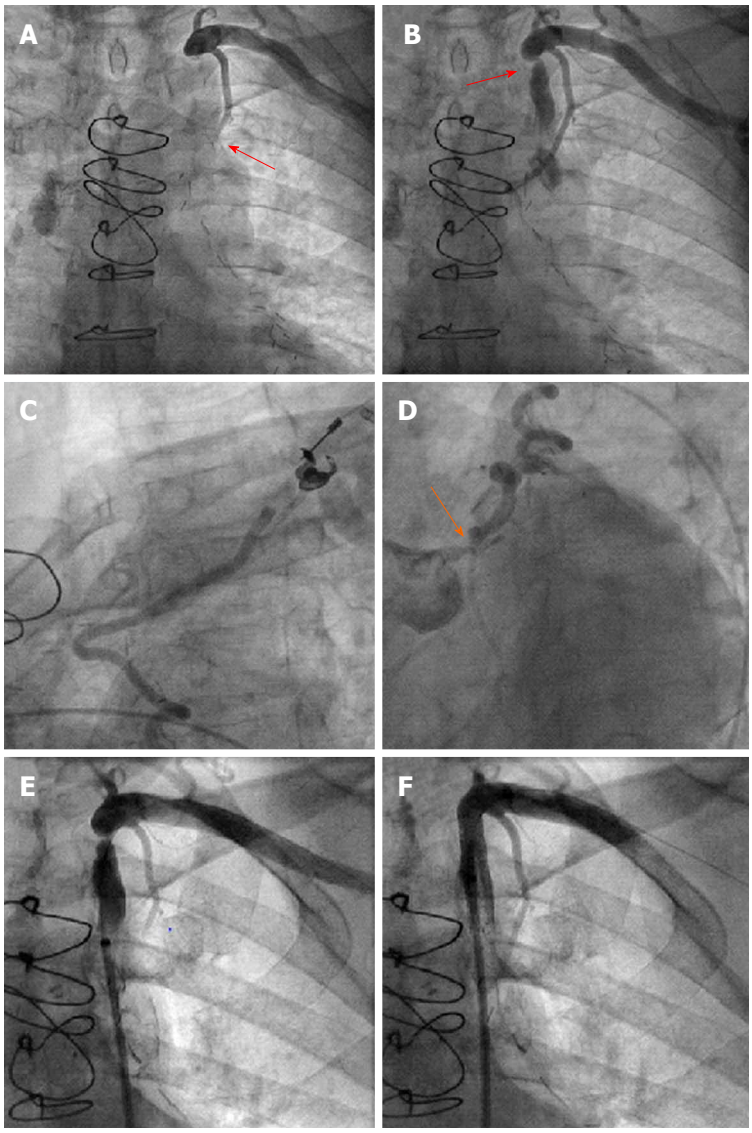

Figure 3 After selective contrast injection into the left internal mammary artery graft no contrast opafication. It was shown in the left artery disease (red arrow in A). Subsequently, a high grade stenosis of the left subclavian artery was observed (red arrow in B). During coronary angiography retrograde flow from the left artery disease up to the origin of the LIMA graft could be demonstrated (C), despite left main stenosis (orange arrow in D). After angioplasty and stent placement (E) antegrade flow could be re-established in the subclavian artery (F). LIMA: Left internal mammary artery.

despite selective contrast injection into the presumably patent vessel (Figure 3). Subsequently, angiography of the left subclavian artery was performed, confirming high grade stenosis of the left subclavian artery (Figure 3), which was already accidentally diagnosed one year earlier during a computed tomography scan. Consistently an interarm blood pressure difference of 20 mmHg (left < right) could be measured with this patient. The subclavian stenosis was located proximally to the origin of the LIMA graft, thus possibly causing a coronary steal syndrome. Coronary angiography confirmed this diagnosis demonstrating retrograde flow from the LAD up to the insertion of the LIMA graft into the subclavian artery (Figure 3) despite the presence of significant left main disease (Figure 3). On the following day, stress echocardiography was performed, demonstrating an inducible hypokinesia in the anterior LV-wall by arm exertion ("hand grip method"), compatible with inducible ischemia in the LAD territory. Subsequently, balloon angioplasty and stent placement of the left subclavian artery was performed using an Armada 6.0 mm × 20 mm balloon and an 8.0 mm × 27 mm VisiPro-Stent with good angiographic result (Figure 3). Importantly, antegrade flow could be reestablished in the subclavian artery after interventional treatment (Figure 3).

Both patients were discharged the day after the procedure. During clinical follow-up patient A showed complete resolution auf his angina symptoms, whereas repeated stress echocardiography showed no signs of inducible ischemia in patient B.

DISCUSSION

Subclavian artery stenosis is a relatively frequent disease, which is more commonly described in patients with diabetes mellitus and was shown to be predictive of poor cardiovascular outcomes[7]. Known PAD accompanied by a interarm blood pressure difference greater than 10% has been suggested as a specific, but unfortunately less sensitive indicator for a subclavian stenosis[8]. The presence of subclavian artery stenosis in patients with previous CABG, who have received a LIMA graft can lead to angina symptoms independent

of atherosclerosis progression in native coronary arteries and bypass grafts. Although several cases of subclavian artery causing a so-called LIMA steal syndrome have been reported in the literature, this syndrome is still considered as relatively uncommon in patients after myocardial revascularization. However, in light of the greater number of LIMA grafts currently used and their long life expectancy its incidence may be higher than expected. In a retrospective study including 226 patients scheduled for CABG, 6 (3%) patients had significant left subclavian artery stenosis, which was successfully treated by angioplasty and stent placement in all cases before bypass surgery[9]. In our case the presence of subclavian artery stenosis was not investigated prior to CABG in our 2 cases. However, due to the long time duration between CABG and angina symptoms of the patient (A: 14 years, B: 9 years) it is more likely that subclavian stenosis developed after CABG. Thus, pre-CABG angiography would probably not have been helpful in our cases.

In the past years, significant technical developments have occurred with endovascular therapy, which offer several distinct advantages over open surgical revascularization techniques in selected lesions[10]. Although no head-to-head trials comparing interventional *vs* surgical treatment of the proximal subclavian artery stenosis are present so far, the effectiveness of percutaneous revascularization seems to be at least equivalent to surgery and that PCI and stent placement may be associated with fewer procedure-related serious complications[11]. In our patients subclavian (in both patients) and vertrebral artery stenosis (in patient B) could be successfully treated by balloon angioplasty and stent placement. This caused restoration of the antegrade flow into the LIMA graft, resulting in resolution of anginal symptoms with patient A and restoration of the inducible wall motion abnormality by echocardiography in patient B. In patient A treatment of the subclavian artery stenosis may have been enough to restore antegrade perfusion of the LAD territory *via* the anatomically patent LIMA graft, without requiring PCI of the left main. However, PCI of the left main had already been performed in the initial session during diagnostic coronary angiography. Due to the fact that symptoms remained, we decided to perform stenting of the subclavian artery stenosis in a second session.

In patients with previous myocardial revascularization apart from CAD, great vessel disease resulting to coronary steal syndromes needs to be considered as a rare but important alternative diagnosis. In such cases, interventional treatment by angioplasty and stent placement may lead to complete resolution of symptoms and possible prevention of ischemic complications.

COMMENTS

Case characteristics

A 75- and 78-year-old male patient, both with known coronary artery disease, peripheral artery disease and prior coronary artery bypass graft who presented with symptoms of myocardial ischemia.

Clinical diagnosis

Peripheral artery disease with subclavian artery stenosis causing coronary steal syndrome.

Differential diagnosis

Progression of coronary artery disease.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

Peripheral artery disease was diagnosed in both patients by digital subtraction angiography.

Pathological diagnosis

Coronary steal syndrome due to subclavian artery disease.

Treatment

Percutaneous balloon angioplasty and stent placement in the left subclavian artery.

Related reports

Coronary steal syndrome is a pathologic entity, which has been previously reported quite rarely so far in the current literature. This disease can sometimes be confused with coronary artery disease due to typical symptoms of myocardial ischemia in such patients.

Term explanation

Coronary steal syndrome is a relatively rare condition, where subclavian artery stenosis causes myocardial ischemia due to reduced blood flow to the left internal mammary artery coronary graft after coronary artery bypass graft operation.

Experiences and lessons

In patients with previous myocardial revascularization apart from coronary artery disease, great vessel disease resulting to coronary steal syndromes needs to be considered as a rare but important alternative diagnosis.

Peer-review

The authors present 2 rare case reports of coronary subclavian steal syndrome after coronary artery bypass graft. The authors have demonstrated that interventional treatment may lead to complete resolution of symptoms and possible prevention of ischemic complications. This manuscript is nicely structured and well written.

REFERENCES

1 **Gallino A**, Aboyans V, Diehm C, Cosentino F, Stricker H, Falk E, Schouten O, Lekakis J, Amann-Vesti B, Siclari F, Poredos P, Novo S, Brodmann M, Schulte KL, Vlachopoulos C, De Caterina R, Libby P, Baumgartner I. Non-coronary atherosclerosis. *Eur Heart J* 2014; **35**: 1112-1119 [PMID: 24595865 DOI: 10.1093/eurheartj/ehu071]

2 **Fowkes FG**, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, Criqui MH. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013; **382**: 1329-1340 [PMID: 23915883 DOI: 10.1016/S0140-6736(13)61249-0]

3 **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]

4 **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: S5-67 [PMID: 17223489 DOI: 10.1016/j.jvs.2006.12.037]

5 **Rothwell PM**, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, Redgrave JN, Bull LM, Welch SJ, Cuthbertson FC, Binney LE, Gutnikov SA, Anslow P, Banning AP, Mant D, Mehta Z. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *Lancet* 2005; **366**: 1773-1783 [PMID: 16298214 DOI: 10.1016/S0140-6736(05)67702-1]

6 **Chang P**, Nead KT, Olin JW, Cooke JP, Leeper NJ. Clinical and socioeconomic factors associated with unrecognized peripheral artery disease. *Vasc Med* 2014; **19**: 289-296 [PMID: 24872403 DOI: 10.1177/1358863X14535475]

7 **Aboyans V**, Criqui MH, McDermott MM, Allison MA, Denenberg JO, Shadman R, Fronek A. The vital prognosis of subclavian stenosis. *J Am Coll Cardiol* 2007; **49**: 1540-1545 [PMID: 17418292 DOI: 10.1016/j.jacc.2006.09.055]

8 **Osborn LA**, Vernon SM, Reynolds B, Timm TC, Allen K. Screening for subclavian artery stenosis in patients who are candidates for coronary bypass surgery. *Catheter Cardiovasc Interv* 2002; **56**: 162-165 [PMID: 12112906 DOI: 10.1002/ccd.10198]

9 **Prasad A**, Prasad A, Varghese I, Roesle M, Banerjee S, Brilakis ES. Prevalence and treatment of proximal left subclavian artery stenosis in patients referred for coronary artery bypass surgery. *Int J Cardiol* 2009; **133**: 109-111 [PMID: 18158191 DOI: 10.1016/j.ijcard.2007.08.108]

10 **White CJ**, Gray WA. Endovascular therapies for peripheral arterial disease: an evidence-based review. *Circulation* 2007; **116**: 2203-2215 [PMID: 17984390 DOI: 10.1161/CIRCULATIONAHA.106.621391]

11 **Eisenhauer AC**. Subclavian and Innominate Revascularization: Surgical Therapy Versus Catheter-Based Intervention. *Curr Interv Cardiol Rep* 2000; **2**: 101-110 [PMID: 11096657]

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CASE REPORT

Optical coherence tomography to identify the cause of an arrhythmic storm: A case report

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Informed consent statement: The patient involved in this study gave her written informed consent authorizing use and disclosure of her protected health information.

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Abstract

A 56-year-old man experienced an aborted sudden death followed by an arrhythmic storm. Angiography revealed a non-severe lesion on the left circumflex artery that was treated medically but an arrhythmic storm recurred. A repeat angiogram was comparable but optical coherence tomography imaging revealed a ruptured plaque with intraluminal thrombosis. Percutaneous coronary intervention was performed and no arrhythmia recurred.

Key words: Optical coherence tomography; Arrhythmic storm; Sudden death

Core tip: A 56-year-old man presented to a community hospital after an aborted sudden death. After initial resuscitation, he presented an arrhythmic storm with multiple episodes of ventricular fibrillation refractory to intravenous amiodarone. Coronary angiogram showed a nonobstructive intermediate lesion in the mid left circumflex artery. Because of repeated ventricular fibrillation episodes, an optical coherence tomography (OCT) was performed and revealed a ruptured thin-cap fibroatheroma with an intraluminal thrombosis at the level of the intermediate lesion. This case suggests that performing OCT to detect vulnerable culprit lesion of less than severe angiographic severity when an ischemic event is likely, such as an aborted sudden death or arrhythmic storm, may be of diagnostic value and alter therapeutic decisions.

Couture EL, Bérubé S, Daneault B. Optical coherence tomography to identify the cause of an arrhythmic storm: A case report. *World J Cardiol* 2017; 9(1): 71-75 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i1/71.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i1.71

INTRODUCTION

Triggers for arrhythmic storms are found in a minority of them. Careful assessment is required as some causes are reversible such as myocardial ischemia. We report the first case of an arrhythmic storm where the trigger was revealed by optical coherence tomography.

CASE REPORT

A 56-year-old man known for smoking presented to a community hospital after an aborted sudden death. A witness immediately began cardiopulmonary resuscitation and the patient received 7 shocks from an automated external defibrillator prior to emergency arrival. Repeated electrocardiograms and a head CT-scan were normal. Five ventricular fibrillation (VF) episodes recurred and were treated with defibrillation and intravenous amiodarone. Given the refractory arrhythmia, the patient was transferred to our center to exclude myocardial ischemia.

Angiogram showed an intermediate lesion (50% stenosis) on the left circumflex artery (LCX) with a TIMI grade 3 flow (Figure 1A and B). The LCX lesion was therefore not judged as the culprit and he was admitted to the intensive care unit (ICU) with a plan to performed cardiovascular magnetic resonance after therapeutic hypothermia. Initial ICU laboratories revealed a hs-TnT of 732 ng/mL as well as normal electrolytes. A transthoracic echocardiogram demonstrated diffuse hypokinesis with a left ventricular ejection fraction of 35%. Within 24 h, 10 episodes of VF recurred and were treated with defibrillation and intravenous xylocaine. Between VF episodes, electrocardiogram transiently revealed inferior and posterior ST-elevation. Emergent angiogram was repeated and was unchanged from the day prior (Figure 1C). Optical coherence tomography (OCT) imaging study was performed in the LCX. OCT revealed a ruptured thin-cap lipid-rich plaque with intraluminal thrombosis (Figure 2). Minimal lumen area was 2.9 mm^2. Because of the unstable characteristics of the plaque and clinical presentation, percutaneous coronary intervention (PCI) with a drug-eluting stent was performed (Figure 3B). Adequate stent expansion and strut apposition was confirmed by OCT (Figure 3A and C). After PCI, no arrhythmia recurred and the patient was discharged home 8 d after admission without neurological deficits and without an implantable cardioverter-defibrillator. Ten months later, he is asymptomatic with no recurrent cardiovascular event.

DISCUSSION

Although coronary artery disease and especially acute coronary occlusion represent the most common cause of sudden cardiac arrest (SCD), diagnosis and treatment of the underlying mechanism remains a challenge[1]. In this case, because of the initial normal ECGs and the coronary angiogram showing a non-obstructive lesion, it was judged that this lesion did not cause active resting ischemia and therefore, was not the cause of the arrhythmia. Subsequent VF recurrences and transient ST-elevation in leads corresponding to the LCX prompted a repeat angiogram and the use of intravascular imaging. The unstable plaque characteristics revealed by OCT lead us to treat the lesion with PCI and the subsequent evolution proved that the arrhythmia's trigger had been effectively treated.

This case is interesting for a multitude of factors. It highlights the limitation of post-resuscitation ECG for the selection of patients who could benefit from immediate coronary angiography. When initial post-resuscitation ECGs do not demonstrate ST-segment elevation or presumably new left bundle branch block, it remains controversial to proceed to immediate coronary angiography. However, as demonstrated recently in SCD survivors, a culprit lesion (defined as > 90% coronary stenosis) was found in 19% of patients presenting with no ECG signs indicating myocardial ischemia[2]. In this case, transient ST-elevation was only documented once despite continuous ECG monitoring and 22 VF episodes.

It also suggests that immediate angiography may have a central role in the management algorithm of SCD. Among initial survivors of SCD caused by VF or pulseless VT, it has been suggested that early coronary angiography was associated with higher rate of survival to discharge and favorable neurological outcome[3]. These observations are however retrospective and need to be validated in adequate trials.

Another important aspect of this case is the normal flow found in the culprit artery. In the PAMI trials, 16% of patients had TIMI 3 flow before PCI indicating spontaneous reperfusion[4]. Therefore, plaque rupture must be seen as a dynamic event as flow could be transiently occluded by thrombus with spontaneous fibrinolysis or by transient vasospasm. In this case, we supposed the arrhythmic storm was caused by multiple transient occlusive coronary spasms triggered by the plaque rupture. This phenomenon increases the difficulty in identifying ischemic causes of SCD and culprit lesion when ECGs are normal. This case demonstrated the additive value of OCT to further stratify intermediate non-obstructive lesion when an ischemic event is likely. Intravascular ultrasound (IVUS) also have been reported to revealed culprit lesion in SCD[5]. In a study of 12 survivors of SCD and high probability of coronary artery disease who underwent cardiac catheterization, 4 of them showed non-obstructive lesion a (< 50% stenosis and TIMI 3 flow) but all had intraluminal thrombosis revealed by intravascular ultrasound. However, none of the previous reports were accompanied by a such an arrhythmic storm[5,6]. Moreover, to rule out plaque rupture in survivors of SCD with non-obstructive intermediate lesion, OCT own a potential advantage over IVUS given its higher spatial resolution. Other modality such as near infrared spectroscopy could be of value in the future[7,8].

The optimal treatment of unstable plaque with

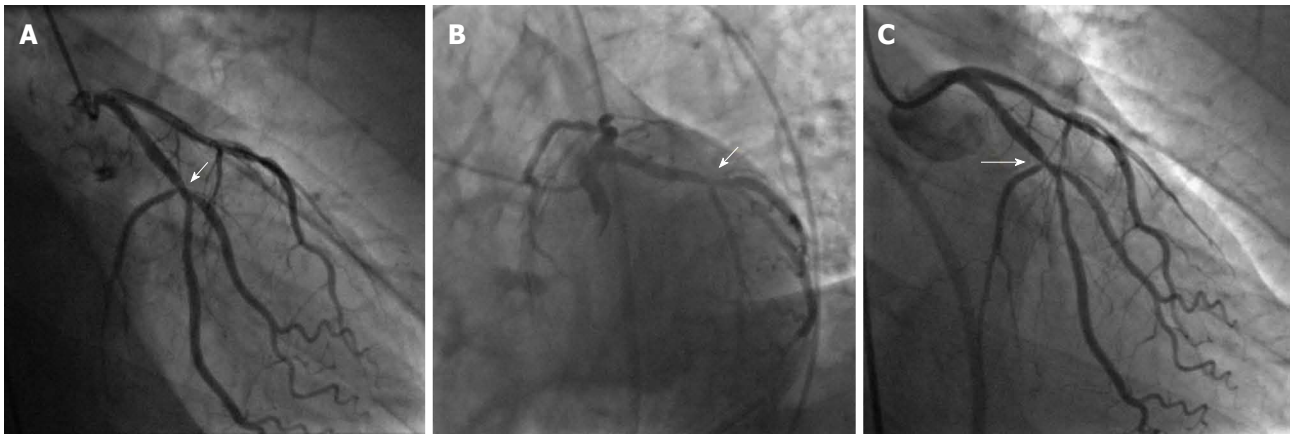

Figure 1 Angiography images at presentation. A, B: First angiogram. Arrows show a 50% lesion on the left circumflex artery with a TIMI grade 3 flow in the RAO/caudal view (A) and LAO/caudal view (B). After documentation of transmural ischemia and recurrence of the arrhythmic storm, the second angiogram revealed the same non-occlusive and intermediate lesion highlighted by the arrow in RAO/caudal view (C). RAO: Right anterior oblique; LAO: Left anterior oblique.

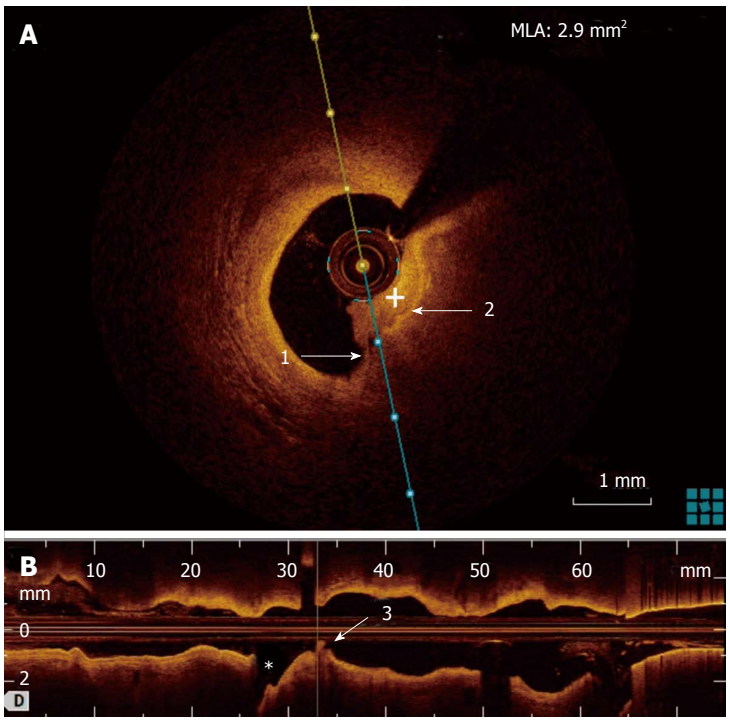

Figure 2 Optical coherence tomography performed during the repeated angiogram. A: OCT showing cross-section lumen reconstruction at the level of the plaque rupture. An intraluminal non-occlusive thrombus (+) is visualized. Arrow 1 shows rupture thin-cap fibroatheroma as visualized by the loss of continuity of the normal intima show by Arrow 2; B: OCT longitudinal lumen reconstruction at the mid left circumflex artery level. Arrow 3 highlights both plaque rupture and intraluminal thrombus be just before the bifurcation with the first marginal (asterisk). OCT: Optical coherence tomography.

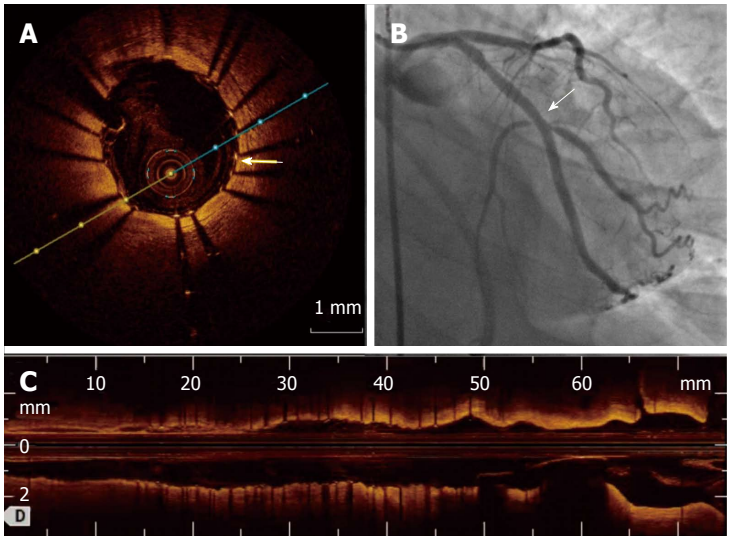

Figure 3 Angiogram and optical coherence tomography images after percutaneous coronary intervention. A, C: OCT confirming stent expansion and apposition in the cross-sectional (A) and longitudinal (C) lumen reconstruction. Arrow in A highlights good strut apposition to the vessel wall and B is final angiogram. The arrow in B highlights the level of the previous stenosis and the percutaneous coronary intervention success. OCT: Optical coherence tomography.

adequate residual lumen area is however uncertain. Prior reports suggest that medical management could be adequate in these circumstances[9]. However, in our case, PCI clearly was of additional value to medical therapy. With the evolution of drug eluting stents and especially bioresorbable vascular scaffold, these technologies may impact the treatment of vulnerable lesions in the future. Large trials will be needed to evaluate the optimal diagnostic modalities and treatments for these unstable lesions.

In conclusion, this case suggests that performing OCT to detect vulnerable culprit lesion of less than severe angiographic severity when an ischemic event is likely, such as an aborted sudden death or arrhythmic storm, may be of diagnostic value and alter therapeutic decisions.

COMMENTS

Case characteristics
A 56-year-old man known for smoking presented to a community hospital after an aborted sudden death.

Clinical diagnosis
Arrhythmic storm (ventricular fibrillation) episodes refractory to intravenous amiodarone.

Differential diagnosis
Ischemic secondary to acute coronary syndrome, electrolytes abnormalities, primary cardiomyopathy.

Laboratory diagnosis
Electrolytes were all normal at intensive care unit arrival, but hs-TnT was elevated.

Imaging diagnosis
Coronary angiogram showed a nonobstructive intermediate lesion in the mid left circumflex artery. Optical coherence tomography (OCT) revealed ruptured thin-cap fibroatheroma with an intraluminal thrombosis at the level of an angiographic intermediate lesion in the mid left circumflex artery.

Pathological diagnosis
Acute coronary syndrome with a plaque rupture.

Treatment
Percutaneous coronary intervention with a drug-eluting stent.

Related reports
Very few cases of sudden death caused by a plaque rupture only detected with intravascular imaging have been described but never with a so dramatic presentation as in this case.

Term explanation
OCT is an intravascular imaging modality that uses light to capture micrometer-resolution, three-dimensional images from within optical scattering media (*e.g.*, coronary artery). Spatial resolution is between 2-10 μm and his penetration varied between 1-10 mm.

Experiences and lessons
This case suggests that performing optical coherence tomography to detect vulnerable culprit lesion of less than severe angiographic severity when an ischemic event is likely, such as an aborted sudden death or arrhythmic storm, may be of diagnostic value and alter therapeutic decisions.

Peer-review
The paper is well written.

REFERENCES

1 **Zipes DP**, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Smith SC, Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B, Blanc JJ, Budaj A, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006; **114**: e385-e484 [PMID: 16935995 DOI: 10.1161/CIRCULATIONAHA.106.178233]

2 **Stær-Jensen H**, Nakstad ER, Fossum E, Mangschau A, Eritsland J, Drægni T, Jacobsen D, Sunde K, Andersen GØ. Post-Resuscitation ECG for Selection of Patients for Immediate Coronary Angiography in Out-of-Hospital Cardiac Arrest. *Circ Cardiovasc Interv* 2015; **8**: [PMID: 26453688 DOI: 10.1161/CIRCINTERVENTIONS.115.002784]

3 **Vyas A**, Chan PS, Cram P, Nallamothu BK, McNally B, Girotra S. Early Coronary Angiography and Survival After Out-of-Hospital Cardiac Arrest. *Circ Cardiovasc Interv* 2015; **8**: pii: e002321 [PMID: 26453686 DOI: 10.1161/CIRCINTERVENTIONS.114.002321]

4 **Stone GW**, Cox D, Garcia E, Brodie BR, Morice MC, Griffin J, Mattos L, Lansky AJ, O'Neill WW, Grines CL. Normal flow (TIMI-3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction: analysis from the primary angioplasty in myocardial infarction trials. *Circulation* 2001; **104**: 636-641 [PMID: 11489767]

5 **Quintanilla J**, Avila C, Meraz M, Jerjes-Sanchez C, de la Peña-Almaguer E, Diaz-Cid A, Sanchez L, Trevino AR, Perez LC. The role of a multimodality imaging approach in diagnosis and stratification of aborted sudden cardiac death. *Can J Cardiol* 2015; **31**: 103.e9-103.e11 [PMID: 25547563 DOI: 10.1016/j.cjca.2014.10.010]

6 **Sánchez-Recalde A**, Merino JL, Moreno R, Jiménez-Valero S, Galeote G, Calvo L, López de Sá E, López-Sendón JL. Clinical implications of intracoronary findings beyond coronary angiograms in patients with sudden death and high probability of coronary artery disease. *Rev Esp Cardiol* 2011; **64**: 819-823 [PMID: 21501916 DOI: 10.1016/j.recesp.2010.11.021]

7 **Madder RD**, Goldstein JA, Madden SP, Puri R, Wolski K, Hendricks M, Sum ST, Kini A, Sharma S, Rizik D, Brilakis ES, Shunk KA, Petersen J, Weisz G, Virmani R, Nicholls SJ, Maehara A, Mintz GS, Stone GW, Muller JE. Detection by near-infrared spectroscopy of large lipid core plaques at culprit sites in patients with acute ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv* 2013; **6**: 838-846 [PMID: 23871513 DOI: 10.1016/j.jcin.2013.04.012]

8 **Madder RD**, Husaini M, Davis AT, VanOosterhout S, Khan M, Wohns D, McNamara RF, Wolschleger K, Gribar J, Collins JS, Jacoby M, Decker JM, Hendricks M, Sum ST, Madden S, Ware JH, Muller JE. Large lipid-rich coronary plaques detected by near-infrared spectroscopy at non-stented sites in the target artery identify patients likely to experience future major adverse cardiovascular events. *Eur Heart J Cardiovasc Imaging* 2016; **17**: 393-399 [PMID: 26800770 DOI: 10.1093/ehjci/jev340]

9 **Hong MK**, Mintz GS, Lee CW, Suh IW, Hwang ES, Jeong YH, Park DW, Kim YH, Han KH, Cheong SS, Kim JJ, Park SW, Park SJ. Serial intravascular ultrasound evidence of both plaque

stabilization and lesion progression in patients with ruptured coronary plaques: effects of statin therapy on ruptured coronary plaque. *Atherosclerosis* 2007; **191**: 107-114 [PMID: 16584733 DOI: 10.1016/j.atherosclerosis.2006.02.040]

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