ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2016 December 26; 8(12): 689-745

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

A peer-reviewed, online, open-access journal of Cardiology

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World Journal of Cardiology

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Monthly Volume 8 Number 12 December 26, 2016

World Journal of Cardiology
Volume 8 Number 12 December 26, 2016

Contents

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

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Xiu-Xia Song, Director
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World Journal of Cardiology
Baishideng Publishing Group Inc
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Telephone: +1-925-2238242
Fax: +1-925-2238243
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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v8.i12.689

World J Cardiol 2016 December 26; 8(12): 689-694
ISSN 1949-8462 (online)

EDITORIAL

Interaction of hyperlipidemia and reactive oxygen species: Insights from the lipid-raft platform

Eisuke Amiya

Eisuke Amiya, Department of Cardiovascular Medicine, Graduate School of Medicine, the University of Tokyo, Bunkyo-ku, Tokyo 113-8655, Japan

Author contributions: Amiya E solely contributed to this paper.

Supported by The Ministry of Education, Culture, Sports, Science and Technology of Japan through grant-in-aid 26461103 (to Amiya E).

Conflict-of-interest statement: The author declares no conflicts of interest.

Manuscript source: Invited manuscript

Correspondence to: Eisuke Amiya, MD, PhD, Department of Cardiovascular Medicine, Graduate School of Medicine, the University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. amiyae-tky@umin.ac.jp
Telephone: +81-33-8155411

Received: July 21, 2016
Peer-review started: July 26, 2016
First decision: September 6, 2016
Revised: September 7, 2016
Accepted: October 5, 2016
Article in press: October 9, 2016
Published online: December 26, 2016

Abstract

Reactive oxygen species (ROS) and oxidative stress are closely associated with the development of atherosclerosis, and the most important regulator of ROS production in endothelial cells is NADPH oxidase. Activation of NADPH oxidase requires the assembly of multiple subunits into lipid rafts, which include specific lipid components, including free cholesterol and specific proteins. Disorders of lipid metabolism such as hyperlipidemia affect the cellular lipid components included in rafts, resulting in modification of cellular reactions that produce ROS. In the similar manner, several pathways associating ROS production are affected by the presence of lipid disorder through raft compartments. In this manuscript, we review the pathophysiological implications of hyperlipidemia and lipid rafts in the production of ROS.

Key words: Lipid raft; Hyperlipidemia; Free cholesterol; Reactive oxygen species; NADPH oxidase

Core tip: Lipid raft is a membrane microdomain in which specific combinations of lipid components such as free cholesterol and proteins function to mediate and amplify a variety of cellular signals. The platform has a significant impact on the cellular reactions such as the production of reactive oxygen species, however, there are limited articles on the clinical relevance of this platform. Lipid disorder, such as hyperlipidemia, is one that significantly affects the platform, with the modification of associating cell functions in various ways. We focused on the effect derived from this platform in hyperlipidemia in this manuscript.

Amiya E. Interaction of hyperlipidemia and reactive oxygen species: Insights from the lipid-raft platform. *World J Cardiol* 2016; 8(12): 689-694 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i12/689.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i12.689

REACTIVE OXYGEN AND VASCULAR INJURY

Reactive oxygen species (ROS) and oxidative stress are considered key mediators of atherosclerosis[1]. ROS are involved in the progression of endothelial-cell dysfunction, which is accompanied by inactivation of endothelial nitric oxide synthase (eNOS) and decrease of nitric oxide (NO) levels[2]. Oxidative stress results from overproduction of ROS, failure of host antioxidant defense, or both. The effects of ROS-associated signal pathways have a meaningful impact on cellular function in endothelial cells. The most important modulator of ROS in endothelial cells is NADPH oxidase[3], and ROS metabolism is constantly modified by the surrounding environment. Pathological conditions associated with hyperlipidemia may be derived from these pathways of ROS, and the suppression of ROS may block the progression of those pathology[4].

RAFT PLATFORMS AS A REGULATOR OF ROS

Lipid rafts or membrane rafts are membrane microdomains in which specific combinations of lipid components and proteins function to mediate and amplify a variety of cellular signals[5]. Rafts are dynamic assemblies of cholesterol and lipids with saturated acyl chains, such as sphingolipids and glycosphingolipids in the exoplasmic leaflet of the membrane bilayer; and cholesterol in the inner leaflet. Intracellular reactions that produce ROS in endothelial cells can occur in lipid rafts, as a plasma membrane-associated NADPH oxidase complex exists within that compartment[6]. Clustering of lipid rafts in the cell membrane of endothelial cells causes the aggregation and activation of NADPH oxidase, thereby forming a redox signaling platform[7].

Raft structure and composition differ in various pathological states. Extracellular free cholesterol can be directly incorporated into the plasma membrane, leading to increase in cellular cholesterol levels[8]. Fang *et al*[9] showed that hypercholesterolemia increased the level of cellular free cholesterol approximately two-to four-fold in vascular endothelial cells[8]. The presence of very low-density lipoprotein (LDL) can cause a 50%-100% increase in total-cell unesterified cholesterol[10]. Indeed, endothelial cells are more likely to accumulate free rather than esterified cholesterol due to low ratio of hydrolysis to esterification. As a result, an increase in free cholesterol in endothelial cells causes a change in plasma membrane cholesterol content and may contribute to alterations in membrane function[11]. Similarly, hypercholesterolemia is also reported to alter the composition of lipid rafts and affect cell function in smooth muscle cells[12].

These pathological modifications of raft components affect ROS production. For example, a reduction of free cholesterol in rafts attenuates ROS production, leading to the suppression of ROS-associated downstream pathways[13]. By contrast, increase of plasma membrane free cholesterol leads to the modification of associated reactions that enhance ROS production[9]. Other conditions are known to affect the lipid components of rafts. For instance, aging has been associated with changes in sphingolipid and cholesterol, leading to the production of long-chain ceramides in plasma membrane[14] and the resulting enhancement of membrane-associated oxidative stress contributes to the progression of Alzheimer disease.

Not only lipid content of rafts but also specific proteins influence the behavior of associated reactions. Caveolin is an essential protein component of caveolae, which are unique raft compartments in the plasma membrane of endothelial cells[15]. Caveolin interacts with both lipids and lipid anchors on the raft proteins, and it functions as a scaffolding protein to organize and concentrate specific lipids and lipid-modified signaling molecules within the rafts[12,16]. In the presence of hypercholesterolemia, caveolin binding to eNOS is enhanced, leading to eNOS inactivation[17]. The resulting decrease in NO production has a significant impact on ROS metabolism. Hypercholesterolemia thus affects the production of ROS by a caveolin-associated pathway. Lobysheva *et al*[18] demonstrated that Caveolin-1 modulated the ROS behavior by regulating the balance of eNOS-derived NO. An increase in caveolin and eNOS interactions that occur with hyperlipidemia, may act to decrease NO production and promote endothelial dysfunction and atherosclerotic lesion formation[17].

The spatial compartmentation of eNOS in the raft compartment also has a significant impact of the behavior of ROS, in especially the cross-talk between NO and ROS. Under normal conditions, eNOS is associated with cholesterol-enriched caveolae in endothelial cells, where its activity can be closely regulated. However, in hyperlipidemia, lipoprotein particles modulate the activity and subcellular distribution of eNOS[19]. Incubation of endothelial cells with LDL, particularly oxidized LDL (ox-LDL), causes an increase in the binding of eNOS to CD36, which attenuates its activity and causes displacement of the protein from endothelial caveolae. In addition, the spatial interaction between eNOS and NADPH oxidase determines net NO and ROS production because the NO produced adjacent to NADPH oxidase is scavenged by the ROS[20]. Therefore, the pathological condition affects localization of ROS-associated molecules, resulting a change in the output from these pathways.

Rafts can also be platforms that enhance the production of reactive nitrogen. Yang *et al*[21] reported that TNF-α enhanced ROS production within these membrane compartments concomitant with recruitment of the p47phox regulatory subunit of NADPH oxidase

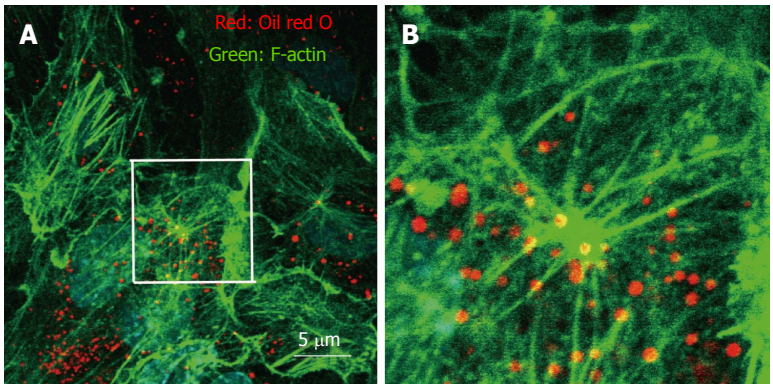

Figure 1 Immunohistochemistry of actin, and visualization of vesicle structures after free cholesterol loading and angiotensin Ⅱ in cultured human aortic endothelial cells. The cells were loaded by cholesterol-saturated methyl-b-cyclodextrin (Sigma, St. Louis, MO) (Chol/MBCD) and angiotensin Ⅱ (Wako, Tokyo, Japan) (200 nmol/L). Following treatment, cell were fixed, and stained using Alexa 546-conjugated phalloidin (Invitrogen, Carlsbad, CA) for visualization of F-actin and oil red O for visualization of vesicle structure. Oil red O-positive vesicles formed, and moved along the F-actin filament in the setting of actin remodeling induced by angiotensin Ⅱ. B is a magnified view of the white square in A.

subunit domains. In addition, TNF-α induced activation and phosphorylation of eNOS present in plasma membrane raft compartments. The dual activation of superoxide-generating and NO-generating systems within the same membrane domains provided a spatially favorable environment for formation of peroxynitrite.

Conversely, raft compartments are also susceptible to the oxidative reactions, resulting the oxidation of lipid components and modifying the associating reactions. For instance, 7-ketocholesterol, one oxidized form of cholesterol, was reported to deplete cholesterol from the raft domains and disrupt it[22,23]. However, the exact results of membrane injury by oxidized lipids are uncertain and are beyond the scope of this manuscript.

RAFT CONDITIONS AND ASSOCIATED REACTIONS

The association of rafts and the actin cytoskeletal network has been reported to affect the endocytic pathway. For instance, when the vacuolating cytotoxin (VacA), a major virulence factor of *Helicobacter pylori*, was continuously associated with raft compartments it was routed to early endosome antigen 1-sorting endosomes and then sorted to late endosomes[24]. We previously reported that intracellular vesicle structures in endothelial cells act as a raft-like domains that move along the actin cytoskeleton network (Figure 1)[13].

The most common raft protein, caveolin, can also be found in these endocytic pathways, such as late endosomes and lysosomes. Once it is ubiquitinated, it is transferred into intraluminal vesicles in endosomes for degradation using the endosomal sorting complex required for transport machinery[25]. During this translocation, caveolin is also recruited by accessory membrane compartments that affect its interactions with other intracellular compartments. Changes in lipid raft-based membrane compartmentation can involve movement of key molecules that modify intracellular dynamics. ROS production is one of the activities affected by the translocation of raft compartments. Indeed, NADPH oxidase-dependent ROS production in endosomes is seen as a proinflammatory immune response. Li *et al*[26] have demonstrated that interleukin-1β (IL-1β) stimulation promotes endocytosis of the IL-1β receptor (IL-1R1), leading to NADPH oxidase-dependent ROS production in early endosomes and subsequent redox-dependent activation of transcription factor NF-κB.

Previous reports demonstrated that visfatin activated lysosomal acid sphingomyelinase (ASM), the formation of raft redox signaling platforms, and consequent local oxidative stress[27]. Lysosome-associated molecular trafficking and the resulting ceramide accumulation in the cell membrane may mediate the assembly of NADPH oxidase subunits and their activation in response to adipokine visfatin in coronary artery endothelial cells, thereby producing endothelial dysfunction in the coronary vasculature.

In addition to intercellular vesicle structures, extracellular vesicle structures have been reported to associate with raft components[28]. Characterization of human B-cell-derived exosomes showed an abundance of membrane raft-associated lipids, including cholesterol and sphingomyelin[29]. Indeed, we found that modification of raft lipid components affected changes of molecules in vesicle structures (unpublished data). In addition, endothelial microparticles induced by angiotensin Ⅱ through the NADPH oxidase pathway, have been shown to associate with lipid raft[30]. These findings suggest that cholesterol metabolism affects the behavior of extracellular vesicles that can have an effect on pathological conditions. However, the physiological and pathological role of extracellular vesicles had not yet been elucidated. Further study of the mechanisms underlying the relationships of raft compartments and the extracellular vesicles produced by endothelial cells is warranted.

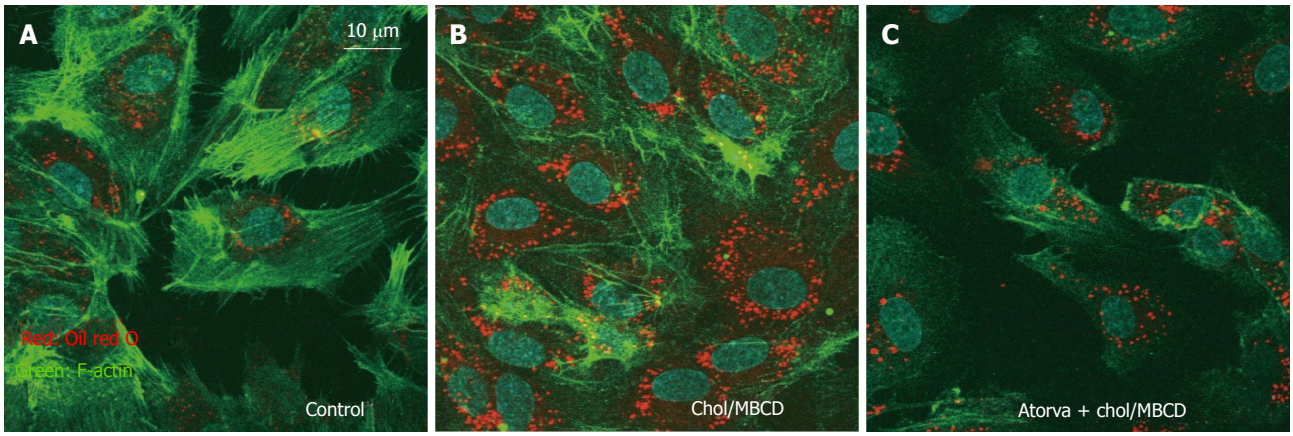

Figure 2 Immunohistochemistry of actin and visualization of vesicle structures after free cholesterol loading and atorvastatin pretreatment in cultured human aortic endothelial cells. The cells were loaded by cholesterol-saturated methyl-b-cyclodextrin (Chol/MBCD) with and without atorvastatin (10 μmol/L) pretreatment. Atorvastatin (Pfizer, New York, NY) pretreatment (C) significantly suppressed formation of vesicles induced by free cholesterol loading, as shown by oil red O as compared with Chol/MBCD loading alone (B); A: Control.

EFFECT OF STATINS ON RAFT COMPLEXES

Statins, inhibitors of HMG-CoA reductase, block cholesterol biosynthesis by inhibiting the mevalonate pathway, thereby producing a dramatic reduction in circulating LDL-cholesterol. Statins also exhibit non-cholesterol-lowering activities, including inhibition of inflammatory responses by immune cells such as macrophages and lymphocytes[31]. Statins also affect intracellular cholesterol pharmacokinetics, leading to other pleiotropic effects.

By interacting with the raft compartment, statins have been reported to inhibit the formation of raft redox signaling platforms and to decrease production of oxidized LDL in endothelial cells stimulated by a proatherogenic factor[32]. The inhibitory effect of statins on raft-redox signaling is associated with their vascular protective effects. Ponce *et al*[33] demonstrated that small reductions of intracellular cholesterol levels by simvastatin were associated with reduction in neuronal excitotoxity. The mechanism was found to be related to the translocation of NMDA receptors from raft compartment[33]. Other groups have found that statins inhibit OxLDL-induced ASM translocation and ceramide production in human aortic endothelial cells[34]. Previous studies have shown that lysosomal trafficking and translocation of ASM into membrane rafts results in ceramide production, membrane raft clustering, and formation of ceramide-enriched macrodomains[27]. Statins inhibit this ceramide formation, leading to the protection of endothelial function.

Raft cholesterol content affects cell function and changes in raft cholesterol content in response to statins have been shown to impact cell function. Zhuang *et al*[35] demonstrated that simvastatin lowered raft cholesterol content, leading to inhibition of Akt/PKB pathway signaling and induction of apoptosis in caveolin-negative and phosphatase and tensin homolog-negative LNCaP prostate cancer cells. On the other hand, cholesterol elevation also promoted tumor growth, increased phosphorylation of Akt, and decreased apoptosis in the xenografts.

We also observed that free cholesterol loading-induced vesicle structures were significantly suppressed by statin pretreatment (Figure 2). Intracellular vesicle structure was considered an intracellular raft platform, and statin affected the behavior of these platforms. As a result, the activity of platforms where key ROS-producing molecules are assembled may be decreased, with reduction of intracellular oxidative stress[13]. However, there had been little reports about the clinical effects of raft modifying agents other than statin. Further studies investigating about it is warranted.

CONCLUSION

This review described how ROS production is affected by the modification of lipid raft compartments in hyperlipidemia. The concept of lipid rafts may stimulate the development of novel therapeutic strategies for hyperlipidemia-associated pathologies. However, there had been little reports that demonstrated the clinical implication and importance of lipid raft compartments in lipid disorder. Further studies investigating about the associations between raft compartment and pathologic changes are needed.

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P- Reviewer: Cheng TH, Fujiwara N, Kukongviriyapan V, Tonks A
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Wu HL

World Journal of Cardiology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v8.i12.695

World J Cardiol 2016 December 26; 8(12): 695-702
ISSN 1949-8462 (online)

FRONTIER

To ventricular assist devices or not: When is implantation of a ventricular assist device appropriate in advanced ambulatory heart failure?

Emily Cerier, Brent C Lampert, Arman Kilic, Asia McDavid, Salil V Deo, Ahmet Kilic

Emily Cerier, Asia McDavid, Ahmet Kilic, Division of Cardiac Surgery, The Ohio State University Wexner Medical Center, Columbus, OH 43210, United States

Brent C Lampert, Division of Cardiovascular Medicine, the Ohio State University Wexner Medical Center, Columbus, OH 43210, United States

Arman Kilic, Division of Cardiovascular Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA 19104, United States

Salil V Deo, Harrington Heart and Vascular Institute, University Hospitals, Case Western Reserve University, Cleveland, OH 44106, United States

Author contributions: All of the authors contributed to this manuscript.

Conflict-of-interest statement: AK serves as consultant for Baxter International and St. Jude Medical; travel grant from HeartWare. BL and EC have no disclosures.

Manuscript source: Invited manuscript

Correspondence to: Ahmet Kilic, MD, Assistant Professor of Surgery, Division of Cardiac Surgery, The Ohio State University Wexner Medical Center, N-816 Doan Hall, 410 W. 10th Avenue, Columbus, OH 43210,
United States. ahmet.kilic@osumc.edu
Telephone: +1-614-2938878
Fax: +1-614-2934726

Received: July 12, 2016
Peer-review started: July 13, 2016
First decision: August 4, 2016
Revised: October 11, 2016
Accepted: October 22, 2016
Article in press: October 24, 2016
Published online: December 26, 2016

Abstract

Advanced heart failure has been traditionally treated *via* either heart transplantation, continuous inotropes, consideration for hospice and more recently *via* left ventricular assist devices (LVAD). Heart transplantation has been limited by organ availability and the futility of other options has thrust LVAD therapy into the mainstream of therapy for end stage heart failure. Improvements in technology and survival combined with improvements in the quality of life have made LVADs a viable option for many patients suffering from heart failure. The question of when to implant these devices in those patients with advanced, yet still ambulatory heart failure remains a controversial topic. We discuss the current state of LVAD therapy and the risk *vs* benefit of these devices in the treatment of heart failure.

Key words: Left ventricular assist device; Mechanical circulatory support; Heart failure; Cardiomyopathy; Diastolic dysfunction

Core tip: Heart failure remains the most common diagnosis in patients discharged from the hospital. In its most advanced stages, it bears a grim prognosis and there are only a limited number of treatments that can truly change the course of the disease. Advancements in left ventricular assist device technology have enticed

clinicians to expand their role in earlier ambulatory, but advanced heart failure. Here, we describe the current equilibrium between early implantation and risks of the current technology.

Cerier E, Lampert BC, Kilic A, McDavid A, Deo SV, Kilic A. To ventricular assist devices or not: When is implantation of a ventricular assist device appropriate in advanced ambulatory heart failure? *World J Cardiol* 2016; 8(12): 695-702 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i12/695.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i12.695

INTRODUCTION

Approximately 5.7 million people in the United States have heart failure (HF) and more than half of those who develop heart failure die within five years of the diagnosis[1]. As the population ages, the incidence of HF is expected to concurrently increase highlighting the importance of a continuation of need for developing more effective therapies. In the current spectrum of options, heart transplantation remains the gold standard for those with advanced heart failure[2]. The limitation of organ availability and unpredictability of rapidly advancing multi-system organ deterioration in patients with advanced heart failure have contributed to the rapid rise of left ventricular assist device (LVAD) implantation.

Since their first inception, there have been marked improvements in LVAD technology making them now a reliable therapeutic option for patients with advanced heart failure. There have been over 15000 mechanical circulatory support devices implanted since 2006 in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry[3]. In addition to improvements in technology, better understanding of patient selection, peri-operative management strategies, and long term management have led to reduced complications with improvements in survival and quality of life in HF patients[4].

Despite tremendous advancements, however, there remain important limitations to LVADs. Gastrointestinal bleeding, infections, thromboembolic events such as stroke, pump thrombosis and right heart failure remain barriers to earlier use of this therapy. Even with these improved clinical outcomes and significant decreases in size of LVADs, many patients and clinicians still view them as bulky machines associated with significant morbidity, mortality and need for life-long hospitalization. Patients with advanced disease who have not quite reached "end-stage heart failure" present lower surgical risk with less end organ dysfunction, better functional capacity, and enhanced capacity to rehabilitate from major surgery. Many experts contend that these "less sick" ambulatory advanced heart failure patients could benefit from earlier LVAD implantation, but in clinical practice this has yet to commonly occur.

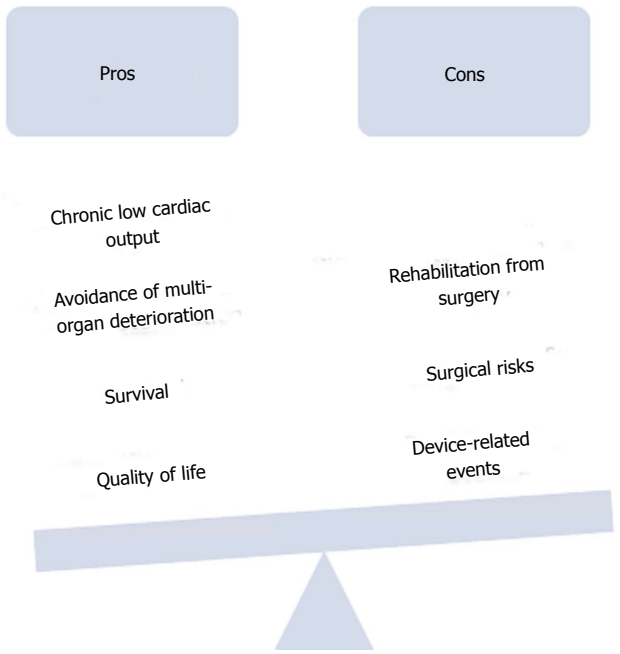

Figure 1 Factors determining timing of left ventricular assist devices implantation. Factors for earlier implantation of left ventricular assist devices are increased survival and quality of life, avoidance of multi-organ deterioration and chronic low cardiac output while factors against earlier implantation are device-related events, surgical risks, and rehabilitation from surgery.

(Cite intermacs report and can find other opinion pieces about early implantation).

This paper aims to review the current advantages and disadvantages of LVAD implantation in patients with advanced, ambulatory heart failure and discuss the pertinent issues in establishing an equilibrium between early surgical and/or device-related risks and benefits of quality and/or quantity of life with earlier implantation (Figure 1).

QUALITY OF LIFE

When asked about their decision to pursue optimal medical management over LVAD, patients stated reasons such as "they didn't like the idea of a major device implantation surgery", "they are worried about the possible complication", and they don't think an LVAD will improve quality of life and survival[5]. Moreover, many patients are never referred for advanced mechanical support due to inadequate understanding of LVAD outcomes by their medical providers and unavailability of the technology locally. However, one-year survival with the current pump technology is near 80%, which is markedly higher compared to the original data that established LVADs as a form of heart failure therapy[3]. To parallel the great advancements in LVAD therapy, it seems natural that the number of patients offered this therapy will continue to increase to the more than 10% of the HF population that will progress to advanced heart failure.

Even with tremendous improvements in survival and device related adverse events over the past

decade, considerable debate persists regarding the optimal timing of LVAD implantation. The benefits of LVAD implantation in inotrope dependent patients and those in cardiogenic shock are generally accepted. However, for patients with advanced heart failure who have not yet progressed to inotrope dependency the decision is more challenging. A single effective model for risk stratification is currently lacking for this large, heterogeneous, group. Traditionally patients have been classified according to the New York Heart Association (NYHA) functional classification, but this system is somewhat subjective and limited by significant inter-reporter variability[6]. While current FDA approval exists for LVAD implantation in NYHA class IIIB and class IV patients, the vast majority (81%) of LVADs are implanted in those identified as class IV on chronic inotropic therapy or in cardiogenic shock[5]. Implantation of LVADs has led to improved symptom burden and quality of life in those with advanced heart failure. In the HeartMate II destination therapy trial, 80% of patients who received a continuous flow LVAD went from NYHA class III or IV to NYHA class I or II. Furthermore, these patients also had a significant increase in a 6-min walk distance by 1 year[7].

SURVIVAL

As previously stated, the one-year survival with the current pump technology is near 80%[5]. The greatest risk for mortality following LVAD implantation falls during the early post-operative period and reaches a low by 3 mo following the procedure[8]. When analyzing factors that are related to survival following LVAD implantation, the 7th INTERMACS Annual Report found that patients with an INTERMACs profile of 2-3, and thus less severe disease, have better survival than those with an INTERMACS profile 1[5]. However, while INTERMACS levels 1-3 have been associated with lower survival rates 3 years post-LVAD implantation when compared to levels 4-7, no graded mortality risk has been demonstrated to help further discriminate the potential benefit between levels 4-7, which could be associated with the subjectivity of assignment in these levels[9]. Per Shah *et al*[8], other factors that have a great impact on LVAD perioperative mortality include age, female sex, prior stroke, mechanical ventilation, LVAD for destination therapy, hepatic or renal dysfunction, right ventricular dysfunction, and prior or concurrent cardiac surgery.

Risk assessments

To better characterize patients' risk to benefit profiles for LVAD implantation, multiple risk assessments have been developed. Unfortunately, few consistent predictors have been identified across models and currently no single model effectively triages potential LVAD patients. In general, however, the predictors that have been recognized in different models are markers of end-organ dysfunction secondary to heart failure or other significant comorbidities, such as age[9,10]. Patients that are "sicker", as reflected by a more acute INTERMACS profile, are also known to have worse outcomes. Moreover, regardless of INTERMACS profile, mortality increases with increasing age at the time of implantation[3]. With this in mind, there is support for considering LVAD implantation earlier in the disease course theoretically leading to lower operative risk and fewer post-operative complications.

In continuing to lower the morbidity and mortality associated with LVADs the balance of patient risk to benefit for LVAD implantation may suggest sooner application of this technology.

Adverse events

Though LVAD implantation can result in significant improvements in morbidity and mortality, their use is associated with complications including infection, stroke, pump thrombosis, gastrointestinal bleeding, and right ventricular failure. Infection occurs in about 20% of patients following implantation and may present as sepsis or a driveline infection. Infection additionally may predispose to pump thrombosis[11]. Pump thrombosis occurs at an annual incidence of 6%-12%, although the exact incidence varies based on device type and anticoagulation regimen employed. One thing for certain; however, is that pump thrombosis is associated with an increase in neurologic events as well as a higher rate of mortality. Cerebrovascular complications occur with an annual incidence of greater than 6%[8]. Furthermore, 30% of patients have major bleeding in the first month, and then following one month, bleeding occurs at a rate of 8%-23% by one year. Overall, 55% of patients will be rehospitalized for any cause[11].

Bleeding

Bleeding, in particular gastrointestinal bleeding, is associated with significant morbidity after LVAD implantation. The cause of increased bleeding is multifactorial and can be attributed to chronic anticoagulation, acquired von Willebrand syndrome, and chronic low pulse pressure leading to increased risk for angiodysplasia. Therefore, screening patients for angiodysplasia and von Willebrand syndrome prior to implantation may allow for preemptive treatment of these conditions to help avoid complications postoperatively[12]. With further understanding of the pathogenesis of bleeding post implantation and research on the prevention and appropriate management, its hopeful the risk of bleeding will decrease to support the earlier implantation of LVADs.

Pump thrombosis

As stated before, Pump thrombosis occurs at an annual incidence of 6%-12% raising awareness that LVAD therapy is not without inherent risks[8]. The lack of equipoise in many physicians' minds of

benefit *vs* risk of LVAD for NYHA Class Ⅲ patients that were highlighted by pump thrombosis led to early termination of the Registry Evaluation of Vital Information for VADs in Ambulatory Life (REVIVE-IT) trial. The PREVENT (Prevention of Heartmate Ⅱ Pump Thrombosis through Clinical Management) study was designed to analyze the impact of clinical practices developed to decrease the risk of Heartmate Ⅱ pump thrombosis. The study followed the "PREVENT protocol" which were recommendations on LVAD implantation, anticoagulation and antiplatelet protocols, and pump management. Preliminary results have been positive and show that the protocol is associated with lower rates of thrombosis without increased incidence in bleeding complications[13].

Furthermore, in the case that pump exchange must occur, the morbidity and mortality of the exchange has decreased. Soleimani *et al*[14] found that off-pump minimally invasive exchange of the Heartmate Ⅱ can be safely accomplished with low morbidity and mortality, resulting in excellent outcomes. Therefore, will evolving clinical guidelines improving the risk of pump thrombosis and minimizing the risk of adverse events in addition to the decreased morbidity and mortality of pump exchange, this supports the shift to earlier implantation of LVADs.

Right ventricle failure

In particular, the risk of right heart failure following LVAD implantation has been extremely difficult to predict. With improved left ventricular decompression, pulmonary congestion should decrease resulting in decreased afterload for the right ventricle. However, increased cardiac output from LVAD support will result in increased right ventricle preload. Also, leftward shift of the interventricular septum shift and change in motion after LVAD implantation may impair the right ventricle contractility, leading to right ventricle dysfunction, and ultimately right heart failure[15]. Right ventricular failure is likewise often the last manifestation of advanced heart failure. There are no durable treatment options currently available for right ventricular failure emphasizing the need to prevent it in LVAD patients, and identify those who may be at increased risk of developing it with extended time with an LVAD.

A study by Santambrogio *et al*[16] showed that early right heart failure will develop in about 25% of patients receiving LVAD support. Furthermore, Argiriou *et al*[15] noted that female sex, existence of pre-operative circulatory failure, presence of end-organ dysfunction, severe right ventricle systolic dysfunction, and presence of pulmonary vascular disease are all pre-operative risk factors for early right heart failure. However, there are limitations to all these risk factor stratification models as has been pointed out by Lampert *et al*[17] that most of the risk scores were developed primarily in BTT patients with pulsatile devices, and so there is a need for further investigation. The report notes that echocardiography, hemodynamic parameters, and biomarkers including neutrophil gelatinase-associated lipocalin, blood urea nitrogen, aspartate aminotransferase and serum creatinine could be of use in predicting pre-operative risk of early right heart failure.

While much has been studied about early right heart failure following LVAD implantation, less is known about the development of late right ventricular failure, which is an important complication to consider when arguing to implant LVADs in patients earlier. As there is a question of whether late right heart failure is a distinct entity, or just undiagnosed early right heart failure, the risk factors are not as well established, although there is likely significant overlap with the risk factors of early right heart failure[17]. Takeda *et al*[18] found that late right heart failure occurred in about 11% of patients at a median of 99 d, with significant predictors including diabetes mellitus, body mass index greater than 29 kg/m^2, and BUN level greater than 41 mg/dL. These patients had significantly worse survival when compared to those who did not develop late right heart failure, but this could also be attributable to their increased incidence of comorbidities. Currently, treatment for late right heart failure is directed at the underlying causes and management of symptoms, however it is thought that optimization of pump speed, which will avoid excessive leftward septal shift and decrease excessive venous return, may help to avoid this late complication[17]. Further research on the effects of more frequent imaging and hemodynamic measurements in patients with LVADs could help develop appropriate post implantation management guidelines to best screen for and prevent late right heart failure. Additionally, avoiding early and aggressive titration of beta-blockers and use of inotropes to support right ventricular function and pulmonary vasodilators to decrease right ventricular afterload may also help[17].

Thus, if these risk factors could be further developed and taken into consideration when selecting patients for early implantation, the risk of late right heart failure could be minimized. With the shift to earlier implantation of LVADs, there is a clear need for continued research in the screening and management of late right heart failure to better care for patients who do receive LVADs earlier in their course of heart failure. However, the development of bi-ventricular failure in non-transplant eligible patients still warrants special consideration. Advancements in total artificial heart technology and a better understanding of right ventricular failure are needed to better care for these patients who do develop right ventricular failure.

Despite these adverse events, The 7th INTERMACS Annual Report demonstrated that with the improved technology of the continuous-flow pumps, there has been a dramatic decrease in the overall adverse event rate when pumps implanted between 2012 to 2014 are compared to pumps implanted between 2008 to

Table 1 Studies analyzing the early implantation of left ventricular assist devices

Study	Objective	Significant findings
ROADMAP	Compare outcomes of HeartMate Ⅱ implantation in destination therapy patients who are not dependent on inotropic support with those on optimal medical management	Early LVAD implantation associated with improved quality of life and more adverse events. Intent to treat analysis showed no survival benefit with early implantation
REVIVE-IT	Compare outcomes of HeartMate Ⅱ implantation in NYHA class Ⅲ patients not severe enough to qualify for transplant or permanent LVAD therapy with those on optimal medical management	Study discontinued due to difficulty recruiting from observed increase in pump thrombosis (enrolled 0/100 patients (randomized study), 0/2500 patients (screening registry)
MedaMACS	Characterize and report on patients with ambulatory advanced heart failure who have not receive an LVAD	Patients desire LVADs and LVAD shows survival benefit compared to medical management for INTERMACS 4 and 5

ROADMAP and REVIVE-IT both evaluated the impact of implanting LVADs earlier in the heart failure progression while MedaMACS created a registry of patients on optimal medical therapy without LVADs to parallel INTERMACS data, and allow for a comparison of patients with LVADs to patients on optimal medical therapy; REVIVE-IT: Registry Evaluation of Vital Information for VADs in Ambulatory Life; NYHA: New York Heart Association; MedaMACS: Medical Arm of the Interagency Registry for Mechanically Assisted Circulatory Support; LVAD: Left ventricular assist devices.

2011[5].

CURRENT TRIALS IN TIMING OF LVAD IMPLANTATION

Appropriate identification of patients with the best chance to benefit from therapy and lowest risk of complications is a perpetual focus of investigation for LVAD implantation. For example, Boyle *et al*[19] found that patients on inotropes before LVAD implantation trended toward a higher incidence of hemorrhagic stroke post-operatively. Boyle *et al*[19] also found that patients in INTERMACS 4-7 had significantly shorter length of stay following LVAD implantation and greater survival when compared to both INTERMACS 1, and 2/3 patients[20]. This suggests that selecting patients earlier on in the progression of heart failure, prior to dependence of inotropic therapy, would reduce the LVAD implantation post-operative risk of complications. Furthermore, studies are currently being conducted which directly show the benefit in both quality of life and survival with earlier LVAD implantation (Table 1, Figure 2).

Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients

The Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (ROADMAP) Study attempted to evaluate the effects of LVAD implantation in less sick patients[5]. ROADMAP was a prospective, multi-center, nonrandomized observational study that evaluated outcomes of LVAD implantation in destination therapy patients who are not dependent on inotropic support (INTERMACS profiles 4-7). Currently, these patients make up roughly 20% of all implantations[5]. In ROADMAP, patients and their providers chose to continue on optimal medical therapy (OMM) or proceed with LVAD implantation. The primary composite end-point was survival on original therapy with increase in 6 min walk distance (6MWD) by at least 75 m. Significantly more patients in the LVAD cohort (n = 97) reached this endpoint than those on OMM (n = 103) (39% *vs* 21%). Furthermore, the LVAD group had greater improvements in self-reported quality of life and depression. Additionally, the LVAD group had 77% of patients change in their NYHA classifications to class Ⅱ or Ⅰ, while the OMM group only had 29% change to class Ⅱ, and none to class Ⅰ (Figure 3). This greater improvement in functional status was also supported by the improvements in the 6MWD, as LVAD patients had a significant increase while there was no significant change in the OMM cohort. The LVAD group also had a significantly greater 12-mo as-treated (event-free) survival (80% *vs* 63%). However, since delayed LVAD implantation counted as a "failure" in OMM patients, the intent-to-treat analysis showed no survival benefit with early LVAD implantation[5].

There were some adverse findings with early LVAD implantation. These patients had more frequent adverse events as compared to the OMM patients. LVAD patients' adverse events were primarily due to bleeding as opposed to the OMM patients' adverse events that were primarily due to worsening heart failure[5]. The ROADMAP results suggest that earlier LVAD implantation in select patients may provide significant benefit, but there remains no consensus on a singular way to identify these patients.

A significant limitation to the ROADMAP trial that prevents generalization of the results is the lack of randomization of patients between LVAD and OMM. At baseline, patients who elected to have an LVAD were sicker than those who elected to continue OMM. The LVAD group had more NYHA class Ⅳ patients (52% *vs* 25%), which is a group that is generally already thought to benefit from LVAD implantation. Moreover, the LVAD group in ROADMAP consisted of more INTERMACS profile 4 patients (65% *vs* 34%), had less beta-blocker use, and a lower predicted Seattle Heart Failure Model 12-mo survival. Also, the LVAD cohort was much less satisfied with their quality of life on average than the OMM group[5]. This could lessen the significance of the greater improvements in self-reported depression and quality of life. Despite these limitations, the LVAD group

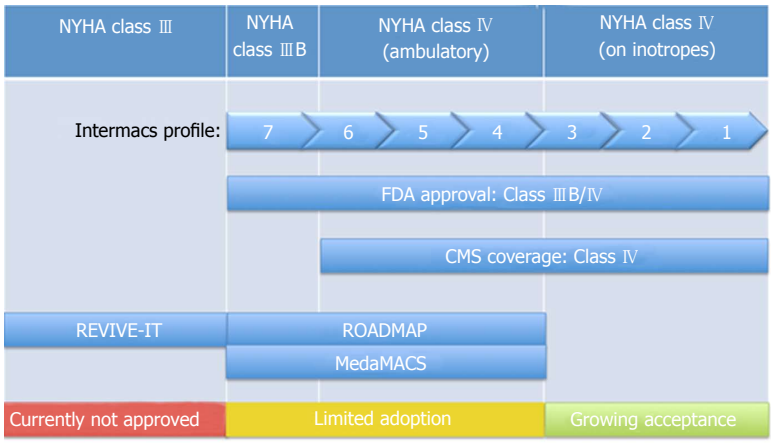

Figure 2 New York Heart Association classes considered for left ventricular assist devices implantation. Currently, FDA approval for LVAD implantation exists for NYHA Class ⅢB and Ⅳ, which encompasses all of the INERMACS profile levels. ROADMAP is evaluating LVAD implantation in patients of NYHA class Ⅲ and class Ⅳ (ambulatory), which has limited adoption in most clinical practices. MedaMACS looked at the same patient population as ROADMAP however focused on those patients without LVADs. REVIVE-IT was evaluating implantation in patients in NYHA class Ⅲ, which is not currently FDA approved. LVAD: Left ventricular assist devices; FDA: Food and Drug Administration; MedaMACS: Medical Arm of the Interagency Registry for Mechanically Assisted Circulatory Support; NYHA: New York Heart Association.

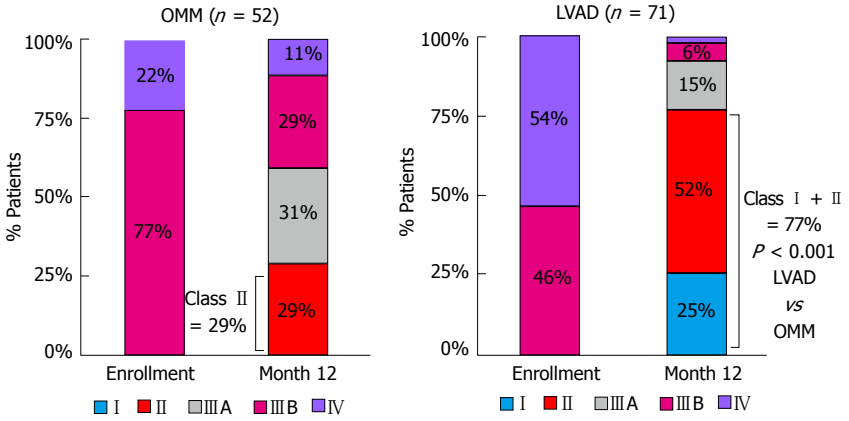

Figure 3 Comparison of baseline and 12-mo after enrollment from the ROADMAP study comparing left ventricular assist device implantation with optimal medical management. OMM: Optimal medical management; LVAD: Left ventricular assist device; Ⅰ-Ⅳ: New York Heart Association classification[5] (Reprinted with permission from *J Am Coll Cardiol*).

still showed much more functional improvement in both the 6 min walk test and NYHA classification.

Medical Arm of the Mechanically Associated Circulatory Support

The Medical Arm of the Mechanically Associated Circulatory Support (MedaMACS) project is an ongoing cross-sectional, observational study following patients with ambulatory advanced heart failure (INTERMACS profile 4-7) that aims to characterize and report on the medical outcomes of those patients who have not yet received an LVAD (include citation). In the MedaMACS screening pilot study, a majority (56%) of patients reported they would "definitely" or "probably" want an LVAD given the alternative was their current symptomatic state. Interestingly, 93% of these patients were at a low or intermediate implant risk based on the HeartMate Ⅱ Risk Score. Furthermore, many patients were willing to consider LVAD surgery despite expectation of a long survival with OMM suggesting that more than HF mortality influences preference for mechanical support[21]. This suggests that patients value the improved quality of life made possible by LVADs and may be willing to take on the risk of adverse events associated with them. Hence an argument can be made for LVAD implantation in the ambulatory heart failure patient by individualized patient desire.

In terms of survival, MEDAMACS showed a one-year survival for patients on medical management of 78% in INTERMACS level 6/7, 67% in INTERMACS level 5, and 39% in INTERMACS level 4[8]. Therefore, when compared to the 80% one-year survival after LVAD implantation, this data would suggest an increase in survival for patients in INTERMACS level 4/5 who undergo LVAD implantation and further supports a shift towards earlier implantation of LVADs and an expansion in their utilization.

REVIVE-IT

The REVIVE–IT study, like the ROADMAP study, also

planned to test the theory that patients with less advanced heart failure will benefit in both survival and quality of life with LVAD implantation as opposed to optimal medical management. This trial however was to analyze LVAD implantation in moderate NYHA class Ⅲ patients with marked limitation of physical activity and LVEF of 35% or less[22]. However, this study was discontinued as it met great challenges with recruiting patients due to the observed increase from 2.2% at 3 mo post-implantation to 8.4% in pump thrombosis in the pump used in the study discovered by Starling *et al*[23]. Therefore, in combination with the perceived increased risk of thrombosis, a renewed hesitancy for wider adoption of LVAD technology grew. As some were already risk aware in patients with NYHA class Ⅳ/INTERMACS profile 4-6 patients, it became clear that routine consideration of patients for NYHA Class Ⅲ/INTERMACS profile 7 were too far out of reach. However, it is clear that controversy persists as, the ROADMAP study has shown the benefits of earlier implantation with regards to quality of life and once again shifting the equilibrium towards early implantation.

CONCLUSION

When considering the earlier implantation of LVADs, its critical for one to account for the extended amount of time these patients will have using the LVADs and how that will impact the potential for adverse events. The increased chance of adverse events will need to be weighed against the increase in quantity and quality of life.

Although LVADs are currently being used to improve quality and quantity of life for those in NYHA class Ⅳ end-stage heart failure, there is anticipation that a much larger group of patients may benefit from this potentially life-saving therapy. Although we are not quite there yet, we are moving towards a balance where the improvement of quality and quantity of life outweigh the risks of adverse events for patients who aren't quite yet at NYHA class Ⅳ end-stage heart failure. Patients who are implanted earlier may experience much greater benefits with lower risks of complication than those currently being treated. Earlier implantation of LVADs, prior to the onset of end organ dysfunction, may have benefits when compared to optimal medical management and could be considered as an alternative for less advanced heart failure patients, who do not have risk factors for adverse events. In continuing to reduce the morbidity and long-term risks of LVAD implantation, LVADs will likely be used earlier in the treatment of advanced heart failure as the technology progresses. In fact the next generation of devices, the HeartMate Ⅲ (St. Jude Medical, St. Paul, MN) and the MVAD (HeartWare International Inc, Framingham, MA) have been developed with this very goal in mind – to push the boundaries of reducing surgical morbidity and long-term reduction of device related adverse events. With continued research in the early implantation of LVADs we can better identify what to expect with extended time on LVAD support. Additionally, with continued research on incidence, management and prevention of adverse events, we can better select patients for early implantation and be more prepared in the case that adverse events occur. As we continue to learn from trials such as the ROADMAP trial and the MedaMACS registry, we hope to clarify the delicate balance between implantation of devices in patients who are too sick to benefit from the therapy and those who are too well to undergo the morbidity of the procedure.

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P- Reviewer: Amiya E, Bonanno C, Cebi N, Kirali K, Skobel E
S- Editor: Kong JX **L- Editor**: A **E- Editor**: Wu HL

World Journal of Cardiology

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DOI: 10.4330/wjc.v8.i12.703

World J Cardiol 2016 December 26; 8(12): 703-718
ISSN 1949-8462 (online)

REVIEW

Hematological disorders and pulmonary hypertension

Rajamma Mathew, Jing Huang, Joseph M Wu, John T Fallon, Michael H Gewitz

Rajamma Mathew, Department of Physiology, New York Medical College, Valhalla, NY 10595, United States

Rajamma Mathew, Jing Huang, Michael H Gewitz, Section of Pediatric Cardiology, New York Medical College, Valhalla, NY 10595, United States

Joseph M Wu, Department of Biochemistry and Molecular Biology, New York Medical College, Valhalla, NY 10595, United States

John T Fallon, Department of Pathology, New York Medical College, Valhalla, NY 10595, United States

Author contributions: All authors contributed to this manuscript.

Conflict-of-interest statement: None of the authors has conflict of interest.

Manuscript source: Invited manuscript

Correspondence to: Rajamma Mathew, MD, Section of Pediatric Cardiology, New York Medical College, Rm A11, Basic Science Building, 15 Dana Rd, Valhalla, NY 10595, United States. rajamma_mathew@nymc.edu
Telephone: +1-914-5943283

Received: June 29, 2016
Peer-review started: July 1, 2016
First decision: August 5, 2016
Revised: September 13, 2016
Accepted: October 5, 2016
Article in press: October 9, 2016
Published online: December 26, 2016

Abstract

Pulmonary hypertension (PH), a serious disorder with a high morbidity and mortality rate, is known to occur in a number of unrelated systemic diseases. Several hematological disorders such as sickle cell disease, thalassemia and myeloproliferative diseases develop PH which worsens the prognosis. Associated oxidant injury and vascular inflammation cause endothelial damage and dysfunction. Pulmonary vascular endothelial damage/dysfunction is an early event in PH resulting in the loss of vascular reactivity, activation of proliferative and antiapoptotic pathways leading to vascular remodeling, elevated pulmonary artery pressure, right ventricular hypertrophy and premature death. Hemolysis observed in hematological disorders leads to free hemoglobin which rapidly scavenges nitric oxide (NO), limiting its bioavailability, and leading to endothelial dysfunction. In addition, hemolysis releases arginase into the circulation which converts L-arginine to ornithine, thus bypassing NO production. Furthermore, treatments for hematological disorders such as immunosuppressive therapy, splenectomy, bone marrow transplantation, and radiation have been shown to contribute to the development of PH. Recent studies have shown deregulated iron homeostasis in patients with cardiopulmonary diseases including pulmonary arterial hypertension (PAH). Several studies have reported low iron levels in patients with idiopathic PAH, and iron deficiency is an important risk factor. This article reviews PH associated with hematological disorders and its mechanism; and iron homeostasis and its relevance to PH.

Key words: Anemia; Hemolysis; Iron homeostasis; Myelofibrosis; Pulmonary hypertension

Core tip: Oxidant injury, inflammation, impaired nitric oxide bioavailability and coagulopathy that

occur in hematological diseases lead to endothelial dysfunction and thrombo-embolism with subsequent development of pulmonary hypertension (PH). In addition, treatment used for these disorders such as immunosuppressive drugs, splenectomy, bone marrow transplantation and radiation therapy are also known to cause endothelial damage and thrombo-embolism leading to PH. Furthermore, there is a causal relationship between vascular and hematopoietic systems. Patients with chronic myeloproliferative diseases are at a risk of developing PH; and the occurrence of myelofibrosis contributing to impaired hematopoiesis is not uncommon in PH.

Mathew R, Huang J, Wu JM, Fallon JT, Gewitz MH. Hematological disorders and pulmonary hypertension. *World J Cardiol* 2016; 8(12): 703-718 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i12/703.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i12.703

INTRODUCTION

Pulmonary hypertension (PH) is a devastating sequela of a number of diverse systemic diseases including cardiopulmonary, autoimmune, inflammatory and myeloproliferative diseases, drug toxicity, acquired immunodeficiency syndrome, portal hypertension, and hemolytic anemia. Based on the clinical diagnosis, PH is classified into 5 major groups, which was updated in 2013[1]. Group 1 is labeled pulmonary arterial hypertension (PAH). Included in this group are idiopathic and heritable PAH, PAH associated with human immunodeficiency viral infection, schistosomiasis, congenital heart defect, connective tissue diseases, portal hypertension and drug-induced PAH. In the current updated classification, PH associated with hematological disorders, myeloproliferative diseases and splenectomy has been moved to Group 5. Pulmonary veno-occlusive disease (PVOD)/pulmonary capillary hemangioma and persistent PH of the newborn are in Group 1 as subcategories (1′ and 1″ respectively). Group 2 comprises PH associated with congenital and acquired left heart diseases, Group 3 includes PH due to lung diseases and/or hypoxia, Group 4 includes chronic thromboembolic pulmonary hypertension (CTEPH). PH associated with hematological disorders, myeloproliferative diseases, splenectomy and a number of miscellaneous systemic and metabolic disorders are included in group 5. PH is defined as a mean pulmonary artery (PA) pressure of $\geqslant$ 25 mmHg at rest as measured by cardiac catheterization. Right heart catheterization is considered the gold standard for the diagnosis of PH. Echocardiography is a useful noninvasive tool to estimate right ventricular systolic pressure (in the absence of right heart obstruction) for screening and monitoring the patients with PH[2].

Pulmonary vascular endothelial injury/disruption is considered to be an important initiating factor in the development of PH. The severity, the extent and the site of endothelial damage may determine the type of PH and the irreversibility of the disease. Endothelial cells (EC), a non-thrombogenic monocellular layer function as an interface between the circulating blood and the underlying tissue. EC produce vasorelaxants such as nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor. In addition, EC inhibit cell proliferation, and participate in inflammation, thrombosis, barrier function, cell cycle and apoptosis; EC control vascular tone and structure, maintain homeostasis, thus, participate in vascular pathobiology. NO, generated from L-arginine by catalytic activity of endothelial NO synthase (eNOS) in vascular EC is a short-lived free radical; it stimulates soluble guanylate cyclase that catalyzes guanosine triphosphate to cyclic guanosine monophopshate (cGMP). Increase in cGMP results in a decrease in Ca^{2+} levels that mediates NO functions including vascular relaxation[3]. eNOS is localized in special cellular domains in EC including Golgi bodies and plasmalemmal caveolae, and is tightly regulated by a variety of transcriptional, post-transcriptional and post-translational mechanisms. The proteins that modulate the eNOS activity include caveolin-1, heat shock protein 90, cationic amino acid transporter 1 (arginine transporter), Ca^{2+}-calmodulin, and others. Caveolin-1 is a scaffolding protein of caveolae found on the plasma membrane of a variety of cells including EC, smooth muscle cells (SMC) and fibroblasts. Caveolin-1 interacts with transducing molecules in caveolae and maintains these molecules in an inhibitory state. It has a dynamic relationship with eNOS. In EC, caveolin-1 inhibits NO signaling by binding to eNOS. In response to various stimuli, eNOS is dissociated from caveolin-1, and generates NO. However, caveolin-1 is essential for agonist-induced eNOS activation[3,4]. In addition, the eNOS activity is controlled by endogenous circulating inhibitors; the most important being the L-arginine analog, asymmetric dimethylarginine (ADMA). ADMA inhibits eNOS-mediated production of NO from L-arginine. A large portion of circulating ADMA is metabolized by dimethylarginine dimethylaminohydrolase (DDAH) to L-citrulline and dimethylamine. DDAH is inhibited by oxidative stress, thereby leading to ADMA accumulation and resulting EC dysfunction[5]. Recent studies have shown that erythrocytes take up and store ADMA. Following lysis of erythrocytes, proteolysis of methylated proteins generate free ADMA which then can inhibit NO production leading to EC dysfunction, and contribute to vascular disease[6]. In a group of 34 healthy individuals (age 2 d-24 years), plasma levels of ADMA has been shown to decrease with age[7].

Hemolysis is a common occurrence in a number of hematological disorders. Released free hemoglobin (Hb) as a result of hemolysis reacts with NO and forms inactive nitrate and methemoglobin, thus leading to endothelial dysfunction. In addition, arginase 1 released

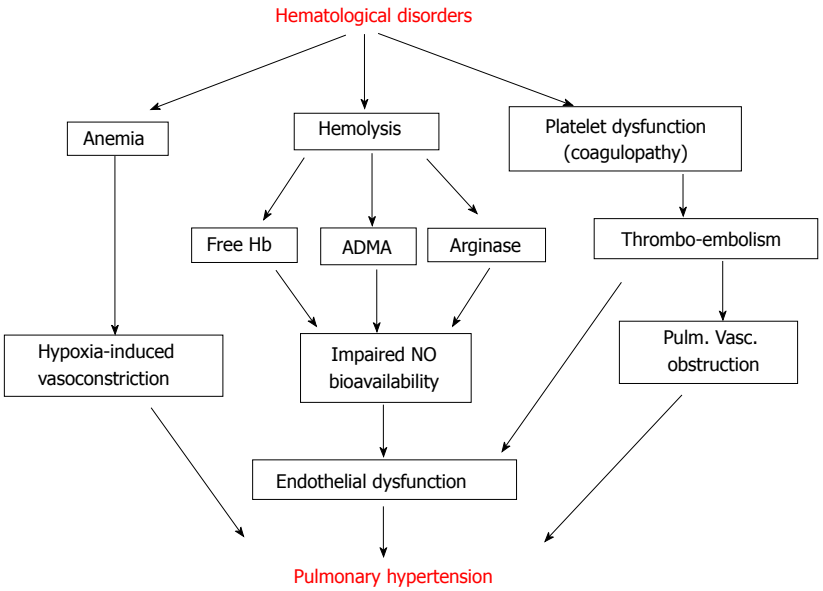

Figure 1 Various pathways of hematological disturbances leading to pulmonary hypertension. ADMA: Asymmetric dimethylarginine; Hb: Hemoglobin; NO: Nitric oxide; Pulm. Vasc.: Pulmonary vascular.

during hemolysis alters arginine metabolism, further reducing NO bioavailability[8,9]. Arginase 1 converts L-arginine to ornithine, a precursor of proline. Proline is an amino acid involved in collagen formation, lung fibrosis and SMC proliferation. Low arginine/ornithine ratio has been reported to be associated with high mortality. Under conditions of low arginine and tetrahydrobiopterin, eNOS is uncoupled generating reactive oxygen species[10]. These changes lead to pulmonary vascular remodeling and increased pressure. Furthermore, therapeutic measures used in patients with hemolytic disorders have been shown to be associated with PH[11]. Figure 1 depicts the alterations observed in hematological disorders that can lead to PH.

Iron is an essential trace element required for a number of biological processes including cellular response to hypoxia, cell proliferation, immune responses and mitochondrial function. It also has the ability to generate free radicals, which cause deleterious effects. Mitochondria use iron for heme synthesis and in iron-sulfur cluster biogenesis. Hepcidin expressed in the liver is thought to be a key regulator of iron homeostasis. Dietary iron is absorbed through the duodenal enterocytes and exported to circulation *via* ferroportin, an iron transporter. Increased levels of hepcidin degrade ferroportin, thus inhibit iron uptake; whereas low levels allow increased iron absorption. Hepcidin is upregulated by BMP6, and inflammatory cytokines including IL-6, IL-1β through JAK2/STAT3 pathway. It is downregulated by iron deficiency, erythropoiesis and hypoxia in order to increase iron levels. Major portion of iron is in erythroid marrow, and erythropoiesis is the major regulator of hepcidin. Erythropoiesis releases erythroferrone that in turn inhibits hepcidin transcription to increase iron absorption. Excess intracellular iron is stored by ferritin that prevents iron-mediated free radical formation[12-15]. Iron circulates bound to a glycoprotein, transferrin, which keeps it soluble; iron is delivered into cells through transferrin receptor (TfR1)[16]. Physiological iron saturation range for transferrin is 20%-45%. Less saturation is indicative of iron deficiency and saturation above 80% is associated with non-transferrin-bound iron which has toxic effect on the tissue[17]. Intracellular iron regulates TfR1 *via* iron responsive elements that are recognized by iron regulatory proteins (IRPs) which bind to iron responsive elements of TfR1, and prevent degradation when the intracellular iron levels are low. Increased cellular iron levels inactivate IRP1 resulting in degradation of TfR. Furthermore, IRP1 and IRP2 are required for mitochondrial iron supply and function[18,19]. Deregulation of iron homeostasis plays an important role in the pathophysiology of hematological disorders and several cardiovascular diseases including PAH. Deregulated iron metabolism can result in iron overload as seen in some of the hematological disorders leading to toxic effects, or to deficiency as seen in anemia. Several recent studies have reported low iron levels in patients with idiopathic PAH, that is considered to be an important risk factor[20].

HEMATOLOGICAL DISORDERS AND PH

Persistent pulmonary hypertension of the newborn associated with anemia

Persistent pulmonary hypertension of the newborn (PPHN) is the result of failure of cardiopulmonary transition at birth. It is associated with cardiovascular anomalies, meconium aspiration syndrome, lung hypoplasia, sepsis, respiratory distress syndrome, or it could be idiopathic. In addition, maternal factors such as diabetes, obesity, elective cesarean section; and maternal drug use such as aspirin, nonsteroidal inflammatory agents and serotonin reuptake inhibitors are known to be associated with PPHN. The incidence of PPHN is about 1.9 per 1000 live births, and the mortality is reported to be 10%. The major findings of PPHN are elevated pulmonary artery pressure, right to left shunt at the foramen ovale or at the ductus level, and

hypoxemia[21,22]. Recent studies have shown that PPHN can also be associated with severe neonatal anemia. However, anemia as a potential cause of PPHN is not well recognized. In a series of 12 infants, 7 were reported to have congenital dysrythropoietic anemia; and three with ε-γ-δ β-thalassemia, one with HbH disease and another one with Diamond-Blackfan anemia[23]. Another report described 3 siblings with dysrythropoietic anemia and PPHN. Two infants survived after blood transfusion, oxygen; and one infant in addition, had received inhaled NO[24]. Others have reported PPHN associated with anemia; one infant with fetal anemia associated with maternal trophoblastic tumor, two infants with fetal anemia due to massive feto-maternal hemorrhage and in the fourth case the reason for anemia was not known. All these infants had received blood transfusion for anemia[25,26]. In addition, neonates with twin-to-twin transfusion syndrome are at a risk of developing PPHN[27]. The reason for PPHN associated with anemia is not clear. Hypoxia secondary to low Hb level could be a contributing factor to PPHN. Interestingly, booster packed red blood cells (RBCs) transfusion has been shown to improve tissue oxygenation in premature infants[25,28]. The increase in plasma Hb levels following transfusion could be an additional factor contributing to high pulmonary artery pressure. Cell-free Hb scavenges NO, thus, leading to vasoconstriction and increased pulmonary artery pressure. Experimental studies have shown transient increase in pulmonary artery pressure following blood transfusion[29]. Furthermore, transfusion with aged stored blood results in increased cell free plasma Hb levels, higher levels of arginase, endothelial dysfunction and increased pulmonary artery pressure[30,31]. Recently, significant reduction in flow-mediated dilatation was reported in adult patients who received old blood (> 21 d) compared with the ones who received fresh blood (< 14 d old)[32]. Inhaled NO prevents the elevation of pulmonary artery pressure induced by aged blood transfusion[31,32]. The possibility of PPHN needs to be considered in the presence of severe anemia in newborns. In addition to blood transfusion, inhaled NO may be necessary to ameliorate PH.

Hemolytic disorders and PH

Hb disorders include sickle cells disease and thalassemia; and RBC membrane diseases include spherocytosis, stomatocytosis and paroxysmal nocturnal hemoglobinurea. PH is one of the leading causes of morbidity and mortality in patients with hemolytic disorders. Major causes of PH in hemolytic disorders are hemolysis, hypercoagulabilty and iron overload resulting from transfusions and splenectomy[9,33-35]. Recently, in a murine model of hemolysis, significant reduction in NO bioavailability due to free Hb was shown to be accompanied by platelet activation and the activation of coagulation pathway resulting in thrombosis, PH, right ventricular failure and death. Interestingly, treatment with sildenafil reduced the mortality rate[36]. Furthermore, Hb has been shown to interact with superoxide and hydrogen peroxide, thus increasing reactive oxygen species formation, lipid peroxidation, and increase inflammatory response. Interestingly, in an experimental model, treatment with haptoglobin, a Hb scavenger was shown to decrease oxidative and inflammatory response and attenuate PH[37]. Free Hb plays a significant role in the pathogenesis of PH in hemolytic disorders; therefore, treatment with Hb scavengers appears to be an attractive therapeutic option.

Sickle cell disease: Hb in patients with sickle cell disease (SCD) is structurally different; valine is substituted for glutamic acid in the 6th position of β-globulin subunit of Hb[38]. This mutation produces abnormal and insoluble HbS. The major genotypes of SCD are homozygous SS, heterozygous SC and S/β thalassemia. In the United States, 0.15% of African-Americans are homozygous for SCD, and 8% have sickle trait. SCD is characterized by anemia, severe pain, potentially life-threatening complications such as bacterial sepsis, splenic sequestration, acute chest syndrome, stroke, chronic organ damage resulting from chronic hemolysis and intermittent ischemia. Vasculopathy in SCD results in irreversible organ damage, a frequent cause of death beyond childhood. Recent studies have shown that chemically-induced RBC stiffness leads to increased pulmonary artery pressure and pulmonary vascular resistance[39]. Importantly, sickled RBCs are stiffer than controls[40], which may partly contribute to PH in SCD. Furthermore, RBCs from SCD patients have an abnormal tendency to adhere to vascular endothelium. This abnormal adhesion plays an important role in facilitating the trapping of sickle cells in post-capillary venules and causing vascular obstruction which is the underlying factor for the characteristic features of SCD such as painful vascular occlusive crises and acute chest syndrome. In addition, the sickle cell adherence to EC results in the activation of EC and a chronic state of inflammation. Endothelial activation is a critical component of the microvascular responses accompanying SCD resulting in inflammatory response, increased expression of cell adhesion molecules and reactive oxygen species, and altered vasomotor tone leading to vasculopathy including PH. Interestingly, hypoxia/reperfusion injury causes inflammatory response in sickle cell transgenic mice[41-43].

Morbidity and mortality in SCD are high, and PH is a serious complication in SCD. Sudden death in patients with SCD and PH is not uncommon[44,45]. In a small series of autopsy cases (12 patients), 75% of patients had right ventricular hypertrophy and 50% revealed large thrombus in pulmonary artery, and 40% exhibited pulmonary vascular remodeling. The mortality in patients with catheterization-confirmed PH is 50% within 2 years compared to 7% at 10 years in SCD patients without PH[46-49]. In adult population with SCD, echocardiography revealed high incidence of PH (27%) as assessed by a tricuspid regurgitation jet velocity

(TRJV) of > 2.5 m/s, however, the incidence was confirmed to be 6%-10% by cardiac catheterization, and > 50% of these patients had post-capillary PH[50-52]. A recent study showed increased TRJV in children to be associated with an increased PA pressure, increased cardiac output due to anemia and normal pulmonary vascular resistance[53]. The incidence of PH in patients with SCD, however, is relatively high (6%-10%), compared with the normal population (2.4-7.6 people/million per year). It is noteworthy that SCD patients with lower pulmonary artery pressure are at a higher risk compared with idiopathic PAH with equivalent pressure. Recent experimental studies in rodents reveal that it is the Hb-induced inflammation and to a lesser extent the Hb-induced oxidant injury leads to vascular injury[54]. Thus, RBC sickling, rheological abnormalities, hypoxemia, heme-induced oxidant injury and resulting inflammatory response leading to endothelial dysfunction play a major role in vasculopathy leading to vaso-occlusive disease including PH.

Thalassemia: Thalassemia diseases are an inherited Hb disorders associated with chronic anemia, impaired erythropoiesis and dysregulated iron metabolism; resulting from defective synthesis of α and β subunits of HbA. Absence or impaired production of α globulin results in β thalassemia and vice versa. PH is quite rare in α thalassemia. β thalassemia is characterized by impaired erythropoiesis and dysregulated iron metabolism. Two types of β thalassemia have been described; thalassemia major (TM) and thalassemia intermedia (TI). Patients at birth are asymptomatic because of the presence of HbF. Diagnosis of TM is usually made during infancy because of anemia. They require frequent transfusion and chelation therapy which have improved their survival. Furthermore, well transfused patients with TM are at a lower risk of developing PH. In contrast, the TI patients remain transfusion-independent for a longer period; the incidence of PH is higher in this group[34,55-57]. Pathophysiology of PH in thalassemia is similar to other hemoglobinopathies. Chronic hemolysis, iron overload, splenectomy, hypercoagulability, vascular inflammation and left ventricular dysfunction contribute to the pathogenesis of PH. Dysregulated arginine metabolism[58] and elevated levels of ADMA[59] have been reported in patients with β-thalassemia associated with PH. Higher incidence of PH was noted in patients with E/β-thalassemia who had more severe hemolysis and had had splenectomy; in addition, inflammatory markers were increased[60]. Increased non-transferrin bound iron and increased transferrin saturation indicative of iron overload increase the risk of cardiopulmonary damage[61]. Interestingly, in a mouse model of β thalassemia, transferrin treatment normalized labile plasma iron levels and RBC survival, and increased hepcidin expression[62]. In addition, increased hepcidin levels were accompanied by increased BMP2 expression in the liver and concomitant decrease in extracellular-signal related kinase (ERK) activation[63].

Compared to β thalassemia, SCD patients do not have iron overload. This difference is thought to be due to the presence of chronic inflammation in SCD which could block iron release from reticulo-endothelial system. In addition, unlike SCD, hepcidin levels are low in β thalassemia, which can further enhance iron absorption[64]. In β thalassemia, transfusion not only improves anemia but also suppresses erythropoiesis and increases hepcidin levels[65]. Globin chain imbalance leads to ineffective erythropoiesis, and erythroferrone suppresses hepcidin production during increased erythropoiesis, resulting in low hepcidin levels and increased iron absorption. In a mouse model of β-thalassemia, ablation of erythroferrone restored hepcidin expression and reduced iron accumulation without affecting anemia[66]. Furthermore, thalassemia carriers have been reported to have abnormal iron metabolism[67].

RBC membrane disorders: RBC membrane-associated abnormalities are found in inherited disorders such as spherocytosis and stomatocytosis. A defect in one or several proteins such as ankyrin, spectrin (α and β), band 3 has been reported. Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired RBC membrane defect. RBCs play a role in regulating membrane properties to undergo reversible deformation while maintaining integrity. In addition, RBCs have a pivotal role in regulating cell volume homeostasis. Inability to regulate cell volume is a feature of hemoglobinopathies[68-70].

Hereditary spherocytosis (HS) is considered not to be associated with thrombo-embolic risk. In a recent study, 26 children who underwent splenectomy, no evidence of PH or coagulation defect was observed during a follow-up period of median 4.5 years[71]. In another study that included 36 patients with HS (28 with splenectomy and 8 without), no evidence of PH was found[72]. However, arterial and venous thrombo-embolic events in patients with HS have been observed after splenectomy[73]; and several cases of CTEPH have been reported in patients with HS several years after splenectomy[74-76]. In a review of 22 patients with CTEPH following splenectomy, 3 patients with HS had had splenectomy 17-35 years before the diagnosis of CTEPH was made[77].

In hereditary stomatocytosis, the RBC membrane shows a leak of univalent cations (Na^+ and K^+). Two clinical variants have been recognized; hydrocytosis (overhydrated) and xerocytosis (dehydrated). Stewart *et al*[78] described 11 patients with stomatocytosis after splenectomy. Most of them had thrombo-embolic episodes, and 3 of them developed PH. Other case reports have described PH in patients with stomatocytosis several years (approx 6-30 years) after splenectomy. One patient underwent successful pulmonary endarterectomy for CTEPH. He had undergone splenectomy as a child because of the family history of spherocytosis[79]. Another patient with dehydrated hereditary stomatocytosis underwent

splenectomy because of splenic infarct following air travel. Approximately 12 years later she developed CTEPH. Because of the worsening condition she underwent successful heart-lung transplantation[80]. The third case of stomatocytosis had splenectomy done for traumatic rupture of the spleen. About 6 years later he developed PH[81]. Splenectomy is not recommended for stomatocytosis, however, stomatocytosis is often mistaken for spherocytosis, and splenectomy is performed. At times it is difficult to distinguish RBC morphology; therefore, intracellular electrolyte measurements or flux studies may be required to make the correct diagnosis[78].

PNH is a progressive hemolytic disorder. It is an acquired clonal genetic deficiency of glycosylphosphatidylinositol-linked protein on the RBC surface that leads to complement-mediated hemolysis[35,82]. One case of PNH was diagnosed to have PH 5 years after splenectomy and associated chronic thromboembolism[83]. In one study, 41% patients with PNH and associated hemolysis (total 29 patients) had echocardiographic evidence of PH. Treatment with eculizumab reduced hemolysis[82,84]. In another study, 23 patients with PNH and hemolysis were examined before and after eculizumab therapy. Importantly, markers of endothelial dysfunction (sVCAM1, vWF) and coagulation activation were significantly reduced after eculizumab therapy[85].

Chronic myeloproliferative diseases and PH

Evidence is accumulating to suggest a link between PH and chronic myeloproliferative diseases (CMPD). CMPD originate in multipotent hematopoietic progenitor cells that are characterized by increases in one or more types of blood cells. CMPD include polycythemia vera, essential thrombocythemia, idiopathic myelofibrosis and chronic myeloid leukemia (CML)[86]. Dingli *et al*[87] examined 26 patients with CMPD and echocardiography based diagnosis of PH (estimated systolic pulmonary artery pressure 35-100 mmHg); 24 patients had symptoms related to PH and 4 had had splenectomy. The mortality rate among these patients was high. Another report[88] described 6 patients with myeloproliferative disease who developed PH (echocardiographic diagnosis, and in 4 confirmed with cardiac catheterization), and all had had splenectomy; 5 patients died within 1-6 mo of PH diagnosis. Lung histology in 3 patients revealed pulmonary myeloid metaplasia and fibrosis. A 72-year-old patient developed PH, right ventricular failure and thrombocytosis after splenectomy. The peripheral blood smear revealed megakaryoblasts. Interestingly, treatment with hydroxyurea not only decreased the platelet counts but also improved right heart failure. It was considered possible that megakaryocytes created obstruction in the pulmonary capillaries leading to PH[89]. In a group of 30 patients with a past history of thromboembolism, high incidence of valve disease (aortic and mitral valve with vegetation) was noted; 13% of patients had PH secondary to venous obstruction[90]. In another study, 46 patients with essential thrombocytosis were compared with 40 patients with reactive thrombocytosis secondary to anemia. In the essential thrombocytosis group, elevated platelet levels and 43% thrombo-embolic events were recorded; and 47.8% (22/46) had echocardiographic evidence of PH. In contrast, the reactive thrombocytosis secondary to anemia group did not have increased platelet levels, thrombo-embolic events or PH[91]. Garypidou *et al*[92] reported incidence of PH by echocardiography to be 41.7% in 24 patients with CMPD. In another report, among 103 patients with various CMPD, echocardiographic diagnosis of PH was made about 15 mo after the initial diagnosis of CMPD. The incidence of PH was found in less than 5%[93]. A 50 years old individual was diagnosed to have PH (confirmed by cardiac catheterization) 15 years after the diagnosis of latent myeloproliferative disorder and portal hypertension. Portal hypertension is a known complication of CMPD[94]. PVOD also has been reported in CMPD. A patient with myeloproliferative and myelodysplastic syndrome was treated with hydroxyurea for 4 years. Because of refractory thrombocythemia and hydroxyurea-induced neutropenia, anagrelide was started. Six weeks later, the patient was admitted with severe dyspnea at rest and was diagnosed to have PVOD[95]. Guilpain *et al*[96], reviewed 10 cases of CMPD (8 polycythemia vera and 2 essential thrombocythemia) and PH; 6 patients developed CTEPH and 4 patients had PAH. Importantly, CTEPH occurred early in the course of the disease and PAH occurred several years after the diagnosis of CMPD. All patients with PAH revealed myeloid metaplasia but none in the CTEPH group.

The patients with CMPD are at a risk of developing PH; and the occurrence of myelofibrosis in patients with PAH is not uncommon and is thought to contribute to impaired hematopoiesis. Popat *et al*[97] reported moderate to severe myelofibrosis in 14/17 patients with PAH. However, platelets and granulocytes in PAH patients were polyclonal unlike monoclonal cells that were found in patients with polycythemia vera and essential thrombocythemia. Erythropoietin facilitates erythroid lineage and proliferation. Erythropoietin has also been shown to induce tyrosine phosphorylation of JAK2 and to associate with it for biological activities including mitogenesis[98]. In a number of patients with CMPD, an acquired somatic *JAK2V617F* mutation has been observed, which confers a selective growth advantage. Interestingly, a small molecule inhibitor of JAK2 has been shown to attenuate myeloproliferative disease in a mouse model[99,100]. However, the patients with PAH (13 Familial PAH, 24 Idiopathic PAH, and 15 Associated PAH) and the controls did not reveal JAK2 mutation[101], nor was the JAK2 mutation noted in 19 patients with myelofibrosis secondary to PH[102]. Circulating $CD34^+CD133^+$ cells were higher in familial PAH compared with idiopathic PAH and the control subjects; interestingly, in non-affected family members, the $CD34^+CD133^+$ cell counts were comparable to

that observed in Familial PAH group[101]. Furthermore, patients with PAH and myelofibrosis have blood vessels morphologically similar to what is observed in myeloproliferative myelofibrosis such as, microvascular density, distended lumina and irregular branching. In addition, VEGF levels are much higher in patients with primary myelofibrosis compared with the controls; and even higher in patients with primary myelofibrosis associated with PH. However, in PH associated with myeloproliferative diseases, the levels of circulating endothelial progenitor cells and the bone marrow pericytes were lower[103,104]. Almost a century ago it was thought that EC and hematopoietic cells have a common progenitor, hemangioblasts. Furthermore, EC and hematopoietic cells affect each other[105], which may explain the increased incidence of PH in CMPD and myelofibrosis accompanying PH. Transplantation of bone marrow-derived $CD133^+$ cells from PAH patients into mice has been shown to result in endothelial injury, angioproliferative remodeling of pulmonary vasculature and right ventricular failure; $CD133^+$ cells from control subjects, however, had no effect[106]. Recent studies have shown that bone marrow cells from BMPR2 mutant mice when transplanted into control mice induce PH, whereas bone marrow cells from the control mice protect mutant mice from developing PH[107]. These results further support a causal relationship between vascular and hematopoietic systems.

Autoimmunity, PH and hematological disorders

Autoimmunity is a well-known underlying feature of hematological disorders as well as of PH. Autoimmune diseases such as systemic sclerosis, systemic lupus erythematosus (SLE), Sjogren's disease, and mixed connective tissue diseases are known to be associated with PH[108-110]. Loss of $CD4^+CD25^+$ cells, the T regulatory (Treg) cell population has been reported in several forms of PAH[110]. Furthermore, normal Treg function has been shown to limit the vascular injury and provide protection from developing PH[111]. In 132 patients with SLE, the incidence of PH was 12.9%. PH patients had longer duration of anemia; oxygen delivery was inversely related to PA pressure, indicating that tissue hypoxia may play a greater role in the lupus-associated PH[112]. Another patient with SLE and associated lupus anticoagulant and clotting disorder was described to have PH[113].

Autoimmunity is also important in thyroid diseases and thyroid disease-associated PH. Scicchitano *et al*[114] in a recent review article have discussed the prevalence of PH in hypothyroid state as well in hyperthyroid state. Interestingly, approximately half of the patients with PAH have been shown to have autoimmune thyroid disease[115]. Coagulation abnormalities associated with thyroiditis[116] may lead to chronic embolism and eventually CTEPH. Furthermore, thyroid hormone participates in EC proliferation and facilitates angiogenesis. Recent studies with an angio-proliferative model (Sugen + hypoxia) of PH have shown that thyrodectomy inhibits angioproliferation and reduces the expression of p-ERK1/2, integrin receptor $\alpha v\beta 3$, fibroblast growth factor (FGF) 2 and FGF receptor[117]. These results suggest that the status of thyroid function in PH is important and it may affect the progression of the disease adversely.

Evan's syndrome includes immune thrombocytopenia and associated autoimmune hemolytic anemia. Connor *et al*[118] reported 2 children with Evan's syndrome and associated PH; both with the evidence of perivascular lymphoid infiltration indicative of vasculitis. Both improved with steroid and rituximab treatment. The incidence of PH in Evans's syndrome, however, is not known. PH has also been reported in an adult patient with autoimmune hemolytic anemia who improved significantly on regular steroid therapy[119].

Therapy-associated PH

A number of alkylating agents including cyclophosphamide, bleomycin, mitomycin used for hematological diseases have been shown to lead to PVOD and PH[11,120]. Other therapeutic measures used for hematological disorders such as tyrosine kinase inhibitor dasatinib, interferon, splenectomy, bone marrow transplantation (BMT) and radiation also contribute to PH as discussed below.

Dasatinib: CML is caused by active BCR/ABL tyrosine kinase. Tyrosine kinase inhibitor, imatinib inhibits BCR/ABL and platelet-derived growth factor (PDGF), and has been used as a first line treatment for CML with good results. However about 29% of patients do not recover completely with imatinib, therefore, newer tyrosine kinase inhibitor, dasatinib is used as a second line treatment. Dasatinib inhibits Src kinase in addition to BCR/ABL and PDGF. Several case reports have appeared showing the development of precapillary PH after about 8-48 mo of dasatinib therapy[121-127]. In the French experience, the incidence of dasatinib-associated PH is 0.45%. The patients, however, did not recover fully after having been taken off dasatinib treatment. Interestingly, in the monocrotaline (MCT) and hypoxia-induced PH models, the pretreatment with dasatinib, unlike imatinib induced increased pulmonary artery pressure and increased inflammatory cells in the perivascular area. Furthermore, *in vitro* studies with human pulmonary EC, dasatinib induced apoptosis in a dose dependent manner through mitochondrial reactive oxygen species generation[128,129]. Interestingly a number of patients with dasatinib-induced PH is accompanied by pleural effusion (as high as 68%), which is not observed in classical PH. In most cases, discontinuing the medication appeared to have reversed PH; however, in a few cases prolonged PH therapy might be required[130]. Recent studies have shown that the inhibition of Src tyrosine kinase or dasatinib increases pulmonary artery pressure, and depolarizes PA SMC by altering potassium channels[131]. Thus, dasatinib-associated Src inhibition and the alterations in potassium channels may be

responsible for the increased vasoconstriction and PH. It is noteworthy that decreased expression of Src tyrosine kinase has been reported in the lungs of patients with PAH[132]. It is suggested that Src function may depend on the state of vascular SMC[133].

Interferon: Interferon (IFN) α and β are used for various hematological disorders, cancer and infection especially hepatitis C. Evidence is accumulating to suggest that IFN pathway may have a role in the pathobiology of PH. INF therapy has been shown to be complicated by vasculopathy. IFN therapy has been shown to lead to reversible PH and in some cases irreversible PH[134-136]. Infusion of IFN-α into sheep has been shown to elevate pulmonary artery pressure associated with increased expression of thromboxane B2, a stable byproduct of thromboxane A2, a vasoconstrictor; that is attenuated by a selective thromboxane A2 synthetase inhibitor, OKY-046[137]. Interestingly, a subgroup of patients treated with INF exhibit increased levels of endothelin-1 (ET-1), which is known to play an important role in PH. Recent studies have shown that IFN induces *ET1* gene and IFN-inducible protein IP10, a mediator of inflammation in vascular SMC; and the combination of IFN and TNF-α produce the highest amount of ET1. These cytokines have direct effect on ET1 transcription and also on increased translocation of NF-κB and STAT1[138]. Importantly, recent studies have shown increased levels of IP10 and ET1 in patients with PAH which correlated positively with serum brain natriuretic peptide and the status of the disease. These Authors have further shown increased type 1 IFN receptor (IFNR1) protein levels in the lungs of patients with PAH compared with the controls. Furthermore, IFNR1 knockout mice exhibit attenuated response to hypoxia[139]. These studies strongly indicate a role for IFN in the pathobiology of PAH.

Splenectomy: A number of patients who undergo splenectomy following trauma or for various hematological disorders develop PH, associated with histological changes in pulmonary arteries such as intimal fibrosis, plexiform lesions and thrombo-embolic lesions. The prevalence of PH in patients in the presence of asplenia is reported to be 11.5%[140]. In another study, 22 out of 257 patients with CTEPH (8.6%) had a prior history of splenectomy, compared with the positive history of splenectomy in 2.5% of idiopathic PAH patients and 0.4% in general population[77]. PH has been shown to occur several years after splenectomy for hereditary spherocytosis[74,75], stomatocytosis[78], thalassemia[141] and Hb Mainz hemolytic anemia[142]. Splenectomy is associated with deep vein thrombosis and un-resolving recurrent thrombosis eventually leading to CTEPH. Loss of spleen results in a loss of filtering function leading to abnormal circulating erythrocytes and the activation of coagulation. The activation of platelets enhances thrombin generation as well as cytokine activation. Human thrombi obtained after pulmonary endarterectomy revealed increased platelet-derived micro-particles and increased anionic phospholipids (phosphotidylserine, phosphotidylethanol and phosphotidylglycerine), reduced angiogenesis related gene expression, and reduced vascular canalization. These micro-particles are pro-coagulant. In addition, in a murine model of CTEPH, inhibition of angiogenesis was associated with delay in thrombus resolution[143,144]. In a rabbit model with splenic artery ligation, transfusion of sonicated blood resulted in platelet rich thrombi in pulmonary circulation; in contrast, transfusion of normal blood did not have any effect[145].

BMT: BMT is used for a number of blood disorders and cancer. Hepatic veno-occlusive disease is a well-established complication of BMT and cytotoxic drugs. In 1984, Troussard *et al*[146] were the first ones to report a child who developed PVOD a few years after having received BMT for a relapse of acute lymphoblastic leukemia. Since then, PVOD following BMT have been reported in several adults and children[147-152]. Hepatic veno-occlusive disease is a recognized complication of cytotoxic therapy used concomitantly with BMT. BMT in combination with cytotoxic drugs and radiation increases the chances of EC damage and PH. Another possibility that has been considered is that malignancy itself may cause PH[151]. Transplantation-associated thrombotic microangiopathy (TM-TMA), a known complication of BMT is caused by EC injury resulting in thrombin and fibrin deposition in microcirculation with ensuing organ damage. Jodele *et al*[153] have described 5 children who developed severe PH 71-205 d after having undergone hemopoietic stem cell transplantation. These children did have TM-TMA 56-101 d before the diagnosis of PH was made. PH can occur from a few months to several years after transplantation**.** In addition, PH without any evidence of PVOD was reported to occur in an adult almost a year after BMT[154]. A 5.25-year-old child underwent BMT after conditioning with cyclophosphamide and antithymocyte globulin; and he was treated with cyclosporine A and a short course of methotrexate to prevent graft-*vs*-host disease. Within a month of BMT, he developed respiratory distress, anemia and thrombocytopenia. Approximately 1.5 mo later, he was diagnosed to have microangiopathic changes. His condition, however, stabilized after cyclosporine A was discontinued and treatment with mycophenolate mofetil was started. About a year or so later he started to have vague respiratory symptoms which was subsequently diagnosed as severe PH[155]. These cases illustrate that PH can occur early or late after BMT. Cytotoxic drugs and radiation used to prepare the patient for BMT and to prevent graft-*vs*-host disease can contribute to EC damage leading to pulmonary vasculopathy. These patients need to be carefully monitored and PH should be considered a possibility when they present with

pulmonary symptoms.

Radiation injury: Lung radiation leads to pneumonitis, fibrosis and vascular injury. Thoracic or whole body radiation is used for several types of lung cancer; and at times radiation in combination with immunosuppressive drugs is used before BMT. PVOD and pulmonary insufficiency have been reported to occur several months to years following therapy for cancer that included chemotherapy and radiation therapy. Histopathological changes in the lungs comprised interstitial fibrosis, thromboemboli, veno-occlusive lesions, and medial hypertrophy of pulmonary arteries, consistent with PVOD[156,157]. In addition, a 14-year-old was reported to have developed PH after receiving radiation therapy during infancy following the surgical removal of neuroblastoma arising from the left of the thoracic spine. At cardiac catheterization significant PH was noted. In addition, the branches of left pulmonary artery were described as hypoplastic, and the pulmonary veins from the left lung were underdeveloped[158].

EC play a pivotal role in radiation-induced vascular injury. Irradiated EC from rectal adenocarcinoma have been shown to induce fibrogenic phenotype in vascular SMC, and increase proliferation and migration[159]. Furthermore, several experimental studies have shown radiation injury resulting in elevated pulmonary artery pressure, and structural remodeling of the small pulmonary arteries. In a sheep model, several weeks after the whole lung exposure to radiation resulted in abnormal vascular reactivity, PH and pulmonary vascular remodeling[160]. In a mouse model, low dose radiation resulted in EC injury, followed by rapid recovery. However, a higher dose resulted not only in EC injury, but also a delay in recovery followed by prolonged EC proliferation, fibroblast proliferation and collagen secretion indicative of significant vascular damage[161]. In a rat model, radiation injury induced pulmonary vascular EC damage followed by medial wall and adventitial thickening, neointima formation and obliteration of vessels similar to what is observed in PAH[162].

These studies underscore the fact that vascular EC are susceptible to radiation injury. The patients who receive radiation therapy with or without alkylating drugs are at a risk of developing PH. PH has been shown to occur several years after the cessation of therapy; therefore these patients need a long careful follow-up.

IRON HOMEOSTASIS AND PAH

Deregulation of iron homeostasis and resulting alterations in iron availability plays an important role in the pathogenesis of cardiovascular diseases including PH. Both iron deficiency and iron overload have deleterious effect on cardiovascular system. Iron deficiency has been shown to have an adverse effect on survival in patients with chronic heart failure[163]. Anemia in PH is associated with worse function and poor survival[164]. Iron deficiency is being recognized as an important factor in the prognosis of PAH. Low transferrin saturation, an indicator of iron deficiency has been reported in PAH patients, particularly the ones with BMPR2 mutation, but not in the CTEPH group. In this group of PAH patients, 72% of iron deficient patients had anemia, whereas only 4% in non-iron deficient patients[20]. In another study, iron deficiency was found in 43% of 70 patients with idiopathic PAH accompanied by low exercise capacity. However, anemia did not affect the exercise intolerance. Interestingly, 8 out of 18 patients did not respond to oral iron therapy[165]. Red cell distribution width (RDW), a biomarker of anemia has a better survival predictive value independent of NT-proBNP levels and 6 min walk distance. Increased RDW was accompanied by other indicators of iron deficiency such as decreased ferritin levels and low transferrin saturation. Patients with increased soluble TfR (sTfR) had higher mortality independent of WHO class or exercise capacity. sTfR levels are a sensitive marker of tissue iron availability, unaffected by inflammation. Interestingly, hepcidin levels were increased in PAH despite iron deficiency. Hepcidin which restricts iron absorption is stimulated by cytokines and BMP6; however, hepcidin levels did not correlate with IL-6 levels. Since a number of patients have BMPR2 mutation and loss of function, it is likely that increased BMP6 levels secondary to BMPR2 loss may increase hepcidin levels. Furthermore, erythropoietin levels are increased in idiopathic PAH despite the fact that these patients were not anemic. The hematocrit and Hb levels were not different compared with the controls. Erythropoietin is known to reduce hepcidin levels in order to increase iron uptake. Increased levels of hepcidin in the presence of increased erythropoietin indicates deregulated erythropoiesis in idiopathic PAH[166,167]. In 29 patients with idiopathic PAH, 46.2% of iron deficient patients belonged to NYHA functional class 3 or higher compared with 12.5% in non-iron deficient. There were no differences in the hematocrit or Hb levels between the two groups. The iron deficiency was related to the severity[168]. In addition, zinc protoporphyrin (ZnPP) levels, indicative of iron deficiency was significantly higher in patients with idiopathic PAH associated with increased RDW; however, ZnPP levels were not altered in "Associated" PAH. Iron containing protein is also required for mitochondrial electron transport and catalyzes reactions that form NO[169]. Intravenous iron therapy in patients with idiopathic PAH was well tolerated and it improved endurance capacity; however, it did not alter cardiac function[170]. Thus, iron deficiency seems to be a more important prognosticator compared with anemia.

Iron deficiency is common in patients with systemic sclerosis (SSc) associated with PH than in the non-PH group. PH was present in 27.8% of patients with SSc. Iron deficiency was associated with poor exercise tolerance and survival. Hepcidin levels were high in the SSc population, but did not correlate with IL-6

levels. Hb levels, however, were not altered. Soluble transferrin receptor (sTfR) levels in both groups were significantly increased associated with iron deficiency[171]. Interestingly, iron-depletion by desferrioxamine infusion in normal individuals resulted in higher systolic pulmonary artery pressure during 8 h hypoxia compared with the iron-repleted individuals. Thus, the alterations in iron availability affect the pulmonary vascular response to hypoxia. HIF is implicated in hypoxia; it is likely that increased iron potentiates HIF hydroxylation and its degradation[172]. Sufficient iron availability is required for adjustment to high-altitude hypoxia. There is a close connection between oxygen and iron homeostasis[173].

Recently it was reported that iron-deficient diet in rats resulted in elevated PA pressure, right ventricular hypertrophy, vascular remodeling, and increased expression of HIF1α, HIF2α, STAT3 activation and aerobic glycolysis, which could be reversed by iron therapy[174]. Furthermore, deletion of iron regulatory protein 1 (IRP1) in mice leads to PH and polycythemia that is exacerbated by low iron diet, resulting in increased HIF2α levels and ET1 in EC. Iron deficiency can stabilize HIF2α by diminishing activity of iron-dependent prolyl hydroxylases involved in HIF2α degradation[175]. In contrast, dietary iron restriction attenuated monocrotaline-induced PH, although, the serum iron concentration in MCT group was not different from the control group. However, the expression of TfR1 in pulmonary arteries was increased. Interestingly, TfR1 hetero-knockout mice showed attenuated hypoxia-induced PH, right ventricular hypertrophy and vascular remodeling[176,177]. Iron chelation has been shown to attenuate hypoxia-induced PH, pulmonary vascular remodeling and right ventricular hypertrophy in rats. In addition, carbonylation of proteins was increased in hypoxia-induced rats as well in the plasma of the patients with PAH indicative of oxidative stress[178]. Furthermore, PH in patients with idiopathic pulmonary fibrosis was shown to correlate with iron deposition in alveolar spaces[179]. These foregoing results show opposite effects of iron levels on pulmonary vasculature. Iron homeostasis is intricately balanced and maintained; any injury and/or stress can alter this balance resulting in iron overload or iron deficiency. Mitochondria play a pivotal role in energy and iron metabolism[180]. The opposing effects of iron levels observed in different forms of PH may depend on the level of non-transferrin-bound iron and on the status/health of mitochondria.

In summary, hemopoietin system, pulmonary vasculature and iron metabolism are intricately related. Hematological disorders affect pulmonary vasculature and PH can cause myelofibrosis. Deregulated iron homeostasis and resulting status and function of mitochondria in PH may have an important effect on prognosis.

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P- Reviewer: Ciccone MM, Nakhoul FM, Ueda H, Wang F
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Wu HL

World Journal of Cardiology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v8.i12.719

World J Cardiol 2016 December 26; 8(12): 719-727
ISSN 1949-8462 (online)

MINIREVIEWS

Cardiac biomarkers in pediatric heart disease: A state of art review

Benedict A Fernandes, Kevin O Maher, Shriprasad R Deshpande

Benedict A Fernandes, Department of Pediatrics, Children's Hospital of Illinois, University of Illinois, Peoria, IL 61637, United States

Kevin O Maher, Shriprasad R Deshpande, Pediatric Cardiology, Children's Healthcare of Atlanta, Emory University, Atlanta, GA 30322, United States

Author contributions: All authors contributed to this paper.

Conflict-of-interest statement: None of the authors have any conflicts of interest to declare. No financial or intellectual conflicts to disclose.

Manuscript source: Invited manuscript

Correspondence to: Shriprasad R Deshpande, MD, MS, Assistant Professor of Pediatrics, Medical Director, Mechanical Circulatory Support Program, Pediatric Cardiology, Children's Healthcare of Atlanta, Emory University, 1405 Clifton Rd NE, Atlanta, GA 30322, United States. deshpandes@kidsheart.com
Telephone: +1-404-6947739
Fax: +1-770-4889480

Received: August 15, 2016
Peer-review started: August 16, 2016
First decision: September 6, 2016
Revised: September 27, 2016
Accepted: October 22, 2016
Article in press: October 24, 2016
Published online: December 26, 2016

Abstract

Every year there are more than 11000 hospitalizations related to heart failure in children resulting in significant morbidity and mortality. Over the last two decades, our understanding, diagnosis and management of pediatric heart failure is evolving but our ability to prognosticate outcomes in pediatric heart acute heart failure is extremely limited due to lack of data. In adult heart failure patients, the role of cardiac biomarkers has exponentially increased over the last two decades. Current guidelines for management of heart failure emphasize the role of cardiac biomarkers in diagnosis, management and prognostication of heart failure. It is also noteworthy that these biomarkers reflect important biological processes that also open up the possibility of therapeutic targets. There is however, a significant gap present in the pediatric population with regards to biomarkers in pediatric heart failure. Here, we seek to review available data regarding cardiac biomarkers in the pediatric population and also explore some of the emerging biomarkers from adult literature that may be pertinent to pediatric heart failure.

Key words: Pediatric heart failure; Biomarkers; Cardiac; Outcomes; Congenital heart disease

Core tip: Biomarkers such as BNP, ST2 are well established in adult heart failure. Emerging data supports the use of some of these biomarkers for diagnosis, monitoring and prognostication of pediatric heart disease. Continued research is needed to better understand these established and emerging biomarkers. Here, we review the available data regarding cardiac biomarkers in the pediatric population and also explore some of the emerging biomarkers from adult literature that may be pertinent to pediatric heart disease.

Fernandes BA, Maher KO, Deshpande SR. Cardiac biomarkers in pediatric heart disease: A state of art review. *World J Cardiol* 2016; 8(12): 719-727 Available from: URL: http://www.

wjgnet.com/1949-8462/full/v8/i12/719.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i12.719

INTRODUCTION

Pediatric acute heart failure is now being increasingly recognized as an important source of healthcare resource utilization with 11000 to 14000 heart failure related hospital admissions in the United States every year[1,2]. Additionally, pediatric heart failure is associated with significant morbidity and mortality. Over the last two decades, our understanding, diagnosis and management of pediatric heart failure is evolving. This is especially true with regards to acute heart failure. However, unlike adult heart failure, underlying mechanisms and etiology is responsible for pediatric heart failure are very heterogeneous from simple congenital heart defects, cardiomyopathies to complex palliated single ventricle patients. Similar to the underlying etiologies, management and outcomes in these groups of patients are also very variable. However, ability to prognosticate outcomes in pediatric heart acute heart failure is extremely limited due to lack of data.

In adult patients with heart failure both related to ischemic and non-ischemic cardiomyopathy, the role of cardiac biomarkers has exponentially increased over the last two decades.

Current American Heart Association guidelines for management of heart failure emphasize the role of cardiac biomarkers in diagnosis, management and prognostication of heart failure[3]. This is especially true for two biomarkers included in these guidelines *viz.* brain-type natriuretic peptide and suppression of tumorigenicity-2 (ST2)[3]. In addition to these there are several biomarkers being studied that have provided additive information beyond the well-established biomarkers. It is also noteworthy that these biomarkers reflect important biological processes that also open up the possibility of therapeutic targets.

There is however, a significant gap present with regards to biomarkers in pediatric heart failure. Here, we seek to review available data regarding cardiac biomarkers in the pediatric population and also explore some of the emerging biomarkers from adult literature that may be pertinent to pediatric heart failure.

B-TYPE NATRIURETIC PEPTIDE AND N-TERMINAL SEGMENT OF PRO-B-TYPE NATRIURETIC PEPTIDE

B-type natriuretic peptide (BNP) and the N-terminal segment of pro-BNP (NT-ProBNP) are used as essential parts of adult cardiologic evaluation. BNP belongs to a larger family of titrated peptides which have a paracrine role in the body. It is primarily secreted by cardiocytes in the form of pre-pro-peptides. These pro-peptides are synthesized within the endoplasmic reticulum of the cardiac cells where they're stored as specific atrial granules. These pre-pro-peptides have a constant basal rate of release and play an important regulatory function in maintenance of salt and water homeostasis. Various stimuli such as myocardial stretch or stress can lead to a very rapid increase in the secretion of these pre-pro-peptides. Once released it undergoes conversion into pro BNP which is cleaved by serine peptidases into the active moiety BNP and inactive moiety NT-proBNP. Outside of the heart, kidneys and blood vessels are the major target organs where natriuretic peptide receptors types A, B and C are present. Once receptor bound, BNP leads to increased diuresis, natriuresis and vasorelaxation. On the cardiac sites, BNP has significant anti-proliferative and anti-hypertrophic properties mediated by the same receptor[4]. Since its first description in 1970s by de Bold[5,6], natriuretic peptides have been extensively studied in various disease conditions both cardiac and non-cardiac. It is one of the most studied biomarker for heart failure. The cumulative data has led to the recognition of its value in diagnosis, management and prognosis of heart failure by the current AHA/ACC heart failure guidelines[3].

BNP and age

BNP and NT-ProBNP levels vary with age especially in the pediatric group. Immediately after birth, BNP and NT-ProBNP are elevated and then rapidly decrease after the first week of life. Reasons for this physiologic fluctuation in the levels are unclear at this point, but hypotheses include removal of the placenta and thereby significant redistribution of blood volume to the heart causing a volume overload and an increase in the afterload at the same time. Rapid increase in pulmonary blood flow with lung expansion further adds to the stimulus. Lastly, renal immaturity may contribute to decreased clearance of the BNP during the first week of life. As a result, the BNP (and NT-proBNP) levels are significantly elevated in newborns and drop rapidly over the first two weeks of life. The BNP concentrations due appear to hold steady until 12 years of age without any differences in gender. However, in the second decade of life, higher BNP levels were seen in girls than in boys. This parallels differences in the activity of the renin-angiotensin-aldosterone system, renin levels (higher in males) as well as the influence of gonadal hormones in the second decade of life[7-10]. BNP, along with the biomarkers reviewed here are also summarized in Table 1.

BNP and congenital heart disease

Before delving into the diagnostic value of BNP, it is important to note that BNP levels are strongly method dependent. This is because different assays that are used to measure BNP use different methods and have varying sensitivities and specificities. The various com-

Table 1 Overview of cardiac biomarkers and their physiologic actions

Name of biomarker	Mechanism of action	Primary effect	Available evidence
BNP/NT-ProBNP	Activates the intracellular Guanylyl cyclase-A moieties after binding to the NPR types A, B and C	Increases diuresis, natriuresis and vasorelaxation Anti-proliferative and anti-hypertrophic properties	[4]
ST2	After binding to its TL/IL-1 receptor like family, interacts with IL-33	Anti-proliferative and anti-hypertrophic properties	[3]
CTGF	Unknown	Deposition of extracellular matrix	[43]
h-FABP	Participate in the uptake, intracellular metabolism and transport of fatty acids	Modulation of cell growth and proliferation	[48]
Pro-adrenomedullin	Releasing nitric oxide from the endothelium Inhibit nicotinic agonist-induced catecholamine secretion and synthesis and nicotinic agonist-induced Na^+ and Ca^{2+} influx	Regulation of hormonal secretion Angiogenesis proliferation Vasodilation	[50]
GDF-15	Unknown	Deposition of extracellular matrix	[55]

ST2: Suppression of tumorigenicity-2; CTGF: Connective tissue growth factor; h-FABP: Serum heart-type fatty acid-binding protein; BNP: B-type natriuretic peptide; NT-ProBNP: N-terminal segment of pro-B-type natriuretic peptide; GDF: Growth differentiation factor.

ponents of pro-BNP cleavage impact measurements to varying degree depending on the method used. Hence, the reference ranges change according to which method was used.

BNP has utility in diagnosis of congenital heart disease (CHD) in newborns. Cantinotti *et al*[11] have shown that while there is a rapid decline in the BNP levels in normal newborns within the first few days of life, newborns with CHD maintain significantly elevated levels beyond 5 d of life. This was true across the spectrum of various congenital heart defects except those leading to volume or pressure overload on the right heart[11]. Maher *et al*[12] studied infants with left-sided obstructive lesions admitted to our center. Infants were divided into 2 groups: Group 1 was diagnosed with cardiogenic/circulatory shock at presentation, and group 2 consisted of infants with ductal-dependent systemic circulation without evidence of shock. In this group of total 122 patients, newborns with cardiogenic shock had a median BNP of 4100 pg/mL at presentation compared to a median BNP of 656 pg/mL ($P < 0.001$) for those without shock. A 100% of patients presenting with shock had significantly abnormal BNP values. They also report an incremental value of BNP such that every 100 units rise in BNP increased the odds of cardiogenic shock by 100 ($P < 0.001$)[13].

A study comparing new diagnosis of CHD in an emergency room setting evaluated the value of BNP compared to patients with diagnosis of respiratory distress due to primary respiratory illness or infection. This study found that in a cohort of critically sick patients with a heart disease, a mean BNP value of 3290 pg/mL was seen in patients with heart disease when compared to 17.4 pg/mL for the patients with respiratory illness or infection[13]. Koulouri *et al*[14] (2004) and Cohen *et al*[15] (2005) report similar findings that plasma BNP or NT-proBNP can differentiate between cardiac or pulmonary etiologies for patients presenting with respiratory distress.

Elevation of BNP/pro-B-type NP are seen due to long term exposure of right heart or left heart to volume and pressure overload. These elevations are especially seen with diseases that causes left ventricular volume overload when compared to right ventricular volume or pressure overload[16]. Furthermore, when comparing pediatric populations with complex CHD *vs* simple cardiac defects (ASD, VSD or PDA), on average, complex defects tend to have higher concentrations. Nir *et al*[9] (2004) showed that patients with higher pressure left to right shunts (VSD, PDA) have higher levels of NT-proBNP when compared to low pressure left to right shunts (ASD). BNP can be used to differentiate preemies with and without a patent ductus arteriosus (PDA) as well as potentially guide therapy. Attridge *et al*[17] showed that by using BNP, fewer doses of indomethacin were used for therapy of PDA. Of note, the pediatric heart can compensate better with pressure overload than volume overload and this can directly impact BNP secretion or level. A normal BNP reflects a compensated heart status but does not rule out heart disease.

BNP can assist in clinical decision making especially when identifying populations at high risks for outcomes after cardiac surgery. Various studies have shown that post-operative BNP, lack of decrease in BNP post-operatively were all strongly related to poor hemodynamics or adverse outcomes after a cardiac surgery[18,19]. Bobik *et al*[20] evaluated the value of NT-pro BNP in patients with atrioventricular septal defects (AVSD) preoperatively. They found that patients with complete AVSD had higher levels of BNP preoperatively compared to partial AVSD. Additionally, NT-proBNP levels predicted longer ICU length of stay, ventilator needs and inotropic support needs post-operatively[20].

For pediatric patients supported on mechanical support (ECMO), Huang *et al*[21] have suggested the utility of serial BNP monitoring before, during and after decannulation from ECMO. In their series, it was noteworthy that after coming off ECMO, BNP levels on the fourth day after removal of ECMO among the

survivors (median, 498 pg/mL) were significantly lower than those among non-survivors (median, 3900 pg/mL; $P = 0.017$)[21].

BNP and heart failure without structural heart disease

As mentioned above, majority of adults have heart failure (ischemic or non-ischemic) in the setting of structurally normal heart. In pediatric patients dilated cardiomyopathy is the most dominant etiology for heart failure[22]. Additional forms such as restrictive, hypertrophic cardiomyopathies are rare but important causes of genetic cardiomyopathies and heart failure. Amongst acquired causes, myocarditis followed by rheumatic heart disease in certain regions of the globe cause acute and chronic heart failure in children.

Although the overall incidence of these clinical conditions is relatively common, our understanding of BNP in these patients is not as robust. Mir *et al*[23] reported significantly higher NT-ProBNP levels in children with heart failure (from various etiologies) than health children. Ohuchi *et al*[24] showed that the BNP levels differentiated NYHA classes regardless of the underlying etiology. Law *et al*[25] in their study used two cutoff values to differentiate between a hemodynamically significant cardiologic process *vs* other disease process with a similar presentation. For neonates, a cutoff value of 170 pg/mL showed a sensitivity of 94% and a specificity of 73%. For the older age group, a cutoff value of 41 pg/mL produced a sensitivity of 87% and specificity of 70% to detect significant cardiovascular disease and related heart failure[25]. For patients presenting with acute heart failure in non-CHDs, our data (currently under review) indicated that mean BNP at presentation in this cohort is very elevated; mean of approximately 1700 pg/mL. In the outpatient setting for pediatric populations with chronic left ventricular systolic dysfunction, BNP values > 300 pg/mL have shown high sensitivity, specificity, positive and negative predictive value for the prediction of adverse cardiovascular events. Price *et al*[26] studied pediatric patients with chronic heart failure. They found that whole blood BNP concentrations were increased in patients who had a 90-d adverse cardiovascular event compared with those who did not (median, 735 pg/mL *vs* median, 37 pg/mL; $P < 0.001$). Patients with a BNP concentration > 300 pg/mL were at increased risk of death, hospitalization, or listing for cardiac transplantation (adjusted hazard ratio, 63.6; $P < 0.0001$)[26].

BNP and other diseases (post-chemotherapy, heart transplantation, Kawasaki disease, cardiac surgery)

BNP can be used to predict cardiac dysfunction in a myriad of conditions such as post-chemotherapy cancer patients, rejection from heart transplantation and Kawasaki disease. It is well known that anthracyclines exposure can lead to significant cardiac dysfunction. As such, serial measurement of BNP maybe of value to detect anthracycline induced cardiomyopathy. Studies have shown BNP to correlate with both early and late effects of anthracycline exposure, correlate well with echocardiographic findings as well as other makers of cardiac dysfunction[27].

Utility of BNP in patients with heart transplantation is being increasing explored. Lan *et al*[28] (2004 showed that BNP was elevated early on after heart transplantation however, falls exponentially early on and reached very low levels around 3 mo post-transplant. Lindblade *et al*[29] and Rossano *et al*[30] showed that BNP was significant elevated in acute rejection and had sensitivities of 96% with BNP > 100 pg/mL 1 year after transplantation. Sparks *et al*[31] have documented reduction in BNP over the first 3 mo and showed correlation it with hemodynamics. Overall, it appears that BNP correlates well with acute episodes of rejection, especially when accompanied by hemodynamic compromise.

Kawasaki disease is an acute febrile vasculitis process that may have cardiac manifestations such as myocarditis, pericarditis and coronary vasculitis leading to coronary ectasia and aneurysms. In one of the earlier studies to assess the utility of BNP in Kawasaki patients, Kurotobi *et al*[32] studied echocardiographic markers of diastolic function during acute phase of Kawasaki disease. They found that diastolic dysfunction occurs during the acute phase of the disease and BNP levels correlated well with the presence of significant diastolic dysfunction[32]. Similarly, Iwashima *et al*[33] have demonstrated the utility of BNP in identifying non-responders. They demonstrated that high level of NT-pro BNP in acute phase KD was associated with systemic inflammatory responses, elevated CRP, and increased vascular permeability. This level was particularly higher in immunoglobulin (IVIg) non-responders compared to responders (1689.3 ± 1168.8 pg/dL *vs* 844.4 ± 1276.3 pg/dL, $P < 0.001$)[33].

ST2

ST2 receptor is a member of toll like/IL-1 receptor family. It interacts with IL-33, a cytokine synthesized by cardiac fibroblasts leading to a cardioprotective stress-induced signaling that produces both antihypertrophic and antifibrotic cell signaling. ST2 is present in a membrane bound and soluble form. Soluble ST2 (sST2) may prevent the binding of IL-33 to a membrane-bound receptor version of ST2. The soluble ST2 has been shown to be of significant value in diagnosis and prognosis of heart failure. One of the key initial studies looked at myocyte stretch induced marked upregulation of myocardial *ST2* gene expression[34,35]. This was followed by multiple, large studies which have corroborated the importance of ST2 in heart failure. An analysis of the patients enrolled in the PRIDE study showed that elevated ST2 levels at presentation to the emergency room with dyspnea was a very strong predictor of death at one year. This was true for both patients with dyspnea as well as those with acute heart failure[36]. In a recent study, Parikh *et al*[37] studied population of

community-dwelling older individuals enrolled in the Cardiovascular Health Study. They found that soluble ST2 levels were significantly associated with incident heart failure, cardiovascular death and that greater ST2 level was continuously associated with increasing hazard for cardiovascular death[37]. Various studies have documented the incremental value of addition of ST2 to pre-existing predictive models of heart failure[37,38]. Accumulation of these data have led the ACC/AHA guidelines to recommend ST2 measurement for additive risk stratification in patients with acute or chronic ambulatory heart failure[3]. Normal concentration of ST2 in adults is less than 18 ng/mL, with a level greater than 35 ng/mL generally accepted as a predictor of morbidity and mortality.

Data regarding pediatric application of ST2 is extremely limited. Meeusen *et al*[39] evaluated healthy children between 2-17 years of age and measured their soluble ST2 levels using the Presage ST2 quantitative assay (Critical Diagnostics, San Diego, CA, United States). The median value for the entire cohort was 21 ng/mL (range: 6 to 122 ng/mL). They found that the ST2 levels normally increase with age, was slightly higher in males and that the central 95th percentile reference interval was 9-50 ng/mL[39].

Mathews *et al*[40] report analysis of patients with heart transplantation and small bowel transplantation and present relationship between soluble ST2 and episodes of rejection. ST2 levels are significantly elevated at the time of acute rejection (cellular and or antibody mediated) in pediatric heart transplant patients. During an episode of biopsy proven rejection, serum sST2 was elevated compared to rejection-free time points (1714 ± 329 pg/mL *vs* 546.5 ± 141.6 pg/mL; $P = 0.0002$). The authors found that, a level of > 600 pg/mL could discriminate time points of acute rejection and nonrejection [area under the curve (AUC) = 0.724 ± 0.053; $P = 0.0003$][40]. Additive value of ST2 as a marker for rejection needs to be validated.

In pediatric patients with idiopathic or primary pulmonary hypertension, Chida *et al*[41] studied the utility of ST2, BNP and other cardiac biomarkers. They report finding to statistically significant relationship between ST2 levels and functional class in these patients. Additionally, ST2 levels along with BNP levels were predictive of poor outcomes. On AUC analysis, a cutoff value of 11.1 ng/mL was identified for mortality prediction, with an AUC of 0.830. The authors conclude that ST2 and BNP levels correlate with clinical status and our predictive of outcome in pediatric patients with pulmonary hypertension[41].

To date, there has been only one published study looking at the utility of ST2 in pediatric heart failure. Hauser *et al*[42] evaluated 114 patients (and 89 controls) with heart failure due to various etiologies, analyzed for different biomarkers along with BNP for diagnostic utility. In this study, MR-proANP was the only novel biomarker that performed in a comparable manner to BNP as far as diagnostic utility was concern. ST 2 levels were not statistically different between controls and heart failure patients[42]. However, it is noteworthy that only 17/114 (15%) of patients with heart failure were in class Ⅲ or class Ⅳ heart failure. The rest of the patients were categorized as class Ⅰ or Ⅱ heart failure. It is therefore not surprising that majority of the levels were not different compared to the controls. Subgroup analysis of the 17 patients with class Ⅲ or class Ⅳ heart failure is not available. Our experience with a pilot group of 15 pediatric heart failure patients was more favorable. In our patients, the ST2 levels ranged from 14 to > 1000 ng/mL, with a mean of 229.7 ng/mL. BNP values ranged from 217 to 18216 pg/mL with a mean of 4179.5 pg/mL. There was a very strong and statistically significant correlation between ST2 and BNP levels in this cohort. We could not establish correlation between functional status or ventricular function (ejection fraction) and ST2 levels probably due to a small sample size (unpublished data).

This biomarker therefore warrants more studies in the pediatric heart failure population to establish its value in diagnosis and prognosis.

CONNECTIVE TISSUE GROWTH FACTOR /CCN2

In addition to the myocardial remodeling seen in heart failure, the role of extracellular matrix is being increasingly recognized. The ultrastructural changes in the extracellular matrix contribute towards both functional as well as structural changes that take place in acute and chronic heart failure. Enhanced collagenous deposition and fibrosis are some of the key changes in the extracellular matrix in CHF. Various mediators and matri-cellular proteins in the extracellular matrix are being increasingly looked at as biomarkers for heart failure. Connective tissue growth factor (CTGF) is one such matri-cellular protein that is involved in pathologic process of fibrosis in addition to other physiologic conditions such as endochondral ossification, vascular growth, cellular growth. Recently CTGF plasma levels have been investigated in patients with chronic and acute heart failure[43]. Koitabashi *et al*[44] studied CTGF levels along with other cardiac biomarkers as well as markers of fibrosis in 52 patients with chronic heart failure. In this study plasma CTGF levels were significantly elevated in patients with symptomatic heart failure and strongly correlated with plasma BNP, TGF beta, matrix metalloproteinase levels. Plasma CTGF levels also correlated with E/E' ratio[44].

Behnes *et al*[45] studied CTGF levels in 212 patients enrolled in the Mannheim NT-proBNP study including 66 patients with acute heart failure. This study showed that CTGF levels were significantly elevated (median 93.3 pg/mL) in patients with heart failure with reduced ejection fraction as well as in patients with acute heart failure (median 77.3 pg/mL) when compared to those with normal heart function (median 25.9 pg/mL). In

addition, CTGF significantly improved the diagnostic capacity of NT proBNP for acute heart failure. There is limited data in pediatric heart failure[45]. Li *et al*[46] studied CTGF and BNP levels in 61 children including 41 with heart failure. They report that CTGF levels were significantly increased in patients with heart failure and that the levels correlated with the severity of heart failure. Addition of CTGF levels to NT-proBNP levels also improved ability to diagnose heart failure in children[46]. The same group has also shown significant correlation of CTGF levels with pulmonary arterial hypertension associated with CHD in children[47].

SERUM HEART-TYPE FATTY ACID-BINDING PROTEIN

The serum heart-type fatty acid-binding protein (h-FABP) is an intracellular transport protein mainly involved in transport of fatty acids. When compared to skeletal muscle, it is highly expressed (about 10 ×) in cardiac muscle. H-FABP has a very strong specificity for diagnosing myocardial injury since it has a small size and so rapidly appears in the blood stream and no isotype mismatch between different types of FABP. Sun *et al*[48] showed both h-FABP and BNP concentrations have good correlation with the degree of heart failure in patients with CHF. In their study, they also evaluated the effects of therapy with carvedilol and found that initiation of carvedilol was associated with decrease in h-FABP and BNP levels. They concluded that h-FABP can be used as biomarkers to evaluate the severity of heart failure in children[48]. In a different study, the group has also demonstrated the utility of h-FABP as a marker of cardiac involvement in patients with Kawasaki disease[49].

PRO-ADRENOMEDULLIN

The adrenomedullin protein (ADM) is protein is cleaved to form adrenomedullin and proadrenomedullin (proADM). This protein has several functions including regulation of hormonal secretion, promotion of angiogenesis, antimicrobial activity and vasodilation. CHF is a complex multifactorial process and since there is neurohormonal activation playing quite an important role in HF, ADM can be implicated in this process. Gegenhuber *et al*[50] found that ADM was found to be elevated and comparable to BNP in patients with acute decompensated heart failure. They also found that high concentrations of ADM predicted 1-year all-cause mortality[50]. Furthermore, ADM may not only be used to evaluate the severity of HF but also a prognostic indicator of this syndrome. In a study by Khan *et al*[51] looking at the value of proADM in heart failure patients post-myocardial infarction, they found that proADM was an excellent predictor of mortality. Additionally, proADM provided further risk stratification in those patients who had NTproBNP levels above the median and therefore could be of additive value[51].

Due to the implication of fluid distribution and vasodilatory properties, this biomarker has been used to predict response to treatment in patients with postural orthostatic tachycardia syndrome (POTS). Zhang *et al*[52] have shown that the levels of midregion-proADM are elevated in patients with POTS and that midodrine responsive patients had higher levels compared to non-responders. ROC analysis showed that a cutoff value for MR-proADM of 61.5 pg/mL produced both high sensitivity (100%) and specificity (71.6%) in predicting the efficacy of midodrine hydrochloride therapy for treating POTS[52].

GROWTH DIFFERENTIATION FACTOR

Growth differentiation factor (GDF-15) is a member of the TGF-B cytokine family that is implicated in the stress response. Unlike h-FABP that is expressed by the myocardium, GDF-15 is not. However, GDF-15 expression is induced in the heart in response to inflammation, tissues injury, ischemia, pressure overload. It is known that GDF-15 is elevated in the setting of left ventricular overload but may also be in response to right ventricular pressure changes as seen in pulmonary embolism. Kempf *et al*[53] found that GDF-15 can provide prognostic information in patients with heart failure. They found that GDF-15 was significantly increased in these patients. They however, concluded that since GDF-15 is non-specific for cardiac myocytes and is involved in stress overload pathways, GDF-15 would need to be compared to specific cardiac makers to get a complete prognostic assessment[53,54]. Raedle-Hurst *et al*[55] found that GDF-15 levels are significantly associated with NYHA functional class and heart function of patients after completing the Fontan procedure for single ventricle. Since Fontan physiology is not a good model of pressure overload on the single ventricle, they found that NT-proBNP failed to be directly related to the echocardiographic measures of heart function. They concluded that GDF-15 is an early marker of decreased heart function in this cohort while NT-proBNP appear to be late markers when clinical heart failure is already present. They used a cutoff of > 613 pg/mL to suggest further cardiac evaluation may be indicated to assess for impaired ventricular function[55]. A recent meta-analysis has found that increased levels of GDF-15 were associated with increased mortality in patients with heart failure (HR of 1.86, 95%CI: 1.37-2.52), although cautions about heterogeneity in the studies as well as potential publication bias[56]. Overall, it appears that GDF-15 studies focused on specific pediatric patient populations (volume load, pressure load) may clarify its role in diagnosis and prognosis of pediatric heart failure.

CONCLUSION

As our understanding of the pathobiology of heart

disease evolves we continue to identify important biomarkers responsible for the same. These biomarkers are indicative of the cascade of events resulting in various forms of heart failure and heart disease. Elucidation of these processes is extremely important as they have the potential to identify new therapeutic targets. Specifically, biomarkers therefore play a vital role in diagnosis, management and prognosis of heart failure. Of all the biomarkers reviewed, BNP continues to be the dominant biomarker even in pediatric heart failure. Our understanding of the role of these novel biomarkers, some of which have already established a role in adult heart failure, will improve with further research. There is therefore an intermediate and an urgent need for undertaking biomarkers research in pediatric heart failure to enable us to improve care of these patients.

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P- Reviewer: Ng TMH, Ong HT, Wang Y **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

World Journal of Cardiology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v8.i12.728

World J Cardiol 2016 December 26; 8(12): 728-734
ISSN 1949-8462 (online)

MINIREVIEWS

Newer perspectives of coronary artery disease in young

Amitesh Aggarwal, Saurabh Srivastava, M Velmurugan

Amitesh Aggarwal, M Velmurugan, Department of Medicine, University College of Medical Sciences and GTB Hospital, Delhi 110095, India

Saurabh Srivastava, Department of Medicine, School of Medical Sciences and Research, Sharda University, Noida 201308, India

Author contributions: All authors contributed to this paper.

Conflict-of-interest statement: None.

Manuscript source: Invited manuscript

Correspondence to: Amitesh Aggarwal, MD, Associate Professor, Department of Medicine, University College of Medical Sciences and GTB Hospital, Dilshad Garden, Delhi 110095, India. dramitesh@gmail.com
Telephone: +91-11-22586262

Received: June 29, 2016
Peer-review started: July 1, 2016
First decision: September 5, 2016
Revised: October 14, 2016
Accepted: November 1, 2016
Article in press: November 2, 2016
Published online: December 26, 2016

Abstract

Coronary artery disease (CAD) occurring in less than 45 years of age is termed as young CAD. Recent studies show a prevalence of 1.2% of CAD cases in this age group. Ethnic wise south Asians especially Indians are more vulnerable to have CAD in young age group with a prevalence of 5% to 10%. Conventional risk factors such as smoking, diabetes, hypertension, obesity and family history seems to be as important as in older CAD subjects. But the prevalence of these risk factors seems to vary in younger subjects. By far the most commonly associated risk factor is smoking in young CAD. Several genes associated with lipoprotein metabolism are now found to be associated with young CAD like cholesterol ester transfer protein (*CETP*) gene, hepatic lipase gene, lipoprotein lipase gene, *apo A1* gene, *apo E* gene and *apo B*. Biomarkers such as lipoprotein (a), fibrinogen, D-dimer, serum Wnt, gamma glutamyl transferase, vitamin D2 and osteocalcin are seems to be associated with premature CAD in some newer studies. In general CAD in young has better prognosis than older subjects. In terms of prognosis two risk factors obesity and current smoking are associated with poorer outcomes. Angiographic studies shows predominance of single vessel disease in young CAD patients. Like CAD in older person primary and secondary prevention plays an important role in prevention of new and further coronary events.

Key words: Young; Coronary artery disease; Risk factors; Epidemiological trends; Prognosis

Core tip: Coronary artery disease (CAD) in patients less than 45 years of age is termed young CAD. South Asians especially Indians are more vulnerable to have CAD in young age group. Although conventional risk factors, mainly smoking, are also important in young CAD but there are numerous other factors that are responsible for it. Several genes associated with lipoprotein metabolism are now found to be associated with young CAD. Gamma glutamyl transferase, vitamin D2 and osteocalcin seem to be associated with premature CAD in some studies. Angiographic studies shows predominance of single vessel disease in young CAD patients.

Aggarwal A, Srivastava S, Velmurugan M. Newer perspectives of coronary artery disease in young. *World J Cardiol* 2016; 8(12): 728-734 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i12/728.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i12.728

INTRODUCTION

Coronary artery disease (CAD) occurring below the age of 45 years is termed as young CAD[1]. However various studies had considered the age limit varying from 35 years to 55 years in the spectrum of young CAD[2-10] (Table 1). This arena of cardiology has gained importance very recently due to increased prevalence in this age group over a last few decades, with varying risk factor profiles and difference in prognosis as well as longevity after an acute coronary episode. Recently, apart from the established biomarkers of CAD, many new markers, specifically associated with young CAD are discovered. The purpose of this review is to analyse the changing epidemiological trends, role of conventional and newer risk factors and prognosis of young CAD population.

TRENDS IN EPIDIMIOLOGICAL PROFILE

Coronary heart disease is the leading cause of morbidity and mortality, worldwide both in developing as well as developed countries, and is responsible for one third or more of all deaths in individuals greater than 35 years of age[11,12]. World Health Organisation has projected that burden due to CAD is going to increase globally from 47 million disability adjusted life years (DALYs) in 1990 to about 82 million DALYs in 2020. Many studies have demonstrated that young CAD contributes to 2% to 6% of all acute coronary events[13]. In the early 1980s, the Framingham study (FHS) reported a 10 year CAD incidence of 12.9 per 1000 in the age of 30 to 34 years and 5.2 per 1000 in the age group 35 to 44 years, in men and women respectively[14].

Studies have shown an increased prevalence of CAD in the subjects with family history of premature CAD, than in general population (35% *vs* 14%)[15]. The original as well as offspring cohort data of Framingham study, by National heart lung and blood institute (NHLBI's), from 1880 to 2003 revealed an annual incidence of cardiovascular disease of 3 per 1000 men between 35 to 44 years of age[16]. Centre of disease control prevalence data for the year 2010 revealed that prevalence of CAD in the age group of 18 to 44 years, 45 to 64 years and more than 65 years was 1.2%, 7.1% and 19.8% respectively[17]. Epidemiological data of United Kingdom published in the year 2000, reported a prevalence of 0.5% and 0.18% in men and women between 35 to 44 years respectively[1]. The prevalence of occult CAD in 112 asymptomatic young individuals, less than 40 years of age, was found to be 11% (9 had single vessel disease and 3 had double vessel disease) in a study done in Korea. The occult CAD in these individuals was defined by performing coronary CT angiography[18].

Table 1 Spectrum of terminology for young coronary artery disease

No.	Terminology	Age group studied	Ref.
1	Young CAD	Less than 45 yr	Ericsson *et al*[2]
2	Young CAD	Less than 40 yr	Konishi *et al*[3]
3	Young CAD	15-39 yr	Gupta *et al*[4]
4	Very young CAD	⩽ 35 yr	Christus *et al*[5]
5	Premature CAD	Men ⩽ 45 yr Female ⩽ 55 yr	van Loon *et al*[6]
6	Premature CAD	Less than 60 yr	Genest *et al*[7]
7	Premature CAD	Less than 45 yr	Pineda *et al*[8]
8	Precocious CAD	2 case reports of familial CAD of 29 and 31 yr	Norum *et al*[9]
9	Early onset CAD	Less than 45 yr	Iribarren *et al*[10]

CAD: Coronary artery disease.

The mean age of onset of CAD in Southeast Asians seems to be 53 years as compared to European figure of 63 years[19]. South Asians especially Indians are at greater risk of developing CAD at a young age (5% to 10%) when compared to other ethnic groups (approximately 1% to 2%)[20]. Reported prevalence of young CAD under the age of 40 years, in a study published from Indian subcontinent, in 1991 was 5% to 10%. This vulnerability of Indians to coronary events may be related to life style, environmental and genetic factors[20].

The median age of presentation of CAD in young women is higher when compared to men. Singapore myocardial infarction registry of CAD in group less than 65 years showed that men have 4 times greater risk of CAD than women[21]. In Asians 9.7% males and 4.4% females develop first episode of MI under 40 years of age[20].

RISK FACTORS PROFILE

Conventional risk factors (Table 2)

Prevalence of conventional risk factors like diabetes, hypertension, smoking, dyslipidemia and obesity accounts for about 85% to 90% of premature CAD patients[22]. Often young CAD patients have multiple coexisting risk factors contributing to the disease[23]. The most common risk factor associated with young CAD seems to be smoking. The prevalence of smoking in younger individuals less than 45 years of age, with CAD, was reported to be 60% to 90% as compared to 24% to 56% in subjects greater than 45 years[13,24]. Smoking in presence of additional risk factors like diabetes, hypertension and obesity predispose a young individual to increased risk of future acute coronary events[25].

The prevalence of diabetes and hypertension seems to higher in young patients with CAD than without CAD. The prevalence of hypertension is 25% in young

Table 2 List of conventional and newer risk factors in young coronary artery disease discussed in the review

Conventional risk factors	Newer risk factors
Age	Polymorphisms in *CETP* gene
Sex	Hepatic lipase gene
Hypertension	Lipoprotein lipase gene
Diabetes mellitus	C-reactive protein gene
Dyslipidaemia	*Apo A1* gene
Obesity	*Apo B* gene
Smoking	*Apo E* gene
Family history of premature CAD	*HIF1A* gene
	Factor 5 leiden
	MTHFR gene
	Methionine synthase gene
	Cocaine use
	Lipoprotein-a, Fibrinogen and D-dimer
	Decreased serum Wnt
	Increased gamma glutamyl transferase
	Raised vitamin D2 and D3
	Decreased osteocalcin
	Hypothyroidism
	Systemic lupus erythematosis
	Rheumatoid arthritis
	HIV patients on HAART
	Homocysteinemia
	Kawasaki disease in childhood,
	Patent foramen ovale
	Spontaneous coronary artery dissection

CETP: Cholesterol ester transfer protein; HAART: Highly active anti retroviral therapy; *MTHFR*: Methylene tetrahydrofolate reductase; *HIF1A*: Hypoxia inducible factor 1 alpha.

CAD as compared to 13% without CAD. Similarly, the incidence of diabetes and pre diabetes is 14.3% and 7.6% in young CAD as compared to only 5.4% and 4.3% in patients without CAD respectively[26]. However, prevalence of these risk factors is much higher in older individuals with CAD as compared to young CAD[27-29]. Various studies have demonstrated a recent increase in the prevalence of hypertension [8.86% (2001-2002) to 27.7% (2009-2010)] and dysglycemia [7.6% (2001-2002) to 36.15% (2009-2010)] in young CAD[30].

Although, dyslipidemia is an important risk factor for young CAD, there seems to be a little difference in prevalence of lipid abnormalities in younger and older patients. One study demonstrated a significantly increased level of LDL and total cholesterol in persons of CAD more than 55 years of age when compared with less than 55 years of age[27]. Conversely in an another study there is high prevalence of lipid abnormalities in young CAD when compared to older CAD group[28]. These differences in lipid parameters may due effect of dietary, genetic and environmental factors on lipid metabolism.

Obesity is a well established risk factor for CAD. There is little difference in the prevalence of obesity in young CAD when compared with older CAD patients[28]. Sagittal abdominal diameter to skin fold ratio seems to be a good indicator in predicting premature CAD, even better than body mass index (BMI) and waist circumference[31].

Family history of premature CAD is an important risk factor for young CAD. It stresses the role of genes in the aetiology of young CAD. Studies have shown that person with a positive family history of premature CAD tend to have severe coronary atherosclerosis and is a very strong predictor of future acute coronary event[32]. The atherosclerosis in coronary vessels, as revealed by increased plaque content is seen in individuals with a positive family history of premature CAD and increases the incidence of severe obstructive CAD[32]. One study revealed around 64% of young CAD patients had a positive family history[13].

The prevalence of conventional risk factors like hypertension (67%), dyslipidemia (67%), obesity (53%), smoking (42%), and diabetes (33%) is higher in women with a family history of CAD[33].

Other risk factors

There are numerous risk factors found to be associated with CAD in younger people. Some of the newer risk factors are discussed in the review. Polymorphisms in cholesterol ester transfer protein (*CETP*) gene, hepatic lipase gene, lipoprotein lipase gene, C-reactive protein gene, *apo A1* gene, *apo E* gene, *apo B*, hypoxia inducible factor 1 alpha gene, factor 5 leiden, Methylene tetrahydrofolate reductase (*MTHFR*) gene and methionine synthase gene have been associated with premature CAD[34-38].

Kuivenhoven *et al*[39] found a significant association between variation at the CETP locus and angiographic progression of coronary atherosclerosis in men with CHD.

The ApoE4 allele has been associated with CAD in several populations. ApoE2/E2 homozygous individuals are at risk for type Ⅲ hyperlipoproteinemia, which is associated with an increased risk for atherosclerosis[40,41].

Homozygosity for the *MTHFR C677T* mutation has been associated with elevated levels of homocysteine, and homocysteine levels have been associated with CAD risk[42,43].

Hepatic lipase (HL) is both a phospholipase and a triglyceride lipase and plays an important role in HDL metabolism and in the conversion of VLDL to LDL. Single nucleotide polymorphisms in the *HL* gene have been shown to associate with plasma lipid concentrations and increased CHD risk[44].

Hypercholesterolemia is the most common and treatable cause of heart disease. Familial Hypercholesterolemia (FH) results from mutations in the LDL receptor, *ApoB*, *PCSK9*, and *ApoE* genes. FH is characterized by isolated elevation of plasma low-density lipoprotein cholesterol and is associated with high risk of premature cardiovascular disease[45].

The prevalence of premature arcus senilis (16.1%), premature greying (34.9%) and premature balding (22.3%) have been found to be significantly increased in young CAD patients when compared to non CAD

subjects of same age[26,46]. Thus young CAD patients are associated with premature ageing as depicted by these markers. The arcus senilis is also a marker of familial hypercholesterolemia which in turn is a risk factor for premature CAD.

Cocaine use is also considered as a risk factor for CAD, it is associated with a number of cardiovascular diseases, including myocardial infarction, heart failure, cardiomyopathies, arrhythmias, aortic dissection, and endocarditis[47].

Young CAD patient shows an increased serum levels of lipoprotein-a, fibrinogen and D-dimer as compared to age matched controls[8]. Decreased serum Wnt, increased gamma glutamyl transferase, raised vitamin D2 and D3 and decreased levels of osteocalcin are found to be associated with premature CAD[48-50]. This association of CAD in young with high levels of vitamin D is in contradiction to the studies done in general population where deficiency of vitamin D is associated with adverse cardiovascular outcomes[51-53].

Diseases such as hypothyroidism, systemic lupus erythematosis, rheumatoid arthritis, HIV patients on highly active anti retroviral therapy (HAART) (especially with protease inhibitors), homocysteinaemia, kawasaki disease in childhood, patent foramen ovale (causing paradoxical embolism) and various other conditions are found to associated with accelerated atherosclerosis[54,55].

The mean age of presentation of spontaneous coronary artery dissection is 35-40 years, and is more common in females. The patients are divided into three groups: A peripartum, atherosclerotic and idiopathic group[56]. Dissection occurs in tunica intima of coronary arteries, the blood penetrates and results in intramural hematoma in tunica media, resulting in restriction in the size of lumen, reduction of blood flow and myocardial infarction[57].

PATHOPHYSIOLOGY OF CAD IN YOUNG

Conventional CAD accounts for about 80% of CAD in young adults. About 4% of heart attacks in young adults are due to congenital abnormalities of the coronary artery anatomy, about 5% due to blood clots that originate elsewhere and are carried to otherwise normal coronary arteries, and block the artery, in another 5%, various disorders of the blood clotting system increase the risk of clot formation. The remaining 6% of CAD in young adults is due to spasm or inflammation of the coronary arteries, radiation therapy for chest tumors, chest trauma, and abuse of cocaine, amphetamines, and other drugs. Coronary segments, with non-significant stenosis and non calcified plaque, shows positive remodeling that might be the cause of CAD in young individuals with normal coronary artery. Positive remodeling is related to plaque instability, suggesting it is more prone to rupture and erosion with subsequent coronary events. Lipid core plaques, in contrast to the severely calcified plaques, showed positive vascular remodeling, thus early plaques are more prone for CAD[58-60].

PROGNOSIS

Obesity and current smoking are the two important conventional risk factors associated with adverse outcomes in the form of increased mortality and future acute coronary events[3]. Mortality of CAD in people of China, less than 40 years of age, was 13.81/100000 in 2006 which increased to 19.07/100000 in 2009[61]. There is a widespread decrease in mortality due to CAD in older age group in the recent years but it not seen in CAD in younger age group[62]. The possible explanation that is proposed is increase in prevalence of risk factors such as diabetes, obesity and hypertension in younger age groups[62]. Mortality after an acute coronary event is two times higher in women than in men under 50 years of age[63,64]. The cause of increased incidence of adverse event in women with premature CAD is still unknown.

In patient with acute coronary event both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are associated with excellent immediate survival (mortality of 0.8% *vs* 1.4% for PCI and CABG respectively at 30 d) as well as long term survival outcomes at end of 5 years[65]. But PCI seems to associated with lower rate of repeated acute coronary events and revascularisation procedures when compared to CABG at the end of 5 years (repeat myocardial infarction 89.9% *vs* 96.6% for PCI *vs* CABG)[66]. Mortality outcomes at 30 d and 3 years after an ST segment elevation myocardial infarction in 3601 patients with and without family history of premature CAD were compared in Harmonizing outcomes with revascularization and stents in acute myocardial infarction (HORIZONS-AMI) trial, which did not show any significant association of family history of premature CAD with mortality outcomes[67]. In patients with young CAD high C-reactive protein have been associated recurrence of future acute coronary event and raised fibrinogen levels seems to be associated with increased mortality[6]. Persons with positive family history of premature CAD and coronary artery calcium scores greater than 80th percentiles benefit from treatment with statins for primary prevention of acute coronary events[68].

Young CAD patients have higher rates of normal coronary vessels on angiography, mild luminal irregularities and increased prevalence of single vessel disease than older CAD patients[24]. In recent study from Nepal of young CAD less than 45 years angiography revealed 7.6% had normal or non critical disease, 6.1% had triple vessel disease, 36.9% had double vessel disease and 53.8% had single vessel disease[69].

Single vessel disease involving left anterior descending artery is much more common in young women when compared with young men with CAD[70,71]. The prevalence of normal coronary arteries in patients with young CAD is about 8% to 22% as reported in various studies[72-74] compared to 3% to 4% in general

CAD population[75]. The cause of this high prevalence of normal angiography in young CAD patients is still unclear. The probable reason could be the natural extra luminal progression of disease in the initial stages, as the vessel wall compensates to maintain unrestricted luminal blood flow[76]. An occlusive thrombus produced by the rupture of an angiographically "invisible" vulnerable plaque totally lysed after few hours or a long-lasting vasospasm leading to complete occlusion of a normal coronary artery or a combination of these two are the most likely mechanism of CAD in patient with normal coronaries[77].

CONCLUSION

The overall prevalence of CAD including the subset of young CAD is on decreasing trend but mortality of CAD doesn't seems to be decreasing when comparing to older CAD patients. In addition to conventional risk factors numerous other risk factors and genes play an important role in the causation of the disease. The prognosis of CAD in younger people is better than older people. Current smoking and obesity have major impact in long term mortality and morbidity. Young CAD patients with an acute coronary event undergoing PCI and CABG have an excellent immediate and long term survival rates.

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P- Reviewer: Pocar M, Sabate M, Tsai WC **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Wu HL

World Journal of Cardiology

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DOI: 10.4330/wjc.v8.i12.735

World J Cardiol 2016 December 26; 8(12): 735-745
ISSN 1949-8462 (online)

ORIGINAL ARTICLE

Retrospective Study

Comparison between the SAPIEN S3 and the SAPIEN XT transcatheter heart valves: A single-center experience

Fadi J Sawaya, Marco Spaziano, Thierry Lefèvre, Andrew Roy, Phillippe Garot, Thomas Hovasse, Antoinette Neylon, Hakim Benamer, Mauro Romano, Thierry Unterseeh, Marie-Claude Morice, Bernard Chevalier

Fadi J Sawaya, Marco Spaziano, Thierry Lefèvre, Andrew Roy, Phillippe Garot, Thomas Hovasse, Antoinette Neylon, Hakim Benamer, Mauro Romano, Thierry Unterseeh, Marie-Claude Morice, Bernard Chevalier, Department of Cardiology, Générale de Santé, Institut Cardiovasculaire Paris-Sud - Hôpital Privé Jacques Cartier, 91300 Massy, France

Author contributions: Both Sawaya FJ and Spaziano M contributed equally to the preparation of this manuscript; Sawaya FJ, Spaziano M designed and performed the research and wrote the paper; Chevalier B designed the research and supervised the report; Roy A designed the research and contributed to the analysis; Garot P, Hovasse T, Neylon A, Benamer H, Romano M, Unterseeh T, Morice MC provided clinical advice; Lefèvre T and Chevalier B supervised the report.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Institut Cardiovasculaire Paris Sud.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: Dr. Thierry Lefèvre is a proctor for Edwards LifeSciences. All other authors report no conflict of interest regarding this manuscript.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

Correspondence to: Bernard Chevalier, MD, Department of Cardiology, Générale de Santé, Institut Cardiovasculaire Paris-Sud - Hôpital Privé Jacques Cartier, 6 Avenue du Noyer Lambert, 91300 Massy, France. bchevali@aol.com
Telephone: +33-78-5949543
Fax: +33-18-7653311

Received: July 22, 2016
Peer-review started: July 26, 2016
First decision: September 6, 2016
Revised: September 26, 2016
Accepted: October 22, 2016
Article in press: October 24, 2016
Published online: December 26, 2016

Abstract

AIM

To investigate the clinical outcomes of transcatheter aortic valve implantation (TAVI) with the SAPIEN 3 transcatheter heart valve (S3-THV) *vs* the SAPIEN XT valve (XT-THV).

METHODS

We retrospectively analyzed 507 patients that underwent TAVI with the XT-THV and 283 patients that received the S3-THV at our institution between March 2010 and December 2015.

RESULTS

Thirty-day mortality (3.5% *vs* 8.7%; OR = 0.44, *P* = 0.21) and 1-year mortality (25.7% *vs* 20.1%, *P* = 0.55) were similar in the S3-THV and the XT-THV groups. The rates of both major vascular complication and paravalvular regurgitation (PVR) > 1 were almost 4 times lower in the S3-THV group than the XT-THV group (major vascular complication: 2.8% *vs* 9.9%, *P* < 0.0001; PVR > 1: 2.4% *vs* 9.7%, *P* < 0.0001). However,

the rate of new pacemaker implantation was almost twice as high in the S3-THV group (17.3% *vs* 9.8%, *P* = 0.03). In the S3 group, independent predictors of new permanent pacemaker were pre-procedural RBBB (OR = 4.9; *P* = 0.001), pre-procedural PR duration (OR = 1.14, *P* = 0.05) and device lack of coaxiality (OR = 1.13; *P* = 0.05) during deployment.

CONCLUSION

The S3-THV is associated to lower rates of major vascular complications and PVR but higher rates of new pacemaker compared to the XT-THV. Sub-optimal visualization of the S3-THV in relation to the aortic valvular complex during deployment is a predictor of new permanent pacemaker.

Key words: SAPIEN-3 valve; Vascular complications; Permanent pacemaker; Lack of coaxiality; Paravalvular regurgitation

Core tip: The SAPIEN 3 transcatheter heart valve (S3-THV) is associated to lower rates of major vascular complications and PVR but higher rates of new pacemaker compared to the SAPIEN XT valve (XT-THV). Sub-optimal visualization of the S3-THV in relation to the aortic valvular complex during deployment is a predictor of new permanent pacemaker (PPM). Our findings highlight the increased importance to adequately visualize the S3-THV in relation to the aortic valvular complex during deployment, in order to improve device positioning and potentially mitigate new PPM requirements.

Sawaya FJ, Spaziano M, Lefèvre T, Roy A, Garot P, Hovasse T, Neylon A, Benamer H, Romano M, Unterseeh T, Morice MC, Chevalier B. Comparison between the SAPIEN S3 and the SAPIEN XT transcatheter heart valves: A single-center experience. *World J Cardiol* 2016; 8(12): 735-745 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i12/735.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i12.735

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has gained rapid acceptance for patients with severe aortic stenosis[1-4] and has recently been associated with excellent short-, mid- and long-term outcomes in patients at intermediate risk[5-7]. However, TAVI is still associated with a higher incidence of paravalvular regurgitation (PVR), permanent pacemaker implantation (PPM) and vascular complications[8-12] when compared to surgical aortic valve replacement. In order to justify the extension of the procedure to lower risk patients, these adverse outcomes have to be mitigated. The development of novel transcatheter heart valves (THVs) and further iterations of delivery systems and prostheses have contributed to the decrease in complications rates in TAVI[13]. One of the recent developments is the balloon-expandable Sapien 3 transcatheter heart valve (S3-THV; Edwards Lifesciences, Irvine, CA). It has been designed with a lower profile to be delivered in a 14 French sheath (for sizes 23 and 26 mm), and with an external sealing cuff. The lower profile should diminish vascular complications while the sealing cuff should diminish PVL[14,15].

Despite positive procedural and short-term outcomes in small single center series and registries, large reports comparing the S3-THV to its predecessor, the Sapien XT (XT-THV), are lacking[16,17]. Recent reports suggest an increased rate of new PPM implantation following TAVI with the S3-THV, compared to the XT-THV[16,17]. Whether procedural characteristics such as depth of implant are related to PPM implantation with this new device remains unclear[18].

The objective of this analysis was to retrospectively compares the procedural outcomes, 30-d clinical outcomes and one-year mortality of TAVI with the S3-THV *vs* the XT-THV in patients with symptomatic severe aortic stenosis in a single high-volume center. We also explored clinical and procedural predictors of new PPM in the S3-THV group.

MATERIALS AND METHODS

Patient population and procedure

To compare clinical outcomes of patients undergoing TAVI with the S3-THV to those undergoing TAVI with the XT-THV, we retrospectively identified all patients treated with TAVI at our institution with either device. Patients underwent TAVI by the transfemoral, transaortic or transapical approach according to previously described techniques[17].

A multidisciplinary heart team involving at least one interventional cardiologist and one cardiac surgeon discussed all cases and consensus was achieved regarding therapeutic strategy. All patients provided informed written consent for the procedure and data collection, and the local ethics committee approved the study.

Pre-procedural planning

All patients underwent TTE examination and native valve function was assessed according to the recommended guidelines[19]. In addition, pre-procedural MSCT evaluation including measurements of the aortic annulus and aortic root was systematically performed. Aortic annulus dimensions were measured according to standard procedures using dedicated software (Philips Brilliance 64-slice multidetector computed tomography scanner, Philips Healthcare, Best, the Netherlands). Valve prosthesis size was selected in accordance with the manufacturer's recommendations after taking into account other anatomic features such as the presence and location of calcification, eccentricity of the aortic

annulus and dimensions of the sinuses of Valsalva and sino-tubular junction in case of borderline sizing ranges. In addition to dimensions, annulus orientation was assessed with MSCT. Implantation projection was selected so that the aortic valve would be seen coaxially, with the three cusps aligned. Cardiac catheterization and femoral angiography were performed prior to the procedure to assess for concomitant coronary artery disease and vessel narrowing or tortuosity.

Study devices

The SXT-THV and the S3-THV designs have been described in detail previously[15,20]. Both consist of bovine pericardium sewn to a balloon-expandable cobalt-chromium tubular frame. The XT-THV was available in the 23, 26, and 29 mm sizes and was implanted with the use of the NovaFlex catheter, which employed an 18- or 19-F introducer sheaths. The S3-THV is available in the 23, 26, and 29 mm sizes. The device's height is about 15% greater than that of the XT-THV. It was implanted with the use of the lower-profile Commander delivery catheter, which employed 14- (sizes 23 and 26 mm) or 16-F (size 29 mm) expandable sheaths (eSheath, Edwards Lifesciences, Inc.). The S3-THV stent was designed with a frame geometry that provides greater radial force. The difference in cell geometry between the inflow and the outflow causes the valve frame to foreshorten more from the ventricular side. The device also includes an outer polyethylene terephthalate fabric seal designed to minimize PVR.

Study procedure

The techniques of SAPIEN XT and SAPIEN S3 valve implantation have been described in detail elsewhere[15,20]. In our center, all trans-femoral cases were performed under local anesthesia and conscious sedation in the catheterization laboratory. The selected femoral artery was "pre-closed" with two 6-Fr suture-mediated closure devices Perclose ProGlide(Abbott Laboratories, Abbot Park, Illinois). With a pigtail in the right coronary cusp, aortography was performed to correct, if necessary, the implantation projection provided by MSCT. Pre-dilatation was performed routinely in the XT-THV group, but only in cases of severe calcification in the S3-THV group. Device positioning was based on fluoroscopy using annular calcification as a landmark along with serial 12 to 15 mL supra-annular aortography to validate its position. The XT-THV was implanted by means of a 2-step inflation technique[21]. The S3-THV was deployed during one-slow inflation (5-10 s). Prosthesis position and function, and patency of the coronary ostia were evaluated by angiography and transthoracic echocardiography. Significant aortic regurgitation was treated by post-dilatation adding 1 to 3 cc of contrast in the balloon delivery system or second valve implantation if the valve was positioned too high or too low. Removal of the sheath was cautiously achieved with serial contralateral angiograms to detect ilio-femoral complications. In the absence of any conduction abnormality, the pacing lead was removed at the end of the procedure. Patients were monitored in the intensive care unit for at least 24 h after valve implantation. For the transapical and transaortic cases, the SXT-THV and S3-THV were deployed with the Ascendra and Certitude delivery systems, respectively. These cases were performed in a hybrid room.

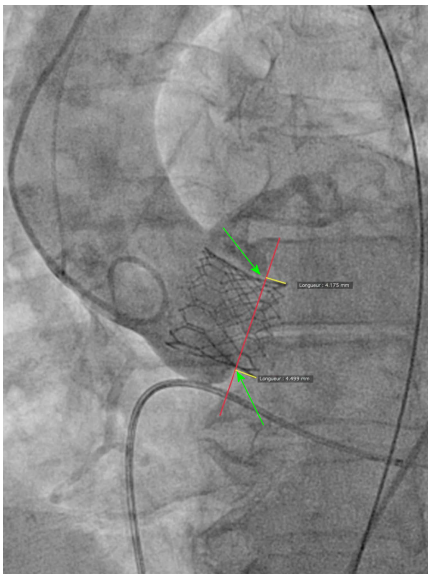

Figure 1 Depth of implant measurement. The arrows show the hinge points between the device and neighboring sinuses of Valsalva. Next, the red line is drawn from the septal to the non-septal hinge point. The yellow lines, drawn perpendicularly from the red line to the extremity of the device frame, represent depth on the septal side (left) and the non-septal side (right).

Data collection and study endpoints

Clinical and echocardiographic data at baseline and follow-up were collected by dedicated personnel and entered in a local database and a national registry (FRANCE-TAVI)[22]. Data from the ECG and MSCT prior to the intervention were retrospectively collected by the co-authors and entered into the local database. The co-authors also retrospectively collected implant depth and device coaxiality from procedure fluoroscopy.

The primary endpoint was 30-d mortality. Secondary endpoints consisted of 1-year mortality, stroke, myocardial infarction, annulus rupture, new PPM implantation, major vascular complication, PVR greater than mild, annulus rupture, acute kidney injury and post-procedural mean gradient. Endpoints were defined according to the VARC-2 criteria[23].

Implant depth and device coaxiality during implant measurement

We reviewed procedural fluoroscopy of all patients in the S3-THV group to measure valve implant depth. A post-implant aortic angiogram with the device coaxial was required for implant depth measurement. First, on a single still frame, the hinge points between the device and the sinus of Valsalva on the septal and non-septal

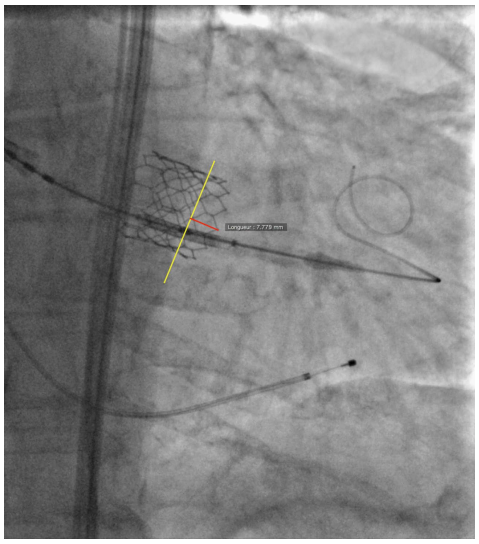

Figure 2 Device coaxiality measurement. On a still frame, immediately after deployment while still under rapid pacing, a line is drawn connecting neighboring valve struts on the ventricular side of the device (yellow line). Next, a perpendicular line is drawn from the yellow line to the tip of the strut that appears the deepest (red line). The length of this red line is recorded as device lack of coaxiality.

side were identified (Figure 1). Next, a line was drawn between both hinge points. The distances between this line and the bottom of the valve frame on both the septal and non-septal sides were then recorded as implant depth. Measurements were performed using the OsiriX sorftware, version 5.9.

In addition to depth, we also measured device lack of coaxiality during deployment. This was done on a single still frame at the end of valve deployment, while still under rapid pacing. The maximal perpendicular distance between the "front" and the "back" struts of the device was measured and recorded as device lack of coaxiality during deployment (Figure 2).

Statistical analysis

Continuous data are reported as mean ± SD, and categorical variables are reported as number of patients and percentages. Categorical data were compared using Fisher's exact test, and continuous data using Student's *t* test or Mann-Whitney's *U* test, as appropriate. Events are reported as counts of first occurrence per type of event. Event probabilities at 30 d were compared for patients treated with the XT-THV *vs* the S3-THV using logistic regression. Crude and adjusted odds ratios (with 95%CI) are reported. Odds ratios are adjusted for procedure date (to account for a potential learning effect of time) and for baseline characteristics with a univariate *P* value < 0.10 for each individual outcome. One-year survival data was fitted in a Cox proportional hazards model and the XT-THV and S3-THV groups were compared using an adjusted hazard ratio. No adjusted analyses were performed for outcomes with less than 15 events overall. Patients with previous pacemaker implantation were excluded from analyses pertaining to the outcome of new pacemaker requirement. A *P* value < 0.05 was considered significant for adjusted models. Statistical analyses were performed with SPSS version 23 (IBM Corp, Armonk, NY).

Table 1 Baseline characteristics

Variable	S3-THV (*n* = 283)	XT-THV (*n* = 507)	*P* value
Age	82.8 ± 7.1	83.5 ± 7.0	0.14
Female sex	137 (48.4)	275 (54.3)	0.12
STS-PROM, %	5.3 ± 3.5	6.4 ± 4.0	< 0.0001
Logistic EuroSCORE, %	15.7 ± 10.8	18.8 ± 11.5	< 0.0001
NYHA class 3 or 4	162 (59.1)	383 (75.8)	< 0.0001
History of syncope	1 (0.5)	10 (2.1)	0.19
Atrial arrhythmia (flutter or fibrillation)	80 (29.5)	135 (27.8)	0.67
Diabetes	71 (25.1)	124 (24.5)	0.86
Hypertension	161 (71.6)	344 (68.8)	0.49
Dyslipidemia	99 (44.0)	263 (52.6)	0.04
Active smoker	4 (1.4)	18 (3.6)	0.11
Previous PPM	35 (12.4)	60 (11.8)	0.91
Previous PCI	81 (29.3)	114 (22.9)	0.06
Previous CABG	25 (9.0)	51 (10.3)	0.62
Previous SAVR	2 (0.7)	7 (1.4)	0.50
Previous stroke	25 (8.8)	39 (7.7)	0.59
Peripheral vascular disease	56 (19.8)	143 (28.4)	0.01
eGFR, mL/min per 1.73 m^2	62.8 ± 24.6	61.4 ± 22.6	0.42
eGFR < 40 mL/min per 1.73 m^2	82 (16.2)	41 (14.5)	0.61
Dialysis	4 (1.5)	13 (2.6)	0.44
Chronic obstructive pulmonary disease	33 (11.7)	110 (21.9)	< 0.0001
Body mass index, kg/m^2	26.5 ± 5.1	26.3 ± 4.9	0.61
LVEF, %	54.9 ± 14.8	53.6 ± 14.2	0.24
LVEF < 30%	55 (11.1)	31 (11.4)	0.91
Mean aortic gradient, mmHg	46.7 ± 15.3	46.9 ± 15.3	0.92
AVA, cm^2	0.67 ± 0.17	0.65 ± 0.14	0.31
Pulmonary artery systolic pressure, mmHg	44.5 ± 13.0	46.5 ± 12.9	0.06
Pulmonary artery systolic pressure > 50 mmHg	64 (28.3)	123 (28.5)	1

Values are mean ± SD or *n* (%). AVA: Aortic valve area; CABG: Coronary artery bypass graft; eGFR: Glomerular filtration rate estimated by the MDRD formula; EuroSCORE: European System for Cardiac Operative Risk Evaluation; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association functional class; PPM: Permanent pacemaker; PCI: Percutaneous coronary intervention; SAVR: Surgical aortic valve replacement; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; S3-THV: SAPIEN 3 transcatheter heart valve; XT-THV: SAPIEN XT transcatheter heart valve.

RESULTS

Between March 2010 and December 2015, 790 patients underwent TAVI with the XT-THV (*n* = 507) or the S3-THV (*n* = 283) in our center. The XT-THV was used from March 2010 to September 2014, after which the S3-THV was used routinely. Patients in the S3-THV group had lower STS scores than those in the XT-THV group (STS score: 5.3% ± 3.5% *vs* 6.4% ± 4.0% respectively, *P* < 0.0001) (Table 1). Patients in the S3-THV group were also less likely to be in NYHA functional class 3 or 4 (59.1% *vs* 75.8%, *P* < 0.0001), and less likely to have peripheral vascular disease (19.8% *vs* 28.4%, *P* =

Table 2 Procedural characteristics

Procedural characteristic	S3-THV (*n* = 283)	XT-THV (*n* = 507)	*P* value
Transfemoral approach	232 (82.6)	273 (53.8)	< 0.0001
Local anesthesia	232 (82.6)	271 (54.2)	< 0.0001
Predilatation	50 (17.7)	440 (86.8)	< 0.0001
Postdilatation	45 (15.9)	61 (12.0)	0.13
Implanted device size			< 0.0001
23 mm	111 (39.8)	127 (25.1)	
26 mm	101 (36.2)	270 (53.4)	
29 mm	67 (24.0)	109 (21.5)	
Valve area oversizing, %	11.5 ± 9.8	22.9 ± 11.2	< 0.0001
Device diameter/annulus diameter (area-derived)	1.05 ± 0.05	1.11 ± 0.05	< 0.0001
Need for seconde valve implantation	7 (2.5)	8 (1.6)	0.42
Annulus rupture	0 (0)	13 (2.6)	0.01
Conversion to SAVR	2 (0.7)	14 (2.8)	0.06
Contrast use (mL)	108.2 ± 42.7	131.6 ± 60.9	< 0.0001
Fluoroscopy time (min)	17.4 ± 9.9	16.5 ± 9.8	0.28

Values are mean ± SD or *n* (%). SAVR: Surgical aortic valve replacement; S3-THV: SAPIEN 3 transcatheter heart valve; XT-THV: SAPIEN XT transcatheter heart valve.

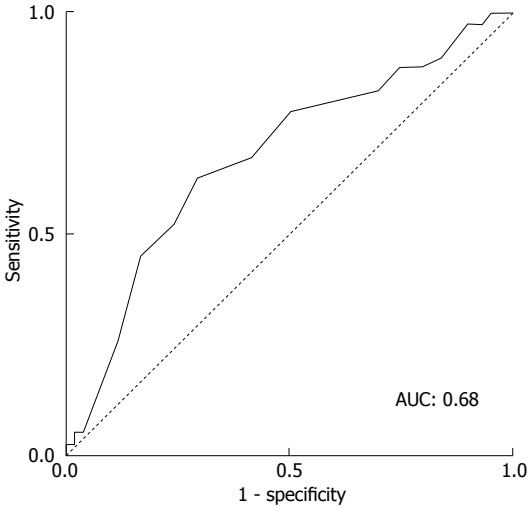

Figure 3 Receiver operating characteristic curve analysis of device diameter to annulus diameter ratio. ROC curve analysis of device diameter to annulus diameter ratio below the threshold of 1.03 increased the risk of post-dilatation or PVR > mild (area under the curve: 0.68). PVR: Paravalvular regurgitation; ROC: Receiver operating characteristic; AUC: Area under curve.

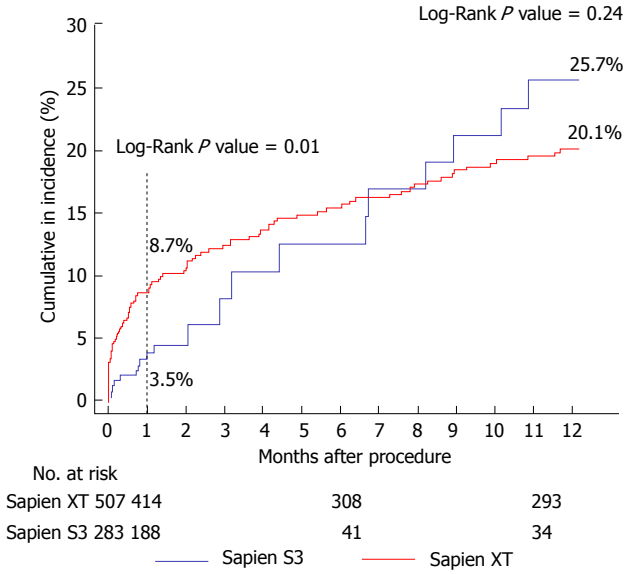

Figure 4 Cumulative incidence of all-cause mortality. Cumulative incidence (%) of all-cause 1-year mortality in the S3-THV group (blue line) and the XT-THV group (red line). S3-THV: SAPIEN 3 transcatheter heart valve; XT-THV: SAPIEN XT transcatheter heart valve.

0.01) or chronic obstructive pulmonary disease (11.7% *vs* 21.9%, *P* < 0.0001). Baseline echocardiographic characteristics were similar between groups.

The use of the transfemoral approach increased from 54% in XT-THV group to more than 80% in the S3-THV group (*P* < 0.0001) (Table 2).

Predilatation was performed routinely in the XT-THV group (86.8%), which was not the case in the S3-THV group (17.7%, *P* < 0001) (Table 2). In the S3-THV group, predilatation was reserved for patients with an extensively calcified aortic valve. The lower use of predilatation in the S3-THV group did not translate into significantly more post-dilatation (S3-THV: 15.9% *vs* XT-THV: 12.0%; *P* = 0.13). As per manufacturer recommendations, device diameter to annulus diameter (area-derived) ratio was reduced from 1.11 ± 0.05 (XT-THV) to 1.05 ± 0.05 (S3-THV; *P* < 0.0001). As a result of this reduced oversizing, smaller device sizes were used in the S3-THV group (*P* < 0.0001). However, according to ROC curve analysis, a device diameter to annulus diameter ratio below the threshold of 1.03 increased the risk of post-dilatation or PVR > mild (area under the curve: 0.68; Figure 3).

While fluoroscopy time was similar between groups, contrast use decreased by more than 15% in the S3-THV group compared to the XT-THV group (131.6 ± 60.9 mL *vs* 108.2 ± 42.7 mL; *P* < 0.0001).

Clinical outcomes

Thirty-day mortality was lower in the S3-THV group than the XT-THV group (3.5% *vs* 8.7%; univariate OR = 0.36; *P* = 0.01) (Figure 4 and Table 3). After adjustment for baseline characteristics, this difference was no longer statistically significant (adjusted OR = 0.44, *P* = 0.21). One-year mortality was also similar between groups (25.7% *vs* 20.1%, adjusted *P* =0.55) (Figure 4). In total, 20 deaths had occurred at 1 year in the S3-THV group. These are listed in Table 4 along with cause of death.

The rates of major vascular complication and PVR > 1 were both almost 4 times lower in the S3-THV group than the XT-THV group (major vascular complication: 2.8% *vs* 9.9%, adjusted *P* < 0.0001; PVL > 1: 2.4% *vs* 9.7%, adjusted *P* < 0.0001) (Figure 5). However, the rate of new pacemaker implantation was almost twice as high in the S3-THV group (17.3% *vs* 9.8%, adjusted *P* = 0.03) (Figure 5).

Acute kidney injury was 10 times lower in the S3-THV group than the XT-THV group (1.1% *vs* 13.6%,

Table 3 Thirty-day and 1-year outcomes

30-d outcomes	S3-THV (*n* =283)	XT-THV (*n* = 507)	Odds ratio (95%CI)	*P* value	Adjusted odds ratio (95%CI)	Adjusted *P* value
Death	8 (3.5)	42 (8.7)	0.36 (0.16-0.81)	0.01	0.44 (0.12-1.56)	0.21
Stroke	4 (1.4)	13 (2.8)	0.51 (0.16-1.58)	0.24	0.59 (0.08-4.33)	0.60
Myocardial infarction	0 (0)	2 (0.4)	0 (0-∞)	1		
New pacemaker implantation[1]	43 (17.3)	44 (9.8)	1.88 (1.19-2.97)	0.007	1.68 (1.05-2.69)	0.03
Major vascular complication	8 (2.8)	50 (9.9)	0.27 (0.13-0.57)	0.001	0.20 (0.09-0.44)	< 0.0001
Paravalvular regurgitation > mild	6 (2.4)	47 (9.7)	0.23 (0.10-0.55)	0.001	0.20 (0.08-0.47)	< 0.0001
Acute kidney injury	3 (1.1)	69 (13.6)	0.07 (0.02-0.22)	< 0.0001	0.12 (0.04-0.39)	< 0.0001
Mean gradient > 20 mmHg	7 (2.8)	6 (1.3)	2.48 (0.78-7.89)	0.13		
Mean gradient, mmHg	11.8 ± 5.8	10.0 ± 5.0		< 0.0001		
Total hospital length of stay, d [median (IQR)]	8 [5-13]	9 [7-14]		< 0.0001		
1-yr outcomes				*P* value	Adjusted hazard ratio (95%CI)	Adjusted *P* value
Death	20 (25.7)	87 (20.1)		0.24	0.86 (0.52-1.42)	0.55

Values are mean ± SD or *n* (%) unless specified otherwise. [1]Patients with previous permanent pacemaker were excluded from this analysis. No adjusted analyses were performed for outcomes with less than 15 events overall. IQR: Inter-quartile range; S3-THV: SAPIEN 3 transcatheter heart valve; XT-THV: SAPIEN XT transcatheter heart valve.

Table 4 Causes of death at 1 year in the SAPIEN 3 transcatheter heart valve group

Patient	Days to death	Cause of death
1	0	Dissection of ascending aorta
2	2	Left main compression/cardiogenic shock
3	3	Iliac rupture
4	5	Sudden cardiac death
5	10	Cardiogenic shock
6	22	Heart failure
7	24	Subdural hematoma
8	25	Unknown
9	31	Stroke
10	36	Acute renal failure
11	62	Unknown
12	87	Heart failure
13	96	Heart failure
14	133	Unknown
15	200	Sudden cardiac death
16	202	Cancer
17	247	Myocardial infarction
18	268	Septic shock
19	305	Chronic obstructive pulmonary disease acute exacerbation
20	326	Major stroke

P < 0.0001). There were no statistically significant differences between groups with respect to stroke, myocardial infarction and post-procedural mean gradient > 20 mmHg.

Predictors of new pacemaker implantation in the S3-THV group

Electrocardiographic and angiographic characteristics of patients in the S3-THV group that required a new PPM are displayed in Tables 5 and 6. Implantation depth in the S3-THV group was 5.1 ± 2.5 mm on the septal side (non-coronary cusp) and 5.2 ± 2.0 mm on the non-septal side (left coronary cusp). According to multivariate analysis, independent predictors of new permanent pacemaker implantation were pre-procedural

Table 5 Electrocardiographic and angiographic characteristics according to new permanent pacemaker requirement in the SAPIEN 3 transcatheter heart valve group

Variable	New PPM (*n* = 43)	No PPM (*n* = 201)	*P* value
Complete RBBB	12 (32.4)	17 (9.5)	0.001
Complete LBBB	0 (0)	14 (7.8)	0.14
Fascicular block	12 (32.4)	33 (18.4)	0.07
QRS duration, ms	108 ± 26	101 ± 23	0.1
PR duration, ms	196 ± 37	183 ± 30	0.04
Implant depth (septal), mm	5.3 ± 2.4	5.0 ± 2.6	0.67
Implant depth (non-septal), mm	4.9 ± 2.4	5.2 ± 1.9	0.64
Device lack of coaxiality during deployment, mm	4.0 ± 3.6	2.9 ± 2.5	0.06

Values are mean ± SD or *n* (%). LBBB: Left bundle branch block; RBBB: Right bundle branch block; PPM: Permanent pacemaker.

complete right bundle branch block (RBBB) (OR = 4.9; 95%CI: 1.88-12.95; *P* = 0.001), PR duration (OR = 1.14 per 10 ms increment; 95%CI: 1.00-1.29; *P* = 0.05) and device lack of coaxiality during deployment (OR = 1.13 per 1 mm increment; 95%CI: 1.00-1.29; *P* = 0.05). Device implantation depth was not a predictor of new pacemaker implantation in our series.

DISCUSSION

To our knowledge, this is one of the largest observational studies to date comparing the newer balloon-expandable S3-THV to the XT-THV in an all-comer population. The major findings are as follows: (1) the S3-THV is associated with similar adjusted 30-d and one-year mortality rates compared to the XT-THV; (2) the S3-THV is associated with 4-fold lower rates of both major vascular complications and PVR compared to the XT-THV; (3) the S3-THV is associated with twice the rate of new PPM implantation compared to the XT-THV; and (4) independent predictors of new pacemaker included

Table 6 Predictors of new pacemaker implantation in the S3 group

Parameter	Univariate analysis		Multivariate analysis		
	OR	*P* value	OR	95%CI	*P* value
Complete RBBB	4.6	< 0.001	4.9	1.88-12.95	0.001
Complete LBBB	1	1	-	-	-
Fascicular block	2.12	0.06	1.88	0.71-5.00	0.20
QRS duration (per 10 ms increment)	1.12	0.1	0.87	0.65-2.72	0.345
PR duration (per 10 ms increment)	1.14	0.05	1.14	1.00-1.29	0.05
Implant depth (septal, per 1 mm increment)	1.05	0.66	-	-	-
Implant depth (non-septal, per 1 mm increment)	0.94	0.63	-	-	-
Device lack of coaxiality during implant (per 1 mm increment)	1.13	0.07	1.13	1.00-1.29	0.049

LBBB: Left bundle branch block; RBBB: Right bundle branch block.

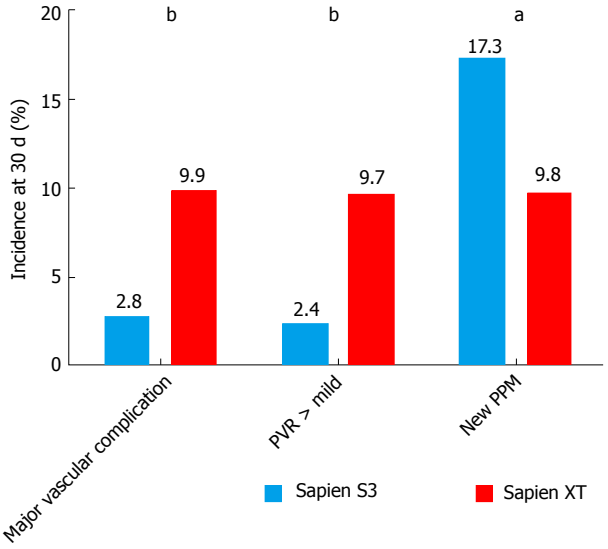

Figure 5 Incidence of major vascular complication, > mild para-valvular regurgitation and new permanent pacemaker. Thirty-day incidence (%) of major vascular complication, > mild PVR and new PPM in the S3-THV group (blue bars) and the XT-THV group (red bars). $^{a}P < 0.05$; $^{b}P < 0.0001$. XT-THV: SAPIEN XT transcatheter heart valve; PPM: Permanent pacemaker; PVR: Paravalvular regurgitation.

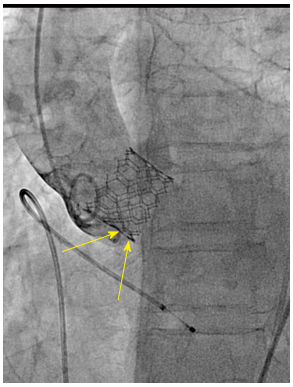

Figure 6 Example of difficult depth measurement. In this case, the projection has been modified after implant so the device appears coaxial. However, the annulus is no longer coaxial: Two aortic cusps are seen at different levels on the septal side (arrows), making difficult the localization of the hinge point and therefore the measurement depth of implant.

pre-procedural complete RBBB and PR duration, and lack of device coaxiality during implant.

Mortality

In a recent study, all-cause 30-d mortality rates were reported between 0% and 17.5%, with a pooled estimate rate of 5.7% for all second-generation THVs[24]. Reported 30-d mortality rates with the S3-THV ranges from 0.5% to 4.5%[16,17,25]. We report also a low 30-d mortality of 3.5% in the S3-THV cohort that was not statistically lower than the 8.7% rate of the XT-THV group after covariates adjustment. The low 30-d mortality speaks to the advancement of TAVI in regard to valve design improvement, increased operator experience, improved patient selection and procedural pre-planning, but also the lower baseline risk profile of TAVI patients.

Vascular complications

One of the shortcomings of TAVI is the association of major vascular complications with mortality[10]. Sheath size, severe ilio-femoral artery calcification, sheath external diameter to minimal femoral diameter artery ratio (≥ 1.05), early site experience and early operator experience, have all been previously associated with major vascular complications[13,26,27]. The S3-THV, with the lower profiles of its 14 and 16-F sheaths and the expanding properties of its E sheath, allows TAVI to be performed in patients with smaller arteries and for it to be safer in patients with larger arteries[28]. This is reflected in our series by the significant increase in proportion of transfemoral procedures. Three studies reported rates of major vascular complications of 4.5%, 5.2% and 3.6%, reflecting increased safety compared to the XT-THV[16,17,25]. We observed a similar rate of 2.9% in our S3-THV cohort, despite seeing the number operators performing TAVI increase from 4 to 9 between 2013 and 2015.

PVR

Patients with more than mild PVR have lower short- and long-term survival than those with trivial or mild PVR, making this an important echocardiographic outcome[29,30]. In the PARTNER trial, moderate or severe PVR was seen in 11.8% of patients implanted with the Edwards SAPIEN valve[31]. In the France 2 Registry,

Table 7 Summary of studies comparing the rate of permanent pacemaker between the S3 and XT device

PPM	S3	XT	*P* value	Predictor/comments
Binder *et al*[40] 2015 Circulation interventions	17%	13%	0.01	Predictors: Depth, RBBB
Binder *et al*[14] 2013 JACC interventions	13.3%			Excluded patient with LBBB, PR > 200 ms No predictors studied
Husser *et al*[25] 2015 JACC interventions	15.2%			Predictors not studied
Binder *et al*[40] 2015 EuroIntervention	20.7%			Predictor > 8 mm depth of implants
Nijhoff *et al*[17] 2015 Circulation interventions	9.8%	8.80%	0.94	High implants: 80/20 in aorta as mentioned by authors

it was reported in 12.2%[32]. We found similar rates of PVR in the XT-THV group. In contrast, the S3-THV group had four times less PVR. Our 2.4% > mild PVR rate in the S3-THV group is comparable to other reports that showed a PVR range between 0% and 3.8%[25,33]. The reduced rate of PVR can be explained by improved annular sealing by the external cuff. Whether the decreased PVR rate with the S3 device could translate into improved long-term outcomes should be evaluated in long-term registries.

Permanent pacemaker implantation

The need for new PPM implantation following TAVI may be correlated to prognosis[34-36]. As the S3-THV valve frame has greater height than the XT-THV, it may extend deeper into the LVOT after deployment[15,16]. Stent frame extension in the LVOT, *i.e.*, depth of implant, has been shown to be a predictor of PPM implantation[37].

Preliminary data on the S3-THV device from the pivotal SAPIEN 3 trial have shown an increased 30-d PPM implantation rate (13.3%), despite excluding patients with LBBB, RBBB and PR > 200 ms[38]. A study by Tarantini *et al*[16] also showed an increased rate of PPM (20.7%) with the S3-THV. This increased risk for PPM was driven by deep implantation of the S3-THV (valve implantation depth ⩾ 8 mm). Similarly, the Swiss registry showed an increased rate of PPM with the S3-THV of 17% compared to 11% with the XT-THV valve[16]. Our study showed similar results with a rate of 17.3% in S3-THV *vs* 9.8% in XT-THV (Table 7). As reported by others, independent predictors of new permanent pacemaker implantation in the S3-THV group included complete right bundle branch block and PR duration[25].

However, implant depth was not a predictor of new PPM in our study. Rather, lack of coaxiality of the device during its deployment was independently associated to new PPM. These findings may be explained by flaws in the way depth is estimated before the prosthesis is deployed, and by flaws in the way depth is measured after it is deployed.

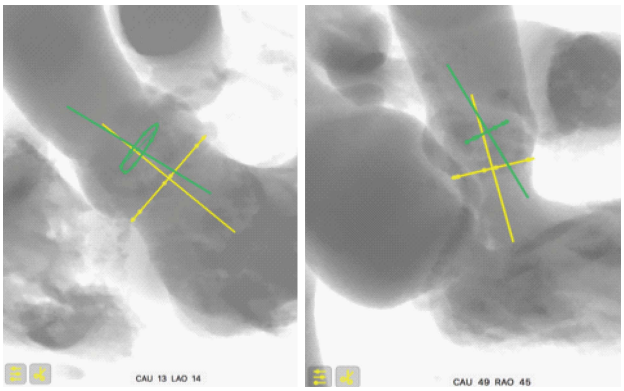

Figure 7 Coaxiality concept. In this example, the aortic annulus is drawn in yellow and the device is in green. Two different C-arm angulations of the same structures are shown. If the operator selects the angulation on the left for deployment, estimation of implant depth will be more difficult as one of the structures (the device) is not coaxial. Notice that in both angulations, the annulus (yellow) is coaxial.

Before the prosthesis is deployed, the aortic annulus is seen in a coaxial projection, with the three cusps aligned. This projection is determined from the MSCT and confirmed during the procedure by aortography. However, the device positioned in the annulus, before deployment, is not necessarily coaxial. This may be difficult to appreciate because, unlike the Corevalve, the XT-THV and the S3-THV do not have a ring at their extremity. This lack of device coaxiality before deployment can induce flaws in the estimation of depth due to parallax error[18,39]. In our experience, lack of device coaxiality induces underestimation of implant depth. In other words, the less coaxial the device, the higher it will look, and the more the operator will want to push it deeper. This increases the true depth of implant and therefore risk of conduction disturbance and new PPM.

After the prosthesis is deployed, measurement of depth of implant can also be flawed by parallax error. As previously described, the projection in which depth is measured is not the one in which the device was deployed. Indeed, after deployment, the device is not necessarily coaxial. The projection is therefore modified to obtain device coaxiality and this is when final aortography is performed and depth is measured. In this new projection, however, the aortic annulus is no longer coaxial[18,39]. An example of this is provided in Figure 6, where two cusps are seen at different levels on the septal side. Proper localization of the hinge point between the device and sinus of Valsalva, and therefore proper implant depth measurement, can be difficult in such circumstances and prone to parallax error. To adequately measure device implantation depth, future studies should rely on post-procedural MSCT. This would allow measurement of depth all around the annulus, and not only on the septal and non-septal sides. Alternatively, computer programs that allow the

operator to find the unique projection where both the device and the annulus are coaxial could be used. This would be the optimal projection to deploy the device, do the final aortography and measure depth.

The premise of this concept is that there is a slight angle between the un-deployed device and the aortic annulus. This is caused by patient anatomy and delivery catheter properties. As a result of this angle, even if the C-arm is perpendicular to the aortic annulus, it may not be perpendicular to the device. Figure 7 illustrates the coaxiality concept.

Limitations

This retrospective study reflects a single-center experience. Groups had significant baseline characteristics differences and adjustment for these may be incomplete or flawed by residual confounding. Although PVR was assessed by experienced echocardiographers and reported according to VARC-2 criteria, the absence of a central core lab may lead to some heterogeneity in assessment of this outcome. In addition, we did not analyze the timing of conduction disturbances. Indeed, one of the possible reasons for higher PPM in the S3-THV group may be a delayed inflammatory process caused by the skirt polymer, in addition to its immediate mechanical effect on the conduction system. To reflect contemporary practice of TAVI, we collected ECG data, depth and device coaxiality only in the S3-THV group. As it is difficult to measure device coaxiality before implant on a crimped valve, we used the device coaxiality at the end of deployment. Measurements were taken as the balloon was deflated and the patient still under rapid pacing so that measurements reflected pre-deployment status. In addition, device coaxiality measurements were only available for procedures done in the catheterization laboratory, thereby excluding patients with non-transfemoral access.

Conclusion

The third generation Edwards S3-THV is associated to improved outcomes with lower rates of major vascular complications and PVR but higher rates of new PPM compared to its predecessor, the XT-THV.

These results are encouraging in the endeavor to take TAVI to lower risk populations. Our findings highlight the increased importance to adequately visualize the S3-THV in relation to the aortic valvular complex during deployment, in order to improve device positioning and potentially mitigate new PPM requirements.

COMMENTS

Background

Since its introduction in 2002, transcatheter aortic valve implantation (TAVI) has evolved tremendously and is now standard of care for high risk and inoperable aortic stenosis patients. However, TAVI is still associated with a higher incidence of paravalvular regurgitation (PVR), permanent pacemaker (PPM) and vascular complications when compared to surgical aortic valve replacement. In order to justify the extension of the procedure to lower risk patients, these adverse outcomes have to be mitigated. The development of novel transcatheter heart valves and refinement of technical skills have contributed to the decrease in complications rates associated with TAVI.

Research frontiers

TAVI indication has now moved to intermediate and lower risk patients and it is crucial to continue careful evaluation of the newer generation devices aimed at improving patient outcomes. The study aimed to compare the different iterations between 2 valves on patient outcomes. New devices with lower profile and different designs have currently been introduced to further improve valve performance and efficacy.

Innovations and breakthroughs

TAVI is still associated with a higher incidence of PVR, PPM and vascular complications when compared to surgical aortic valve replacement. However, the third generation Edwards SAPIEN 3 transcatheter heart valve (S3-THV) the newest approved valve have improved TAVI outcomes by lowering complication rates and have recently been associated with improved outcomes compared to surgical aortic valve replacement in high risk patients. This breakthrough technology will without a doubt become the standard care of all patients in the near future with the continue improvement in device designs.

Applications

The third generation Edwards S3-THV is associated to improved outcomes with lower rates of major vascular complications and PVR but higher rates of new PPM compared to its predecessor, the SAPIEN XT transcatheter heart valve (XT-THV). These results are encouraging in the endeavor to take TAVI to lower risk populations. The authors' findings highlight the increased importance to adequately visualize the S3-THV in relation to the aortic valvular complex during deployment, in order to improve device positioning and potentially mitigate new PPM requirements. Dedicated software devices that can align the annulus and the prosthesis during deployment could help in coaxial implantation of the valve.

Terminology

TAVI: Transcatheter aortic valve implantation; PVR: Paravalvular regurgitation.

Peer-review

The paper is well written and offers a fairly large comparison of the performance of these 2 valves.

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P- Reviewer: Dizon JM, Sochman J, Said SAM **S- Editor**: Ji FF
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