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EDITORIAL

Angiotensin receptor blocker drugs and inhibition of adrenal beta-arrestin-1-dependent aldosterone production: Implications for heart failure therapy

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Abstract

Aldosterone mediates many of the physiological and pathophysiological/cardio-toxic effects of angiotensin II (AngII). Its synthesis and secretion from the zona glomerulosa cells of the adrenal cortex, elevated in chronic heart failure (HF), is induced by AngII type 1 receptors (AT_1Rs). The AT_1R is a G protein-coupled receptor, mainly coupling to $G_{q/11}$ proteins. However, it can also signal through β-arrestin-1 (βarr1) or -2 (βarr2), both of which mediate G protein-independent signaling. Over the past decade, a second, $G_{q/11}$ protein-independent but βarr1-dependent signaling pathway emanating from the adrenocortical AT_1R and leading to aldosterone production has become appreciated. Thus, it became apparent that AT_1R antagonists that block both pathways equally well are warranted for fully effective aldosterone suppression in HF. This spurred the comparison of all of the currently marketed angiotensin receptor blockers (ARBs, AT_1R antagonists or sartans) at blocking activation of the two signaling modes (G protein-, and βarr1-dependent) at the AngII-activated AT_1R and hence, at suppression of aldosterone *in vitro* and *in vivo*. Although all agents are very potent inhibitors of G protein activation at the AT_1R, candesartan and valsartan were uncovered to be the most potent ARBs at blocking βarr activation by AngII and at suppressing aldosterone *in vitro* and *in vivo* in post-myocardial infarction HF animals. In contrast, irbesartan and losartan are virtually G protein-"biased" blockers at the human AT_1R, with very low efficacy for βarr inhibition and aldosterone suppression. Therefore, candesartan and valsartan (and other, structurally similar compounds) may be the most preferred ARB agents for HF pharmacotherapy, as well as for treatment of other conditions characterized by elevated aldosterone.

Key words: Adrenal cortex; Adrenocortical zona glomerulosa cell; Aldosterone; Angiotensin receptor blocker; Angiotensin II type 1 receptor; β-arrestin-1; Heart failure;

Suppression efficacy

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Core tip: The angiotensin II type 1 receptor (AT_1R) endogenously expressed in adrenocortical cells was known for decades to induce aldosterone production *via* a well-defined G_q protein-mediated signaling pathway. Over the past decade, a number of studies have elucidated another, β-arrestin-1 (βarr1)-dependent signaling cascade, which proceeds in parallel to, and independently of the G_q-mediated one, and also results in aldosterone synthesis and secretion from the adrenal cortex. Importantly, although all of the Food and Drug Administration-approved angiotensin receptor blocker (ARB) drugs (AT_1R antagonists) are very effective at blocking the G_q-mediated pathway, as expected, since they were designed to do so (*i.e.*, to block the G protein signaling of the AT_1R), they seem to display varying efficacies at blocking this new, βarr1-dependent pathway, which translates into significant variation at aldosterone suppression efficacies. In that context, candesartan and valsartan appear the most effective agents at blocking also the βarr1 pathway emanating from the adrenocortical AT_1R, and thus, these two agents may be the best aldosterone suppressors within the ARB drug class.

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INTRODUCTION

Aldosterone is a mineralocorticoid hormone with several cardio-toxic actions, whose plasma levels are extremely high in chronic heart failure (HF) negatively affecting progression of the disease[1]. Amongst its main actions on the failing myocardium is overall promotion of adverse remodeling *via* maladaptive hypertrophy, chamber dilatation, collagen deposition and fibrosis, increased inflammation and reactive oxygen species production, *etc*. The net result of all of these effects is acceleration of cardiac functional decline[2-4]. The main source of circulating aldosterone is the adrenocortical zona glomerulosa (AZG) cells, which synthesize and secrete it in response to high serum K^+ levels (hyperkalemia), since its main action on the kidneys is K^+ excretion (along with Na^+ and water reabsorption)[5]. Another powerful physiological stimulus for aldosterone secretion from AZG cells is the octapeptide hormone angiotensin II (AngII), which activates its type 1 receptors (AT_1Rs), endogenously expressed in AZG cells[5,6].

The AT_1R is a 7-transmembrane-spanning or G protein-coupled receptor (GPCR); upon agonist activation, it couples primarily to the $G_{q/11}$ family of G proteins[6]. Nowadays however, it is known to signal also through other types of G proteins, like $G_{i/o}$ and G_s, as well as through G protein-independent pathways mediated by the universal GPCR adapter proteins β-arrestin-1 (βarr1) and βarr2 (also known as arrestin-2 and -3, respectively)[7-9]. The βarrs bind agonist-activated and GPCR-kinase (GRK)-phosphorylated GPCRs to uncouple them from G proteins (receptor desensitization) and to target them to clathrin-coated vesicles for internalization (receptor endocytosis). At the same time, they initiate their own, "second wave" of signal transduction independently of G proteins[10-13].

ANGII-DEPENDENT ALDOSTERONE PRODUCTION: THE SUM OF TWO SIGNALING MODALITIES

The $G_{q/11}$ protein-dependent signaling pathway elicited by the AngII-activated AT_1R that culminates in aldosterone synthesis and secretion in AZG cells has been well characterized (Figure 1)[14]. More specifically, diacylglycerol (DAG) and inositol trisphosphate (IP_3), the two second messengers produced by this pathway, ultimately lead to: (1) aldosterone secretion, *via* elevated intracellular free Ca^{2+} concentration, which directly stimulates exocytosis and hormonal (in the context of AZG cells, aldosterone) secretion; and (2) aldosterone synthesis, *via* extracellular signal-regulated kinase (ERK) MAPK activation, which, in turn, stimulate aldosterone biosynthesis in AZG cells by transcriptionally upregulating the StAR (steroidogenic acute regulatory) protein[14]. This protein mediates the mitochondrial uptake of the precursor of all adrenal steroids cholesterol and is the rate-limiting enzyme of aldosterone biosynthesis in AZG cells[14].

In the chronic HF setting, adrenal GRK2 is upregulated and, along with βarr1, hyperphosphorylates and severely desensitizes the sympatho-inhibitory α_2-adrenergic receptors (ARs) of chromaffin cells in the adrenal medulla[15-21]. The result of this is chronic elevation of adrenal catecholamine secretion, which significantly contributes to the heightened sympathetic nervous system outflow and increased norepinephrine and epinephrine levels that further damage the failing heart[22-26]. Since aldosterone is also increased in HF and its production is stimulated by the AT_1Rs of the adrenal cortex[1], which are also GRK2 and βarr1 substrates, it was theorized that the upregulated (in HF) adrenal GRK2 could lead to excessive interaction of βarr1 also with the AT_1R in the adrenal cortex, thereby modulating aldosterone secretion in the chronic HF setting, as well. Indeed, this was found to be the case[27]. *Via* a combination of *in vitro* experiments in the human AZG cell line H295R and *in vivo* experiments in experimental rats developing HF following an acute, surgically induced myocardial infarction (MI), we were

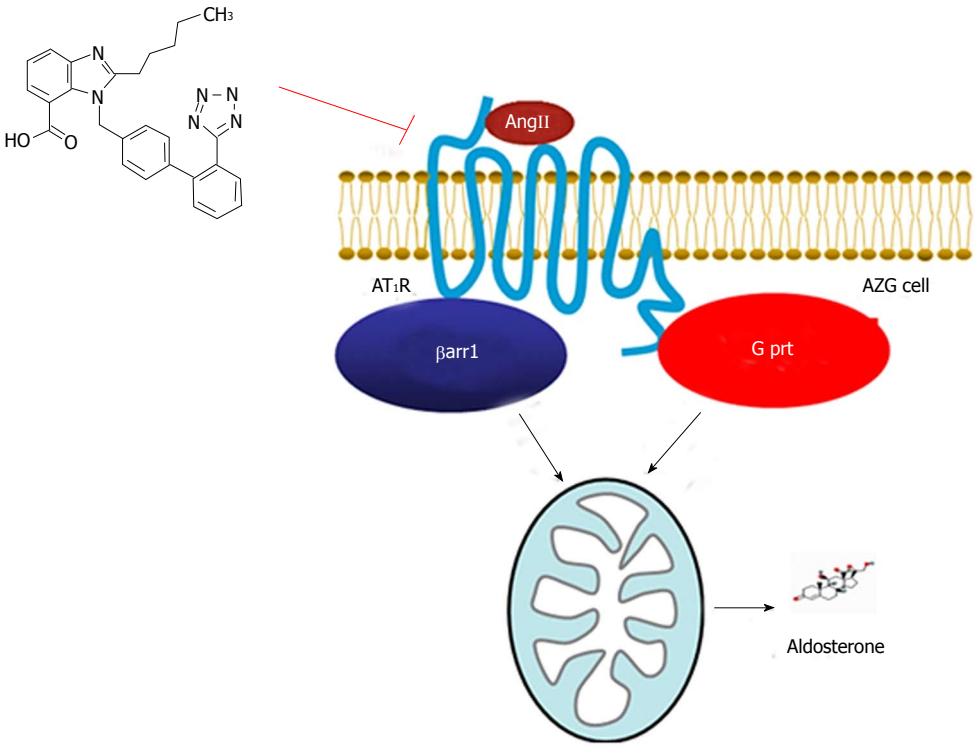

Figure 1 Angiotensin II type 1 receptor and aldosterone production. Schematic representation of the parallel G prt- and βarr1-mediated, AngII-bound AT1R signaling cascades that converge on mitochondrial aldosterone synthesis in adrenocortical zona glomerulosa (AZG) cells. The structure of the proposed AT1R antagonist (2-pentyl-1-({4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1H-1,3-benzodiazole-7-carboxylic acid)[40], discussed in the text, capable of suppressing both pathways equally well, is also shown (upper left corner). See text for details. G prt: G_q protein; βarr1: β-arrestin1; AngII: Angiotensin II; AT_1R: AngII type 1 receptor.

able to show that adrenal βarr1 actually promotes AngII-dependent aldosterone synthesis and secretion by also mediating AT_1R signaling to ERK-dependent StAR upregulation independently of G proteins (Figure 1)[27,28]. This finding was somewhat surprising, given that βarr1 would normally be expected to reduce AngII-dependent aldosterone production thanks to desensitizing the AT_1R (terminating its G protein-dependent signaling, see above). Nevertheless, it was discovered that, after abolishing the G_q-dependent signaling by the AT_1R in AZG cells, AT_1R-bound βarr1 initiated its own signaling to aldosterone synthesis by recruiting a DAG-kinase to the activated receptor[29], which converted the second messenger lipid DAG to phosphatidic acid (PA)[27]. PA can directly activate the small (monomeric) G protein Ras at the plasma membrane, which then initiates the cascade that results in ERK phosphorylation and activation[30]. Thus, AT_1R-activated βarr1 elicits a "second (delayed) wave" of signaling leading to sustained ERK activation in AZG cells in its own right (*i.e.*, independently of G proteins), which, as discussed above, promotes aldosterone production *via* StAR upregulation[27]. Importantly, since StAR regulates synthesis not only of aldosterone but of all adrenal steroids throughout the three anatomical zones of the adrenal cortex[14], adrenal βarr1 may also affect the synthesis of glucocorticoids and of androgens in the adrenal cortex.

Notably, adrenal βarr1 may not only stimulate the AT_1R-dependent aldosterone synthesis *via* its "second wave" of signaling to ERK-dependent StAR upregulation but also facilitate the acute AT_1R-dependent aldosterone secretion at the plasma membrane of AZG cells and in parallel to the G protein-mediated signaling by the receptor (Figure 1). Recent evidence in transfected heterologous systems suggests such a role in the "first wave" of GPCR signaling for the βarrs[31,32] and a very intriguing study, done specifically in the adrenal medulla, suggested an acute stimulation of catecholamine secretion and of Ca^{2+}-dependent exocytosis by AT_1R-activated βarr1 (but interestingly not by βarr2) in adrenal chromaffin cells, thanks to its direct interaction with the plasma membrane Ca^{2+} channel short transient receptor potential channel-3 (TRPC3)[33]. Thus, it is quite plausible that AT_1R-bound βarr1 can directly stimulate TRPC3-dependent Ca^{2+} currents and hence, exocytosis, also in AZG cells, thereby acutely stimulating AngII-dependent aldosterone secretion within seconds of agonist binding (and in parallel to the G_q-mediated signaling by the AT_1R). This interesting possibility of another signaling mechanism by which βarr1 can induce aldosterone production in AZG cells is definitely worthy of investigation in future studies.

Most importantly, adrenal βarr1-dependent aldosterone production has been documented to occur also *in vivo*, both under physiological (in normal, healthy animals) and pathophysiological (in the post-MI HF setting) conditions[27,28]. Specifically, adrenal-targeted

βarr1 overexpression increased aldosterone serum levels *in vivo* in normal rats[27], and caused severe hyperaldosteronism also in post-MI rats on top of the circulating aldosterone elevation normally occurring due to the MI injury[28]. Importantly, in the latter animals, adrenal-specific βarr1 blockade *in vivo* with a βarr1 C-terminal fragment during post-MI HF progression helped stall the decline of cardiac function and even reversed several aspects/markers of adverse cardiac remodeling courtesy of normalization of circulating aldosterone levels[28]. What's more, aldosterone levels remarkably show no increase in βarr1-knockout mice post-MI, which further highlights the importance of adrenal βarr1 in regulation of circulating aldosterone levels[34]. Together, these *in vivo* studies strongly suggest adrenal βarr1, in conjunction with GRK2, as an attractive therapeutic target for diseases associated with, and aggravated by hyperaldosteronism, such as post-MI HF[9,25]. Adding to its importance as a therapeutic target is also the fact that aldosterone can produce effects independently of its mineralocorticoid receptor (MR) (the so-called "non-genomic" actions of aldosterone)[4]. Obviously, these effects cannot be countered by MR antagonist drugs (*e.g.*, eplerenone, finerenone, spironolactone) and thus, suppression of aldosterone production at its source, *i.e.*, the adrenal cortex, *via* adrenal βarr1 blockade would be much more preferable from the therapeutic standpoint.

WHICH ARB DRUG WINS THE ALDOSTERONE SUPPRESSION "CONTEST"?

The realization that AngII-dependent aldosterone production from the adrenal cortex proceeds through two independent signaling modalities, *i.e.*, G_q protein- and βarr1-dependent (Figure 1), signaled that complete blockade of both of these modalities is needed to attain full suppression of adrenal aldosterone production and effectively lower circulating aldosterone levels in HF and in other diseases. This, coupled with the fact that some AT_1R antagonist drugs (angiotensin receptor blockers, ARBs, or sartans) appear ineffective at lowering aldosterone in HF, despite their full capacity to block AT_1R-G protein coupling[35-38], prompted us to test the relative efficacy of the currently available ARBs at inhibiting the βarr1-dependent aldosterone production by the AT_1R in an effort to identify the most effective agent(s). Indeed, the prototypic agent of this class, losartan, was found totally ineffective at preventing adrenal βarr1-dependent aldosterone production and combatting hyperaldosteronism post-MI due to very weak antagonism of βarr1 activation by the AT_1R[28]. Interestingly however, the active metabolite of losartan EXP1374 was found quite effective at blocking AT_1R-dependent aldosterone production and βarr1 activation[39,40].

Upon subsequent head-to-head testing of all the currently Food and Drug Administration (FDA)-approved ARB drugs, it was found that, although all ARBs (including losartan) are potent inhibitors of G protein activation by the AT_1R, their potencies at preventing βarr1 activation by the human AT_1R *in vitro* varied enormously[40]. Specifically, candesartan and valsartan appeared the most potent blockers of βarr1 activation and the most efficacious aldosterone suppressors *in vitro* and *in vivo*[39,40]. At the opposite end of the spectrum and in addition to losartan, was irbesartan, which was found to be a very weak βarr1 inhibitor and hence, a very ineffective aldosterone suppressor both *in vitro* and *in vivo*, despite its excellent G protein-blocking ability[39,40]. The rest of the class fell more or less in the middle of the βarr1 inhibition and AT_1R-dependent aldosterone suppression scales, *i.e.*, their potency values were lower than candesartan's and valsartan's but much higher than losartan's and irbesartan's[39,40]. Importantly, their effects on cardiac function of in post-MI HF animals *in vivo* were in complete concordance with their effects on circulating aldosterone levels; candesartan and valsartan induced significant improvements in cardiac function and remodeling post-MI, whereas irbesartan and losartan were not able to alter the course of progression of post-MI animals to full-blown HF[39].

IMPLICATIONS FOR HF PHARMACOTHERAPY

It is widely recognized nowadays that the members of the ARB drug class display significant variation in their pharmacological and clinical properties, which has significant repercussion for their use in HF pharmacotherapy[41]. In fact, certain agents have already been shown to afford larger improvements in morbidity and mortality of chronic HF than others[42-45]. Part of the reason for these differences among these agents that belong to the same pharmacological class and share the same mechanism of action (AT_1R antagonism) may be differences in their efficacies at combating the hyperaldosteronism that accompanies and burdens chronic HF[1]. In other words, agents that suppress aldosterone effectively are bound to work better for HF therapy and, since adrenal βarr1 plays a pivotal role in regulation of this cardio-toxic hormone's levels, the ARBs that are most effective at blocking the AT_1R-βarr1 interaction in the adrenal cortex would be expected to be preferred agents. In that vein, our aforementioned recent findings that candesartan and valsartan are the most efficacious βarr1 inhibitors at the AT_1R, coupled with their excellent efficacy at lowering aldosterone *in vitro* and *in vivo*, point to these two ARBs as being the most preferable agents of their class to use in HF treatment (and in other hyperaldosteronic conditions, *e.g.*, salt-sensitive hypertension). In contrast, irbesartan and losartan were found very weak βarr1-dependent aldosterone inhibitors, a finding that may have some bearing on the lack of therapeutic benefit of these two

agents demonstrated in HF with preserved ejection fraction (HF-PEF) and on their therapeutic inferiority to candesartan in terms of HF mortality reduction[44,45]. Of course, future trials providing data on the serum aldosterone levels of the ARB-treated HF patients are needed to confirm such a link between adrenal βarr1-dependent aldosterone suppression efficacy and clinical benefit for this important cardiovascular drug class.

On the other hand, failure of these agents to suppress aldosterone, otherwise referred to as "aldosterone breakthrough" or "aldosterone escape", is a clinically well-documented phenomenon[46-49] and the efficacy of each agent at inhibiting βarr1-dependent aldosterone production may be inversely proportional to the probability of the ARB to exhibit it. In other words, the more potent βarr1-dependent aldosterone suppressor an ARB is, the lower the likelihood is that the treated patient will suffer from "aldosterone breakthrough". Thus, candesartan and valsartan may be the safest ARB drugs to use in HF patients in terms of the risk of "aldosterone breakthrough". However, large trials closely monitoring the circulating aldosterone levels of treated patients are again needed in order to confirm this hypothesis.

IMPLICATIONS FOR AT$_1$R BLOCKER MEDICINAL CHEMISTRY

The studies on the relative potencies/efficacies of the currently FDA-approved ARBs at inhibiting AT$_1$R-βarr1 interaction and βarr1-dependent aldosterone turnover provided some interesting medicinal chemistry and pharmacological insights, as well. Specifically, as far as the ARBs that are tetrazolo-biphenyl-methyl derivatives are concerned, which is a subgroup that includes losartan (and its metabolite EXP1374), irbesartan, candesartan, valsartan, and olmesartan, it was concluded that a substitution both bulky and negatively charged attached to the one side of the methylene group of the biphenyl-methyl backbone (the other end has the tetrazolo-biphenyl group attached) is needed to confer good inhibitory potency of βarr1 at the AT$_1$R and consequently, effectively suppress aldosterone[40]. Indeed, both candesartan and valsartan, as well as EXP1374, have spacious, long aliphatic chain-containing and anionic (carboxylic acid) groups attached to that end of the biphenyl-methyl backbone[40]. In contrast, both losartan and irbesartan possess neutrally charged (unionizable) groups (albeit also bulky) at that biphenyl-methyl backbone end[40]. Finally, olmesartan, which also has an anionic (carboxylic acid) substitution but of intermediate bulkiness (*i.e.*, less long aliphatic chain) compared to candesartan and valsartan on that side of its backbone, displays intermediate potency at inhibiting βarr1 activation and suppressing aldosterone[40]. Based on these observations, we have designed the compound 2-pentyl-1-({4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1H-1,3-benzodiazole-7-carboxylic acid (Figure 1)[40], which carries a bulky, carboxyl acid group with a long aliphatic chain on the other end of the tetrazolo-biphenyl-methylene backbone, and we are currently testing both its potency at blocking βarr1 activation by the human AT$_1$R and its efficacy at suppressing aldosterone secretion *in vitro* and in the post-MI HF setting *in vivo*. Our hope is that it will prove to be even more efficacious than candesartan and valsartan at suppressing aldosterone levels and thus, an even better drug for HF treatment than all currently available ARBs. Of course, the above mentioned ARB structure-activity relationship inferences have to be confirmed by crystal structure resolutions of the AT$_1$R bound to βarrs. The first glimpse into the human AT$_1$R crystal structure was recently provided and it was the first step towards that goal[50]. Unfortunately however, that crystal structure lacked the intracellular C-terminal tail of the receptor, which is exactly the AT$_1$R region that interacts with βarrs[51].

CONCLUSION

A head-to-head comparison of the ARBs currently on the United States market identified candesartan and valsartan as the most potent βarr1 antagonists and the most efficacious aldosterone suppressors at the human AT$_1$R. Conversely, irbesartan and losartan were found to be largely G protein-"biased" inhibitors, with minimal efficacy towards inhibition of AngII-dependent aldosterone production. Thus, from a therapeutic standpoint, candesartan and valsartan may be the most preferable agents of this drug class, as they provide the biggest benefit for cardiac function and patient survival in post-MI HF and have the lowest propensity to cause the "aldosterone escape" adverse effect (failure to suppress aldosterone). Future studies on this class of drugs and on the effects of βarrs at the adrenal AT$_1$R will help solidify these inferences and will also provide additional important information regarding AngII/AT$_1$R pharmacology for clinicians and medicinal chemists alike.

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EDITORIAL

Coronary stenting: A matter of revascularization

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Abstract

In the last few decades, the recommended treatment for coronary artery disease has been dramatically improved by percutaneous coronary intervention (PCI) and the use of balloon catheters, bare metal stents (BMSs), and drug-eluting stents (DESs). Catheter balloons were burdened by acute vessel occlusion or target-lesion re-stenosis. BMSs greatly reduced those problems holding up the vessel structure, but showed high rates of in-stent re-stenosis, which is characterized by neo-intimal hyperplasia and vessel remodeling leading to a re-narrowing of the vessel diameter. This challenge was overtaken by first-generation DESs, which reduced re-stenosis rates to nearly 5%, but demonstrated delayed arterial healing and risk for late in-stent thrombosis, with inflammatory cells playing a pivotal role. Finally, new-generation DESs, characterized by innovations in design, metal composition, surface polymers, and anti-proliferative drugs, finally reduced the risk for stent thrombosis and greatly improved revascularization outcomes. New advances include bioresorbable stents potentially changing the future of revascularization techniques as the concept bases upon the degradation of the stent scaffold to inert particles after its function expired, thus theoretically eliminating risks linked with both stent thrombosis and re-stenosis. Talking about DESs also dictates to consider dual antiplatelet therapy (DAPT), which is a fundamental moment in view of the good outcome duration, but also deals with bleeding complications. The better management of patients undergoing PCI should include the use of DESs and a DAPT finely tailored in consideration of the potentially developing bleeding risk in accordance with the indications from last updated guidelines.

Key words: Drug-eluting stent; Bare metal stent; In-stent re-stenosis; Stent thrombosis; Coronary artery disease

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Core tip: Percutaneous coronary intervention (PCI) has made progress in leaps and bounds in the last 20 years. Complications occurring with catheter balloons and bare metal stents have been overwhelmed by drug-eluting

stents (DESs), especially the new-generation ones. They are characterized by innovations in design, metal composition, surface polymers, and anti-proliferative drugs, thus reducing the risk for stent thrombosis and greatly improving revascularization outcomes. DESs also need dual antiplatelet therapy (DAPT), but the latter implies bleeding complications, too. Patients undergoing PCI should be implanted with DESs and DAPT should be tailored on each patient considering the bleeding risk.

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INTRODUCTION

Since the 1990s, percutaneous coronary intervention (PCI) has brought a revolution in the field of coronary artery disease (CAD). Coronary stents have been found to efficiently halt dissection flaps and restore the round lumen in order to decrease the possibility of acute occlusion of the vessel. Bare metal stents (BMSs) have been demonstrated to limit early vessel recoil and late remodeling, justifying the lower rates of re-stenosis with respect to balloon angioplasty[1] and the favorable outcomes in terms of mortality, myocardial infarction, and stent thrombosis (ST) (Figure 1)[2]. Nonetheless, they also increased the formation of the neo-intima layer leading to re-stenosis, which was partially limited by the thinning of stent struts[3,4]. Hence, the development of drug-eluting stents (DESs) was required (Figure 1). Early DESs are characterized by a metallic structure coupled with anti-proliferative drugs, usually controlled by surface polymers demonstrating a lower risk of clinical re-stenosis compared to BMSs[2] and reduced angiographic target-vessel revascularization[5]. New-generation DESs featured durable or biodegradable polymer-coated, metallic, thin scaffold releasing anti-proliferative drugs, thus improving the post-PCI vessel injury and the healing response leading to neo-intimal hyperplasia[6]. In general, DESs naturally limiting healing processes can lead to an incomplete endothelization, which appears as a main contributor to ST resulting in acute myocardial infarction and mortality rates ranging from 20% to 40%[6].

According to the 2014 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines, revascularization by either PCI or coronary artery by-pass graft (CABG) is generally indicated in coronary stenoses leading to a reduced flow in order to limit myocardial ischemia, relieve symptoms, and improve the prognosis[7]. Several studies concluded that neither PCI nor CABG alone provided a definitive solution for the entire spectrum of stable CAD needing revascularization, which should be considered as a complementary to the medical therapy. We believe that an exhaustive discussion about PCI or CABG indications would deserve appropriate focus in systematic reviews, meta-analyses or position papers. Therefore, additional speculation appears out of the scope to the present editorial[7].

As stated by the 2014 ESC/EACTS guidelines, no indication for BMSs over new-generation DESs is stated, irrespective of patient and lesion subset[7]. Similarly, in randomized clinical trials, BMSs and DESs did not significantly differ in long-term rates of death or myocardial infarction[2,8]. DESs have been described to better prevent coronary re-stenosis[9]. New-generation DESs have been found to reduce ST rates[10-12], being safer and more efficient than early DESs[13,14]; finally, new-generation DESs were demonstrated to decrease the rates of death and myocardial infarction[10,11,15].

ST AND IN-STENT RE-STENOSIS

ST

ST is a relatively rare complication (around 1% up to 3 years) characterized by angiographic or post-mortem evidence of a thrombus in a stented segment of the coronary tree[6]. The definition includes definite, probable, and possible ST according to the presence of a thrombus and the angiographic detection of an occlusion or not[16]. Moreover, ST can be divided between early (within the first 30 d from stent implantation) and late (beyond 30 d), with the former accounting for the great majority of the cases[17]. Recognized risk factors can be attributed to patient characteristics, such as diabetes, impaired left ventricular function, and premature anti-platelet disruption; stent features (BMS *vs* DES); and procedure-related problems, such as primary PCI, stent undersizing, and residual dissection or stenosis. The most important mean to prevent ST is represented by the prescription of an appropriate duration of a post-PCI dual antiplatelet therapy (DAPT).

In-stent re-stenosis

Re-stenosis is defined as a re-narrowing of more than 50% of the vessel diameter when evaluated by angiography technique or as a re-narrowing of more than 75% of the reference vessel area in cross-section when measured by intravascular imaging techniques[6]. The pathophysiology starts with the vessel injury caused by BMS implantation, followed by neo-intimal hyperplasia, inflammation and remodeling of the coronary vessel[18]. Risk factors for in-stent re-stenosis can be considered as patient-dependent (such as diabetes and chronic renal disease), stent-dependent (such as BMS *vs* DES and early *vs* new-generation DESs), and procedure-related (such as small vessel, residual stenosis, longer stented segment, and bifurcation lesion)[6].

BMS AND DES: IS IT TIME FOR A RE-APPRAISAL?

In light of new stent design and different scaffold

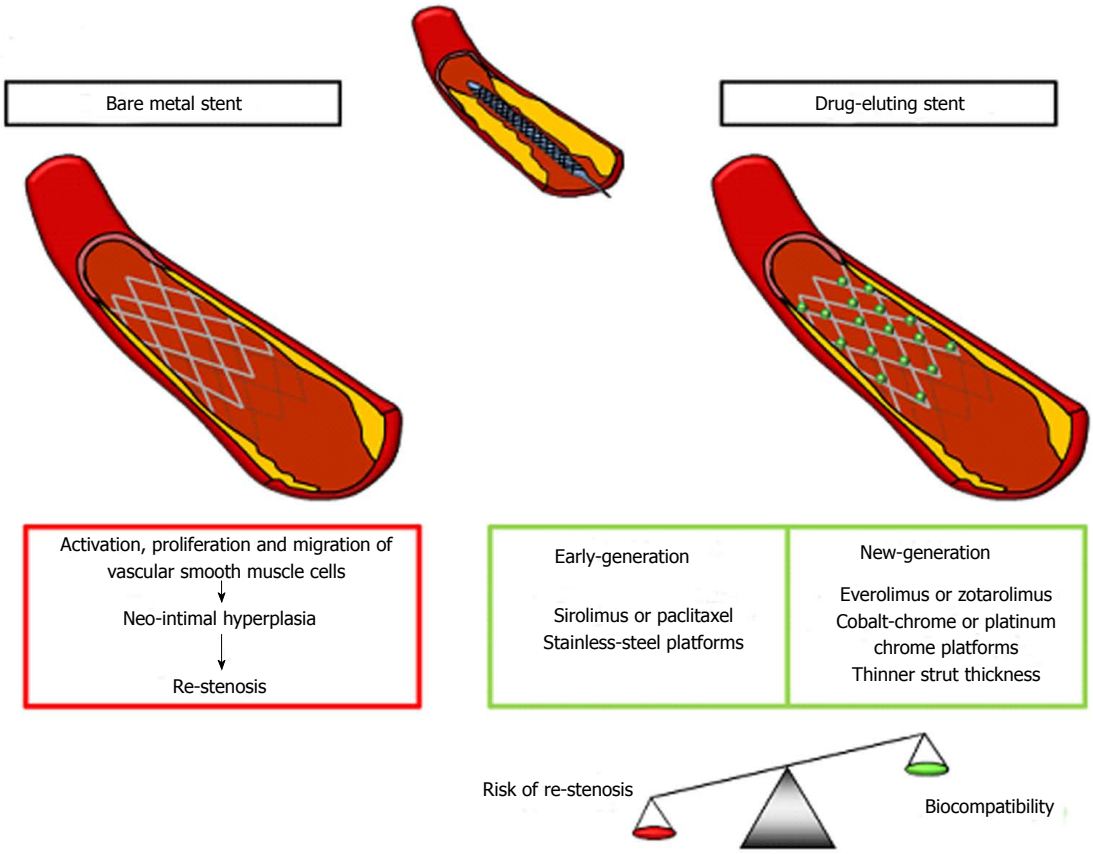

Figure 1 Bare metal stents and drug-eluting stents. Percutaneous coronary intervention for coronary artery disease has seen important evolution in last few decades. Early bare metal stents showed a high rate of in-stent re-stenosis. Drug-eluting stents tried to overcome this complication using anti-proliferative molecules; in this sense, new-generation ones, with thinner strut thickness, showed more biocompatibility and less complications with respect to previous models.

composition, Bønaa *et al*[19] have evaluated new-generation DESs and new-generation BMSs in a randomized trial conducted in eight centers in Norway, named Norwegian Coronary Stent Trial (NORSTENT). Among more than 20000 patients undergoing PCI between 2008 and 2011, 12425 met the eligibility criteria and 9013 were randomly assigned to either DESs or BMSs. After a 5-five year follow-up period, no significant differences were found between groups for either the primary outcome (composite of death from any cause and non-fatal spontaneous myocardial infarction) or the secondary ones (death; fatal and non-fatal spontaneous and peri-procedural myocardial infarction and stroke; hospitalization for unstable angina pectoris). Interestingly, even if not considered as the primary end-point, new-generation DESs have shown better performances than BMSs in terms of rates of any revascularization (16.5% *vs* 19.8%, respectively, $P < 0.001$), target-lesion revascularization (5.3% *vs* 10.3%, respectively, $P < 0.001$) both for PCI and coronary artery bypass graft surgery, and definite ST (0.8% *vs* 1.2%, $P = 0.0498$).

This trial is worth being considered not only for its results, but also because it is well-designed, correctly powered, and especially not sponsored by industry. Results are very interesting as they partly oppose to those who claimed that there is no longer a role for BMSs in PCI because of the larger superiority of DESs; these conclusions are surely derived from studies which were underpowered, only observational or from meta-analyses pooling results[15,20,21]. Moreover, results from the NORSTENT trial are important because they are not centered on death or recurrent myocardial infarction, certainly reduced also by lifestyle modifications and appropriate drugs, but rather on reduction of need for revascularization and ST. Indeed, in the latter case, the result in absolute terms is very encouraging, but between-group difference is to be considered to the extreme limit of the statistical significance ($P = 0.0498$).

As things stand at present, new-generation DESs are to be preferred in the majority of clinical situations. Recent recommendations from the American College of Cardiology/American Heart Association allow a shorter duration of DAPT to 6 mo in patients developing a high risk of bleeding[22]. If this possibility is considered, the choice of DESs with respect to BMSs becomes surely more attractive. Moreover, several trials have demonstrated that a prolonged DAPT (over 12 or 24 mo) did not add benefits in terms of major cardiovascular events, including ST, across a median 2- or 5-year follow-up period, but rather increased the frequency of bleeding complications[23,24]. These data have also been confirmed in a meta-analysis by Valgimigli *et al*[25], who did not find any significant difference in

ischemic end-points, such as cardiac death, myocardial infarction with or without stroke, and death from any or cardiovascular causes. Indeed, in spite of the poor number of ST, prolonged DAPT duration has not been shown to provide a decrease in the definite or probable ST when compared to shorter DAPT duration. Moreover, clear evidence for prolonged DAPT for 1 year or more was found for major bleeding events and the risk of stroke[25]. Recently, Helft *et al*[26] partially confirmed the same results in the OPTImal DUAL antiplatelet therapy trial showing no reduction in adverse clinical events in the prolonged DAPT group and no apparent difference in the major bleeding rate, even if the reduced trial power has to be considered in this case; interestingly, STs were rare with no between-group differences.

Anyway, it is important to underline that BMSs might be recommended in patients with a large vessel diameter, and they show low re-stenosis rates, with poor compliance to DAPT or need for non-cardiac surgery, with reimbursement problems, and with increased risk of bleeding (such as patients with recent bleeding or under concurrent anticoagulation therapy), as indicated by Morice *et al*[27]. The latter study showed how the choice of BMSs seems to be guided mainly by the concern of bleeding or poor compliance, considering only 1 mo of DAPT for BMSs compared to 6-12 mo for DESs according to European or American guidelines, and neglecting the potential, future need for revascularization, which is accordingly an ineluctable matter to be considered in terms of costs and quality of life.

In conclusion, DESs have to be considered as the first choice in patients undergoing PCI both in stable CAD and in acute coronary syndrome as they demonstrated to reach better outcomes in terms of mortality, recurrent myocardial infarction, and revascularization. The DAPT duration is still debated depending on bleeding and ischemic risks following stent implantation both changing over time. The known rule of one-year DAPT duration cannot be applied to all patients, but rather the therapy should be tailored for each patient according to the latest guidelines. For example, those treated with new-generation DES for stable coronary disease can be administered DAPT for 6 mo or 3 mo in case of bleeding risk, while for those treated for acute coronary syndrome the choice should be at least 12 mo, which can be reduced to 6 mo in case of developing a high risk bleeding.

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REVIEW

Patient selection for transcatheter aortic valve replacement: A combined clinical and multimodality imaging approach

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Abstract

Transcatheter aortic valve replacement (TAVR) has been validated as a new therapy for patients affected by severe symptomatic aortic stenosis who are not eligible for surgical intervention because of major contraindication or high operative risk. Patient selection for TAVR should be based not only on accurate assessment of aortic stenosis morphology, but also on several clinical and functional data. Multi-Imaging modalities should be preferred for assessing the anatomy and the dimensions of the aortic valve and annulus before TAVR. Ultrasounds represent the first line tool in evaluation of this patients giving detailed anatomic description of aortic valve complex and allowing estimating with enough reliability the hemodynamic entity of valvular stenosis. Angiography should be used to assess coronary involvement and plan a revascularization strategy before the implant. Multislice computed tomography play a central role as it can give anatomical details in order to choice the best fitting prosthesis, evaluate the morphology of the access path and detect other relevant comorbidities. Cardiovascular magnetic resonance and positron emission tomography are emergent modality helpful in aortic stenosis evaluation. The aim of this review is to give an overview on

TAVR clinical and technical aspects essential for adequate selection.

Key words: Aortic stenosis; Doppler echocardiography; Cardiac computed tomography; Two-dimensional strain; Three dimensional echocardiography; Cardiac magnetic resonance; Transcatheter aortic valve replacement

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Core tip: Transcatheter aortic valve replacement (TAVR) has been validated as a new therapy for patients affected by severe symptomatic aortic stenosis who are not eligible for surgical intervention because of major contraindication or high operative risk. Patient selection for TAVR should be based not only on accurate assessment of aortic stenosis morphology, but also on several clinical and functional data. Multi-Imaging modalities are preferred for assessing the anatomy and the dimensions of the aortic valve and annulus before TAVR. The aim of this review is to give an overview on TAVR clinical and technical aspects essential for adequate selection.

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INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has been validated as a new therapy for patients affected by severe symptomatic aortic stenosis who are not eligible for surgical intervention because of major contraindication or high operative risk[1,2]. Recently this option, performed in experienced centers, using next generation devices has demonstrated to be not inferior to standard surgery also in intermediate-risk patients[3].

The safety and efficacy of prosthesis implantation depends on a proper patient selection and procedural guidance, based on a multimodality imaging approach[4,5]. A precise measurements of annulus and aortic root allow to make a correct "sizing", that means to choose the best fitting prosthesis in native aortic seat, representing one of the most important predictor of a successful procedure[6,7].

CLINICAL EVALUATION

Patient selection requires a multidisciplinary team approach including interventional cardiologists, surgeons, anesthesiologists and imaging specialists in order to delineate risk profile, study the anatomy of aortic valve, aorta and peripheral vascular structures.

First line risk evaluation is usually performed using the Logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) and/or the STS Predicted Risk of Mortality Score, defining a high risk in case of logistic EuroSCORE $\geqslant$ 15%-20% or a STS score $\geqslant$ 10%. These scores present clear limitations mostly in elderly population and have not been created for TAVR procedures but for surgery so that their suitability in percutaneous valve implantation has been questioned and a risk overestimation suspected in this contest[8].

In patient with prior cardiac surgery, including degeneration of an implanted aortic bioprosthesis (valve in valve implantation), chest radiation therapy, porcelain aorta, liver cirrhosis, pulmonary hypertension and/or right ventricular dysfunction a TAVR approach should be reasonably preferred.

On the other hand, in elderly population, frailty has been associated with worst prognosis in several pathological conditions and also after TAVR and must be considered in patient evaluation. It can be definite as a syndrome of impaired physiologic reserve with decreased resistance to stressors[9] and can be quantified using a composite of four markers: Serum albumin, dominant hand grip strength, gait speed on a 15 ft (4.57 m) walk and independence in activities in daily living. These components can be summed to derive a frailty score (ranging 0 to 12) able to identify frail patients in case of score $\geqslant$ 5.

Moreover, patients with poor life expectancy (less than 1 year) or in which TAVR has not expected to significantly improve quality of life should be excluded from this selection[10].

Relative and absolute contraindications to TAVR are listed in Table 1.

One of the main advantages of TAVR *vs* SAVR is the more rapid recovery from TAVR and this benefit is different according to access site and is greater for transfemoral approach. Transapical access for TAVR is an accepted approach for patients in whom vascular anatomy do not permit a transfemoral approach and if on one hand it avoids potential site complications of iliac and femoral vessels, on the other hand has some limitations including an increase in respiratory complications[11].

ECOCARDIOGRAPHY

Role of transthoracic echocardiography

Echocardiography represents the first line tool in the setting of pre- and post-interventional evaluation and planning of Transcatheter Aortic Valve Replacement procedures (Figures 1-3).

Transthoracic echocardiography (TTE) gives detailed anatomic description of aortic valve complex and allows to estimate with enough reliability the haemodynamic entity of valvular stenosis.

An adequate TTE examination in a patient presenting with aortic valve stenosis should include information

Table 1 Contraindications for transcatheter aortic valve implantation

Absolute contraindications
Absence of heart team or surgery on the site
Estimated life expectancy < 1 yr
Improvement of quality of life by TAVI unlikely because of comorbidities
Severe primary associated disease of other valves with major contribution to the patient's symptoms, that can be treated only by surgery
Inadequate annulus size (< 18 mm, > 29 mm)
Thrombus in the left ventricle
Active endocarditis
Elevated risk of coronary ostium obstruction (asymmetric valve calcification, short distance between annulus and coronary ostium, small aortic sinuses)
Plaques with mobile thrombi in the ascending aorta, or arch
For transfemoral/subclavian approach: inadequate vascular access (vessel size, calcification, tortuosity)
Relative contraindications
Bicuspid or non-calcified valves
Untreated coronary artery disease requiring revascularization
Haemodynamic instability
LVEF < 20%
For transapical approach: severe pulmonary disease, LV apex not accessible

TAVI: Transcatheter aortic valve implantation; LVEF: Left ventricular EF.

about valve anatomy (bicuspid or tricuspid valve) and severity of impairment of cusp motion. Moreover TTE provides an accurate evaluation of alterations in left and right ventricular morphology and function induced by the increase in afterload and allows to structurally and functionally investigate the other cardiac valves[12].

Ultrasounds allow to underlie factors associated with outcome: In a longitudinal study of echo parameters in cohort A of the PARTNER trial authors showed that the TAVR and the SAVR groups had different univariate factors associated with outcome. In fact, in TAVR group, baseline low peak gradients predicted worse outcome expressing a low stroke volume status while in SAVR population the strongest determinant of mortality was mitral regurgitation[13].

Severity of aortic stenosis

An appropriate haemodynamic evaluation of aortic valve stenosis requires the assessment of functional aortic valve area (AVA) or indexed AVA by body surface area, derived using continuity equation, peak transvalvular gradient and velocity (Vmax), mean transvalvular pressure gradient (MPG) and Stroke Volume index (SVi). According to latest recommendations by American College of Cardiology/American Heart Association, aortic valve stenosis is considered severe when Vmax is above 4 m/s, mean pressure exceeds 40 mmHg and estimated or measured AVA is under 1 cm^2 (< 0.6 cm^2/m^2 if indexed for body surface area), assuming a normal left ventricular EF (LVEF)[14].

When performing continuity equation it should be remembered that diameter of left ventricular outflow tract (LVOT) diameter should be taken within 1 to 5 mm

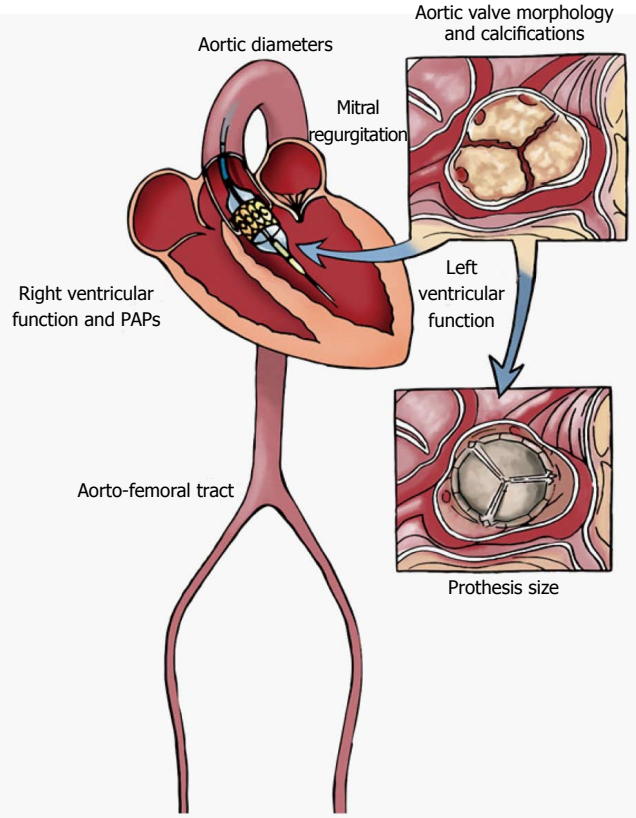

Figure 1 Main morphologic and functional parameters to assess by Multi-Imaging approach in the setting of pre-interventional evaluation and planning of Transcatheter Aortic Valve Replacement procedures (illustrator by Germano Massenzio). PAPs: Pulmonary arterial systolic pressure.

from aortic valve annulus in order to obtain maximum diameter[15]. LVOT often is elliptical so in case of measurement of the shortest dimension the continuity equation may still under-estimate the AVA and the stroke volume.

The calculation of the valvuloarterial impedance (*Z*va) should be part of a routine echocardiographicexaminationbecause this parameter provide an estimate of the global hemodynamic load[16] and can be an useful parameters in the evaluation of paradoxical aortic stenosis.

In clinical practice discordance between these parameters is often encountered so that commonly a severely restricted AVA can be found concomitantly with mean and peak pressure gradients falling into the moderate or mild category. This pattern is typically observed when systolic stroke volume and consequently transvalvular flow are reduced, thus realizing a so called low-flow low-gradient (LF-LG) aortic stenosis. In this condition visual assessment of structure, calcification and mobility of aortic valve is a crucial element as it can allow suspecting the diagnosis of severe aortic stenosis regardless of Doppler values.

Two forms of LF-LG aortic stenosis have been described[17]: (1) classical LF-LG aortic stenosis defined as an AVA < 1 cm^2 in presence of LVEF < 50% and MPG < 40 mmHg or Vmax < 4 m/s; (2) paradoxical LF-LG aortic stenosis in presence of an AVA < 1 cm^2,

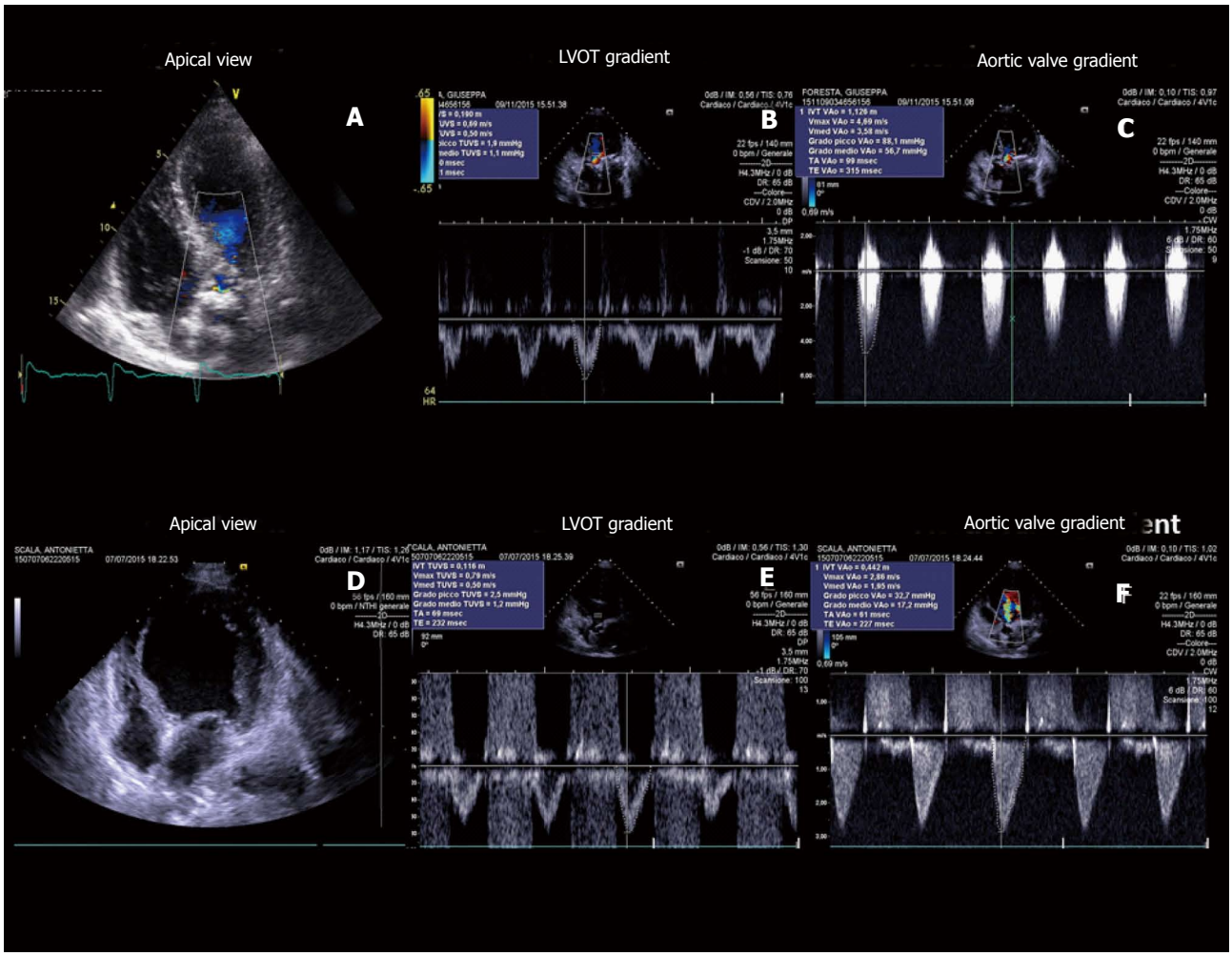

Figure 2 Transthoracic echocardiography gives detailed anatomic description of aortic valve complex and allows to estimate with enough reliability the haemodynamic entity of valvular stenosis by assessment of functional aortic valve area, derived using continuity equation. Two examples of severe aortic stenosis with normal ejection fraction and gradients (A-C), and with classical "low flow-low gradient" pattern (D-F). LVOT: Left ventricular outflow tract.

LVEF > 50%, a reduced left ventricular stroke volume (< 35 mL/m^2), MPG < 40 mmHg or Vmax < 4 m/s. In this case stroke volume is low usually because of a markedly hypertrophied left ventricle with a small cavity that is unable to be filled appropriately and subsequently eject a normal stroke volume, in case of reduced volume load due to diuretic therapy[18,19] or in presence of a high valvulo-arterial impedance (ZVa > 5.5 mmHg/mL/mq)[20]. These patients seem to have a dismal prognosis, which can be improved by aortic valve replacement or TAVI, as demonstrated in a PARTNER study sub-group analysis[21].

On the other hand, a severely reduced functional AVA associated with low transvalvular gradient may be consequent to a reduced transvalvularflowdue to left ventricular dysfunction that cannot allow cusps opening, defined as "pseudo-severe" aortic stenosis. It is important to distinguish these two conditions since in this last case aortic valve intervention may not improve prognosis. In patients with reduced EF low-dose dobutamine stress echocardiography (⩽ 20 μg/kg per minute) can be used to discriminate LF-LG severe aortic stenosis from pseudosevere aortic stenosis as,in the case of a severely stenotic valve, estimated AVA remains < 1 cm^2 and contemporarily transvalvular gradient increase[14,10], but this variation can only be achieved in presence of a significant flow reserve (stroke volume increase > 20%).

In patients with asymptomatic severe aortic stenosis echo stress can be used, with caution and in expert centre, for unmask exercise-limiting symptoms, a drop in systolic blood pressure by > 20 mmHg, exercise increase in mean gradient ⩾ 18 to 20 mmHg, the absence of contractile reserve (no or < 5% exercise increase in LVEF) or the presence of exercise pulmonary hypertension (> 60 mmHg) that are all strong predictors of cardiac events[22-25].

When performing TTE evaluation of a stenotic aortic valve multiple windows should be investigated, including apical three or five chambers views and right parasternal approach, in order to obtain the best alignment of Doppler beam to transvalvular flow, thus avoiding inconsistency between estimated functional AVA and pressure gradient[26-28]. Recently in a study including 100 patients it has been shown that right parasternal window is more accurate than apical approach; in fact, when

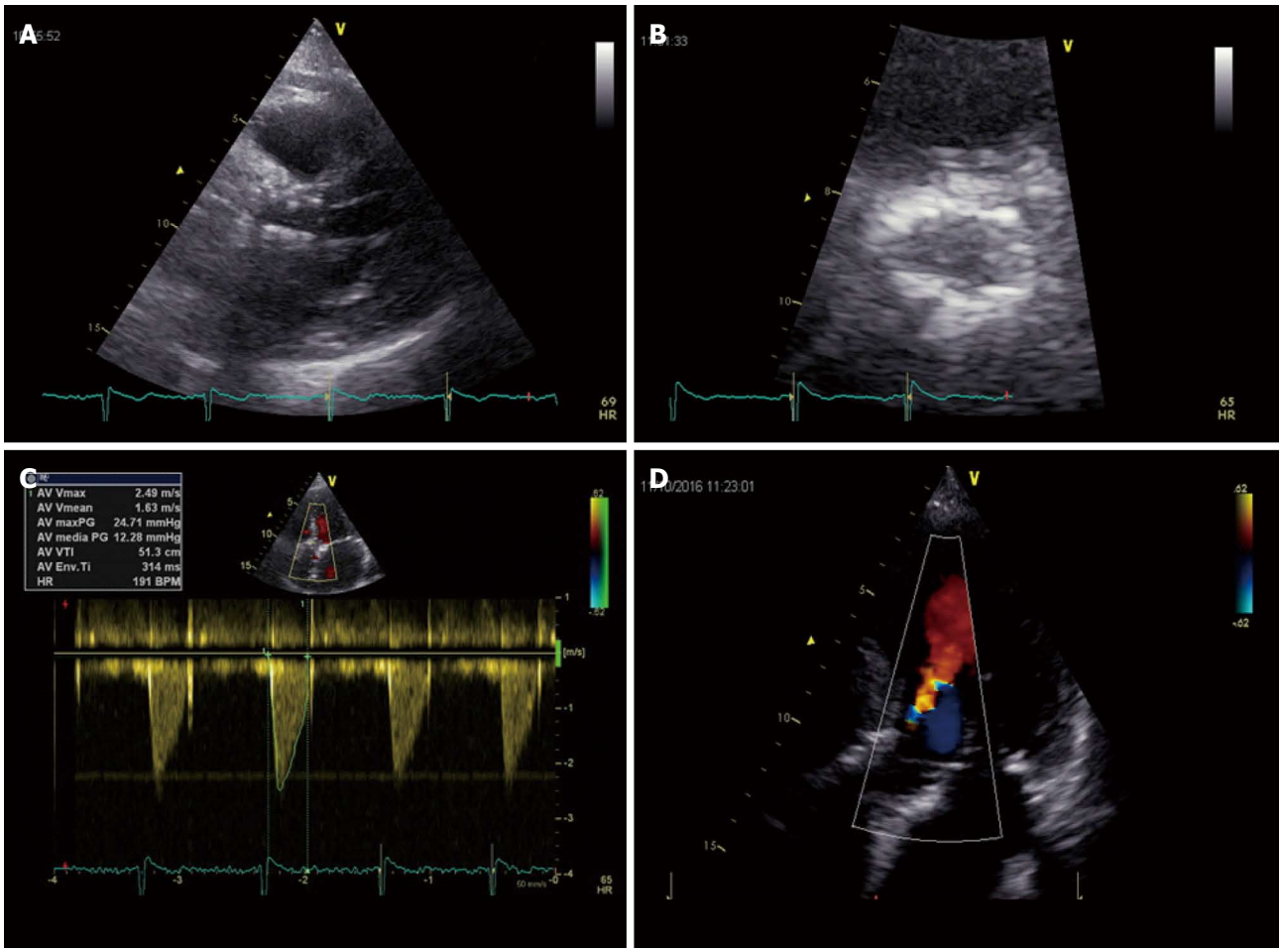

Figure 3 Post-implantation echocardiographic transcatheter aortic valve replacement assessment in long-axis (A) and short-axis (B) parasternal views; Normal trans-prothesis flow gradient by Doppler analysis (C); Mild paravalvular aortic regurgitation in this apical 5-chamber view of the same patient (D).

only apical approach is used a quarter of patients was incorrectly classified, underestimating severity in two thirds of patients deemed as moderate and misjudging a third as paradoxical LF-LG[29].

Systemic blood pressure and calibre of ascending aorta can influence severity estimation, increased left ventricular global afterload due to hypertension may cause a reduction in transvalvular flow, thus leading to stenosis underestimation[30].

Whereas if ascending aorta diameter is smaller than 30 mm, transvalvular pressure gradient may be overestimated because of a pressure recovery phenomenon distally to the aortic valve[31].

Aortic valve morphology

Conventional 2D-TTE allows in majority of patients to determine the number and disposition of aortic valve cusps. Bicuspid aortic valve with its asymmetrical closure line tends to develop degenerative alterations earlier than normal tricuspid valves and has a markedly elliptical annulus with eccentrically disposed calcium deposition[32].

In presence of a bicuspid aortic valve percutaneous implanted prosthesis may fail to expand completely with consequent periprosthetic regurgitation (up to 28% of cases) and the risk of valve misplacement[33,34]. Dilation of ascending aorta, which can be a contro-indication to TAVI, is also common in bicuspid aortic valve disease, moreover TAVR could increase the risk of aortic dissection in these subjects[35] Because of these technical conundrums PARTNER trial did not include subjects with bicuspid aortic valvular stenosis[1]. Anyway TAVR is still possible in these patients and several cases have been reported up today[36]. Phan *et al*[37] have published a meta-analysis and systematic review of literature collecting 149 patients undergone TAVR procedure there was no significant difference for patients with bicuspid aortic valves in 30-d mortality, post-procedural prosthetic haemodynamics and presence of moderate to severe perivalvular aortic regurgitation or rate of bleeding or vascular complications, indicating that TAVR can be an effective treatment also in this setting. No difference in 30-d and one year mortality between bicuspid and tricuspid stenotic valves undergoing TAVR was also found in the Poland National Registry[38]. In light of this evidence more and more centres are proposing TAVR as a valuable option for treatment patients carrying a bicuspid aortic valve, considering this condition no more an absolute but a relative contraindication to the procedure.

Evaluation of left ventricular function

The presence of a left ventricle systolic dysfunction, defined as aEF < 50%, constitutes a negative prognostic marker both in symptomatic and asymptomatic severe aortic stenosis. In patients considered unsuitable for surgical aortic valve replacement enrolled in PARTNER B cohort 30-d and 1-year prognosis was not different for patients with a LVEF over 50% confronted with those with reduced LVEF[39] Moreover in this arm of PARTNER study an increase in LVEF > 10% subsequently TAVR was found in 50% of patients considered unfit for surgery, especially for those with smaller LV chamber diameters and lower grade of mitral regurgitation before TAVR. Although LVEF improvement was not associated with improvement in survival, in those with no post-procedural increase in LVEF there was a worse prognosis at one year of follow-up.

In light of these evidences TAVR represents a valuable option in severe aortic stenosis and markedly reduced left ventricular systolic function and should be taken in consideration by the Heart Team, because in these very high risk patients for surgery TAVR may show a better outcome.

Furthermore an alteration in LV structure and function has been demonstrated in patients with severe aortic stenosis regardless a preserved LVEF and this phenomenon can be studied also with speckle tracking echocardiography, a relative new technique that provides non-Doppler evaluation of myocardial deformation as expression of systolic and diastolic dynamics[40]. In this context, in fact, a reduced GLS (global longitudinal score) has been documented with a more evident alteration in the basal LV segments and a value > -15.9% correlated with adverse prognosis[41,42].

In patients with severe aortic stenosis undergoing TAVR, LV reverse remodelling and improvement of longitudinal myocardial function assessed by speckle tracking echocardiography have been observed together with a decrease of aorto-valvular impedence and an improvement of atrial morphology and function[43]. In fact, our group evaluated 55 patients before and 6 mo after CoreValve implantation demonstrating a significant reduction in mean transaortic gradient, LV mass, LA volume index, and an improvement of ejection fraction (P < 0.0001). In addition, LV GLS and LA longitudinal strain significantly increased after TAVI and at the multiple logistic regression analysis, LV mass before TAVI (P < 0.001) and peak CK MB mass after TAVI (P < 0.0001) were powerful independent predictors of lower improvement of LV GLS. Moreover, LV mass index (P < 0.001) and LV GLS strain (P < 0.001) before TAVI was powerful independent predictor of LA longitudinal strain after TAVI (Figure 4).

Mitral regurgitation

Haemodynamically relevant mitral regurgitation is present in a substantial amount of patients with severe valvular aortic stenosis. It may have many different underlying mechanisms, both organic and functional. Functional mitral regurgitation may be also of ischemic nature, because of the common occurrence of coronary artery disease in these subjects. Moreover left ventricular systolic dysfunction and dilatation and concomitant aortic regurgitation may contribute to cause or aggravate mitral regurgitation[44].

In addition high grade mitral regurgitation may result in reduced transvalvular flow and lead to incorrect classification of stenosis severity, so it has to be taken in consideration in pre-procedural TTE for a comprehensive global assessment of aortic valve disease.

Interestingly in these subset of patients improvement of mitral insufficiency is reported in around 50%, more often in the case of secondary mitral regurgitation[45,46]. This finding was consistent with the results of a recently published meta-analysis which demonstrated that MR improvement was associated with pre-procedural grade and not with causative mechanism[47].

Right ventricular function and pulmonary hypertension

Pre-procedural TTE should include a comprehensive evaluation of right ventricular dimensions and function, in addition to estimation of pulmonary arterial systolic pressure (PAPs) from tricuspid regurgitation velocity.

Registries report that after TAVR moderate or severe tricuspid regurgitation is frequent (occurring in about 15%) and in most cases it is not improved after the procedure[48].

Pulmonary hypertension (PH) can be found in up to 25% of subjects affected by severe aortic stenosis, secondary to post-capillary increase of left ventricular filling pressure and the eventual presence of associated mitral regurgitation. PH is a predictor of worse prognosis following surgical aortic valve replacement and recently there is increasing evidence that it is a negative prognostic marker together with tricuspid regurgitation also in the setting of transcatheter aortic intervention[49].

Evidence from TAVR registries suggests that PH (estimated PAPs over 40 mmHg on TTE) does not negatively influence success rate, amount of complications in the early phase and 30-d survival, but a negative prognostic effect is present regarding 1 year mortality, which is raised up to 22% (or higher if estimated PAPs is above 60 mmHg)[50].

Role of transoesophageal echocardiography

Transesophageal echocardiography (TEE) allows to better visualize aortic cusps, define etiology (bicuspid *vs* tricuspid) and directly measure aortic valve area by planimetry in doubt cases, when TTE is not conclusive. TEE can be used in association with other imaging techniques for optimal pre-procedural planning in the setting of TAVI.

Annulus size measurement

Aortic valve annulus can be defined as a ring-shaped structure virtually identifiable at the level of basal attachment of aortic cusps measured in systole[46]. A correct measurement of annular size allows an appro-

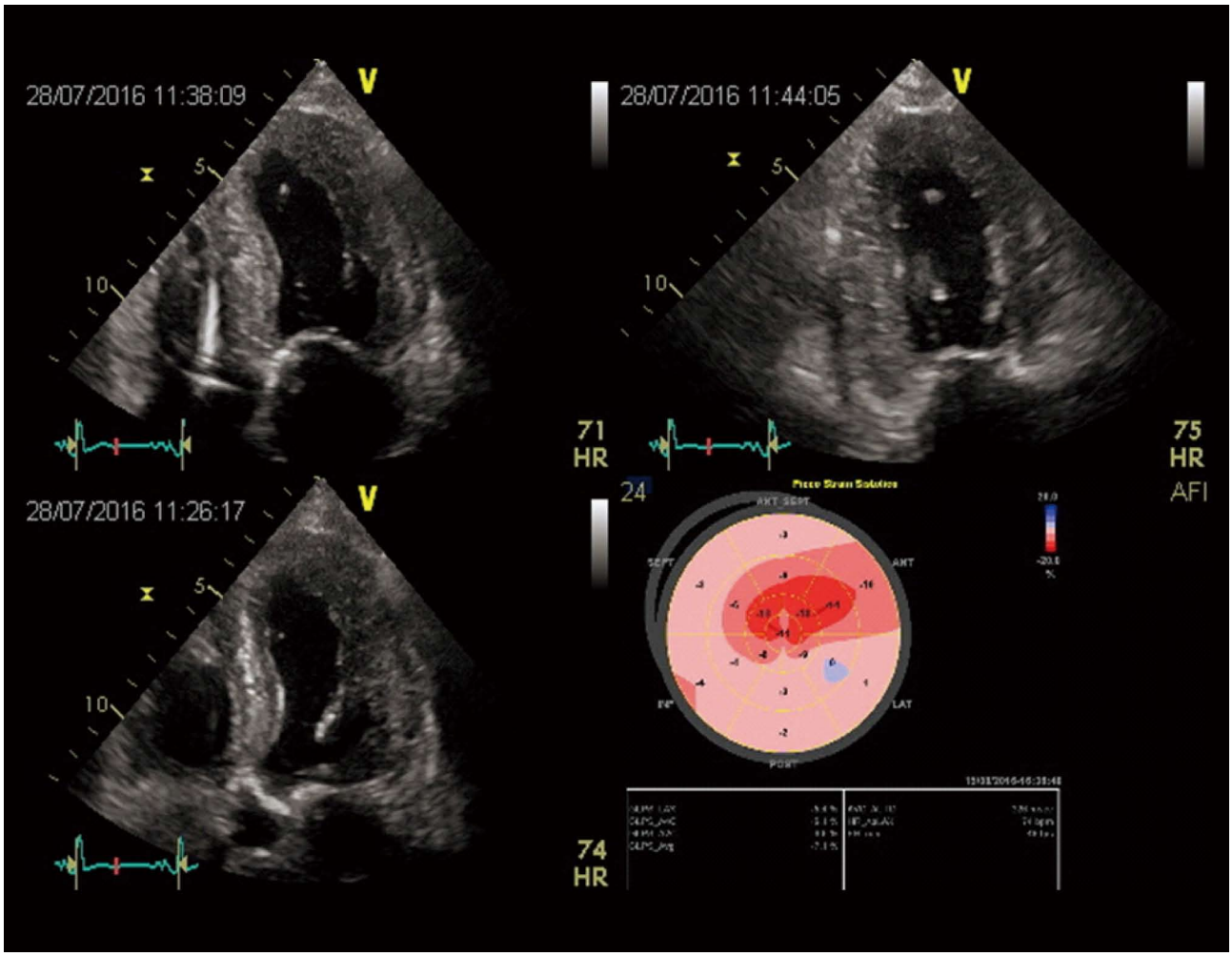

Figure 4 Two-dimensional LV strain in a patient with low flow-low gradient aortic stenosis, showing a severe and diffused impairment of myocardial deformation.

priate delivery of aortic valve prosthesis and reduce the incidence of complications[51].

When aortic annulus is underestimated the delivery of a prosthesis too small can be followed by displacement or paraprosthetic regurgitation[4]. On the other hand prosthesis oversizing can cause insufficient expansion and valvular or paraprosthetic regurgitation or annular rupture. Optimal annular sizing aims to deliver a valve of an adequate dimension large enough to avoid paravalvular regurgitation, but not exceeding more than 20% the measured annular diameter, which increases risk of rupture.

In practice antero-posterior annular diameter is measured by TEE in mid-esophageal long axis view (120°-150°) in correspondence of basal hinge points of aortic cusps to aortic root.

Three dimensional TEE allows to visualize the real shape of LVOT, which is oval in 90% of patients[52]. 3D-TEE has proved more effective in providing optimal annular measurement and was more useful in predicting paravalvular aortic regurgitation compared to 2D-TEE[53,54] (Figure 5).

3D-TEE has been directly compared with cardiac CT demonstrating the two imaging modalities were equally effective in predicting paraprosthetic aortic regurgitation[55], although annulus diameter and planimetric area determined by 3D-TEE tend to result smaller than those measured by cardiac CT, except for sagittal dimensions. Considering sagittal dimensions both diagnostic techniques were equally accurate in predicting prosthetic dimensions with good post-procedural results. In conclusion before TAVI, 3D-TEE can be considered a valuable alternative to cardiac CT in pre-procedural planning, especially in patients with chronic kidney disease.

Root anatomy

Transesophageal Echocardiography is able to evaluate the distance of coronary arterial ostia from aortic annulus and to correlate this distance with aortic cusp length, in long axis view. If cusp length is longer than coronary-annular distance there is a risk of coronary occlusion after valve delivery, when aortic valve cusps are displaced by the prosthesis expansion.

In clinical practice in order to avoid coronary occlusion, coronary-annular distance should be higher than

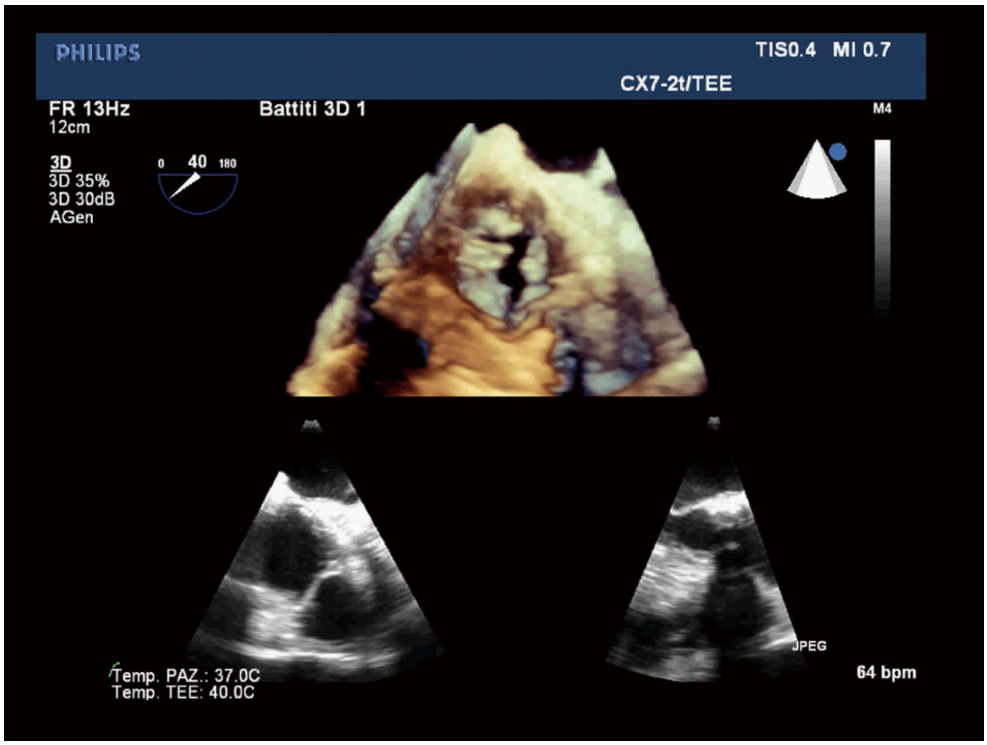

Figure 5 Three dimensional transesophageal echocardiography allows to visualize the real shape of left ventricular outflow tract, and has proved more effective in providing optimal annular measurement and was more useful in predicting paravalvular aortic regurgitation compared to 2D-transesophageal echocardiography.

10 mm[56,57]. Moreover aortic valve calcium burden should be always assessed and confronted with aortic sinus capacity. Although it is possible to measure coronary-annular distance with 2D-TEE, in the majority of patients it is necessary to use Multi Slice Computed Tomography (MSCT) or as an alternative 3D-TEE.

Distribution of calcium

TEE allows visualization of calcium deposits, which are present in almost all subjects affected by degenerative aortic stenosis, and their distribution. The presence of extensive aortic valve calcifications may cause paravalvular regurgitation due to formation of gaps between prosthetic and native valve and increase the risk of coronary ostium obstruction after TAVI delivery[58]. In addition extensively calcified sino-tubular junction may impair the expansion at the aortic end of the prosthesis eventually causing ventricular displacement of the prosthetic valve during delivery[59,60]. Great amount of calcification, particularly in subvalvular region, is also associated with increased risk of periprocedural annular rupture or sinus rupture.

Characteristics of aorta and significant left ventricular septal hypertrophy

TEE examination provides an higher spatial and temporal resolution and in pre-procedural phase allows to evaluate the ascendingaorta and the descending thoracic tract in order to exclude the presence of extensive and soft atheromas which are associated with higher risk of peri-procedural ischemic stroke because they can be mobilized and hinder the passage of delivery system[61,62]. It remains a suboptimal tool for the assessment of the distal ascending aorta and the proximal arch (TEE "blind spot" due to tracheal air shadowing) as well as for the abdominal aorta. Finally TEE may show a significant basal septal hypertrophy that may lead to prosthesis displacement in periprocedural or postprocedural phase[63,64].

CORONARY ANGIOGRAPHY AND PCI

Coronary angiography represents an essential part of patient evaluation before planning a TAVR procedure. Significant coronary artery disease is commonly found in patients with indication to TAVI, however there is no universal agreement about if and how it should be treated[61,65]. Secondary left ventricular hypertrophy may cause myocardial ischemia irrespectively of the presence of obstructive atherosclerotic lesions in major coronary arteries, in fact manifestations of angina are reported also by patients without evidence of relevant coronary artery disease (CAD) on angiographic examination[66].

Moreover even though degenerative stenotic aortic valve disease has the same risk factors of CAD, there is substantial variability in CAD prevalence in aortic stenosis population between different studies, ranging from 34% to 75%[67,68]. A possible explanation for this inconsistency can be found in the definition adopted for significant CAD and which method is used for its diagnosis, usually angiographic examination,

which shows relevant interobserver variability. Usually angiographic cut-off for coronary obstruction is considered ⩾ 50%[69-72], but some authors use a cut off value of ⩾ 70%[73-75].

Latest recommendations about myocardial revascularization released from European Society of Cardiology suggest PTCA for patients undergoing TAVI in the presence of coronary obstructive lesions of more than 70% (class IIa, level of evidence C), despite the impact on long term survival of obstructive CAD is controversial according to different TAVI registries[76-78]. In order to definite the prognostic benefit of percutaneous revascularization of anatomically relevant CAD in patients undergoing TAVR a randomized controlled trial, the ACTIVATION study, is ongoing[79].

In addition the burden of CAD in this setting fall in a broad spectrum going from a simple single lesion to multiple complex lesions, with different prognostic implications. Currently CAD treatment can be guided by coronary angiography and Anatomical Scoring Systems. Moreover in patients with borderline risk profile the assessment or the exclusion of coronary artery disease can induce the Heart Team to lean towards SAVR or TAVR.

Angiography-guided revascularization

According to angiographic data significant obstructive CAD is found in 40%-60% of TAVR patients, evaluated through quantitative coronary angiography (QCA). Khawaja *et al*[66] in a retrospective study "Coronary artery disease in patients undergoing TAVI- why not to treat" including 271 patients evaluated through QCA, reported an incidence of obstructive CAD of 34% (defined as a 70% or more stenosis of a major coronary artery or 50% or more in left main stem or a venous graft); 26.9% of them underwent revascularization before TAVR procedure. Moreover no significant increase in mortality for patients carrying obstructive CAD was found in this study, either at 30 d or at 1 year and among them, those treated by revascularization also did not show any significant prognostic improvement.

However QCA has several pitfalls: (1) eccentric and markedly calcific plaques are difficult to assess through this technique because of calcium pools projection by X-rays; and (2) extremely tortuous epicardial coronary arteries may cause mistakes in vessel measurement and thus in stenosis evaluation[80]. Alternatively markedly calcific and contorted lesions may be more reliably evaluated through optical coherence tomography or intravascular ultrasonography, but at present the use of these techniques has not been investigated in TAVR population.

Finally according to old fashioned studies using QCA of left coronary artery in aortic valve stenosis it was demonstrated a progressive increase in coronary vessel dimensions as aortic valvular stenosis progresses, such phenomenon was reverted by SAVR, so angiographic evaluation may not reliably predict CAD extension after TAVR procedure[81].

Anatomical score system

Anatomical scores are used to grade coronary artery disease extension in everyday clinical practice, among them the most frequently used is SYNTAX score[82]. Recently these scoring systems have been applied in small TAVR registries, taking in consideration the location and complexity of coronary lesions in order to estimate procedural risk of coronary revascularization[83,84].

In the previously cited retrospective analysis by Khawaja *et al*[66] a SYNTAX score > 33 (which defines an high risk according to SYNTAX study) had an higher rate of periprocedural complications during TAVR, whereas a SYNTAX score between 0 and 22 identified patients with a lower risk. Moreover a cut off value of 9 was a predictor of all-cause death at one month and at one year of follow-up so that revascularization may be indicated for patients with a SYNTAX score ⩾ 9.

Furthermore comparing surgical aortic valve replacement with TAVR in the setting of low flow-low gradient aortic stenosis, which represent an higher risk population, the extent of CAD evaluated through SYNTAX score or remaining CAD severity assessed by residual SYNTAX score after revascularization were both predictors of worse prognosis and cardiovascular death after 1 year follow-up[85].

Fractional flow reserve guided revascularization

No methods are validated to assess ischemia in patient with severe aortic stenosis and also evaluation offunctional significance of coronary artery stenosis by fractional flow reserve (FFR) is not recommended in this population. In fact the mechanism of ischemia in severe aortic stenosis is more complex and due to multiple hemodynamic factors so that aortic pressure waveform and coronary blood flow regulation is altered by left ventricular hypertrophy leading to an impaired coronary flow reserve also in absence of coronary obstruction[86]. In addition, the increased left ventricular filling pressure will rise left ventricular diastolic wall stress, this phenomenon together with reduced diastolic time may contribute to impair diastolic coronary blood flow per se.

On the other hand the administration of vasodilator drugs, necessary to asses FFR, could induce critical fall in systemic arterial pressure with potentially hemodynamic instability.

MULTISLICE COMPUTED TOMOGRAPHY

Among the imaging modalities, computed tomography (CT) plays a central role in the evaluation of patients with severe aortic stenosis prior to TAVR since it allows to study anatomical details in order to choice the best fitting prosthesis, evaluate the morphology of the access path, select the best fluoroscopic projection angles and detect other relevant comorbidities (Figure 6).

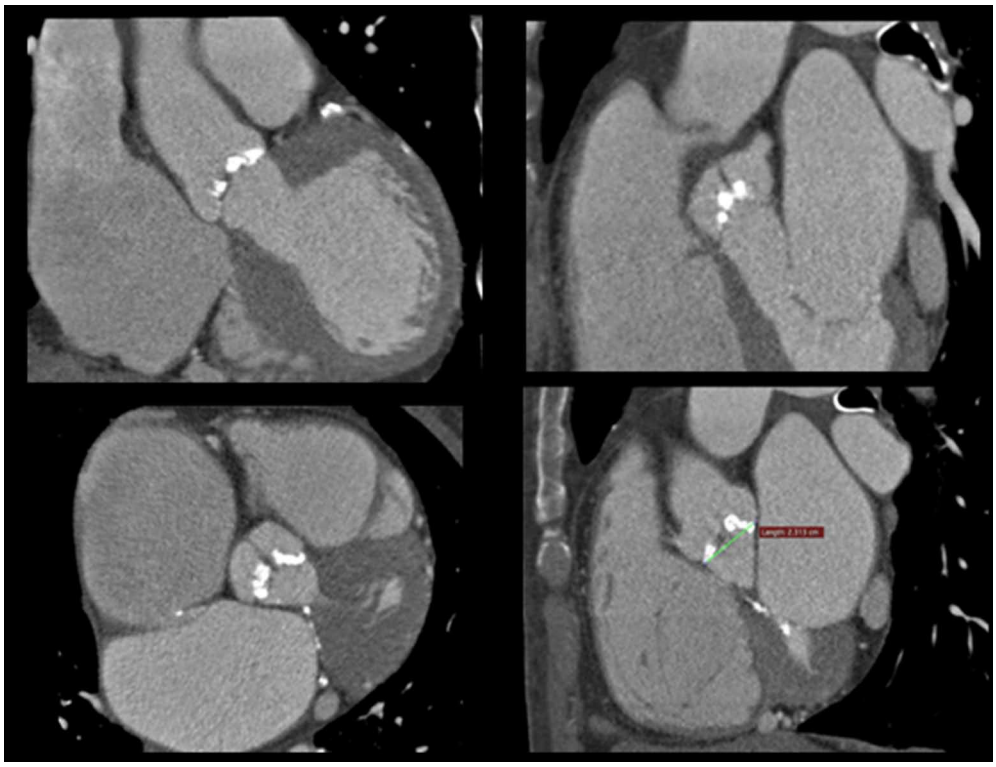

Figure 6 Multi-slice enhanced computed tomography images showing the aortic valve cusps and the first tract of the ascending aorta, with associated presence of extensive valvular calcifications.

Measurement of aortic annulus and evaluation of aortic root

Multidetector scanners allow multiplanar reformation and 3-dimensional reconstruction of aortic root, ascending tract, arch and descending segments of aorta. Novel technological advances in CT result in higher imagine quality with substantially reduced scan duration, contrast volume and radiation exposure. CT provide an accurate measurement of anatomic AVA by a cross-sectional view of the aortic valve derived from left sagittal and left coronal oblique views[52]. Moreover this modality gives precise measurements diameters, expressed also as mean value between different planar reliefs, area and perimeter of aortic annulus which are essential information for a correct prosthesis choice. The annulus size is larger when measured by MSCT than by 2D transthoracic or transoesophageal echocardiography with an absolute difference $\leqslant$ 1.52 ± 1.1 mm. Comparing the measurements of aortic annulus size as obtained by CT angiography and 2-dimensional transesophageal echocardiography with direct surgical measurement in patients undergoing surgical valve replacement, CTA overestimates aortic annulus diameter in 72.2% of cases, with 46.3% > 1 TAVI valve-size (> 3 mm) overestimations, whereas TEE underestimated aortic annulus diameter in 51.1% of cases, with 16.7% > 1 valve-size underestimations[87,88].

MSCT allows also to give precise measurements of the distance between annulus and coronary ostia and represents the gold standard for this purpose,providing a more comprehensive assessment, showing an average annular-right coronary artery distance of 13.6 ± 2.8 mm and annular-left coronary artery distance of 13.4 ± 3.2 mm[89,90]. The distance between the aortic valve annular plane and the coronary ostia should be at least of $\geqslant$ 10-11 mm for both type of most used prosthesis (Corevalve and Edwards). It is important also to evaluate the dimensions of ascending aorta at 45 mm above the annulus plane when the strategy foresees the implantation of a Corevalve prosthesis as this value should not exceed 40 mm for the 26-mm valve and 43 mm for the 29-mm and 31-mm.

This technique is useful to make many reconstructions with adjunctive information about calcification severity, plaque burden and prohibitive risk findings as dissections and complex atheroma of aorta[91].

Aortic valve calcium score

CT permits to calculate aortic valve calcium scoring. In severe aortic annular calcification the protrusion of calcium into the lumen > 4 mm can lead to an undersizing of the prosthesis valve and predict a post procedural paravalvular regurgitation[92]. Furthermore a high calcium score can help to distinguish between severe and pseudosevere aortic stenosis in patients with low left ventricle ejection fraction. Different cutoff values of calcium score in aortic stenosis have been described for men ($\geqslant$ 2000 AU or $\geqslant$ 480 AU/cm^2) and women ($\geqslant$ 1200 AU or $\geqslant$ 290 AU/cm^2) to identify severe AS[93]. In risk stratification, mostly in asymptomatic or paucisymptomatic patients, the aortic valve calcium load assessed by MSCT is a powerful predictor of rapid

Table 2 Magnetic resonance sequences used for pre transcatheter aortic valve implantation evaluation[96]

Three-plane localizer	To localize aortic valve plane
Axial SSFP non ECG gated without contrast	To identify potential ascending aorta and subclavian access sites
	To determinae size, calcification, and presence of aneurysmal dilatation of aorta
Breath held free breathing 2D ECG gated SSFP	To evaluate aortic annulus,aortic valve structure, and sinus higher
Coronal aorta, LVOT and aortic root	Planimetry valve orifice area
SSFP ECG gated images:short axis stak	Calculate ejection fraction, ventricular volumes and mass
Breath held free breathing phase contrast at aortic orifice	Calculate blood flow velocity, pressure gradient, and flow volume across the aortic valve
	Calculate Aortic regurgitant volume
3D Navigator assisted SSFP	Coronary ostia height
	Aortic diameter
T2 black blood	Useful in presence of susceptibility artifacts from sternal wires of prosthetic valves

LVOT: Left ventricular outflow tract; SSFP: Steady state free procession; ECG: Electrocardiography.

stenosis progression and of cardiac events[94].

Detection of coronary artery disease

Invasive coronary angiography remains the gold standard diagnostic modality for the detection of significant CAD in patients with severe aortic stenosis. The role of coronary computed tomography angiography (CTA) in selection of patients for TAVR until now remains not established mainly because there are few data regarding on its diagnostic accuracy in this contest. In a large unselected cohort of patients with severe aortic stenosis, the identification of significant CAD has been limited by feasibility and an overall moderate accuracy (driven by the high rate of false-positive observations) so that this test cannot be used instead of invasive coronary angiography[95]. In fact, also in patients without arrhythmias, high heart rate and coronary stents up to 25% of the CTA images were found to be not fully evaluable representing coronary calcification the major confounding factor[96-98]. On the other hand, CTA has shown a good sensitivity (97%) and negative predictive value (97%) so that it can be reasonably be used as a rule-out test in some selected cases mostly inpatients without prior known CAD and little calcifications[95].

Comorbidities detection

Computed tomography as a part of pre-TAVR diagnostic work-up is often able to detect other concomitant pathologies with important influence on outcome and sometimes questioning the indication to the procedure as in case of detection of potentially malignant diseases with poor prognosis. In fact, during CT aortography, images are acquired throughout the thorax and abdomen, and potentially significant incidental findings can be found. Until today patients candidates to TAVR tend to be elderly and it has been shown a very high overall incidence of incidental pathological findings in this population (more than 50%) and in 18.1% of cases a clinical signification has been documented[99].

Assessment of peripheral accesses

Appropriate approach selection is crucial for a good results of TAVR and is based on minimal aorto-femoral tract diameter detected by projection aortography or CTA. In addition to conventional angiography (XA), CTA provides more detailed 3D imagines including calcification and tortuosity and allows to exclude a transfemoral access in patients with poor vessel quality or small diameter in aorto-femoral tract considering that the 18 Fr sheath requires a minimal arterial diameter of 6 mm of the aorto-femoral tract for prosthesis delivery[100,101]. It is important to know that the semi-automated CTA diameter measurement of the aorta-iliac tract resulted statistically significantly smaller compared to XA-based measurements.

Patients not suitable for transfemoral TAVR should be considered for transapical implantation or conventional surgery[102].

MAGNETIC RESONANCE IMAGING

Cardiovascular magnetic resonance (CMR) is an emergent modality for evaluation of patients before TAVR and it is expected to gain more and more space in this setting, mostly in patients with contraindications to contrast medium. As MSCT, this technique provides precise measurements of aortic valve, annulus, aortic root, coronary ostia,definition of the thoraco-abdominal aorta and luminal caliber of the iliofemoral branches (Table 2)[103]. Moreover it is able to study LV function with the advantage of not using ionizing radiation (Figure 7).

Non contrast MR should have an important role in preoperative evaluation in selected groups of patients with aortic stenosis: (1) patients affected by severe renal function impairment with GFR < 30 mL/min/mq; (2) patients with inadequate acoustic window mostly in the contest of low gradient detection and/or reduced left ventricle ejection fraction; (3) discrepancy between parameters obtained by echocardiography and symptoms; and (4) History of allergic reactions to iodated contrast medium.

MRI technique are influenced by some limitations. In the first place multiple breath holds, claustrophobia and the presence of arrhythmias can interfere with an adequate acquisition. Aneurism clips, carotid vascular clamp, neurostimulator devices, insulin or infusion pumps, ear implant and ocular foreign bodies represent

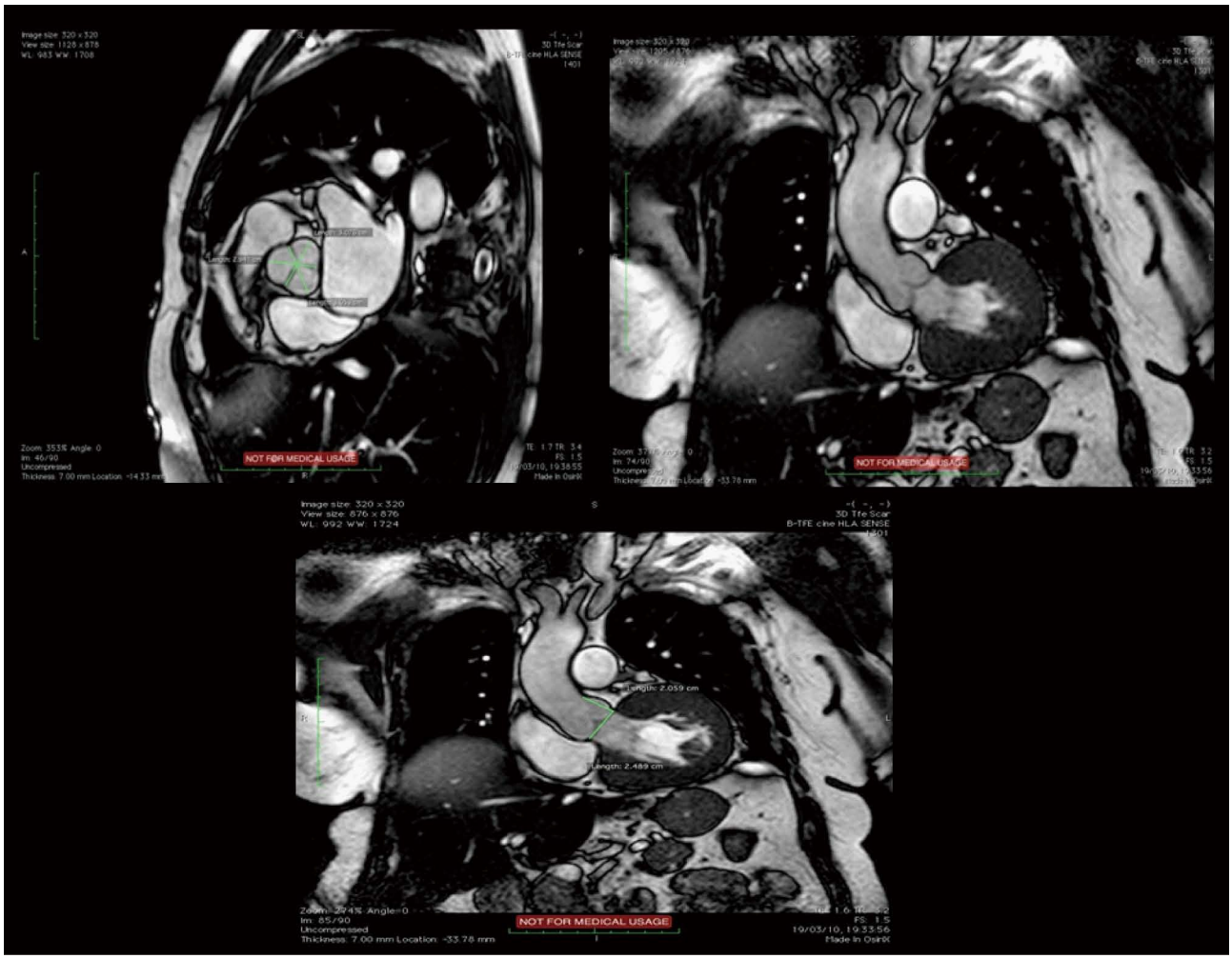

Figure 7 Balanced fast-field echo unenhanced magnetic resonance images showing the normal tricuspid aortic valve, with the typical "Mercedes-Benz Sign" and the first tract of the ascending aorta.

absolute contraindications.

Aortic valve and root evaluation

MRI is able to provide accurate measurements of aortic annulus that in terms of capacity to predict the presence and the severity of post-implantation aortic regurgitation is similar to MSCT[104]. A good concordance between MSCT, CMR and echocardiography has been documented for aortic valve morphology definition and aortic valve area measurements[105]. In fact MRI is able to provide the planimetry of aortic valve opening area which is similar to other diagnostic modality as 3D TEE and flow-derived area calculation by catheterization using the Gorlin equation or by Doppler echocardiography using the continuity equation[106]. Although anatomic planimetry of aortic stenosis and assessment of valvular anatomy and motion is possible with MRI, this became less than optimal in patients with severe calcifications mostly in the presence of non-planar orifices. Furthermore assessment of severity of aortic stenosis can be completed by velocity-encoded cine MRI with other standard measures as peak anterograde velocity and pressure gradient but it is necessary to know that velocities and gradients are usually underestimated if compared with Doppler echocardiography[107].

MRI can be an alternative to 3D imaging modality for the measurement of aortic annulus (minor an major diameters, area and perimeter) having showed a good agreement with CT in this context also in presence of oval shape of the structure in which, after adequate plane orientation and 3 dimensional reconstruction, generally the coronal diameter is larger than the sagittal one[108]. As for MSCT, MRI diameters were found to be larger than those measured by 2D TEE modality.

Measurements of sinus of Valsalva diameters and definition of aortic root orientation are also possible with this approach but conversely this doesn't represent a good modality to thoracic aorta plaque burden definition as calcifications cause signal voids[103].

The concordance with CT has been documented also for the assessment of the distance between the annulus and the ostium of the left coronaryartery in relation to the length of the left coronary leaflet but at the moment more studies are needed to determine whether a strategy based on a different imaging method could

Table 3 Multimodality imaging in pre transcatheter aortic valve replacement evaluation

Technique	Principal advantages	Disadvantages
Transthoracic echocardiography	Widespread availability	Poor acoustic window
	First line diagnostic tool	Frequent discrepancy between different parameters
Transesophageal echocardiography	Good spatial resolution	Suboptimal for distal ascending aorta and arch
3 D reconstruction	Semi-invasive exam	Anatomic definition and annulus measurement
Multislice computed tomography	Multiplanar reconstruction	Potential nephrotoxicity of contrast medium
	Quantification of calcium score	Radiations exposition
	Evaluation of aorto-femoral tract	Controlled heart rate
Magnetic resonance imaging	Tissue characterization	Reduced availability
	Multiplanar reconstruction	Poor evaluation of calcifications
	Evaluation of aorto-femoral tract	Contraindicated in metallic devices wearers
	Controlled heart rate	
Positron emission tomography	Evaluation of calcification and inflammation	Poor spatial resolution

achieve better results. A3-D SSFP free breathing stack in late diastole with a respiratory navigator allows to measure the height of coronary ostia from the annular plane.

Moreover magnetic resonance angiography can characterize aorto-ilio-femoral arteries in order to plan the more adequate access[109].

Ventricular volume and function

MRI provides quantitative evaluation of left ventricle volumes and function and late gadolinium enhancement at T1-weighted sequences allows to detect myocardial fibrosis which is more often localized in mid-wall of myocardium, like in pressure-overload cardiomyopathies, and represents a predictor of poor prognosis[110]. Fibrosis represents one of the most important factors implicated in progression of hypertrophy towards heart failure and an early detection can be useful in risk profile definition mostly in asymptomatic patients or in case of borderlines parameters at conventional echocardiography evaluation. Advanced fibrosis replacement of left ventricle myocardium predicts a lack of improvement in LV systolic function after aortic valve replacement and is an independent predictor of all-cause mortality[111,112].

POSITRON EMISSION TOMOGRAPHY/CT

An emergent role in pre-TAVR evaluation is attributable to positron emission tomography (PET)/CT with the advantage of combining the anatomic definition derived from CT and the functional and metabolic characterization gained from PET[15]. ^{18}F-sodium fluoride (18F-NaF) is a tracer used to detect calcification and in aortic stenosis the amount of uptake correlates with disease severity and is able to predict the progression of the disease[113-115]. On the other hand ^{18}F-fluorodeoxyglucose uptake, representing the burden of inflammation, is higher in patients with mild or moderate aortic stenosis and decrease with stenosis progression.

CONCLUSION

Patient selection for TAVR should be based not only on accurate assessment of aortic stenosis morphology, but also on several clinical and functional data. The Heart Team is key in the overall risk evaluation of this population. Multi-Imaging modalities are preferred for assessing the anatomy and the dimensions of the aortic annulus before TAVI (Table 3). In any case, we should tailor our patient selection and prosthesis selection on a case-to-case basis.

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MINIREVIEWS

Paroxysmal atrial fibrillation ablation: Achieving permanent pulmonary vein isolation by point-by-point radiofrequency lesions

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Abstract

Pulmonary vein isolation by point-by-point radiofrequency catheter ablation constitutes the cornerstone of catheter ablation strategies for the treatment of atrial fibrillation. However, despite advances in pulmonary vein isolation ablation strategies, long-term success rates after ablation remain suboptimal, which highlights the need to develop techniques to achieve more durable lesions. Strategies proposed to improve the durability of pulmonary vein isolation can be divided into two groups: Those addressed to improving the quality of the lesion and those that optimize the detection of acute PV reconnection during the ablation procedure. This manuscript reviews the role and potential benefits of these techniques according to current clinical evidence.

Key words: Atrial fibrillation; Pulmonary vein isolation; Lesion durability; Contact force; Pulmonary vein reconnection

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Core tip: Results of pulmonary vein isolation remains suboptimal in terms of long-term outcomes. Improving lesion durability could reduce atrial fibrillation recurrence rate after pulmonary vein isolation. This manuscript reviews current techniques proposed in order to achieve more durable pulmonary vein isolation by point-by-point radiofrequency ablation. The role and potential benefits of these techniques are discussed according to current clinical evidence. Furthermore a stepwise approach to achieve permanent pulmonary vein isolation is proposed.

Pedrote A, Acosta J, Jáuregui-Garrido B, Frutos-López M, Arana-Rueda E. Paroxysmal atrial fibrillation ablation: Achieving permanent pulmonary vein isolation by point-by-point radiofrequency lesions. *World J Cardiol* 2017; 9(3): 230-240 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i3/230.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i3.230

INTRODUCTION

Atrial fibrillation (AF) is one of the major causes of stroke, heart failure, and cardiovascular morbidity worldwide[1]. Since Haïssaguerre *et al*[2] identified the pulmonary veins (PVs) as triggers capable of initiating AF paroxysms, radiofrequency (RF) catheter ablation through pulmonary vein isolation (PVI) has been developed and now constitutes the cornerstone of catheter ablation strategies for the treatment of AF[3]. Current indications for PVI include symptomatic paroxysmal or persistent AF, in general as second-line treatment after failure of or intolerance to antiarrhythmic drug therapy, but also as first-line therapy in selected cases[4].

According to the most recent consensus statement on catheter ablation of AF[3], the technique for achieving PVI should target a wide area around the PVs, called the antrum, with complete electrical isolation as the endpoint of the procedure. However, despite advances in PVI ablation strategies, long-term success rates after ablation remain suboptimal, which has led to the development of new techniques to achieve more durable lesions.

PV RECONNECTION AS THE MAIN CAUSE OF AF RECURRENCE AFTER PVI

In the majority of patients with AF recurrence, an electrical reconnection between the PV and LA can be observed[5-7]. The probability of AF recurrence during follow-up after a PVI procedure has been linked with the presence of gaps, defined as poor isolation areas between the PV and LA, due to suboptimal RF lesions[8]. A recent meta-analysis of 11 studies[9] including 683 patients showed that 85.5% of patients with AF recurrence had at least one PV reconnected, opposed to 58.6% of those without AF recurrence. Although not fully established, it has been suggested that the biological mechanism underlying PV reconnection may be related to the recovery of tissue conduction after a transient phase of reversible tissue injury with inflammation and edema[10]. Therefore, achievement of permanent PV isolation should be considered the main goal of current AF ablation approaches in order to avoid recurrences.

PERMANENT PV ISOLATION AS THE ENDPOINT OF AF ABLATION: HOW TO ACHIEVE IT?

The reasons for long-term failure of AF ablation are largely based on a suboptimal ability to effectuate a durable transmural lesion using the contemporary ablation toolset. While electrical PVI may be achieved acutely, the combination of inadequate electrode-tissue contact, insufficient power delivery, and tissue edema may prevent RF-induced heating of myocardium to lethal temperatures. With time, as the acute effects of RF energy resolve, the transient injury induced at the time of index ablation recovers, revealing gaps in the initial line of ablation and allowing PV triggers to excite the adjacent LA and induce AF[6,10]. Several techniques to improve the durability of PVI have been proposed, and can be divided into two groups: Those addressed to improving the quality of the lesion and those that optimize the detection of acute PV reconnection during the ablation procedure.

TECHNIQUES TO IMPROVE LESION DURABILITY

The use of irrigated catheters for PVI was associated with a dramatic decrease in PV reconnection rate[11]. However, even when irrigated catheters are used, the recurrence rate after a single PVI procedure remains high (30%-35%)[12]. Further strategies are required in order to improve long-term durability of the lesions obtained with this type of catheters.

Use of sheaths

Efficient catheter contact can be facilitated through the use of non-steerable and steerable sheaths that allow easy maneuverability, access, and contact to target sites. Piorkowski *et al*[13] compared the use of steerable sheaths with the use of non-steerable sheaths during AF ablations in a prospective randomized trial. Although the rate of acute PVI and total RF application time did not differ between the study groups, single procedure success was significantly higher in patients treated with a steerable sheath (76% *vs* 53% at 6 mo). The difference persisted at 12 mo (75.7% success) after a single AF catheter ablation procedure using steerable sheath[14]. Therefore, use of a steerable sheath may help to improve the maneuverability of the ablation catheter, catheter stability, and tissue contact. This could potentially reduce recurrence through the enhancement of lesion continuity and transmurality.

General anesthesia

In a multicenter trial, Di Biase *et al*[15] randomized 257 consecutive patients undergoing a first AF ablation procedure to general anesthesia or conscious sedation. During follow-up (mean 17 ± 8 mo), fewer patients randomized to conscious sedation were free of atrial arrhythmias while off antiarrhythmic drugs (69% *vs* 88% of patients randomized to general anesthesia). In their study, all patients with recurrence had a second procedure. Interestingly, 42% of PVs in the conscious sedation arm at the repeat procedure had recovered PV conduction, compared with 19% in the general anesthesia group[15]. Better and more stable tissue-catheter contact due to controlled breathing patterns and elimination of patient movements may explain this finding.

Contact force sensing catheters

Contact force (CF) sensing is a novel technology used to assess the degree of catheter-tissue contact through a sensor at the distal tip of the ablation catheter. Studies based on animal models have shown that catheter-tissue CF is directly correlated with lesion size, and that excessive CF (> 50 g) could even provoke steam pops[16,17]. The concept of force-time integral (FTI) has also been proposed as a major factor in RF lesion size[18]. Shah *et al*[18] calculated the FTI by measuring the area under the CF curve beyond 60 s and found a linear correlation with lesion size during RF ablation. Despite similar power and peak CF values, lesions were larger with constant contact and smaller with intermittent contact.

CF and lesion transmurality

Several studies have assessed the relationship between CF and lesion transmurality by means of electrogram analysis, cardiac imaging, and histopathology. Squara et al assessed the CF and FTI needed to create effective transmural lesions during AF ablation by analyzing bipolar electrograms before, during, and after RF application. Based on post-ablation changes in electrogram characteristics, they identified a cutoff FTI of > 392 gs to predict transmurality with 89% sensitivity and 93% specificity[19]. Two cardiac MRI studies have demonstrated a direct correlation of CF and FTI with lesion transmurality. In the first study, Sohns *et al*[20] performed contrast-enhanced cardiac MRI in patients treated with AF ablation using CF catheters. They found a correlation between regions where higher FTI (> 1200 g) was maintained during ablation and those showing increased late gadolinium enhancement on MRI at 3 mo after ablation[20]. In the second study, Andreu et al performed cardiac MRI at 3 mo after PVI ablation to assess CF thresholds required to create permanent lesions using a dragging catheter (as opposed to a point-by-point lesion delivery) technique[21]. They reported that PV segments where MRI gaps were seen had lower maximal CF values, compared to segments without gaps, and a CF threshold of > 12 g predicted the formation of a complete PV lesion with 94% specificity and 91% positive predictive value.

Results from a recent study question the correlation between CF and chronic lesion formation. Williams *et al*[22] placed linear intercaval right atrial lesions in eight pigs using high (> 20 g) or low (< 10 g) CF, intentionally leaving a gap between segments. Voltage maps and cardiac MRI were performed before, immediately after, and 2 mo after ablation. The authors found that tissue edema was greater in the acute post-ablation setting with high CF, but there was no difference in chronic lesion size or volume by voltage mapping or cardiac MRI between high *vs* low CF regions at 2 mo. Their results suggest that a transmural lesion can be created whenever continuous tissue-catheter contact is achieved (independently of the CF value) and adequate power is delivered with a stable catheter position throughout the lesion.

CF variability according to left atrium anatomy

Obtaining adequate CF can be difficult in certain portions of the LA, and certain LA regions may require less CF to achieve transmurality with RF ablation. This may explain the observation that PV reconnection tends to recur at specific regions in the LA. For example, Schluermann *et al*[23] reported lower CF obtained in left PVs than in right PVs and found the lowest values in the anterior segments, where the ridge between the left upper PV and the LA appendage represents anespecially challenging region for obtaining appropriate CF. Consistently with these data, our group observed that when operators were blinded to CF, the lowest CF values were recorded at the anterior segments of left PVs[24] (Figure 1).

On the other hand, given the differences in LA wall thickness, the amount of CF needed to achieve transmural lesions may vary in different portions of the LA. Sotomi *et al*[25] showed that higher CF may be necessary in certain regions such as the inferior right PV and posterior-superior right PV regions (22 g CF), while other areas such as the posterior-inferior right PV region may require only 10 g CF to assure acute PVI. Knowledge of CF requirements in various regions of the LA can improve safety during ablation by allowing the operator to control RF power based on CF to prevent steam pops without compromising lesion durability.

Impact of CF on ablation outcomes-clinical studies

Several studies (Table 1) have assessed the role of CF technology in short and long-term ablation outcomes.

The TOCCATA study was the first multicenter, prospective study to demonstrate the safety of CF-sensing catheters (Tacticath, Endosense) for ablation of cardiac arrhythmias[26]. The study included 34 patients undergoing PVI for paroxysmal AF and showed that low CF was associated with higher rates of AF recurrence[26]. Specifically, all patients treated with a CF < 10 g experienced AF recurrences, whereas 80% of the patients treated with an average CF > 20 g remained free from AF recurrence at 12 mo[26].

In order to demonstrate the correlation between CF parameters during initial procedure and PV reconnection, the EFFICAS-I study of PVI using CF-sensing catheters assessed the incidence of isolation gaps at 3-mo follow-up (Tacticath, Endosense)[27]. Interestingly, operators were blinded to CF information during the initial procedure. Isolation gap sites correlated with lower minimum CF and FTI during the initial ablation, and the authors proposed an optimal CF target of 20 g with minimum FTI of 400 gs. These cut-off values were prospectively tested in the EFFICAS-II study, which showed that 85% of PVs treated within the proposed CF guidelines were chronically isolated, suggesting a more durable PVI[28].

The SMART-AF trial, a prospective, multicenter, non-randomized single-arm study, examined the efficacy

Table 1 Clinical studies on contact force monitoring and mid/long-term outcomes

Study	*n*	Type of study	CF catheter	Control catheter	Follow-up (mo)	Findings
Andrade *et al*[55], 2014	75	Prospective observational	Thermocool SmarTouch	Navistar Thermocool	13.3	CF reduced dormant conduction (16% *vs* 52%) and improved long-term arrhythmia-free survival (88% *vs* 66%)
Kimura *et al*[31], 2014	38	Randomized controlled trial	Thermocool SmarTouch	Thermocool SmarTouch (blinded operador)	6	CF reduced procedure time and additional touch-up ablation
Marijon *et al*[61], 2014	60	Prospective observational	Thermocool SmarTouch	EZ Steer Thermocool	12	CF reduced AF recurrence at 12 mo (10.5% *vs* 35.9%)
Shurrab *et al*[33], 2015	42	Observational	Thermocool SmarTouch	Navistar Thermocool	2.5	CF reduced reconnection rate at 30 min postablation
TOCCASTAR, 2015	300	Randomized controlled trial	Tacticath	Thermocool Navistar	12	No differences in arrhythmia-free survival
Pedrote *et al*[24], 2016	50	Randomized controlled trial	Thermocool SmarTouch	Thermocool SmarTouch (blinded operador)	12	CF reduced PV gaps (20% *vs* 68%). No benefits in arrhythmia-free survival
Ullah *et al*[34], 2016	117	Randomized controlled trial	Thermocool SmarTouch	Thermocool SmarTouch (blinded operador)	12	CF reduced acute reconnections (22% *vs* 32%). No benefits in arrhythmia-free survival

CF: Contact force.

and safety of AF ablation using a SmartTouch CF-sensing catheter[29]. Only 2.5% of the 172 patients included had severe complications, suggesting that safety was not inferior to non-CF-sensing catheters. On the other hand, CF-sensing ablation that remained within target range > 80% of the time resulted in superior 1-year ablation success (81% of patients free from AF recurrence *vs* 66%, $P = 0.005$)[29].

The TOCCASTAR study was a prospective, multicenter, randomized clinical trial that compared AF ablation with CF (TactiCath) *vs* non-CF (ThermoCool Navistar) catheters in 300 patients[30]. Achieving optimal CF resulted in higher rates of acute PVI and no differences were observed in long-term success (freedom from AF or atrial tachycardia recurrence at 12 mo, excluding 3-mo blanking period).

Kimura *et al*[31] compared acute bidirectional block after PVI in 38 patients randomized to non-CF guided *vs* CF-guided (target CF 10-20 g) ablation using Thermocool Smart Touch catheter. This study showed that CF-guided PVI reduces procedure time and the need for additional touch-up ablation. Furthermore, a nonsignificant trend towards lower AF recurrence rate at 6 mo post-PVI was observed in the CF-guided group.

Two large meta-analyses have compared AF ablation with CF *vs* non-CF catheters. Afzal *et al*[32] examined data on 1148 patients in 9 studies and found that the use of CF-sensing technology reduced AF recurrence 37% overall at a median 12 mo of follow-up. Those treated with CF catheters also had reduced RF ablation duration, although no significant difference was seen in total procedure length or fluoroscopic exposure, compared to non-CF catheters. Shurrab *et al*[33] subsequently published another meta-analysis, which included 1428 patients from 11 studies (an overlap of 6 studies from the previous meta-analysis). They found a similar 38% overall reduction in AF recurrence at long-term follow-up. However, in addition to reduced RF ablation time, overall procedure length and fluoroscopic exposure duration were significantly lower in patients treated with CF technology. This meta-analysis also demonstrated a non-significant trend toward lower complication rates in the CF group.

It should be noted that the studies mentioned above assessed the impact of CF parameters in PVI performed with a circular catheter inside the PV. The use of circular catheters allows continuous recording of the electrical signal inside the PV, which can condition the endpoint of the procedure and prevents "naïve" assessment of the potential benefit of CF monitoring. In order to test the benefits of CF monitoring in PVI with an exclusively anatomic approach (blinded to the PV catheter), our group conducted a randomized, controlled study in which 50 patients with paroxysmal atrial fibrillation were randomized into CF-on (CF > 10 g) or CF-off (CF blinded; $n = 25$) groups. In the CF-on group, there was a reduction in the PV gaps at the expense of the left PVs and shortening of the procedure and radioscopy times. This confirms the benefits of operator monitoring and control of a mean CF > 10 g during PVI[24]. However, at 12 mo the AF recurrence rate was similar in both groups[24]. Consistent with these data, a larger study by Ullah *et al*[34] using the same methodology showed that access to CF data during the procedure was associated with reduced acute PV reconnection, although no benefit was observed in terms of 1-year success rate. These results suggest that CF monitoring during PVI may not impact long-term clinical outcome because it is only one of multiple factors that determine lesion durability.

Ablation index

As has been explained, previously described endpoints (CF and FTI) do not take the power used during RF

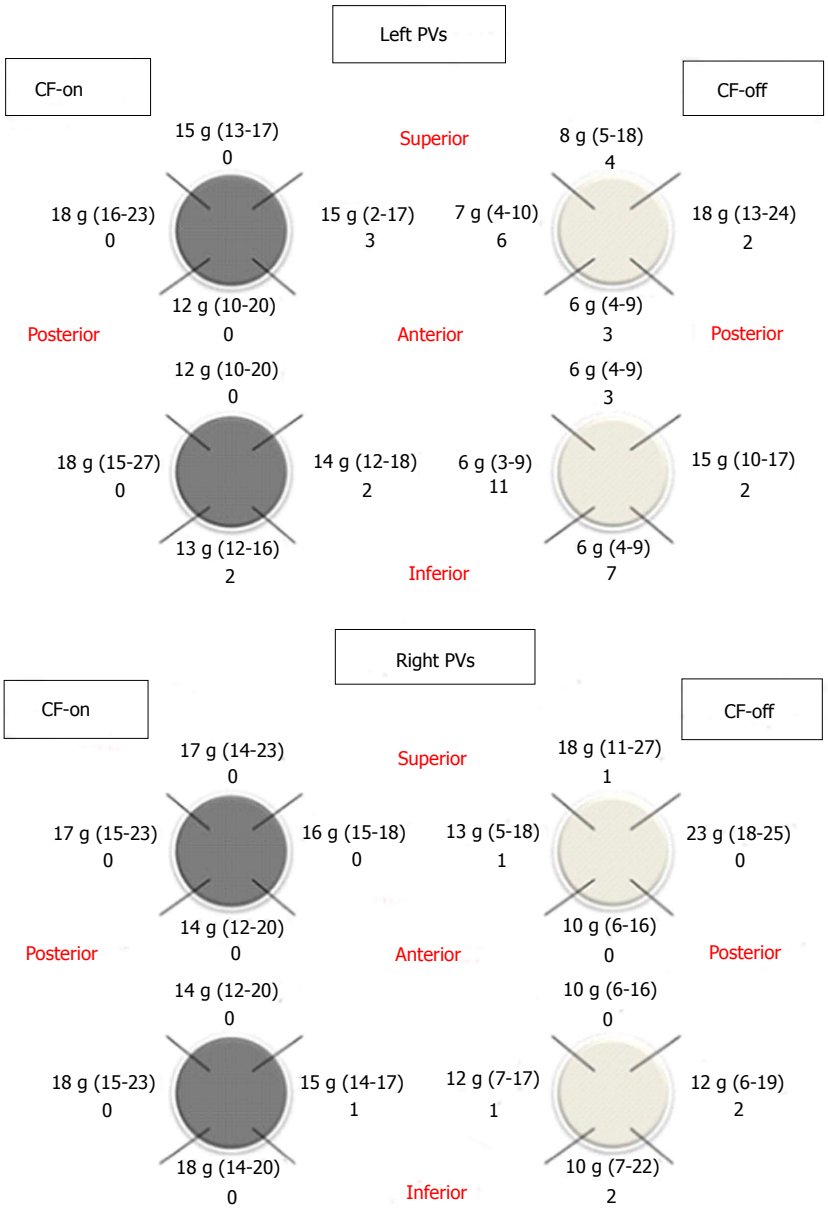

Figure 1 Contact force variability according to left atrium anatomy. Contact force (CF) is expressed in grams (g; median and 25th-75th percentile) and the number of pulmonary veins segments with conduction gaps (bold) in the CF-on group (dark gray) and the CF-off group (light gray). Reproduced with permission from Pedrote *et al*[24].

application into account. In order to resolve this limitation, the ablation index has been proposed as a marker of ablation lesion quality that incorporates CF, ablation time, and RF power in a weighted formula (the greater the impact of power over CF, the greater the impact on the initial phase of ablation). A recent study by Das *et al*[35] showed that the minimum ablation index was an independent predictor of conduction recovery after PVI. Furthermore, in this study, higher ablation index values were required to prevent reconnection of anterior/roof segments, compared to posterior/inferior segments[35].

Lesion contiguity

The EFFICAS-II study demonstrated that lesion contiguity is an essential component of effective PVI. The analysis of the contiguity index revealed that even with effective use of optimized CF, 15% of PVs were reconnected after ablation due to non-contiguity between point-by-point lesions along ablation line[28]. Consistent with these data, Park *et al*[36] showed that acutely durable PVI can be achieved in CF-guided ablation when RF lesions are delivered with a mean CF > 10 g and an inter-lesion distance < 5 mm.

A novel automated technology for tagging ablation lesions (VisiTag module) allows real-time assessment of catheter stability, contact force, power, and impedance drop during radiofrequency applications (Figure 2). This technology improves lesion efficiency and reduces the number of ineffective applications[37]. Catheter stability tracking during PVI is essential in order to achieve appropriate lesion contiguity. Okumura *et al*[38] reported

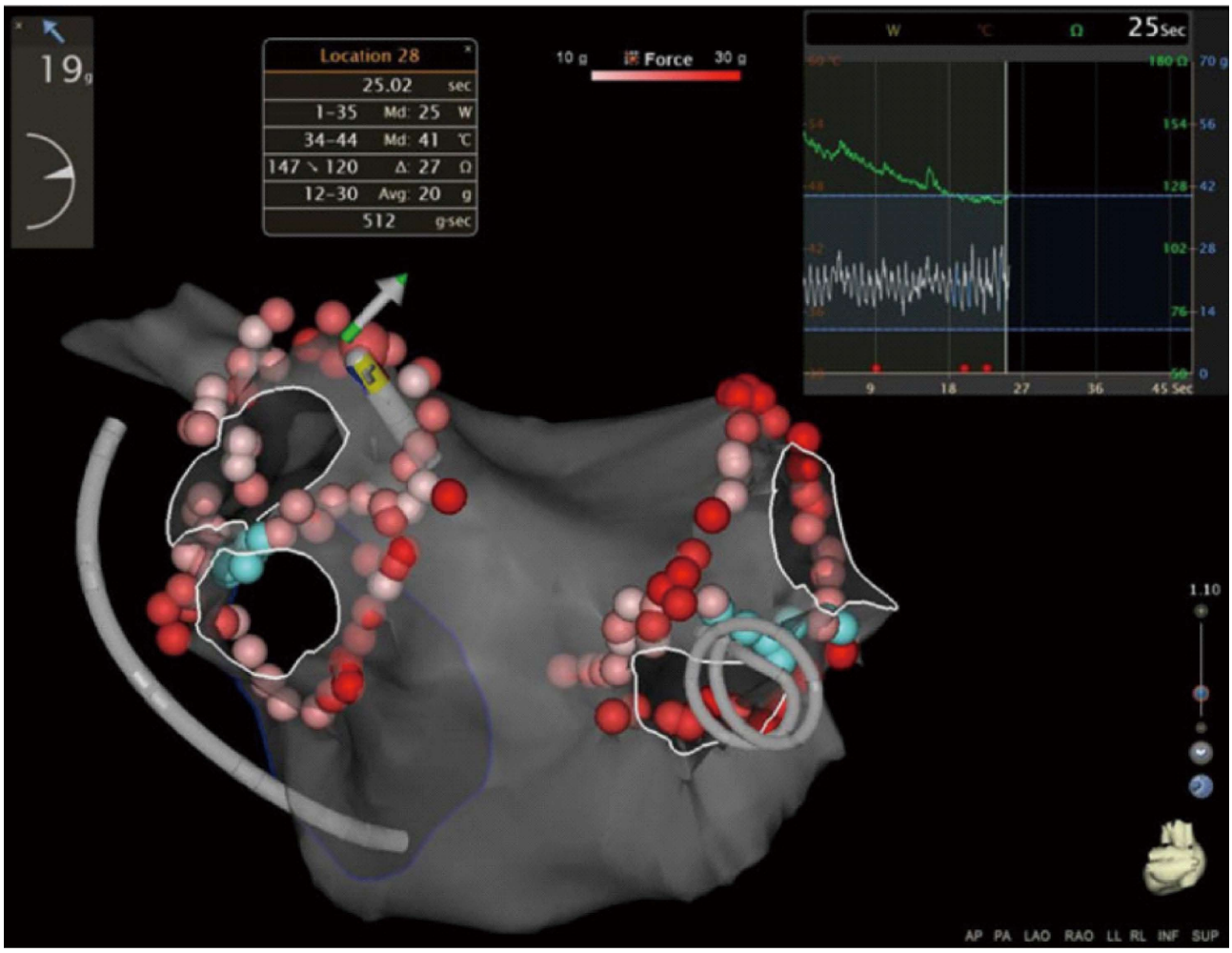

Figure 2 Automatic tagging of radiofrequency lesions. The contact force (CF) of each application is color-coded (color bar). The manually acquired RF applications are displayed in green. The central box shows the information collected by the VisiTagTM module on each point, including average CF, time, force-time integral, temperature, power, and delta impedance. The force and impedance graphs from this RF point are shown on the right, and the real-time CF and direction dashboard are shown on the left. Reproduced with permission from Pedrote *et al*[24]. RF: Radiofrequency.

that a strict stability setting (3-mm distance limit for at least 10 s) for VisiTag reduced acute PV reconnection, although no benefit was observed in mid-term outcomes.

HOW TO OPTIMIZE THE DETECTION OF ACUTE PV RECONNECTION DURING THE ABLATION PROCEDURE

Circular mapping catheters

Circumferential PVI guided by nonfluoroscopic electroanatomic mapping systems, without confirmation of electrical isolation with a circular mapping catheter, has been shown to be ineffective in achieving long-term arrhythmia control[39]. Additionally, a randomized study comparing PVI guided by circular mapping catheter *vs* PVI using only RF catheter showed that the use of circular mapping catheter is associated with better acute results and lower recurrence rates[40]. Therefore, electroanatomic mapping-guided circumferential PV ablation without use of the circular mapping catheter has been demonstrated to be less reliable to achieve PVI and significantly less effective than circular mapping catheter-guided PVI in terms of arrhythmia-free survival.

Identification of dormant conduction

The identification of dormant tissue that has been rendered unexcitable by "stunning" or edema is a significant challenge that may potentially increase risk of AF recurrence. The detection of such "dormant conduction" during the initial ablation procedure may therefore help identify PVs with the potential to reconnect after the index procedure, and targeted ablation at these sites may reduce the risk of recurrent AF. Adenosine has been shown to effectively uncover dormant conduction. Following ablation, adenosine selectively hyperpolarizes PV cells by increasing inward rectifier potassium current, thereby restoring excitability of inactivated voltage-dependent Na^+ (INa) and reestablishing conduction in dormant PVs[41]. Multiple studies have shown that adenosine is clinically useful in identifying PV reconnection, as well as cavotricuspid isthmus reconnection[42]. An early study reported that

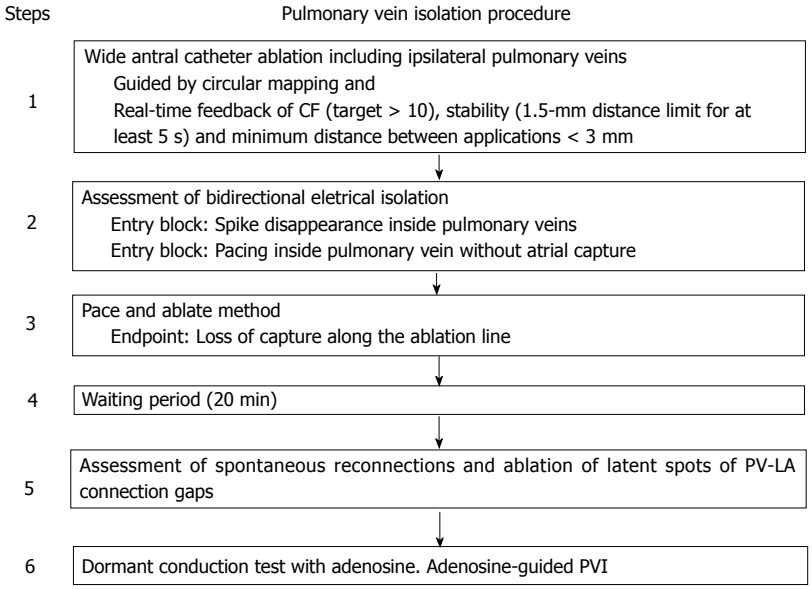

Figure 3 Stepwise approach for permanent pulmonary vein isolation. CF: Contact force; PVI: Pulmonary vein isolation.

adenosine induced reconnection in 25% of PVs immediately after successful isolation[43]. Tritto *et al*[44] further demonstrated that delivering additional RF lesions at electrical gap sites elicited by adenosine definitively eliminated recovery of PV reconnection in all cases. Subsequent studies have shown that AF recurrence after PV isolation could be reduced by delivering additional ablation lesions to eliminate adenosine-induced dormant PV conduction[45-47]. Other studies[48,49] did not confirm the usefulness of adenosine in AF recurrence after PVI, fueling a need for randomized trials.

Two randomized trials (ADVICE and UNDER-ATP) have assessed whether elimination of dormant PV conduction after PVI is better than conventional PVI in terms of arrhythmia-free survival. The ADVICE study showed that the use of adenosine to identify and target areas of dormant conduction significantly improved long-term arrhythmia-free survival, compared to PVI alone[50]. In contrast, the UNDER-ATP trial found no significant reduction in arrhythmia-free survival by ATP-guided PVI, compared with conventional PVI[51]. The discrepancy between ADVICE and UNDER-ATP trials may be due to differences in the rate of dormant conduction, around 50% in the ADVICE trial and 28% in UNDER-ATP. This suggests that the benefit of using adenosine after PVI depends on how frequently dormant conduction is observed; which is highly affected by the ablation procedural method.

Pace and ablate

Entrance and exit block confirmed by the absence of PV potentials and by pacing inside the PVs is a common procedural endpoint of encircling PVI. However, it has been suggested that pacing along the ablation line may identify latent spots of PV-LA antrum connection gaps not detected by circular mapping catheters. Steven *et al*[52] showed that more RF ablation energy was required to achieve loss of pace capture along the ablation line than for entrance block into the PVs, suggesting that reaching the endpoint of loss of capture along the ablation line may be associated with more durable lesions. Consistent with this hypothesis, a randomized study confirmed that the use of pacing to ensure an unexcitable gap along the ablation line improved success rates at 12 mo post-PVI, compared to reliance on bidirectional block alone (83% *vs* 52%, respectively)[53]. However, it should be noted that adenosine was not used to identify dormant conduction after PVI in this study. In contrast to these findings, two recent studies showed that although PVI followed by the pace and ablate method reduced dormant PV conduction unmasked by adenosine, there was no difference in 1-year AF recurrence, compared to adenosine-guided ablation[54,55].

Although the available results suggest that both techniques achieve similar long-term outcomes, the potential effect on recurrence rates of combining pace and ablate with adenosine-guided PVI remains unknown. A recent study by Kogawa *et al*[56] showed that sites with adenosine-induced dormant PV reconnection did not match the excitable gaps identified by pacing, suggesting a difference in the underlying mechanism to elucidate potential PV-antrum gaps. Thus, the authors proposed that an adenosine provocation test followed by pace and ablate method could be useful in reducing AF recurrence. Further prospective and randomized studies are required to confirm this hypothesis.

NON-PV SOURCES OF AF RECURRENCE

It should be noted that a variable proportion of patients may have AF recurrence despite persistent PVI. This could be due to the existence of non-PV triggers[57]. Typically, these non-PV triggers are located in specific

regions such as the crista terminalis, the superior vena cava, the Eustachian ridge, the fossa ovalis, the left atrial appendage, the inferior mitral annulus and the coronary sinus. Empirical ablation of these common origins of triggers is not recommended. However, once a trigger is identified, it should be eliminated in order to achieve better outcomes[58].

EXPERT RECOMMENDATIONS

Based on our own experience, we propose the following step-wise approach to achieve permanent PVI (Figure 3). Our unit adopted this strategy two years ago, with good arrhythmia-free survival at 12 mo (84%), a very low complication rate (1%), and no increase in procedure time[24,59].

FUTURE PERSPECTIVES

The implementation of non-fluoroscopic navigation systems in the electrophysiology laboratory has improved anatomic definition of cardiac structures. However, the increased complexity of ablation procedures demands better intra-procedural anatomic definition and improved accuracy in catheter positioning. Novel non-fluoroscopic systems have been proposed for catheter guidance during PVI procedures. In animal studies, Ranjan *et al*[60] showed the feasibility of catheter tracking, electrogram recording, and RF energy delivery in a real-time MRI environment. Intra-procedural MRI allowed real-time visualization of lesion formation and tissue characterization, which could permit the assessment of lesion depth and transmurality. Furthermore, their work demonstrates the utility of MRI-guided PVI to identify gaps intra-procedurally and guide catheter positioning to target them. However, this proof-of-concept has not been tested in humans. In order to use this technology in clinical settings, several technical challenges must be overcome to obtain better signals and develop more maneuverable and easily visible catheters. However, this promising technology will provide considerable benefits by delivering accurate anatomic definition and monitoring of RF lesions.

CONCLUSION

PVI is the cornerstone of catheter-based therapies for AF. PV reconnection after PVI represents the main limitation of AF ablation techniques. Efforts should be made to develop strategies that achieve more durable lesions. Current techniques associated with better acute (and probably long-term) outcomes include antral PVI guided by circular mapping catheters, the use of CF catheters, lesion contiguity, and the assessment of dormant PV conduction by adenosine and/or pace and ablate. Finally, a subset of patients may still have AF recurrences despite persistent PVI, due to the presence of non-PV triggers. Efforts should be made in order to individualize the treatment according to each patient's specific mechanism of recurrence (drivers, rotors, focal activity…).

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ORIGINAL ARTICLE

Retrospective Cohort Study

Accuracy of gestalt perception of acute chest pain in predicting coronary artery disease

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Abstract

AIM

To test accuracy and reproducibility of gestalt to predict

obstructive coronary artery disease (CAD) in patients with acute chest pain.

METHODS

We studied individuals who were consecutively admitted to our Chest Pain Unit. At admission, investigators performed a standardized interview and recorded 14 chest pain features. Based on these features, a cardiologist who was blind to other clinical characteristics made unstructured judgment of CAD probability, both numerically and categorically. As the reference standard for testing the accuracy of gestalt, angiography was required to rule-in CAD, while either angiography or non-invasive test could be used to rule-out. In order to assess reproducibility, a second cardiologist did the same procedure.

RESULTS

In a sample of 330 patients, the prevalence of obstructive CAD was 48%. Gestalt's numerical probability was associated with CAD, but the area under the curve of 0.61 (95%CI: 0.55-0.67) indicated low level of accuracy. Accordingly, categorical definition of typical chest pain had a sensitivity of 48% (95%CI: 40%-55%) and specificity of 66% (95%CI: 59%-73%), yielding a negligible positive likelihood ratio of 1.4 (95%CI: 0.65-2.0) and negative likelihood ratio of 0.79 (95%CI: 0.62-1.02). Agreement between the two cardiologists was poor in the numerical classification (95% limits of agreement = -71% to 51%) and categorical definition of typical pain (Kappa = 0.29; 95%CI: 0.21-0.37).

CONCLUSION

Clinical judgment based on a combination of chest pain features is neither accurate nor reproducible in predicting obstructive CAD in the acute setting.

Key words: Acute chest pain; Clinical judgment; Gestalt; Coronary artery disease; Acute coronary syndrome

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Core tip: In the scenario of acute chest pain, individual features of chest pain presentation are intuitively combined to form physician's impression, by a process called "gestalt". Physicians commonly assess probability of disease by unstructured clinical judgment. Although commonly used and presumed to be accurate, diagnostic assessment by gestalt of acute chest pain lacks validation. In the present manuscript, we investigated the accuracy of gestalt in the prediction of coronary artery disease (CAD). Our results indicate that clinical judgment (gestalt) of acute chest pain characteristics has low diagnostic accuracy for obstructive CAD. Thus, physicians should be cautious when relying on chest pain characteristics and investigators should redirect their focus to identify validated predictors.

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INTRODUCTION

In the scenario of acute chest pain, specific features of symptoms have either null or weak association with coronary artery disease (CAD) etiology[1-3]. However, in clinical practice, these characteristics are not analyzed separately. Individual features of chest pain presentation are intuitively combined to form the physician's impression by a process called "gestalt". Although presumed to be accurate, diagnostic assessment by gestalt of acute chest pain lacks validation[4,5]. In fact, it remains uncertain how much physicians should rely on acute chest pain characteristics to estimate pretest probability of CAD.

Our aim was to test the hypothesis that physicians' gestalt accurately estimates probability of CAD. Since gestalt accuracy depends on chest pain characteristics, and knowing that these findings have a broad and variable spectrum, we focused our analysis exclusively on clarifying the reliability of this component. In order to isolate chest pain characteristics variables, we invited an experienced cardiologist, blind to patient's demographic and clinical features, to estimate probability of CAD based on 14 symptom characteristics obtained by remote standardized interview. The accuracy of unstructured clinical judgment was tested against non-invasive or invasive tests that were used as reference standards. Additionally, a second cardiologist performed the same evaluation in order to test for reproducibility of clinical judgment.

MATERIALS AND METHODS

Sample selection

During a period of 24 consecutive months, all patients admitted in the Chest Pain Unit of our Hospital due to chest discomfort were included in the study, regardless of electrocardiogram or troponin results. The study was approved by an institutional review committee and all subjects gave informed consent.

Clinical judgment of chest pain

Data collection was planned a priori and performed prospectively. At admission, chest pain characteristics were collected by standardized interview performed by 3 investigators (MC, NS, FL), trained to diminish bias and improve reproducibility of data collection. Fourteen standardized questions were recorded on a specific form: Precordial location (lower left side), compressive

nature, radiation to left arm, radiation to neck, severe intensity, similarity to previous infarction (if applicable), presence of vagal symptoms, worsening with body movement, worsening with palpation, worsening with arms movement, worsening with deep breath, and relief by nitrate. Characteristics were considered positive if patient's answer was clearly affirmative. Dubious answers ("maybe", "sometimes", "not sure") were taken as negative. In addition, 3 numeric variables were recorded: Intensity of chest pain from 0 to 10 (defined by the patient according to a visual scale), number of pain episodes at rest and duration of the longest episode in minutes. No additional information regarding demographic or clinical characteristics was recorded on this form.

Subsequently, a cardiology faculty member (CV, with 23 years of experience in the field of acute chest pain) assessed the forms and classified chest pain according to the 14 characteristics. This investigator did not have any contact with the patients, and was completely blind to additional information such as name, gender, age, previous history or additional tests. This method guaranteed that medical judgment was based exclusively on chest pain characteristics. In order to assess reproducibility of medical judgment, the same procedure was independently performed by a second faculty member (LLJ) in all patients and his classification was compared with the first.

Chest pain was classified in four ways: (1) typical or atypical; (2) Non-anginal, Undefined or Anginal Chest Pain; (3) definitely angina, probably angina, probably not or definitely not; and (4) numeric probability of coronary etiology from 0 to 100. No objective predefinition of these classifications was provided to the evaluators of chest pain, enabling the definition to be a result of the physician's unstructured discretion. This method guaranteed that answers reflected authentic clinical judgment.

Obstructive CAD

Outcome data was collected by 3 other independent investigators (MC, FK, FF) and adjudicated by a fourth investigator (LC). Obstructive CAD was defined by a stenosis $\geqslant$ 70% on angiography. For diagnostic evaluation, patients underwent invasive coronary angiography or a non-invasive test (perfusion magnetic resonance imaging or nuclear single-photon emission computed tomography), at the discretion of the assistant cardiologist. In case of a positive non-invasive test, patients underwent angiography for confirmation. A negative non-invasive test indicated absence of obstructive CAD and no further test was required. In case of a dominant alternative diagnosis as confirmed by imaging (such as pericarditis, pulmonary embolism, aortic dissection or pneumonia), the etiology was defined as non CAD.

Statistical analysis

Frequencies were compared by Pearson's χ^2 test and means by Student's *t* test. The accuracy of clinical judgment in predicting CAD was described by point-estimate and 95%CI of sensitivity, specificity, likelihood ratios and predictive values. The accuracy of numerical estimative of CAD probability was described by the area under the ROC curve with 95%CI.

For analysis of reproducibility, the Kappa test was utilized to assess agreement between two observers regarding the different forms of categorical classification. For numeric estimation of CAD probability, the Bland-Altman analysis was used: mean absolute error between the two observers (mean of differences without the signal), mean signed difference (bias) and 95% limits of agreement.

Sample size was calculated based on an expected CAD prevalence of 50%. Thus, a sample size of 300 would provide 150 patients with and 150 patients without CAD. Considering assumptions of 70% sensitivity and specificity, 150 patients would yield a ± 8% precision for the 95%CI.

RESULTS

Sample characteristics

From 2011 to 2013, a sample of 330 patients was studied, 59 ± 15 years old, 58% males, 54% presented ischemic electrocardiographic changes and 48% had positive troponin. All individuals had gestalt evaluation and reference standard performed during the same admission. Obstructive CAD was identified according to study protocol in 48% of the individuals. Baseline characteristics are depicted on Table 1.

Accuracy of clinical judgment

Typical *vs* atypical chest discomfort: Chest discomfort was classified as typical in 41% of patients. Obstructive CAD was present in 56% of individuals with typical symptoms, compared with 42% of those with atypical symptoms (P = 0.02). Among 158 individuals with obstructive CAD, the discomfort was defined as typical in 75, yielding a sensitivity of 48% (95%CI: 40%-55%). Conversely, in 172 individuals free of CAD, 113 had symptoms defined as atypical, leading to a specificity of 66% (95%CI: 59%-73%). Consequently, typical pain had a negligible positive likelihood ratio of 1.4 (95%CI: 0.65-2.0), as well as a negative likelihood ratio of 0.79 (95%CI: 0.62-1.02). The positive predictive value of typical chest pain was only 56% (95%CI: 48%-64%), while the negative predictive value was 58% (95%CI: 51%-65%), Table 2.

Non-anginal, undefined or anginal chest pain: Patients were equally distributed among the 3 classifications, 36% defined as non-anginal, 34% as undefined and 30% as anginal. Prevalence of CAD was respectively 38%, 49% and 55% (P = 0.04). Among 158 individuals with CAD, only 66 had anginal pain, leading to a sensitivity of 42% (95%CI: 34%-50%), positive likelihood ratio of 1.35 (95%CI: 0.89-2.1) and

Table 1 Clinical characteristic *n* (%)

Variable	Description
Sample size	330
Age (yr)	59 ± 15
Male gender	192 (58)
History of coronary disease	112 (34)
Diabetes	104 (32)
Ischemia on EKG	179 (54)
Positive troponin	157 (48)
Signs of left ventricular failure	28 (8.5)
Final diagnosis	
Unstable angina	52 (16)
Myocardial infarction	142 (43)
No CAD, but undefined diagnosis	103 (31)
Gastrointestinal disorder	5 (1.5)
Osteo-muscular disorder	1 (0.3)
Pericarditis	12 (3.6)
Pulmonary embolism	2 (0.6)
Aortic dissection	2 (0.6)
Pneumonia	2 (0.6)
Other	9 (2.7)

CAD: Coronary artery disease.

positive predictive value of 56% (95%CI: 47%-65%). Conversely, in 172 individuals free of CAD, 62 had symptoms defined as non-anginal, leading to a specificity of 36% (95%CI: 29%-43%), negative likelihood ratio of 0.67 (95%CI: 0.40-1.1) and negative predictive value of 62% (95%CI: 53%-62%) (Table 2).

Definitely angina, probably angina, probably not and definitely not: Patients were equally distributed among the 4 categories, with 25% classified as definitely angina, 32% as probably angina, 23% as probably not and 20% as definitely not. Prevalence of CAD was similar among the first 3 groups, respectively 49%, 56% and 51%, while patients classified as definitive no-angina had a lower prevalence of 30%, which was responsible for the statistical difference among the 4 groups (P = 0.008). Thus, the threshold of definitely not was utilized for accuracy. Among 158 individuals with CAD, 138 were not classified as definitely not, leading to sensitivity of 83% (95%CI: 77%-89%). Among the 172 patients free of disease, only 47 were definitely not, yielding 27% specificity (95%CI: 20%-34%). Thus, the negative likelihood ratio of definitely not was a negligible 0.63 (95%CI: 0.32-1.15), with a negative predictive value of 70% (95%CI: 59%-81%) (Table 2).

Subjective estimation of CAD probability: Probability of CAD had a mean of 59% ± 34%, with a median of 70% (interquartile range = 30%-90%). Individuals with CAD had a median probability of 80% (interquartile range = 50%-95%), compared with 60% in patients free of disease (interquartile range = 10%-90%) - P < 0.001. The diagnostic area under the ROC for numeric probability was 0.61 (95%CI: 0.55-0.67) (Figure 1).

Reproducibility of clinical judgment

The two observers agreed in 62% of the patients regarding typical *vs* atypical chest pain, yielding a weak Kappa of 0.29 (95%CI: 0.21-0.37; P < 0.001). For non-anginal, undefined or anginal chest pain, agreement was 53% (Kappa = 0.28; 95%CI: 0.20-0.36; P < 0.001). For definitely angina, probably angina, probably not and definitely not, agreement was 42%, leading to a weak Kappa of 0.21 (95%CI: 0.14-0.28; P < 0.001).

Regarding numeric estimation of probability, mean absolute error was 23% ± 23%, with a mean signed difference (bias) of - 9.7% ± 31%, with 95% limits of agreement from - 71% to + 51%. The Bland-Altman plot showed a diamond pattern with reasonable agreement in very low (< 20%) or very high (> 80%) ranges of probability, with increasing disagreement as probability becomes more intermediate (Figure 2).

DISCUSSION

The present study indicates that clinical judgment (gestalt) of acute chest pain has low diagnostic accuracy for obstructive CAD. In addition, there was poor agreement between the gestalt of two physicians, indicating low precision of intuitive interpretation of chest pain features. These findings confront the common belief that physicians should take into account the typicality of symptoms when evaluating patients with acute chest pain.

Our primary interest was to assess the role of chest pain features on clinical evaluation. Thus, our methods were designed to evaluate accuracy of clinical judgment that comes specifically from chest pain characteristics, as opposed to the entire clinical presentation. In order to do this, we blinded the physician to demographics, clinical characteristics or patient's appearance. Secondly, we tested physician's intuitive judgment that comes from the combination of all features, instead of the accuracy of specific symptom characteristics. Thus, there was not an a priori criterion for classifying chest pain, allowing the physician to use his own intuition (unstructured clinical judgment).

Physicians commonly assess probability of disease by unstructured clinical judgment. Although medical doctors normally put confidence into this type of judgment, it tends to be inaccurate. As described by Nobel Prize laureates and psychologists Kahneman and Tversky, judgment under uncertainty is vulnerable to cognitive bias, due to heuristics utilized in the process of intuitive thinking[6]. A common example of heuristics is "representativeness": If A resembles B, when A is present we think B is highly probable to be present. Oppressive chest pain resembles angina. Hence, a physician may jump to conclude that a patient with oppressive chest pain has a high probability of CAD. However, the likelihood ratio of oppressive chest pain is very low. These cognitive biases that are present in intuitive thinking explain why mechanical models are

Table 2 Accuracy of the 3 classifications of chest pain according to medical judgment

	Sensitivity	Specificity	Positive LR	Negative LR	Positive PV	Negative PV
Classification 1 (2-level)						
Typical (*vs* atypical)	48% (40%-55%)	66% (59%-73%)	1.4 (0.65-2.0)	0.79 (0.62-1.02)	56% (48%-64%)	58% (51%-65%)
Classification 2 (3-level)[1]						
Angina (*vs* undefined/no-angina)	42% (34%-50%)	69% (62%-76%)	1.35 (0.89-2.1)		56% (47%-65%)	
No-angina (*vs* undefined/angina)	76% (69%-83%)	36% (29%-43%)		0.67 (0.40-1.1)		62% (53%-72%)
Classification 3 (4-level)[1]						
Definitely no-angina (*vs* the other 3 groups)		27% (20%-34%)		0.63 (0.32-1.15)		70% (59%-81%)

Numbers in parenthesis are 95%CI. [1]Because only no-angina distinguished itself from the other 3 classifications, only specificity, negative LR and negative PV were calculated. LR: Likelihood ratio; PV: Predictive value.

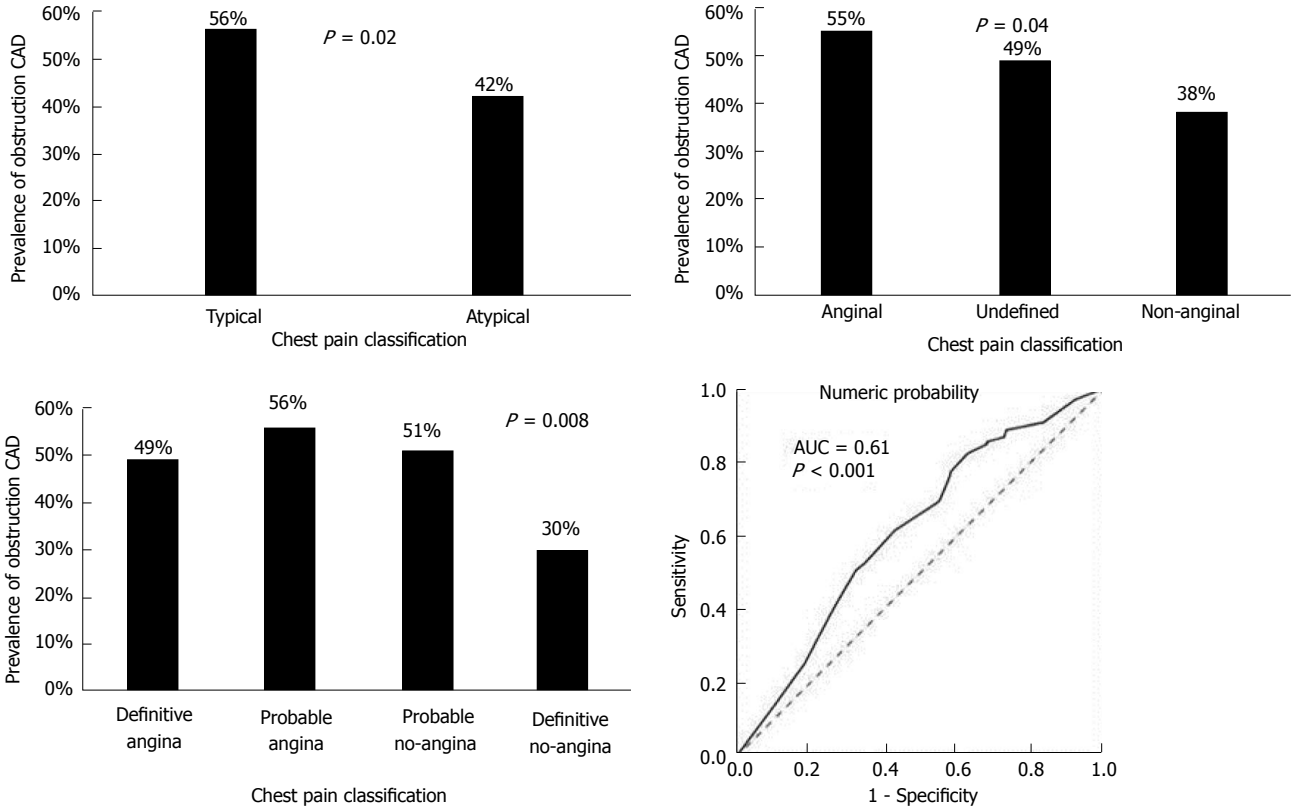

Figure 1 Categorical and numerical accuracy of gestalt, regarding the prediction of obstructive coronary artery disease. CAD: Coronary artery disease.

usually better predictors than medical judgment. For instance, a systematic review of several medical and non-medical situations consistently showed better predictability of probabilistic models, in comparison with specialist' decision[7]. Therefore, in order to avoid heuristics when evaluating a chest pain scenario, physicians should increase awareness of the low diagnostic value of chest pain characteristics or invest in probabilistic models able to predict obstructive disease more precisely.

The lack of reproducibility between two independent cardiologists also deserves attention. While lack of accuracy promotes diagnostic errors, lack of agreement impairs consensus regarding medical management. Thus, relying too much on chest pain characteristics does not only promote probabilistic errors, but also promote differences in clinical impressions, leading to confusion and discordance among the medical team.

Although an experienced physician made clinical judgment, we cannot guarantee that his analysis is similar to most physicians. In fact, this would be unlikely, considering the low level of reproducibility found in our head-to-head comparisons. Nevertheless, the concept of accuracy is somewhat independent of agreement. Accuracy depends on the proportion of correct predictions. Two models can have the same proportion of correct predictions and not be related to the same patients. Indeed, we should not expect different people to have the same intuition regarding diagnosis. This rationale is the basis for testing the concept of accuracy of physician judgment by using one specific professional as a proxy of the average physician. Nevertheless, we recognize that further studies are needed to validate our findings, extending it to different populations of

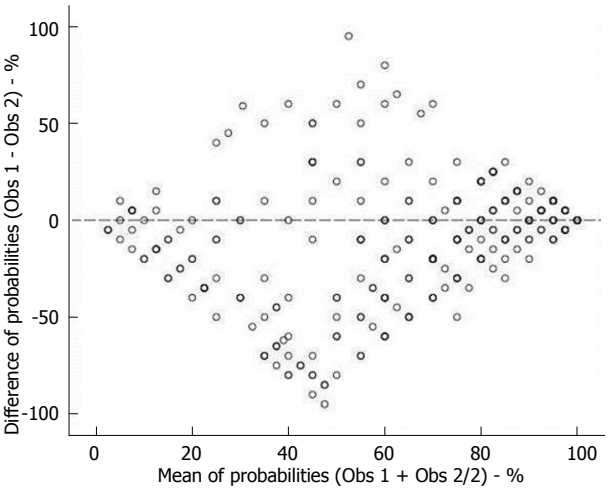

Figure 2 Bland-Altman plot of agreement between two observers regarding gestalt's numerical probability of coronary disease.

physicians and patients.

Usually, accuracy studies of acute chest pain utilize myocardial infarction as the outcome of interest. Differently, we opted to use obstructive CAD as the outcome to be predicted by clinical judgment, because it is has a more objective definition than myocardial infarction. This objectiveness was important because we were evaluating physician's cognitive judgment based on clinical data, and definition of myocardial infarction as an outcome is also influenced by clinical judgment. Therefore, to avoid this redundancy, we used obstructive CAD defined by angiography or functional tests.

A sense of surprise regarding our results may arise from the traditional belief that a careful history is important. Firstly, our findings do not undermine the value of the history as a whole, because our analysis only refers to chest pain characteristics. Secondly, our data is in line with chest pain characteristics being consistently demonstrated to be inaccurate. The novelty of our study is the gestalt evaluation of these characteristics taken together. And the main application of our results prompts us to reconsider how much value we should assign to classifications such as typical or atypical chest pain, as these have little or no influence on probability of CAD. The fact that typicality of pain did not show significant differences on predicting CAD probability has important practical implications, since decision-making during the clinical management of patients can be initially guided by these subjective classifications. The overvaluing of the current categorization may be misleading, resulting in under or overdiagnosis of CAD and mismanagement of cases. Therefore, the use of probabilistic models is supposed to be a more effective way to avoid representativeness heuristics.

In conclusion, our findings indicate that physician's gestalt based on acute chest pain features lacks accuracy and reproducibility in estimating the probability of CAD. Physicians should be cautious when relying on chest pain characteristics and investigators should redirect their focus to identify validated predictors.

COMMENTS

Background

Traditionally, physicians tend to strongly rely on chest pain characteristics to define whether a patient has low or high probability of having coronary artery disease, through a process called gestalt. This kind of clinical judgment, however, does not seem to have good diagnostic accuracy in predicting coronary artery disease (CAD) etiology.

Research frontiers

Many authors have compared the accuracy of scores *vs* medical judgment in acute coronary syndromes. However, the study intends to clarify a current non-scientific trend of the physician community to make cardiovascular inferences directly from chest pain characteristics. This research establishes a new perspective for chest pain analysis, and reinforces the need to identify strong diagnostic clinical predictors of obstructive disease and then develop a multivariate model to help the emergency physician to assess this condition, instead of intuitive univariate diagnostic association currently applied.

Innovations and breakthroughs

The main idea presented was the evaluation of the diagnostic accuracy of chest pain characteristics in predicting the probability of CAD. This was performed by using only pain characteristics and with no further information. The novelty of the study is the gestalt evaluation of these characteristics taken together, while previous others had analyzed the diagnostic probability of each symptom separately. Additionally, previous literature has tested medical gestalt *vs* probabilistic scores, while the authors have tested medical gestalt *vs* real diagnosis.

Applications

The main application of the results relies on avoiding putting too much value of classifications such as typical or atypical chest pain. These classifications merely refer to chest pain characteristic and this isolated aspect has little or no influence on probability of CAD.

Terminology

Clinical gestalt refers to the theory that physicians and healthcare professionals organize clinical perceptions into "unified wholes". This means that physicians can make clinical decisions without necessarily having complete information, posteriorly using this information to create solutions that can be generalized from one situation to another. Clinical gestalt represents an overall analysis, cultivated mainly by personal experience, history and examination.

Peer-review

The present study essentially supports that the elements of the chest pain history are only a little bit associated with increasing accuracy of diagnosis with CAD. Furthermore, it is very interested that there were poor agreement between the two cardiologists. The methods are sound, and the used statistics seem also sound.

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ORIGINAL ARTICLE

Retrospective Study

Validity of electrocardiographic criteria for increased left ventricular mass in young patients in the general population

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Author contributions: Sklyar E designed and supervised the study; Ginelli P collected and analyzed the data and drafted the manuscript; Barton A assisted with data collection; Peralta R provided statistical analysis; Bella JN revised the manuscript for important intellectual content; all authors have read and approved the final version to be published.

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Abstract

AIM

To investigate validity of electrocardiographic (ECG) criteria for left ventricular hypertrophy (LVH) in young adults.

METHODS

Retrospectively, echocardiograms showing LVH and concomitant electrocardiograms were collected in patients 18 to 39 years old. A control group of patients without LVH was collected. Using echocardiogram as the gold standard, electrocardiograms were analyzed using common voltage criteria.

RESULTS

Study included 100 subjects (52% male, mean age = 28 ± 6.8 years, 96% Hispanic or African-American) with 50% LVH prevalence. Sensitivity and specificity for Sokolow-Lyon criteria were 24% (95%CI: 13.5%-38.4%) and 88% (95%CI: 74.9%-95%). For Cornell criteria, sensitivity was 32% (95%CI: 19.9%-46.8%) and specificity 98% (95%CI: 87.9%-99.8%). For R in aVL criteria, sensitivity was 12% (95%CI: 4.9%-25%) and specificity 100% (95%CI: 91.1%-100%).

CONCLUSION

In young adults common ECG voltage criteria have low sensitivities and high specificities similar to other age groups. Low sensitivities preclude these ECG criteria from serving as effective screening tests.

Key words: Electrocardiographic; Left ventricular hypertrophy criteria; Young adults

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Core tip: The electrocardiographic (ECG) has been used for years to diagnose left ventricular hypertrophy (LVH). However, to the best of our knowledge, there were no prior studies validating most common ECG criteria for LVH in young adults. The authors believe that this is important group of population, as athletes screening for pre participation to professional sport falls into this category. ECG is one of the proposed screening tools and we think that it should be validated for diagnosis of LVH. This study showed that common ECG criteria for LVH can be used in young adults with similar sensitivity and specificity to other age groups.

Sklyar E, Ginelli P, Barton A, Peralta R, Bella JN. Validity of electrocardiographic criteria for increased left ventricular mass in young patients in the general population. *World J Cardiol* 2017; 9(3): 248-254 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i3/248.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i3.248

INTRODUCTION

Epidemiologic studies have demonstrated that increased left ventricular mass (LVM) is a risk factor for cardiovascular disease and death[1-4]. Left ventricular hypertrophy (LVH) has a significant prevalence in the general population with some estimates approaching 16%-20% in population based samples[5,6], and up to 50% in those with hypertension[7-9]. As a result of the obesity epidemic, even the adolescent population has had a higher incidence of hypertension and LVH[10], with some estimates showing LVH in nearly 30% of younger hypertensive[11]. Thus, with the high prevalence of LVH that extends even into the young population and the increased cardiovascular risk it confers, it is important to identify patients with increased LVM so that they may receive appropriate care.

Another important indication for detecting LVH, specifically in younger individuals in the general population, is in the setting of pre-participation screening prior to partaking in athletic activities. Current screening methods often involve looking for evidence of LVH on electrocardiogram (ECG) and transthoracic echocardiogram (TTE) to help identify those who may be at risk for sudden cardiac death[12]. Unfortunately, LVH is often misdiagnosed during these pre-participation screenings which can lead to unwanted outcomes[13]. Due to the immense importance of detecting increased LVM in the screening process of this younger population, a reliable screening tool is vital for this age group.

The ECG is the simplest and most commonly used method to detect LVH, but to date there has been no study evaluating the correlation between the established ECG criteria and increased LVM detected by TTE in adults from the general population with a mean age of 18 to 39 years old. Although numerous investigations have been conducted to validate the ECG criteria for LVH in individuals of the pediatric and older populations, the data for younger adults have been limited. Thus, with the growing number of young individuals with hypertension and LVH, along with the need for effective pre-participation screening, the quick and simple electrocardiographic methods for detecting increased LVM and obtaining prognostic information need to be validated for use in the younger members of the general population. Therefore, the aim of this study is to examine this particular subset of the population in order to determine the efficacy of this potentially valuable tool for identifying patients at increased risk for cardiovascular morbidity and mortality.

MATERIALS AND METHODS

This was a single-center, retrospective study involving ECG and TTE data conducted in the Cardiology Division of the Department of Medicine at Bronx Lebanon Hospital Center, a large teaching medical center in Bronx, New York. After receiving approval from the Institutional Review Board, the hospital's electronic database was used to collect all consecutive TTEs with the finding of LVH performed between January 2010 and July 2011 on male and female patients aged 18-39 years old who were referred or admitted to the hospital. A control group of age-matched patients without LVH on TTE was also collected in the same manner from the database. Subjects were also required to have a standard 12-lead ECG within 30 d before or after the reference TTE. Excluded were patients with ECGs showing myocardial infarction, bundle branch block, paced rhythm, pre-excitation, or any intraventricular conduction delay, as these ECG findings can interfere with voltage measurements and were not included in the original studies from which the ECG criteria for detecting increased LVM were derived[14,15]. After creating the study and control groups based on the presence or absence of increased LVM using TTE as the gold standard for diagnosis, the subjects' ECGs were analyzed using several ECG criteria for detecting LVH in order to determine their efficacy in this cohort of patients.

Study subjects had previously completed the prerequisite two-dimensional (2-D) rest echocardiogram using a standard, commercially available ultrasound transducer and machine (M3S probe, Vivid 7, GE Medical Systems). In each patient, standard parasternal views (long and short axis) and apical views (4- and 2-chamber) were obtained. TTE images were saved digitally in raw data format for off-line analysis using GE Medical Systems' EchoPAC PC software. These TTEs

were previously read by board-certified cardiologists on the day of acquisition, and it was these interpretations that were used to extract the study population from the hospital database. In order to ensure uniformity of the echocardiographic data used in this study, all subjects' TTEs were reread by a single board-certified noninvasive cardiologist who was blinded to the study arm in which the TTE's belonged. This reader remeasured left-ventricular end-diastolic dimension (LVEDd), end-diastolic posterior wall thickness (PWTd), and end-diastolic septal wall thickness (SWTd) in the standard 2-D parasternal long axis view as detailed by the American Society of Echocardiography (ASE)[16]. These measurements were then used to calculate LVM using the ASE recommended formula for estimation of LVM from left ventricular linear dimensions[16]: LVM = 0.8 × {1.04[(LVEDd + PWTd + SWTd)^3 - (LVEDd)^3]} + 0.6 grams. The LVM was then indexed to body surface area (BSA) which was obtained from the original reference TTE reports. The ASE gender specific cut-off values for LVM[16] were used to classify patients as having increased LVM if the LVM indexed to BSA was greater than 88 g/m^2 for women and greater than 102 g/m^2 for men.

All subjects had previously undergone a standard 12-lead rest ECG at 25 mm/s speed, 10 mm/mV sensitivity, and 0.05 Hz to 150 Hz frequency within 30 d of the index TTE. Of the various ECG criteria for LVH including, Sokolow-Lyon voltage[14], Sokolow-Lyon product[17], R in aVL voltage[14], Cornell voltage[15], Cornell product[17], and Gubner voltage[18], three of the most commonly used criteria in many clinical trials[19-21], Sokolow-Lyon voltage, Cornell voltage, and R in aVL voltage, were then selected to analyze the ECGs. For Sokolow-Lyon voltage, the amplitude of the S wave in lead V1 was added to the largest amplitude of the R wave in either lead V5 or V6, with a value greater than or equal to 35 mm meeting criteria for LVH. For Cornell voltage, the amplitude of the S wave in lead V3 was added to the amplitude of the R wave in lead aVL, with a value greater than 28 mm for men and greater than 20 mm for women signifying LVH. For R in aVL voltage, an amplitude of the R wave in lead aVL greater than or equal to 11 mm was indicative of LVH. All study ECGs were evaluated for these three criteria using manual calipers by each of two trained readers who were blinded to the study group in which the ECGs belonged. Any discrepancies in measurements between the two readers were evaluated by a board-certified electrophysiologist who made the final decision on the ECG findings.

Statistical analysis

Data management and descriptive analysis were performed with IBM SPSS 20 (Statistical Packages for the Social Sciences). Data are presented as mean (SD) for continuous variables and proportions for categorical variables. For measurements of sensitivity and specificity, increased LVM as detected by TTE was used as the reference standard against which the performance of the ECG criteria was compared. Mean values of continuous variables were compared by using an independent sample t-test. Linear correlations were evaluated with the Pearson's r correlation. Receiver operating characteristic (ROC) curves were constructed for each ECG criteria to evaluate test performance over a wide range of possible partition values. A two-tailed value of $P < 0.05$ was considered statistically significant.

RESULTS

The initial database query revealed 1107 subjects who had a TTE performed during the search period. Of these 1107 patients, 239 had LVH documented in their TTE report. Using the aforementioned inclusion and exclusion criteria, 84 subjects were then found for the increased LVM group. After left ventricular dimensions were re-measured by our expert reader, there were 50 remaining subjects with increased LVM by ASE criteria. Fifty subjects without increased LVM were found for the control group, resulting in a prevalence of increased LVM by TTE of 50%. The total study population had a mean age of 28 ± 6.8 years and consisted of 52 men and 48 women, of which 96% were either Hispanic or African-American. The 1007 excluded subjects had similar demographics with a mean age of 29 ± 6.2 years, 38% men, and 96% Hispanic or African-American. There were no significant differences noted in age, gender, or BSA between the increased LVM and control arms (Table 1). As expected, the increased LVM group had a mean LVM indexed to BSA of 130.35 ± 36.76 g/m^2 which was significantly higher ($P < 0.001$) than the control group's value of 63.61 g/m^2 ± 11.73 (Table 1). The increased LVM group also had significantly higher values ($P < 0.001$) for SWTd, PWTd, and LVEDd as compared to the control group (Table 1).

Sensitivities and specificities for detecting increased LVM with each ECG criteria are displayed in Table 2. Sensitivity and specificity for the Sokolow-Lyon criteria were 24% (95%CI: 14%-38%) and 88% (95%CI: 75%-95%), respectively. For the Cornell voltage criteria, sensitivity was 32% (95%CI: 19%-47%) and specificity was 98% (95%CI: 88%-99%). For the R in aVL criteria, sensitivity was 12% (95%CI: 5%-25%) and specificity was 100% (95%CI: 91%-100%). Positive predictive values (PPV) and negative predictive values (NPV) are also shown in Table 2. PPVs were 67% (95%CI: 41%-86%) for Sokolow-Lyon, 94% (95%CI: 69%-99%) for Cornell, and 100% (95%CI: 52%-100%) for R in aVL. NPVs were 54% (95%CI: 42%-65%) for Sokolow-Lyon, 59% (95%CI: 48%-69%) for Cornell, and 53% (95%CI: 43%-63%) for R in aVL.

ROC curves illustrating the performance of each ECG criteria in detecting increased LVM are shown in Figures 1-3. Areas under the ROC curve were 0.560 for Sokolow-Lyon, 0.650 for Cornell, and 0.560 for R in aVL. All three ECG criteria also demonstrated good statistical correlation with increased LVM by TTE (Table 3).

Table 1 Clinical characteristics of the study population

Parameter	Increased LVM (n = 50)	Controls (n = 50)	P value
Age (yr)	29.7 ± 5.9	26.9 ± 7.4	0.05
Male/female	27/23	25/25	0.69
BSA (m^2)	1.95 ± 0.34	1.88 ± 0.32	0.30
SWTd (cm)	1.09 ± 0.16	0.79 ± 0.08	< 0.001
LVEDd (cm)	5.70 ± 0.68	4.69 ± 0.43	< 0.001
PWTd (cm)	1.05 ± 0.11	0.76 ± 0.09	< 0.001
LVM/BSA (g/m^2)	130.35 ± 36.76	63.61 ± 11.73	< 0.001

LVM: Left ventricular mass; BSA: Body surface area; SWTd: Septal wall thickness at end diastole; LVEDd: Left ventricular end-diastolic dimension; PWTd: Posterior wall thickness at end diastole.

Table 2 Sensitivity, specificity, positive and negative predictive values for electrocardiographic criteria for left ventricular hypertrophy

ECG criteria	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
Sokolow-lyon	0.24 (0.14-0.38)	0.88 (0.75-0.95)	0.67 (0.41-0.86)	0.54 (0.42-0.65)
Cornell	0.32 (0.19-0.47)	0.98 (0.88-0.99)	0.94 (0.69-0.99)	0.59 (0.48-0.69)
R in aVL	0.12 (0.05-0.25)	1 (0.91-1)	1 (0.52-1)	0.53 (0.43-0.63)

PPV: Positive predictive value; NPV: Negative predictive value.

Table 3 Correlation between left ventricular mass index and electrocardiographic criteria for left ventricular hypertrophy

ECG criteria	Pearson's r correlation	P value[a]
Sokolow-lyon	0.28	0.005
Cornell	0.51	< 0.001
R in aVL	0.26	0.01

[a]Correlation is significant when $P < 0.05$. ECG: Electrocardiographic.

DISCUSSION

This investigation found that three frequently used ECG voltage criteria are effective in identifying increased LVM in the subset of the general population aged 18 to 39 years old. Sensitivity was highest with the Cornell criteria at 32%, as compared to 24% with the Sokolow-Lyon criteria and 12% with the R in aVL criteria. The highest specificity was found with the R in aVL criteria at 100%, while the Cornell and Sokolow-Lyon criteria had somewhat lower specificities of 98% and 88%, respectively. Although there is some minor variation among these values, all three criteria demonstrated a low sensitivity but high specificity for detecting increased LVM in this young adult population. These findings are similar to those previously published for other age groups and populations.

Prior studies examining the accuracy of these ECG criteria in older individuals of the general population encompassing mean ages from 45 to 70 years old[21-24] have shown similar findings with values for sensitivity ranging from 4% to 52% for the Sokolow-Lyon criteria and 2% to 41% for the Cornell criteria, and specificities ranging from 53% to 100% for the Sokolow-Lyon criteria and 89% to 100% for the Cornell criteria, as reported in a large meta-analysis[21]. In another large study in patients with mean age of 65 years old, the Sokolow-Lyon criteria had a sensitivity of 17% and

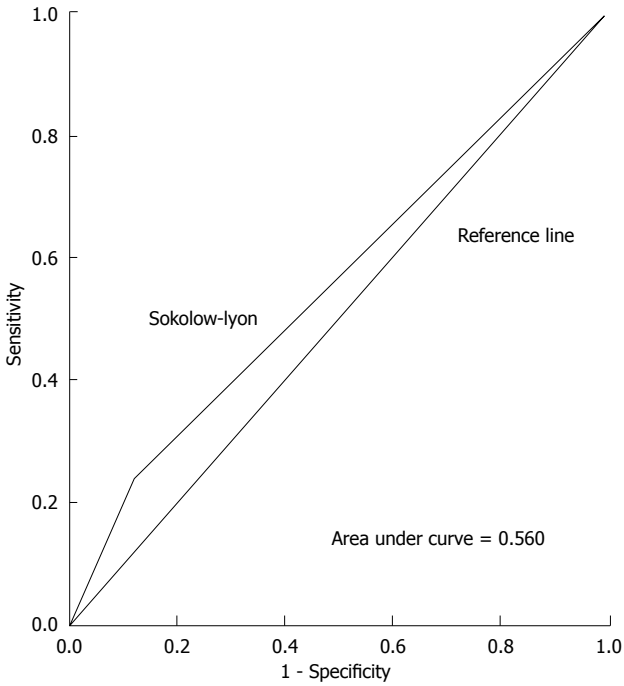

Figure 1 Receiver operating characteristic curve for Sokolow-lyon criteria.

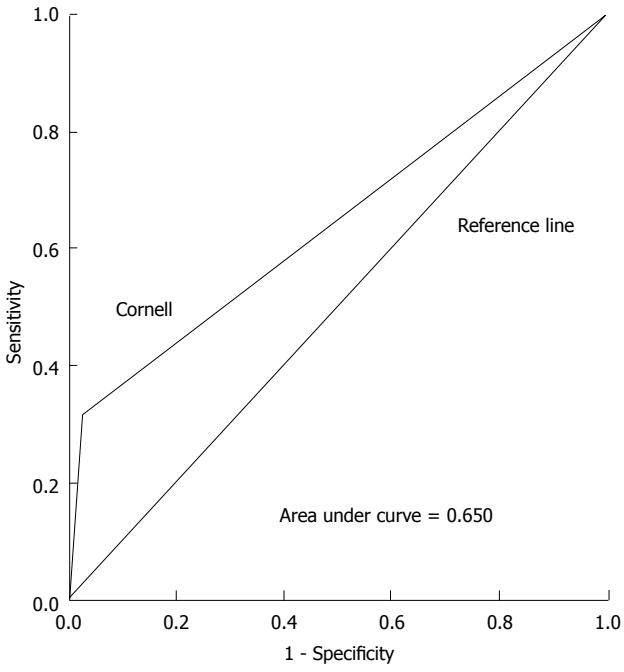

Figure 2 Receiver operating characteristic curve for Cornell criteria.

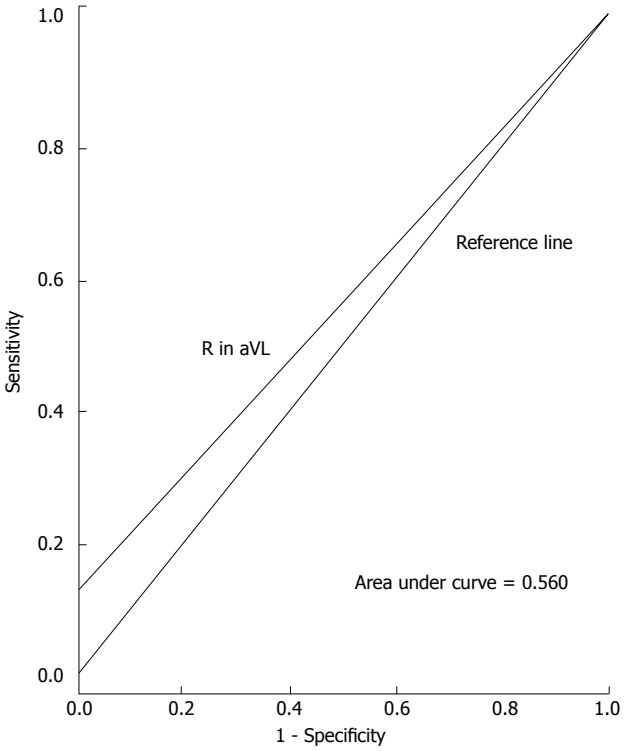

Figure 3 Receiver operating characteristic curve for r in aVL criteria.

specificity of 90%, the Cornell criteria had a sensitivity of 5.9% and a specificity of 99%, and the R in aVL criteria had a sensitivity of 8% and specificity of 94%[25]. The original Cornell criteria study[15] and a follow-up paper[26] by the same authors also found similarly low sensitivities and high specificities in the older population. Evaluation of the Sokolow-Lyon criteria in a pediatric population encompassing infants to 15 year olds also yielded a low sensitivity of 25% and high specificity of 95%[27].

In young adults from the general population there have been no data for ECG voltage criteria until the present study was conducted and demonstrated that these commonly used criteria perform equally well as in other age groups. Prior studies involving young adults were conducted in very distinct subsets of the population. In a recent study of healthy male Air Force candidates, the Sokolow-Lyon and Cornell criteria were found to have a sensitivity of 55% and specificity of 87%[28]. Another study involving healthy young male military recruits found the Sokolow-Lyon criteria to have a sensitivity of 50% and specificity of 71%, and the Cornell criteria to have a sensitivity of 25% and specificity of 88%[29]. Other studies in the young adult population involved highly trained athletes and found poor correlation between the Sokolow-Lyon criteria and increased LVM[30,31].

Hypertension has become more prevalent in the young adult population[10], and has been shown to cause increased LVM and even heart failure if left untreated[32]. With proper antihypertensive therapy LVH can regress and left ventricular dysfunction can improve[33,34]. Thus, with our findings that ECG voltage criteria are highly specific for increased LVM in young adults, it is reasonable to conclude that such a patient meeting ECG criteria for LVH may benefit from further testing, including TTE, to identify and treat increased LVM, a known and modifiable risk factor for cardiovascular disease and death[1-4]. Our results also suggest that ECG voltage criteria may not be suitable for pre-participation screening prior to partaking in athletic activities. Some screening methods often involve looking for evidence of LVH on ECG to identify those who may be at risk for sudden cardiac death[12], but with this study demonstrating such low sensitivities for detecting increased LVM, ECG voltage criteria may not perform adequately as screening tools. This finding is in agreement with the current United States guidelines for pre-participation screening, as laid forth by the American Heart Association, which do not recommend performing an ECG as part of pre-athletic screening[35]. Despite their low sensitivities, the ECG voltage criteria showed rather high specificity for detecting increased LVM in young adults. This result brings into question the notion that the presence of ECG voltage criteria in young adults is merely a normal variant[36]. Regardless of the initial indication, if an ECG performed in a young adult meets voltage criteria for LVH, the finding should not be assumed normal until completing further investigation with an imaging modality such as TTE.

In conducting a retrospective analysis it was necessary to accept certain limitations inherent with this type of design, the most significant being the lack of randomization. In analyzing the study and control groups, however, there were no significant differences in baseline characteristics as shown in Table 1. Although this was a study of the general population, the majority of subjects were Hispanic or African-American, with few Caucasian individuals. It is likely that the ECG voltage criteria tested would also show efficacy in other races, but this cannot be concluded from this study alone. This study examined only three of the numerous ECG criteria that have been developed for detecting LVH, but this was done intentionally as those chosen are among the most commonly used and simplest to perform, with no difficult calculations or point systems.

In conclusion, three commonly used ECG voltage criteria, Sokolow-Lyon, Cornell, and R in aVL, show efficacy in detecting increased LVM in young adults of the general population and have sensitivities and specificities that are similar to those found in other age groups. Although their low sensitivities preclude these ECG criteria from serving as effective screening tests, their relatively high specificities would necessitate further evaluation if the criteria were present in a young individual. Our results provide evidence that these simple diagnostic tools can be utilized in a population subset that may benefit from the valuable prognostic information that they provide.

COMMENTS

Background

Electrocardiographic (ECG) is a very common test to evaluate for structural heart disease, including left ventricular hypertrophy (LVH). The ECG criteria for LVH are widely studies in older patients; its utility in young adults is unknown. ECG was proposed to be a screening test for detection of structural abnormality of the heart, however in order to be a screening test is should have high sensitivity for detection of pathology. Thus, it's important to evaluate sensitivity and specificity of ECG criteria for LVH in young adults.

Research frontiers

ECG has been used for years to diagnose LVH. However, to the best of the authors' knowledge, there were no prior studies validating most common ECG criteria for LVH in young adults.

Innovations and breakthroughs

The results of this study contribute to clarifying the ECG diagnostic criteria for LVH in young adults in compression to older patients and its sensitivity and specificity.

Applications

In young adults common ECG voltage criteria have low sensitivities and high specificities similar to other age groups. Although their low sensitivities preclude these ECG criteria from serving as effective screening tests, their relatively high specificities would necessitate further evaluation if the criteria were present in a young individual. The results provide evidence that these simple diagnostic tools can be utilized in a population subset that may benefit from the valuable prognostic information that they provide.

Peer-review

The authors have done a good job analyzing retrospectively common electrocardiographic criteria for LVH in young adults.

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ORIGINAL ARTICLE

Retrospective Study

Pheochromocytoma and stress cardiomyopathy: Insight into pathogenesis

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Abstract

AIM

To investigate the occurrence of cardiomyopathy (CMP) in a cohort of patients with histologically proven pheochromocytoma (pheo), and to determine if catecholamine excess was causative of the left ventricular (LV) dysfunction.

METHODS

A retrospective chart review spanning years 1998 through 2014 was undertaken and patients with a diagnosis of pheo confirmed with histopathologic examination were included. Presenting electrocardiograms and cardiac imaging studies were reviewed. Transthoracic echocardiography (TTE), ventriculography or single positron emission computed tomography imaging was evaluated and if significant abnormalities [left ventricular hypertrophy (LVH) or LV dysfunction] were noted in the pre operative period a follow up post-operative study was also analyzed. Multivariate analysis using logistic regression was used to investigate independent predictors for outcomes of interest, LV dysfunction and LVH.

RESULTS

We identified 18 patients with diagnosis of pheo confirmed on pathology. Mean age was 54.3 ± 19.3 years and 11 (61.1%) patients were females. 50% of such patients had either resistant hypertension or labile blood pressures during hospitalization, which had raised suspicion for a pheo. Cardiac imaging studies were available for 12 (66.7%) patients at the time of inclusion into study and preceding the adrenalectomy.

7 (58.3%) patients with a TTE available for review had mild or more severe LVH while 3 (25%) patients had LV dysfunction of presumably acute onset. In a multivariate analysis, elevated catecholamine levels as assessed by urinary excretion of metabolites was not an independent predictor of development of LV systolic dysfunction or of presence of LVH on TTE. Two female patients with a preceding history of hypertension had marked LV hypertrophy and systolic anterior motion of the mitral valve. Prolongation of the QTc interval was noted in 5 (27.8%) patients but no acute arrhythmias were observed in any patient.

CONCLUSION

This study adds to the growing body of literature on the predilection of patients with pheochromocytomas to develop non-ischemic CMP. Degree of catecholamine excess as measured by urinary secretion of metabolites did not predict the development of CMP but 2 of 3 patients developed CMP in the setting of significant acute physiologic stress. Our findings provide support to the proposed etiologic role of elevated catecholamines in TC and other stress induced forms of CMP, however, activation of a brain-neural-cardiac axis from acute stress and local release of catecholamines but not chronic catecholamine elevations are likely to be responsible in pheo related CMP.

Key words: Pheochromocytoma; Cardiomyopathy; Stress

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Core tip: A non-ischemic cardiomyopathy (CMP) may be observed in patients with pheochromocytoma and shares several features with takotsubo cardiomyopathy. Although it is believed that pheochromocytoma related CMP is due to the catecholamine excess, the exact pathogenesis is unclear. CMP in pheochromocytoma patients often follows acute stress and while clinical course maybe complicated by acute hemodynamic compromise, prognosis is good. On the basis of our findings, where 3 of 18 pheochromocytoma patients developed an acute CMP, we suggest that activation of a brain-neural-cardiac axis from acute stress and local release of catecholamines but not chronic catecholamine elevations may likely be responsible for pheo related CMP.

Agrawal S, Shirani J, Garg L, Singh A, Longo S, Longo A, Fegley M, Stone L, Razavi M, Radoianu N, Nanda S. Pheochromocytoma and stress cardiomyopathy: Insight into pathogenesis. *World J Cardiol* 2017; 9(3): 255-260 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i3/255.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i3.255

INTRODUCTION

Pheochromocytomas (pheo) are rare tumors of chromaffin cells originating most frequently in the adrenal medulla[1]. Catecholamines are secreted by these tumors in varying amounts and proportions[1] accounting for the various associated clinical symptoms. Cardiovascular manifestations of this catecholamine excess are several. Hypertension (both sustained and paroxysmal), ventricular hypertrophy, myocardial infarction, and arrhythmias (supraventricular and ventricular) are reported to occur in relation to this hormonal excess[2]. Left ventricular (LV) dysfunction may develop in patients with pheo and is termed catecholamine cardiomyopathy (CC)[2]. Although thought to arise from the incident catecholamine excess, the exact mechanism of such cardiac dysfunction remains elusive[3]. "Stress" or takotsubo cardiomyopathy (TC) is a syndrome characterized by transient acute LV systolic dysfunction encompassing multiple vascular territories in the absence of flow-limiting epicardial coronary artery disease (CAD)[4,5] and is purported to be caused by myocardial stunning resulting from exaggerated adrenergic signaling[6]. A similar morphologic pattern of LV dysfunction characterized by apical akinesis with preservation of contractility of more basal LV segments and described classically as apical ballooning has been described for both TC and CC[3,7]. It is therefore plausible that a common etiologic link exists between these two entities. We sought to investigate the occurrence of cardiomyopathy (CMP) in a cohort of patients with histologically proven pheo and to determine if catecholamine excess was causative of this LV dysfunction.

MATERIALS AND METHODS

Patient characteristics

A retrospective chart review spanning years 1998 through 2014 was undertaken to search for patients with a diagnosis of pheo. Medical records of patients with a probable diagnosis of pheo were perused and patients were included in this study only if such diagnosis had been confirmed with histopathologic examination. The institutional review board approved the study protocol. Data on patient demographics, clinical characteristics, radiologic imaging, laboratory investigations (specifically plasma and urine catecholamine levels); and surgical and pathologic findings were collected. Presenting electrocardiograms (ECG) and cardiac imaging study results were reviewed. Transthoracic echocardiography (TTE), ventriculography and single positron emission computed tomography (SPECT) imaging was evaluated and if significant abnormalities [LV hypertrophy (LVH) or LV dysfunction] were noted in the pre-operative period a follow up post-operative study was also analyzed if available. Two physicians unaware of the knowledge of the diagnoses independently interpreted the ECG and imaging studies. LVH on ECG was diagnosed if any of the accepted voltage criteria was judged to be satisfied[8]. Echocardiograms were obtained according to a standardized institutional protocol [parasternal, apical, subcostal and suprasternal imaging planes were

Table 1 Patient demographics

	n = 18
Age (yr)	54.33 ± 19.30
Female gender (*n*, %)	11 (61.1)
Hypertension (*n*, %)	12 (66.7)
Acute hypertension (*n*, %)	6 (33.3)
DM (*n*, %)	5 (27.8)
HLD (*n*, %)	4 (22.2)
CAD (*n*, %)	1 (5.6)
Migraine (*n*, %)	2 (11.1)

DM: Diabetes mellitus; HLD: Hyperlipidemia; CAD: Coronary artery disease.

Table 2 Tumor characteristics

	n (%)
Left	9 (50)
Right	4 (22.2)
Bilateral	1 (5.6)
Extra-adrenal	2 (11.1)
Metastatic	2 (11.1)
Size (range) (c.c.)	15.63-3025
Incidental diagnosis	14 (77.8)
Open adrenalectomy	9/17 (52.9)

scanned using Vivid 7 machine (GE® medical systems, Waukesha, Wisconsin, United States)]. Two dimensional (2D), M-mode and Doppler modalities were utilized. LVEF was calculated using the Simpson's method of disc summation and adjudicated independently by two reviewers. Our primary outcome of interest was the incidence of LV dysfunction, which was defined as an LVEF ⩽ 50%, with or without regional wall motion abnormalities. LVH was defined as an increase in LV mass indexed for body surface area per guideline recommendations of the American Society of Echocardiography[9]. Disagreements in ECG or TTE interpretation were resolved by a consensus meeting or after consultation with a third author. Plasma and urine catecholamine levels were measured by a method of liquid chromatography according to current diagnostic guidelines[10].

Statistical analysis

Results are expressed as numbers (frequencies) for categorical variables and mean ± standard deviation (SD) for continuous variables. Differences between groups were analyzed with the use of the Student's *t* test for continuous variables and the chi-square test for categorical variables respectively. Multivariate logistic regression analysis was used to investigate predictors for outcomes of interest. A two sided *P*-value less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS, Statistics version 20.0 (IBM Corp., Armonk, New York).

RESULTS

We identified 18 patients with pathologically confirmed pheo. The demographics, clinical presentations and co-morbidities for these patients are described in Table 1. Mean age was 54.3 ± 19.3 years (range 17-83 years) and 11 (61.1%) patients were females; 9 (50%) tumors were localized to the left adrenal gland while 5 (27.8%) tumors were bilateral, extra-adrenal or metastatic (Table 2). Two (11.1%) patients presented with a recurrence and both had metastatic disease. One patient, a young male had an extra-adrenal paraganglioma in close proximity to the urinary bladder. All except for one patient who had diffuse metastatic disease underwent surgical removal of pheo. Open (52.9%) and laparoscopic approaches were utilized for tumor removal. A history of hypertension was present in 12/18 (66.7%) patients of which 50% was either resistant or labile. Prior history of CAD was uncommon; one patient had known history of obstructive CAD and another was found to have non-flow limiting atherosclerosis. Two patients were admitted for acute cardiovascular events. The first was a 37-year-old woman with a large ischemic stroke in the middle cerebral artery territory. She had experienced a self-resolving episode of LV dysfunction presumed to be secondary to a viral myocarditis 5 years before this event. Bilateral adrenal cystic tumors were found on CT and she subsequently underwent successful bilateral adrenalectomy. No LV dysfunction was noted during this time or subsequently. The other patient was a 77-year-old woman who was admitted originally with complaint of chest pain accompanied by headache and nausea suspicious for an acute coronary syndrome. Coronary angiography was negative and systolic blood pressure (BP) elevation of more than 200 mmHg had initiated a search for pheo. Overall, 14 (77.8%) patients had incidentally noted adrenal masses. One of these patients had an existing diagnosis of multiple endocrine neoplasia syndrome type 2b and was undergoing serial biochemical testing to rule out hormonal production for a known history of an enlarging adrenal mass. Plasma catecholamine secretion and 24-h urine catecholamine excretion were elevated to varying degrees in most patients (Tables 3 and 4). All patients survived to discharge after adrenalectomy.

LV function was evaluated in 12 (66.7%) patients at the time of inclusion into study and preceding the adrenalectomy (Table 5) and, thus, no assessment of LVEF was available for 6 patients and these patients were excluded from statistical comparisons. Seven (58.3%) patients with a TTE available for review had mild or more severe LVH while 3 (25%) patients had LV dysfunction of presumably acute onset. LVH and LV dysfunction patients were serially compared with patients without these findings serving as controls. Clinical characteristics, catecholamine secretion, TTE and ECG findings were compared using multivariate analysis, and elevated catecholamine levels as assessed by urinary excretion of metabolites was not found to be an independent predictor of development of LV systolic dysfunction or of presence of LVH on TTE.

Two of the 3 patients with LV dysfunction had global

Table 3 Plasma catecholamine secretion

(*n*) (lab normal, pg/mL)	Mean ± SD (ρg/mL)
Epi (7/18) (< 99)	873.86 ± 2074.92
NE (7/18) (< 339)	4121.43 ± 4833.55
NM (10/18) (< 111)	1506.1 ± 1856.72
Meta (9/18) (< 60)	1065.33 ± 1668.24

Epi: Epinephrine; NE: Norepinephrine; NM: Normetanephrine; Meta: Metanephrine.

Table 4 Urine catecholamine excretion

(*n*) (lab normal, υg/24 h)	Mean ± SD (υg/ 24 h)
NE (11/18) (< 140)	1099.27 ± 1233.70
Epi (11/18) (< 24)	307.73 ± 520.34
Dopa (11/18) (< 610)	377.91 ± 239.94
NM (9/18) (< 1050)	12960.67 ± 15197.26
Meta (10/18) (< 640)	22030.4 ± 40060.17
VM (6/18) (< 6.7 mg/dL)	3498.17 ± 8380.88

Epi: Epinephrine; NE: Norepinephrine; NM: Normetanephrine; Meta: Metanephrine; Dopa: Dopamine; VM: Vanillylmandelic acid.

hypokinesia. The first patient was an apparently healthy 47-year-old male who had a precipitous decline in BP after an initial malignant elevation shortly after elective endotracheal intubation and induction of anesthesia. Acute ST-segment elevation was noted on an ECG and warranted an emergent coronary angiography. No significant CAD or spasm was reported but severe diffuse hypokinesis was observed on TTE. Peak cardiac troponin I level was 6.8 ng/mL. Elevated 24-h urine catecholamine levels prompted a CT scan at which time a large left adrenal tumor was identified and subsequently excised. The second patient was a 64-year-old man who was admitted for severe anaphylactic reaction following multiple Hymenoptera stings. Clinical course was complicated by acute pulmonary edema and BP was labile. Acute severe diffuse LV hypokinesis and elevated cardiac troponins suggested an acute coronary syndrome, which was subsequently ruled out with a normal coronary angiogram. Pheo was detected and the tumor was excised. A follow up TTE (10 d) showed resolution of LV dysfunction and mild LVH. The third patient was a 67-year-old woman who was undergoing evaluation for severe systemic hypertension. No obstructive CAD was found on coronary angiography done previously when she was noted to have an abnormal ECG in the setting of dyspnea and chest pressure. A diagnosis of "classic" TC was made at that time in view of mid to distal wall segment hypokinesis consistent with "apical ballooning". An adrenal mass and elevated catecholamine levels were noted on a second presentation and a right adrenalectomy was performed for a moderate sized pheo.

Two women with preceding history of hypertension had marked LV hypertrophy. One such patient with septal and posterior wall thickness of 18 mm had systolic anterior motion of the mitral valve but no resting gradient across the LV outflow tract (LVOT). The LVH resolved post adrenalectomy in this patient. The second patient had asymmetric septal hypertrophy and a resting LVOT gradient of 23 mmHg. LVH was present on admission ECG in 11.1% patients, which resolved after tumor removal in 1 patient. Prolongation of the QTc interval (> 440 ms in males and > 460 ms in females) was noted in 5 (27.8%) patients. A univariate analysis for predictors of QTc prolongation was attempted, three of those patients were females, 4 had LVH by echo criteria and 2 had acute LV dysfunction. No acute arrhythmias were observed in any patient.

Table 5 Echo and electrocardiograms findings of study cohort

	n (%)
Echo available	12
LV dysfunction	3/12 (25)
LVEF (%) (mean ± SD)	50 ± 16.88
Prior LV dysfunction	1/12 (8.3)
Asymmetric hypertrophy with mitral SAM	2/12 (16.67)
LVH	7/12 (58.3)
LVH on ECG	2/18 (11.1)
Prolonged QTc	5/18 (27.78)

QTc prolongation defined as > 440 ms in males; > 460 ms in females. LV: Left ventricle; LVH: Left ventricle hypertrophy; LVEF: LV ejection fraction; SAM: Systolic anterior motion; ECG: Electrocardiogram.

DISCUSSION

In our study, 3 out of 18 patients with histologically proven pheochromocytoma were found to have de-novo non-ischemic CMP which was defined as acute onset of systolic dysfunction with LVEF ⩽ 50% in the absence of flow limiting CAD on coronary angiogram. The prevalence of this "idiopathic" pheo-related CMP was therefore 17% in the overall cohort, and 25% for patients who underwent any imaging for assessment of LV function. Previous studies have reported that the incidence of such pheo-related CMP is approximately 11%[11,12]. Overall, 7.5% of patients with TC have been found to have a pheo subsequently[13] and therefore it is recommend that pheo be excluded in patients with TC[14]. Elevation of circulating catecholamine levels in TC[6] and with pheo suggests excess catecholaminergic activity may be a shared pathogenic mechanism. Catecholamines cause myocardial toxicity by enhancing lipid mobility, calcium overloading, oxygen derived free radical production, increased sarcolemmal permeability as well as by provoking a state of oxygen supply-demand mismatch[15]. Further, recurrence of CMP in patients with unresected pheo[3] and resolution of CMP after treatment of adrenergic excess also suggest a causal relationship between catecholamine excess from pheo and CMP.

Provocation of a brain-heart-neural axis by various emotional and physical "stressors" has been theorized to result in massive releases of catecholamines locally into cardiac tissue while only a small leak occurs into

the systemic circulation[16,17]. In 2 of 3 patients that developed acute LV dysfunction in our study such events followed acute stress, suggesting that increases in catecholamine levels over and above the background elevation precipitated by "stress" may provoke acute LV dysfunction in pheo patients in a manner similar to TC. No independent predictors of LV dysfunction were found in this study including degree of adrenergic excess as assessed by urinary catecholamine excretion. In a study of 5 patients with TC like LV dysfunction, catecholamines levels were elevated in coronary sinus but not peripheral blood suggesting local norepinephrine release[18]. Endogenous release of catecholamines from myocardial sympathetic nerve terminals rather than circulating catecholamines may therefore mediate neurocardiogenic injury explaining the noted lack of higher catecholamine levels in pheo patients with acute LV dysfunction despite an attendant "acute stress"[19]. The absence of universal LV dysfunction despite the chronic adrenergic excess in all pheo patients is also intriguing. Persistent elevation of plasma catecholamine levels might induce adrenergic receptor desensitization *via* mechanisms that include receptor modulation and uncoupling from down-stream effectors[20,21]. Genetic susceptibility mediated through adrenergic receptor[22,23] and G protein coupled receptor kinase polymorphisms (GRK5)[24] may also account for differences in predisposition to cardiac dysfunction in pheo and TC related LV dysfunction despite similar catecholamine elevations.

Despite sharing a common morphology and possibly a shared etiology, pheo related CMP tends to differ from "idiopathic" TC in terms of patient demographics and clinical features. A study based on a population of 38 cases assimilated from published case reports of pheo related TC found such patients to be younger; and although the majority was still females, the sexual inequality was less skewed compared to TC patients without pheo[3]. Such patients experienced an inciting event less often but experienced more recurrent episodes (13.2% *vs* 3.5%).

Our study has some limitations. First, the sample size is small. However, this is related to the rare incidence of the disease process being studied. Second is the utilization of a retrospective design, again necessitated by the infrequent occurrence of the disease.

In conclusion, this study adds to the growing body of literature on the predilection of patients with pheo to develop non-ischemic CMP. In doing so it provides support for the proposed etiologic role of elevated catecholamines in TC and other stress induced forms of CMP. Degree of catecholamine excess as measured by urinary secretion of metabolites did not predict the development of CMP but 2 of 3 patients developed CMP in the setting of significant acute physiologic stress. Thereby acute stress mediated activation of a brain-neural-cardiac axis and local release of catecholamines as has been described previously but not chronic catecholamine elevations are likely to be responsible in pheo related CMP.

COMMENTS

Background

Pheochromocytomas are adrenal medullary tumors associated with a chronic elevation in catecholamine levels. They can rarely be associated with a non-ischemic cardiomyopathy.

Research frontiers

Acute cardiomyopathy which may develop in patients with a pheochromocytoma is similar to "stress" or "takotsubo" cardiomyopathy in several ways including an elevated levels of catecholamines in both conditions. This suggests that the two forms of cardiac dysfunction might share a common etiologic link.

Innovations and breakthroughs

Pheochromocytoma related cardiomyopathy developed in 3 of 18 patients. Two of these patients experienced an acute stressful event in a manner similar to classic takotsubo cardiomyopathy. The authors did not find an association between urinary excretion of catecholamines and development of cardiac dysfunction.

Applications

The findings of this study need to be confirmed in a larger multicenter international registry.

Terminology

Pheochromocytoma: Adrenal medulla tumors that may secrete varying amounts and combinations of catecholamines; Takotsubo cardiomyopathy: A form of acute cardiac dysfunction that develops classically after an acute stressful events and without obstruction of epicardial coronary arteries.

Peer-review

This paper is interesting review concerning association pheochromocytoma and cardiomyopathy. Therefore, this article should be published.

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ORIGINAL ARTICLE

Observational Study

Significance of inferior wall ischemia in non-dominant right coronary artery anatomy

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Abstract

AIM

To investigate the relationship of inferior wall ischemia on myocardial perfusion imaging in patients with non-dominant right coronary artery anatomy.

METHODS

This was a retrospective observational analysis of consecutive patients who presented to the emergency department with primary complaint of chest pain. Only patients who underwent single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) were included. Patients who showed a reversible defect on SPECT MPI and had coronary angiography during the same hospitalization was analyzed. Patients with prior history of coronary artery disease (CAD) including history of percutaneous coronary intervention and coronary artery bypass graft surgerys were excluded. True positive and false positive results were identified on the basis of hemodynamically significant CAD on coronary angiography, in the same territory as identified on SPECT MPI. Coronary artery dominance was determined on coronary angiography. Patients were divided into group 1 and group 2. Group 1 included patients with non-dominant right coronary artery (RCA) (left dominant and codominant). Group 2 included patients with dominant RCA anatomy. Demographics, baseline characteristics and positive predictive value (PPV) were analyzed for the two

groups.

RESULTS

The mean age of the study cohort was 57.6 years. Sixty-one point seven percent of the patients were males. The prevalence of self-reported diabetes mellitus, hypertension and dyslipidemia was 36%, 71.9% and 53.9% respectively. A comparison of baseline characteristics between the two groups showed that patients with a non-dominant RCA were more likely to be men. For inferior wall ischemia on SPECT MPI, patients in study group 2 had a significantly higher PPV, 32/42 (76.1%), compared to patients in group 1, in which only 3 out of the 29 patients (10.3%) had true positive results (*P* value < 0.001 *Z* test). The difference remained statistically significant even when only patients with left dominant coronary system (without co-dominant) were compared to patients with right dominant system (32/40, 76.1% in right dominant group, 3/19, 15.8% in left dominant group, *P* value < 0.001 *Z* test). There was no significant difference in mean hospital stay, re-hospitalization, and in-hospital mortality between the two groups.

CONCLUSION

The positive predictive value of SPECT MPI for inferior wall ischemia is affected by coronary artery dominance. More studies are needed to explain this phenomenon.

Key words: Myocardial perfusion imaging; Single photon emission commuted tomography; False positive results; Coronary artery dominance; Inferior wall ischemia

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Core tip: A positive test for ischemia on single photon emission computed tomography (SPECT), myocardial perfusion imaging (MPI) is often followed up with coronary angiography. The aim of our study was to assess the relationship of inferior wall ischemia on SPECT MPI with non-dominant right coronary artery (RCA) anatomy. We found that positive predictive value of inferior wall ischemia on SPECT MPI was significantly lower in patients with non-dominant RCA anatomy. We postulate that in non-dominant RCA anatomy flow tracer may show relatively decreased uptake in the inferior wall that might not be indicative of flow limiting stenosis.

Malik AO, Abela O, Devabhaktuni S, Malik AA, Allenback G, Ahsan CH, Malhotra S, Diep J. Significance of inferior wall ischemia in non-dominant right coronary artery anatomy. *World J Cardiol* 2017; 9(3): 261-267 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i3/261.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i3.261

INTRODUCTION

Single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is most often used to assess the likelihood of obstructive coronary artery disease (CAD), presence of ischemia in a patient with known CAD, and evaluating the extent of ischemia for prognostic value[1]. In essence SPECT MPI accomplishes this by measuring relative changes in perfusion of myocardial territories before and after augmenting coronary blood flow[1]. SPECT MPI has enjoyed widespread clinical use because of its well documented diagnostic and prognostic utility in CAD[2].

Coronary artery dominance is determined by the artery supplying the posterior portion of interventricular (IV) septum[3]. In a right dominant system, the right coronary artery (RCA) supplies this territory and feeds the posterior descending artery, in contrast to left dominant system in which the left circumflex artery (LCX) accomplishes this role[3]. In a co-dominant system, the supply of posterior IV septum is shared by both RCA and LCX[3]. Right dominant system is the more prevalent variant occurring in approximately 70% of people, followed by left dominant and co-dominant system[4].

The prognostic significance of coronary artery dominance in patients with CAD has been studied. Left dominant system has been shown to be an independent risk factor of morbidity and mortality in patients undergoing both surgical and percutaneous revascularization, especially in patients with ST segment elevated myocardial infarction (STEMI)[4-7].

The effect of coronary anatomy on diagnostic accuracy of cardiac magnetic resonance imaging (CMR) has been studied[8]. However, no study to our knowledge has evaluated the effect of coronary artery dominance on diagnostic accuracy of SPECT (MPI studies). We present the first report showing the effect of coronary artery dominance on positive predictive value of SPECT MPI.

MATERIALS AND METHODS

Study design

The study was a single center retrospective analysis conducted at a tertiary care center.

Inclusion and exclusion criteria

All patients who underwent rest and stress SPECT MPI from January 1st 2013 to June 30th 2014, for diagnostic purposes were included in our study. All patients who did not undergo a coronary angiogram during the same hospital stay were excluded. Furthermore, all patients who did not have evidence of reversible ischemia on SPECT MPI were excluded.

These patients presented with chest pain that were deemed to be of intermediate pre-test probability for ischemia. The images were initially read by an experienced radiologist and results verified by the cardiologist.

Institute review board approval

The study was approved by the Institute Review Board at University Medical Center of Southern Nevada. This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of

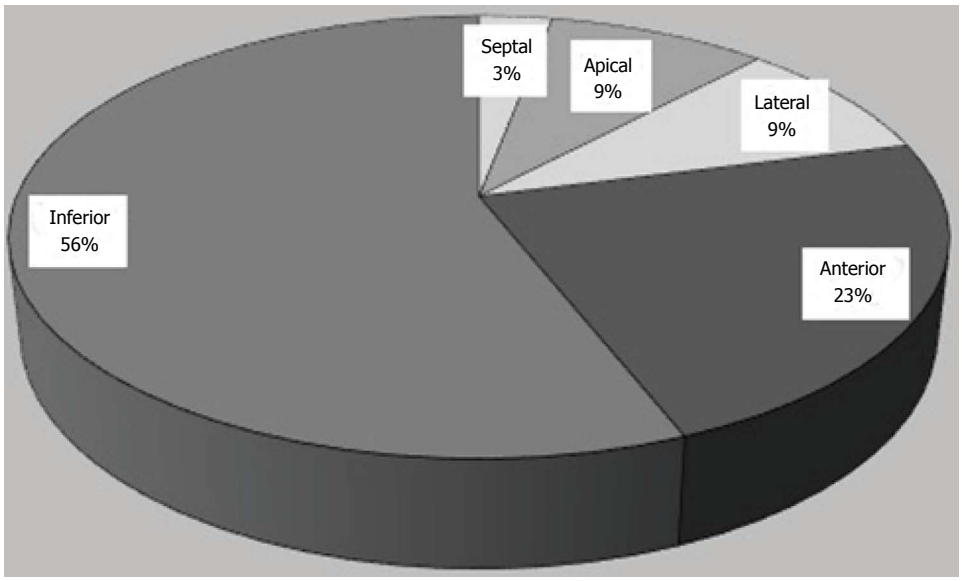


Figure 1 Defect location on single photon emission computed tomography myocardial perfusion imaging.

Helsinki and its later amendments or comparable ethical standards.

Coronary angiography and defining obstructive CAD

All of the patients subsequently underwent a coronary angiogram during the same hospital stay after the SPECT MPI. Patients were divided into two groups on the basis of coronary artery dominance. Group 1 included patients with a non-dominant RCA (left dominant and co-dominant). Group 2 included patients with right dominant coronary artery system.

The coronary angiogram was performed by an experienced interventional cardiologist. It was noted if there was obstructive CAD, in the same distribution as shown by the SPECT MPI the study was deemed to be true positive. Obstructive CAD was defined as maximal coronary artery stenosis of more than 70%.

SPECT MPI and determination of reversible ischemia

SPECT MPI was performed using standard protocols approved by the American Society of Nuclear Cardiology[9]. An experienced radiologist initially read the images and the presence of any reversible ischemia was verified by the cardiology team. Figure 1 shows representative images of SPECT MPI, showing inferior wall ischemia and normal scan respectively.

Study outcome

The primary study outcome was determining diagnostic accuracy of the SPECT MPI, with the coronary angiogram as gold standard. The positive predictive value of SPECT MPI was compared in both groups.

Statistical analysis

Data for each study variable were summarized initially for the whole cohort and then by dominant coronary artery group, using means for continuous variables and frequencies/percentages for categorical variables. Means for the non-dominant RCA and dominant RCA groups were compared using independent-samples *t*-tests (or Mann Whitney *U* tests, for variables with non-normally distributed data). Frequencies/percentages were compared using χ^2 tests. Positive predictive values for were compared *via Z* tests of proportions. The significance level (alpha) was set at 0.05, and all analyses were completed *via* SPSS, version 22 (IBM).

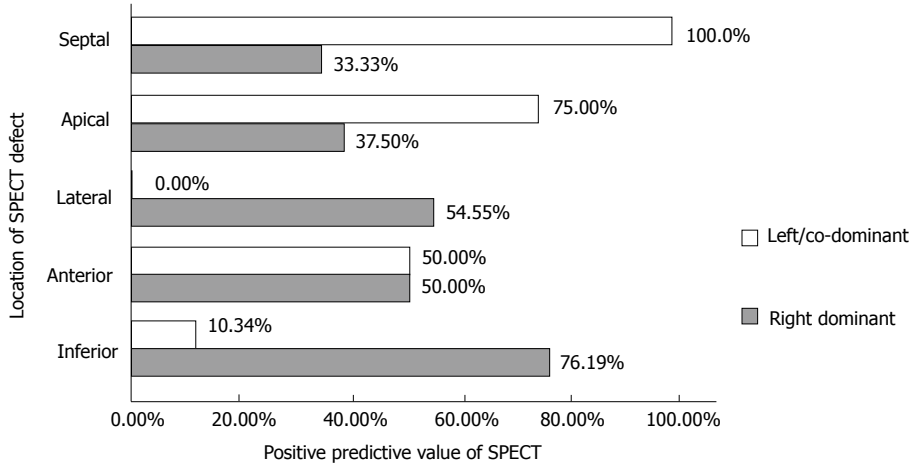
RESULTS

The mean age of the study cohort was 57.6 years. Sixty-one point seven percent of the patients were males. The prevalence of self-reported diabetes mellitus, hypertension and dyslipidemia was 36%, 71.9% and 53.9% respectively. A comparison of baseline characteristics between the two groups showed that patients with a non-dominant RCA were more likely to be men. Table 1 shows comparison of other baseline characteristics.

The most common location for the reversible defect was seen the inferior wall (Figure 2).

The positive predictive value (PPV) was analyzed and compared between the two study groups. Sub-group analysis showed that for inferior wall ischemia on SPECT MPI, patients in study group 2 had a significantly higher PPV, 32/42 (76.1%), compared to patients in group 1, in which PPV was 10.3% (3/29) (*P* value < 0.001 *Z* test) Figure 2 illustrates the results. The difference remained statistically significant even when only patients with left dominant coronary system (without co-dominant) were compared to patients with right dominant system. (32/40, 76.1% in right dominant group, 3/19, 15.8% in left dominant group, *P* value < 0.001 *Z* test).

There was no significant difference in mean hospital stay, re-hospitalization, and in-hospital mortality between the two groups as shown in Table 2.



Significant difference between left/co-dominant and right dominant, $P < 0.001$.

Figure 2 Positive predictive value of single photon emission computed tomography for patients in group 1 and group 2. SPECT: Single photon emission computed tomography.

Table 1 Baseline characteristics of study groups *n* (%)

	Dominant RCA *n* = 87	Non- dominant RCA *n* = 41	*P* value (test)
Age	56.92 yr	59.24 yr	0.252 (*t* test)
Male gender	48/87 (55.17)	31/41 (75.61)	0.026 (χ^2)
BMI	28.29	28.87	0.459 (Mann-Whitney)
PMH of DM	33/87 (37.93)	14/41 (34.15)	0.679 (χ^2)
PMH HTN	64/87 (73.56)	27/41 (65.85)	0.369 (χ^2)
PMH dyslipidemia	51/87 (58.62)	18/41 (43.90)	0.119 (χ^2)
PMH of a fib	2/87 (2.30)	1/41 (2.45)	1.000 (χ^2)
PMH of PVD	17/87 (19.54)	8/41 (19.51)	0.997 (χ^2)
PMH of COPD	5/87 (5.75)	7/41 (17.07)	0.053 (χ^2)
Current smoker	27/87 (31.03)	15/41 (36.59)	0.533 (χ^2)
Drug abuse	10/87 (11.49)	7/41 (17.07)	0.386 (χ^2)
Alcohol use	23/87 (26.45)	11/40 (27.50)	0.900 (χ^2)
PMH of sleep apnea	3/87 (3.45)	1/41 (2.44)	1.000 (χ^2)
PMH of CKD	9/87 (10.34)	2/41 (4.88)	0.501 (χ^2)
ESRD on HD	4/87 (4.60)	2/41 (4.88)	1.000 (χ^2)

RCA: Right coronary artery; BMI: Body mass index; PMH: Past medical history; DM: Diabetes mellitus; HTN: Hypertension; a fib: Atrial fibrillation; PVD: Peripheral vascu-lar disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney dis-ease; ESRD: End stage renal disease; HD: Hemodialysis.

DISCUSSION

Around 15 million patients seek medical attention for symptoms concerning for CAD[10]. In stable patients, not having acute coronary syndrome non-invasive testing like SPECT MPI, act as gatekeepers to coronary angiography because of risks and costs associated with coronary angiography[11,12]. Despite the use of conventional non-invasive testing such as SPECT MPI an analysis of almost 400000 coronary angiograms in patients with no prior history of CAD disease revealed no obstructive disease in more than 60% of the cases, resulting in unnecessary risks and costs[13,14]. Hence, from a public health standpoint, it is imperative that we study the reasons for false positive diagnoses associated with non-invasive tests such as SPECT MPI.

SPECT MPI is widely used for diagnostic purposes in patients presenting with chest pain when acute coronary syndrome (ACS) has been ruled out[2]. A recent study showed that SPECT MPI is widely used for diagnostic and risk stratification purposes in the United States and patient's socio-economic status did not significantly affect the use of SPECT MPI by physicians[15]. In the developing world several studies have shown the widespread use of SPECT MPI by physicians to aid in diagnosis in management[16,17]. One such report from Iran regarding SPECT MPI referral practices showed that 72.5% (211/291) of the referrals found to be appropriate per ASNC recommendations[16].

The utilization of SPECT MPI is often on the physician's assessment of pre-test probability. The American College of Physicians pre-test probability assessment and Duke chest pain score are two common objective tools used for this assessment[18]. In our retrospective analysis, SPECT MPI was done, on the physician's assessment of the patient's pre-test probability.

Our study shows that SPECT MPI in patients with non-dominant RCA has significantly high false positive results for inferior wall ischemia. In a study using positron emission tomography measuring absolute myocardial blood flow (MBF) in low risk normal patients' authors found baseline MBF in the inferior region was significantly ($P < 0.0001$) lower than either the anterior or lateral regions[19]. However, coronary anatomy was not available in this study population. Nonetheless this finding may contribute to our observation as well. One study using stress CMR also showed a statistically significant difference in false positive rate correlating with dominance[8]. They also showed a correlation with the vessel size, postulating that the smaller vessel size that usually comes with non-dominant vessels was the factor leading to false positive readings[8].

Table 2 Comparison of outcomes between study groups

	Dominant RCA *n* = 87	Non-dominant RCA *n* = 41	*P* value (test)
Mean hospital stay (d)	4.33	4.29	0.713 (Mann-Whitney)
In-hospital mortality	0/87	0/41	-
30-d re-hospitalization for chest pain	10/87 (11.49%)	2/41 (4.88%)	0.231 (χ^2)

RCA: Right coronary artery.

Gender differences in vessel caliber and coronary artery dominance could also play a role. As shown in our results patients with non-dominant RCA were more likely to be men. This is consistent with the report by Gebhard *et al*[5] in which patients with left dominant coronary artery anatomy were more likely to be males. In contrast in a cohort of patients with STEMI, lower percentage of patients with left dominant circulation were men compared to patients with right dominant circulation[7]. This was not statistically significant. Vessel caliber was not available in either of these studies. Whether gender differences affect coronary artery, dominance is not clear at this time.

Regardless our study finding has important consequences. First, it has been shown that patients with left dominant system are at high risk in terms of cardiovascular events[6]; hence, it is important that significant CAD is promptly addressed in these patients. If the diagnostic accuracy of SPECT MPI is particularly low in this sub group of patients, then it is important that more studies are done to evaluate the negative predictive value (NPV) in this subset to reach a better understanding about role of SPECT MPI in excluding significant CAD in these patients. In our retrospective analysis patients with negative SPECT MPI imaging did not have a coronary angiogram, hence analysis of NPV was not possible.

Second, if the diagnostic accuracy of inferior wall ischemia on SPECT MPI is affected by coronary artery dominance and it has a significantly lower PPV in patients with non-dominant RCA, it would mean that many patients in this sub-group are exposed to unnecessary invasive procedures. This is in addition to utilizing the resources when it will not help the patient.

In conclusion, based on our findings we hypothesize that the flow tracer in a non-dominant RCA may show relatively decreased uptake in the inferior wall that might not be indicative of flow limiting stenosis. More multi-center studies to explore the relationship of coronary artery dominance on SPECT MPI are needed to reach a better understanding regarding positive or negative results in patients in the context of non-dominant RCA anatomy.

Study limitations

This study was done only at a single center and the SPECT MPI results were only read by one group of physicians. Prone imaging was not done. Also some patients could have could have had inferior wall abnormality and coronary computed tomography angiogram was not utilized. Coronary angiograms were not done on patients with normal SPECT MPI results. Hence we could not analyze the effect of coronary dominance on NPV. We did not strictly use objective validated models to quantify SPECT MPI defect so some measurement bias may be present.

COMMENTS

Background

Single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is most often used to assess the likelihood of obstructive coronary artery disease (CAD), presence of ischemia in a patient with known CAD, and evaluating the ex-tent of ischemia for prognostic value. SPECT MPI has enjoyed widespread clinical use be-cause of its well documented diagnostic and prognostic utility in CAD. The authors' study aims to understand the effect of coronary artery dominance on the positive predictive value (PPV) of SPECT MPI.

Research frontiers

The effect of coronary anatomy on diagnostic accuracy of cardiac magnetic resonance imaging (CMR) has been studied. However, no study to our knowledge has evaluated the effect of coronary artery dominance on diagnostic accuracy of SPECT MPI studies. The authors' present the first report showing the effect of coronary artery dominance on PPV of SPECT MPI.

Innovations and breakthroughs

They studied the effect of coronary artery dominance on the PPV of SPECT MPI. The effect of coronary anatomy on diagnostic accuracy of cardiac magnetic resonance imaging (CMR) has been studied. In a study using positron emission tomography measuring absolute myocardial blood flow (MBF) in low risk normal patients' authors found baseline MBF in the inferior region was significantly lower than either the anterior or lateral regions. However, coronary anatomy was not available in this study population. They studied the effect of coronary artery dominance on the PPV of SPECT MPI.

Applications

In stable patients, not having acute coronary syndrome non-invasive testing like SPECT MPI, act as gatekeepers to coronary angiography because of risks and costs as-sociated with coronary angiography. Despite the use of conventional non-invasive testing such as SPECT MPI an analysis of almost 400000 coronary angiograms in pa-tients with no prior history of CAD disease revealed no obstructive disease in more than 60% of the cases, resulting in unnecessary risks and costs. Hence, from a public health standpoint, it is imperative that the study the reasons for false positive diagnoses associated with non-invasive tests such as SPECT MPI. They show in the study that the PPV of SPECT MPI for inferior wall ischemia in stable patients no having ACS, is affected by coronary artery dominance. Although more studies are needed to explain this phenomenon, maybe this subset of patients should undergo further non-invasive testing before proceeding to invasive coronary angiography.

Terminology

SPECT MPI: SPECT MPI is most often used to assess the likelihood of obstructive CAD, presence of ischemia in a patient with known CAD, and evaluating the ex-tent of ischemia for prognostic value. In essence SPECT MPI accomplishes this by measuring relative changes in perfusion of myocardial territories before and after aug-menting coronary blood flow; coronary artery dominance: Coronary artery dominance is determined by the artery supplying the posterior portion of interventricular (IV) septum. In a right dominant system, the right coronary artery (RCA) supplies this territory and feeds the posterior descending artery, in contrast to left dominant system in which the left circumflex artery (LCX) accomplishes this role. In a co-dominant system, the supply of

posterior IV septum is shared by both RCA and LCX.

Peer-review

This is an interesting manuscript about the association of a positive test for inferior wall ischemia on MPI with non-dominant RCA anatomy.

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ORIGINAL ARTICLE

Observational Study

Risk of ventricular arrhythmia in patients with myocardial infarction and non-obstructive coronary arteries and normal ejection fraction

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Abstract

AIM

To assess the arrhythmic determinants and prognosis of patients presenting with myocardial infarction and non-obstructive coronary arteries (MINOCA) with normal ejection fraction (EF).

METHODS

This is an observational analysis of 131 MINOCA patients with normal EF. Three cardiac magnetic resonance (CMR) diagnosis classes were recognized according to the late gadolinium enhancement (LGE) pattern: Myocardial infarction (MI) (n = 34), myocarditis (n = 47), and "no LGE" (n = 50). Ventricular events occurring during hospitalization were recorded and the entire population

was followed-up at 1 year.

RESULTS

Ventricular arrhythmia was observed in 18 (13.8%) patients during hospitalization. The "no LGE" patients experienced fewer ventricular events than the MI and myocarditis patients [4.0% *vs* 26.5% and 14.9%, respectively (P = 0.013)]. There was no significant difference between the MI and myocarditis groups. On multivariate analysis, LGE transmural extent [OR = 1.52 (1.08-2.15), P = 0.017] and ST-segment elevation [OR = 4.65 (1.61-13.40), P = 0.004] were independent predictors of ventricular arrhythmic events, irrespective of the diagnosis class. Finally, no patient experienced sudden cardiac death or ventricular arrhythmia recurrence at 1-year.

CONCLUSION

MINOCA patients with normal EF presented no 1-year cardiovascular events, irrespective of the CMR diagnosis class. LGE transmural extent and ST segment elevation at admission are risk markers of ventricular arrhythmia during hospitalization.

Key words: Ventricular tachycardia; Myocarditis; Myocardial infarction; Late gadolinium enhancement; Cardiac magnetic resonance; Myocardial infarction and non-obstructive coronary arteries

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Core tip: Out of 131 myocardial infarction and non-obstructive coronary arteries patients, 18 experienced a ventricular arrhythmic event during hospitalization, consisting of 17 ventricular tachycardia and one ventricular fibrillation. No patient died during the 1-year follow-up. Cardiac magnetic resonance classified the underlying diagnosis in 61.8% of the cases, as a myocarditis or a myocardial infarction. Rather than the diagnosis itself, late gadolinium enhancement and ST-segment elevation were found as valuable tools to stratify the risk for arrhythmia of these patients. These findings may be useful to select patients who might be eligible for either arrhythmia prevention or secondary prevention therapy.

Bière L, Niro M, Pouliquen H, Gourraud JB, Prunier F, Furber A, Probst V. Risk of ventricular arrhythmia in patients with myocardial infarction and non-obstructive coronary arteries and normal ejection fraction. *World J Cardiol* 2017; 9(3): 268-276 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i3/268.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i3.268

INTRODUCTION

Sudden cardiac death is still the most common cause of death worldwide, accounting for over 50% of all deaths from cardiovascular disease. Coronary artery disease represents approximately 80% of all cases[1]. However, 1%-12% of patients with chest pain and cardiac troponin elevation present with normal coronary arteries on angiography analysis[2]. This pathological entity is called myocardial infarction and non-obstructive coronary arteries (MINOCA) and encompasses myocarditis, transient apical ballooning syndrome, and authentic ischemic injuries[2]. Cardiac magnetic resonance (CMR) imaging is helpful for providing detailed information on myocardial tissue characteristics, and has become the gold standard for *in vivo* detection of necrosis, notably in acute myocardial infarction (MI) and myocarditis[3].

Early-sustained ventricular arrhythmias complicate 2%-20% of acute MIs and are associated with increased hospital mortality rates[4,5]. While the arrhythmic prognosis of MI with abnormal coronary angiography is well known, there is little data concerning MINOCA, even when the arrhythmic prognosis seems to be relatively good[6,7]. As a result of the lack of data concerning this entity, there are no specific guidelines concerning hospitalization duration, follow-up, or treatment for this specific setting.

Our study sought to evaluate the risk of ventricular arrhythmias of presumed low-risk MINOCA patients at both early-stage consultation and 1-year follow-up, based on the diagnosis class established by CMR imaging.

MATERIALS AND METHODS

One hundred and sixty-seven patients were retrospectively enrolled between 2007 and 2012 in the French university hospitals of Nantes and Angers. The inclusion criteria were: (1) hospitalization for acute anginal chest pain; (2) increase in troponin rates superior to the normal range; (3) left ventricular ejection fraction (LVEF) $\geqslant$ 45%; and (4) absence of coronary artery stenosis or thrombosis (stenosis < 50% of the diameter of the epicardial vessel).

All patients underwent CMR and the arrhythmic evaluation included at least 48 h of electrocardiography (ECG) monitoring after admission.

In order to avoid overestimating the arrhythmic risk in this population, patients hospitalized for sustained ventricular tachycardia (n = 8) or cardiopulmonary arrest were not included in the study. Patients presenting with Tako-Tsubo (n = 21) were therefore also from the study due to this syndrome's specific pathophysiology. Seven more patients could not be included due to poor CMR quality so that the study was performed on 131 patients (Figure 1). The study complies with the Declaration of Helsinki and local ethics committee has approved the research protocol.

Ventricular tachycardia (VT) was defined as at least three consecutive ventricular beats with a rate > 100 bpm[8]. Prolonged VT was defined as at least eight consecutive ventricular beats[9]. Ventricular fibrillation

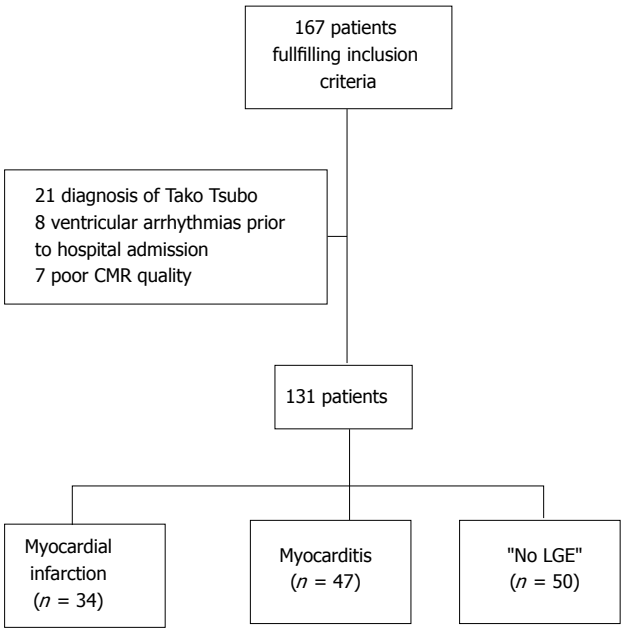

Figure 1 Flow chart of the study population. CMR: Cardiac magnetic resonance; LGE: Late gadolinium enhancement.

was defined as an irregular ventricular rhythm with marked variability in the QRS cycle length, morphology, and rapid amplitude, usually over 300 bpm/200 ms (cycle length: 180 ms or less)[8].

All data concerning the initial hospitalization were recorded from the patient medical files. Repolarization abnormalities were defined as ST-segment depression $\geqslant$ 0.1 mV at 0.08 s from the junction (J point) (STD), asymmetrical T wave inversion $\geqslant$ 0.1 mV deep in two or more leads except lead aVR, and ST-segment elevation $\geqslant$ 0.2 mV (STE). Q waves > 0.3 mV in depth or > 0.04 s in duration in at least two leads, except lead aVR, were considered abnormal.

At the 1-year follow-up, the following outcomes were collected: Ventricular arrhythmia, death from any cause, cardiovascular (CV) death, and particularly sudden cardiac death. The chosen treatments were evaluated on hospital discharge and at 1 year. If necessary, the referring cardiologists or general practitioners were contacted to obtain information concerning the patients at 1-year follow-up. Data on 1-year survival was completed for every patient.

CMR was performed using 1.5T scanners (Avanto, Siemens, Erlangen, Germany) with 8-element phased-array cardiac receiver coils. The median time from presentation of MINOCA to CMR was 7 d (interquartile range: 4; 13).

LV function was determined by means of cine imaging, in multiple short-axis views covering the entire LV. The typical in-plane resolution was 1.6 mm × 1.9 mm and 7.0-mm thickness sections were used. Temporal resolution was around 35-45 ms.

Late gadolinium enhancement (LGE) was performed 10 min after administering the gadolinium-based contrast agent, at a cumulative dose of 0.2 mmol/kg, by means of a two-dimensional segmented inversion recovery gradient-echo pulse sequence. The inversion time was set to null the signal of the viable myocardium, typically ranging from 240 to 300 ms.

A post-hoc core analysis was specifically performed for this study, using a dedicated software package (Medis 7.1, Mass, Leiden, The Netherlands). For all qualitative assessments, the recommended 17-segment system was applied, requiring the consensus of two blinded observers.

On all the short-axis cine slices, the endocardial and epicardial borders were outlined manually on the end-diastolic and end-systolic images, with the exclusion of the trabeculae and papillary muscles. The reproducibility of the LVEF and LV volumes assessments was good, the details of which are published elsewhere[10].

The cine imaging was assessed visually by analyzing the LV wall thickening using a three-grade scale: 0 = normal, 1 = hypokinesia, 2 = akinesia. We counted the number of segments affected in order to determine the extent of hypokinesis. Furthermore, pericardial effusion was noted when considered exceeding trivial effusion[3].

LGE was evaluated by means of visual analysis. We estimated the maximal transmural extent of LGE within each segment as a percentage of the LV using a five-grade scale: 0% = 0, 0%-25% = 1, 25%-50% = 2, 50%-75% = 3, and > 75% = 4 (Figure 2). The number of segments with LGE defined the LGE transversal extent.

Following analysis by means of CMR, the patients were classified according to LGE pattern, as described: Subendocardial LGE was revealed in the MI group, subepicardial or medioventricular LGE in the myocarditis group, and absence of LGE in the "no LGE" group[11].

When the extent of LGE was transmural (> 75%), the border zones were analyzed to more precisely determine the CMR diagnosis, for example, if the signal of LGE borders was subendocardial, myocardial infarction was diagnosed.

Statistical analysis

Statistical analyses were performed using SPSS Version 15.0 software for Windows (SPSS Inc., Chicago, Illinois, United States). The data was presented as mean ± standard deviation (SD) or median (25^{th}; 75^{th} percentiles) in cases of non-normal distribution, with categorical data expressed as frequencies and percentages. Continuous variables were compared by means of the unpaired *t* test or Wilcoxon rank-sum test, when necessary. Non-continuous variables were compared using the χ^2 test. Differences were considered significant with a $P < 0.05$. For the multivariate analysis of ventricular events during hospitalization, clinical and CMR data were tested by means of an ascending step-by-step binomial logistic regression analysis, including variables with *P* values < 0.05 in univariate analysis. The Hosmer-Lemeshow goodness-of-fit test was used to assess the applied models.

Table 1 Patient characteristics

	All patients (n = 131)	MI (n = 34)	Myocarditis (n = 47)	"No LGE" (n = 50)	P
Age, yr	48.5 ± 16.1	52.4 ± 14.2	40.5 ± 13.5[1]	53.4 ± 16.9[3]	< 0.001
Risk factors, n (%)					
Male gender	87 (66.4)	22 (64.7)	39 (83.0)	26 (52.0)[2,3]	0.005
Hypertension	39 (29.8)	13 (38.2)	8 (17.0)	18 (36.0)	0.06
Diabetes	11 (8.4)	4 (11.8)	2 (4.3)	5 (10.0)	0.42
Dyslipidemia	38 (29.0)	9 (26.5)	10 (21.3)	19 (38.0)	0.18
Current smoker	45 (34.4)	14 (41.4)	12 (25.5)	19 (38.0)	0.27
Family history of premature CHD	25 (19.1)	11 (34.2)	5 (10.6)	9 (18.0)	0.05
Time from symptom onset to admission, h	9 [2; 24]	3.5 [2; 13.5]	13 [4; 48][1]	9.5 [2; 24]	0.01
Hospitalization duration, d	6 [4; 7]	5.5 [4; 7]	6 [5; 7]	5 [4; 7]	0.42
ECG monitoring duration, d	5 [4; 6]	5 [4; 6]	5 [4; 7]	4 [3; 6]	0.12
Primary ECG abnormality, n (%)	91 (69.5)	26 (76.5)	34 (72.3)	31 (62.0)	0.32
ST-segment elevation	46 (35.1)	9 (26.5)	22 (46.8)	15 (30.0)	0.10
ST-segment depression	8 (6.1)	2 (5.9)	4 (8.5)	2 (4.0)	0.65
T-wave inversion	31 (23.7)	11 (32.4)	8 (17.0)	12 (24.0)	0.27
Q wave	2 (1.5)	2 (5.9)	0	0	0.06
Atrioventricular block	1 (0.8)	0	0	1 (2.0)	0.28
Laboratory measurements					
Peak troponin, μg/L	2.1 ± 5	3.6 ± 6.1	2.9 ± 6.3	0.5 ± 0.6[2,3]	0.013
Leucocytes on admission, G/L	9.3 ± 3.6	9.3 ± 3.9	9.2 ± 3.5	9.2 ± 3.4	0.99
CRP on admission, mg/L	28.2 ± 41.1	8.8 ± 18.9	39.5 ± 38.4[1]	31.0 ± 50.4[2]	0.004
Coronary atheroma, n (%)	45 (34.6)	15 (45.5)	14 (29.8)	16 (32.0)	0.31
β-blocker use, n (%)					
During hospitalization	91 (69.5)	27 (79.4)	31 (66.0)	33 (66.0)	0.34
At 1 yr	16 (12.2)	10 (29.4)	1 (2.1)	5 (10.0)	0.05
ACEI use, n (%)					
During hospitalization	56 (43.1)	16 (48.5)	16 (34.0)	24 (48.0)	0.29
At 1 yr	17 (13.0)	10 (29.4)	1 (2.1)[1]	6 (12.0)	0.042

[1]P significant between MI and myocarditis groups; [2]P significant between MI and "no LGE" groups; [3]P significant between myocarditis and "no LGE" groups. MI: Myocardial infarction; LGE: Late gadolinium enhancement; ACEI: Angiotensin converting enzyme inhibitor; CHD: Coronary heart disease; CRP: C-reactive protein.

RESULTS

A total of 131 patients (87 men, median age: 48.5 ± 16 years) fulfilled our criteria. LGE was present in 81 of the 131 patients (61.8%). There were 34 (25.9%) patients classified in the MI group, 47 (35.9%) in the myocarditis group, and 50 (38.2%) in the "no LGE" group (Table 1). The myocarditis group exhibited a specific pattern of myocarditic lesions, located predominantly in the free lateral wall (42/47 cases) and in the subepicardial layers (45/47 cases). The ischemic lesions were distributed homogeneously (Figure 2).

Patients classed in the myocarditis group were younger (P < 0.001) and more frequently male (P < 0.005) than the others. No differences in cardiovascular risk factor were noted.

The median time between symptom onset and hospital admission was 9 h (2; 24). Patients from the MI group were admitted to the hospital more quickly than those in the myocarditis group (P = 0.002).

The prevalence of ECG abnormalities was 69.5%, predominantly consisting of STE (35.7%) and T-wave inversion (23.1%). There were no differences in the frequency of ECG abnormalities between the groups.

Troponin rates were lower in the "no LGE" group compared to those of the MI and myocarditis groups (P = 0.001 and P = 0.013, respectively).

The MI patients presented with lower C-reactive protein (CRP) rates than the myocarditis and "no LGE" patients (P < 0.001 and P = 0.020, respectively). Elevated CRP was observed in 42 (93.3%), 22 (66.7%), and 37 (82.2%) patients from the myocarditis, MI, and "no LGE" groups, respectively.

During hospitalization, 69% of patients were treated with β-blockers and 43% received angiotensin-converting enzyme inhibitors (ACEIs), with no difference observed between the different groups. At 1 year, only 13% of the patients were receiving either β-blockers or ACEIs, with a trend for higher rates of treatment seen in the MI group, though this difference was not statistically significant. Notably, no other antiarrhythmic drug than β-blockers was given at any time of the study.

The mean LVEF was 58.6% ± 8.2%. No significant differences were observed in either LVEF or LV end-diastolic volume between the groups. The "no LGE" group exhibited smaller LV end-systolic volumes than those of the MI and myocarditis patients. LV wall thickening was more often altered in the MI group. Moreover, the MI patients presented with higher rates of akinesia compared to the myocarditis and "no LGE" patients (58.8% *vs* 4.3% and 2.0%, P < 0.001). Pericardial effusion was detected nonspecifically in 20 patients (15.4%) (Table 2).

During hospitalization, 18 patients experienced

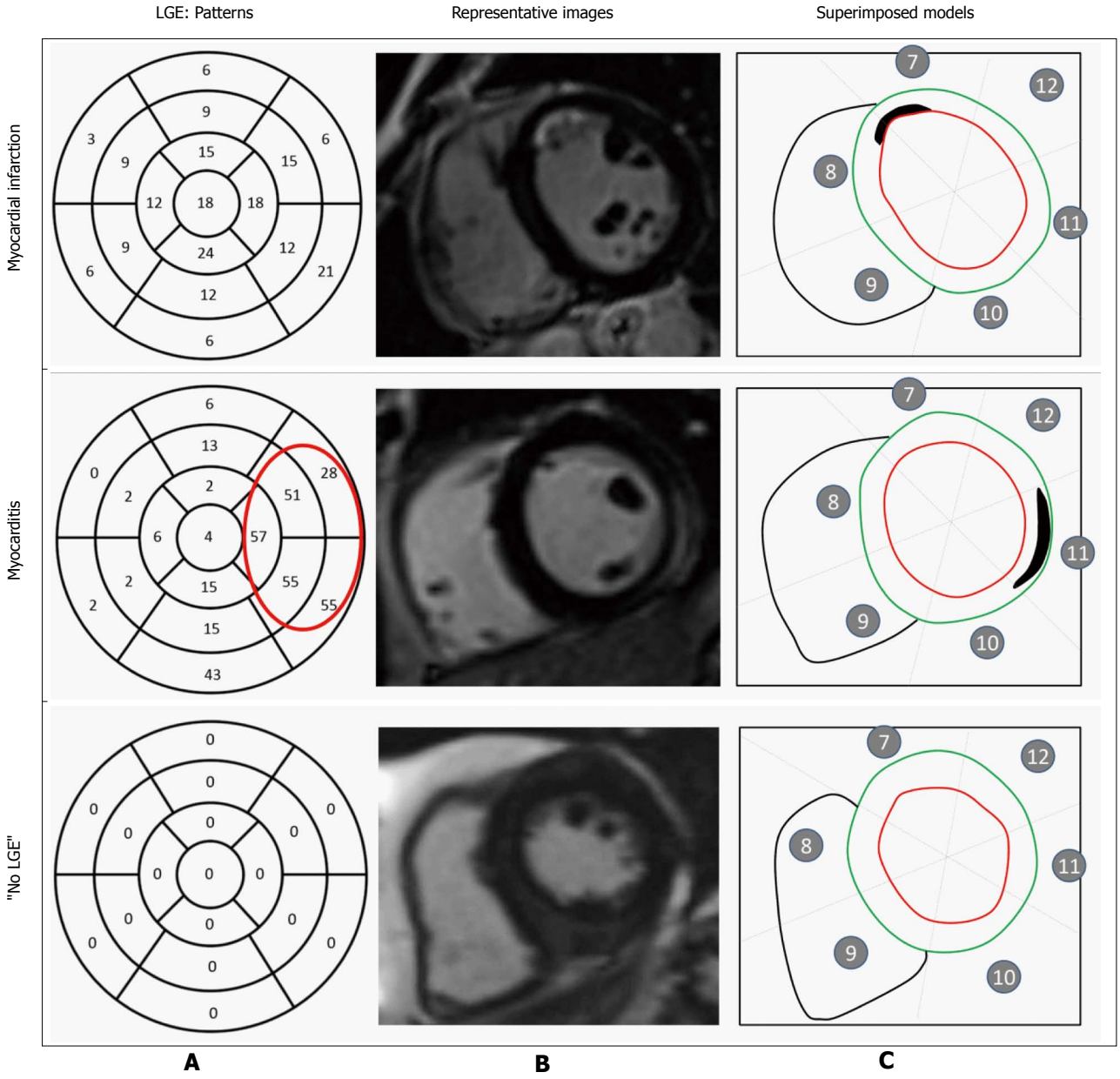

Figure 2 Pattern of late gadolinium enhancement. A: Incidence of late gadolinium enhancement (LGE) within each segment (percentage) of all patients, including those with and without LGE. In myocarditis cases, LGE was predominantly on the lateral wall. In myocardial infarction, no specific pattern of LGE could be identified; B: Representative short-axis slice images showing LGE location; C: Superimposed segmental models showing location and spatial extent of LGE (outlined).

a ventricular arrhythmic event, consisting of 17 VTs and one ventricular fibrillation (Tables 3 and 4). No differences were observed between the MI and the myocarditis groups (n = 9, 26.5% *vs* n = 6, 12.8%, P = 0.10), whereas the MI patients exhibited higher rates of VT than the "no LGE" group (n = 2, 4.0%, P = 0.001). All these events occurred in the early stages of hospitalization, with a median onset of 1 (0-1) d. One episode of ventricular fibrillation occurred in a myocarditis patient on day 3, who was successfully defibrillated. We found no differences in cardiovascular risk factor, CRP, coronary atheroma, or use of β-blockers and ACEIs in correlation with the ventricular events.

The transmural extent of LGE was more marked in the MI group (P < 0.001). An LGE transmural extent > 50% was observed in 32 patients (94.1%) in the MI group, in contrast to 16 patients (34.0%) in the myocarditis group (P < 0.001). LGE was more contained in the MI group, exhibiting lower transversal extents than the myocarditis group. Only eight patients (23.5%) were found to have more than two segments with LGE presence in the MI group, *vs* 27 (57.4%) in the myocarditis group (P = 0.002).

Of note, the concordance among Cine and LGE data was higher in the MI group compared to the myocarditis group (88.2% *vs* 41.3%, P < 0.001).

The multivariate analysis demonstrated that STE [OR = 5.72 (1.77-18.46), P = 0.004] and LGE transmural extent [OR = 1.50 (1.02-2.20), P = 0.039] were both independently related to ventricular events during hospitalization (Table 5). STE presented high sensitivity for the diagnosis of prolonged VT (83%), achieving a

Table 2 Cardiac magnetic resonance parameters

	Total (n = 131)	MI (n = 34)	Myocarditis (n = 47)	"no LGE" (n = 50)	P
LVEF (%)	58.6 ± 8.2	57.1 ± 7.8	57.9 ± 8.6	60.2 ± 7.8	0.18
LVEDV (mL)	154.7 ± 37.7	158.8 ± 41	159.6 ± 28.6	147.3 ± 42.1	0.21
LVESV (mL)	64.5 ± 22.1	69.5 ± 25.5	67.1 ± 16.9	58.6 ± 22.9[2,3]	0.048
LV wall thickening abnormality, n (%)	62 (47.3)	30 (88.2)	22 (46.8)[1]	10 (20.0)[2,3]	< 0.001
Hypokinetic extent, segments	1.1 ± 1.5	2 ± 1.6	1.2 ± 1.6[1]	0.4 ± 1.1[2,3]	< 0.001
0 segment, n (%)	69 (52.7)	4 (11.8)	25 (53.2)	40 (80.0)	
1-2 segments, n (%)	43 (32.9)	20 (58.8)	14 (29.8)	9 (18.0)	
> 2 segments, n (%)	19 (14.5)	10 (29.4)	8 (17.0)	1 (2.0)	
LGE transmural extent, segments	0.9 ± 0.8	3.6 ± 0.6	2.1 ± 0.9[1]	0	< 0.001
< 50%, n (%)	83 (73.4)	2 (5.9)	31 (66.0)	0	
> 50%, n (%)	48 (36.6)	32 (94.1)	16 (34.0)	0	
LGE transversal extent, segments	1.9 ± 2.2	1.9 ± 1.3	3.5 ± 2.4	0[2,3]	< 0.001
0 segment, n (%)	50 (38.2)	0	0	50 (100.0)	
1-2 segments, n (%)	46 (35.1)	26 (76.5)	20 (42.6)	0	
> 2 segments, n (%)	35 (26.7)	8 (23.5)	27 (57.4)	0	
LGE/CINE concordance, n (%)	49 (37.4)	30 (88.2)	19 (41.3)[1]	0	< 0.001
Pericardial effusion, n (%)	20 (15.3)	4 (11.8)	8 (17.4)	8 (16)	0.8

[1]P significant between MI and myocarditis groups; [2]P significant between MI and "no LGE" groups; [3]P significant between myocarditis and "no LGE" groups. MI: Myocardial infarction; LGE: Late gadolinium enhancement; LV: Left ventricle; LVEDV: Left ventricular end diastolic volume; LVESV: Left ventricular end systolic volume; LVEF: Left ventricular ejection fraction.

Table 3 Acute event rates

	All patients (n = 131)	MI (n = 34)	Myocarditis (n = 47)	"No LGE" (n = 50)	P
Ventricular event, n (%)	18 (13.8)	9 (26.5)	7 (14.9)	2 (4.0)[1]	0.013
VT, n (%)	17 (13.0)	9 (26.5)	6 (12.8)	2 (4.0)[1]	0.011
Prolonged VT or VF, n (%)	8 (6.1)	4 (11.8)	4 (8.5)	0[1]	0.06
VF, n (%)	1 (0.8)	0	1 (2.1)	0	0.41

[1]P significant between MI and "no LGE" groups. MI: Myocardial infarction; LGE: Late gadolinium enhancement; VF: Ventricular fibrillation; VT: Ventricular tachycardia.

specificity of 77% and negative predictive value of 92%. At 1 year, no patients presented with sudden cardiac death or recurrence of symptomatic ventricular event. One patient died of cancer.

DISCUSSION

The key point of the study is to demonstrate that none of the patients presenting with MINOCA and normal LVEF died of cardiovascular death or sudden cardiac death following the initial phase of hospitalization. ST segment elevation and LGE extent were the best predictors of in-hospital ventricular arrhythmic events, irrespective of the etiology.

During hospitalization, 13.8% of the patients experienced a ventricular arrhythmic event, primarily consisting of VT, with one case of ventricular fibrillation. Most of these events occurred during the first 48 h following symptom onset. These results are consistent with the literature, with previous reports of similar rates of early arrhythmic outcomes among patients with MINOCA[7,12-14] or in cases of myocarditis[15]. Our study demonstrated that, in the absence of decreased LVEF, MI and myocarditis patients are affected by the same arrhythmic risks. Following the initial phase of the disease, where the risk of ventricular arrhythmia is present, the arrhythmic risk appears very low.

The initial arrhythmic risk of myocarditis is well known and studies have shown that in patients < 35 years, myocarditis was the second most common identified cause of sudden cardiac death after coronary artery disease[16].

Our study demonstrated that STE is an independent predictor of ventricular arrhythmia at early-stage disease, achieving a good negative predictive value of 92% for prolonged VT. Data on the prognostic role of ECG abnormalities are currently scarce. This finding was assumed to be in relation to the transient character of the ST changes in myocarditis[17], as well as the weak relationship between STE and LGE localization[17,18].

The adverse prognostic value of LGE-CMR in ischemic and non-ischemic cardiomyopathy has been proven in patients with reduced LVEF[19]. Conversely, Grün *et al*[20] demonstrated a relevant cardiac mortality of 15% in 203 patients with myocarditis, which was primarily driven by the presence of LGE. Nevertheless, a large proportion of their patients presented with heart failure and decreased LVEF. In another report of fewer selected patients with suspected myocarditis, LGE was found in only 28% of cases, and LGE and LVEF were defined as predictors for a composite of cardiac death and heart failure[15]. In our study, considering the

Table 4 Acute event characteristics

Patient	Gender	Age (yr)	ECG	Troponin (μg/L)	LVEF (%)	Diagnosis	LGE transmural extent[1]	β-blocker use	ACEI use	VT	VF	CMR delay (d)	Ventricular arrhythmia length
13	Male	39	STE	0.3	51.7	MI	4	1	0	1	0	1	10 VPBs
52	Male	45	Normal	0.4	57.7	MI	3	0	0	1	0	1	10 VPBs
53	Female	30	STE	17.3	45.5	MI	4	1	1	1	0	0	30 VPBs
63	Male	51	Normal	0.3	57.8	MI	3	1	1	1	0	1	6 VPBs
64	Male	56	STE	1.6	61.2	MI	4	1	1	1	0	1	15 VPBs
75	Male	32	STE	0.8	63.2	MI	4	1	0	1	0	0	7 VPBs
92	Male	57	STD	0.4	48.1	MI	3	1	0	1	0	0	6 VPBs
128	Female	55	STD	0.6	49.8	MI	4	1	1	1	0	1	5 VPBs
97	Male	83	STD	0.2	46.5	MI	2	1	1	1	0	0	6 VPBs
3	Male	45	STE	0.1	66.9	Myocarditis	3	1	0	1	0	2	9 VPBs
37	Male	40	STE	4.8	56.1	Myocarditis	2	0	1	1	0	2	5 VPBs
44	Male	25	STE	36.6	65.7	Myocarditis	3	0	0	0	1	3	VF
94	Male	28	STE	1.4	57.1	Myocarditis	2	1	0	1	0	0	4 VPBs
76	Male	53	STE	1.4	69.6	Myocarditis	2	1	1	1	0	0	7 VPBs
104	Female	42	STE	21.2	57.1	Myocarditis	4	1	0	1	0	1	13 VPBs
131	Female	31	STD	0.6	51.7	Myocarditis	1	1	0	1	0	1	8 VPBs
80	Male	34	STE	0.4	53.1	No LGE	0	0	1	1	0	0	7 VPBs
125	Male	56	Normal	0.1	62.4	No LGE	0	1	1	1	0	4	3 VPBs

[1]LGE transmural extent: 0 = 0%, 1 = 0%-25%, 2 = 25%-50%, 3 = 50%-75%, and 4 > 75%. LGE: Late gadolinium enhancement; ECG: Electrocardiography; LVEF: Left ventricular ejection fraction; STD: ST-segment depression; STE: ST-segment elevation; VT: Ventricular tachycardia; VF: Ventricular fibrillation; VPBs: Ventricular premature beats; MI: Myocardial infarction; ACEI: Angiotensin-converting enzyme inhibitor.

Table 5 Univariate and multivariate analysis for ventricular arrhythmia

	Univariate analysis		Multivariate analysis	
	Odds ratio (95%CI)	*P*	Odds ratio (95%CI)	*P*
STE	4.65 (1.61-13.40)	0.004	5.72 (1.77-18.46)	0.004
STD	-	0.06		
T-wave inversion	-	0.99		
Troponin	1.10 (1.02-1.20)	0.02	-	0.27
Hypokinetic extent	-	0.09		
LGE transmural extent	1.52 (1.08-2.15)	0.017	1.50 (1.02-2.20)	0.039
LVEF	-	0.31		
LVEDV	-	0.3		
LVESV	-	0.17		
Pericardial effusion	-	0.24		
Coronary atheroma	-	0.68		
CMR diagnosis	-	0.12		
MI or myocarditis	0.17 (0.04-0.77)	0.022		

LVEDV: Left ventricular end-diastolic volume; LVESV: Left ventricular end-systolic volume; LVEF: Left ventricular ejection fraction; STD: ST-segment depression; STE: ST-segment elevation; MI: Myocardial infarction; CMR: Cardiac magnetic resonance.

excellent prognosis of the population, we have found that LGE is not useful for evaluating cardiac outcomes.

Despite this, however, the transmural extent of LGE was identified as an independent predictor for ventricular arrhythmia during the acute phase of the disease. This could therefore be of great value, if performed very early after the hospitalization, to identify at-risk patients requiring special attention and perhaps more prolonged rhythmic monitoring.

In our study, CMR imaging provided etiological diagnosis in 81 patients (61.8%), which is consistent with previous reports[21,22]. Clinical evaluations including biopsy have demonstrated that myocarditis could be present in patients with normal CMR results in 32% to 47% of cases[20,23]. It is likely that the frequency of myocarditis was underestimated in our study, especially in the "no LGE" group, as suggested by the CRP levels that were similar to those with myocarditis. It has been suggested that global LV involvement in myocarditis may be the cause of LGE absence[24].

The choice of medical management strategy for these patients remains controversial. There is little data, which is also conflicted, on the use of a secondary prevention treatment involving at least β-blockers in patients affected by myocarditis mimicking acute MI[25]. In our cohort, 69.5% of the patients received β-blockers during hospitalization, reflecting the management of a recent MI. Regarding the relatively-high percentage of patients who experienced ventricular arrhythmia, there is no doubt that this treatment is of interest during this period of time.

In our study, the absence of sudden cardiac death at 1 year suggests that β-blockers should not be continued over the long term, even if the β-blocker treatment had already been stopped in most of the population, with only one myocarditis patient still undergoing treatment. The need to prolong the treatment immediately after the hospital discharge is, however, a more controversial topic. LGE and ST segment elevation may represent valuable tools to stratify the risk of these patients and select those eligible for secondary prevention therapy.

The first limitation of our study was the sample size, which was too small to detect any statistical difference between the myocarditis group and the MI group. Secondly, the retrospective study design also, evidently, posed a limit. Finally, no systematic rhythm

monitoring was organized to screen the last recurrence of ventricular events after discharge. Similarly, the therapeutic management that may be chosen based on such preclinical events was left to the discretion of the referring cardiologist, and the use of β-blockers or ACEIs was extremely low at follow-up (12.2% and 13.0%, respectively). Nevertheless, none of our patients presented with sudden cardiac death or severe arrhythmia during follow-up. We must also admit that prognosis may differ by ethnicity but are not stressed in our study.

In conclusion, our study indicated that patients with MINOCA and normal LVEF did not present any 1-year CV events, particularly no sudden cardiac death, after hospital discharge. Most of them had even stopped treatment at 1-year follow-up.

STE on admission and LGE transmural extent appear to be good markers for identifying patients at risk of ventricular events in the early stages of disease.

COMMENTS

Background

About 1%-12% of patients with chest pain and cardiac troponin elevation present with normal coronary arteries on angiography analysis. While the arrhythmic prognosis of myocardial infarction with abnormal coronary angiography is well known, there is little data concerning myocardial infarction with non-obstructive coronary arteries (MINOCA). This study sought to evaluate the risk of ventricular arrhythmias of presumed low-risk MINOCA patients, based on the diagnosis class established by cardiac magnetic resonance (CMR) imaging.

Research frontiers

Numerous patients are affected by MINOCA, and yet prognosis is expected to be favorable as soon as left-ventricular ejection fraction (LVEF) is good. Nevertheless, the mere presence of a myocardial injury/scar/fibrosis, let us empirically dare for the occurrence of ventricular arrhythmia.

Innovations and breakthroughs

CMR was used systematically to identify MINOCA's aetiology, but also to assess myocardial injury and its extent. Continuous electrocardiography was also systematically performed to solve the question of arrhythmic risk during the first days after symptoms onset. It was continued by a one-year clinical follow-up. Nevertheless, this study does not focus on medical therapy, including the effect of β-blockers on ventricular arrhythmia.

Applications

This study provides evidence on the good prognosis (including arrhythmic events) presented by patients with MINOCA and preserved LVEF. When ventricular arrhythmias occurred, they correlated with myocardial injury, as assessed by transmural late gadolinium enhancement (LGE) by CMR. Therefore, this study provides reassuring data about survival but also point out the need to stress the effect of antiarrhythmic therapies on the newly-identified risk markers that are LGE and ST segment elevation.

Terminology

MINOCA is a recent terminology that relates to ischemic injuries, myocarditis, tako-tsubo cardiomyopathy, hypertrophic cardiomyopathy, dilated cardiomyopathy, and other causes such as pericarditis and amyloidosis.

Peer-review

This paper is interesting, novel, and an overall well-conducted study. It provides a timely study on this field.

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ORIGINAL ARTICLE

Prospective Study

Children with transposition of the great arteries: Should they actually be born in Nigeria?

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Abstract

AIM

To describe the clinical and echocardiographic features of Nigerian children with transposition of the great arteries and emphasize the need for collaboration with cardiac centres in the developed countries to be able to salvage the children.

METHODS

Prospective and cross sectional involving consecutive patients diagnosed with transposition of the great arteries using clinical evaluation and echocardiography at the Paediatric Department of Lagos State University

Teaching Hospital, Lagos Nigeria as part of a large study between January 2007 and December 2015.

RESULTS

There were 51 cases of transposition of the great arteries within the study period with a male to female ratio of 2:1 and a prevalence of 1.55 per 10000 among population of children who presented to centre during the study. Its proportion amongst children with congenital heart disease was 4.9%, while it was 15.4% among those with cyanotic congenital heart disease. The mean age ± SD of the subjects was 10.3 ± 21.8 mo. Up to 70% of the patients were less than 6 mo of age at initial presentation. The most common mode of presentation was cyanosis. The most common associated intracardiac anomaly was ventricular septal defect which occurred in 56% of the patients.

CONCLUSION

Transposition of the great arteries is as common in Nigeria as in the other parts of the world. The most common mode of presentation was cyanosis. There is an urgent need to establish paediatric cardiac centres in Nigeria if these children are to be salvaged.

Key words: Transposition; Cyanosis; Children; Salvage; Nigeria

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Core tip: Transposition of the great arteries is as common in Nigeria as in the other parts of the world. The most common mode of presentation in our subjects was cyanosis. Palliative and definitive interventions are currently not available for them in Nigeria. A lot of lives are being wasted yearly because of unavailable and inaccessible surgical care.

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INTRODUCTION

Transposition of the great arteries (TGA) affects children of all races as documented earlier[1,2] and African children are no exception[3,4]. Advance surgical techniques to manage children with congenital heart lesions is still in infancy stage in Nigeria[5,6]. That notwithstanding, cases of TGA are seen and managed within the available limitations. There are only very few reports on TGA in Africa especially from sub-Saharan Africa. At best TGA is only mentioned as part of other congenital heart disease or as case reports. There has been no report on cohorts of children with TGA in West Africa. This article will describe the pattern and presentation of children diagnosed with TGA and the management and outcome of such patients in a tertiary hospital in sub-Saharan Africa. This is to make data available on these group of subjects for reference purpose for future research in the region, create awareness on TGA among health professionals in the region and for advocacy on the urgent need to establish paediatric cardiac centres in Nigeria so that these children can be salvaged, especially the need for collaboration with established paediatric cardiac centres in the developed countries in order to improve the outcome of children born with TGA in the West Africa region through early diagnosis and prompt intervention.

MATERIALS AND METHODS

This was a review of prospectively collected data of all patients less than 13 years of age diagnosed with TGA using echocardiography at the Paediatric Department of Lagos State University Teaching Hospital Lagos Nigeria between January 2007 and December 2015.

The hospital is a tertiary institution in Southwestern Nigeria and receives referral from the region. Patients with suspected cardiac lesion are referred to the department for evaluation from within the state and sub-region. A paediatric cardiologist is in charge of the cardiology unit. Patients referred to the cardiology unit of the department are evaluated with chest radiograph, electrocardiography other ancillary investigations as required including echocardiography.

One echocardiography machine was used on all the subjects throughout the study period, a GE Vivid Q echocardiography machine reference number 14502 WP SN 2084. It has facility for two dimensional, M-mode and color flow Doppler imaging. The paediatric cardiologist performed the echocardiography on all the subjects.

Definitive diagnosis is based on echocardiography which demonstrates the characteristic bifurcation of the pulmonary artery arising posteriorly from the left ventricle in the parasternal long axis view and the aorta anterior and to the right of the pulmonary artery. Other associated cardiac anomalies such as the atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus, double outlet right ventricle (DORV), pulmonary stenosis (PS) and abnormal coronary arteries were documented for all the patients. A diagnosis of TGA was made based on the combination of clinical signs and symptoms, with or without a chest radiograph features described above with the characteristic echocardiographic features[7,8].

All the patients were followed up at the paediatric cardiology clinic. Surgical correction was required by all the subjects but this is not available in Nigeria and thus the patients were referred outside Nigeria for the correction. The patients who had surgical correction were referred back to the unit after the correction and they were followed up in the unit.

The data were imputed in a personal laptop and

Table 1 Yearly incidence and percentage of transposition of the great arteries amongst the congenital heart disease

Year	Total patients seen	Patients with CHD (*n*)	Patients with TGA (*n*)	Prevalence of TGA amongst CHD (%)	Prevalence of TGA per 10000 children
2007	47343	87	1	1.15	0.21
2008	49387	119	8	6.72	1.62
2009	49141	90	2	2.22	0.41
2010	36400	103	14	13.59	3.84
2011	37404	153	6	3.92	1.60
2012	28475	143	4	2.79	1.40
2013	32220	180	6	3.33	1.86
2014	32800	108	7	6.48	2.13
2015	13492	140	3	2.14	2.22
Total	326662	1123	51	4.54	1.56

TGA: Transposition of the great arteries; CHD: Congenital heart disease.

analysed using Statistical Package for Social Sciences version 20. The children's age, sex, indication for echocardiograph, echocardiographic findings and outcome and were documented. Tables and charts were used to depict those variables. Means of continuous variables were compared using the Student *t* test, and proportions using χ^2 test. Level of significance set at $P < 0.05$.

RESULTS

Prevalence of TGA

Prevalence rates were based on 51 cases of TGA diagnosed between January 2007 and December 2015. A total of 326662 children were seen at the department during the study period and 1693 had echocardiography done. Of the 1693 who had echocardiography done, 1123 had congenital heart diseases (772 and 351 for acyanotic and cyanotic congenital heart defects respectively).

Table 1 shows the yearly distribution, prevalence of TGA and proportion of subjects with TGA amongst the cases of congenital heart disease. The prevalence of TGA within the study period was 1.55 per 10000 populations of children who present to the hospital. The percentage of TGA amongst children with congenital heart disease was 4.5% and 14.5% amongst those with cyanotic congenital heart disease.

Clinical presentation

There were 51 cases of TGA within the study period. They comprised 34 males and 17 females with a male to female ratio of 2:1. The mean age of the children at initial presentation in month was 10.3 ± 21.8 with a median age of 4 mo and a bimodal age of 1 and 4 mo. The mean age of the males was 9.3 ± 24.3 while that of the females was 12.2 ± 16.8 ($P = 0.28$). The distribution of the age of the patients was the same across both sexes. The median age for the males and females was 3.5 and 5.5 mo respectively. The modal age for the males was 4 mo while that of the females was bimodal, 2 and 6 mo. Up to 70% of the patients were less than 6 mo of age at initial presentation. The youngest patient was 14 d old while the oldest patient was 11 years old. Table 2 depicts the age distribution of the children at diagnosis.

Table 2 Ages at echocardiography and sex distribution of the patients

Age (mo)	Male	Female	χ^2	*P*
0-6	25	11	2.0	0.36
6.1-12	4	2		
⩾ 12.1	5	4		
Total	34	17		

$\chi^2 = 2.0$, $P = 0.36$.

All the children were ill at presentation. Forty-seven children were cyanosed while 4 were acyanosed at presentation. The indications for echocardiography are depicted in Table 3. In most cases there were more than one reasons/indication for echocardiography. All the study subjects had d-TGA. Other associated intracardiac anomaly are as highlighted in Table 4. The most common associated intracardiac anomaly was ventricular septal defect which occurred in 56% of the patients and this co-existed alone or in combination with other intracardiac connections.

Treatment and outcome

The patients received anti-congestive agents and angiotensin converting enzyme inhibitors. Five patients had surgical intervention done outside the study centre. One patient had atrial switch and is doing well on follow up three years post surgery. The other four had arterial switch surgeries. One patient succumbed at the immediate post up period. Another died about two months' post surgery in a secondary centre. Another died about one-year post surgery secondary to a non-cardiac illness. The remaining patient is on followed up in the department eight-year post-surgery and is stable. The other patients who could not afford treatment succumbed while sourcing for funds to do surgery. More than 90% of the patients died at infancy, a few at about 14 mo of age. All the patients who had surgery were operated in India.

DISCUSSION

TGA is the most common cyanotic congenital heart lesion in the newborn[9]. The Center for Disease Control (CDC) estimated that each year, 1901 babies in the United States are born with TGA or an approximate of 5 in 10000 babies born yearly with it[10]. It is present in 5%-7% of all patients with congenital heart disease[11]. There is a male predominance with a male to female ratio of 1.5:1 to 3:2[12-14]. The mortality in untreated patients is up to 50% in the first month and 90% by the end of the first year[7]. Maron *et al*[1] in the United States over four decades ago, documented that there was no racial difference in the frequency of TGA.

Table 3 Indication for cardiac evaluation of the subjects

Indication	Frequency	% of all patients
Cyanosis	47	92
ACHD	4	7.8
Breathlessness	10	19.6
CCF	1	1.9
Stroke	1	1.9
Murmur	1	1.9
Failure to thrive	1	1.9
Suspected TGA	1	1.9
Dextro Cardia	1	1.9
Down syndrome	2	3.9

Some patients had more than one indication. ACHD: Acyanotic congenital heart disease; CCF: Congestive cardiac failure.

Table 4 Associated intracardiac connections in subjects

Cardiac anomaly	Frequency	% of all TGA
ASD	19	37.3
AVCD	3	5.9
DORV	10	19.6
HLH	1	1.9
PDA	15	29.4
PFO	2	3.9
PS	6	11.8
TAPVC	1	1.9
TOF	1	1.9
TR	3	5.9
VSD	27	52.9

Most patients had more than one intracardiac connections. TGA: Transposition of the great arteries; ASD: Atrial septal defect; AVCD: Atrioventricular canal defect; DORV: Double outlet right ventricle; HLH: Hypoplastic left heart; PDA: Patent ductus arteriosus; PFO: Patent foramen ovale; TAPVC: Total anomalous pulmonary venous connections; TOF: Tetralogy of fallot; TR: Tricuspid regurgitation; VSD: Ventricular septal defect.

However, a more recent study by Botto *et al*[2] in the same country documented a higher occurrence of TGA in whites compared to negroes. In 10% of cases of TGA association with noncardiac malformations have been documented[15].

The aetiology is largely unknown. Associated risk factors include gestational diabetes mellitus[16,17], maternal exposure to rodenticides and herbicides[18] and maternal use of antiepileptic[19]. Genetic mechanisms have been implicated and some genetic mutations have been implicated[20,21].

The prevalence of TGA in this study was 1.55 per 10000 populations of children who presented to the hospital. This result is less than the CDC report of 5 in 10000 live births in the United States[12]. However the CDC report is a study on the proportions of live birth which is a different denominator compared to the present study. We have also documented the yearly prevalence of TGA. It was highest in 2010, 3.84 per 10000 children and lowest in 2007, 0.21 per 10000 children per year. Reasons why it may have been low in the first year is because the echocardiography machine was just made available and there was little awareness of its availability for evaluation of children with structural heart disease within the region. Thus there were little referral for cardiac evaluation at that time. The prevalence rate documented in this study may be a far cry from the actual prevalence rate because a lot of cases may have been missed in the neonatal period and early infancy for a number reasons. Firstly, prenatal cardiac evaluations are rarely done in Nigeria thus a sizeable number may have been missed at birth. Secondly, the clinical presentation of TGA is non-specific and thus a number of cases may have been ill and in the absence of proper evaluation with a high index of suspicion of a congenital heart disease some babies may have be managed for other morbidities and died without a cardiac evaluation. Thirdly, because of cultural practices prevalent in the region, infants who died before a proper evaluation was done may not have autopsy done to confirm a suspicion of a congenital heart disease and TGA to be specific[22].

TGA was documented in 4.5% of all congenital heart disease within the study period. Two decades ago, Jaiyesimi *et al*[23] in UCH Ibadan documented a prevalence rate of 4.8% in cardiac lesions which is similar to findings in the present study. International rate of TGA amongst all congenital heart lesion is 5%-7%[14] and this is also similar to the value documented in the present study. We also documented a male predominance in TGA with a male to female ratio of 2:1. This is consistent with international ratio of 1.5:1-3.2:1[12-14].

The mean age of the children with TGA was 9.3 ± 24.3. The mean age was not different in both sex. The youngest child was 2 wk and the oldest was 11 years old. Although 70% of the patients were ≤ 6 mo old there were three patients who were three, six and eleven years old and those values significantly affected the mean age and resulted in a large standard deviation. In an earlier study by Adegboye *et al*[4] in Ibadan, southwestern Nigeria, the mean age of the children with TGA who underwent palliative surgery was 6.8 ± 2.4. The mean age recorded in Ibadan was not significantly different from that documented in this study although the subjects were fewer in the later study. In contrast, in advanced countries, diagnosis of TGA is made in neonatal period.

Patients with TGA present with central cyanosis from the first month of life with varying clinical manifestation based on the degree of mixing between the two circulations[17]. Patients with a large ventricular septal defect and or a patent ductus arteriosus (PDA) may present early with congestive cardiac failure. Long term complications are secondary to cyanosis. A definitive diagnosis of TGA is made with an echocardiogram[8].

The most common mode of presentation in our subjects was cyanosis and some patients presented with more than one presentation. This is not an unusual finding as the signs and symptoms of TGA varies depending on the associated intracardiac lesion[8].

Cyanosis may go unnoticed in some patients with large ventricular septal defects without right outflow. Similarly, 8% of our study subjects were not cyanosed at presentation and one had congestive cardiac failure.

Complications from cyanosis and polycythemia may occur especially in untreated cases. One of the subjects was a 3.25-year-old male who had been cyanosed from infancy, he presented to the hospital for the first time with cerebrovascular accident and cardiac evaluation revealed a TGA.

D-TGA is the common form of TGA worldwide and all our study subjects had d-TGA. Simple TGA is not compatible with extra-uterine life except there are intracardiac connections for admixture of blood[24,25]. All our subjects had intracardiac connections and not surprisingly the most common was a VSD which occurred either alone or in combination with other intracardiac lesions. ASD was the second most common closely followed by a PDA in 37.3% and 29.4% respectively. Left ventricular outflow obstruction may occur in one eight to a third of patients with TGA. We report in this study 12.5% of cases of pulmonary stenosis and all but one of those subjects had an associated VSD while the other patient had an atrioventricular canal defect. Other complex lesions documented in this study are TOF, hypoplastic left heart, TAPVC, DORV and tricuspid atresia.

TGA is known to be associated with other congenital disorder in 10% of cases[6]. Sporadic association of TGA with trisomy 8, 18, VACTERL and CHARGE syndrome have been documented[26,27]. Two (3.9%) of our subjects had Down syndrome and the others had no dysmorphologies.

Treatment of patients with TGA is both medical and surgical. Initial palliative care is instituted to achieve optimal intercirculatory mixing and optimize the clinical condition[7,18]. Mechanical ventilation and oxygen may be needed for unstable infants, correction of metabolic acidosis and administration of prostaglandin E_1 to maintain arterial duct patency[7]. Balloon atrial septostomy may be done to maintain admixture of blood at atrial level. Surgery provides the definitive treatment. It may be offered within the first month of life depending on the clinical setting. The arterial switch procedure can be done. Others include the Rastelli operation and Nikaidoh's procedure[8].

In the current study, all our patients required definitive surgical corrections which is currently not available in Nigeria. Only three (5.9%) could afford to do corrective surgery outside Nigeria. Three patients presented within the first two weeks of life and all three had a PDA with either a VSD or an ASD. They required palliative surgery but could not afford one. Almost 90% of the patients could not access the much needed surgical care and succumbed before help could be provided. This was not surprising because the case fatality rate for TGA is as high as 50% by the end of the first month and 90% at one year for untreated cases. These are largely preventable deaths if diagnosis can be made on time and appropriate treatment instituted timely.

In conclusion, transposition of the great arteries is as common Nigeria as in the other parts of the world. The most common mode of presentation in our subjects was cyanosis. Palliative and definitive interventions are currently not available for them in Nigeria. A lot of lives are being wasted yearly because of unavailable and inaccessible surgical care. There is an urgent need to establish paediatric cardiac centres in Nigeria so that these children can be salvaged. Collaboration is needed from established paediatric cardiac centres from developing and developed world if this is to be achieved.

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COMMENTS

Background

Transposition of the great arteries (TGA) affects children of all races as documented earlier including African children. Prompt and advance surgical intervention needed to salvage these children is currently not available in Nigeria.

Research frontiers

Arterial switch is one of the surgical option for correction of TGA is preferable done during the neonatal period.

Innovations and breakthroughs

This article described pattern and presentation of children diagnosed with TGA and the management and outcome of such patients in a tertiary hospital in sub-Saharan Africa. Data on these group of subjects has been provided by this study for reference purpose.

Applications

The data provided in this study is useful for, future research in the region on the subject, awareness creation on TGA among health professionals in the region, for advocacy on the urgent need to establish paediatric cardiac centres in Nigeria if these children can be salvaged, especially the need for collaboration with established paediatric cardiac centres in the developed countries in order to improve the outcome of children born with TGA in the West Africa region through early diagnosis and prompt intervention.

Terminology

TGA is a congenital heart anomaly that occurs when the two main arteries of the heart, aorta and pulmonary arteries, are switched in position so that the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. Other names or synonyms used to describe TGA are: Physiologically uncorrected transposition, complete transposition and atrioventricular concordance with ventriculoarterial discordance. TGA is classified based on the spatial relationship between the great arteries to each other and or the infundibular morphology. dextro-TGA (D-TGA) is when the aorta is anterior and to the right of the pulmonary artery and it is the most common form. levo-TGA (L-TGA) describes the aorta that is anterior and to the left of the pulmonary artery. Furthermore, irrespective of either the L- or D-TGA, the patients may still have a subaortic infundibulum, absence of a subpulmonary infundibulum and a fibrous continuity between the mitral and pulmonary valves. Aside the above classifications, different presentations and exceptions have been described. However, the unifying hallmark is the ventriculoarterial discordance. In TGA, the pulmonary and systemic circulations run in parallel rather than in series. Oxygenated blood flows through a closed circuit that involves the lungs and left

cardiac chambers, while deoxygenated blood also flows in a closed circuit that starts from the systemic circulation and ends in the right heart chambers. This parallel circulation is incompatible with prolonged survival, so there is usually admixture of blood through the atrial or ventricular septum and or a patent ductus arteriosus.

Peer-review

The paper is well-written and provides an appropriate view about the current situation and future interventions.

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CASE REPORT

Early stent thrombosis secondary to food allergic reaction: Kounis syndrome following rice pudding ingestion

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Author contributions: Tzanis G contributed to acquisition of data, reviewed the literature and drafted the manuscript; Bonou M and Biliou S contributed to acquisition of data, reviewed the literature and helped to draft the manuscript; Koniari I reviewed the literature, and helped to draft the manuscript; Mikos N performed the allergology tests; Barbetseas J critically revised the manuscript; Kounis NG critically revised the manuscript; all authors have read and approved the final manuscript.

Institutional review board statement: This case report conforms to the ethical standards of our institution.

Informed consent statement: The patient involved in this study gave his verbal informed consent authorizing use of his protected health information.

Conflict-of-interest statement: All the authors have no conflicts of interests to declare.

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Abstract

Kounis syndrome is the concurrence of coronary spasm, acute myocardial infarction or stent thrombosis, with allergic reactions in the setting of mast-cell and platelet activation. In this report Kounis syndrome manifesting as stent thrombosis with left ventricular thrombus formation was triggered by a food-induced allergic reaction. The allergic reaction to food was confirmed by oral rice pudding ingredients challenge test while skin tests were inconclusive. To our knowledge, this is first report of early stent thrombosis secondary to food allergic reaction in a 70-year-old man patient who was found to have left ventricular thrombus and undiagnosed hypertrophic cardiomyopathy.

Key words: Allergic myocardial infarction; Allergic reaction; Kounis syndrome; Stent thrombosis

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Core tip: Kounis syndrome highlights, the role of anaphylactic mediated acute coronary syndromes complicating stent thrombosis in the era of invasive treatment of coronary artery disease. Drugs, stings,

bites, contrast material, atopic diathesis and even food ingestion could be the culprits. Managing the complex pathophysiology of this condition is a challenging issue, especially in the emergency setting, that requires rapid treatment decisions. The role of detailed past history and of preventive anti-allergic medication in high risk patients with anaphylactic reactions should be considered in randomized studies.

Tzanis G, Bonou M, Mikos N, Biliou S, Koniari I, Kounis NG, Barbetseas J. Early stent thrombosis secondary to food allergic reaction: Kounis syndrome following rice pudding ingestion. *World J Cardiol* 2017; 9(3): 283-288 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i3/283.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i3.283

INTRODUCTION

Kounis syndrome is a variety of acute coronary syndromes triggered by the release of inflammatory mediators following an allergic insult[1]. Stent thrombosis is a rare, but serious, complication that is strongly associated with severe morbidity and mortality. Stent thrombosis associated with allergic mediated inflammatory reaction has been described as a serious manifestation of Kounis syndrome[2-4]. Several reports exist in the medical literature on patients with coronary stent implantation who developed stent thrombosis, concurrently with an allergic reaction manifesting as Kounis syndrome. Such reactions had been triggered by non anionic contrast material iopromide, flavonate-propyphenazone, non steroidal anti-inflammatory agent acemetacine, insect stings, snake bite and clopidogrel, the drug that is given itself to prevent stent thrombosis[5-10]. In the following report we describe a patient who suffered early stent thrombosis with left ventricular thrombus formation triggered by an allergic reaction following food consumption. To the best of our knowledge, this is the first case of early stent thrombosis associated with food-induced allergy reaction.

CASE REPORT

A 70-year-old man smoker with a previous history of a transient ischemic attack, was referred to the emergency department of our hospital because of a pain to the left shoulder and arm that had started 4 d ago and was unresponsive to analgesics.

Upon admission, the electrocardiogram showed anteroseptal ST elevation myocardial infarction (Figure 1A) and transthoracic echocardiography revealed left ventricular hypertrophy, that was more pronounced at the interventricular septum, compatible with hypertrophic cardiomyopathy. Additional findings were an apical aneurysm, and moderate attenuation of systolic function. High sensitivity troponin I was elevated to 11037 ng/L. The patient was transferred to the coronary care unit and the next day coronary angiography revealed left anterior descending artery occlusion at the mid-level (Figure 1B). Subsequently, he was submitted to balloon angioplasty with placement of a drug-eluting stent (Resolute Integrity, 3 mm × 18 mm, Figure 1C). The patient remained asymptomatic and was discharged under optimal medical treatment including aspirin, clopidogrel, simvastatin, metoprolol, furosemide, lisinopril and eplerenone.

Four days later and about 20 min after taking his evening medication that was metoprolol and simvastatin and during ingestion of Greek rice pudding made of sheep milk, rice and sugar, the patient started gradually to develop lip swelling and itching followed by erythematous rash in all over his body. Within, approximately, 15 min he complained of chest pain and discomfort spreading to the left shoulder and arm. He was immediately transferred to the emergency department of our hospital. On arrival, the patient was covered in all his body with rash accompanied by itching and angioedema of the lips. The electrocardiogram showed ST elevation in V1-V4 leads (Figure 2A). Hydrocortisone and dimetindene maleate was given intravenously together with oral desloratadine and he was transferred to the catheterization laboratory, where coronary angiography revealed stent thrombosis with left anterior descending coronary artery occlusion (Figure 2B). The patient underwent thrombus aspiration that was followed by an additional stent placement (stent in stent procedure, drug eluting stent 3 mm × 16 mm, Figure 2C). However, mild chest pain remained for about 2 h and was attributed to "no reflow" phenomenon. Transthoracic echocardiography revealed, apart from hypertrophic cardiomyopathy with asymmetrical septal hypertrophy, also thrombus formation in an apical aneurysm (Figure 2E and F) necessitating heparin infusion. Contrast-echocardiography with Sonovue-Sulfur hexafluoride microbubbles revealed sessile apical thrombus (Figure 2F). Tryptase was elevated confirming an allergic reaction. The patient had an uneventful recovery and was scheduled for discharge after an allergology investigation.

Oral food challenge test

In order to identify what had triggered the allergic reaction, skin prick tests were performed, under strict hemodynamic monitoring, for simvastatin and metoprolol that were the drugs the patient was taking after the first episode, and were inconclusive. Subsequently, it was decided to proceed to an oral food challenge test, again under strict hemodynamic monitoring, using the rice putting ingredients that were sheep milk, rice and sugar according to the protocol described previously[11]. Following an initial amount of 0.6 g of sheep milk given slowly and 15 min after swallowing of 5 g of sheep milk the patient suddenly felt unwell, dizzy, started sweating, developed urticarial rash and complained of severe dyspnea. Soon after, he became

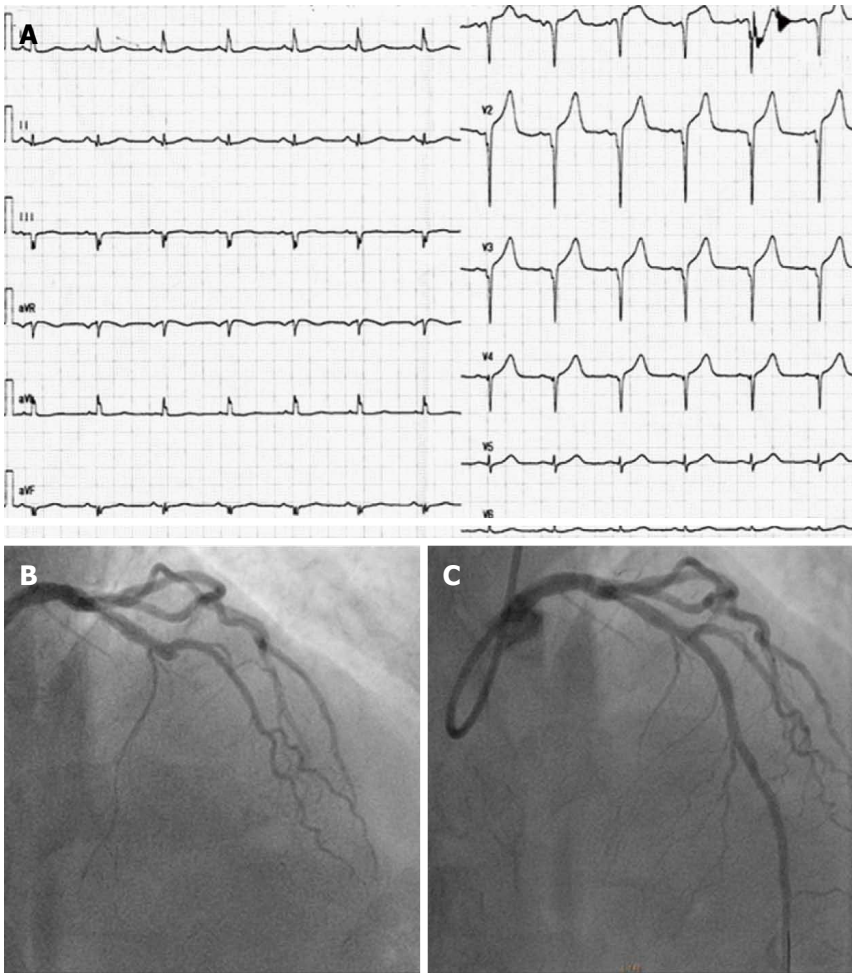

Figure 1 First presentation with acute coronary syndrome. A: Electrocardiograph upon admission; B: Coronary angiography showing critical stenosis in left anterior descending; C: After implantation of resolute integrity drug-eluting stent.

disorientated and sleepy. On examination, he was pale with bronchospasm accompanied by hypoxemia (SpO_2 82%), and sinus tachycardia (110/60 mmHg, 125 bpm), feeling itchy but without electrocardiographic changes. He was immediately treated with 250 mg hydrocortisone intravenously, 4 mg dimetindene maleate intravenously and 5 mg desloratadine orally with improvement in signs and symptoms. He gradually became stable and asymptomatic. Blood examinations, 10 min after onset of symptoms were performed for troponin, IgE antibodies and tryptase. Troponin was not increased, eosinophils were 70/μL, but IgE levels were increased to > 1000 IU/mL (normal values: 1-183 IU/mL). We did not proceed to challenge the patient with rice or sugar on ethical grounds, while the patient recalled that he was apprehended to sheep milk in the past.

He had an uncomplicated hospital follow-up and was discharged with the advice neither to eat rice pudding nor to drink sheep's milk again.

DISCUSSION

Acute myocardial infarction after a prolonged allergic reaction was firstly described in 1950[12]. However, a detailed description of the allergic angina syndrome progressing to acute myocardial infarction was described in 1991 by Kounis *et al*[13]. Three variants of Kounis syndrome have been described so far[14]: Type Ⅰ that includes patients with normal coronary arteries in whom the acute release of inflammatory mediators can induce coronary artery spasm that could progress to acute myocardial infarction. Type Ⅱ that includes patients with culprit and quiescent atheromatous disease in whom the acute release of inflammatory mediators may induce plaque erosion or rupture manifesting as acute myocardial infarction. The type Ⅲ variant includes coronary artery stent thrombosis in the setting of allergic or hypersensitivity and anaphylactic or anaphylactoid insults. In this type, the thrombus is infiltrated by eosinophils and/or mast cells.

The patient was found to have a previously undiagnosed hypertrophic cardiomyopathy with septal hypertrophy and apical thrombus formation. Coexisting of hypertrophic cardiomyopathy with coronary spasm is not frequent and clinical characteristics in patients with both diseases have not been clarified yet. However, in a study of 36 patients with hypertrophic cardiomyopathy challenged with acetylcholine provocation test coronary

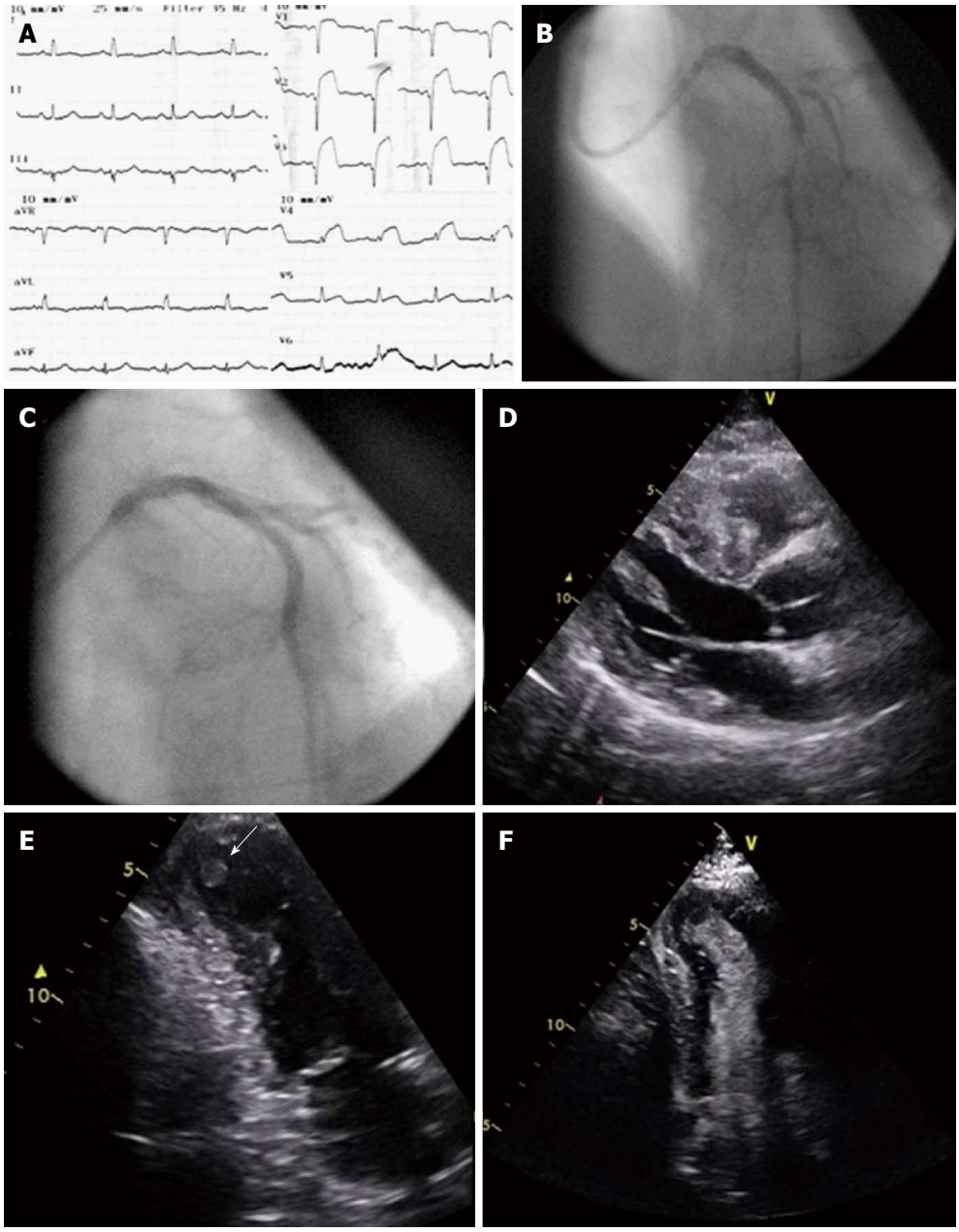

Figure 2 Kounis syndrome following rice pudding consumption. A: Electrocardiograph upon admission; B: Coronary angiography showing stent thrombosis; C: After implantation of drug-eluting stent (stent in stent); D: Parasternal long axis view showing excessive hypertrophy of the septum; E: Thrombus in aneurysmatic apex, apical 2-chamber view; F: Contrast derived image, with thrombus in the apex, apical 2-chamber view.

vasospasm was induced in 10 (28%). The conclusion was that coronary vasospasm appears to play a significant role in the etiology of myocardial ischemia in patients with hypertrophic cardiomyopathy and smoking, as in our patient, might be a major risk factor for coexistence of coronary vasospasm[15].

The apical thrombus formation could be attributed to pre-existing ischemic disease with aneurysmal dilatation of the apex. However, the activation of the thrombotic path during Kounis syndrome may have played an additional role. Indeed, platelet surface membrane contains, not only the well known receptors for thromboxane, adenosine diphosphate, IIb/IIIa but additional receptors for multiple exogenous agonists which contribute to platelet activation. These include receptors for thrombin, serotonin, epinephrine collagen, platelet activating factor and histamine[16]. Additionally, a subset of platelets bear in their surface high and low affinity FCγRI, FCγRII, FCεRI and FRεRII IgE receptors[17] that are activated during hypersensitivity responses.

The anaphylactic reaction was confirmed during hospitalization with oral food consumption test and it was found that the patient was allergic to sheep milk. Tryptase levels were not elevated and this might be due to blood sample collection soon after the onset of symptoms, and according to tryptase kinetics these levels are found to elevate later[18]. Immunoglobulin E antibodies were highly elevated that explains the IgE-mediated allergic reaction. In a study comparing cow milk allergy with sheep and goat milk allergy, it was

found that the latter affects older children and appears at a later age. In sheep or goat milk allergic patients, the IgE antibodies recognize the caseins but not the whey proteins. Moreover, IgE specificity and affinity was high to sheep-goat milk and lower to cow milk caseins despite their marked sequence homology[19].

Both physicians and susceptible individuals should be aware that high risk patients and patients with predisposition to allergies, especially allergy to sheep or goat milk require strict avoidance of such milk and milk derived products as reactions could be severe and life threatening. Vigorous anti-allergic medication and standardized treatment protocol is mandatory in order to prevent allergic insults and catastrophic cardiovascular adverse events.

COMMENTS

Case characteristics

A 70-year-old man with coronary artery disease who suffered early stent thrombosis with left ventricular thrombus formation triggered by a food-induced (sheep milk in rice pudding) allergic reaction and was found by oral food challenge test to be sensitized to sheep milk.

Clinical diagnosis

Clinical diagnosis Kounis syndrome, complicating early stent thrombosis following Greek rice pudding consumption, in a patient with coronary artery disease and hypertrophic cardiomyopathy.

Differential diagnosis

Acute coronary syndrome and anaphylactic shock. Both of them are the two sides of the same coin when investigating the complex pathophysiology of Kounis syndrome.

Laboratory diagnosis

Increased cardiac enzymes, IgE antibodies and tryptase levels.

Imaging diagnosis

Coronary angiography revealed stent thrombosis completely occluding left anterior descending artery. Echocardiography demonstrated left ventricular hypertrophy compatible with hypertrophic cardiomyopathy, an apical aneurysm and moderate attenuation of systolic function with thrombus formation in the apical aneurysm.

Pathological diagnosis

In the acute setting of the coronary syndrome, no thrombus was kept for pathological analysis.

Treatment

The patient underwent balloon angioplasty with placement of a drug-eluting stent in the acute setting of the stent thrombosis. In the second allergic reaction, during the allergic skin tests and the oral food challenge test, he was treated with hydrocortisone, dimetindene maleate and desloratadine with improvement in signs and symptoms of the allergic reaction.

Related reports

To our knowledge, this is the first report of Kounis syndrome with the clinical manifestation of early stent thrombosis after food allergic reaction.

Experience and lessons

Kounis syndrome is "a new twist on an old disease", which is frequently misdiagnosed. The early diagnosis could improve patients' outcome and prognosis, while original randomized studies could investigate the role of preventive anti-allergic medication in high risk patients with anaphylactic reactions.

Peer-review

This manuscript is well-written and an interesting case report with addressing type III Kounis syndrome (anaphylactic reaction) induced by food allergy.

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CASE REPORT

Importance of a second spasm provocation test: Four cases with an initial negative spasm provocation test

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Author contributions: Teragawa H wrote the manuscript; Fujii Y, Uchimura Y and Ueda T collected and evaluated the data.

Institutional review board statement: This case report was exempt from the Institutional Review Board standards at JR Hiroshima Hospital.

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

Conflict-of-interest statement: All authors have no conflicts of interest to declare.

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Abstract

The spasm provocation test (SPT) is an important test in the diagnosis of vasospastic angina (VSA). In many cases, this test is performed as the gold standard test, and VSA is considered not present if the SPT is negative. However, some patients continue to experience chest symptoms despite a negative SPT. In this study, we report four cases in which SPT was repeated to evaluate chest symptoms despite the negative results of the first SPT. Two men in their 70s, one woman in her 60s, and one woman in her 70s, all with chest symptoms, underwent a second SPT at 4, 3, 2, and 3 years, respectively, after the first SPT, which was negative. Three patients had positive results in the second SPT (75%). In conclusion, even when SPT is negative, the diagnosis of VSA should be made with clinical symptoms in consideration. In some cases, a second SPT may be required to confirm the diagnosis of VSA.

Key words: Coronary spasm; Acetylcholine; Spasm provocation test; Pressure wire

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Core tip: The spasm provocation test (SPT) is an important examination when diagnosing vasospastic angina (VSA). In general, if the SPT is negative, VSA is considered not present. However, we encountered four patients who underwent a second SPT although the first SPT was negative. In these patients, some show a positive second SPT result. SPT is not a perfect examination, and in the clinical setting, the diagnosis of VSA should be made with the consideration of their clinical symptoms and examinations.

Teragawa H, Fujii Y, Uchimura Y, Ueda T. Importance of a second spasm provocation test: Four cases with an initial negative spasm provocation test. *World J Cardiol* 2017; 9(3): 289-295

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INTRODUCTION

Coronary spasm is characterized by transient vasoconstriction of the epicardial coronary artery, leading to myocardial ischemia. Coronary spasm is the cause of not only typical rest angina but also exertional angina, acute myocardial infarction, and sudden cardiac death[1,2]. Therefore, the diagnosis of vasospastic angina (VSA) should be made with certainty. VSA is diagnosed by the presence of chest symptoms accompanied by transient ST deviation on the electrocardiogram (ECG)[3,4]. This can, however, be difficult in the clinical setting because angina attacks do not necessarily occur during the one day of ECG monitoring or because ST changes are not always documented by ECG even in the presence of chest symptoms. In such cases, the spasm provocation test (SPT) can be used[3-5]. In the clinical setting, SPT is the gold standard examination to diagnose VSA. However, we observed some cases in which chest symptoms continued despite a negative SPT. Here, we report four such cases in which a second SPT was performed to evaluate chest symptoms despite negative results in the first SPT.

CASE REPORT

At our institution, SPT is performed in the afternoon. Vasodilators are stopped 2 d before SPT. For SPT, acetylcholine (ACh) is usually used as the provocation drug, with 30 and 50 μg for the right coronary artery (RCA) and 50 and 100 μg for the left coronary artery (LCA). If the SPT results are negative with these doses, additional doses of ACh (80 μg for the RCA and 200 μg for the LCA) and/or ergonovine maleate (EM; 20, 40, and 60 μg for the LCA) are sometimes added. A positive SPT is defined as the presence of transient vasoconstriction > 90% in response to intracoronary infusions of provocative drugs on coronary angiograms. The positive result is accompanied by the usual chest symptoms and/or ischemic ST deviations in the patient's ECG[3].

Case 1

A man in his 70s underwent an SPT because of chest pain at rest. His coronary risk factors were smoking (30 cigarettes per day for 30 years) and hypertension. The SPT showed negative results after intracoronary infusions of ACh with 50 μg for the RCA and 100 μg for the LCA (Figure 1A). Thereafter, he continued to experienced chest pain at rest but did not seek further help for his chest symptoms. Four years later, he felt severe chest pain at rest in the early morning, which was relieved by sublingual nitroglycerin (NTG). Therefore, he underwent a second SPT, which was positive for the RCA with an intracoronary infusion of 30 μg ACh. The result was accompanied by the usual chest symptoms and ECG changes, despite negative LCA results after an intracoronary infusion of NTG (Figure 1B). At that time, we used a pressure wire inserted into the distal RCA. The distal intracoronary pressure /aortic pressure (Pd/Pa) decreased from 0.99 at baseline to 0.73 after the ACh infusion. He was diagnosed with VSA and discharged with a prescription for a calcium channel blocker (CCB).

Case 2

A male in his 70s underwent an SPT because of chest pain at rest, which occurred for 1-2 min and frequently 3-4 times/wk. He had no coronary risk factors. The SPT showed moderate vasoconstriction of the RCA after 50 μg ACh and moderate vasoconstriction of the LCA after 100 μg ACh (Figure 2A). However, he did not experience chest symptoms or ST deviation on ECG during the SPT. Hence, the SPT result was judged as negative. His chest symptoms continued thereafter, and he had severe chest pain at midnight 3 years later; therefore, he underwent a second SPT 3 years after the first SPT. The second SPT showed positive results for both the RCA after intracoronary infusions of 50 μg ACh and the LCA after infusions of 100 μg ACh (Figure 2B). The test was accompanied by the usual chest symptoms. The Pd/Pa decreased from 0.96 at baseline to 0.75 during the RCA spasm and from 0.93 at baseline to 0.74 during the left anterior descending coronary artery (LAD) spasm. He was diagnosed with VSA and was discharged with CCB medication.

Case 3

A female in her 60s underwent an SPT due to 1-2-min chest pain at rest during the night. She had no coronary risk factors. The SPT showed negative RCA results after 50 μg ACh and for the LCA after an intracoronary infusion of 100 μg ACh (Figure 3A). Nevertheless, her symptoms continued. CCB did not help, and she underwent the second SPT 3 years after the first SPT. The second SPT showed negative RCA results after 80 μg ACh and for the LCA after 200 μg ACh (Figure 3B). The Pd/Pa did not change significantly, from 1.00 at baseline to 0.92 with 80 μg ACh in the RCA and from 0.95 at baseline to 0.93 with 200 μg ACh in the LAD. She was discharged with analgesic and anti-depressive medication.

Case 4

A female in her 70s underwent an SPT to evaluate chest pain in the evening lasting for 1 min. Her coronary risk factors were hypertension and lipid disorder. The SPT showed negative RCA results after 50 μg ACh and for the LCA after 100 μg ACh (Figure 4A). Thereafter, her chest symptoms were infrequent, but she felt severe

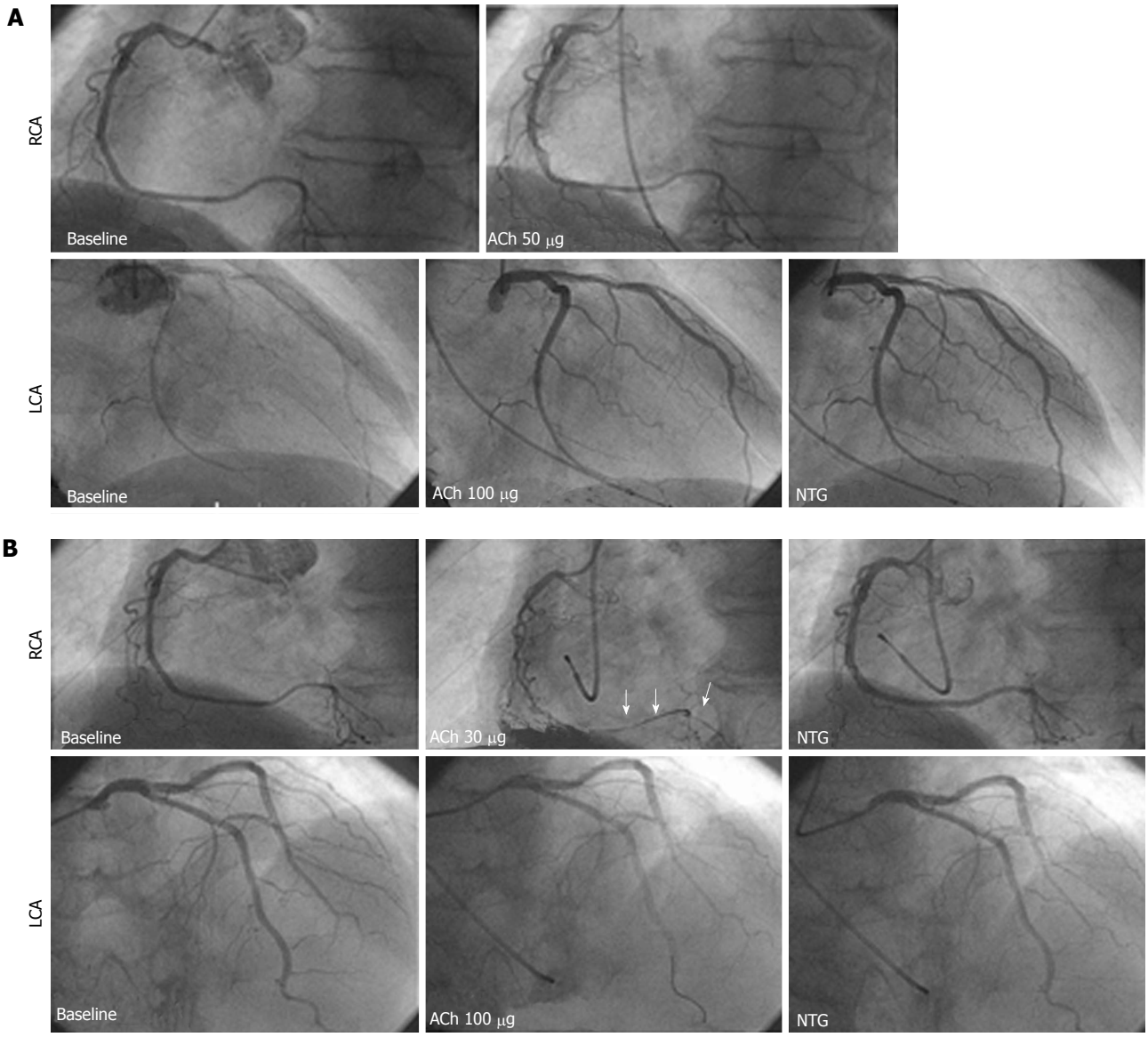

Figure 1 Coronary angiograms during the first and second spasm provocation test in case 1. A: The first spasm provocation test (SPT) showed negative results after intracoronary infusions of acetylcholine (ACh) with 50 μg for the right coronary artery (RCA) and 100 μg for the left coronary artery (LCA); B: The second SPT showed positive RCA results with an infusion of 30 μg ACh, accompanied by the usual chest symptoms and electrocardiogram changes, despite negative LCA results after an intracoronary infusion of nitroglycerin (NTG). Arrows indicate coronary spasm.

chest pain at rest 3 years later, when she presented at our institution for the second SPT. The second SPT showed negative RCA results after an intracoronary infusion of 50 μg ACh, and severe vasoconstriction at the distal LAD without chest symptoms and ECG changes after an intracoronary infusion of 100 μg ACh (Figure 4B). At the time, the Pa/Pa decreased from 0.90 at baseline to 0.73 after the ACh infusion. Based on the angiograms and pressure wire findings, she was diagnosed with VSA. She was discharged with CCB medication and has not experienced chest symptoms since.

In summary, there were three positive results from a second SPT (75%) of four cases that experienced chest symptoms and had negative results for the first SPT.

DISCUSSION

In the present report, we present four patients who underwent a second SPT for the evaluation of chest symptoms, despite negative results from the first SPT. Of the four cases, there were three positive cases (75%). From these cases, we learned that SPT is not an absolute and final examination for diagnosing VSA.

SPT has been widely adopted as the final examination for the diagnosis of VSA. However, several factors may affect a positive SPT finding, such as VSA activity, time of day when the SPT is performed, and the duration of the withdrawal of vasodilators. VSA activity is variable, not only daily but also seasonally or yearly[3], and this may contribute to the difference in SPT results. According to the time spent performing the SPT, it may

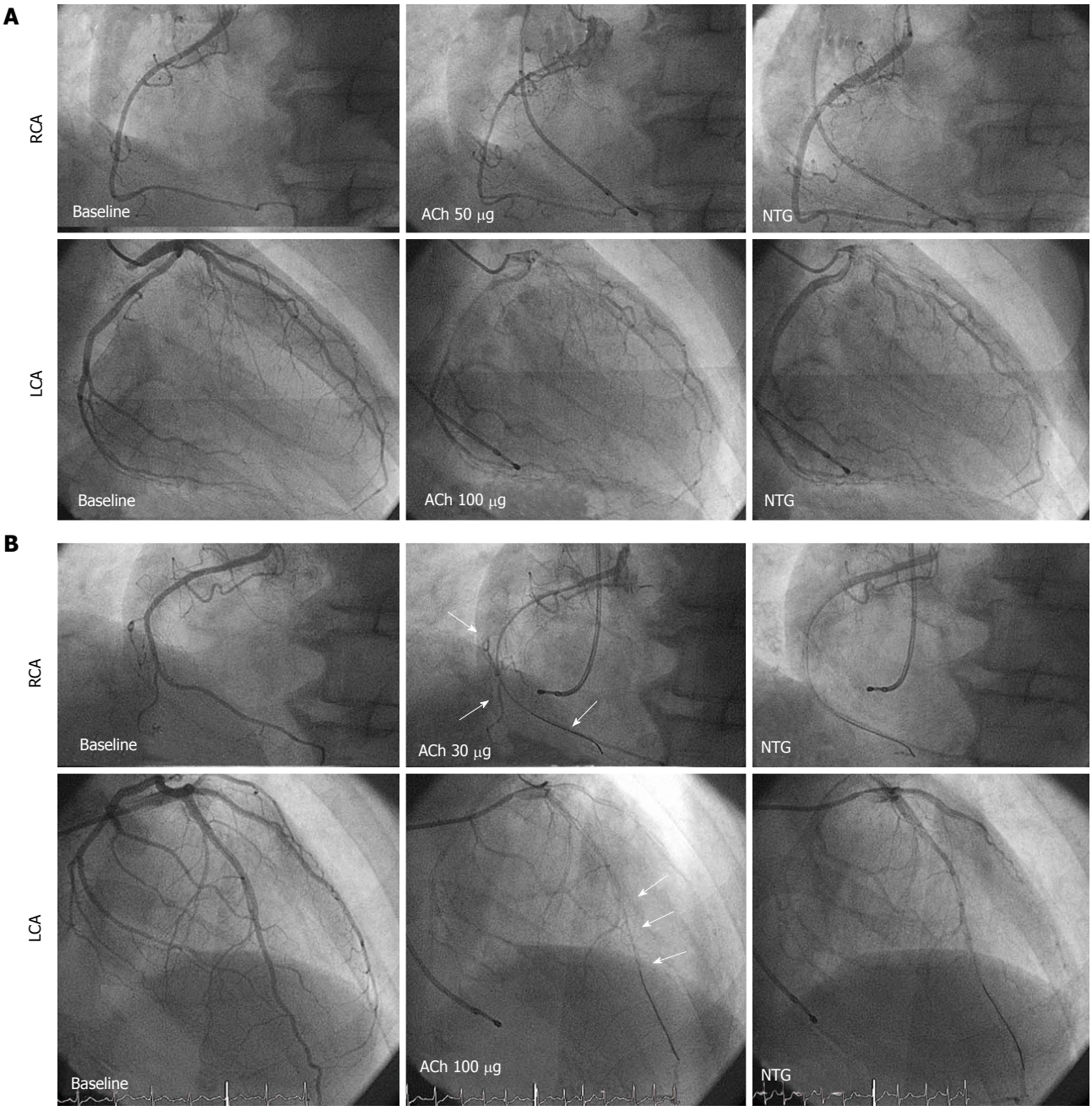

Figure 2 Coronary angiograms during the first and second spasm provocation test in case 2. A: The first spasm provocation test (SPT) showed moderate vasoconstriction of the right coronary artery (RCA) after infusions of 50 μg acetylcholine (ACh) and moderate left coronary artery (LCA) vasoconstriction after infusions of 100 μg ACh. However, neither chest symptoms nor ST deviation of the electrocardiogram occurred during the SPT; B: The second SPT showed positive results with both the RCA after intracoronary infusions of 50 μg ACh and the LCA after infusions of 100 μg ACh, accompanied by the usual chest symptoms. Arrows indicate coronary spasms.

be ideal to perform the SPT when VSA angina attacks occur easily, particularly in the morning. However, at our institution, SPTs are performed only in the afternoon. In these four cases presented here, both the first and second SPTs were performed at the same time in the afternoon. For the withdrawal of vasodilators before SPT, vasodilators were withheld at least 48 h before SPT[3,6]; however, 2 d may be insufficient for the withdrawal of long-acting CCBs. This factor may contribute to the discrepancy of SPT results.

The SPT procedure is another important problem. The maximal doses of 50 μg ACh for the RCA and 100 μg for the LCA, in general, are recommended[3]. However, SPT using higher ACh doses of 80 μg for the RCA and 200 μg for the LCA[7,8] and/or using a combination of ACh and EM[6,8], have recently been recommended. The use of higher ACh doses and/or a combination of ACh and EM may decrease the number of incomplete SPTs. In case 3, we judged the results as negative after higher ACh intracoronary infusion doses for the second SPT. To deny the possibility of VSA, it may be ideal to perform the SPT using higher

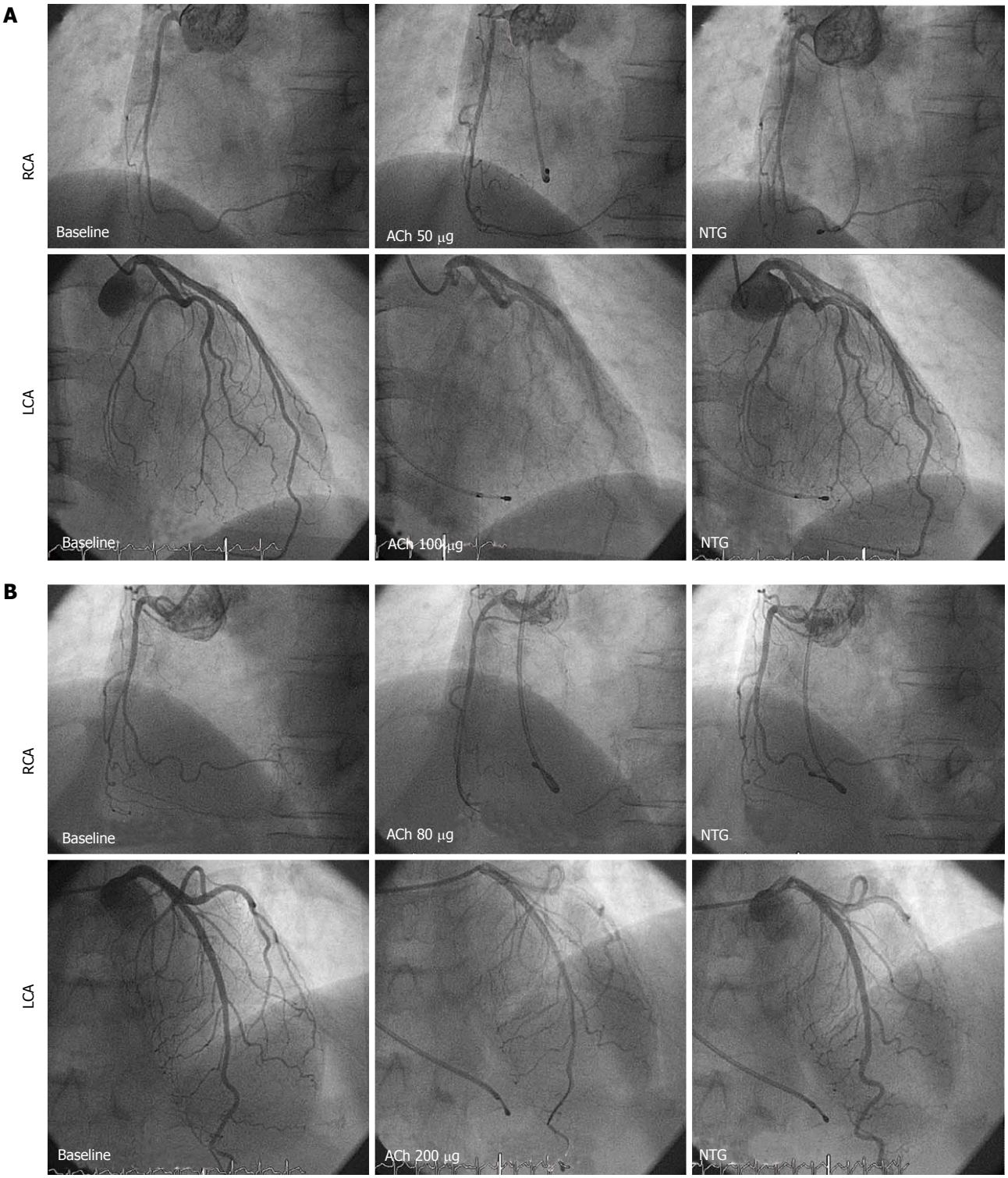

Figure 3 Coronary angiograms during the first and second spasm provocation test in case 3. A: The first spasm provocation test (SPT) showed negative right coronary artery (RCA) results after an intracoronary infusion of 50 μg acetylcholine (ACh) and of the left coronary artery (LCA) after an intracoronary infusion of 100 μg Ach; B: The second SPT also showed negative RCA results after an intracoronary infusion of 80 μg ACh and of the LCA after an intracoronary infusion of 200 μg ACh.

concentrations of ACh. In addition, we used a pressure wire in all four cases. Using a pressure wire in SPT may be useful for diagnosing VSA[9] because the presence of myocardial ischemia can be detected promptly when the Pd/Pa is continuously monitored. Although an SPT using a pressure wire is not always recommended in all patients, this technique may provide additional information for VSA diagnosis and may, therefore, be useful for the second SPT.

In our cases shown here, there were the gaps of 3 to

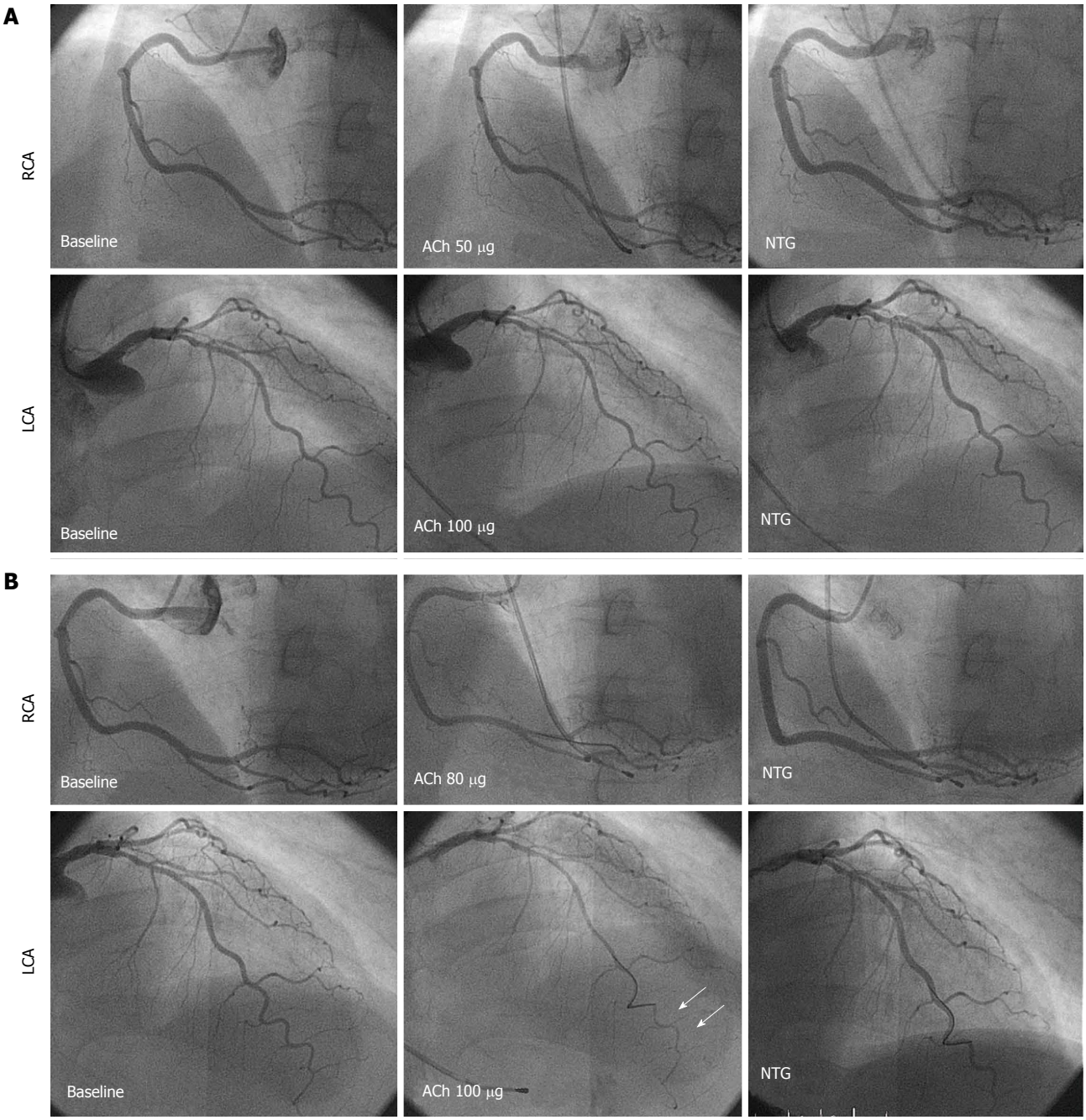

Figure 4 Coronary angiograms during the first and second spasm provocation test in case 4. A: The first spasm provocation test (SPT) showed negative right coronary artery (RCA) results after an intracoronary infusion of 50 μg acetylcholine (ACh) and of the left coronary artery (LCA) after an intracoronary infusion of 100 μg Ach; B: The second SPT showed negative RCA results after an intracoronary infusion with 50 μg ACh, and severe vasoconstriction at the distal left anterior descending coronary artery, after an intracoronary infusion of 100 μg ACh. Arrows indicate coronary spasms.

4 years between the first and second SPT. During these periods, vascular dysfunction and/or atherosclerotic changes were newly developed. Thus, we cannot deny the possibility that coronary spasticity emerges during such periods, leading to a positive result for second SPT despite a negative result of the first SPT.

Even when the SPT is negative, the diagnosis of VSA should be with clinical symptoms in consideration. In some cases, a second SPT may be needed to confirm the diagnosis of VSA. Cardiologists should keep these concepts in mind.

COMMENTS

Case characteristics

There are four patients who underwent a spasm provocation test (SPT) for a second time to evaluate chest symptoms despite negative results for the first SPT.

Clinical diagnosis

Vasospastic angina, which was diagnosed with the second SPT.

Differential diagnosis

Microvascular angina, chest pain syndrome and gastroesophageal reflux

disease.

Laboratory diagnosis
All labs were within normal limits.

Imaging diagnosis
In 3 of 4 patients, the second SPT showed positive results with the angiographical coronary vasoconstriction, accompanied by usual chest symptoms and reduced intracoronary pressure measured with a pressure wire and/or ischemic changes of the electrocardiogram (ECG).

Treatment
Vasodilators, including calcium-channel blockers, were administered in 3 patients who had positive results in the second spasm SPT, and analgesics and antidepressive medication were administered in 1 patient with a negative result for the second SPT.

Related reports
There are many case reports and studies of the spasm provocation test; however, this is the first report showing positive results for the second SPT despite negative results for the first SPT.

Term explanation
Vasospastic angina (VSA) is characterized by the transient vasoconstriction of the epicardial coronary artery, leading to myocardial ischemia. It is the cause of not only rest angina but also exertional angina, acute coronary syndrome and ischemic cardiac arrest. VSA is diagnosed with chest symptoms and transient ischemic changes of the ECG, mainly at rest, but there are many cases in which the diagnosis is difficult when only based on chest symptoms and ECG monitoring. In such cases, an SPT using acetylcholine and/or ergonovine are performed and the results of the SPT are considered the final decision.

Experience and lessons
Even when SPT is negative, the diagnosis of VSA should be made with the consideration of clinical symptoms. In some cases, a second SPT may be needed to confirm the diagnosis of VSA.

Peer-review
This paper is interesting.

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