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EDITORIAL

Percutaneous pulmonary and tricuspid valve implantations: An update

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Abstract

The field of percutaneous valvular interventions is one of the most exciting and rapidly developing within interventional cardiology. Percutaneous procedures focusing on aortic and mitral valve replacement or interventional treatment as well as techniques of percutaneous pulmonary valve implantation have already reached worldwide clinical acceptance and routine interventional procedure status. Although techniques of percutaneous pulmonary valve implantation have been described just a decade ago, two stent-mounted complementary devices were successfully introduced and more than 3000 of these procedures have been performed worldwide. In contrast, percutaneous treatment of tricuspid valve dysfunction is still evolving on a much earlier level and has so far not reached routine interventional procedure status. Taking into account that an "interdisciplinary challenging", heterogeneous population of patients previously treated by corrective, semi-corrective or palliative surgical procedures is growing inexorably, there is a rapidly increasing need of treatment options besides redo-surgery. Therefore, the review intends to reflect on clinical expansion of percutaneous pulmonary and tricuspid valve procedures, to update on current devices, to discuss indications and patient selection criteria, to report on clinical results and finally to consider future directions.

Key words: Congenital heart disease; Right ventricular outflow tract dysfunction; Pulmonary regurgitation; Percutaneous pulmonary valve implantation; Percutaneous tricuspid valve implantation

Core tip: The field of percutaneous valve implantation/repair is rapidly developing within interventional cardiology. Percutaneous procedures focusing on aortic, mitral or pulmonary valve dysfunction have almost reached daily routine. In contrast, percutaneous treatment of tricuspid valve dysfunction is still evolving on a much earlier level. Taking into account that an "interdisciplinary challenging" population of patients previously treated by corrective, semi-corrective or palliative surgery is growing inexorably, there is an increasing need of options besides redo-surgery. This review intends to report on clinical application of pulmonary and tricuspid valve procedures. It updates on current devices, patient selection criteria, results and future directions.

Wagner R, Daehnert I, Lurz P. Percutaneous pulmonary and tricuspid valve implantations: An update. *World J Cardiol* 2015; 7(4): 167-177 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i4/167.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i4.167

INTRODUCTION

Isolated pulmonary and tricuspid valve dysfunction, whether acquired or in the context of congenital heart disease, can be clinically asymptomatic and be tolerated for a long time[1]. In the western world, acquired primary tricuspid or pulmonary valve diseases are rare conditions and mostly related to rheumatic fever, infective endocarditis or rarities (*e.g.*, carcinoid syndrome).

For those cases with underlying congenital heart disease, dysfunction of these valves is both a primary component of many anatomical conditions and a secondary, but common consequence of several early repair strategies[2].

Increasing knowledge about potential harmful effects of chronic pulmonary artery (PA) regurgitation has made the surgical revision of the right ventricular (RV) outflow tract (RVOT) a frequently performed operation in this population[3]. Typically, most of these patients require several redo-operations during their lifetime to halt the detrimental effects of valvular dysfunction. Since techniques of percutaneous pulmonary valve implantation (PPVI) were first described by Bonhoeffer *et al*[4] more than a decade ago, the procedure has reached worldwide clinical acceptance and routine interventional procedure status. Several devices have been investigated for purposes of PPVI, but so far only the MELODY™ device (Medtronic, MN, United States) has obtained regulatory approval. Interventional procedures focusing on percutaneous tricuspid valve replacement or interventional treatment of severe tricuspid regurgitation are evolving, but yet remain at a much earlier stage and have so far not reached levels of standard procedures[5]. The authors review on clinical expansion of this revolutionary technology, discuss current indications and patient selection criteria, report on clinical results and finally consider future directions.

PPVI

Background and clinical indications

Over the last decades, advances in cardiac surgery, interventional procedures, intensive care and non-invasive imaging have led to a substantial increase in life expectancy for many patients with congenital heart disease. Therefore, an "interdisciplinary challenging", heterogeneous population of patients treated by corrective, semi-corrective or palliative surgical procedures, sometimes decades ago, is growing inexorably. For approximately 20% of these patients RVOT dysfunction caused by predominant obstruction, by predominant pulmonary regurgitation or both in combined conditions, becomes clinically evident.

Undeniably, surgical pulmonary valve replacement is the most frequent mode of redo-operation in patients with congenital heart disease[3]. Surgery for RVOT dysfunction can be performed with low morbidity and mortality[3]. However, an important drawback of this treatment is the limited lifespan of used conduits that has been reported to be around ten years[6-9]. As a consequence, the majority of patients have to undergo several open-heart procedures during their life that raise potential individual risks for a diversity of complications. To limit the need for redo-operations delaying surgery for as long as possible is the strategy of choice in any individual patient. If the necessary treatment is delayed beyond a certain point of no return, adverse RV loading conditions might lead to irreversible ventricular dysfunction, reduced exercise capacity and ultimately to an increased risk for sudden cardiac death[10-13]. Decision making on ideal timing of pulmonary valve replacement is still challenging in most cases and represents one of the most controversial issues of cardiologists who take care of children and adults with congenital heart disease[3,14,15]. RV volume thresholds on magnetic resonance imaging (MRI) have been proposed as predictors for outcome after conduit placement[14]. An RV end-systolic volume of 150-170 mL/m^2 has been reported to deserve as cut-off point above which normalisation of RV dimensions is unlikely following pulmonary valve replacement[13-17]. Nevertheless, the impact of the timing of pulmonary valve replacement on RV function, exercise performance and patient long-term survival remains undefined[13].

With the evolution of PPVI, an effective and feasible non-surgical technique was introduced. It offers a minimally invasive method which can potentially avoid open-heart surgery for RVOT dysfunction in children and adults by restoring acceptable RV loading conditions.

Since the first description of PPVI in 2000[4], more than 3000 percutaneous pulmonary valves have been implanted worldwide[18]. PPVI is performed to prolong the lifespan of RV-to-PA conduits and thereby delaying redo-operations in children and adults with congenital heart disease. Over the last decade, a marked learning curve in outcome post-PPVI could be demonstrated, with improved safety, efficacy and freedom from redo-surgery or re-intervention for pediatric or adult patients who underwent this procedure[13,19-25].

Current devices

The MELODY™ transcatheter pulmonary valve is designed of a segment of bovine jugular vein with a central valve (Figures 1 and 2) that is sewn inside an expanded platinum-iridium stent. The current carrying

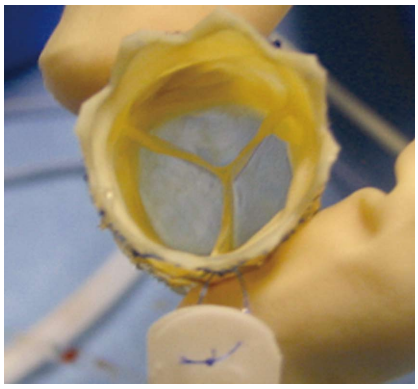

Figure 1 The MELODY™ percutaneous pulmonary valve (Medtronic, MN). The Melody device in "en face" view. Note the blue outflow line to identify the outflow end of the device (courtesy of P.Lurz).

Cheatham platinum stent (NuMED CP Stent CP8Z34) is of a length 34 mm, "crimpable" to minimum of 6 mm and re-expandable up to 22 mm. The balloon in balloon (BiB) delivery system (Ensemble™, Medtronic, MN) is commercially available with different outer balloon diameters of 18, 20 and 22 mm.

The Edwards SAPIEN™ valve (Edwards Lifesciences LLC, Irvine, CA) is radiopaque and made of a trileaflet bovine pericardial valve hand-sewn into a stainless-steel stent (length of 14 or 16 mm) (Figure 3). A sealing cuff covers the proximal part of the stent designed to prevent paravalvular leakage. Currently, the valve is commercially available in 23 and 26 mm diameter sizes and is crimped onto a designated balloon delivery system Retroflex™ Ⅲ. A 29 mm diameter valve is also available (Edwards SAPIEN™ XT). The delivery system requires either 22 Fr (SAPIEN™ 23 mm valve) or 24 Fr hydrophilic sheaths (SAPIEN™ 26 mm and SAPIEN™ XT 29 mm valve) (Figure 3). Promising improvements of design (Edwards eSheath™) offer even smaller sheath sizes.

Technical details regarding both devices for PPVI are summarized in Table 1.

Patient selection criteria

Although sophisticated MR data have been reported, the clinicians' dilemma of the right timing for treatment of RVOT dysfunction, whether predominantly caused by obstruction or regurgitation has not been solved yet[13]. According to current guidelines for the management of grown-up congenital heart disease[26], patients with RVOT obstruction should be treated if the RV to PA gradient exceeds 60 mmHg or in presence of symptoms due to RVOT obstruction regardless of RVOT gradients. Pulmonary regurgitation can be clinically asymptomatic and be tolerated for a long time[1]. When to intervene is subject to ongoing discussions. It is common sense to base the indication criteria for transcatheter or surgical treatment on a combined assessment of MR-imaging derived RV EDV and systolic function, cardiopulmonary exercise testing and the presence of atrial or ventricular dysrhythmia[13]. According to the 2010 recommendations of the ESC task force PPVI can therefore be indicated, if severe pulmonary regurgitation (as assessed on echocardiography or MR imaging) is accompanied by severe RV dilatation, severe RV dysfunction, clinical symptoms and/or impaired exercise capacity[13,26].

In 2011, the American Heart Association (AHA) stated: "It is reasonable to consider the percutaneous pulmonary valve replacement in patient with RV-to-PA conduits with moderate to severe pulmonary regurgitation or stenosis provided the patient meets inclusion/exclusion criteria for the available valve". The AHA writing committee recommended this procedure with a Class IIa evidence (Level of evidence: B)[27]. Clinical indications applicable regardless of the device used for valve implantation (MELODY™ and SAPIEN™) are summarized in Table 2.

Although there is no absolute lower age limit, an adequate body size (*e.g.*, weight > 20 kg) is required to accommodate femoral placement of the introducer[21].

Size and shape of the implantation site ("landing zone") and its anatomical relation to coronary arteries are decisive morphological criteria which have to be appropriate when considering patients as potential candidates for PPVI: In regulatory approved routine use, current MELODY™ devices are not intended for dilatations to diameters of more than 22 mm. Patients with (non-dilated) conduits between the RV and PA of 22 mm and less offer an ideal environment to perform PPVI. In contrast, native or patched RV outflow tracts after surgical repair for Tetralogy of Fallot are often enlarged (> 22 mm) and therefore do not provide a secure landing zone for MELODY™ valves[14]. In these cases (but not larger than 29 mm) the SAPIEN™ valve might be a possible alternative[28-30]. Furthermore, in our experience the RVOT shape (after prior pre-stenting) is of importance: due to its "engineered" nature of sutured pericardial tissue, optimal valved stent function in SAPIEN™ procedures is guaranteed by a circular RVOT shape. In PPVI procedures with the MELODY™ valve the RVOT shape itself appears to have less impact on valvular competence.

Coronary artery anatomy varies due to a broad spectrum of complex congenital heart defects or after surgical re-insertion into the aorta. In some cases there is relevant proximity of one or more of the relevant coronary artery branches to the main PA. This exposes patients who undergo interventions of the RVOT to the risk for fatal coronary artery obstruction due to expansion of the RVOT[31,32]. Therefore, it is essential to assess the course of proximal coronary arteries in relation to the RVOT prior to PPVI deployment. Some centers prefer MR 3-D whole heart images (Figure 4), but we recommend performing selective coronary angiography and particularly aortic root angiography and simultaneous high-pressure balloon inflation within the landing zone at the time of catheterization in all patients to rule out the risk of coronary compression

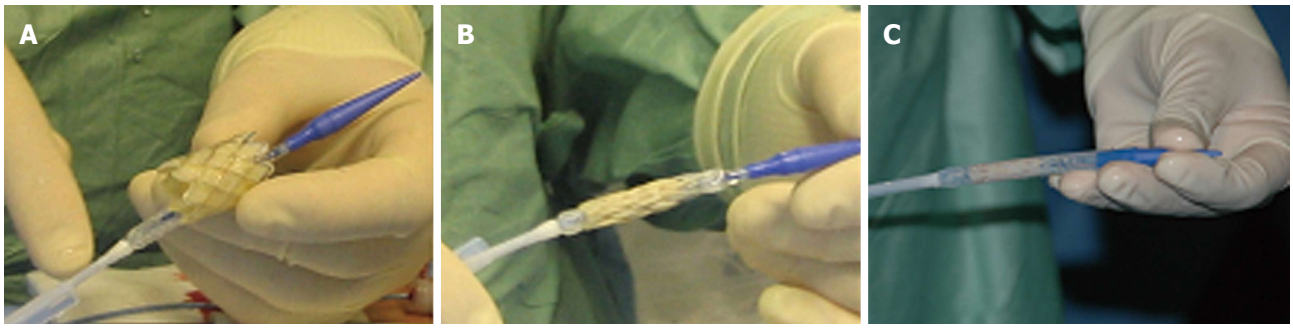

Figure 2 MELODY™ device and its delivery system. A: Uncrimped device on the delivery system with a retractable sheath; B: Crimped device before covering the device to protect it during the delivery; C: Crimped and covered device prepared for delivery (courtesy of Lurz P).

Table 1 Devices and delivery systems for percutaneous pulmonary valve implantation

	The MELODY™ transcatheter pulmonary valve	The SAPIEN™ pulmonic transcatheter heart valve
Manufactor	Medtronic Inc., MN, United States	Edwards Lifesciences LLC, Irvine, CA, United States
Regulatory approval	CE 9/2006 FDA 01/2010	CE 5/2010 FDA 10/2012
(Tissue) characteristics	Segment of bovine jugular vein with a central valve hand-sewn inside a stent	Trileaflet bovine pericardial valve hand-sewn inside a stent
Stent type	Cheatham platinum stent (NuMED CP Stent CP8Z34) Length 34 mm Expandable up to 22 mm	Stainless-steel stent Length of 14 or 16 mm
Available sizes	18, 20, 22 mm (depending on the favoured Ensemble™ delivery (system)	23, 26, (XT 29[a]) mm
Delivery system	Ensemble™ (Medtronic, MN) with balloon in balloon (BiB) deployment design	Edwards Retroflex™ Ⅲ containing a balloon catheter and a deflectable guiding catheter
Sheats for implantation	One-piece 22 Fr Teflon sheath	(18 Fr[b]) 22 Fr for 23 mm valves (19 Fr[b]) 24 Fr for 26 mm valves (16 Fr[b]) 24 Fr for 29 mm XT valves

Technical comparision of the commercially available devices for percutaneous pulmonary valve implantation: the MELODY™ device and the SAPIEN™ pulmonic transcatheter heart valve as non-surgical treatment options for RV outflow tract dysfunction ([a]"Off label-use" in pulmonary position; [b]Manufacturer's data given for the Edwards eSheath™). RV: Right ventricle.

Table 2 Clinical and morphological requirements for percutaneous pulmonary valve implantation

Clinical indications in the context of RV pressure overload/pulmonary stenosis
RV systolic pressure > 65% of systemic pressure in symptomatic patients
RV systolic pressure > 75% of systemic pressure in asymptomatic patients
Clinical indications in the context of RV volume overload/pulmonary regurgitation
Severe pulmonary regurgitation on echocardiography or MR imaging and
Severe RV dilatation > 150 mL/m^2 or the RV to LV end-diastolic ratio of > 1.7 and/or
Rapid progressiv RV dilatation and/or
Severe RV dysfunction and/or
Symptoms and/or
Sustained atrial or venticular arrhythmia and/or
Impaired exercise capacity [< 65% compared to norm peak oxygen consumption related to bodyweight (VO_2/kg)]
Morphological indications
Circumferential RV to PA conduit with dimensions ranging from 16 to 22 mm (Melody™)
Circumferential RV to PA conduit with dimension at surgical implantation of at least 18 mm but no larger than 29 mm (with some degree of conduit narrowing) (SAPIEN™)
Exclusion of risk for coronary compression

RV: Right ventricle; PA: Pulmonary artery.

(Figure 5).

To facilitate superior immediate haemodynamic results several peri-procedural interventions should be considered: (1) pre-dilatation of the landing zone to resolve relevant stenosis and facilitate positioning of the system; (2) pre-stenting of the RVOT to mark, cover and enhance the "landing zone" and avoid stent fractures; and (3) post-dilatation in any case of residual stenosis more than > 20 mmHg of invasively measured gradient[13].

The optimal timing of pre-dilatation/stenting in relation to definitive PPVI is unknown. Some centers

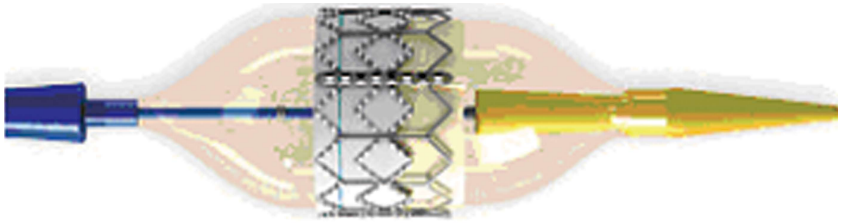

Figure 3 The Edwards SAPIEN™ pulmonic transcatheter heart valve (Edwards Lifesciences LLC, Irvine, CA). The SAPIEN™ device in lateral view mounted on its delivery system Retroflex™ III (courtesy of Edwards Lifesciences LLC).

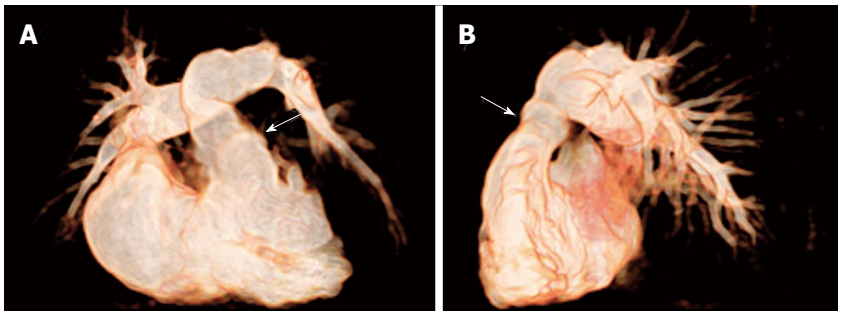

Figure 4 Non-invasive 3D whole heart imaging by magnetic resonance tomography. Non-invasive 3D whole heart imaging by magnetic resonance tomography was performed in a patient with pulmonary atresia with intact ventricular septum after repair by pulmonic homograft implantation (arrows) with RVOT dysfunction prior to PPVI (A) in a.p. and (B) in lat. view. (Courtesy of Wagner R). RVOT: Right ventricular outflow tract; PPVI: Percutaneous pulmonary valve implantation.

allow stent ingrowth for two to three months. Combined procedures as well as a two-staged procedure are valid options.

Results

Data regarding the haemodynamic outcome post PPVI reported by major reports using MELODY™ [18,19,21,24,33] and using the SAPIEN™ device[28,30] are summarized in Table 3.

Several mono- and multicenter trials consistently reported a low periprocedural complication rate of six percent using the MELODY™ pulmonic valve[19,33]. Data analysis of the "MELODY™ Registry" data distinguishes between major procedural complications [*e.g.*, homograft rupture, perforation of branch pulmonary arteries, guidewire injury, damage to tricuspid valve, device dislodgement, compression of coronary arterie(s) or obstruction of PA] in 2.7% and 11.9% of minor complications in total of 1003 MELODY™ procedures[34].

The "Early Phase 1 International Multicenter Clinical Trial" reporting on SAPIEN™ PPVI in 36 patients reported on a successful valve deployment of 97 percent, but seven patients (20.5%) experienced adverse events[30]. The major complication was device dislodgement. In none of the patients, homograft rupture occurred. All of the SAPIEN™ patients received pre-stenting (33.3%) or peri-procedural stenting procedures (66.6%).

Coronary compression due to RVOT interventions with bare metal stenting of the RVOT is a well-known and previously described complication[31]. Approximately five to six percent of all patients who are potential candidates for PPVI will have a coronary artery anatomy which bears the risk for coronary obstruction[24]. There are several reports of this potential catastrophic complication[35,36] which is strongly related to early procedural mortality[21]. Ruling out the risk for this complication represents one of the most difficult steps in pre-procedural planning for PPVI. In any case of doubt about the risk of coronary compression, we recommend to abandon the implant in either MELODY™ or SAPIEN™ valve procedures (Figure 5).

Follow-up

Short- and medium-term results of PPVI with the MELODY™ and SAPIEN™ are thought to be similar, although more data are available for the former. Long-term outcome data for both valved stent types are not yet available.

Overall mortality of PPVI during follow-up procedures was zero to five percent and seems not related to the device itself.

Failure of the device either for the MELODY™ or the SAPIEN™ could be related to malfunction of its stent or its sewn valve. Relevant dysfunction of the engrafted valve leads to pulmonary regurgitation which is rare condition that almost only occurs in the context of graft endocarditis[37-40], However, the most common reason for re-operation and re-intervention is re-stenosis of the stent portion of the device. Re-stenosis of the stent can be caused by late recoil or lost of radial strength of the device due to stent fractures. Novel data by Nordmeyer reported of a rate of 11 percent cases of stent fractures[34] representing the most common reason for re-intervention.

Overall, data are available from the major four short- and medium-term observational studies with a total of over 450 patients with one- to five-year follow-up[19,21,25,33]: freedom from valve dysfunction or re-intervention was approximately 94% at one year follow-up. Patients who did not require re-intervention had consistently mild or none pulmonic valve regurgitation at one-year follow-up. Pulmonary regurgitation decreased from median values of 16% to 27% to one to two percent. Median peak velocity over the RVOT was 1.9 to 2.7 m/s at one-year

Table 3 Haemodynamic outcome immediately post-percutaneous pulmonary valve implantation

	US Melody Valve Trial (n = 124)		London Melody experience (n = 151)		Munich/Berlin Melody experience (n = 102)		Philadelphia Melody experience (n = 104)		Early Edwards experience (n = 7)		Later Edwards experience (n = 36)	
Parameter	Pre (median)	Post (median)	Pre (mean)	Post (mean)	Pre (mean)	Post (mean)	Pre (mean)	Post (mean)	Pre (mean)	Post (mean)	Pre (mean)	Post (mean)
RV systolic pressure, mmHg	65	41[b]	63	45[b]	NA	NA	72	47[b]	NA	NA	55	42[b]
Peak RV to PA gradient, mmHg	37	12[b]	37	17[b]	37	14	39	11[b]	NA	NA	27	12[b]
RV to systemic pressure, %	0.74	0.42[b]	0.69	0.4[b]	0.62	0.3[b]	NA	NA	0.78	0.3[b]	0.6	0.4[b]

Invasively measured pressures and gradients pre and post percutaneous pulmonary valve implantation within the largest trials (n > 100) of the MELODY™[18,19,21,33] and of SAPIEN™ implants[28,30] in pulmonary position. In all studies, a profound improvement in RV to systemic pressure ratio in response to PPVI was seen ([b]$P \leq 0.001$) (all parameters expressed by medians). RV: Right ventricular; PA: Pulmonary artery. NA: Not available.

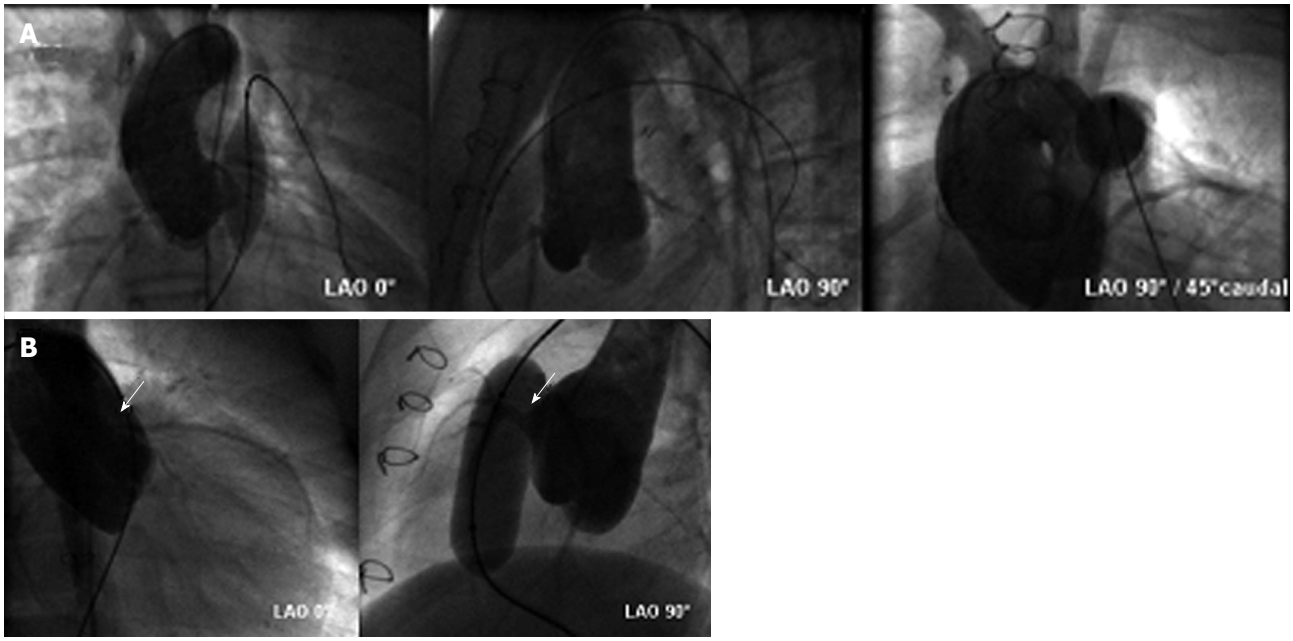

Figure 5 Assessment of risk for coronary compression. A: Aortic root angiogram and simultaneous (high-pressure) balloon inflation within the eligible landing zone is performed to rule out potential for coronary compression (courtesy of Wagner R); B: Aortic root angiogram showing compression of the left anterior descending coronary artery (arrows) during balloon inflation in the conduit. The procedure was therefore abandoned in this patient and no percutaneus pulmonary valve implantation was performed (courtesy of Wagner R).

echocardiographic follow-up. Nordmeyer recently reported preliminary but promising MELODY™ Registry data with a one-year freedom for all case events with 92.5% and 94.2% for PPVI-related events[34].

Data on device function of the SAPIEN™ valve are limited and available from smaller short- and medium-term observational studies with a total of less than 100 patients[28,30,41,42]. In the largest series (COMPASSION trial), successful valve deployment was achieved in 33 of 34 attempts[30]. Freedom from re-intervention at six-month follow-up was 97%. Haas *et al*[41] demonstrated a significant reduction of the RVOT to PA gradient, reduction in RV systolic pressure, increasing of diastolic pulmonary pressure from 6.3 to 14.5 mmHg as a sign of tremendously decreased pulmonary regurgitation with freedom from re-intervention after six months[41].

As for the MELODY™ valve, there are no comparison studies with conventional surgery regarding pulmonary valve replacement by SAPIEN™ valves.

Regarding the functional outcome, several studies have shown a marked improvement in NYHA functional class post-PPVI[18,19,33]. The improvement has been maintained consistently for the duration of follow-up, irrespective of the treated lesion (predominant stenosis *vs* predominant regurgitation)[24].

Parameters of exercise cardiopulmonary function such as peak oxygen consumption related to body weight (VO_2/kg), ventilatory efficiency and anaerobic oxygen consumption have been assessed in several studies addressing PPVI[20,43-45]. Only patients with a predominant stenotic lesion showed an improvement in peak VO_2/kg. Assuming that significant RVOT

obstruction may limit the increase of cardiac output in exercise testing resolving of the obstructive lesion at least partially reverses limited exercise capacity in these patients[45,46]. Recently, we reported on the ability to recovery from exercise as described by VO_2 and VCO_2 decay after maximal exercise. Recovery form exercise after PPVI improves in both groups (predominant stenosis *vs* predominant regurgitation). These findings could explain the symptomatic improvement observed in patients with predominant regurgitation despite the lack of increased maximal exercise capacity and might have implications for how we judge procedural success[47].

Right and left ventricular function and calculation of great vessel blood flow analyzed by functional and morphologic MR imaging performed prior to and within one month after PPVI has shown mixed data regarding changes in RV ejection fraction following PPVI, with some studies finding no change[21,33] and others reporting on improvements in the acute or short term[23,43,44,46]. Importantly, PPVI also results in improved left ventricular filling[13,44,48].

Extended indications and future directions

Many patients are not ideal candidates for PPVI procedures due to their small physical size, limited vascular access or, most important, due to the size and shape of the RVOT[49]. The majority of patients suffering from dysfunction of the RVOT have enlargement of the patched RVOT as part of the initial surgical repair strategy[24]. This unmet clinical challenge led to the development of novel approaches to treat RVOT dysfunction using existing interventional pulmonic valve technology. A small case series reveals an approach to implant or post-dilate the MELODY™ valve using 24 mm balloons. This practice does not compromise function of the engrafted valve and may effectively broaden the pool of eligible patients[24,50].

However, RVOT dysfunction with predominant regurgitation and marked dilatation are not be eligible to this approach. Treatment strategies, *e.g.*, MELODY™ valve implantation into the branch pulmonary arteries[51,52] or a "jailing" procedure of the pulmonary bifurcation by implanting a bare metal stent across the main pulmonary into a pulmonary branch have been described as potential options[53].

A hybrid approach combining intra-operative PPVI with simultaneous conduit down-sizing[54] or direct exposure of the RV or RVOT (*e.g.*, after failed percutaneous attempt, "bailout" procedure) have also proven to be feasible[55].

Innovative (experimental) technologies, *e.g.*, the self-expanding Medtronic Native Outflow Tract device[56], infundibular reducer devices[57] or newer low-profile pulmonary valves such as the Colibri Heart Valve (Colibri Heart Valve, LLC, CO, United States) indicate future treatment alternatives and hopefully will offer a non-surgical treatment to a much broader patient population[58].

PERCUTANEOUS TRICUSPID VALVE IMPLANTATION

Background and clinical indications

Primary tricuspid valve disease is rare: the underlying etiology can be of either congenital (Ebstein, tricuspid valve dysplasia) or of acquired nature (*e.g.*, rheumatic, endocarditis or carcinoid disease). RV volume and/or pressure overload, left heart failure or mitral valve dysfunction can result in secondary RV enlargement, geometric distortion and tricuspid annular dilation. These circumstances can promote concomitant tricuspid regurgitation, thus called functional tricuspid regurgitation (80 percent of all cases)[59,60]. Patients with tricuspid regurgitation may be asymptomatic for prolonged periods. Surgical treatment is often reserved for advanced stages of tricuspid disease when dysfunction, particularly in patients with congestive heart failure, has led to symptomatic right heart failure[61]. For that reason, patients undergoing tricuspid repair or replacement procedures tend to be at higher risk with poorer outcome[61]. European and American guidelines on surgical management of valvular heart disease were updated in 2012[62] and confirmed in 2014[60]. The level of indication was raised to Class I and IIa for most situations of functional tricuspid regurgitation[62]. A transcatheter approach for tricuspid valve repair or replacement seems to be desirable and beneficial to his high-risk population but is still a long way ahead[2].

Patient selection criteria (in selected series)

Van Garsse *et al*[63] reported on the first "Percutaneous Transcatheter Valve-in-Valve Implantation in stenosed Tricuspid Valve Bioprosthesis" in 2011 amongst other case reports with small patient numbers[64-66].

A multicenter series by Roberts *et al*[67] enrolled 15 patients with failing tricuspid prostheses of whom ten underwent implantation into various failing bioprosthetic valves after careful (echocardiographic) confirmation of a suitable anchor point that allows safe positioning of the stented-valve. Median NYHA class was III and all patients were considered to be "high risk" for conventional surgery for tricuspid prothesis failure. The primary lesion was predominant stenosis (mean gradient > 5 mmHg, mean inflow gradient 12.9 mmHg), although a few had significant regurgitation.

Recently, Cullen *et al*[5] has reported a single-center series on transvenous Melody "Valve-in-Valve" implantation for bioprosthetic valve dysfunction that enrolled ten "high risk" patients with failing tricuspid prosthesis among others. Patients were considered candidates for the interventional procedure if they had significant bioprosthetic tricuspid valve dysfunction (either stenosis, regurgitation, or both) with co-morbid

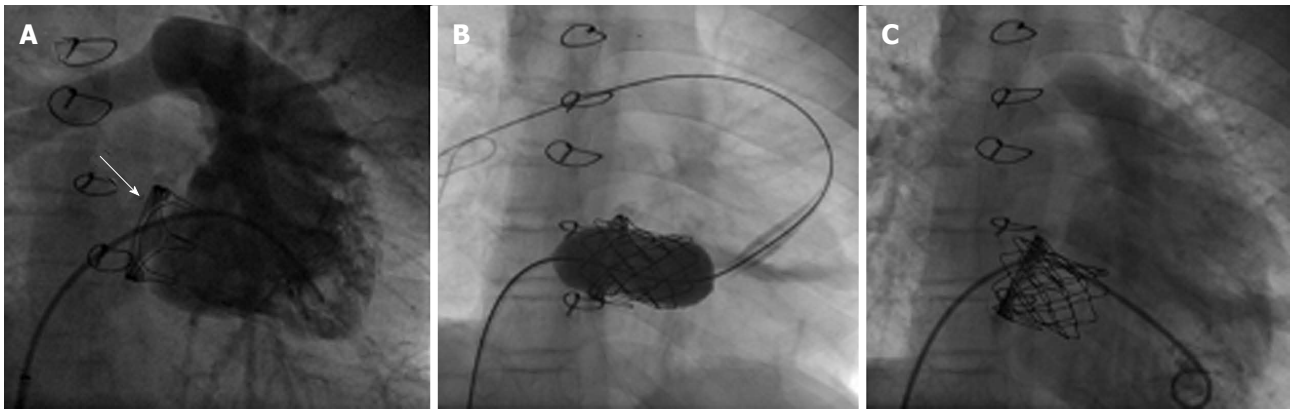

Figure 6 MELODY™ device for "Valve-in-Valve" implantation in tricuspid position. MELODY™ valve implantation procedure in a patient with severe stenosis of a prosthetic biological tricuspid valve (arrow): fluroscopy reveals (A) a RV angiogram in systoly prior to implantation (B) guidewire in the right PA and stable device position after inflating of both balloons of the BiB-delivery system and (C) RV angiogram showing stent position within the biological prosthesis and relative to the ventricle. There is no tricuspid regurgitation. (Courtesy of Wagner R). RV: Right ventricular; PA: Pulmonary artery.

conditions which would preclude surgery. Median NYHA class was Ⅲ with seven of the ten tricuspid patients suffering from moderate or worse tricuspid valve regurgitation with a mean inflow gradient 10 ± 4.3 mmHg.

After all, patient selection criteria for percutaneous tricuspid valve replacement are yet based on (very) limited data. Principally, if a percutaneous approach seems to be an option of treatment in clinical practice, the clinical indication for "Valve-in-Valve" implantation should be based on the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) or the American College of Cardiology/American Heart Association guidelines for tricuspid valve surgery. The percutaneous approach should be reserved particularly for those cases considered to be high-risk cases for conventional surgery[68].

Devices for tricuspid valve implantation

Two percutaneous devices have been described for transcatheter valve implantation in failing bioprosthetic valves so far. These are the Edwards SAPIEN™ and its iterations and the Medtronic MELODY™ valve as described previously (Figure 6).

So far, none of them have been approved or certified to be delivered in tricuspid position. Therefore, implantation of these devices in tricuspid position is off-label-use.

Results

In both series procedural success with device deployment was achieved in all of the tricuspid patients[5,67]. There were no early periprocedural complications in the Cullen series. Procedural complications occurred in one of Roberts' patients (atrioventricular block requiring a pacemaker). Another patient suffered endocarditis eight weeks post-procedural. In both series mean tricuspid gradient decreased significantly (drop to 5.6 ± 2.5 mmHg in Cullen's patients, drop to 3.9 mmHg in Roberts' series). The level of regurgitation revealed to be mild or none in all but one case of the Cullen's series.

Follow-up and outcome

Mean follow-up was nine months in the series by Roberts but with 41 d (range 11 to 209) shorter and more heterogeneous in Cullen's patients. As reported by Roberts *et al*[67] functional class improved in 12 of the treated patients. Nine of the patients sustained the good interventional result nine months after implantation with one percutaneous valve-in-valve which had to be replaced. Cullen's group observed a 30-d readmission rate with three out of ten in the tricuspid patients. And NYHA functional class improvement in nine of the ten treated patients.

Extended indications and future directions

Several groups selected similar patients to demonstrate the feasibility of percutaneous deployment of stent-mounted valves (SAPIEN, SAPIEN™ XT or MELODY™) into the venous system (inferior and/or superior vena cava). The focus is not on the tricuspid regurgitation itself, but rather on its hemodynamic disturbance. These procedures are therefore called "Caval-valve Implantation"[69-72].

Although, a number of animal studies examined the experimental feasibility of percutaneous valve implantation into a native tricuspid valve[2,73,74], Kefer *et al*[75] recently demonstrated feasibility of SAPIEN™ valve implantation into a "native" tricuspid annulus after failed repair without bioprothesis but mixed tricuspid disease.

SUMMARY AND PERSPECTIVE

The aim of PPVI is to prolong the lifespan of surgically placed conduits. The prolonged conduit lifespan, and hence delayed surgery, should limit the number of needed open chest redo-operations over the

patients' total lifespan in cases of congenital and acquired heart disease that indicated the implantation of pulmonic conduits. This sophisticated strategy potentially improves these patients' life expectancy. Pulmonary valve replacement with stent-mounted with stent-mounted valves containing xenograft materials represents the derived valves represents the non-surgical treatment of choice in patients with dysfunction of the RVOT. Although indications continue to extend even to patients with "native", but dysfunctional RV outflow tracts, the diameter of the proposed implantation site limits the feasibility in a relevant number of patients. Even though significant improvement has been achieved in early and late outcomes after PPVI, the risk of stent fractures and graft rupture have not yet been sufficiently explored. Further research is necessary to avoid these complications.

Besides, the extending use of PPVI, the percutaneous approach to tricuspid valve replacement has briefly moved beyond its experimental character. It has been shown to be feasible, but should mainly be reserved for high-risk patients with conditions that preclude surgery.

In conclusion, evolution of the interventional treatment of dysfunctional valves/RVOTs can only be achieved by continuous creative thinking and encouraged teamworking of cardiologists, surgeons, specialists in imaging and bio-medical engineers.

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EDITORIAL

Practical update on imaging and transcatheter aortic valve implantation

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Abstract

After very rapid advances in the development of the technique and devices, transcatheter aortic valve implantation (named TAVI or TAVR), is today a reality that is here to stay. It has become the minimally-invasive treatment option for high-risk and non-surgical patients with severe symptomatic aortic stenosis. Requiring the participation of a multidisciplinary team for its implementation, cardiac imaging plays an important role. From pre-assessment to determine the suitability of the patient, the access site, the type of device, to the guidance during the procedure, and ultimately the long term monitoring of the patient. Correct selection of the patient and device, correct placement of the stent-valve and early detection of complications are of paramount importance for procedural success and for patient outcome. Each technique has advantages and disadvantages, being the cardiologist who will determine the best approach according to the type of patient and the expertise of the center in each one of them. This article summarizes the last contributions of the most common used imaging techniques, in each step of the procedure.

Key words: TAVI; TAVR; Echocardiography; Multislice tomography; Cardiac magnetic resonance; Aortic stenosis

Core tip: Cardiac imaging is of crucial importance in the whole process of transcatheter aortic valve implantation, from initial evaluation, intraprocedural guidance and post implantation evaluation and early detection of complications. Multiple techniques are available for this, and as the rapid development of new devices and equipments, the greater the necessity of being aware of these advances. We provide current data and tips for this purpose. This is the reason of this work.

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INTRODUCTION

Since its beginnings 20 years ago, with first implantations in animals, transcatheter aortic valve implantation (TAVI or TAVR) has evolved substantially[1].

With the advancement of cardiovascular imaging, the application of the most innovative techniques acts jointly to obtain the best clinical results. At present, TAVI is a serious alternative treatment for inoperable or high risk patients with aortic stenosis (AS). In addition, is expected to expand quickly to other subgroups (intermediate risk and aortic regurgitation), since trial results are encouraging compared with medical treatment and cardiac surgery.

Several bioprosthesis types are available, being by far the most commonly used the self-expandable porcine Medtronic CoreValve (Medtronic Inc, Minneapolis, MN, United States), available in the sizes 23 mm, 26 mm, 29 mm, and 31 mm, and the balloon-expandable Edwards Sapien XT bovine valve (Edwards Lifesciences Inc, Irvine, CA, United States), available in multiple sizes: 20 mm, 23 mm, 26 mm, and 29 mm. Both models recently introduced their latest valve generations: Corevalve Evolut R and the Sapien 3, with several advantages and thinner sheaths-introducers (up to 14F). There are now being marketed other valves with different delivery systems, like for instance the Direct Flow valve, the Jena Valve or the Lotus valve, between others.

The preferred implantation route is usually transfemoral. If this is not possible because of patient characteristics, both valve types can be implanted via the subclavian artery, and the Edwards Sapien valve can be implanted *via* a transapical access.

Here we review the contribution of imaging techniques to the whole process of selection of patients and prosthesis, intraprocedural guidance and evaluation of deployment and complications.

PRE-IMPLANTATION EVALUATION

Aortic stenosis severity

Invasive cardiac catheterization used to be the standard for quantification of AS, but nowadays echocardiography is used for diagnostic purposes and in its replacement. Transthoracic echocardiography (TTE) allows evaluation of a calcified valve with restricted leaflet opening and quantification of peak and mean aortic valve (AV) gradient by applying the simplified Bernoulli equation ($\Delta p = 4v2$) to the maximal velocity recorded through the AV by continuous wave Doppler. Severe aortic stenosis is defined as a peak velocity > 4.0 m/s (peak gradient of 64 mmHg), a mean gradient > 40 mmHg, or valve area (AVA) < 1.0 cm^2 (0.6 cm^2/m^2) whith normal left ventricular (LV) systolic function[2]. In cases of low gradient with small area, a dobutamine stress study (maximum dose 20 mcg/kg per minute), may be helpful to determine if the valve is truly severely stenotic, when the maximum jet velocity rises over 4 m/s with the dobutamine-induced increase in stroke volume, whereas the AVA remains less than 1.0 cm[2]. The AS is only mild to moderate in severity if stroke volume increases but there is a small rise in gradient (and therefore the valve area increases greatly), and thus other causes are the origin of LV dysfunction[3].

Annular size

Particularly in the candidates selected for TAVI, other parameters than the severity of the stenosis and the ejection fraction must be evaluated previously to the intervention.

The most important aspect of anatomical screening includes assessment of the arterial vasculature and aortic valvar complex [left ventricular outflow tract (LVOT), aortic annulus, sinus of Valsalva, sinutubular junction and ascending aorta]. All this data will guide physicians to choose the most appropriate access route (subclavian, transfemoral, transaortic or apical) and transcatheter valve size, and it will help to be alert in the detection of potential complications during the procedure[4].

An annular size accurate evaluation is of utmost importance. Underestimation of its dimension could lead to selection and deployment of a smaller valve, with possible complications like paravalvular regurgitation, poor hemodynamics, valve migration and embolism. Overestimation of annular size and deployment of a larger valve can lead to incomplete unfolding (with the consequence of valvular and paravalvular regurgitation) or annular rupture. TAVIs are designed to be utilized in slightly smaller annuli than the prosthesis size[5]. The annular size and the correspondent prosthesis are listed in Table 1.

Aortic annulus can be evaluated using various techniques. Echocardiography is extensively available, repeatable, and easy to perform even taking into account that transesophageal echocardiography (TEE) is semi-invasive and usually requires sedation[6] (Figure 1). We use the sagital plane obtained from a 2-dimensional (2D) parasternal long axis image (TTE) or a mid-esophageal long axis (TEE) image among 120° and 140°, during early systole, measuring from the right coronary cusp to the left noncoronary commissure. To obtain measurements in the coronal and sagittal planes three-dimensional (3D) reconstructions and biplane imaging can be performed.

Multislice computed tomography (MSCT) can give appropriate measurements and may provide important additional information like the anatomy of the coronary arteries, the aortic valve anatomy and area, the plane of the valve and the amount and distribution of calcifications, but iodine injection and radiation are relative limitations. It is important to remember that the aortic annulus is not only a complex 3-dimensional structure, but also that its shape is oval and not circular in the vast majority of patients, as it was demonstrated in previous MSCT studies[7]. The aortic annulus plane is acquired by a reconstruction using two orthogonal planes, the short and long axis of the virtual basal ring, and measurements are taken from systolic phase reconstructions from 20% to 45% of the R-R interval. MSCT multiplanar reconstructions

Table 1 The annular size and the correspondent prosthesis

Prosthesis type	Prosthesis size (mm)	Annular size (mm)	Introducer profile (F)	Minimun vessel diameter (mm)
Edwards Sapien	23	18-22	22	⩾ 7
	26	21-25	24	⩾ 8
Edwards Sapien XT	20	16-19		
	23	18-22	16	⩾ 6
	26	21-25	18	⩾ 6.5
	29	24-27	20	⩾ 7
Edwards Sapien 3	23	18-22	14	⩾ 5.5
	26	21-25	14	⩾ 5.5
	29	24-28	16	⩾ 6
CoreValve	23	18-20	18	⩾ 6
	26	20-23	18	⩾ 6
	29	23-26	18	⩾ 6
	31	26-29	18	⩾ 6
CoreValve evolut R	23	18-20	12	⩾ 6

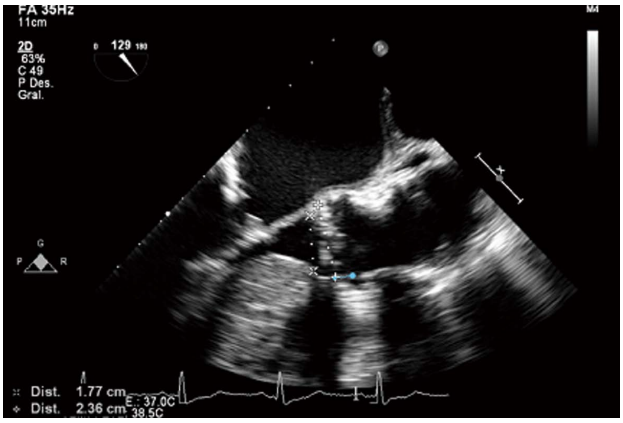

Figure 1 Transesophageal echocardiography 2D at 129° in long axis view in systole with measurements of the left ventricular outflow tract and aortic annulus. The measurement in blue is the distance to the rigth coronary artery.

(MPRs) can provide coronal, sagittal and axial images of the aortic root, with accurate measuraments, almost always underestimated by 2D echocardiography.

On the other hand, cardiac magnetic resonance (CMR) permits an anatomic and functional evaluation of the aortic valve and aortic root, with most sequences in 2D and the selection of the imaging plane during the examination. However, whole heart, echogated 3D CMR with contrast allows obtaining images for multiplanar reconstruction and demonstrates the oval shape of the annulus with minimal and maximal diameters.

Every technique has its advantages and disadvantages. The annulus size is in general 1 mm smaller by TTE than by TEE, and the TEE measurement is 1 to 1.5 mm smaller than MSCT measurements[8,9]. Echocardiography (TTE or TEE) still is the most used technique to assess the aortic annulus, nevertheless, with the acquisition of more data in the near future, MSCT will probably become the first imaging modality to do this.

Aortic anatomy

The characteristics of the aortic valve, like the number of cusps, grade of calcification, thickness and mobility are important to predict the procedure success. Congenital or acquired bicuspid aortic valve stenosis were initially considered a contraindication for TAVI, nevertheless, several successful case reports have been documented and today is considered a relative issue[10-12]. It is frequently not easy to examine cusp anatomy in the severely calcified valves, but in these cases, MSCT or review of old echocardiograms may permit better evaluation of the underlying anatomy. With echocardiography important calcification might cause acoustic shadowing, so MSCT is nowadays the technique of choice in evaluating severity and showing the location of aortic cusp calcification. CMR is not a good choice because of the signal void caused by calcium. Large aortic valve calcifications raise the risk of gaps between the external face of the prosthesis and the patient's native valve, allowing paravalvular regurgitation leaks. Also, the asymmetry, severity and the prosthesis "landing zone" calcification, may produce differences in the tension-force across the valve, with the consequent asymmetric deployment of the device and increased risk of obstruction of the coronary arteries ostium; and important sinotubular junction calcifications may cause limitation during balloon dilatation at the aortic end and may produce ventricular displacement of the prosthesis at the moment of unfolding[13].

Another important issue to consider is the distance from the annulus to the coronary ostia, in order to avoid its compromise during the valve deployment. The distance to the right coronary ostia is easily determined with TEE (Figure 1), but not to the left coronary ostia, which requires 3D TEE (Figure 2). MSCT provides 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[5]. The distance between the aortic valve annular plane and the coronary ostia should be at least of ⩾ 10-11 mm for both type of prosthesis.

Aorta evaluation

Evaluation of the aortic root and tubular portion of the aorta is as well essential, specially when using Core Valve, because its length is greater compared with regular valves, ranging from 52 mm (31-mm valve) to 55 mm (26-mm valve, *i.e.*,). It is advised that the dimensions of the tubular aorta measured at 45 mm above the annulus be 40 mm for the 26-mm valve and 43 mm for the 29-mm and 31-mm CoreValve prosthesis. MSCT can provide an excellent reconstruction and evaluation of the aortic sinus diameter, sinotubular junction, ascending and descending aorta and its iliofemoral branches (Figure 3). This is very important for the selection of the vascular

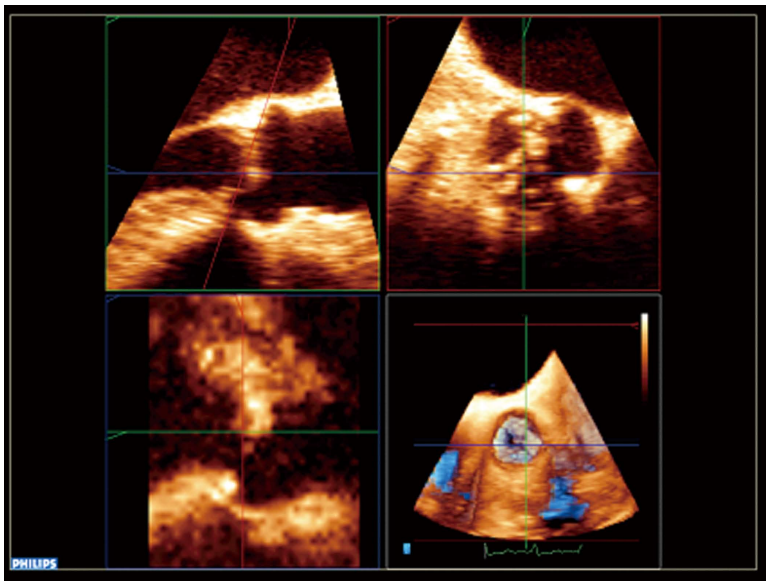

Figure 2 Transesophageal echocardiography 3D with multiplanar projection showing the measurements at annulus level.

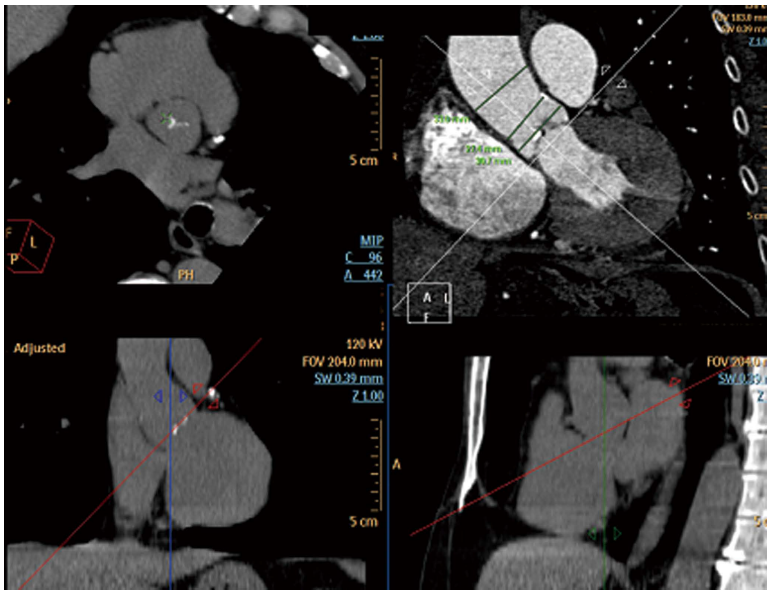

Figure 3 Computed tomography with multiplanar reconstruction showing measurements at different levels of the aorta.

access, because its complications rates range from 5% to 25%[14], and are associated with a striking increase in early mortality risk. Its evaluation often begins with conventional angiography, but it proportionates a very limited data. MSCT provides many reconstructions, as 3D volume rendered imaging, curved multiplanar reformats, and maximum intensity projection images allowing evaluation of vessel size, minimal luminal diameter, calcification severity, plaque burden, vessel tortuosity and identification of high risk characteristics like dissections and complex atheroma[15] (Figure 4). Calcification of less than 180º or eccentric calcification usually do not cause procedural trouble like would nearly circumferential and luminal calcification do. Vascular complications and 30 d mortality can be predicted with the use of a sheath/femoral artery ratio of 1.05 or higher[16]. It is remarkable that the existence of significant aneurysmal dilatation in ascending aorta is a contraindication for the use of CoreValve.

Like MSCT, CMR can give exhaustive evaluation of the aortic valve, annulus, aortic root, coronary ostia, course of the thoracoabdominal aorta and luminal caliber of the iliofemoral branches, and LV function, with the advantage of not using ionizing radiation (Figure 5). Also, free-breathing noncontrast navigator-gated 3D whole-heart acquisition can be acquired, similar to the volumetric acquisition of CT[17].

Other issues

Calcification in other areas, as dense calcification in the intertrigonal area rises the risk of paravalvular aortic regurgitation (AR) due to asymmetric unfolding of the valve[18]. The angle between the aorta and the LV and proximal septal hypertrophy are essential issues to consider when planning the procedure. A very prominent proximal septum is an important consideration to have in mind during the placement of the valve because can cause valve repositioning when stopping the pacing run[15]. LV function must be evaluated in order to minimize the number of pacing

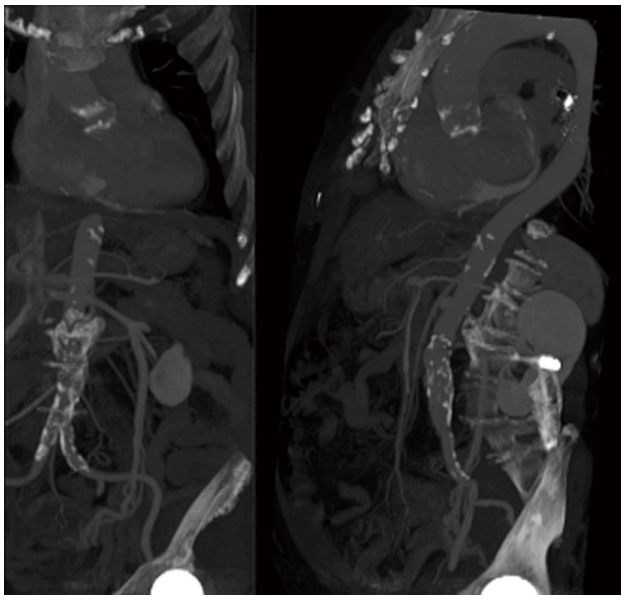

Figure 4 Computed tomography images showing aortic anatomy and calcifications, previous to transcatheter aortic valve implantation procedure.

runs to prevent hemodynamic compromise in those with severe dysfunction. The degree of baseline aortic regurgitation is also very important, since balloon inflation might aggravate regurgitation and cause hemodynamic deterioration.

In conclusion, echocardiography (in all modalities, TTE, TEE, 2D and 3D), MSCT and CMR can be used to make a pre-implantation evaluation, but it is very important to remind that the imaging technique used might influence TAVI size selection and strategy.

INTRAPROCEDURE GUIDANCE

During the procedure, fluoroscopy and angiography are the principal techniques used to guide device placement (Figure 6). However, they involve several shortcomings, for example: (1) radiation use; (2) restricted 2D visualizations with scarce soft-tissue contrast, sometimes preventing early identification of complications (cardiac tamponade, *etc.*); and (3) the reiterated use of nephrotoxic contrast media to observe the aortic annulus and coronary ostia during the procedure.

Nevertheless, other imaging modalities, like TEE, may overcome the lower soft tissue contrast resolution of fluoroscopy and do not use radiation or contrast. Specially 3D-TEE permits a good visualization of the guide wire path and allows a good assessment of the prosthesis position on the balloon, with respect to the native valve annulus and other structures. Using mid-esophagus long axis view is possible to observe the guide wire across the aortic valve in its delivery, retrograde (transaortic, transubclavian, transfemoral) or anterograde (transapical)[13]. For the adequate position of the prosthesis, TEE can be very useful. In

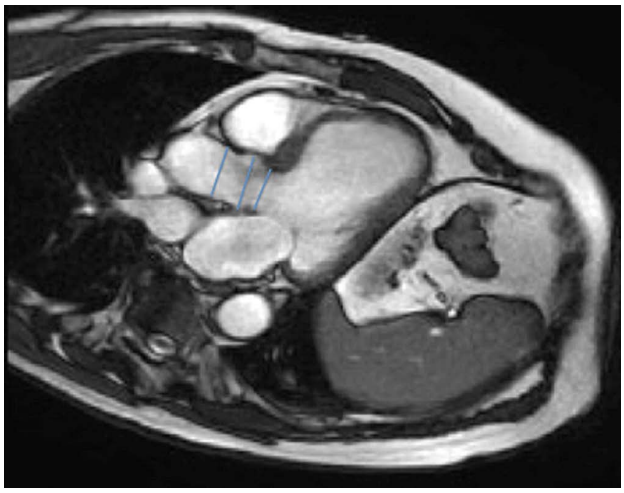

Figure 5 T1 weighted cardiac magnetic resonance image depicting aorta measurements.

the case of Sapien valve, about half of the prosthesis should be below and above the aortic annulus, and when using CoreValve, the nitinol stent must be well within the borders of the calcified native annulus. With 3D TEE it is feasible to observe ortogonal planes simultaneously, aortic valve's views in long and short-axis in realtime, very helpfull for every step of the procedure (aortic valve pass, balloon inflation and prosthesis unfolding).

Intracardiac echocardiography has also been used for TAVI guidance, but imaging abilities are worse than with TEE[19].

In patients with preserved LV systolic function, it was described an improvement in diastolic function, evaluated minutes after deployment with TEE, evaluated through E wave deceleration time, E wave velocity and isovolumetric relaxation time[20].

Immediately after deployment, it is very important to discard complications, for example AR, the most common one. This must be performed rapidly and in multiple echocardiographic views to permit possible reballooning or up delivery of a second prosthesis if the AR is severe and cannot be controlled in another way. It is of utmost importance to differentiate between paravalvular and valvular regurgitation (Figures 7 and 8). Because of irregular calcification in the native valve, small paravalvular leaks are usually observed due to gaps between the annulus and the device, particularly at the commissural areas.

In the case of paravalvular jets, the recommendations indicate that the rate of the circumference of the annulus occupied by the jet offers a guide to severity: < 10% mild, 10%-29% moderate, and ⩾ 30% severe[21]. In a work of our group, we found that the vena contracta planimetry on 3D TTE was better correlated with AR volume than vena contracta width on 2D TTE [Kendall's τ = 0.82 (P < 0.001) *vs* 0.66 (P < 0.001)]. The areas under the receiver operating characteristic curves were 0.96 for vena contracta

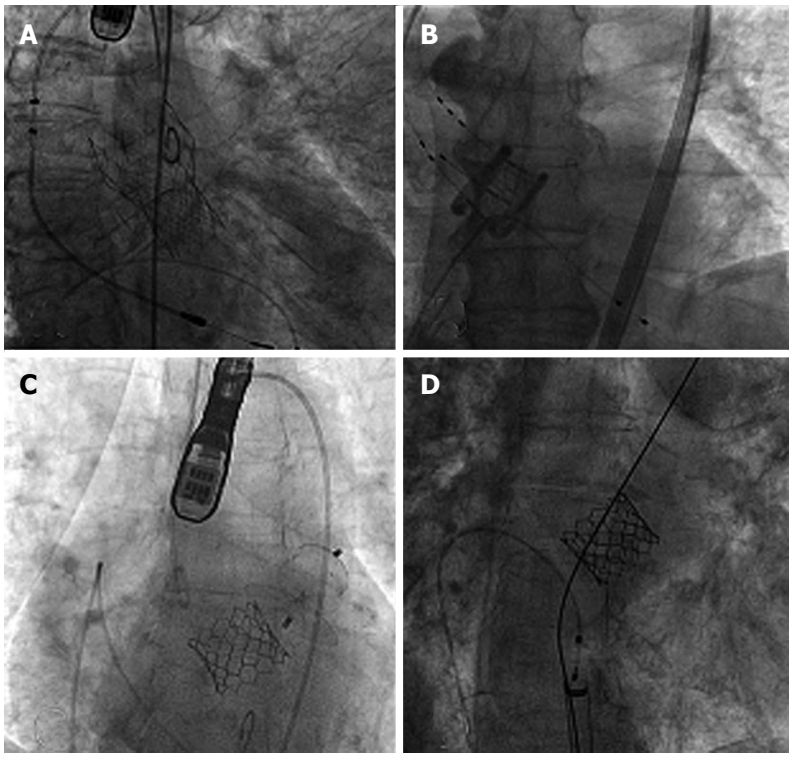

Figure 6 Fluoroscopy images showing different prosthesis models. A: CoreValve evolut R; B: Direct Flow valve; C: Edward Sapien 3; D: Edward Sapien XT.

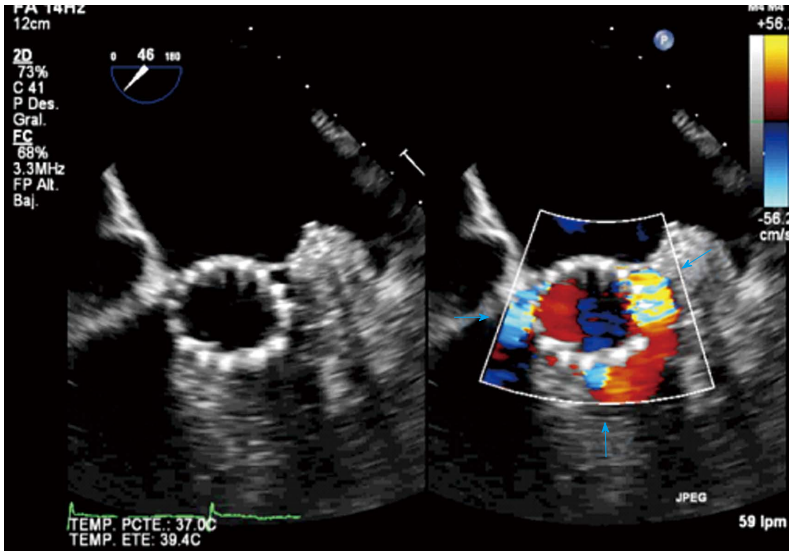

Figure 7 Transesophageal echocardiography at 46° without and with color Doppler showing 3 paravalvular leaks (arrows) after valve implantation.

planimetry and 0.35 for vena contracta width[22]. To avoid paravalvular leak, is required that the covered portion of the prosthesis must be well-apposed to the host valve and interleaflet triangles and the ventricular border of the device just under the hinge points of the AV. It is also common the presence of mild central valvular regurgitation that frequently resolves with removal of the guidewire; otherwise, it must be assessed looking for underexpansion of the prosthesis (Figure 9). Significant valvular AR is generally due to AV harm in the course of the procedure, too large a device for a little annulus with consequent valve distortion, or severe calcification of the patient's AV producing deformation of the frame of the valve[23].

Obstruction of a coronary artery by the prosthesis or displaced calcium is another possible complication. This situation can be seen as regional hypokinesis, best evaluated from the transgastric view and, if it is possible, assessing the coronary arteries flow. If there is LVOT obstruction, this may cause hypotension because of rapid drop in afterload. Other causes must also be considered, like severe mitral regurgitation, pericardial tamponade, displacement of the device, air embolism, right ventricule perforation by a pacemaker lead, aortic dissection and vascular access bleeding.

Other imaging techniques in vogue at the moment are fusion imaging modalities, like C-arm computed tomography with valve landmark detection and automatic aorta segmentation, that tries to make simpler the procedure using 3D over fluoroscopic

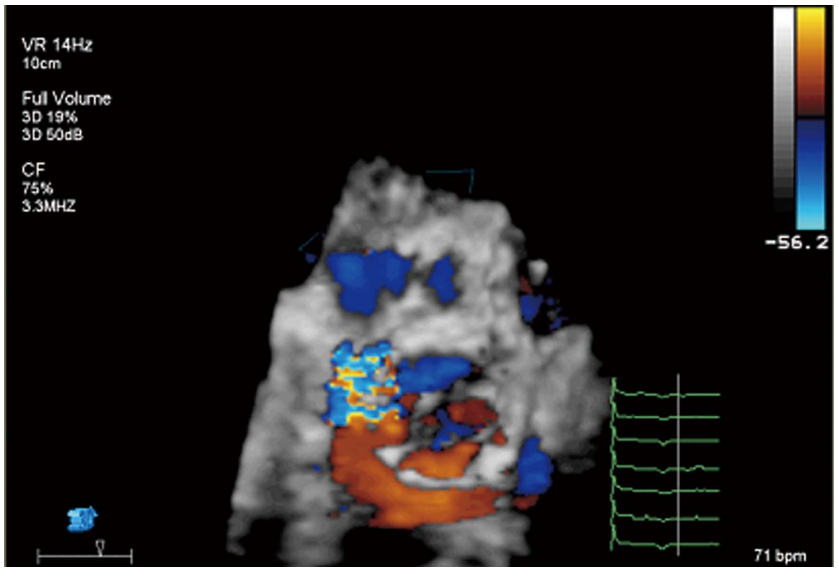

Figure 8 Transesophageal echocardiography 3D full volume showing the exact position of an important paravalvular leak.

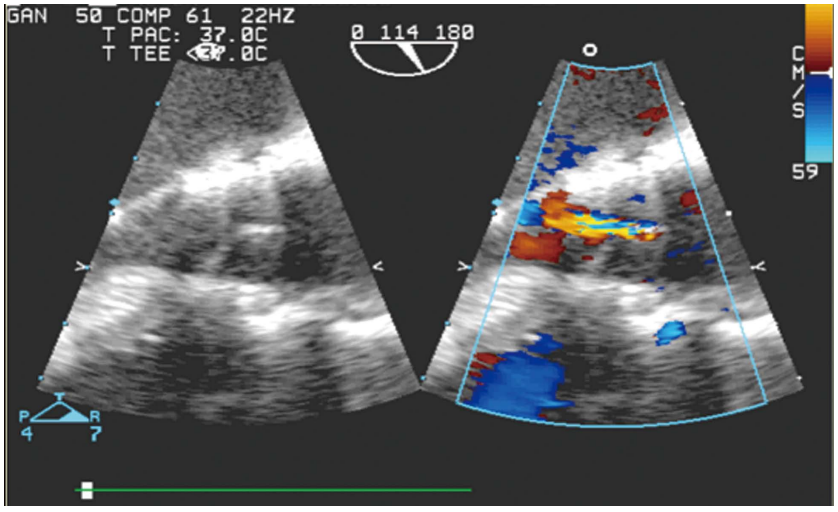

Figure 9 Transesophageal echocardiography at 114° without and with color Doppler depicting the presence of central aortic regurgitation due to underexpansion of the prosthesis.

imaging[24]. CMR capacities are real-time image without restricted scan plane orientation and incomparable soft-tissue contrast, with concomitant display of the prosthesis; and it seems convenient over X-ray angiography and fluoroscopy during all of complete procedure. It allows on-line monitoring cardiac performance, instant recognition of vascular and cardiac harm, and real-time orientation for axial placement and unfolding of the device[25].

POST-IMPLANTATION ASSESSMENT

After TAVI implantation, the imaging evaluation will contribute to determine the valve hemodynamic condition, like effective valve area and gradients; the presence and quantity of valvular and paravalvular regurgitation; the effect of the procedure in ventricular function, hypertrophy, *etc*. and the recognition of long term problems like device migration, endocarditis, ventricular perforation, mitral valve impingement and thrombus formation.

Echocardiography remains the technique of choice for this, because of its wide availability, avoidance of ionizing radiation, together with real time hemodynamic and structural assessment. MSCT and CMR can also provide and excellent anatomic detail and detection of complications like pseudoaneurysm of the root or the apex. Postprocedural evaluation of remaining AR by CMR might have a possible part in TAVI patients[26]. Nevertheless, CMR is a time-intensive method, and this could be an important factor, especially in older patients. In cases of renal disfunction the advantages for the use of gadolinium must be greater than the risks of nephrogenic systemic fibrosis[27]. Also CMR is not warranted in patients with defibrillators, pacemakers or intracranial aneurysm clips, even though the prosthesis used now are CMR compatible.

LV function and hemodynamics

Echocardiography is most common used tool to evaluate the changes described after TAVI, like reductions in LV mass[28], recovery in EF[29], amelioration in diastolic function, and reduction of mitral regurgitation[30].

Although, CMR evaluation of LV mass provides a greatly precise calculation[31].

Valve area and gradients

Determination of mean and peak transvalvular pressure gradients and the calculation of effective orifice area are easily obtained with continuous wave Doppler with TTE, not forgetting suprasternal notch and right parasternal windows to confirm that maximum gradients are catched. CoreValve and Edward Sapien valves have very good flow features with mean gradients of 10-15 mmHg, with relatively stable gradients[32] or little rise in mean transvalvular gradient (3.8%/year) and a low decrease in valve area (0.06 cm^2/year)[33].

Aortic regurgitation

Follow-up echocardiograms should recognize the existence, position, and severity of valvular and paravalvular AR, using all the possible views in case of eccentrical jets. Paravalvular regurgitation is generally produced by imperfect device apposition to the host annulus because of to remaining calcium, undersized prosthesis, or too low position of the valve[34], so imaging in multiple planes is necessary. Valvular and paravalvular AR affect LV hemodynamic condition, determined by raised volume burden, consequently affecting chamber dilatation, LV performance, and progress to pulmonary hypertension, so total AR should routinely be calculated combining information from color and spectral Doppler. Three-dimensional TTE allows quantification of AR with greater accuracy than 2D TTE. CMR might be the technique of election in cases of severe AR, or disagreement in gradients with echocardiography[35].

Although it is always difficult to predict the future, TAVI seems a truly promising therapeutic alternative with settled indications nowadays and expanding indications (intermediate risk, aortic regurgitation, valve in valve[36], *etc.*). What seems clear is that cardiovascular imaging will be needed in this field in order to achieve all its potential objetives.

To sum up, although at the begining multiple test and measurements were required, as experience grows, patients and devices selection are improving, with a more rational imaging algorithm, based in local expertise and availability.

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EDITORIAL

Helicobacter pylori vs coronary heart disease - searching for connections

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Abstract

In this review, we discussed the findings and concepts underlying the potential role of *Helicobacter pylori* (*H. pylori*) infections in the initiation, development or persistence of atherosclerosis and coronary heart disease (CHD). This Gram-negative bacterium was described by Marshall and Warren in 1984. The majority of infected subjects carries and transmits *H. pylori* with no symptoms; however, in some individuals these bacteria may cause peptic ulcers, and even gastric cancers. The widespread prevalence of *H. pylori* infections and the fact that frequently they remain asymptomatic may suggest that, similarly to intestinal microflora, *H. pylori* may deliver antigens that stimulate not only local, but also systemic inflammatory response. Recently, possible association between *H. pylori* infection and extragastric disorders has been suggested. Knowledge on the etiology of atherosclerosis together with current findings in the area of *H. pylori* infections constitute the background for the newly proposed hypothesis that those two processes may be related. Many research studies confirm the indirect association between the prevalence of *H. pylori* and the occurrence of CHD. According to majority of findings the involvement of *H. pylori* in this process is based on the chronic inflammation which might facilitate the CHD-related pathologies. It needs to be elucidated, if the infection initiates or just accelerates the formation of atheromatous plaque.

Key words: *Helicobacter pylori*; Coronary heart disease; Inflammation; Microbiota; Lipopolysaccharide

Core tip: *Helicobacter pylori* (*H. pylori*) is a Gram-negative spiral bacterium which colonizes gastric mucosa of nearly half of human population. A characteristic feature of *H. pylori* infection is an excessive inflammatory response. The majority of *H. pylori* infections remain asymptomatic. However, still it leads to the development of histological gastritis with the recruitment of immune cells. About 10% of infected subjects develop symptomatic gastritis, erosions or peptic ulcer. Gastric cancer is the most severe consequence of *H. pylori* infection. Recently, a possible association between chronic infections with *H. pylori* and extragastric disorders - including coronary heart disease, has been intensively investigated. Here we have revised recent studies confirming or excluding possible

connections between chronic bacterial infections and the occurrence of coronary heart disease (CHD) within different populations, especially in the context of *H. pylori* infections. We have also presented various study approaches investigating direct and indirect interplay between *H. pylori*-driven consequences and CHD development to clarify already gained knowledge and suggest future directions. Considering the significance of already conducted research studies, the involvement of *H. pylori* infection in the process of CHD development is highly probably, however, still a lot need to be done to clarify whether this association is direct (with the involvement of *H. pylori* antigens and products) or indirect (with the involvement of inflammatory-related molecules accelerating/initiating CHD development).

Chmiela M, Gajewski A, Rudnicka K. *Helicobacter pylori vs* coronary heart disease - searching for connections. *World J Cardiol* 2015; 7(4): 187-203 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i4/187.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i4.187

INTRODUCTION

Since classic risk factors do not explain all cases of coronary heart disease (CHD) the concept that atherogenesis may have infectious background should be considered. The role of virus and bacterial pathogens including *Helicobacter pylori* (*H. pylori*) are now considered as factors implicated in the development of CHD. Chronic infections may influence the course of CHD *via* different mechanisms such as chronic inflammatory reactions, an autoimmune processes and modification of classic CHD risk factors. The pioneer finding of Mendall and co-workers, published in 1994, showed that CHD patients have elevated levels of serum anti-*H. pylori* antibodies. Following this finding, some authors confirm and some exclude the existence of this connection. Still there is no consensus on the role of *H. pylori* in either causation or progression of CHD. In order to describe the involvement of *H. pylori* in the development of CHD, it is necessary to find the largest number of reliable research studies confirming this relationship.

PATHOGENESIS OF CHD

CHD is one of the most severe chronic diseases of the coronary vessels - an important health and social problem - often life-threatening. It occurs due to endothelial dysfunction within the vessels, accompanied by an increased blood pressure, remodeling of vascular wall, local inflammation, platelet aggregation and blood clotting. These disorders promote the formation of atheromatous plaque, which is often unstable and subsequently ruptures. This might impair the blood flow leading to vascular blockage or myocardial infarction. Classic risk factors of CHD include cigarette smoking, hypertension, elevated levels of total cholesterol, triglycerides and low density lipoproteins (LDL) *vs* decreased high density lipoproteins (HDL) fraction, diabetes mellitus, as well as raised homocysteine and coagulation factors. Predisposing factors that increase the probability of CHD development are obesity, lack of physical activity, previous incidents of CHD in relatives, male gender, low socioeconomic status, as well as ethnic and behavioral factors that[1,2].

CHD is a group of symptoms resulting from chronic malnutrition and hypoxia of myocardial cells which is accompanied by oppression, burning, feeling the burden, discomfort and chest choking. These disorders are a consequence of atherosclerosis, which histologically is characterized by the accumulation of macrophages (MØ), LDL fractions, foam cells derived from macrophages filled with oxidized (ox) LDL and extracellular cholesterol complexes deposited within the vessels. On the inner surface of the vessel, lipid deposits are formed, which are gradually surrounded by a connective tissue and undergo fibrosis[3,4]. According to the statistics of World Health Organization (WHO), ischemia associated with atheromatous plaque is the main reason for CHD development, 70% of heart failure cases and 80% of sudden cardiac deaths. The natural history of atherosclerosis suggests that lesions in the arteries may occur already in the uterus or in early childhood. However, clinical manifestations of atherosclerosis are associated with the presence of atherosclerotic plaques, which in men usually develops after the age of 50 and in women postmenopausally[1].

DYSFUNCTION OF VASCULAR ENDOTHELIUM AS AN INITIATOR OF ATHEROMATOUS PLAQUE FORMATION

The interior of blood vessels is covered with a single layer of adjacent endothelial cells (size 0.2-0.3 mm) attached to the basal membrane and extracellular matrix molecules through integrin adhesion molecules[3]. Endothelium contacts with smooth muscle cells through gap junctions, which are permeable to the electric current, ions and low molecular weight compounds. Human vascular endothelium is a barrier that separates blood containing clotting proteins, platelets and inflammatory cells, from connective tissue and muscle layers of the blood vessel wall. The balance between the internal and external environment of the vessel depends on mechanical, chemical and immune reactions occurring within endothelial cells[1]. The endothelium is affected by physical pressure of blood flow (hemodynamic forces), various soluble substances and immune cells. Endothelium delivers many effector substances such as vasolidation and vasoconstrictioning factors (determining the proper tension of the vessel wall), cytokines and adhesion molecules (responsible for interactions with blood

cells and the development of the inflammatory response), factors involved in blood coagulation and fibrinolysis. All together the endothelium plays a role in the maintenance of the vascular homeostasis which is determined by its large mass, distribution and the ability to receive and respond to signals from external environment (hemodynamic and chemical stimuli, pO_2), by changing the expression of various active substances and proteins[1,5]. The endothelium expresses structures that are necessary for adhesion, migration, activation and diapedesis of immune cells and platelets, which allows for the development of inflammatory response[6,7]. These are mostly adhesion molecules (selectins) such as: P-selectin (platelet), E-selectin (endothelial) and L-selectin (leukocyte) and immunoglobulin-derived adressins, including: intracellular adhesion molecules (ICAM)-1 and -2, vascular cell adhesion molecule 1 (VCAM-1), platelet endothelial cell adhesion molecule 1, and macrophage chemotactic protein-1 (MCP-1). If endothelium is damaged it loses its functional integrity and homeostasis which initiates the occurrence of multiple lesions[5,8]. This dysfunction is usually leads to increased tension, vascular wall remodeling, vascular inflammation, increased platelet adhesion and aggregation. These processes contribute to the development of atherosclerosis or destabilization of existing atherosclerotic plaques[2].

CHD AS AN INFLAMMATORY PROCESS

In the late 90s we believed that the atherosclerotic process is a response to a mechanical trauma, resulting in the loss of endothelial cell lining in the vessels. Since the majority of CHD symptoms are induced by both local and systemic inflammatory responses, recently the attention is focused on the role of inflammation in the development of atherosclerosis[9-12]. Inflammatory markers, such as C-reactive protein (CRP) have been found to be higher in CHD patients than in controls, similarly to the concentration of interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α) in plasma and supernatants of immune cells stimulated *in vitro* with bacterial lipopolysaccharide (LPS). Increased expression of E-selectin, L-selectin and P-selectin as well as higher expression of VCAM-1 and ICAM-1 was also noted in CHD cases[9,13]. It is difficult to identify factors that initiate cascade of inflammation and plaque formation. However, it is clear that endothelial dysfunction and raised cholesterol play a major role in the inflammation. Cholesterol contributes to the localization of atherosclerotic lesions, preferentially in the sites where it leads to the activation of endothelial NF-κB signal transduction pathway[14]. The inflammatory response is characterized by the influx of MØ and monocytes to the endothelium, with the latter being transformed first into MØ and subsequently to foam cells prior ingestion of oxLDL. Protein components of the LDL particles are processed by macrophages and dendritic cells and presented to T cells in the context of class Ⅱ major histocompatibility complex[15]. Activated MØ and other inflammatory cells release chemokines that stimulate the migration of smooth muscle cells which together with foam cells, form a fibrous cap. This process is facilitated by interferon gamma (IFN-γ) and TNF-α secreted by T helper (Th)-1 lymphocytes, as well IL-12 produced by macrophages and foam cells[16]. The latter undergo apoptosis, and together with cholesterol crystals form lipid plaque cover[13,17]. It has been revealed that atherosclerotic lesions are associated with the increased reactivity of immune cells. The injured tissue releases IL-33 which alarms the immune system, induces expression of adhesion molecules and attracts Th2 lymphocytes delivering IL-4-considered anti-inflammatory cytokine[18-20]. However, a growing body of evidence indicates that IL-4 may play a role in atherosclerosis through induction of inflammatory responses, such as upregulation of VCAM-1 and MCP-1[21]. The main population of cells in newly formed atherosclerotic lesions are T lymphocytes, while in chronic lesions this proportion is reversed towards MØ that initiate immune processes by presenting antigens to T cells and the production of cytokines and chemokines[1,15,16,22].

MØ and neutrophils contains granules where myeloperoxidase and metalloproteinase are stored - the inflammatory markers correlated with a risk of atherosclerosis[23,24]. Myeloperoxidase contributes to leukocyte migration and the accumulation of foam cells. Indirectly it is involved in endothelial dysfunction and the induction of apoptosis with a consequence of plaque rupture and its destabilization. Due to the this, occurrence of vascular tissue factor is released and the activation of the blood coagulation cascade take place. Myeloperoxidase reduces the availability of endothelial nitric oxide and inhibits its diastolic and anti-inflammatory function. Moreover, it is involved in the oxidative modification of LDL to its atherogenous form, recognized by MØ receptors[3,10]. Prominent inflammation markers, activated by myeloperoxidase are delivered by macrophage-derived metalloproteinases (MMPs), hydrolyzing the components of extracellular matrix such as elastin and collagen, leading to the destabilization of atherosclerotic plaque. Metalloproteinases are also involved in the lipid peroxidation process and accelerated consumption of nitric oxide[22]. CRP belonging to the group of acute phase proteins which raises during infection or tissue damage, is an important marker of inflammation and is considered as an indicator of coronary events associated with endothelial damage. The upregulation of CRP is correlated with the elevation of IL-6, TNF-α, obesity and insulin resistance, which may indicate a link between chronic inflammation and endothelial dysfunction[12]. It has also been shown that CRP is more accurate marker of coronary events than the LDL cholesterol. This was based on the observation that women with the highest levels of CRP and low LDL

were more susceptible to acute coronary insufficiency compared with those with high LDL and low CRP levels[25].

INFECTIOUS RISK FACTORS OF CHD

Classic risk factors do not explain all cases of CHD. Many data indicate that atherogenesis may be associated with chronic infections, accompanied by a long-term persistent inflammation[26-30]. Compelling evidence supports also the concept that gut microbiota actively promotes weight gain as well as fat accumulation, and indirectly sustains a condition of low-grade inflammation, thus escalating the risk of CHD[31-33]. The occurrence of microbiota favors not only intestinal but also the systemic exposure to the LPSs of Gram-negative bacteria. This microbiome-derived compound can cause a condition called "metabolic endotoxemia" characterized by low-grade inflammation, insulin resistance, and augmented cardiovascular risk. LPS is a powerful trigger for the cells of the innate immunity[34]. Variety of immune cells (monocytes, macrophages, Kupfer cells, and preadipocytes) and non-immune cells (adipocytes, hepatocytes, and endothelial cells) express Toll like receptor (TLR) 4 complex recognizing bacterial LPS[35]. Upon binding to TLR, it induces the release of proinflammatory molecules that interferes with metabolic paths of glucose and insulin, promotes development of the atherosclerotic plaque, and favors progression of fatty liver diseases[36,37].

Chronic infections may influence the development of CHD *via* various mechanisms such as chronic inflammatory reactions, an autoimmune responses and the modifications of classic risk factors for CHD[26,38]. They may pose direct effect on the vessel wall by inducing foam cell formation[39]. Therefore, *Herpes simplex* and Hepatitis C viruses as well as bacteria such as *Chlamydophila pneumoniae, Mycoplasma pneumoniae, Porphyromonas gingivalis, Streptococcus mutans* and *H. pylori* have been considered as factors involved in the development of CHD[40-45]. It has also been suggested, that *Ch. pneumoniae* promotes atherogenesis by inducing the synthesis of MCP-1, IL-8 and ICAM-1 in endothelial cells[44]. Among various pathogens possibly involved in atherogenesis *H. pylori* is particularly interesting, since it induces chronic long-term infection within gastric epithelium which leads not only to local but also systemic inflammation[45-48].

H. PYLORI A VERSATILE PATHOGEN

H. pylori is a Gram-negative bacterium demonstrating the affinity to gastric epithelial cells and perfect adaptation to the acidic environment of the stomach. In the majority of infected patients the interplay between *H. pylori* and the host cells are transformed into some sort of long lasting homeostasis. The majority of infected individuals (80%-90%) carry and transmit *H. pylori* with no symptoms, however, in some patients these bacteria induce pathological changes like gastroduodenal ulcers, as well as gastric cancers[49]. *H. pylori* are acquired early in life, and if not successfully treated persist for lifetime[50]. It is believed that the history and adaptation of *H. pylori* is associated with the evolution and migration of *Homo sapiens*. This bacterium has evolved to successfully colonize the hostile environment of the human stomach in the face of innate and adaptive immune responses[51]. In some ways, *H. pylori* resemble commensal bacteria. Contrary to this assumption, stays the fact that *H. pylori* expresses virulence factors with unquestionable pathogenic properties. For these reasons *H. pylori* infections should be monitored since, even if asymptomatic, they may cause systemic complications[52,53].

The interactions between *H. pylori* and gastric tissue cells determines the establishment and development of the disease[54]. Colonization of gastric epithelial cells by *H. pylori via* bacterial adhesins is followed by the occurrence of the acute phase of inflammation accompanied by the infiltration of gastric mucosa with granulocytes and MØ. *H. pylori* survives inside epithelial cells, also temporarily in MØ or in other niches within gastric tissues[55]. When infection becomes persistent, acute phase becomes chronic and is accompanied by an infiltration of lymphocytes. Inflammation is necessary for the proper recognition and elimination of infectious agents and tissue healing. But in case of *H. pylori* the inflammatory reaction is excessive and results in the development of pathological processes in gastric epithelium such as erosions, ulcers, modifications in the cells phenotype, their excessive proliferation as well as secretion of proinflammatory cytokines[56-58]. *H. pylori* possess an abundant composition of antigens[59]. Urease and vacuolating cytotoxin (VacA) stimulate inflammatory responses by damaging gastric epithelial cells, whereas cytotoxin-associated gene A (CagA) antigen, when introduced into the host cells through secretion system Ⅳ, evokes structural and functional changes. Also soluble forms of CagA may influence the activity of host gastric epithelial cells stimulating them to secrete IL-8 with chemotactic properties[60-62]. It inhibits proliferation of lymphocytes[63] and enhances expansion of gastric epithelial cells[64]. *H. pylori* modulates the activity of immune cells *via* different mechanisms such as molecular mimicry, antigen variation and immunomodulation of nonspecific and specific adaptive responses[65,66]. Some antigens of *H. pylori* enhance, while others inhibit the activity of immune cells. The first group includes surface lectins whereas CagA, VacA and LPS represents the second group[63,67-70]. *H. pylori* LPS shares some features common with human tissues. These are Lewis (Le) determinants: Le^X, Le^Y, Le^{XY} present in the O-specific chain of *H. pylori* LPS and on the surface of host cells: erythrocytes, granulocytes, monocytes, epithelial and vascular endothelial cells. In consequence, *H. pylori*

can impair its recognition by host immune cells and pose a risk of autoreactive antibody production[71]. *H. pylori* LPS of Le^{XY} type impairs phagocytic activity of granulocytes, cytotoxic activity of NK cells and lymphocyte proliferation[68,70]. It binds with dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) and may interfere with the development of specific immune response[72].

Recently, possible association between *H. pylori* infection and extragastric disorders, including iron deficiency anemia, chronic idiopathic thrombocytopenic purpura, growth retardation, diabetes mellitus and CHD is being considered[73]. Also, an inverse correlation between *H. pylori* prevalence and an increase in allergies, has been suggested. However, since the understanding of *H. pylori*-related pathologies continues to evolve, the idea that *H. pylori* might confer benefit to humans generates serious controversy. Postulated role of *H. pylori* in the pathogenesis of extragastric disorders is based on the following facts: (1) local inflammation induced by these pathogens has also systemic effects; (2) *H. pylori* infection induces chronic low grade process lasting for decades; and (3) persistent infection induces immune responses, which may have local and remote consequences.

The widespread prevalence of *H. pylori* infection and the fact that they are frequently asymptomatic may suggest that, similarly to intestinal microflora, *H. pylori* can be a source of antigenic components that stimulate not only local, but also systemic inflammatory response. Possibly *H. pylori* together with intestinal microbiota may enhance a risk of cardiovascular disorders, probably through a mechanism that involves an increased exposure to bacterial products translocated from the gut to the circulation[74,75]. Both *H. pylori* proteins and LPS demonstrate pro-inflammatory properties. Considering the role of *H. pylori* LPS as a proinflammatory compound, the different structure of its lipid A is taken into account[76,77]. This component of *H. pylori* LPS determines its diminished proinflammatory properties in comparison to other bacterial LPSs discussed in previous review[75]. Moreover the impact of Le determinants on the severity of *H. pylori* induced-inflammation has also been investigated. For instance, it has been shown that *H. pylori* LPS with or without Le^{XY} determinants exhibits different effectiveness in stimulating the secretion of proinflammatory cytokines: IL-8 and TNF-α[78].

Recent knowledge on the pathoetiology of atherosclerosis together with current findings in the area of *H. pylori* infections constitute the background for the newly proposed hypothesis that those two processes may be related. To describe the involvement of *H. pylori* infection in the development of atherosclerosis, multiple study approaches have been undertaken. To discover a significance of *H. pylori* compounds, in the modulation of cell barrier function and its contribution to CHD development complex studies have to be undertaken. The understanding of subsequent stages of *H. pylori* infections and the processes induced on the level of cellular barriers: gastrointestinal epithelium, vascular endothelium and the cells of innate immunity seem to be crucial.

Local chronic inflammation induced by *H. pylori* in the gastric epithelium, may be reflected on the periphery by the appearance of acute phase proteins and cytokines produced by immune cells and particular tissues[58,59,79]. These soluble systemic inflammatory markers may enhance the development of lesions within vascular endothelium. Also, it cannot be excluded that certain *H. pylori* components crossing the epithelial barrier in the stomach or intestines can have a direct influence on the vascular endothelial cells as well as circulating immune cells maintaining their constant activation (Figure 1). So far, it has been shown that *H. pylori* vacuolating toxin and urease contribute to the intercellular tight junction degradation[80]. If so, bacterial agents penetrating lamina propria may interact with immune cells or even enter the circulation. Although *H. pylori* colonize particularly the gastric epithelium its antigens are translocated to a deeper parts of gastrointestinal tract where they may be easily detected in feces[81]. In the jejunum components of *H. pylori* affect the expression of surface molecules, secretion of cytokines, epithelial permeability and its barrier function. Probably in Peyer's patches *H. pylori* antigens initiate specific adaptive immunity and from this site could be spread into the circulation[79,82]. It has been hypothesized that *H. pylori* antigens may affect vascular endothelium by direct interactions with endothelium, indirectly in a form bound with leukocytes or as complexes with LDL/oxLDL fractions - classic risk factors of CHD[75]. The vascular endothelium can also be affected by *H. pylori* - driven cytokines and chemokines[57,78,83].

In order to evaluate the involvement of *H. pylori* infection in the development of CHD, it is necessary to find the largest number of research studies and possible connections confirming this relationship. The search for such connections should combine serological, biochemical, immunological as well as molecular markers. Serological and molecular studies on the material derived from patients with clinically confirmed CHD can provide markers helpful in defining individual susceptibility to chronic infections and extensive inflammation, predisposing to CHD. These cellular and molecular study approaches would describe the background of *H. pylori*-driven proinflammatory mechanisms directed towards epithelial and endothelial barrier functions, and innate immune cells, which would help to define their role in the atherogenesis.

H. PYLORI VS CHD - CURRENT STATE

Serological studies

The role of *H. pylori* infection in the development of CHD was suggested by Mendall *et al*[84] in 1994, where he observed for the first time the elevation of anti-*H.*

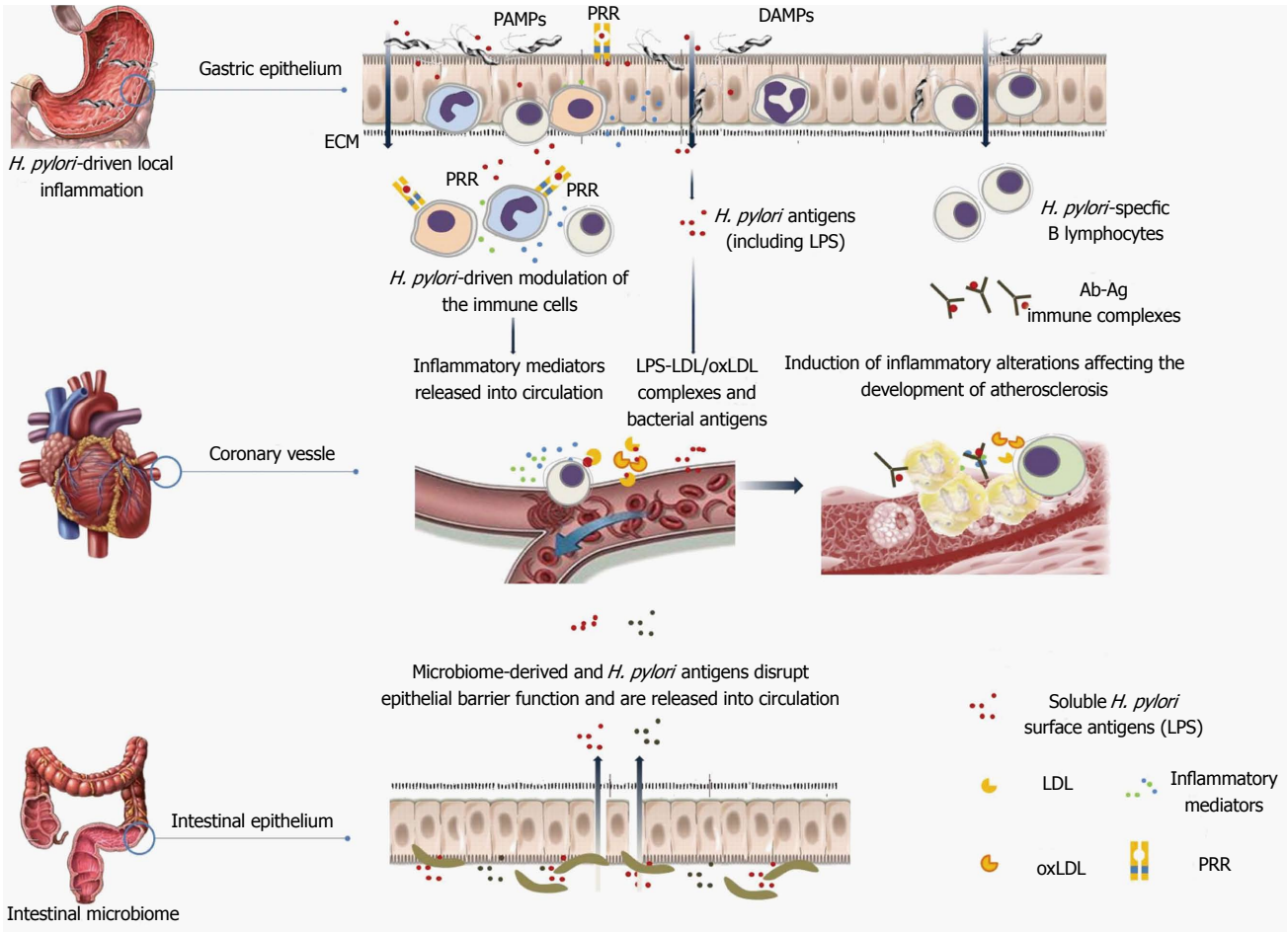

Figure 1 A possible link between local inflammation induced by *Helicobacter pylori* on surface of the gastric epithelium and the inflammatory response within vascular endothelium. *H. pylori*: *Helicobacter pylori*; LDL: Low density lipoproteins; LPS: Lipopolysaccharide; PRR: Pattern recognition receptor; PAMPs: Pathogen associated molecular patterns; DAMPs: Damage associated molecular patterns.

pylori antibodies in the sera of CHD cases[84]. Following this pioneer finding, some authors made confirmed this association in several serological studies[85-88]. Searching for that connection other groups concentrated on the evaluation of bacteriological, biochemical, inflammatory and epidemiological parameters related with CHD and *H. pylori* infection (Table 1). The *H. pylori* seropositivity in CHD group varied from 40% up to 90%. Several studies also supported the association between CagA$^+$ *H. pylori* infection and CHD prevalence. This relation is probably based on the increased levels of trombin - Factor Ⅶ and the prothrombin subunits: F1 + 2 or through the stimulation of low-grade persistent inflammatory response in CHD cases infected with *H. pylori* CagA$^+$ strains[88-92]. However several authors obtained contrary data[93,94]. The findings coming from other studies showed no increase in the production of anti-*H. pylori* antibodies in CHD patients.

Thus, still there is no consensus on the role of *H. pylori* infections in either causation or progression of CHD[95-98]. Possible reasons of these controversies may result from differences in: (1) magnitude of the study groups; (2) exclusion/inclusion criteria used in study groups selection; (3) the usage of serological tests for the *H. pylori* diagnostics; and (4) approaches for data analysis and statistical tests or insufficient knowledge on possible mechanisms involved. However, a new approach suggesting a role of gut microbiota in the development of chronic diseases prompts to continue the research[32]. Particularly stimulating are the results of research conducted in ethnic groups with low incidence of classic risk factors for CHD, and high prevalence of *H. pylori* infection. Recently published data[99] showed that high levels of anti-*H. pylori* IgG were significantly associated with the increased risk for CHD in a group of Central Africans. After adjusting with classic risk factors of CHD, *H. pylori* infection was found to be the only independent predictor of carotid plaque and stroke incidence in this group. Also Sealy-Jefferson *et al*[100] (2013) showed that the exposure to *H. pylori* in Mexican Americans may constitute a risk factor for stroke. Taking into consideration the increased prevalence of *H. pylori* in this population, the infection itself may contribute to the ethnic differences in stroke risk. It has also been suggested that *H. pylori* seroprevalence may influence long term prognosis for patients with unstable angina[101,102]. This finding is supported by several studies where genomic material (16S rRNA) of *H. pylori* was identified in the coronary

Table 1 Major results of the clinical and basic research studies on the relationship between coronary heart disease and *Helicobacter pylori* infection

Study characteristic	Ref.
Serological parameters	
Higher prevalence and concentrations of anti-*H. pylori* antibodies in CHD *vs* non-CHD individuals	[84-88]
Association between *H. pylori* CagA positive infections and CHD; exposure of endothelial and smooth muscle components within atherosclerotic plaques to the anti-CagA antibodies	[88-92]
Autoimmunity hypothesis: the presence of the immune complexes $Le^{X/Y}$-anti-$Le^{X/Y}$ IgG in CHD patients infected with *H. pylori*	[47,127,134]
Bacteriological parameters	
Detection of *H. pylori* genomic material (16S rRNA) in the coronary arteries and atheromatous plaques from patients with cardiologic disorders	[43,91,103-105]
Presence of viable *H. pylori* bacteria in atherogenic plaques	[106]
Biochemical parameters	
Association of *H. pylori* infection with the increased biochemical and inflammatory parameters of CHD as well as coronary lumen reduction	[85,92,107-109]
Higher prevalence of LDL-hiperchlesterolemia, HDL-hypocholesterolemia and elevated levels of CRP in *H. pylori* infected than uninfected individuals	[110,127-129]
Lower activity of serum paraxonase-1 (a major anti-atherogenous component of HDL) and higher carotid-intima media thickness (one of the surrogate marker of atherosclerosis) in *H. pylori* positive in comparison to negative subjects	[108]
Positive correlation between raised LBP levels and the severity of CHD with co-existing *H. pylori* infection. The escalation of inflammatory process occurring *via* Toll-like receptors and LPS-LDL complexes	[127]
Increased levels of homocysteine in *H. pylori* infected individuals caused by malabsorption of vitamine B12 and foliate from diet, leading to obesity-related resistance to insulin	[48,130,131]
Inflammation and inflammation-related parameters	
Increased concentrations of IL-6, IL-8, TNF-α, plasminogen, activator inhibitor type-1, and von Willebrand factor in CHD patients infected with *H. pylori*	[3,38,69,83]
High levels of fibrinogen, a marker of systemic inflammation – putative link between *H. pylori* infections and pathophysiology of CHD	[133]
Recruitment of immune cells to the infectious foci and survival of *H. pylori* within the endothelium due to interaction of *H. pylori* LPS Le determinants with E- and L-selectins	[38,136]
Stimulation of Th1 lymphocytes to produce cytokines by *H. pylori* HspB	[47, 127,134]
Epidemiological studies	
Higher risk of CHD in ethnic groups of Central Africans and Mexican Americans with increased prevalence of *H. pylori* infections	[100-102]
Genetic susceptibility to infections and predisposition to strong inflammatory response	[140,145-146]

CagA: Cytotoxin-associated gene A; CHD: Coronary heart disease; CRP: C-reactive protein; Ig: Immunoglobulines; HDL: High density lipoprotein; Hsp: Heat shock protein; LBP: Lipopolysaccharide binding protein; IL: Interleukin; LDL: Low density lipoprotein; Le: Lewis; TNF: Tumor necrosis factor.

arteries and atheromatous plaques from patients with cardiologic disorders including myocardial infarction and coronary artery disease - suggesting the direct involvement of *H. pylori* in CHD pathogenesis[43,91,103-105]. Some authors postulate the presence of viable *H. pylori* in atherogenic plaques supporting their results by the culture of bacteria on solid media[106].

Inflammatory markers

It has been epidemiologically reported that *H. pylori* infections are associated with the changes in biochemical and inflammatory parameters as well as coronary lumen reduction[85,92,107-109]. In both *H. pylori* infected and CHD patients local inflammation occurring in gastric mucosa or in blood vessels, respectively turns into a chronic phase, which leads to a constitute presence of an inflammation-inducing agents. Increased concentrations of systemic inflammatory markers, both in patients with atherosclerosis and *H. pylori* infected individuals are usually considered a symptom or a result of a local inflammation. However, it has been claimed that systemic inflammation might be a cause and not a result of a local inflammatory reaction within atherosclerotic lesions[110]. Inflammation occurring in both, CHD and *H. pylori* infected individuals is determined by innate immune mechanisms with a participation of cell receptors called "alarmins". They recognize conservative structures of infectious agents - pathogen associated molecular patterns (PAMPs) as well as host endogenous ligands - damage associated molecular patterns (DAMPs) appearing on MØ, dendritic cells (DC) and natural killer (NK) cells, as well as on epithelial and endothelial cells. It is supposed that the activation of immune or epithelial cells *via* pattern recognition receptors (PRRs) may be a reason for subacute inflammation in chronic diseases including CHD[11,69,111,112]. Local inflammation results with increased cytokine levels including IL–6 and TNF-α. Both stimulate the liver to produce acute phase proteins such as CRP, lipopolysaccharide binding protein (LBP) and MMP including MMP-9. Since, acute phase proteins are ligands for PRRs, they enhance the primary inflammation. However, chronic *H. pylori* infection leads to an excessive activation of inflammatory cells and a release of active radicals into the environment. This, due to oxidative stress, leads to tissue damage and apoptosis, therefore providing endogenous DAPMs such as heat shock protein (Hsp) 70, galectin-1, IL-1α, IL-33, mitochondrial damage motifs (mtDNA) and high mobility group box1 protein. Their probable role is a maintenance of inflammation, stimulation of tissue healing within the gastric ulcer

niche, or removing damaged cells from the ischaemic niche, in the vascular endothelium. Mitochondrial DAMPs may increase endothelial permeability through neutrophil dependent and independent pathways[113]. Also specific microRNA expression is associated with the inflammatory response to damaged cells with possible deleterious implications[114]. Prolonged exposure to PAMPs and DAMPs is an apparent reason for a transformation of a local inflammation into a chronic form. The damage of vascular endothelium results in an increased production of reactive oxygen species and inactivation of nitric oxide, which has an anti-atherosclerotic properties. These changes lead to the activation of nuclear transcription factor NF-κB and result with a transformation of endothelium to a proinflammatory phenotype characterized by an increased expression of adhesins and chemokines, including MCP-1 and IL-8, with chemotactic activity towards inflammatory cells[1,14,22]. Proinflammatory phenotype of vascular endothelium exhibits an increased expression of PRR receptors including Toll-like receptors *e.g.*, TLR4, CD14 and TLR2 recognizing bacterial LPS. The enhanced expression of these receptors also occurs on MØ accumulated in the atherosclerotic plaques[6,115,116].

Signaling pathways involving PRR receptors

In recent considerations recognizing CHD as an inflammatory disease, much attention has been paid to the role of signaling pathways involving PRR receptors present on MØ, DC and NK cells as well as endothelial and smooth muscle cells. There are different classes of PRR, including scavenger receptors, and the TLRs. Their role in the pathogenesis of CHD is still unclear and the results obtained in this issue vary greatly[112,117]. Toll-like receptors have been identified as molecules belonging to primary innate immunity. The studies on TLR4 and TLR2 knockout mice confirmed pro-atherogenous effect of TLR4/TLR2 signaling induction[118,119]. Although the expression of TLR2 and TLR4 on endothelial cells in normal arteries is rather low, it was found to be increased in the endothelium from atherosclerosis lesions[112]. Certain studies made an attempt to find a link between the susceptibility to CHD and TLR polymorphisms. Two single nucleotide polymorphisms of TLR4 - Asp299Gly and Thr399Ile were suspected to impair TLR signaling in response to LPS, in carriers of these alleles. It was suggested that both alleles were associated with the protection from carotid artery atherogenesis and the reduction of myocardial infarction risk up to 30%, in carriers of the Asp299Gly polymorphism[112,116,120]. Several TLR types: 1, 2, 4 and 5 are expressed in atherosclerotic plaques by resident cells and leukocytes that migrate into the arterial wall. The upregulation of TLR4 on MØ induced by proatherogenic oxidized LDL suggests that TLRs may provide a potential pathophysiological link between lipids, infection, inflammation and atherosclerosis[115]. The oxidized lipids may also serve as endogenous ligands of TLR2 and TLR4[121]. The study by Talreja *et al*[122] (2004) showed that mast cell-derived histamine up-regulates TLR4 and TLR2 expression on the host cells and by this enhances their sensitivity to cell wall components of Gram-positive and Gram-negative bacteria[122] - with Hsp and LPS considered as potential mediators linking bacterial infections with atherosclerosis. Moreover, it was shown that standard *E. coli* LPS induces the overexpression of TLR4, NF-κB, ICAM-1, VCAM-1 and the endothelial growth factor (VEGF), as well as the production of nitric oxide and IL-8[14,123].

The escalation of inflammatory process occurring in atherosclerosis does not exclude the participation of *H. pylori* LPS, which has low endotoxic activity, however, its proinflammatory potential is preserved. It stimulates MØ to secrete TNF-α, that inhibits lipoprotein lipase activity. This implies an increase in triglycerides and lower HDL cholesterol levels[124]. The recognition of *H. pylori* LPS by the immune cells and its interaction with vascular endothelium are not well understood. In the context of the correlation between the CHD incidence and *H. pylori* infection the interactions of LPS with TLR4 and TLR2 are taken into consideration, especially in regard to the variability of Le determinants in *H. pylori* LPS. It has been shown that *H. pylori* LPS without Le determinants (Le^{X-Y-}) stimulates monocytes to produce lower concentrations of IL-8 and TNF-α than the LPS of Le^{X+Y+} type. Cytokine production induced by the latter type was inhibited by anti–CD14 and anti–LBP antibodies which confirms the involvement of both Le determinants and lipid A in those interactions[78].

H. pylori LPS exhibits weaker activity than the LPS of *E. coli* and express antagonistic properties towards TLR4. Current data do not rule out a role of TLR2 in the signaling induced by LPS of non-enterobacterial origin and its cooperation with TLR4[36]. It was shown that low stimulation of the TLR4 signaling by bacterial LPS may induce the expression of TLR2 in endothelial cells, probably *via* NADPH oxidase released by neutrophils[125]. Chronic *H. pylori* infection favors the formation of LPS-LDL complexes, directly or with the involvement of LBP. Such complexes, when deposited in the vascular endothelium, may enhance proinflammatory atherosclerotic processes[126]. It was shown that the presence of LBP is required for the LPS-dependent activation of intracellular TLR4 in endothelial cells. LBP acts as a catalyst of this process by the translocation of serum sCD14-LPS complexes into the cells[111]. In this context, the positive correlation between raised LBP and the severity of CHD with co-existing *H. pylori* infection seems to be of great importance[127]. It is also possible that *H. pylori* LPS contributes to CHD due to its anti-phagocytic, anti-cytotoxic and anti-proliferative properties, towards phagocytes, NK cells and lymphocytes respectively[68-70].

The expression of TLR4 and TLR2 is intensified in the inflamed endothelium. Recent data indicate that

the binding of *E. coli* LPS with TLR4 may increase the permeability of the vascular epithelium[36]. Any kind of endothelial dysfunction, including a reduction of cell integrity may result in inflammatory cascade. The involvement of TLRs in the development of atherosclerosis is associated with the ability of those receptors to bind ox-LDL, which initiate atherogenesis. Binding of such complexes induces a cascade of signals that activate the transcription factor NF-κB and results in the upregulation of inflammasome components such as cytokines and acute phase proteins[14]. In the context of atherosclerosis the key NF-κB-dependent proteins include inflammatory cytokines: IL-1β and TNF-α, chemokines: IL-8, MCP-1 and MMPs hydrolyzing the extracellular matrix[1]. The role of IL–1β in the development of CHD is associated with the stimulation of endothelial cells to produce IL–6, fibrinogen, CRP and adhesins resulting in a activation of signal cascade leading to the destabilization of atherosclerotic plaques[8].

Acute phase response, lipid metabolism, homocysteine and fibrinogen related mechanisms

Significant association of *H. pylori* infection with LDL-hipercholesterolemia, HDL-hypocholesterolemia and elevated levels of CRP was found. This indicates a possible impact of chronic infection on a lipid metabolism, which is associated with the increased CHD risk[110,128,129]. It was also noted that seropositive patients with unstable angina develop diabetes more frequently than seronegative individuals. *H. pylori* infection increases obesity-related resistance to insulin causing malabsorption of vitamin B12 and foliate from diet, ultimately leading to an increase in circulating homocysteine levels[48,130,131]. Since raised homocysteine may disturb the function of vascular endothelium it might be implicated in the coronary slow flow phenomenon. However, there are also suggestions that homocysteine is a marker rather than a cause of CHD[132]. In *H. pylori* positive subjects the activity of serum paraoxonase-1 (a major anti-atherogenous component of HDL) was lower while carotid-intima media thickness (one of the surrogate marker of atherosclerosis) was higher[108]. The sera of *H. pylori* infected subjects contain increased concentrations of inflammatory cytokines, particularly IL-6, IL-8 and TNF-α, plasminogen, activator inhibitor type-1, and von Willebrand factor - a sensitive indicator of atherosclerosis and a predictive factor of acute coronary syndrome[133]. Certain studies also showed that high levels of fibrinogen, a marker of systemic inflammation can constitute a probable link between *H. pylori* infections and CHD pathophysiology[47]. The putative mechanism of this association might involve *H. pylori*-driven stimulation of mononuclear cells to produce a tissue-factor-like pro-coagulant that, converts fibrinogen to fibrin though the extrinsic blood coagulation pathway. Fibrinogen also stimulates macrophage chemokine secretion through TLR4, promoting immune surveillance at sites of inflammation[134]. However, there are also contradictory results and hypotheses that the occurrence of CHD is positively associated with age and lower social class[135]. It would be of great importance to check, whether *H. pylori* eradication is associated with the decrease in the level of the above markers and lower CHD incidence. To date, anti-*H. pylori* eradication therapy confirmed only some suggestions. Mean coronary artery lumen loss in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) with stent and anti-*H. pylori* eradication therapy was significantly smaller compared to PTCA and placebo treated group. Similarly, cytokines such as TNF-α, IL-1β and IL-8 were significantly lower in plasma of PTCA patients after *H. pylori* eradication, while there were no changes in plasma lipids, homocysteine and clotting factors[85].

Autoimmunity hypothesis

Bacterial pathogens, including *H. pylori* might contribute to CHD pathogenesis. This approach is supported by the fact that CHD is starting to be considered as an autoimmune inflammatory process. The antigenic structures of infectious agents can induce the expansion of potentially autoreactive T and B cells, or B cells producing antibodies cross-reacting with host tissues. This phenomenon is defined as antigenic mimicry. For instance *H. pylori* HspB (60 kDa) might be implicated in CHD pathogenesis *via* stimulation of Th1 lymphocytes to secrete IFN-γ and IL-12 or activation of MØ to express metalloproteinases and adhesins[38]. Antigenic mimicry as a cause of inflammation in CHD is also related to Le determinants. In human tissues Le antigens serve as ligands for endothelial (E and P–selectin) and leukocytes (L–selectin) adhesins. This interaction drives cell migration into the inflammatory milieu and plays an important role in the accumulation of immune cells in peripheral lymph nodes. It was shown that *H. pylori* bearing Le antigens in their LPSs are able to bind E- and L-selectins. This linkage enables the recruitment of immune cells to the infectious foci and may promote survival of *H. pylori* within the endothelium[136]. The activity of *H. pylori* LPS is also manifested by the activation of monocytes, MØ and secretion of proinflammatory cytokines: IL-1, IL-6 and IL-8[69]. *H. pylori* strains bearing Le^X or Le^A attract circulating lymphocytes that express L–selectin. It was shown that *H. pylori* expressing Le determinants induce higher colonization rates and more excessive infiltration of gastric mucosa with neutrophils and lymphocytes - a phenomenon also observed in individuals infected with *H. pylori* expressing Le^X determinants[137]. Due to the ongoing inflammation the endothelial and smooth muscle components within atherosclerotic plaque might be revealed and exposed to the anti-CagA antibodies. The formation of such immune complexes facilitates the risk for further damage of the endothelium caused by lytic complex of complement proteins[46].

INDIVIDUAL SUSCEPTIBILITY TO INFECTION AND INFLAMMATION IN RESPECT TO THE DEVELOPMENT OF CHD

The risk for cardiovascular diseases might also be considered on the genetic level-determining the susceptibility to CHD development related to inflammatory process[138]. For example, one of the explanations for elevated levels of CRP in CHD patients might lay in chronic, bacterial or viral infection. However, since viral as well *H. pylori* and *Ch. pneumoniae* infections, are very common, it is believed that an individual susceptibility to infections and accompanying inflammation could explain the role of infectious agents in the course of CHD. This individual predisposition to persistent infections and chronic inflammatory response can be determined, to some extent, by the Le antigens, receptors for PAMPs and proinflammatory cytokines. It is believed that Lewis antigens can play a key role in shaping the individual susceptibility to CHD development: by directing the adverse effects of infection and excessive inflammatory response[41]. There are also clear examples of protection against infectious diseases (particularly to *H. pylori*, norovirus, and *Vibrio cholerae*) based on polymorphisms in genes encoding and regulating the expression of ABH blood group and Lewis antigens[139]. There are two types of Lewis antigens in humans: Le a and Le b. Their expression depend on genes located on chromosome 1 encoding fucosyltransferases: *FUT2* and *FUT3*. Depending on the genotype, and thus the expression of one or both Le antigens, in the Caucasian population, there are three dominating phenotypes: Le^{a+b-}, Le^{a-b+}, Le^{a-b-}, and Le^{a+b+} which occurs very rarely. Le antigens expressed on cell surface and released in body fluids are associated with the susceptibility to infections especially related to the mucus layer, such as those caused by *H. pylori*[140]. It is assumed that Le antigens promote adhesion-dependent infections[141]. There are speculations on the link between the Le^{a-b-} phenotype and several disorders constituting a risk factors for CHD development, with examples such as insulin resistant diabetes, elevated levels of clotting factor VIII and von Willebrand factor. This phenotype is considered a genetic marker for the risk for CHD development[142,143]. It is also believed that the polymorphism in *FUT3* associated with the presence of point mutations 59T > G, 202T > C, 314 C > T, 1067 T > A, may determine the individual susceptibility to infections and the development of atherosclerotic lesions and strong inflammatory response[144].

The polymorphism of inflammation-related genes, may indirectly contribute to the development of CHD, and the dynamics of the disease. Such a possibility appears especially when the mutations accumulate in several genes related with inflammatory response. Thus, while searching for the relationship between *H. pylori* infections and their role in the development of CHD, mutations in the genes encoding TLR4/CD14 receptors (binding LPS), and IL–1β should be taken into consideration[145]. IL-1β acts as a stimulating mediator of IL-6, fibrinogen, CRP or adhesive molecules expression by endothelial cells within a cascade leading to the development and destabilization of the atherosclerotic plaques. In regard to IL-1β the most frequently considered gene mutations are: -511C > T and -31C > T[145,146]. It was showed that carriers of the two relatively frequent variants of *IL-1β* gene at -31 and -511 positions, *i.e.*, -31 TT and -511 CC, are at a higher risk of developing CHD requiring surgical treatment or two-stage percutaneous angioplasty. In patients prone to the development of atherosclerosis, polymorphism of *IL-1β* gene cluster may be associated with the extent and dynamics of lesions in the coronary arteries[146]. For gene encoding TLR4: Asp299Gly and Thr399Ile and for *CD14* gene: 159C > T mutations are considered to play a role in CHD and chronic infections[112,116]. Patients carrying Asp299Gly, a common variant of the *TLR4* gene presented reduced prevalence of angiographic artery disease and low levels of CRP. This common variant of the TLR4 gene, probably attenuates receptor signalling and diminishes inflammatory response to Gram-negative pathogens[147].

Since neither infection nor the activation of TLR4/TLR2 is sufficient to induce atherosclerosis in animal models[148], it is rather unlikely that microbes and/or TLRs signaling play a causative role in this disease. Instead, it is thought that they may be important as associates of silent disease. For instance, microbial components such as LPS or lipoteichoic acid released during acute infection or exacerbation of chronic infection might activate plaque cells. It has been suggested that such local "echos" of infections could lead to increased local production of cytokines and initiate plaque activation and rupture. The expression of TLRs in plaques suggests a pathway through which such an echo effect could occur[6]. Because *H. pylori* infection is located in the stomach, the question arises why the possible inflammation should only be transferred to the heart blood vessels and not to other vessels of the body? Various activities of the immune cells are mediated by endothelial cells, which form specialized microcirculatory networks used by the immune cells under both physiological and pathological circumstances. Endothelial cells represent a highly heterogenous population of cells with the ability to interact with and modulate the function of immune cells[149]. Atherosclerotic lesions occur at distinct sites within the arterial tree, such as branches, bifurcations, and curvatures, where they cause characteristic alterations in the blood flow, including decreased shear stress and increased turbulence. The nature of the flow appears to determine whether lesions occur at these vascular sites. The low-shear hypothesis of

atherosclerosis has been validated[150]. Decreasing shear stress at branches, bifurcations, and curvatures results in endothelial activation, adhesion molecule expression, and greater monocyte transmigration. It has been shown that atherosclerotic lesions appear first at lesion-prone sites, where activated endothelium expresses specific molecules, which favors the recruitment of monocytes and T cells. For instance, it has been hypothesized that the regiospecitifity of atherosclerotic lesions might be determined by the lower expression of TLR2 molecules[111]. The localization of atherosclerotic lesions could be also related to the local overexpression of NF-κB/IκB pathways[14].

FUTURE RESEARCH PERSPECTIVES

To describe the role of *H. pylori* in the initiation, acceleration or the development of CHD a few fundamental questions need to be addressed. It needs to be elucidated, whether viable *H. pylori* or bacterial compounds are able to break the single layer of epithelial cells and have unimpeded access to the systemic circulation. Also, it is not clear, whether classic risk factors such as hypercholesterolemia may act synergistically with *H. pylori* or their compounds to destabilize or disrupt gastric epithelial barrier function. It is also interesting whether CHD as systemic disease can lead independently to the disruption of gastric epithelial barrier function. The use of well-defined cell lines which mimic the *in vivo* conditions and exclude the naturally occurring phenotypic variations or the influence of external agents will enable to clarify the relationship between *H. pylori* as effective colonizer of gastric mucosa and inflammatory response. Methodology of culturing the cells using trans-well systems can help to examine whether *H. pylori* antigens alone or in combination with classic CHD risk factors interfere with the integrity of gastric epithelial and endothelial cells, cytotoxicity, the cell cycle, chemokines as well as cytokines and cell signaling. Microfluidic culture systems enable to explain if *H. pylori* compounds might be delivered to the inflammatory sites within vascular endothelium and interact with both endothelial and the immune cells[151].

Since, *H. pylori* infection has been defined as class I gastric carcinogen and many epidemiological studies demonstrated positive correlation between serum lipids and the risk of gastrointestinal malignancies, it is tempting to evaluate the prevalence of malignancies in CHD patients infected with *H. pylori*. Although it has been shown that *H. pylori* infection is related with increased LDL level, the association between abnormal concentrations of serum lipid components, the infection with *H. pylori* and the risk of gastrointestinal cancer is unknown[152].

CHD patients are recommended for antitrombocythic therapy with aspirin, which can be beneficial to individuals who already have experienced a heart attack, stroke, angina or peripheral vascular disease, or have had certain procedures such as angiography or bypass. However, aspirin can be prescribed to prevent heart disease and stroke in same individuals who have not previously experienced these events. The United States Preventive Services Task Force recommends that men with no history of heart disease or stroke aged 45-79 years should use aspirin to prevent myocardial infractions and that woman with no history of heart disease or stroke aged 55-79 should use aspirin to prevent stroke[153]. On the other hand, NSAIDs such as aspirin is positively correlated with the incidence of gastrointestinal tract disorders. Such damage can take a form of mucosal erosions or ulcers. NSAIDs can stimulate leukocytes, particularly neutrophils, such that they adhere to the vascular endothelium within the gastrointestinal microcirculation. Moreover NSAIDs impair the rapid restitution that occurs through cell migration following damage to the superficial epithelium of the stomach, reduce rates of epithelial turnover and thus impair the healing process. It is necessary to elucidate, whether ulcers are more likely to develop in long-term NSAIDs users who have mucosal erosions or in individuals infected with *H. pylori*, or both – and what is the role of NSAIDs on the course of CHD and *H. pylori*-related pathologies[153,154].

Proinflammatory agents released directly due to damage induced by *H. pylori* or indirectly by neutrophils recruited to the site of infection break the epithelial barrier. An initial effect of *H. pylori* infection is amplified significantly and impairs the proper action of cellular barrier. The question is whether inflammatory mediators generated in the stomach can reach and harm distant tissues, leading to systemic disorders related with CHD.

Tissue inflammation, cell injury or death result in the release of molecules that are endogenous PRR ligands. DAMPs stimulates cells to produce acute phase cytokines and activates other inflammatory compounds. Depending on the affected tissue, various stromal cells, including epithelial and endothelial cells, may function as sentinels for detection of DAMPs, which felicitate neutrophil recruitment. It was hypothesized that IL-33 may have protective effects during atherosclerosis by inducing a Th1-to-Th2 switch of immune responses[19]. However, many questions regarding the role of specific DAMPs during *H. pylori* infections and cardiovascular diseases remain to be solved.

Since initial moment of *H. pylori* infection is almost impossible to identify, little is known about the natural history and kinetics of infection and immune responses. There is an urgent need to establish and optimize the animal model mimicking human immune system, sensitive for *H. pylori* infection and CHD development. Immunologic similarities between guinea pigs and humans in regard to: leukocyte antigens, complement system, antigen presenting molecules, patterns of IFN-γ, IL-8, IL-12 release, as well as their receptors

suggest that this animal model may be suitable for studies on the relation between *H. pylori* infection and the development of its extragastric consequences. Antigen-specific lymphocyte proliferation has been found a suitable marker of immune response in guinea pigs with sustained *H. pylori* infection. Recently guinea pigs were successfully used to show the role of endotoxemia in the myocardial injury and sepsis-associated dysfunction[42,72,155].

It is believed that an individual susceptibility to infections and accompanying inflammation could help to explain the role of infectious agents in the course of CHD. Using the samples from patients with clinically confirmed CHD infected or not with *H. pylori* in comparison with control group it is necessary to look for cellular and molecular markers which may determine an individual susceptibility to chronic infections and extensive inflammation, predisposing to CHD.

These cellular and molecular studies would help to understand the role of *H. pylori* infections in the pathogenesis of CHD. Describing the background of *H. pylori* - driven proinflammatory mechanisms directed towards epithelial and possibly endothelial barrier, would help to allocate their role in the process of atherogenesis. In case of proven causative role of this bacterium in the pathogenesis of CHD, its eradication will be important for diminishing one of CHD infectious risk factors.

CONCLUSION

CHD, one of the most severe chronic diseases of the coronary vessels is a multifactorial disorder. Since classic risk factors do not explain all cases of CHD it has been suggested that chronic infections and even commensal microorganisms may affect the development or maintenance of CHD. Among various pathogens possibly involved in atherogenesis *H. pylori* is particularly interesting, since it induces chronic long-term infection within gastric epithelium which leads to not only local but systemic inflammation. Recent knowledge on the pathogenesis of atherosclerosis together with current findings in the field of *H. pylori* related diseases constitute the background for the newly proposed hypothesis that those two processes may be related.

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MINIREVIEWS

Autonomic and endocrine control of cardiovascular function

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Abstract

The function of the heart is to contract and pump oxygenated blood to the body and deoxygenated blood to the lungs. To achieve this goal, a normal human heart must beat regularly and continuously for one's entire life. Heartbeats originate from the rhythmic pacing discharge from the sinoatrial (SA) node within the heart itself. In the absence of extrinsic neural or hormonal influences, the SA node pacing rate would be about 100 beats per minute. Heart rate and cardiac output, however, must vary in response to the needs of the body's cells for oxygen and nutrients under varying conditions. In order to respond rapidly to the changing requirements of the body's tissues, the heart rate and contractility are regulated by the nervous system, hormones, and other factors. Here we review how the cardiovascular system is controlled and influenced by not only a unique intrinsic system, but is also heavily influenced by the autonomic nervous system as well as the endocrine system.

Key words: Heart; Cardiovascular function; Autonomic nervous system; Endocrine system; Regulation

Core tip: The function of the heart is to contract and pump oxygenated blood to the body and deoxygenated blood to the lungs. To achieve this goal, a normal human heart must contract regularly and continuously, and respond to the changing requirements of the body's tissues. Here we review how the cardiovascular system is controlled and influenced by not only a unique intrinsic system, but is also heavily influenced by the autonomic nervous system as well as the endocrine system.

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INTRODUCTION

The cardiovascular system is a closed system connecting a pump to blood vessels (*i.e.*, arteries, capillaries, veins). The heart serves as the pump that moves blood through blood vessels thereby providing the needed oxygen and nutrients to the body. The

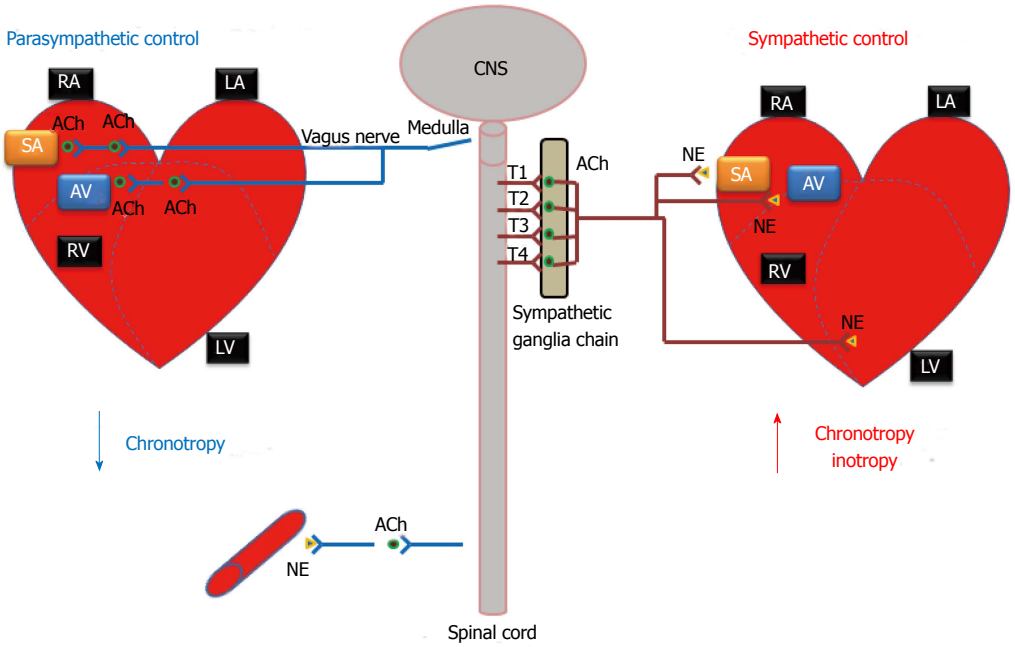

Figure 1 Autonomic nervous system regulation of the heart function. The autonomic nervous system affects the rate and force of heart contractions. CNS: Central nervous system; RA: Right atria; LA: Left atria; RV: Right ventricle; LV: Left ventricle; SA: Sino-atrial node; AV: Atrioventricular node; NE: Norepinephrine; ACh: Acetylcholine.

heart consists of four chambers: right atrium, right ventricle, left atrium and left ventricle. The right atrium receives oxygen-poor blood from the systemic veins; this blood then moves across the tricuspid valve to the right ventricle. From the right ventricle the de-oxygenated blood is pumped pass semilunar valves out through the pulmonary arteries to the lungs. In the lungs, the blood becomes oxygenated and returns to the left atrium *via* the pulmonary veins. This oxygen-rich blood next moves across the mitral valve to the left ventricle and is pumped out across semilunar valves to the systemic arteries and to body tissues. To achieve this goal, a normal human heart must beat regularly and continuously for one's entire life. Autorhythmic cardiac cells initiate and distribute impulses (action potentials) throughout the heart. The intrinsic conduction system coordinates heart electrical activity. This electrical activity in the heart corresponds to electrocardiogram (ECG) wave tracings. On a normal ECG recording, the P wave reflects atrial depolarization followed by atrial contraction. The QRS wave reflects ventricular depolarization followed by ventricular contraction and the T wave reflects ventricular repolarization and ventricular relaxation.

In the intrinsic conduction system, heartbeats originate from the rhythmic pacing discharge from the sinoatrial node (SA node) within the heart itself. The SA node, located in the right atrium, is a part of the intrinsic conduction (or nervous) system found in the heart. This conduction system in order of rate of depolarization starts with the SA node or pacemaker and results in atrial depolarization and atrial contraction, the internodal pathway, the AV node (where the impulse is delayed), AV bundle, the left and right branches of the bundle of His and lastly the Purkinje fibers, both of which result in ventricular depolarization and contraction. All of the components of the intrinsic conduction system contain autorhythmic cells that spontaneously depolarize. In the absence of extrinsic neural or hormonal influences, the SA node pacing rate would be about 100 beats per minute (bpm). The heart rate and cardiac output, however, must vary in response to the needs of the body's cells for oxygen and nutrients under varying conditions. In order to respond rapidly to changing requirements of the body's tissues, the heart rate and contractility are regulated by the autonomic nervous system, hormones, and other factors.

AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system (ANS) is the component of the peripheral nervous system that controls cardiac muscle contraction, visceral activities, and glandular functions of the body. Specifically the ANS can regulate heart rate, blood pressure, rate of respiration, body temperature, sweating, gastrointestinal motility and secretion, as well as other visceral activities that maintain homeostasis[1-4]. The ANS functions continuously without conscious effort. The ANS, however, is controlled by centers located in the spinal cord, brain stem, and hypothalamus.

The ANS has two interacting systems: the sympathetic and parasympathetic systems. As illustrated in Figure 1, sympathetic and parasympathetic neurons exert antagonistic effects on the heart. The sympathetic

system prepares the body for energy expenditure, emergency or stressful situations, *i.e.,* fight or flight. Conversely, the parasympathetic system is most active under restful conditions. The parasympathetic counteracts the sympathetic system after a stressful event and restores the body to a restful state. The sympathetic nervous system releases norepinephrine (NE) while the parasympathetic nervous system releases acetylcholine (ACh). Sympathetic stimulation increases heart rate and myocardial contractility. During exercise, emotional excitement, or under various pathological conditions (*e.g.,* heart failure)[5], the sympathetic nervous system is activated. The stimulation of the sympathetic nervous system causes pupil dilatation, bronchiole dilatation, blood vessel constriction, sweat secretion, inhibits peristalsis, increases renin secretion by the kidneys, as well as can induce reproductive organ contraction and secretion. In contrast, parasympathetic stimulation decreases heart rate and constricts the pupils. It also increases secretion of the eye glands, increases peristalsis, increases secretion of salivary and pancreatic glands, and constricts bronchioles. Most organs receive innervations from both systems, which usually exert opposing actions. However, this is not always the case. Some systems do not have a response to parasympathetic stimulation. For example, most blood vessels lack parasympathetic innervations and their diameter is regulated by sympathetic nervous system input, so that they have a constant state of sympathetic tone. It is a decrease in sympathetic stimulation or tone that allows vasodilatation. During rest, sleep, or emotional tranquility, the parasympathetic nervous system predominates and controls the heart rate at a resting rate of 60-75 bpm. At any given time, the effect of the ANS on the heart is the net balance between the opposing actions of the sympathetic and parasympathetic systems.

Unlike the somatic nervous system, where a single neuron originating in the spinal cord typically connects the central nervous system and a skeletal muscle *via* a neuromuscular junction, both sympathetic and parasympathetic pathways are composed of a two-neuron chain: a preganglionic neuron and a postganglionic neuron. The neurotransmitter between the preganglionic and postganglionic neurons is acetylcholine, the same as that in neuromuscular junctions. Messages from these systems are conveyed as electrical impulses that travel along axons and cross synaptic clefts (using chemical neurotransmitter).

In the sympathetic system (thoracolumbar division), these nerves originate from the thoracolumbar region of the spinal cord (T1-L2) and radiate out towards the target organs. In contrast, the nerves of the parasympathetic system originate within the midbrain, pons and medulla oblongata of the brain stem and part of these fibers originate in the sacral region (S2-S4 sacral spinal nerves) of the spinal cord. While sympathetic nerves utilize a short preganglionic neuron followed by a relatively long postganglionic neuron, parasympathetic nerves (*e.g.,* the vagus nerve, which carries about 75 percent of all parasympathetic fibers) have a much longer preganglionic neuron, followed by a short postganglionic neuron.

Cardiac sympathetic nervous system

The sympathetic nervous system is the component of the ANS that is responsible for controlling the human body's reaction to situations of stress or emergency (otherwise known as the "fight-or-flight" response), while the parasympathetic nervous system is generally responsible for basal organ system function.

Cardiac sympathetic preganglionic nerves (typically all myelinated) emerge from the upper thoracic segments of the spinal cord (T1-T4). After traveling a short distance, preganglionic fibers leave the spinal nerves through branches called white rami and enter sympathetic ganglia. The cardiac sympathetic neurons form the sympathetic chain ganglia located along the side of the viscera column (*i.e.,* paravertebral ganglia). These ganglia comprise the sympatheric trunks with their connecting fibers. The postganglionic fibers, extend to the viscera, such as the heart. In general, sympathetic preganglionic neurons are shorter than sympathetic postganglionic neurons (Figure 1).

Sympathetic neurotransmitters: Neurotransmitters are chemical substances released into the synaptic cleft from nerve terminals in response to action potentials. They transmit signals from a neuron to a target cell across a synapse, *e.g.,* acetylcholine for neuromuscular junctions. While the preganglionic neurons of both the sympathetic and parasympathetic system secret acetylcholine (ACh) which is why they are referred to as cholinergic, the majority of the postganglionic endings of the sympathetic nervous system release NE, which resembles epinephrine (*i.e.,* adrenalin). Thus, these sympathetic postganglionic fibers are commonly called adrenergic fibers.

Sympathetic receptors: There are two types of adrenergic receptors: β and α. In the cardiovascular system there are β_1, β_2, α_1, and α_2 adrenergic receptors (Table 1).

β_1 adrenergic receptors are expressed in the heart (in the SA node, AV node, and on atrial and ventricular cardiomyocytes). The activation of β_1 receptors increases heart rate (*via* the SA node), increases contractility as result of increased intracellular calcium concentrations and increased calcium release by the sarcoplasmic reticulum (SR), and increased AV node conduction velocity. Additionally, activation of this receptor also induces renin release by the kidneys to help maintain blood pressure, plasma sodium levels and blood volume.

β_2 adrenergic receptors are mainly expressed in vascular smooth muscle, skeletal muscle, and in

Table 1 Sympathetic and parasympathetic receptors and their functions in the heart and vessels

	Heart				Vessels	
	Receptor	Function			Receptor	Function
		Inotropy	Chronotropy	Dromotropy		
Norepinephrine	α_1	+	+	+	α_1	Vasoconstriction
	β_1	+	+	+	β_1	Vasoconstriction
	β_2	+	+	+	β_2	Vasodilation
Acetylcholine	M_2	-	-	-	M_2	Vasodilation

the coronary circulation. Their activation elicits vasodilatation, which, in turn increases blood perfusion to target organs (especially the liver, heart, and skeletal muscle). These receptors are not innervated and thus are primarily stimulated by circulating epinephrine. There are also some low expressions of β_2 receptors in cardiomyocytes.

α_1 adrenergic receptors are expressed in vascular smooth muscle proximal to sympathetic nerve terminals. Their activation elicits vasoconstriction. There are also some low expressions of α_1 receptors in cardiomyocytes.

α_2 adrenergic receptors are expressed in vascular smooth muscle distal from sympathetic nerve terminals. Their activation also elicits vasoconstriction.

Sympathetic nervous system control and heart function: Stimulation by the sympathetic nervous system results in the following effects on the heart (Table 1): Positive chronotropic effect (increase in heart rate): The sinoatrial (SA) node is the predominate pacemaker of the heart. It is located within the upper posterior wall of the right atrium, and is responsible for maintaining a sinus rhythm of between 60 and 100 beats per minute. This rate is constantly being affected by innervations from both the sympathetic and parasympathetic nervous systems. Stimulation by the sympathetic system nerves results in an increase of heart rate, as occurs during the "fight-or-flight" response.

Positive inotropic effect (increase of contractility): Myocardial contractility represents the ability of the heart to produce force during contraction. It is determined by the incremental degrees of binding between myosin (thick) and actin (thin) filaments, which in turn depends on the concentration of calcium ions (Ca^{2+}) in the cytosol of the cardiomyocyte. Stimulation by the sympathetic nervous system causes an elevation in intracellular (Ca^{2+}) and thus an increase in contraction of both the atria and ventricles.

Positive dromotropic effect (enhancement of conduction): Stimulation by the sympathetic nervous system also enhances the conductivity of the electrical signal. For example, it increases AV conduction velocity.

Parasympathetic nervous system

As previously mentioned, the parasympathetic nervous system is responsible for the unconscious regulation of the body's systems, most notably, salivation, lacrimation, urination, digestion, and defecation (acronym SLUDD). Importantly, the parasympathetic nervous system plays an antagonistic role in regulating heart function.

The parasympathetic system has preganglionic neurons (craniosacral division) that arise from neurons in the mid-brain, pons and medulla oblongata. The cell bodies of parasympathetic preganglionic neurons are located in the homologous motor nuclei of the cranial nerves. Parasympathetic preganglionic fibers associated with parts of the head are carried by the oculomotor, facial, and glossopharygeal nerves. The fibers that innervate organs of the thorax and upper abdomen are parts of the vagus nerve which as previously mentioned carries approximately 75% of all parasympathetic nerve fibers passing to the heart, the lungs, the stomach, and many other visceral organs. Preganglionic fibers arising from the sacral region of the spinal cord make up parts of S2-S4 sacral spinal nerves and carry impulses to viscera in the pelvic cavity. The short postganglionic neurons reside near effector organs, *e.g.,* lacrimal gland, salivary glands, heart, trachea, lung, liver, gallbladder, spleen, pancreas, intestines, kidney, and urinary bladder, *etc*. Unlike the sympathetic system, most parasympathetic preganglionic fibers reach the target organs and form the peripheral ganglia in the wall of the organ. The preganglionic fibers synapse within the ganglion, and then short postganglionic fibers leave the ganglia to the target organ. Thus, in the parasympathetic system, preganglionic neurons are generally longer than postganglionic neurons (Figure 1).

Parasympathetic neurotransmitters: Acetylcholine is the predominant neurotransmitter from the parasympathetic nervous system, in both the preganglionic and postganglionic neurons. Although excitatory in skeletal muscle by binding to nicotinic receptors and inducing the opening of ligand gated sodium channels, acetylcholine inhibits the contraction of cardiomyocytes by activating muscarinic receptors (M_2). These parasympathetic postganglionic fibers are commonly called cholinergic fibers because they secrete acetylcholine at their nerve endings.

Acetylcholine is synthesized by choline acetlytransferase in cholinergic neurons by combining choline and acetyl-COA molecules. Once assembled in synaptic vesicles near the end of the axon, the entry of calcium causes the vesicles to fuse with the membrane of the

neuron and to release acetylcholine into the synaptic cleft (the space between the neuron and post-synaptic membrane or effector cell). Acetylcholine diffuses across the synaptic cleft and binds to receptors on the post-synaptic membrane increasing the permeability to sodium causing depolarization of the membrane and propagation of the impulse. This chemical transmission is much slower than the electrical "all or none" transmission of the action potential seen in the intrinsic nervous system of the heart. To regulate the function of these neurons (and thus, the muscles they control), acetylcholinesterase is present in the synaptic cleft. It serves to hydrolyze the acetylcholine molecule by breaking it down into choline and acetate, which are then both taken back up by the neuron, to be again synthesized into acetylcholine.

Parasympathetic receptors: The parasympathetic postganglionic fibers are cholinergic. Acetylcholine can bind to two types of cholinergic receptors called nicotinic receptors and muscarinic receptors. Muscarinic receptors are located in the membranes of effector cells at the end of postganglionic parasympathetic nerves and at the ends of cholinergic sympathetic fibers. Responses from these receptors are excitatory and relatively slow. The nicotinic receptors are located at synapses between pre- and post-ganglionic neurons of the sympathetic and parasympathetic pathways. Nicotinic receptors in contrast to muscarinic receptors produce rapid, excitatory responses. Neuromuscular junctions found in skeletal muscle fibers are nicotinic.

In relation to the cardiovascular system the parasympathetic nervous system has two different kinds of muscarinic receptors: the M_2 and M_3 receptors (Table 1).

The M_2 receptors are expressed in the heart; abundant in nodal and atrial tissue, but sparse in the ventricles. The binding of acetylcholine to M_2 receptors serves to slow heart rate till it reaches normal sinus rhythm. This is achieved by slowing the rate of depolarization, as well as by reducing the conduction velocity through the atrioventricular node. Additionally, the activation of M_2 receptors reduces the contractility of atrial cardiomyocytes, thus reducing, in part, the overall cardiac output of the heart as a result of reduced atrial kick, smaller stroke volume, and slower heart rate. Cardiac output is determined by heart rate and stroke volume (CO = HR x SV).

The M_3 receptors are mainly expressed in vascular endothelium. The predominate effect of M_3 receptor activation is dilatation of the vessels, by stimulating nitric oxide production by vascular endothelial cells[6]. M_3 receptors impact afterload and vascular resistance which can again alter cardiac output and blood pressure.

Parasympathetic nervous system control and heart function: As mentioned earlier, parasympathetic activity produces effects that are, in general, opposite to those of sympathetic activation. However, in contrast to sympathetic activity, the parasympathetic nervous system has little effect on myocardial contractility.

Negative chronotropic effect (decrease in heart rate): The vagus nerve directly innervates the sinoatrial node; when activated, it serves to lower the heart rate, thus exhibiting a negative chronotropic effect.

Negative inotropic effect (decrease in myocardial contractility): Currently, it is a matter of debate whether parasympathetic stimulation can exhibit negative inotropic effects, as the vagus nerve does not directly innervate cardiomyocytes other than that of the sinoatrial and atrioventricular nodes, however, recent *in vivo* studies may suggest otherwise, at least in the atrium.

Negative dromotropic effect (decrease conduction velocity): Stimulation of the parasympathetic system serves to inhibit AV node conduction velocity.

Cellular signal transduction

Most sympathetic and parasympathetic receptors are known to be G protein-coupled receptors (GPCRs). In the heart, the G-protein-cAMP-PKA signaling pathway mediates the catecholaminergic control on heart rate and contractility.

Signaling pathway of sympathetic stimulation: The sympathetic stimulation-induced effects in the heart result from activation of β_1-adrenoceptors, which are GPCRs (Figure 2). The sympathetic neurotransmitter NE (as well as other catecholamines) bind to β_1 receptors and activate stimulatory G proteins (G_s) by causing a conformational change within the G_s, so that the disassociated α_s subunit can then bind to and activate adenylyl cyclase (AC). The activation of this enzyme then catalyzes the conversion of ATP into cyclic adenosine monophosphate (cAMP). This second messenger may then activate a myriad of other pathways, ion channels, transcription factors, or enzymes. With regards to the cardiovascular system, the most important enzyme that cAMP activates is protein kinase A (PKA). PKA, which in turn, phosphorylates multiple target proteins, such as L-type Ca channels (LTCC), the SR Ca handling protein phospholamban, and contractile machinery such as troponin C, I and T. Additionally, cAMP binds directly to ion channels responsible for the funny current (I_f), thus increasing the heart rate[7].

Signaling pathway of parasympathetic stimulation: The parasympathetic stimulation-induced effects in the heart result from activation of muscarinic (M_2) receptors, which are also GPCRs by acetylcholine (Figure 2). The parasympathetic neurotransmitter ACh binds to M_2 receptors thereby activating inhibitory G proteins (G_i) by causing a conformational change within the G_i subunit, so that the disassociated α_i

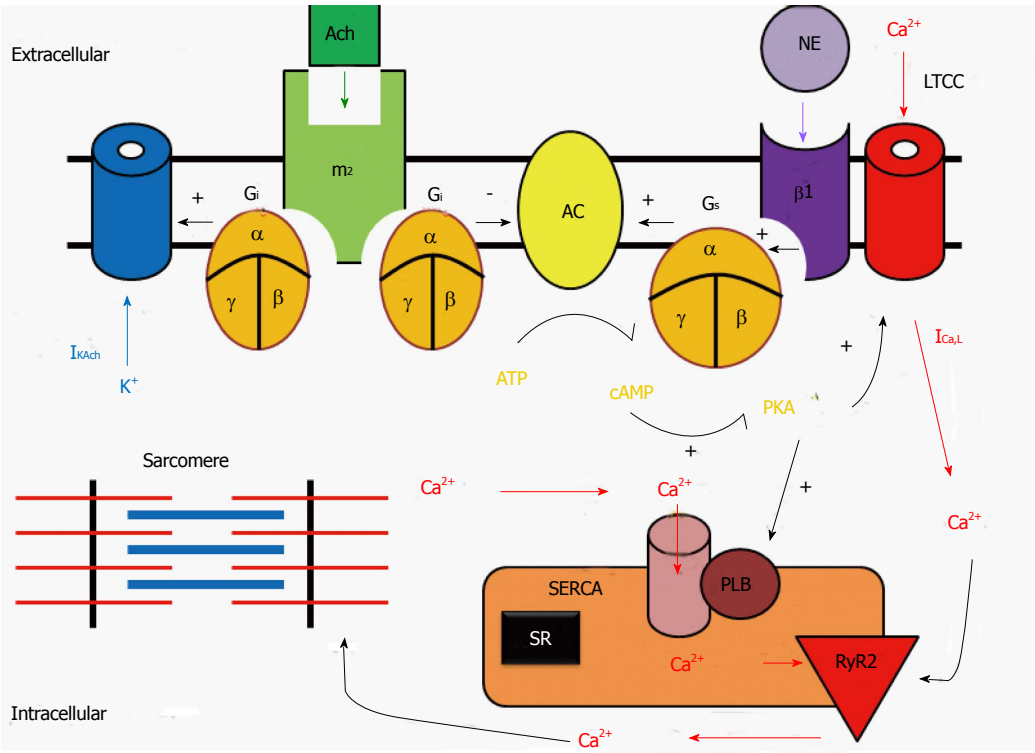

Figure 2 Signal transduction systems for β-adrenergic receptor and muscarinic-receptor stimulations in a cardiac myocyte. NE: Norepinephrine; β1: Beta1-adrenergic receptor; G_s: Stimulatory G-protein: Ach: Acetylcholine; m_2: Type-2 muscarinic receptors; G_i: Inhibitory G-protein; AC: Adenylate cyclase; PKA: Protein kinase A; $I_{Ca,L}$: L-type Ca channel; RyR2: Ryanodine receptor 2; SERCA: Sarcoplasmic reticulum Ca^{2+}-ATPase2a; PLB: Phospholamban.

subunit can then bind to and inhibits AC. Since M_2 receptors are negatively coupled to AC and thus reduce cAMP formation, M_2 receptors act to inhibit PKA activity and exert an opposite effect on ion channels, Ca^{2+} handling proteins, and contractile machinery, compared to sympathetic stimulation.

Autorhythmic cells: Regulation of pacemaking current and heart rate: The funny current (I_f) is thought to be the pace making current in the SA node. It is a non-selective cation channel that can inwardly conduct both sodium and potassium ions. As the membrane potential becomes increasingly hyperpolarized during phase 3 and 4 of the action potential, I_f increases inward potassium and sodium currents, which causes the phase 4 diastolic depolarization. I_f channels are activated by direct binding of cAMP[7].

In addition to the funny current, one of the other driving mechanisms behind the automaticity of the pacemaking cells within the SA node is the calcium clock[8]. As the SR fills with calcium, the probability of spontaneous calcium release increases; in contrast, when the SR calcium stores are depleted, the probability of spontaneous calcium release is reduced. Increased Ca^{2+} entry also increases automaticity because of the effect of $[Ca^{2+}]_i$ on the transient inward current carried by the sodium-calcium exchange current (I_{NCX}). When these pacemaking mechanisms depolarize the resting membrane potential and reach the threshold voltage, which induces the opening of L-type Ca channel (LTCC), an action potential is fired.

On the other hand, M_2 receptor stimulation opens muscarinic potassium channels (K_{ACh})[9]. These channels are opened by M_2 receptors binding to ACh and produce a hyperpolarizing current that opposes the inward pacemaker current. Therefore, the parasympathetic stimulation increases outward K^+ permeability, slowing the heart rate and reducing automaticity.

Cardiomyocytes: Regulation of cellular Ca^{2+} handling and cardiac contraction: Excitation-contraction coupling in cardiomyocytes is dependent on calcium-induced calcium release, whereby an action potential initiates an increase in cellular calcium through opening of the LTCC on the cellular membrane. This creates a positive feedback loop by activating the ryanodine receptors of the SR causing the release of an even greater amount of calcium. This calcium then binds to troponin C, moving the tropomyosin complex off the actin active site, so that the myosin head can bind to the actin filament. Hydrolysis of ATP then causes the myosin head to pull the actin filament toward the center of the sarcomere. Free intracellular calcium is then resequestered into the SR *via* the SR ATPase pump (SERCA), or is pumped from the cell *via* the sodium-calcium exchanger on the cellular membrane. Finally, the troponin complex returns the actin filament to its binding sites to tropomyosin.

Sympathetic stimulation leads to the elevation

of cAMP levels and the activation of PKA, which phosphorylates the α_1 subunits of the LTCCs. This increases the opening probability of LTCCs and the inward Ca^{2+} current, and thus enhances the force of cardiac contraction. In addition, PKA phosphorylates phospholamban, thus relieving its inhibition of SERCA, which in turn facilitates Ca^{2+} uptake by the SR and increases the amount of Ca^{2+} (*i.e.,* SR Ca^{2+} content) available for release by the action potential. Furthermore, activation of β_1-adrenoceptors also increases the Ca^{2+} sensitivity of the contractile machinery, mediated by phosphorylation of troponin C. Taken together, the net result of sympathetic stimulation is to elevate cardiac function and steepen both contraction and relaxation.

Since M_2 receptors are negatively coupled to AC and thus reduce cAMP formation, they act to decrease the open probability of LTCCs and reduce Ca^{2+} current. In opposition to sympathetic stimulation, parasympathetic stimulation reduces the activity of Ca^{2+} handling proteins in cardiomyocytes.

Autonomic regulation of vascular function: In contrast to the heart, most vessels (arteries and veins) only receive sympathetic innervation, while capillaries receive no innervation. These sympathetic nerve fibers tonically release norepinephrine, which activates α_1-adrenergic and β_2-adrenergic receptors on blood vessels thereby providing basal vascular tone. Since there is greater α_1-adrenergic than β_2-adrenergic receptor distribution in the arteries, activation of sympathetic nerves causes vasoconstriction and increases the systemic vascular resistance primarily *via* α_1 receptor activation. On the other hand, modified sympathetic nerve endings in the adrenal medulla release circulating epinephrine, which also binds to α_1 and β_2-adrenergic receptors in vessels. However, β-adrenergic receptors show greater affinity for epinephrine than for norepinephrine. Therefore, circulating epinephrine at low concentrations activates only β_1-adrenergic (mainly in the heart) and β_2-adrenergic (mainly in vessels) receptors, which increase cardiac output and cause vasodilation, respectively. It should be noted that vessels at different locations may react differently to sympathetic stimulation. For example, during the "fight or flight" response the sympathetic nervous system causes vasodilation in skeletal muscle, but vasoconstriction in the skin.

Cardiovascular reflexes and the regulation of blood pressure

In the human body, the ANS is organized as functional reflex arcs (Figure 3). Sensory signals from receptors distributed in certain parts of the body are relayed *via* afferent autonomic pathways to the central nervous system (*i.e.,* spinal cord, brain stem, or hypothalamus), the impulses are then integrated and transmitted *via* efferent pathways to the visceral organs to control their activities. The following reflexes play major roles in regulating cardiovascular functions.

Baroreceptor reflex: Baroreceptors located within the aortic arch and the carotid sinuses detect increases in blood pressure. These mechanoreceptors are activated when distended, and subsequently send action potentials to the rostral ventrolateral medulla (RVLM; located in the medulla oblongata of the brainstem) which further propagates signals, through the autonomic nervous system, adjusting total peripheral resistance through vasodilatation (sympathetic inhibition), and reducing cardiac output through negative inotropic and chronotropic regulation of the heart (parasympathetic activation). Conversely, baroreceptors within the venae cavae and pulmonary veins are activated when blood pressure drops. This feedback results in the release of antidiuretic hormone from cell bodies in the hypothalamus into the bloodstream from the nerve endings in the posterior lobe of the pituitary gland. The renin-angiotensin-aldosterone system is also activated. The subsequent increase in blood plasma volume then results in increased blood pressure. The final baroreceptor reflex involves the stretch receptors located within the atria; like the mechanoreceptors in the aortic arch and carotid sinuses, the receptors are activated when distended (as the atria become filled with blood), however, unlike the other mechanoreceptors, upon activation, the receptors in the atria increase the heart rate through increased sympathetic activation (first to the medulla, then subsequently to the SA node), thus increasing cardiac output and alleviating the increased blood volume-caused pressure in the atria[10].

Chemoreceptor reflex: Peripheral chemoreceptors located in the carotid and aortic bodies monitor oxygen and carbon dioxide content as well as the pH of the blood. Central chemoreceptors are located on the ventrolateral medullary surface in the central nervous system and are sensitive to the surrounding pH and CO_2 levels. During hypovolemia or severe blood loss, blood oxygen content drops and/or pH is decreased (more acidic), and levels of carbon dioxide are likely increased, action potentials are sent along the glossopharyngeal or vagus nerves (the former for the carotid receptors, the latter for the aortic) to the medullary center, where parasympathetic stimulation is decreased, resulting in an increase in heart rate (and thus an increase in gas exchange as well as respiration). Additionally, sympathetic stimulation is increased, resulting in further increases to heart rate, as well as stroke volume, which in turn results in an even greater restoration of cardiac output.

Cardiovascular autonomic dysfunction and heart rate variability: It has been known that sympathetic stress/dominance occurs during heart failure or after myocardial infarction, and may trigger

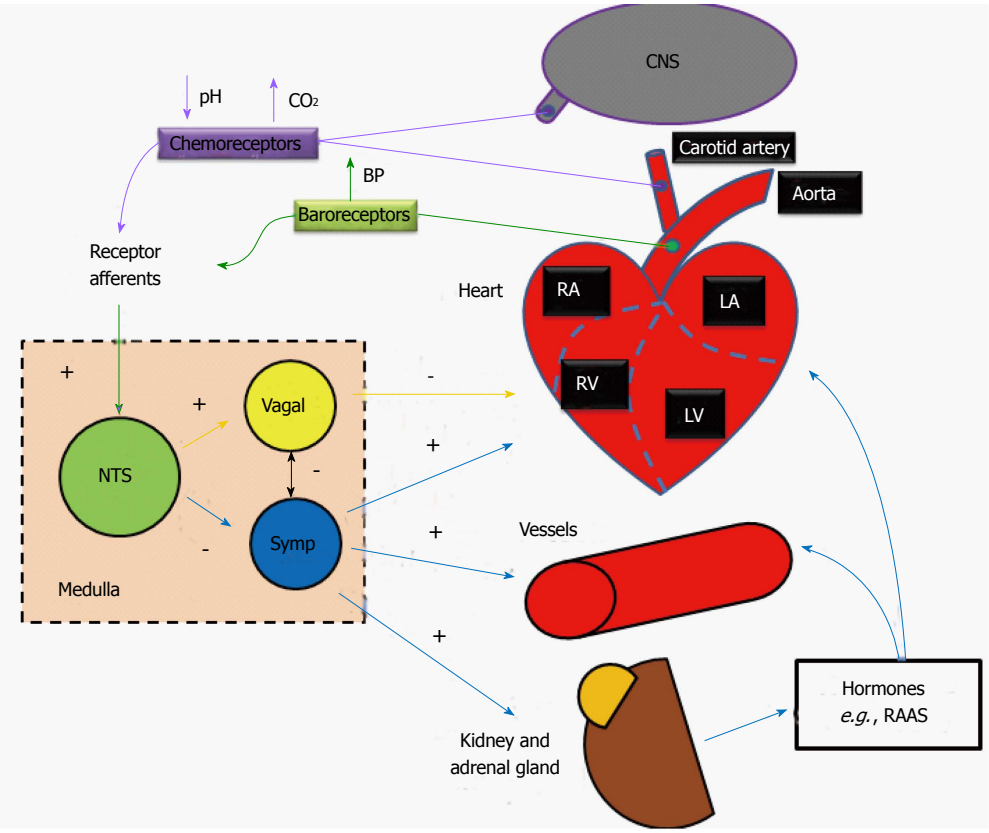

Figure 3 Schematic of cardiovascular reflexes and their influences on heart and vessels functions. NTS: *Nucleus tractussolitarii*; Symp: Sympathetic; CNS: Central nervous system; RAAS: Renin-angiotensin-aldosterone system.

lethal arrhythmias. This sympathovagal imbalance is reflected by reduced heart rate variability (HRV). HRV is determined from ECG and has currently been used clinically as both a diagnostic as well as a prognostic factor for assessing cardiovascular autonomic dysfunction including cardiac autonomic neuropathy. Please refer a recent review article for specific HRV indicators and their interpretations[11].

ENDOCRINE/PARACRINE REFLEXES AND THE REGULATION OF BLOOD PRESSURE REGULATION

In addition to the ANS, cardiovascular function is also influenced by numerous endocrine hormones. Released from the adrenal gland, epinephrine and dopamine (and ultimately, norepinephrine) are all involved in the initiation of the "fight-or-flight" response, while vasopressin, renin, angiotensin, aldosterone, and atrial-natriuretic peptide are all involved in water reabsorption for the purpose of blood pressure regulation.

Adrenal medulla (epinephrine)

An important exception to the usual arrangement in sympathetic fibers is the set of preganglionic fibers that pass through the sympathetic ganglia and extend to the medulla of the adrenal glands. These fibers terminate on special hormone secreting cells, *i.e.*, chromaffin cells, that release norepinephrine (20%) and epinephrine (80%) when stimulated. Epinephrine and norepinephrine are the two main catecholamines that can activate or deactivate sympathetic receptors within the cardiovascular system. Another neurotransmitter dopamine that has limited actions in the autonomic nervous system may excite or inhibit depending on the receptors. Dopamine can be converted into norepinephrine and thus can increase heart rate and blood pressure. Epinephrine is produced (from phenylalanine and tyrosine) and released from chromaffin cells in the adrenal medulla of the adrenal glands. It can stimulate all major adrenergic receptors, including α_1, α_2, β_1, and β_2 receptors. Epinephrine at low concentrations is β_2-selective, producing vasodilatation, while at high concentrations it also stimulates α_1, α_2, and β_1 receptors, producing vasoconstriction (mediated by α_1 and α_2 receptors), and increases heart rate and contractility (mediated by β_1 receptor). Blood pressure is regulated through a system of vasoconstriction and vasodilatation (*i.e.*, vascular resistance). The change in vessel resistance is proportional to the length (L) of the vessel and the viscosity (η) of the blood and inversely proportional to the radius of the vessel to the fourth power (r^4). It is clear from this relationship that vessel diameter controlled by the sympathetic nervous system can have a tremendous impact on

blood pressure regulation *via* small changes in vessel diameter.

$$R \propto \frac{\eta.L}{r^4}$$

Importantly, epinephrine serves to initiate the fight or flight response system by boosting the oxygen and glucose supplies to the brain and skeletal muscle through increased cardiac output and vasodilatation.

Posterior pituitary gland

Vasopressin (antidiuretic hormone) is released during hypovolemic shock as a homeostatic attempt to increase blood pressure and maintain organ perfusion. Vasopressin serves to regulate water retention and vasoconstriction. Vasopressin is produced and released from the parvocellular neurosecretory neurons. It is synthesized in the hypothalamus, and then stored in the posterior pituitary gland, until it is secreted in response to a reduction in plasma volume, an increase in plasma osmolarity, or an increase in cholecystokinin[12]. Within the kidney, vasopressin causes water retention by increasing water permeability of the distal tubule and collecting duct cells, by inserting Aquaporin-2 channels, thus resulting in the inner medullary collecting duct becoming more permeable to urea. Within the cardiovascular system, vasopressin is a vasoconstrictor which increases arterial blood pressure. An increase in blood volume results in increased cardiac output and improved cardiovascular function.

Kidney

There are three hormones produced in the kidneys: calcitriol, thrombopoietin and renin. Of these three, only renin is involved in cardiovascular reflexes and the regulation of blood pressure. Calcitrol works in conjunction with parathyroid hormone to increase the absorption of calcium and phosphate from the gastrointestinal tract[13]. Abnormal calcium metabolism in the cardiovascular system can result in medial arterial calcification and increased vascular stiffness, plaque formation and rupture. Thrombopoietin is made by the proximal convoluted tubule cells, and is responsible for stimulating the production of megakaryocytes of the bone marrow to eventually produce platelets[14]. Low numbers of platelets can lead to hemorrhage and anemic states. Anemia is known to result in high output heart failure.

In the kidney renin is released from the juxtaglomeruler cells, and activates the renin-angiotensin system. The renin-angiotensin-aldosterone system can play both physiological and pathological roles in the cardiovascular system. Angiotensin is known to be involved in heart failure. A main stay in the treatment of heart failure is the use of angiotensin converting enzyme inhibitors.

Renin-angiotensin-aldosterone system: The renin-angiotensin-aldosterone system serves to regulate blood pressure and fluid balance during for example instances of hypovolemia or blood loss. There are three mechanisms by which this system can be activated: baroreceptors with the carotid sinus can detect decreases in blood pressure, a decrease in sodium chloride concentration and/or a decreased rate of blood flow through the macula densa. Once a decrease in blood volume is detected, renin is released by the kidney and cleaves angiotensinogen (produced in the liver) into angiotensin Ⅰ. Angiotensin Ⅰ is further converted to angiotensin Ⅱ by the angiotensin converting enzyme (which is produced in the capillary beds of the lungs). Angiotensin Ⅱ then acts upon the proximal tubules to increase sodium reabsorption, thus helping to retain water while maintaining the glomerular filtration rate and blood pressure. It also serves to constrict the renal arteries, as well as the afferent and efferent arterioles. Through contraction of the mesangial cells, it can also decrease the filtration rate of the kidneys. Angiotensin Ⅱ also increases the sensitivity to tubuloglomerular feedback by increasing the afferent arterioles responsiveness in the macula densa. It can also reduce medullary blood flow. Finally, it causes the adrenal cortex to release aldosterone, which causes sodium retention and potassium excretion.

Angiotensin Ⅱ has three major effects on the cardiovascular system: it is a potent vasoconstrictor, causing a direct increase in systemic blood pressure; it also exhibits prothrombotic effects, stimulating platelet aggregation and causing the production of PAI-1 and PAI-2[15]; finally, it acts as a Gq stimulator when released in an autocrine-paracrine fashion from cardiomyocytes, causing cell growth through protein kinase C during myocardial hypertrophy.

Hormones released by the heart

There are two major hormones produced by the heart. The first, atrial-natriuretic peptide (ANP), is produced by atrial cardiomyocytes, and serves to reduce blood pressure through several mechanisms.

ANP is produced, stored, and released by atrial myocytes (while also being produced in the ventricles, brain, suprarenal glands, and renal glands). There are five major causes for ANP release: distention of the atria, β-adrenergic stimulation, hypernatremia, increases in angiotensin Ⅱ, and increases in endothelin[16]. Upon the vasculature, atrial-natriuretic peptide blocks catecholamines, while in the heart, it inhibits hypertrophy by blocking norepinephrine-stimulated protein synthesis. It is also believed to exhibit cardioprotective properties related to its ability to block cardiac fibrosis following ischemia-reperfusion injuries[17].

The other major hormone, brain-natriuretic peptide

(BNP), is produced by ventricular cardiomyocytes, and works in a similar fashion to ANP. BNP is secreted by the ventricles of the heart in response to excessive stretching of ventricular myocytes and its level is typically increased in patients with left ventricular dysfunction. Therefore, clinically BNP levels are used to monitor heart function. Elevated levels of BNP are thought to be indicative of poor left ventricular function and heart failure.

Additional hormones that may impact cardiovascular function

Endothelin-1: Endothelin-1 is a potent vasoconstrictor that is produced by endothelial cells. There are four endothelin receptors, which are mainly expressed in vascular smooth muscles, each with varying actions upon activation. Activation of ET_A results in smooth muscle vasoconstriction; ET_B causes the release of nitric oxide from endothelial cells, thus resulting in vasodilatation; while activation of ET_{B2} causes vasoconstriction. ET_A receptors also function like G-protein coupled receptors in ventricular cardiomyocytes[18,19]. The effects of ET_C activation are currently unknown[20]. Endothelin-1 may play a role in cardiac hypertrophy *via* intracellular alkalinization.

Thyroxin: Thyroxin (T_4) is a hormone produced by the follicular cells of the thyroid gland. While it acts on nearly every cell type within the human body, one of its most important functions is to increase the effect of epinephrine. Through this permissive relationship, thyroxin increases the number of β_1 receptors and is thus indirectly responsible for increasing cardiac output (in both an inotropic and chronotropic manner) and increasing respiration rates. It is directly responsible for increasing basal metabolic rates by increasing protein and carbohydrate metabolism[21]. Clinical increases in thyroxin are associated with the occurrence of atrial fibrillation, a common cardiac arrhythmia. Elevated heart rates from thyroxin induced atrial fibrillation or other arrhythmias can result in myocardial decompensation and heart failure if not returned to normal sinus rhythm.

CONCLUSION

In conclusion, the heart is not simply an isolated actor. The cardiovascular system responds to not only acute but also chronic changes in blood pressure and homeostasis. Body homeostasis and survival are therefore the main functions of the cardiovascular system. Factors actively influencing the cardiovascular system range from the central nervous system including the brain and spinal cord to the peripheral nervous system with fibers being transported through spinal nerves to the glands, *e.g.*, adrenals, vasculature and even to the urinary system (kidneys). The cardiovascular system is controlled and influenced by not only a unique intrinsic conduction system, but is also heavily influenced by the autonomic nervous system as well as the endocrine system.

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ORIGINAL ARTICLE

Prospective Study

Effective treatment of depression improves post-myocardial infarction survival

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Clinical trial registration: This study is registered at http://clinicaltrial.gov/ct2/show/NCT00000557?term=ENRICHD&rank=1, The clinical Trials.gov Identifier: NCT00000557.

Informed consent: This study is a secondary data analysis using data from the ENRICHD randomized trial and received in a de-identified format.

Conflict-of-interest: The authors have no relationships with industry to report and have no conflict of interest including financial, personal, political interest in this study.

Data sharing: Technical appendix and statistical code are available from the corresponding author at sbana001@umaryland.edu. The ENRICHD limited use data set is available from NIH by application through BIOLINCC at https://biolincc.nhlbi.nih.gov/home/

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Abstract

AIM: To examine the contribution of treatment resistant depression (TRD) to mortality in depressed post-myocardial infarction (MI) patients independent of biological and social predictors.

METHODS: This secondary analysis study utilizes the Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial data. From 1834 depressed patients in the ENRICHD study, there were 770 depressed post-MI patients who were treated for depression. In this study, TRD is defined as having a less than 50% reduction in Hamilton Depression (HAM-D) score from baseline and a HAM-D score of greater than 10 in 6 mo after depression treatment began. Cox regression analysis was used to examine the independent contributions of TRD to mortality after controlling for the biological and social predictors.

RESULTS: TRD occurred in 13.4% (n = 103) of the 770 patients treated for depression. Patients with TRD were significantly younger in age (P = 0.04) (mean = 57.0 years, SD = 11.7) than those without TRD (mean = 59.2 years, SD = 12.0). There was a significantly higher percentage of females with TRD (57.3%) compared to females without TRD (47.4%) [χ^2 (1) = 4.65, P = 0.031]. There were significantly more current smokers with TRD (44.7%) than without TRD (33.0%) [χ^2 (1) = 7.34, P = 0.007]. There were no significant differences in diabetes (P = 0.120), history of heart failure (P = 0.258), prior MI (P = 0.524), and prior stroke (P = 0.180) between patients with TRD and those without TRD. Mortality was 13% (n = 13) in patients with TRD and 7% (n = 49) in patients without TRD, with a mean follow-up of 29 mo (18 mo minimum and maximum of 4.5 years). TRD was a significant independent predictor of mortality (HR =

1.995; 95%CI: 1.011-3.938, *P* = 0.046) after controlling for age (HR = 1.036; 95%CI: 1.011-1.061, *P* = 0.004), diabetes (HR = 2.912; 95%CI: 1.638-5.180, *P* < 0.001), heart failure (HR = 2.736; 95%CI: 1.551-4.827, *P* = 0.001), and smoking (HR = 0.502; 95%CI: 0.228-1.105, *P* = 0.087).

CONCLUSION: The analysis of TRD in the ENRICHD study shows that the effective treatment of depression reduced mortality in depressed post-MI patients. It is important to monitor the effectiveness of depression treatment and change treatments if necessary to reduce depression and improve cardiac outcomes in depressed post-MI patients.

Key words: Depression treatment; Post-myocardial infarction; Mortality; Anti-depressant; Cognitive behavioral therapy

Core tip: Treatment resistant depression (TRD) was associated with increased mortality in post-myocardial infarction (MI) patients with depression. Conversely, effective treatment of depression with cognitive behavioral therapy with or without medication decreased mortality in post-MI patients who were depressed. Since TRD post-MI patients are at higher risk for mortality, closer follow-up and more aggressive treatment for depression and risk factor modification is needed to improve patient outcome. It is important to monitor the effectiveness of depression treatment and change treatments if necessary to reduce depression and improve cardiac outcomes in post-MI patients with depression.

Banankhah SK, Friedmann E, Thomas S. Effective treatment of depression improves post-myocardial infarction survival. *World J Cardiol* 2015; 7(4): 215-223 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i4/215.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i4.215

INTRODUCTION

Depression predicts morbidity and mortality in patients after myocardial infarction (MI)[1-5]. Depression in post-MI patients is associated with increased mortality. A meta-analysis of 29 studies with an average of 16 mo follow-up and a total of 16889 patients revealed that post-MI depression is associated with more than doubling in odds of all cause mortality (OR = 2.25, 95%CI: 1.73-2.93; *P* < 0.001)[6]. Prevalence of depression is about 20% in patients with MI, compared to 5% in the general population[7,8]. Depression predicts a poorer prognosis and lower functional status in post-MI patients[4].

Treating depression in depressed post-MI patients should improve their long-term prognosis; however, in randomized clinical trials treating depression in depressed post-MI patients, did not improve their survival[9-12].

Cognitive behavioral therapy, plus adjunctive sertraline treatment in the case of insufficient response, did not improve mortality or nonfatal re-infarction with a mean 29 mo follow-up in post-MI patients with depression and/or low perceived social support (LPSS) enrolled in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial[9]. There was no difference in event-free survival between the intervention and usual care groups (75.5% *vs* 74.7%). The intervention resulted in a temporary reduction in depression, which was present at 6 mo but disappeared by 30 mo after randomization[9]. Similarly, depression treatment did not improve cardiac event-free survival (treatment group 86.2% *vs* usual care group 87.3%) during the 18 mo of follow-up in the Myocardial Infarction and Depression-Intervention Trial (MIND-IT)[11]. Antidepressant medication (sertraline) for depressed patients with heart disease (*n* = 369) resulted in a slight, but non-significant reduction in recurrent MI and death after an average of 30 mo of follow-up (RR = 0.77; 95%CI: 0.51-1.16) in the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART)[10]. The recent 8-year follow-up of the MIND-IT trial that evaluated the effects of antidepressant treatment in depressed post-MI patients revealed that the treatment group's mortality was not reduced when compared usual care group[12]. However, patients who actually received treatment for depression, regardless of group assignment, had an improved mortality (HR = 0.52, 95%CI: 0.28-0.97).

Secondary analyses of data from subgroups within clinical trials hint that the effectiveness of the treatment of depression might be a factor in whether treatment improves health outcomes. In an on-treatment secondary analysis of the 1834 depressed patients from the ENRICHD intervention and control groups showed significantly lower risk of recurrent MI and death in patients taking selective serotonin reuptake inhibitors (SSRIs) from both the usual care and treatment group. During an average of 29 mo of follow-up, 26% of patients who did not receive antidepressants died or had a recurrent MI *vs* 21.5% of patients on antidepressant therapy. Use of SSRIs was associated with significant reduction in risk of death or nonfatal MI (HR = 0.72; 95%CI: 0.44-1.22) and of all-cause mortality (HR = 0.73; 95%CI: 0.34-1.38)[13].

In patients with at least 1 prior episode of major depression in the ENRICD intervention group whose depression did not improve over the first 6 mo had higher late mortality (unimproved 21.2% *vs* improved 10.4%) and were more likely to be taking antidepressant medication and have a higher body mass index at enrollment than patients whose

depression symptoms improved. In the usual care arm of ENRICHD, improvement in depression was not related to mortality[2].

In a 7-year follow-up analysis of SADHART, patients whose major depression did not respond to medication experienced 2.39 times as much mortality (28.4%) as those whose depression was treated effectively (15.6%)[14].

The ENRICHD study did not find that randomized treatment of depression in depressed post-MI patients decreased mortality or morbidity. Even with extensive effort to treat their depression, many patients in the intervention arm did not improve their depression symptoms after 6 mo of treatment. Instead, they seem to have a treatment refractory depression that was resistance to current available therapy. This finding and other subsequent analysis of ENRICHD studies left health professionals without clear direction for the treatment of depression in post-MI patients.

Clinical studies show that not all depressed patients respond adequately to treatment. Fava *et al*[15] meta-analysis of 36 clinical trials demonstrated that about 50% of depressed patients have an adequate response to antidepressant therapy, 15% had partial response, and 20%-35% did not respond to depression treatment. Patients who do not respond adequately labeled as treatment resistant. Depression was considered treatment resistant when at least 2 trials of different antidepressant therapy with adequate dose/duration/compliance failed to produce a significant clinical improvement in depression symptoms[16].

Patients with treatment resistant depression (TRD) in previous studies may have masked the effect of reducing depression on improvement of survival of depressed post-MI patients. In a cohort study of 4037 depression post-MI patients, 12.1% of the patients had treatment-resistant depression and they were 1.71 times as likely to die than treated patients[17].

The current study focuses on TRD and compares survival of patients with TRD to survival of patients who responded to treatment of depression.

MATERIALS AND METHODS

Research design

This secondary data analysis uses longitudinal data from the ENRICHD randomized clinical trial. The limited use de-identified data set was obtained from the National Heart, Lung, and Blood Institute (NHLBI) after University of Maryland full IRB review.

Data source

ENRICHD was the first randomized multi-center study to examine the effect of psychosocial intervention on survival in patients who were depressed and/or had LSSP after an MI. This study was sponsored by the NHLBI, and recruitment started in October 1996 and ended in October 1999. Patients were enrolled in the ENRICHD study within 28 d of an acute MI.

All patients with an acute MI admitted to 1 of the 73 participating hospitals were screened for acute MI eligibility including MI documented by cardiac enzymes and by chest pain with typical ST-T changes or new Q waves. Complete ENRICHD inclusion and exclusion criteria are published elsewhere[9]. After informed consent was obtained, patients were screened for depression and/or LPSS. If either depression or LPSS was present, patients were randomly assigned to the intervention or usual care arm. Participants had follow-up examinations at 6 and 18 mo and annually thereafter. The primary end-point of the study was the occurrence of re-infarction or all cause mortality[9].

ENRICHD intervention

Cognitive behavioral therapy (CBT) was utilized as the standard of the ENRICHD intervention[18]. Intervention group patients with scores higher than 24 on the Hamilton rating scale for depression (HAM-D) or who had < 50% reduction in BDI score after 5 wk were referred to study psychiatrists for pharmacotherapy consideration. If there were no contraindications, sertraline hydrochloride was used as the drug of choice. The maximum CBT duration was 6 mo[9].

Patients in the usual care arm of the study received only the care provided by their primary care providers, which was standard medical care for post-MI patients. Patients in both groups received health education regarding cardiovascular disease and its management and both groups received standard medical treatment as practiced in that institution.

ENRICHD measures

Baseline assessment in ENRICHD included demographics, cardiovascular health history, risk factors, current medications, detailed medical record documentation of the course of treatment for the acute MI, an electrocardiogram, the Depression Interview and Structured Hamilton (DISH), beck depression inventory (BDI), and ENRICHD social support inventory (ESSI).

The DISH is a semi-structured interview developed for ENRICHD trial and was used for screening and diagnosing depression[19] using principles and criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-Ⅳ)[20]. The DISH incorporated material from the 17-item version of the Hamilton Rating Scale for Depression (HAM-D)[21], the Structured Interview Guide for the Hamilton Depression Scale (SIGH-D)[22], the Diagnostic Interview Schedule (DIS)[23], and the modified versions of the DIS[24]. The DISH depression severity score was based on the 17-item HAM-D. The first 9 items on HAMD-D are 5 point Likert format ranging from 0 (absent) to 4 (severe). The last 8 items are 3 point Likert format ranging from 0 (absent) to 2 (clearly present). The possible score ranges from 0 to 50. Scores of > 10 indicates the presence of depression symptoms. Hig-

her total scores indicate more depression symptom severity. The concurrent validity of DISH was evaluated using the Pearson correlation coefficient between 17-item HAM-D embedded in the DISH and BDI scores that resulted in a correlation of 0.76 ($P < 0.001$)[19]. The DISH was administered at the screening phase of the ENRICHD study and at 6 mo follow-up.

The BDI[25] was used in the ENRICHD study to evaluate baseline depression status and assess progress during treatment and follow-up. The BDI is the most widely use depression instrument in clinical and research settings. The BDI is considered 1 of the best methods to assess presence and severity of depression. It is easy to use and only takes 5 min to complete by the patient or provider. The BDI is a 21-item inventory, and each item is rated on a 0 to 3 scale with a total score ranging from 0 to 64. BDI scores > 10 indicate depression, scores of 10-15 mild depression, 16-23 moderate depression, and 24-64 severe depression. Concurrent validity of BDI was established by comparing BID to HAM-D that positively correlated (r = 0.71, $n = 87$). This indicates an acceptable concurrent validity of BDI. The BDI was administered to all participants at baseline, 6, 12, 18 mo and annually thereafter.

The ESSI was used in the ENRICHD study to assess perceived social support at baseline and durng treatment and follow-up. It was developed for ENRICHD study to measure functional social support. The ESSI was used as a screening tool to determine patients' eligibility for ENRICHD based on low social support, and to assess changes in patients' social support following treatment. The ESSI is a 7-item inventory, and item 1 to 6 is rated on a 1 to 5 scale, which indicates none to all respectively. Item 7 is not rated on numeric scale. The total score ranges from 6 to 30 with lower scores indicating LPSS. A score < 3 on 2 or more items and a total score < 18, or a score of 2 on 2 items without regard to total score indicated LPSS which was the criteria for inclusion in ENRICHD trial[26]. In this study, 3 variables derived from ESSI instrument that were: live alone, perceived social support, and social isolation. Live alone was the seventh question on the ESSI questionnaire ("do you live alone?") that was separated and transferred into the study dataset. Perceived social support was the total score on the ESSI and social isolation was dichotomous value based on scoring the ESSI. Social isolation was defined as meeting the ENRICHD criteria for LPSS. The reliability of ESSI was estimated by using test-retest reliability that showed no significant differences in mean scores administered 1 mo apart ($P = 0.98$). The internal reliability was measured with the use of Cronbach's alpha that revealed an alpha of 0.88, which indicates a high internal consistency. The intra-class correlation coefficient was 0.94, reflecting excellent reproducibility[26]. The ESSI was administered to all participants at baseline, 6, 12, 18 mo and annually thereafter.

Sample

The study sample consists of the depressed patients in either arm of ENRICHD who received treatment for depression and completed the DISH at 6 mo. Treatment was defined as any combination of CBT and/or antidepressant medication. TRD was defined as < 50% improvement of 6-mo HAM-D score from baseline in patients with 6-mo HAM-D > 10. The outcome variable in this study was all cause mortality. All deaths were documented and verified by the ENRICHD investigators.

Statistical analysis

Data analysis: Normality of distributions of continuous variables was examined; no variables had extreme values that needed transformation[27]. Missing data was < 5% thus there was not a need to examine patterns of missing data[27]. All inferential tests were conducted at the 0.05 level of significance. Statistical procedures were performed using SPSS version 20.0 software.

Cox regression analyses was used to examine the hypothesis. The proportional hazards assumption of Cox regression was confirmed. The contribution of each biological (age, female gender, minority status, and presence of diabetes, history of heart failure, hypertension, prior MI, prior stroke, and current smoker), social (lives alone, perceived social support, social isolation), and psychological (baseline depression symptoms and TRD) predictor to mortality was initially examined in individual Cox regression analyses. Age was centered on 34 years, the lowest age in the study for ease of interpretation. The reference group (0) for dichotomous predictors was the un-named category. A combined model was constructed with biological, psychological, and social factors that predicted mortality at $P < 0.20$ in the individual analyses. Based on prior research showing differences between men and women in reporting depression[28,29], the interaction of TRD and female gender was added to the model. Similarly, based on prior research showing differences between minorities and non-minorities in reporting depression[30], the interaction of TRD and minorities status was added to the model. Neither of the interaction were significant predictors of mortality so they were not included in the final parsimonious Cox regression combined model. Biostatistician reviewed the statistical methods of this study.

Sample description: A total of 770 ENRICHD participants were depressed at the study entry and received depression treatment (Table 1). These participants received cognitive behavior treatment (CBT) ($n = 469$, 60.9%), or antidepressant medication ($n = 85$, 11%), or both ($n = 216$, 28.1%). The sample included 365 (47%) women and 239 (31%) minority participants.

Table 1 Summary of demographic biological, social, and psychological characteristics of depressed post-myocardial infarction patients treated for depression and comparison of those with treatment resistant and non treatment resistant depression (n = 770) n (%)

Characteristics	Treated Depressed Post-MI[1]	TRD n = 103[1]	Non TRD n = 667[1]	
Demographics and biological characteristics				
Age, mean (SD), yr	59.2 (12.0)	57.0 (11.7)	59.5 (12.0)	t = -2.07, P = 0.04
Gender, female	365 (47.4)	59 (57.3)	306 (45.9)	χ^2 (1) = 4.65, P = 0.031
Ethnicity, minority	239 (31.0)	32 (31.1)	207 (31.0)	χ^2 (1) = 0.0, P = 0.995
Education:				χ^2 (2) = 3.76, P = 0.153
Basic or no HS degree	187 (24.3)	25 (24.3)	162 (24.3)	
HS without college degree	419 (54.4)	64 (62.1)	355 (53.2)	
Advanced education	146 (19.0)	13 (12.6)	133 (19.9)	
Body mass index, mean (SD)	29.2 (6.1)	29.7 (6.3)	29.2 (6.1)	t = 0.77, P = 0.444
Diabetes	264 (34.3)	42 (40.8)	222 (33.3)	χ^2 (1) = 2.41, P = 0.120
History of heart failure	101 (13.1)	17 (16.5)	84 (12.6)	χ^2 (1) = 1.28, P = 0.258
Hypertension	458 (59.5)	70 (68.0)	388 (58.2)	χ^2 (1) = 4.56, P = 0.033
Prior MI	187 (24.3)	22 (21.4)	165 (24.7)	χ^2 (1) = 0.41, P = 0.524
Prior stroke	70 (9.1)	13 (12.9)	57 (8.7)	χ^2 (1) = 1.80, P = 0.180
Current smoker	254 (33.0)	46 (44.7)	208 (31.2)	χ^2 (1) = 7.34, P = 0.007
Social characteristics				
Live alone	322 (41.8)	46 (44.7)	276 (41.4)	χ^2 (1) = 0.32, P = 0.570
Social support	356 (46.2)	54 (52.4)	302 (45.3)	χ^2 (1) = 1.84, P = 0.176
Psychological characteristics				
Depression				χ^2 (2) = 16.7, P > 0.001
Major depression	398 (51.7)	69 (67.0)	329 (49.3)	
Minor depression	348 (45.2)	28 (27.2)	320 (48.0)	
Dysthymia	24 (3.1)	6 (5.8)	18 (2.7)	
Psychosocial measures				
Baseline Depression Symptom Severity (BDI), mean (SD)	17.7 (7.8)	22.4 (9.3)	17.0 (7.4)	t = 6.62, P < 0.001
Baseline Perceived Social Support (ESSI), mean (SD)	24.5 (6.4)	22.9 (7.0)	24.7 (6.3)	t = -2.74, P = 0.006
Baseline Depression Symptom (HAM-D), mean (SD)	17.9 (6.3)	20.9 (6.5)	17.4 (6.1)	t = 5.07, P < 0.001

[1]Except where mean (SD) is noted. BDI: Beck Depression Inventory; ESSI: ENRICHD Social Support Inventory; HAM-D: Hamilton Depression Rating Scale; HS: High school; TRD: Treatment resistant depression; MI: Myocardial infarction.

Ages ranged from 34 to 85 with a mean of 59 (SD = 12) years. Treatment resistant depression was present in 103 (13.4%) of the patients who were treated for depression.

Biostatistics

The statistical methods of this study were reviewed by Erika Friedmann from University of Maryland.

RESULTS

Baseline characteristics of patients with and without TRD were compared (Table 1). Patients with TRD were significantly younger (P = 0.04), more likely to be female (P = 0.031), be hypertensive (P = 0.033), and have lower perceived social support (P = 0.006) than those without TRD. Major depression was significantly more common (P < 0.001) and baseline depression symptom severity assessed with the BDI was significantly worse (P < 0.001) among patients who experienced TRD.

Of the 770 participants, there were 62 (8%) deaths with an average follow-up of 29 mo. All cause mortality tended to be higher in the patients with TRD (13/103: 13%) than those whose depression responded to treatment (49/667: 7%) (χ^2 = 3.35, P = 0.05).

In univariate Cox regression analysis (Table 2), age (P < 0.001), female gender (P = 0.005), diabetes (P < 0.001), history of heart failure (P < 0.001), hypertension (P = 0.002), prior MI (P < 0.001), prior stroke (P < 0.001), current smoker (P = 0.002) and live alone (P = 0.032) were significant predictors of mortality. Minority status (P = 0.943), perceived social support (P = 0.279), social isolation (P = 0.446), and baseline depression symptoms (P = 0.978) did not predict mortality.

In the combined simultaneous Cox regression model, TRD (P = 0.046), age (P = 0.004), diabetes (P < 0.001), and history of heart failure (P = 0.001) were significant independent predictors of mortality; current smoker tended to predict mortality (P = 0.087) (Table 3).

When the interaction between female gender and TRD and minority status and TRD were each added to the model, the interactions were not significant (P = 0.467, P =0.87, respectively). Neither interaction was added to the final model. In the final model TRD contributed significantly to mortality (P = 0.046) after controlling for age, diabetes, heart failure, and currently smoking. Patients with TRD had approximately double the risk of all cause mortality compared with patients without TRD (95%CI: 1.011-3.938). Other significant independent predictors of mortality were age, diabetes and heart failure.

This study showed a significant improvement in survival in depressed post-MI patients whose depre-

Table 2 Results of separate Cox regression analyses to examine the contributions of each biological, social and psychological predictor to mortality among treated post- myocardial infarction patients with depression (*n* = 770)

	B	SE	Wald	Sig.	HR	95%CI
Biological factors						
Age[1]	0.048	0.011	19.205	< 0.001	1.05	1.027-1.073
Female gender	0.741	0.266	7.791	0.005	2.098	1.247-3.531
Minority status	0.020	0.272	0.005	0.943	1.020	0.599-1.737
Diabetes	1.448	0.272	28.401	< 0.001	4.255	2.498-7.247
Heart failure	1.495	0.275	29.507	< 0.001	4.461	2.601-7.652
Hypertension	1.002	0.322	9.675	0.002	2.723	1.449-5.120
Prior MI	0.961	0.261	13.533	< 0.001	2.616	1.567-4.365
Prior stroke	1.165	0.306	14.496	< 0.001	3.207	1.760-5.843
Current smoker	-1.128	0.361	9.781	0.002	0.324	0.160-0.656
Social factors						
Live alone	0.552	0.258	4.591	0.032	1.737	1.048-2.880
Perceived social support	-0.046	0.028	2.768	0.096	0.955	0.904-1.008
Social isolation	-0.197	0.258	0.582	0.446	0.822	0.496-1.361
Psychological factor						
Baseline depression symptom severity	< 0.001	0.016	0.001	0.978	1.000	0.968-1.032
Treatment resistant depression	0.534	0.312	2.927	0.087	1.705	0.925-3.143

[1]Age centered on the lowest age of 34 years. For dichotomous variables reference group is the absence of the named predictor. MI: Myocardial infarction.

ssion was effectively treated (Figure 1). Among treated depressed post-MI patients, TRD was a significant independent predictor of mortality after controlling for biological and social factors.

DISCUSSION

Not all depressed patients respond adequately to treatment, and their depression does not improve significantly with current depression treatments. These depressed patients are treatment resistant[13]. Recent studies do not show improved mortality of acute myocardial infarction patients after treatment for depression[8-12]. One explanation of this may be that previous studies of post-MI patients included a subgroup of patients with TRD who may have impacted the results. The presence of the TRD subgroup may cause a failure in the study's ability to show improved survival in the intervention group.

The purpose of this study was to examine the differences in mortality between patients with TRD and those without TRD. The significant predictors for mortality among depressed post-MI patients whose depression was treated were; age, diabetes, and history of heart failure. The presence of TRD significantly predicted mortality after controlling for these other factors (HR = 1.995). TRD was associated with an increased risk of mortality when compared to non-TRD patients. This finding is consistence with the 7-year follow-up analysis of the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) [10]. Initial findings of SADHEART revealed a non-significant reduction in re-current MI and death (RR = 0.77; 95%CI: 0.51-1.16) in treated depressed individuals. At that time, they did not examine the difference between survival in those individuals who responded and not respondent to depression treatment. Subsequently, the 7-year follow-up analysis of the SADHART trial found that patients with major depression who responded to treatment with sertraline had a reduction in mortality *vs* non-responders (15.6% *vs* 28.4%; HR = 2.39)[14]. The current study extends this finding from post MI patients with major depression to less psychologically distressed patients, namely post MI patients with dysthymia through major depression. Further the current study began treatment with cognitive behavioral therapy and added medication if depression was not responsive. This study is also consistent with Scherrer *et al*'s[17] cohort study's finding that post-MI patients with TRD had increased mortality. The criteria for TRD in that study were that: the patient received (1) electroconvulsive therapy, (2) a monoamine oxidase inhibitor, or (3) two or more antidepressant at the same time. In contrast, the current study uses depression measurement tools to identify post-MI patients with TRD.

This re-analysis of the ENRICHD study data clearly shows that successful treatment of depression decreases mortality in post-MI patients. It also demonstrates that current depression treatments are not effective in treating all depressed post-MI patients. According to this study, over 13% of treated patients still suffered from depression at the end the treatment. This is consistent with the Scherre study, which showed 12.1% of post-MI patients experienced TRD. Perhaps a treatment that is more effective in alleviating depression would improve survival in post-MI patients. Until more effective treatments are developed, closer follow-up of depression symptoms, aggressive treatment of depression, actively treating other modifiable risk factors, and modifying risky health behaviors may lead to a better survival in post-MI patients with TRD.

Strengths and limitations

This study was a secondary data analysis of an existing trial. This places limitation to this study regarding

Table 3 Final model: Results of Cox regression analysis to examine the independent contributions of biological, social, and psychological predictors and treatment resistant depression to all cause mortality among post-myocardial infarction patients treated for depression (n = 770)

	B	SE	Wald	Sig.	HR	95%CI
Biological factors						
Age[1]	0.035	0.012	8.280	0.004	1.036	1.011-1.061
Diabetes	1.069	0.294	13.243	0.000	2.912	1.638-5.180
Heart failure	1.007	0.290	12.089	0.001	2.736	1.551-4.827
Current smoker	-0.690	0.403	2.932	0.087	0.502	0.228-1.105
Social factors						
None						
Psychological factor						
Treatment resistant depression	0.691	0.347	3.967	0.046	1.995	1.011-3.938

[1]Age centered on the lowest age of 34 years. For dichotomous variables, reference group is the absence of the named predictor.

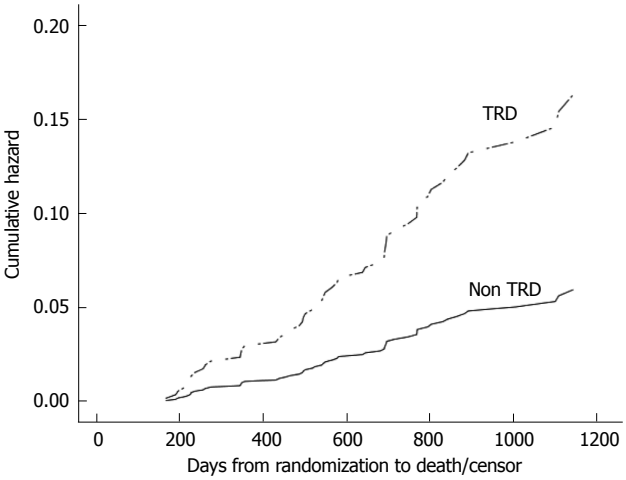

Figure 1 Hazard function for treatment resistant depression and non-treatment resistant depression participants to mortality after myocardial infarction. TRD: Treatment resistant depression.

control over the variable definition, measurement, data collection and other crucial aspects of the study design. With this study, we were not able to establish causality of the contributions of TRD for mortality. The study findings were only able to provide evidence of the associations between the variables. Despite the limitations of this study, the strengths outweigh the limitations of the study. Using a large existing database, this study has the advantage of providing a representative sample. Women and minorities were well represented in the ENRICHD data. ENRICHD included detailed questionnaire development, data collection procedures, data management, and quality control measures. The use of ENRICHD dataset provided an opportunity to use high quality dataset without the high cost and effort of obtaining this type and amount of data.

Implications for practice and future research

The analysis of TRD in ENRICHD shows that treatment of depression in the ENRICHD sample was effective in reducing mortality in those whose depression was effectively reduced by cognitive behavioral therapy and/or anti-depressant medication. By separating out those who were depressed and whose treatment was effective it was possible to evaluate the contribution of effective treatment of depression to mortality in post-MI patients. The findings of this study provided evidence that depressed patients with TRD have more than double the risk of mortality when compared with patients whose depression is effectively treated. This sub-group of depressed patients with TRD did not improve their depression symptoms with their current depression treatment. Closer follow-ups of depression symptoms, aggressive treatment of depression, aggressively treating other modifiable risk factors, and modifying risky health behaviors may lead to a better chance of survival in TRD post-MI patients.

As shown in this current study, depression is a risk factor for mortality among TRD post-MI patients. Yet the question remains how to best treat it. Future research is needed to address the development of effective treatment for depression. Both ENRICHD and SADHART trials reported small effect size using current depression interventions, this suggest a need to increase efficacy of current interventions for depressed post-MI patients. The results of the present study accentuate the need for future research for drug development and effective interventions to alleviate depression symptoms in order to improve cardiac outcomes.

The potential mechanisms linking depression and impaired cardiovascular prognosis are still poorly understood and remain an area that is in need of more research. Future studies are needed to give insight and provide evidence that will direct us toward a future in which we, health providers, are able to help and improve survival in post-MI patients who have TRD.

This study provided evidence that TRD is associated with increased mortality in post-MI patients who are depressed. Conversely, effective treatment of depression with cognitive behavioral therapy without or with medication decreased mortality in post-MI patients who were depressed. Since, TRD post-MI patients are at higher risk for mortality, closer follow-up and more aggressive treatment for depression and risk factor modification is needed to improve patients' outcomes. This may lead to an integrated treatment strategy that may decrease risk of mortality in post-MI patients. It is important to monitor the effectiveness of depression treatment and change treatments if necessary to reduce depression and improve cardiac outcomes in post-MI patients who are depressed.

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limited access dataset obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the ENRICHD Study or the NHLBI. The authors thank the investigators, coordinators, staff, and patients of the ENRICHD Study.

COMMENTS

Background

Depression increases mortality after myocardial infarction (MI). Clinical trials have not demonstrated a reduction in mortality with depression treatment. Depression treatment is not effective in a substantial proportion of the depressed patients. The presence of treatment resistant depression (TRD) may explain why previous clinical trials did not demonstrate decreased mortality when depression was treated.

Research frontiers

Recent clinical studies show that not all depressed patients respond adequately to treatment, and their depression does not improve significantly with current depression treatments. These patients have TRD. Presently, there is no study that shows improved outcome of depressed patients with acute MI by treating depression. This can be explained by the presence of TRD in some post-MI patients, which would impact the results of the study. The presence of TRD may cause a failure in the study's ability to show improved survival in the intervention group.

Innovations and breakthroughs

This study considers the presence of TRD in depressed post-MI patients and its influence on prior analysis. Treatment resistant depression is a possible explanation for why previous clinical trials did not demonstrate decreased mortality when depression was treated. The result of this study reveals that TRD significantly predicts mortality after controlling for biological and social factors. Among depression treated post MI patients, TRD was associated with an increased risk of mortality when compared to non-TRD patients. Depressed patients with TRD have double the risk of mortality when compared with patients whose depression is effectively treated.

Applications

This study provides new evidence that depressed patients with TRD did not improve their mortality with current depression treatment, and they are in desperate need for more efficacious depression treatment. Closer follow-ups of depression symptoms, aggressive treatment of other modifiable risk factors, and modifying risky health behaviors may lead to a better chance of survival in depressed post-MI patients. This knowledge may assist primary care providers regarding clinical decision making that provides a better treatment options for patients.

Terminology

TRD is a term describing patients with depression symptoms that do not improve after treatment is completed. In other words, the total hamilton depression (HAM-D) score does not decrease more than 50% from baseline with a total HAM-D score above 10 after completing depression treatment.

Peer-review

Authors showed that effective treatment of depression improved survival of patients after AMI. This paper is well described, and includes important clinical findings.

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CASE REPORT

Limitations of multimodality imaging in the diagnosis of pannus formation in prosthetic aortic valve and review of the literature

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Abstract

Pannus formation is a rare complication and occurs almost exclusively in mechanical prosthetic valves. It consists of fibrous tissue that covers the surface of the prosthesis either concentrically or eccentrically, resulting in valve dysfunction. The pathophysiology seems to be associated to a chronic inflammatory process that explains the late and insidious clinical presentation. This diagnosis should be considered in patients with high transvalvular gradients on transthoracic echo, and workup should be completed with fluoroscopy and transesophageal echocardiography. Treatment is always surgical and recurrence is rare. We present a case of pannus formation in a prosthetic aortic valve and a review of the literature regarding this disorder.

Key words: Pannus formation; Prosthetic aortic valve; Fluoroscopy; Transthoracic echocardiography; Transesophageal echocardiography

Core tip: Pannus is an infrequent complication that mainly affects mechanical prosthetic valves. Its diagnosis requires clinical suspicion and the association of fluoroscopy, transthoracic and transesophageal echocardiography. The case presented is a characteristic example of pannus, given its clinical presentation

(progressive dyspnea), the steps followed to reach diagnosis and the surgical resolution. Suspecting this disorder and making an accurate diagnosis is of paramount importance, to implement adequate treatment and to avoid prolonging the natural course of the disease and its repercussion on the left ventricle and the quality of life of affected patients.

Soumoulou JB, Cianciulli TF, Zappi A, Cozzarin A, Saccheri MC, Lax JA, Guidoin R, Zhang Z. Limitations of multimodality imaging in the diagnosis of pannus formation in prosthetic aortic valve and review of the literature. *World J Cardiol* 2015; 7(4): 224-229 Available from: URL: http://www.wjgnet.com/1949-8462/full/v7/i4/224.htm DOI: http://dx.doi.org/10.4330/wjc.v7.i4.224

INTRODUCTION

Mechanical prosthetic valve dysfunction caused by pannus or thrombosis is an unusual but serious complication of heart valve replacement. Thrombotic complications are most common early postoperatively, whereas pannus occurs later, especially in bileaflet valves in the aortic position. Pannus formation consists of fibrous tissue usually covering the circumference of a prosthetic valve, and causing valve dysfunction[1]. The incidence of this rare complication is 1.6%-2% in the different series published[2,3] and occurs almost exclusively in mechanical prostheses. Its most frequent location varies according to the authors, but in most series prostheses in the aortic position were affected more often[4] than those in mitral position[3,5].

CASE REPORT

The patient is a 55-year-old man with multiple cardiovascular risk factors (type 2 diabetes, hypertension, past history of smoking, obesity, dyslipidemia, and family history of cardiovascular disease) and intermittent claudication at 200 meters. Also, in 1998 he underwent aortic valve replacement with a mechanical #23 St. Jude valve, and coronary artery bypass grafting (CABG) with three grafts (left internal mammary artery to the left anterior descending artery and saphenous vein graft to the right coronary artery and circumflex coronary artery). In 2009 he began experiencing dyspnea in FC Ⅱ [New York Heart Association (NYHA) classification], that progressed to FC IV. Upon clinical consultation, a meso-telesystolic murmur radiating to the neck was detected, as well as a pulsus tardus et parvus and an apical beat in the anterior axillary line. No other relevant findings were reported.

His chest X-ray showed a cardiothoracic index slightly above 0.5, an old posterior infarction (R/S > 1 in lead V2) was seen on ECG, and routine laboratory results were within normal values. Transthoracic echocardiography (TTE) and two-dimensional transesophageal echocardiography (TEE) showed a bileaflet mechanical prosthesis in aortic position with normal opening of both discs (Figure 1A), with severely increased mechanical aortic valve gradients (peak instantaneous gradient: 97 mmHg, mean gradient: 58 mmHg) and decreased effective prosthetic area (0.67 cm^2). No detectable image suggestive of pannus or thrombus was seen in the left ventricular (LV) outflow tract. There was infero-posterior akinesis and mild LV dysfunction (EF: 40%). Fluoroscopy revealed normal opening of both tilting discs (Figure 1B). Cardiac multiple detector computed tomography (MDCT) did not showed any soft tissue mass on the ventricular side of the prosthetic aortic. Coronary angiography showed a severe lesion in the venous graft to the right coronary artery, without significant lesions in the other grafts or native arteries.

In spite of absence of any tissue mass on the ventricular side of the prosthetic aortic and absence of limitation of motion of the tilting disc to allow suggest pannus, given the clinical suspicion of prosthetic valve obstruction due to pannus formation, the decision was made to replace the aortic prosthesis with a new mechanical valve (ATS # 23) and perform CABG (venous graft to the right coronary artery); there were no postoperative complications. On pathological examination (Figure 2), the explanted specimen exhibited fibrous tissue with a smooth, annular surface, in contact with the ventricular surface of the mechanical prosthesis, consistent with pannus. Histological examination confirmed the diagnosis (Figure 3).

DISCUSSION

Pannus formation consists of fibrous tissue usually covering the circumference of a prosthetic valve, and causing valve dysfunction[1]. The incidence of this rare complication is 1.6%-2% in the different series published[2,3] and occurs almost exclusively in mechanical prostheses. Its most frequent location varies according to the authors, but in most series (Table 1) prostheses in the aortic position were affected more often[4] than those in mitral position[3,5].

Pathology studies of valves explanted due to pannus formation have shown that it consists of fibrous tissue ingrowth, with a generally smooth surface and a ring-like shape covering the valve surface. Pannus formation may be an isolated finding or associated to various degrees of thrombosis[2,5,6]. According to the type of growth, pannus may be classified as concentric or eccentric[7,8], the latter being more frequent[5]. However, the morphology of pannus could be associated to the type of prosthetic valve affected, which would explain the higher frequency of the eccentric type on single-disc valves[5], while the concentric type is more common in bi-leaflet valves[2].

On histological examination, pannus consists of a structure of collagen fibers interspersed with small

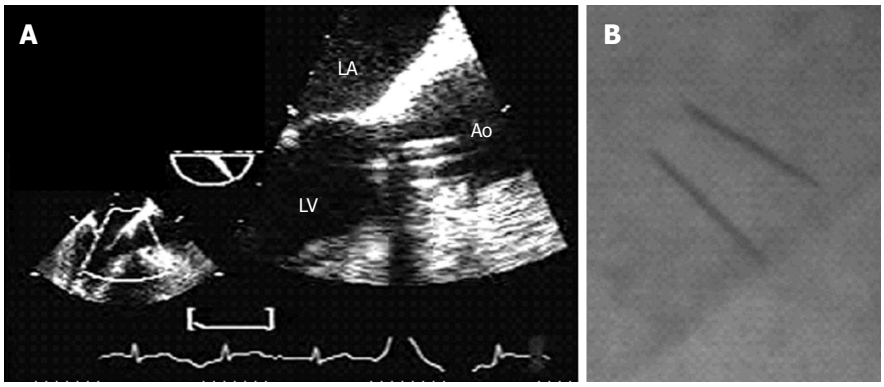

Figure 1 Transesophageal echo and fluoroscopy. A: Transesophageal Echo: 3-chamber view at 129°, with zoom in the LV outflow tract, showing the prosthetic valve with its parallel discs; B: Fluoroscopy showing the almost parallel tilting discs. Both exams confirm an adequate prosthetic valve opening. LA: Left atrium; LV: Left ventricle; Ao: Aorta.

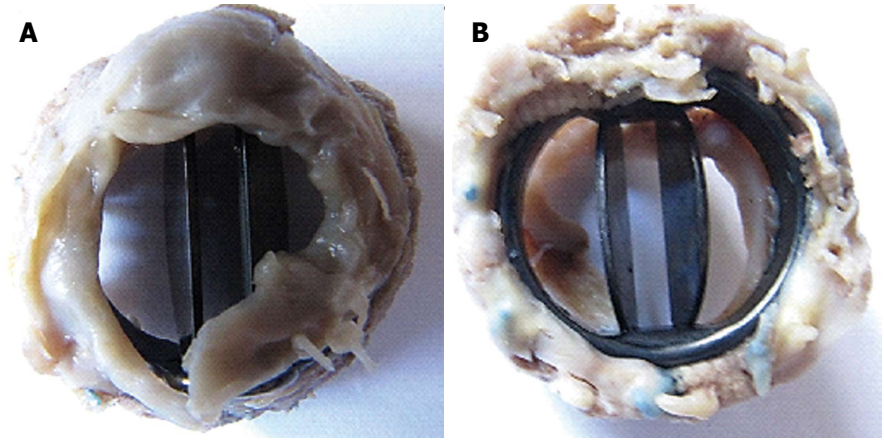

Figure 2 Explanted prosthetic valve. A concentric pannus formation is seen, obstructing the effective prosthetic orifice. A: Ventricular side; B: Arterial side.

Table 1 Characteristics of the different series that assessed the presence of pannus *n* (%)

Ref.	Year	Total number/No. of re-interventions	Pannus (*n*)	Location of pannus			Type of valve affected		Time to re-intervention (mo)	Follow-up (yr)
				Aortic	Mitral	Combined	Biologic	Mechanical		
Vitale *et al*[5]	1997	1878/87	66	0 (0)	66 (100)	0 (0)	0 (0)	66 (100)	51.5 ± 41.4[1]	0.26-20.1
Deviri *et al*[9]	1998	ND/100	51	ND	ND	ND	0 (0)	51 (100)	48 (1.5-144)[1]	13
Barbetseas *et al*[4]	1998	ND/23	10	7 (70)	3 (30)	0 (0)	0 (0)	23 (100)	178 ± 52[2]	ND
Rizzoli *et al*[3]	1999	2680/334	44	13 (30)	27 (61)	4 (9)	0 (0)	44 (100)	156[3]	27
Girard *et al*[18]	2001	ND/92	27	27 (100)	0 (0)	0 (0)	1 (4)	26 (96)	Vmec 156 ± 98[3] Vbio 84 ± 48[3]	ND
Roudaut *et al*[10]	2003	17250/126	26	ND	ND	ND	0 (0)	26 (100)	ND	23
Teshima *et al*[2]	2003	615/12	12	12 (100)	0 (0)	0 (0)	0 (0)	12 (100)	83 ± 52[2]	19
Toker *et al*[19]	2006	63	45	ND	ND	ND	0 (0)	45 (100)	58.9 ± 56.1[1]	ND

[1]Patients with a diagnosis of obstructive prosthetic dysfunction; [2]Patients with a diagnosis of pannus alone; [3]Patients with obstructive or non-obstructive prosthetic dysfunction. ND: No data; Vmec: Mechanical valve; Vbio: Biologic valve.

vessels and capillaries surrounded by giant cells, especially around and over suture stitches[5]. Pannus can be systematically divided into three layers and one core[2]. From the surface in contact with blood flow, the three layers towards the prosthetic material are: the lumen (which consists of endothelial cells, is found in the surface of the pannus), the internal lamina media (is composed of myofibroblasts) and the external lamina media (is composed of collagen and elastic fibers).

The core is located between the prosthetic tissue and the pannus, and consists mainly of a chronic inflammatory infiltrate comprising macrophages, lymphocytes, giant cells, plasmocytes and mastocytes[2].

The pathophysiology of this disorder is not yet completely understood. After implantation of a prosthetic valve, two inflammatory events occur. The first involves replacement of the damaged myocardium around the valve ring by a scar formed by nonspecialized connective tissue. The second event involves a foreign body-like inflammatory response to the presence of the prosthetic material. Prolonged exposure to the non-degradable prosthetic material is a persistent stimulus for inflammatory cells such as macrophages (which cluster as giant cells) and for proliferation of fibroblasts; both phenomena are characteristically seen in chronic inflammation. The presence of giant cells should be construed as a severe reaction, in which the foreign material is not well

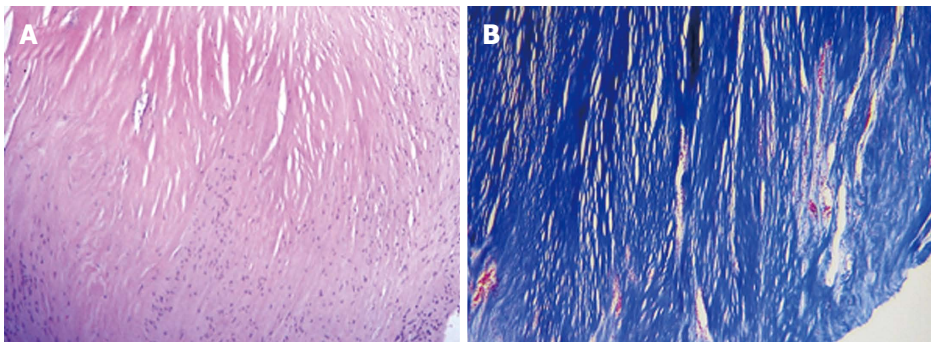

Figure 3 Histology of the pannus. Structure of collagen fibers, interspersed with small vessels and capillaries, surrounded by giant cells. A: Hematoxylin and Eosin staining; B: Masson's Trichrome staining.

tolerated and hence is a target for phagocytosis. This explanation allows to infer that the presence of pannus in only one valve surface represents an early stage of a chronic progressive inflammatory disorder[5].

The clinical presentation of pannus is variable; in most cases signs and symptoms of the disease occur as a consequence of prosthetic valve obstruction. The most common symptom is dyspnea, which may occur as a manifestation of obstruction in valves implanted both in aortic and in mitral valve position. Other less common clinical presentations are: low cardiac output syndrome, shock, embolization, chest pain, absence of a valve click on auscultation, exercise intolerance, cardiorespiratory arrest, and in many cases, patients may be asymptomatic[4,9,10]. In a study[4] that assessed the clinical characteristics of patients with pannus formation *vs* patients with thrombosis, the first group had a longer delay in appearance of symptoms, a longer duration of symptoms at the time of re-intervention, a greater time interval between the first and second surgical intervention and a higher rate of adherence to anticoagulation treatment.

The imaging techniques that are used most often for the diagnosis of this disorder are fluoroscopy, TTE and/or TEE HYPERLINK\l "Cia05"[11], although currently other techniques offer promising results, such as three-dimensional echocardiography and multislice Angio-CT[12-14].

For mechanical prostheses, the use of fluoroscopy is simple and allows to clearly identify the valve ring, cage, ball, the tilting disc/discs and the opening and closure angles; however, in biologic valves its use remains limited[1,11,15-17]. Specifically, in the case of pannus formation, fluoroscopy allows to detect absent motion of the disc/s; a frequent finding in pannus as well as in prosthetic valve thrombosis, albeit more frequent in the latter. In patients with normal leaflet motion, in whom high gradients are found and possible causes are prosthesis-patient mismatch, pannus or thrombosis, the echocardiographic findings shall define the final diagnosis[11]. In a study by Girard *et al*[18] that assessed 16 patients before their second aortic valve replacement, 63% of patients with a post-operative diagnosis of pannus had an abnormal fluoroscopy.

Pannus is suspected in patients who exhibit high gradients on echocardiography. Once structural failure and patient-prosthesis mismatch are ruled out, the only two differential diagnoses that remain to be defined are: pannus or thrombus. Since the advent of thrombolytics as an option for the treatment of valve thrombosis, making an accurate diagnosis has become of utmost importance, since such patients could benefit from the use of thrombolytics, and thus avoid the need for surgical reintervention. Although TTE is most useful in the initial approach to the diagnosis of pannus and thrombus, its usefulness to assess disc/s motion or the etiology of valve obstruction remains limited. However, where TTE fails, TEE appears as a more sensitive and specific method at the time of assessing the etiology of prosthetic valve obstruction. Thus, TEE has allowed to determine certain characteristics associated with pannus, such as: preserved prosthetic disc motion and evidence of a hyper-reflective mass of decreased length and motion, associated to the prosthetic valve[4]. Currently available diagnostic tools including TTE and 2D-TEE are insufficient to detect pannus formation, and detection rate is so poor that a preoperative diagnosis is almost impossible. Real-time three-dimensional transesophageal echocardiography may provide data to the diagnosis of pannus formation.

The treatment of pannus formation is surgical re-intervention to perform a new valve replacement. Occasionally, when pannus does not make contact with the prosthetic ring, the fibrotic tissue could be resected without replacing the prosthetic valve, but certain authors suggest that this surgical option is associated to a greater recurrence of pannus formation. All series agree in that the time to re-intervention is prolonged (Table 1). During follow-up of 63 patients with an obstructed mitral or aortic prosthetic valve, or both (pannus in 71.4% of cases), of whom 100% underwent valve replacement, in-hospital mortality was 20.6%. The main cause of death was low cardiac output syndrome and the only predictor of high mortality on multivariate analysis was LV systolic impairment[19]. In the series by Vitale *et al*[5] which

included 87 patients with obstructive mitral disease, of whom 75.8% had pannus either alone or associated to thrombus, 100% of patients underwent valve replacement (mechanical valve in 88.8%, biologic valve in 11.8%) with a 30-d mortality of 12.5%.

Recurrence is a finding of low prevalence and high mortality, and occurred predominantly in patients who underwent pannus resection without valve replacement[5,10].

Pannus is an infrequent complication that mainly affects mechanical prosthetic valves. Its diagnosis requires clinical suspicion and the association of fluoroscopy + TTE/TEE. Currently, the treatment of choice is a new valve replacement and prognosis depends mainly on LV function. The case presented is a characteristic example of pannus, given its clinical presentation (progressive dyspnea), the steps followed to reach diagnosis and the surgical resolution. Suspecting this disorder and making an accurate diagnosis is of paramount importance, to implement adequate treatment and to avoid prolonging the natural course of the disease and its repercussion on the LV and the quality of life of affected patients.

COMMENTS

Case characteristics

A 55-year-old man with a mechanical aortic prosthetic valve presented with clinical suspicion of prosthetic valve obstruction due to pannus formation.

Clinical diagnosis

The patient began experiencing dyspnea in FC II (NYHA) that progressed to FC IV. A meso-telesystolic murmur radiating to the neck was detected, as well as a pulsus tardus et parvus, with severely increased mechanical aortic valve gradients and decreased effective prosthetic area. No detectable image suggestive of pannus or thrombus was seen in the left ventricular outflow tract in multimodality imaging.

Differential diagnosis

Mechanical prosthetic valve dysfunction caused by pannus or thrombosis.

Imaging diagnosis

Fluoroscopy, transthoracic echocardiography, two-dimensional transesophageal echordiography and cardiac multiple detector computed tomography, failed to diagnose pannus formation.

Treatment

Given the clinical suspicion of prosthetic valve obstruction due to pannus formation, the decision was made to replace the aortic prosthesis with a new mechanical valve (ATS # 23). On pathological examination, the explanted specimen exhibited fibrous tissue with a smooth, annular surface, in contact with the ventricular surface of the mechanical prosthesis, consistent with pannus. Histological examination confirmed the diagnosis.

Related reports

The case presented is a characteristic example of pannus, given its clinical presentation (progressive dyspnea), the steps followed to reach diagnosis and the surgical resolution.

Experiences and lessons

Multimodality imaging in the diagnosis of pannus formation may have limitations. Suspecting this disorder and making an accurate diagnosis is of paramount importance, to implement adequate treatment and to avoid prolonging the natural course of the disease and its repercussion on the left ventricle and the quality of life of affected patients.

Peer-review

Authors have made good and fluent review of pannus formation and presented a clinical case ignored by transesophageal echocardiography and fluoroscopy.

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