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Review Article

Circulating MicroRNAs as Potential Novel Biomarkers in Cardiovascular Diseases: Emerging Role, Biogenesis, Current Knowledge, Therapeutics and the Road Ahead

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Abstract

Cardiovascular diseases (CVD) are the leading cause of morbidity and mortality worldwide. Although considerable progress has been made in the diagnosis, treatment, and prognosis of CVD, there still remains a critical need for novel diagnostic biomarkers and new therapeutic interventions to reduce the incidence of diseases. Recently, there has been increasing evidence that circulating MicroRNAs (miRNAs), which are endogenous, stable, single-stranded, short, noncoding RNAs (ncRNAs), can be used as diagnostic biomarkers. miRNAs are small ncRNA having approximately 21–25 nucleotides in length, and they mainly act as transcriptional regulators of gene expression in diverse biological processes such as cellular proliferation, differentiation, and tumorigenesis and death. miRNAs regulate in several cardiovascular pathologies, not only limited to hypertrophy, heart failure, arrhythmias, hypertension, myocardial infarction, dyslipidemias, and congenital heart diseases but are also present and circulate in various body fluids such as blood, pericardial fluid, and saliva and act as potential novel biomarkers in various cardiovascular pathologies. Furthermore, miRNAs represent potential novel therapeutic targets for several of above-mentioned CVD. This review presents detailed information about miRNAs regarding its structure and biogenesis, functions, expression profiles in serum/plasma of living organisms, diagnostic and prognostic potential as a novel biomarker and therapeutic applications in various CVD.

Keywords: Cardiovascular disease, microRNA, noncoding RNAs

Introduction

Cardiovascular diseases (CVD) are one of the most common causes of mortality in both developing and developed nations worldwide.[1] Even though there have been improvements in primary prevention, the prevalence of CVD continues to increase in recent years. It is also important to know about the pathophysiology of CVD at molecular level that may help in finding a novel biomarker which may aid in early diagnosis and treatment. While nearly 80% of genes in the human body undergo transcription, only 1% to 2% of them get translated into proteins, which leaves many noncoding RNA (ncRNA) transcripts.[2,3] ncRNAs are composed of small nuclear and nucleolar RNAs, Y-RNAs, microRNAs (miRNAs), and long ncRNAs. ncRNAs are very important in regulating gene expression and also in epigenetic applications. Furthermore, they may be one of the most important etiologic factors for the development of cardiovascular disease. To date, miRNAs are the most studied and characterized ncRNAs in the literature.[4]

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miRNAs are endogenous, conserved, single-stranded ncRNA s of 21-25 nucleotides in length.[5] Lin-4 was the first miRNA discovered in Caenorhabditis elegans in 1993. The second miRNA or the first miRNA to be discovered in humans was let-7 discovered in 2000 with its target protein lin-41.[6] Unlike the first miRNA, let-7 is highly conserved in many species including humans where it is regulated at transcriptional and posttranscriptional levels. Let-7 recognizes 3'UTR in the lin-41 gene and binds to it and hence downregulates lin-41 translation. Lin-41 is associated with different protein ubiquitin ligase in an autoubiquitination assay.[7] In addition, mouse lin-41 is found to be more pronounced during the early development of mouse limb bud, nervous tissue, and craniofacial tissue.[8] The let-7 family of miRNAs have also been found to modulate the immune response against opportunistic human pathogen like *Pseudomonas aeruginosa*.[9] Since the discovery of lin-4 and let-7 attention of researchers have been drawn toward this new promising RNA biology and its revolution. Moreover, the primary miRNA database was released in 2002 with only 218 entries, and it continued to increase over the years. The latest miRNA base Sequence Database includes 28,645 entries standing for hairpin precursor miRNAs which includes 35,828 mature miRNAs in 223 species. To date, over 2500 miRNAs have been discovered in the human body.[10,12] Furthermore, many novel computational programs have been found to predict target mRNAs of each specific miRNA, such as Target scan (http://www. targetscan. org), miRanda (http://www. microRNA. org), and Tarbase (http://www. microrna. gr/tarbase). A diverse role of dysregulated miRNAs in various pathologies including CVD in the human body were reported in several literature.[11,12] This review presents detailed information about miRNAs regarding its structure and biogenesis, function, expression profiles in serum/plasma of living organisms, diagnostic and prognostic potential as a novel biomarker, and therapeutic applications in various diseases.

Biosynthesis of MicroRNAs s

miRNA biogenesis starts with the processing of RNA polymerase II/III transcripts post or co-transcriptionally.[13] About half of all presently identified miRNAs are intragenic and are processed mainly from introns and relatively few exons of protein-coding genes, while the remaining are intergenically transcribed independent of the host gene and are regulated by their own promoters.[14,15] miRNAs at several instances are also transcribed as a single long-length transcript chain known as clusters, that may have similar seed regions and in such cases, they are considered to be a family.[16] The biogenesis of miRNA is classified into canonical and noncanonical pathways [Figure 1].

The Canonical Pathway of MicroRNAs Biosynthesis

The canonical biosynthesis pathway is the dominant pathway by which miRNAs are processed. In this pathway, primary miRNAs are transcribed from their genes and then processed into primi RNAs by the microprocessor complex, consisting of an RNA binding protein DiGeorge Syndrome Critical Region 8 (DGCR8) and a ribonuclease III enzyme Drosha.[17] DGCR8 recognizes an N6-methyladenylated GGAC and other motifs within the primi RNA, while Drosha cleaves the primi miRNA duplex at the base of the characteristic hairpin structure of primi miRNA. This results in the formation of a 2 nt 3′ overhang on precursor-miRNA (pre-miRNA).[18,19] Once pre-miRNAs are generated, they are exported to the cytoplasm by an exportin 5 (XPO5)/RAs-related nuclear protein (Ran) guanosine triphosphate (GTP) complex and then processed by the RNase III endonuclease Dicer.[20] This processing involves the removal of the terminal loop, resulting in a mature miRNA duplex.[21] The directionality of the miRNA strand determines the name of the mature miRNA form. The 5p strand arises from the 5′ end of the pre-miRNA hairpin while the 3p strand originates from the 3′ end. Both strands derived from the mature miRNA duplex can be loaded into the Argonaut (AGO) family of proteins (AGO1-4 in humans) in an ATP-dependent manner.[22] For any given miRNA, the proportion of AGO-loaded 5p or 3p strand varies greatly depending on the cell type or cellular environment, ranging from near equal proportions to predominantly one or the other.[23] The selection of the 5p or 3p strand is based in part on the thermodynamic stability at the 5′ ends of the miRNA duplex or a 5′ U at nucleotide position 1. In general, the strand with lower 5′ stability or 5′ uracil is preferentially loaded into AGO and is deemed to be the guide strand. The unloaded strand is called the passenger strand which will be unwound from the guide strand through various mechanisms based on the degree of complementarity. The passenger strands of miRNA that contain no mismatches are cleaved by AGO2 and degraded by cellular machinery which can produce a strong strand bias. Further, miRNA duplexes with central mismatches or non-AGO2-loaded miRNA are passively unwound and are degraded.[24]

Noncanonical MicroRNAs Biosynthesis Pathways

To date, multiple noncanonical miRNA biogenesis pathways have been elucidated [Figure 1]. These pathways make use of different combinations of the proteins involved in the canonical pathway mainly Drosha, Dicer, XPO5, and AGO2. In general, the noncanonical miRNA biogenesis can be grouped into Drosha/DGCR8-independent and Dicer-independent pathways. Pre-miRNAs produced by the Drosha/DGCR8-independent pathway resemble Dicer substrates. An example of such pre-miRNAs is mirtrons, which are produced from the introns of mRNA during splicing.[25,26] Another example is the 7-methylguanosine (m7G)-capped pre-miRNA. These nascent RNAs are directly exported to the cytoplasm through exportin 1 without the need for Drosha cleavage. There is a strong 3p strand bias most likely due to the m7G cap preventing 5p strand loading into AGO.[27] On the other hand, Dicer-independent miRNAs are processed by Drosha from endogenous small hairpin RNA (shRNA) transcripts. These pre-miRNAs require

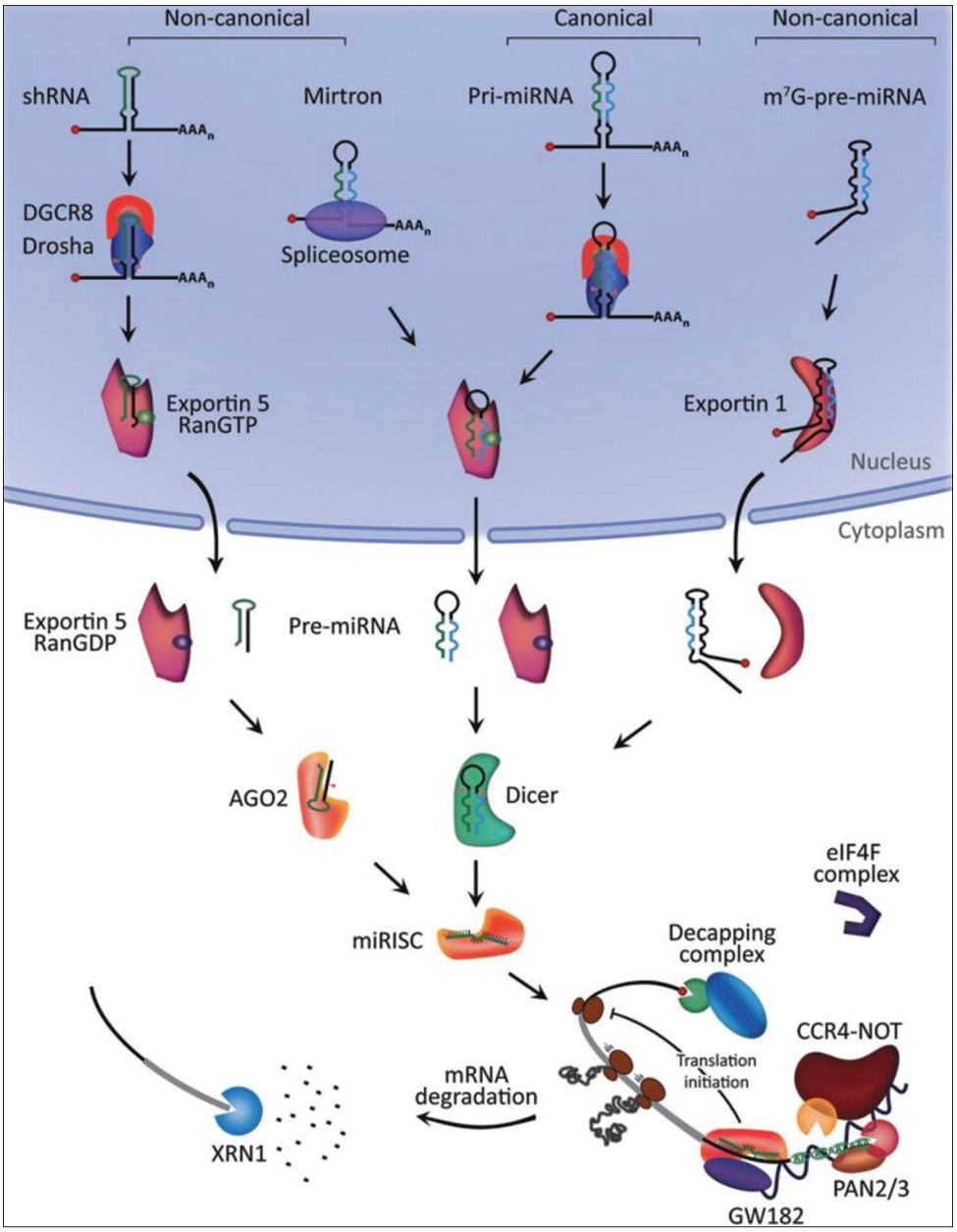


Figure 1: MicroRNA biogenesis and mechanism of action

AGO2 to complete their maturation within the cytoplasm because they are of insufficient length to be Dicer-substrates.[28] This, in turn, promotes the loading of the entire pre-miRNA into AGO2 and AGO2-dependent slicing of the 3p strand. The 3′-5′ trimming of the 5p strand completes their maturation.[29]

Figure 1 shows MicroRNA biogenesis and mechanism of action. Canonical miRNA biogenesis begins with the generation of the primi-miRNA transcript. The microprocessor complex, comprised of Drosha and DGCR8, cleaves the primi-miRNA to produce the pre-miRNA. The pre-miRNA is exported to the cytoplasm in an Exportin5/RanGTP-dependent manner and processed to produce the mature miRNA duplex. Finally, either the 5p or 3p strands of the mature miRNA duplex is loaded into the AGO family of proteins to form a miRNA-induced silencing complex (miRISC). In the noncanonical pathways, small hairpin RNA (shRNA) is initially cleaved by the microprocessor complex and exported to the cytoplasm via Exportin5/RanGTP. They are further processed via AGO2-dependent, but Dicer-independent, cleavage. Mirtrons and 7-methylguanine capped (m7G) pre-miRNA are dependent on Dicer to complete their cytoplasmic maturation, but they differ in their nucleocytoplasmic shuttling. Mirtrons are exported via Exportin5/RanGTP while m7G-pre-miRNA are exported via Exportin1. All pathways ultimately lead to a functional miRISC complex. In most cases, miRISC binds to target mRNAs to induce translational inhibition, most likely by interfering with the eIF4F complex. Next GW182 family proteins bound to AGO e recruit the poly (A)-deadenylases

PAN2/3 and CCR4-NOT. PAN2/3 initiates deadenylation while the CCR4-NOT complex completes the process, leading to the removal of the m7G cap on target mRNA by the decapping complex. Decapped mRNA may then undergo 5′−3′ degradation via the exoribonuclease XRN1 Hayder *et al*.[30]

MicroRNA in Cardiac Development and Physiology

From the embryonic period to the fully developed heart, miRNAs are constantly found in cardiac tissues. miR-21, miR-29a, miR-129, miR-210, miR-211, miR-320, miR-423, and let-7c are highly expressed in normal fetal heart tissue which plays a major role in embryonic and postnatal cardiac development.[31] Decreased levels of above-mentioned miRNAs are due to depleted levels of Dicer, an enzyme whose role is essential for miRNA processing and its absence may lead to pericardial edema, poorly developed ventricular myocardium, and rapid necrosis which were studied in mouse models. Similarly, tamoxifen inducible recombinase deletion of dicer causes heart failure and death in the adult heart. In other words, inhibition of miRNA expression is due to dicer deletion. Deletion of dicer during the embryonic phase may result in hypoplastic ventricular muscle and pericardial edema.[32,33] Postnatal deletion of dicer in heart muscle cells may result in cardiomyocyte contractility dysfunction and disarrays which ultimately results in dilated cardiomyopathy and progresses to heart failure.[34] miRNA 1 and miRNA 133 plays a crucial role in cardiac development which has been proved experimentally in mice model. miRNA-1 (miR 1–1, miR 1–2) and miR-133 (miR 133a–1, miR 133a–2, and miR 133b) and miR-206 are muscle-specific miRNA which are regulated by different enzymes in different cells. The main functions of miRNA-1 on heart development are favoring apoptotic mechanisms and inhibition of cardiac development.[35,36] miRNA-1 targets Hand 2, a transcription factor which favors the proliferation of cardiomyocytes in zebrafish embryo hearts.[37] This suggests that during cardiac development rise in miRNA-1 level causes a decrease in Hand 2 transcription factor level and for a healthy heart this needs to be balanced in miRNA homeostasis. If there is an excessive increase in miRNA-1 in early embryogenesis, it may lead to dysregulation of cardiac myocyte proliferation, myoblast differentiation, and ventricular septal defect by interfering with cardiac morphogenesis.[38] Histone deacetylates 4 (HDAC4) is another transcriptional repressor protein of muscle gene expression and miR-1 targets this protein and promotes myogenesis. The role of miR-133 in cardiac development works as a regulator of cardiogenesis

MicroRNA in Cardiac Remodeling

The term "remodeling" is adaption in response to any chronic stress in the heart, for example chronic hypertension can lead to hypertrophy in cardiac myocytes which is required to maintain adequate cardiac output. However, if cardiac remodeling process remains for long duration it may lead to heart failure, myocardial infarction, and other cardiac diseases. miR-1 and miR-133 are found to be downregulated in a heart where cardiac remodeling processing is active, especially in pressure overload-induced hypertrophy. Calcium-dependent gene expressions are crucial for myocyte growth and differentiation. Calmodulin, Mef2a, and Gata4 are the main calcium-dependent transcription factors and miR-1 inhibits these transcription factors as shown by a study in mice model.[39] Other classes of miRNA such as miR-208, miR-195, miR-214, and miR-21 are overexpressed in hypertrophied heart.[39] During pressure-induced stress, cardiac-specific intron of alpha myosin heavy chain gene 6 encodes a cardio-specific miR-208 and then miR-208 further upregulates beta myosin heavy chain, thereby promoting cardiac hypertrophy.[40] A recent study by Bang *et al*.[41] showed that in response to stress, cardio-fibroblast releases miRNA enriched exosomes, miR-21 also known as "star" miRNA which is potent paracrine acting RNA molecule and their overexpression may result in cardiomyocyte hypertrophy. If miR-195 is overexpressed, it may lead to cardiac hypertrophy. Upregulation of microRNA-195 in failing hearts can result in dilated cardiomyopathy which was experimentally shown in transgenic mice model.[41,42]

MicroRNA in Cardiovascular Disease

Arrhythmia

miRNA levels are found to be altered from its normal hemostasis in both atrial and ventricular arrhythmia. Both upregulation and downregulation of miR-1 may cause arrhythmias, especially in ventricle and atria, respectively. In ventricular arrhythmia, miR-1 represses KCNJ2 and GJA1. KCNJ2 encodes Kir2.1 which is a potassium channel subunit and GJA1 encodes connexin 43 which is a cardiac gap junction. This leads to slowed conduction and depolarization of cytoplasmic membrane which has arrhythmogenic potential and elimination of miR-1 has shown to improvement in arrhythmic potential in infarcted rat hearts. This has opened a window for future anti-arrhythmic therapy-targeting miR-1.[43] Another mechanism by which overexpression of miR-1 causes arrhythmia is by CaM-KII-dependent phosphorylation of the L-type Ca2 + channels and ryanodine receptors 2, leading to a burst of calcium from the sarcoplasmic reticulum responsible for the arrhythmia.[44] miR-328 is associated with atrial fibrillation. Lu *et al*.[45] in their study, found that miR-328 was elevated by 3.5-fold in atrial fibrillation as compared to those without atrial fibrillation.

Hypertension

Several studies have highlighted the involvement of miRNAs in blood pressure regulation, particularly by affecting the renin-angiotensin-aldosterone system. Marques *et al*.[46] compared both miRNA and mRNA expression in renal tissue from untreated hypertensive and normotensive individuals using microarray technology. The authors screened 850 miRNAs and identified nine miRNAs which exhibited expression differences with two of the miRNAs (miR-181a and miR-663) linked to

repression of renin expression in the human kidney.[46] Boettger *et al*.[47] demonstrated that miR-143/145 knocked out mice exhibited significantly reduced blood pressure compared with wild-type littermates and identified angiotensin-converting enzyme mRNA as a target for miR-145. Furthermore, it was found that miR-145 was overexpressed in atherosclerotic plaques of hypertensive versus normotensive patients undergoing carotid endarterectomy implicating miR-145 as a potentially key regulator of blood pressure mediated vascular damage.[48]

Pulmonary hypertension

Pulmonary arterial hypertension is characterized by an increase in the resistive and reactive components of pulmonary vascular impedance which ultimately leads to right ventricular failure.[49,50] Over 30 circulating miRNAs have been associated with the development and progression of pulmonary arterial hypertension.[51] The levels of these miRNAs correlate with pulmonary arterial dispensability and pulmonary vascular resistance index and decrease response to oxygen and or inhaled nitric oxide.

Heart failure

No doubt that heart failure remains a significant burden in present-day world and for the treating physician with the leading cause of hospital admissions elderly population. According to Health Management Organization, Kaiser permanent coronary artery disease (CAD), hypertension, diabetes mellitus, atrial fibrillation, and valvular heart disease are the five major causes of heart failure globally.[52] Advancement in miRNA research has raised the possibility of its appearance in heart failure cases using circulating miRNAs as a novel biomarker tool [Figure 2]. Goren *et al*.[53] found that levels of specific miRNAs such as miR-423-5p, miR-320a, miR-22, and miR-92b are found to be elevated in a patient with systolic heart failure. Further, a study by Devaux *et al*.[54] revealed that panels of four miRNAs, namely miR-16, miR-27a, miR-101, and miR-150 are associated with improved prediction of left ventricular contractility 6 months after acute myocardial infarction (AMI). Among various miRNAs, expressions of miR-122, 423-5p,-210,-499,-622 are found to be increased in patients with heart failure. The significance of the increased level of miR-423-5p has been further supported by Tijsen *et al*.[55] where six other miRNAs were found to be elevated, but miR-423-5p was strongly correlated with the clinical diagnosis of heart failure. miR-1 plasma levels were found to be elevated in acute myocardial-induced heart failure.[56] A recent study of myocardial biopsy in 34 Chinese patients were performed who developed recent heart failure and were compared with a group of patients without heart failure undergoing routine cardiac surgery. It was found that miR-1,-21,-23,-29,-130,-195, and -199 levels were significantly raised in the heart failure group.[57]

Acute myocardial infraction

Several studies have investigated the role of miRNAs in identifying patients with AMI. Although a number of promising candidates have emerged including miR-1, miR-133a, miR-133b, miR-208a, miR-499, and miR-499-5p further validation is required for most of them [Figure 3]. In a study conducted by Devaux *et al*.[58] the authors measured the levels of six miRNAs in 1155 patients attending the cardiac emergency department with acute-onset chest pain. 224 patients were diagnosed with AMI and their miRNA assay was performed which showed significantly raised levels of miR-208b, miR-499, and miR-320a in AMI compared with other diagnostic and investigative tools. However, none were able to outperform cardiac troponin T (cTnT) or high-sensitivity cTnT (hsTnT) or add to their diagnostic ability.[58] This highlights a major obstacle in the identification of miRNAs as diagnostic biomarkers in AMI. Further, the diagnostic criteria for AMI place significant emphasis on cardiac troponins as it becomes extremely difficult if not impossible, for any new biomarkers to outperform them. Furthermore, such use of miRNAs as biomarkers in acute coronary syndromes is also

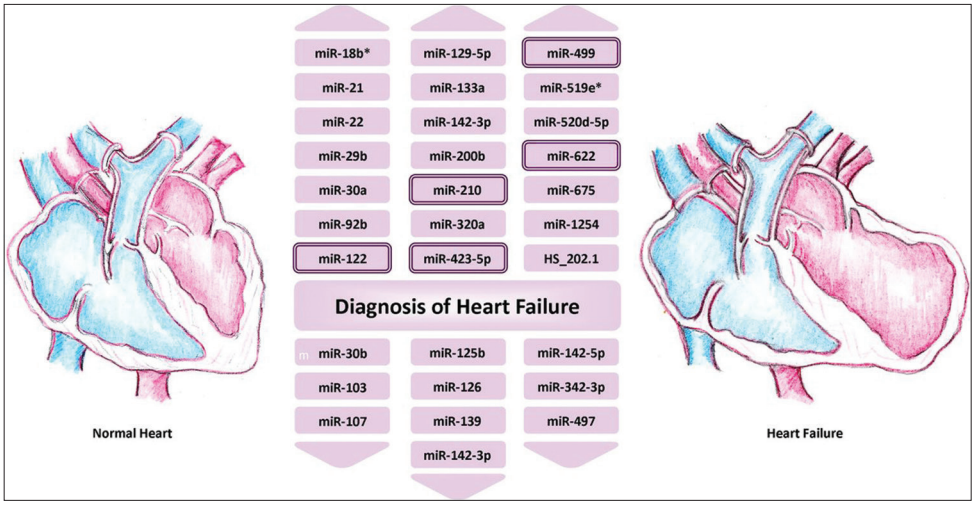


Figure 2: Circulating microRNAs associated in the diagnosis of heart failure. MicroRNAs with a double border have been linked to heart failure in more than one study

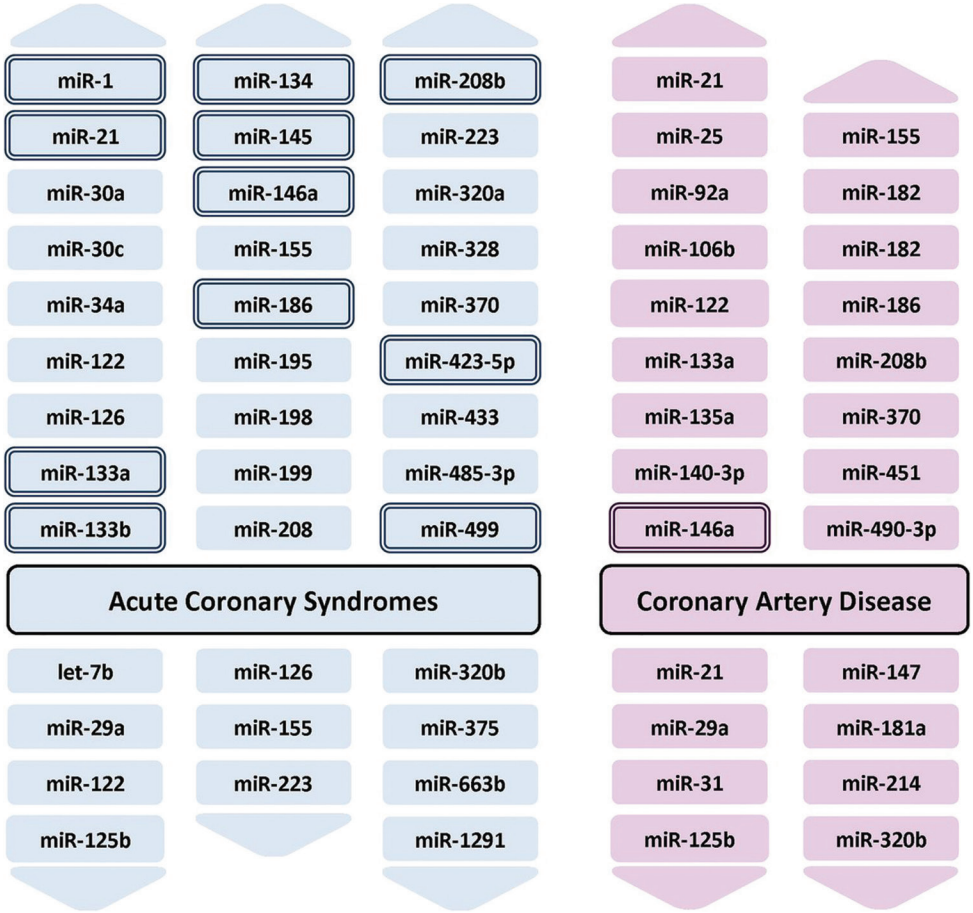


Figure 3: Circulating microRNAs associated with acute coronary syndromes and coronary artery disease. MicroRNAs with a double border have been linked to the associated trait by more than one study

limited by the time taken to investigate the level of candidate miRNAs in a single sample. Owing to this at present this cannot be achieved within a timeframe of clinical utility. In one study, which recruited 175 patients with AMI admitted within 12 h of symptom onset and 90 healthy controls as the control group, the results demonstrated that circulating miR-19a levels were significantly raised in patient groups compared to the control group. The authors concluded that circulating miR-19a possibly has a prognostic value which can be used as a promising molecular target for early diagnosis and prognosis of AMI provided the results are available in desired less time frame.[59]

However, the role of miRNAs as a diagnostic biomarker in less time-sensitive diagnoses and also their role as prognostic biomarkers may herald its diagnostic potential.

Coronary artery disease

A number of miRNAs have been linked to a diagnosis of CAD [Figure 3]. Zampetaki *et al*.[60] identified three miRNAs (miR-126, miR-197, and miR-223) that were predictive of incidental CAD in a prospective study of cardiovascular disease (with 10-year follow-up). Furthermore, the addition of these three miRNAs to the Framingham Risk Score improved classification to a greater degree than hsTnT. While further validation is required, these results suggest a potential role for miRNAs in predicting the risk of future AMI due to CAD.

Atherosclerosis

Atherosclerosis is a complex and chronic inflammatory interaction of the blood vessel wall with altered lipoprotein monocyte-derived macrophages, T-cells, and the normal arterial elements. Patients with CAD have reduced expression of different miRNAs such as miR-126, miR-145, and miR-155 in their blood.[61] The detailed role of miRNAs 126,145 and 155 *in vivo* studies have been studied by Wei *et al*.[62] They found that downregulation of miR145 in smooth muscle cells disrupts smooth muscle cell normal hemostasis and favors atheroma formation. In one study, it was shown that miR-33 which is located in the SREBF2 gene is responsible for reducing the expression of cholesterol transporter ABC transporter A1 which leads to a decrease the level of high-density lipoprotein (HDL) which might act as a trigger factor for atherosclerosis.[63]

miRNA in aortic valve disease

In aortic stenosis, miRNAs were also found to be altered in stenotic aortic valve leaflets compared to insufficient ones. The reduced levels of miR-26a and miR-30b were responsible for a higher risk of developing valvular leaflet fusion. The change

of morphology is due to accelerated calcium accumulation compared to regurgitant aortic valves without morphological fusion of valve leaflets. These miRNAs were involved in the biological processes that modulate calcification-related genes *in vitro*.[64] Several studies have recorded an important association of miRNAs with posttranscriptional regulation of gene expression in aortic valve stenosis. miR-141 was found to be a regulator of the levels of bone morphogenetic protein 2, whereby unrestrained activity led to calcification of the aortic valve mediated by a stimulation of osteogenesis. miR-141 was markedly attenuated in patients with aortic stenosis associated with the bicuspid aortic valve [Figure 4]. Yanagawa *et al*.[65] proposed this new key role of miR-141 in the modulation of aortic valve calcification disorders, highlighting the strategic therapeutic target that emerged in the assessment of progressive calcification in stenotic aortic valve disease. Song *et al*.[66] analyzed the progression of calcified aortic valve disease and suggested the crucial role of myofibroblastic and osteoblast-like phenotypes. The authors reported substantial differences in the levels of two miRNA classes: MiR-486 and miR-204. The levels of miR-486 were increased in calcific aortic valves where the myofibroblastic transition was induced by upregulation of the expression of Runx2 and Osx and miR-204 levels were deficient, which leads to high cellular and valvular pro-osteogenic activity.

MicroRNAs in mitral valve disease

Over the recent years, miRNAs have represented an emerging class of widely circulating biomarkers in various pathological states including degenerative mitral valve disease.[67] Concerning the prolapse of the mitral valve, only a small number of circulating miRNAs have been studied focusing on the degenerative disorders of the mitral valve. These findings were limited to the experimental animal models. Hulanicka *et al*.[68], in their study, evaluated plasma miRNA levels as potential biomarkers for chronic myxomatous mitral disease in dogs. Investigators evaluated the expression of 9 miRNAs that had already been discovered and were involved in CVD.[68] Using a real-time polymerase chain reaction (PCR) method, they found that the plasma levels of two out of nine miRNAs were significantly downregulated, recording an evident involvement of these molecules in developing endocardiosis and mitral valve lesion in dogs. Various miRNAs that have been studied including miR-125, miR-126, miR-21, miR-29b, and miR-30b showed a significant expression in the pathogenesis of mitral valve disease.

Congenital heart disease

miRNA plays an important role from embryogenesis to a fully developed adult heart. Several congenital cardiac defects have been found to be associated with altered expression of miRNA. Alteration of miR-1 and miR-181c levels is found to be associated with Ventricular septal defects (VSD). In humans presenting with VSD, their cardiac cells show decreased expression of miR-1 and increased expression of miR-181c.[69,70] Congenital heart disease in Down syndrome patients has been found to have overexpressed five major miRNAs, namely miR-99a, let-7c, miR-125b-2, miR-155, and miR-802 in chromosome 21.[71] Several cardio facial neural crest defects may result due to abnormalities in neural crest cell migration and dicer deletion, which is mainly responsible for the miRNA maturation. Noonan's Syndrome, DiGeorge Syndrome, LEOPARD Syndrome, and cardio-facio-cutaneous syndrome are some of the examples. Tetralogy of Fallot (TOF) is the most common congenital cyanotic heart disease. The association of TOF with miRNAs has been recently reported by O'Brien *et al*.[72] in 33 infants with nonsyndromic TOF without a 22q11.2 deletion. They found that 33 miRNAs were downregulated in patients who have nonsyndromic TOFs. Another study in 2015 by this group found that overexpression of miR-421 in the ventricular cell is associated with TOFs.[73] Liang *et al*.[74] demonstrated that miRNA-940 is most significantly downregulated in patients with TOF.

Circulating MicroRNAs as a diagnostic indicator of cardiovascular disease

The detection of miRNAs in body fluids is done by various methods, namely real-time PCR or microarray assay. Circulating miRNAs are stable nucleic acids whose sequences can be amplified and are easily detectable with appropriate methods in a wide range of bodily fluids from blood, urine, saliva, cerebrospinal fluid, and breast milk. Despite the advancement in medical science, early and effective diagnosis or treatment for myocardial infarction still remains a clinical challenge.[75] The role of cardiac-specific miRNAs for the detection of AMI have been described by various researchers. Cardiac-specific miRNAs 1, 133, 208b, 499 may have the

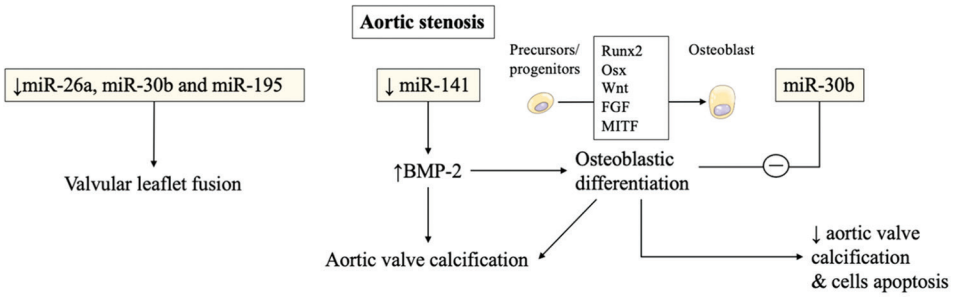


Figure 4: The role of miRNA in aortic stenosis severity and valve calcification. Reduced levels of miRNA-26a, miRNA-30b, and miRNA-195 contribute to further damage to the valve. The negative regulation exerted on osteoblastic differentiation by miRNA-30b favours a better prognosis

future for upcoming diagnostic markers for AMI.[76,77] miR-1, -21,-22,-23,-29,-122,-130,-195,-199,-320a, 423-5p,-499,-622 levels were found to be overexpressed in heart failure patients. Particularly increased levels of miR-423-5p were well correlated with heart failure in different studies. Similarly, levels of miR-122 and miR-370 were positively correlated with total cholesterol, triglycerides, and low-density lipoprotein cholesterol and CAD progression.[78]

Circulating MicroRNAs as the therapeutic role and future prospects

Since single miRNA can target multiple mRNA-making proteins on gene regulation, presently it is feasible to use miRNA as a therapeutic target. Elimination of miR-1 has shown to improvement in arrhythmic potential in infarcted rat hearts and this has opened a new window for future anti-arrhythmic therapy-targeting miR-1. *In vivo* delivery of lentivirus miR-24 can interact with tissue growth factor β 1 to decrease the cardiac fibrosis resulting from various heart conditions such as MI, cardiomyopathies, and heart failure.[79] miRNAs-based therapeutics have been more studied in atherosclerosis. The atheroprotective effect of miR-126 has been explained by Wei *et al*.[63] Similarly, anti-miR-33 therapy has been found to be atheroprotective by increasing circulating HDL in mice models.[80] Moreover, combining miRNAs with traditional biomarkers can be a logical approach to improve risk stratification and long-term prognosis in CVD. miRNA-based therapeutics may be more beneficial to treat CVD using novel platforms and computational tools in combination with traditional methods of analysis.

Conclusions

The discovery of miRNAs has opened a new door for insight into the biology of the cardiovascular system and our understanding of disease pathogenesis. The recent increase in interest of miRNAs in cardiovascular biology and diseases among researchers signifies its bright future in the coming days. Although much has happened within this short period, still it needs further research to completely understand cardiovascular disease pathogenesis. Contrary to its name "microRNA," it has a wider macro function in the heart, including cardiac embryogenesis, differentiation, and from hypertrophy to disease pathogenesis. miRNA might outweigh cardiac sensitivity troponins in the coming days for the early and accurate diagnosis of AMI with predictive future complications risk and their treatment. Therefore, it seems there is a possibility to treat cardiomyopathies in the near future. This will definitely be an important landmark and the availability of more durable and permanent treatment options for treating CVD.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Pulmonary Hypertension and Exercise Tolerance in Heart Failure Patients

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Abstract

Background: The 6-min walk test (6MWT) is a useful tool in assessing patients' outcomes: morbidity and mortality in heart failure (HF) patients. It also helps in monitoring the effect of medications being developed for treatment of pulmonary hypertension (PH) as well as response to therapeutic interventions in HF and may better reflect the functional exercise level for daily physical activities of HF patients. **Aim:** This study aims to describe how exercise tolerance of HF patients with PH may differ from that in HF patients without PH as assessed using the 6MWT. **Materials and Methods:** This was a descriptive cross-sectional study in which 65 patients each in two groups of HF patients with and without PH were sampled. All patients had their body mass index (BMI) and blood pressure assessed. In addition, all patients had echocardiography done and 6-min walk distance assessed. Data obtained were analyzed using SPSS version 23.0. **Results:** There were more females than men who participated in the study. That heart failure (HF) patients with PH walked less distance in six minutes compared to HF without PH. The total distance walked in 6 min was farther in males, younger HF patients <50 years, patients with a higher BMI, and patients with HF with reduced ejection fraction. Furthermore, a negative significant correlation was observed between mean pulmonary artery pressure (MPAP) and total distance walked in 6 min in all 130 HF patients ($r = -0.17$; $P = 0.005$) with a significant correlation between left ventricular ejection fraction ($r = 0.50$; $P < 0.001$), MPAP ($r = -0.24$; $P = 0.050$), and total distance walked in HF patients with PH. **Conclusion:** This study's findings indicate that worse outcomes await HF patients with concurrent PH. Thus, continuous monitoring of their exercise tolerance capacity using the 6MWT is of significant clinical benefit as part of their overall management.

Keywords: Echocardiography, heart failure, pulmonary hypertension, 6-min walk test

Introduction

Heart failure (HF) is a major health problem worldwide affecting all ages, races, and sexes. It affects over 20 million people worldwide, with an estimated prevalence of 2% in developed countries.[1] The prevalence of HF increases with age with about 6%–10% of people aged 65 years and above in developed countries affected.[2,3]

The 6-min walk test (6MWT) was first used in patients with heart disease in 1985 by Guyatt *et al*.[4] They applied the test six times, over 12 weeks, in 18 patients with chronic HF (CHF). The same patients also carried out the cycle ergometer test. The 6MWT and standard cycle ergometry cardiopulmonary exercise testing (CPET) are commonly used for assessing exercise capacity in patients with HF. Other measures of exercise capacity include the shuttle walk test and treadmill walk time.

The test has gained preferred because it is simple, affordable, reproducible, and well standardized.[5,6] In addition, it shows a good correlation with CPET which patients with PH may not be able to complete[7,8] and may better reflect the functional exercise level for daily physical activities of HF patients. However, this test is known to be influenced by body weight, gender, height, age, and patient motivation.

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Earlier studies have shown that the distance walked in 6 min correlates with cardiovascular morbidity and mortality, particularly for those who perform in the lowest quartile (<300–370 m).[9] It also helps in monitoring the effect of medications being developed for treatment of pulmonary hypertension (PH) as well as response to therapeutic interventions in HF[10] and used to measure physical fitness in some rehabilitation programs.[10]

Although there is abundant literature on the less common idiopathic PH, data are scarce on PH in HF or type 2 PH which is the most common type of PH. There are very few studies in West Africa on PH in HF patients and even rare studies on exercise tolerance capacity of these patients although clinicians do recommend the test.

Chikodi and Olufunke[11] evaluated the cardiovascular responses of adult Nigerians with CHF to the 6MWT. The study concluded that the 6MWT is a safe and simple instrument for demonstrating cardiovascular responses to submaximal exercise in patients with heart disease, especially in communities with limited resources.[11] Furthermore, Adedoyin *et al*.[12] suggested that the 6MWT could be useful to evaluate exercise tolerance in patients with CHF, while bicycle ergometry is more appropriate in the assessment of maximum functional capacity and has also shown a significant correlation between distance walked and VO_2[13] in CHF patients.

Furthermore, new therapeutic strategies for PH due to HF are being developed and there is need for more studies in Nigeria and Africa at large on management outcomes (as exercise tolerance is an indicator for outcome) of PH in HF patients.

This will eventually lead to better monitoring of treatment in PH in HF, thereby reducing morbidity and mortality. In particular, this study seeks to describe how exercise tolerance of HF patients with PH may differ from that in HF patients without PH as assessed using the 6MWT.

Materials and Methods

There are few works in this area. Results from this study could lead to exercise tolerance being used more freely to monitor recovery in HF patients with PH.

This study is a descriptive cross-sectional study that was carried out at the University of Benin Teaching Hospital (UBTH). The sample selection was based on convenience sampling method as patients admitted consecutively for HF were recruited for this study within a period of 6 months. Sample size was estimated using the G*Power software for comparing means of independent groups with the following parameters: minimum power = 0.90, minimum effect size = 0.5 (medium), minimum significant level = 0.05, and allocation ratio = 1. This resulted in a sample size of 130, 65 patients in each group. A total of 130 consecutively admitted HF patients (65 HF patients with and without PH in each group) who met the inclusion criteria were recruited for this study.

Patients with myocardial infarction, chronic obstructive airway disease, musculoskeletal abnormalities, ophthalmologic abnormalities (e.g., blindness), cognitive impairment, deafness, and poor echocardiographic images were excluded from the study. All patients underwent transthoracic echocardiography. The diagnosis of PH was made using estimated mean pulmonary artery pressure (MPAP) of >25 mmHg. The MPAP was derived from the pulmonary artery acceleration time (PAAT) using the following equation: "MPAP = 79–0.45 (PAAT)".[14] The PAAT was obtained from parasternal short-axis view at the level of the pulmonary valve using continuous-wave Doppler. Three measurements were taken, and the average time was taken as the PAAT. Subsequently, the 6MWT was performed for all patients and the distance walked in 6 min was recorded.

The 6MWT was carried out at the Special Investigation Unit, UBTH, with emergency crash cart readily available which included: sublingual nitroglycerin, aspirin, oxygen cylinder, Ambu bag, and an automated electronic defibrillator. The tests were carried out by two cardiologists with certification in basic and advanced life support using the ATS Statement: Guidelines for the 6MWT, March 2002.[15] The parameters that were measured in the patients include: height, weight, systolic blood pressure at rest, systolic blood pressure at 6 min, diastolic blood pressure at rest, diastolic blood pressure at 6 min, heart rate at rest, and heart rate at 6 min. A standard method was used to administer the 6MWT in a corridor of 30 m, with markings every 5 m. Patients were instructed to walk at their pace while trying to cover as much distance as possible in 6 min. The time was called out every 2 min. Participants were encouraged every 30 s with words like "You are doing well" or "Keep up the good work." During the test, patients were allowed to rest and then continue as soon as they can resume the walk. The total distance covered within 6 min was recorded. There was no adverse effect noted in any of the participants.

Statistical Analysis

Data obtained were entered into and analyzed using the IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. (Armonk, NY: IBM Corp). Categorical data were expressed as frequencies and percentages and compared using the Chi-square test. Continuous data were expressed as means (standard deviation [SD]) and compared using the independent *t*-test. A Pearson correlation test was done where applicable. $P \leq 0.05$ was considered statistically significant.

Ethical statement

Ethical clearance was obtained from the Ethics and Research Committee of the UBTH, Benin City, Edo State, on April 15, 2015.

Informed consent was obtained from patients before participation in the study.

Autonomy

Respect for respondents and confidentiality was maintained throughout the process of extracting the data.

Results

One hundred and thirty HF patients were studied. As seen in [Tables 1-5]. There were more females than males in the study, with the mean (SD) age of HF patients with PH being 56.85 (18.30) and 59.40 (16.60) in HF patients without PH.

HF with reduced ejection fraction (HFrEF) was present in 67.7% and 58.5% of patients with and without PH, respectively. About 20% of patients were obese in both groups with 36.9% and 20.0% of patients noted to be overweight. The SBP, DBP, and heart rate at rest, 1 min, and 1 min post 6MWT were not significantly different between both groups.

There was a significant difference ($P < 0.001$) between the lower total distance walked in 6 min observed in PH patients (249.90 ± 79.38) and that observed in patients without PH (310.96 ± 87.39).

The left ventricular ejection fraction (LVEF), PAAT, and body mass index (BMI) were higher in HF patients without PH while HF patients with PH had a higher MPAP.

Twenty-three and 16 patients were in NYHA Class III while 42 and 49 patients were in NYHA Class IV in patients without and with PH respectively. The total distance walked was farther in NYHA Class III patients in both groups compared to those in NYHA Class IV. There was a significant difference in the total distance walked between NYHA Class III and Class IV patients in HF patients with PH ($P < 0.001$).

There was also a statistically significant difference in the numerical values observed for MPAP ($P < 0.001$), PAAT ($P < 0.001$), and BMI ($P = 0.002$) when compared between the two groups.

In addition, there was a positive significant correlation between LVEF ($r = 0.32$; $P = 0.011$), BMI ($r = 0.33$; $P = 0.009$), weight ($r = 0.37$; $P = 0.003$), and total distance walked in 6 min in HF patients without PH.

Furthermore, there was a significant correlation between LVEF ($r = 0.50$; $P < 0.001$), MPAP ($r = -0.24$; $P = 0.050$), and total distance walked in HF patients with PH.

Furthermore, a positive significant correlation was found between BMI ($r = 0.29$; $P < 0.001$), LVEF ($r = 0.42$; $P < 0.001$), PAAT ($r = 0.34$; $P < 0.001$), and total distance walked in 6 min in the total population ($n = 130$). Furthermore, a negative significant correlation was observed between MPAP and total

Table 1: Demographic and clinical variables of patients

	Heart failure patients		χ^2	*P*
	PH absent	PH present		
Age (years)				
≤50	17 (26.2)	26 (40.0)	2.81	0.093
>50	48 (73.8)	39 (60.0)		
Sex				
Male	39 (60.0)	20 (30.8)	11.20	<0.001
Female	26 (40.0)	45 (69.2)		
BMI				
Normal	29 (44.6)	39 (60.0)	4.78	0.091
Overweight	24 (36.9)	13 (20.0)		
Obese	12 (18.5)	13 (20.0)		
LVEF				
Reduced	38 (58.5)	44 (67.7)	1.19	0.276
Normal	27 (41.5)	21 (32.3)		

LVEF: Left ventricular ejection fraction, BMI: Body mass index, PH: Pulmonary hypertension

Table 2: Total distance walked

	Heart failure patients		*t*	*P*
	PH absent	PH present		
Age (years)	59.40 (16.60)	56.85 (18.30)	0.83	0.406
LVEF	45.31 (18.24)	40.01 (21.41)	1.51	0.133
PAAT	136.65 (18.04)	97.42 (19.92)	11.77	<0.001
MPAP	16.31 (5.79)	37.84 (27.58)	−6.16	<0.001
BMI	26.62 (5.98)	23.59 (4.81)	3.18	0.002
Total distance walked in 6 min	310.96 (87.39)	244.90 (79.38)	4.48	<0.001

LVEF: Left ventricular ejection fraction, BMI: Body mass index, PAAT: Pulmonary artery acceleration time, MPAP: Mean pulmonary artery pressure, PH: Pulmonary hypertension

Table 3: Total distance walked in heart failure patients and demographic/clinical variables

	PH present	*t*	*P*
Age (years)			
≤50	263.53 (78.56)	2.40	0.019
>50	216.95 (73.47)		
Sex			
Male	251.56 (73.37)	1.02	0.314
Female	229.91 (91.77)		
BMI			
Normal	267.53 (83.62)	1.92	0.060
Overweight/obese	229.81 (75.69)		
LVEF			
Reduced	228.93 (73.67)	2.58	0.012
Normal	282.16 (82.46)		

LVEF: Left ventricular ejection fraction, BMI: Body mass index, PH: Pulmonary hypertension

Table 4: Right ventricular Doppler echocardiographic parameters in study population

	Mean±SD		*t*-test	*P*
	PH present (*n*=65)	PH absent (*n*=65)		
TRVmax	3.03±0.51	1.93±0.72	−10.91	<0.001*
RVET	266.71±90.16	295.01±31.56	2.46	0.015*
PAAT	98.62±19.56	137.78±16.56	13.07	<0.001*
PADP	17.15±6.49	12.26±5.70	−3.90	<0.001*

*P value < 0.05, SD: Standard deviation, PAAT: Pulmonary artery acceleration time, PH: Pulmonary hypertension, TRVmax: Tricuspid regurgitant velocity, RVET: Right ventricular ejection time, PADP: Pulmonary artery diastolic pressure

Table 5: Right ventricular function

	PH present ($n=65$), n (%)	PH absent ($n=65$), n (%)	Total ($n=130$), n (%)	χ^2	P
RVSD					
Present	43 (59.7)	29 (40.2)	72 (48)	10.50	0.001*
Absent	26 (33.3)	52 (66.7)	78 (52)		
RVDD					
Present	51 (63.0)	30 (37.0)	81 (54)	5.69	0.017*
Absent	30 (43.5)	39 (56.5)	69 (46)		

*P value < 0.05, PH: Pulmonary hypertension, RVSD: Right ventricular systolic dysfunction, RVDD: Right ventricular diastolic dysfunction

distance walked in 6 min in all 130 HF patients ($r = -0.17$; $P = 0.005$).

The total distance walked in 6 min was farther in males, younger HF patients <50 years, patients with a higher BMI, and patients with HFrEF. A significant difference was observed between the total distance walked when compared between the two classes of age ($P = 0.019$) and LVEF ($P = 0.012$).

Discussion

The 6MWT is a dependable tool in predicting morbidity and mortality in HF patients and a very useful prognostic tool in patients with PH.[16]

Our study showed that the total distance walked in 6 min was reduced in HF patients compared to recommended values. In addition, the distance walked was lower in HF patients with PH. The standard recommended 6-min walk distance (6MWD) has been set by earlier research at 498 m in 6 min by Lerner-Frankiel.[17] while McLaughlin *et al.*[18] set the 6MWD at 380–440 m: values not met by patients in this study indicating impaired exercise capacity.

In addition, this study showed better outcomes in younger patients, males, HF with reduced ejection fraction patients, and a normal BMI. Earlier research supports our findings of a longer 6MWD in males and younger patients than their older and female counterparts.[19]

Furthermore, our results suggest that exercise capacity is worse in HF patients with PH. Earlier research suggests that these findings may be of multiple etiologies ranging from effects of obesity, diabetes, age, and other chronic inflammatory states which cause changes resulting in decreased myocardial function[20,21] and inability of the heart to adjust proportionately to changes that occur during exercise.[22]

It is also notable that the prognostic value of the 6MWT is more practicable in the clinical setting with respect to continuous monitoring[23] although some improvements in patient test outcomes are less important compared to improvement over time. These improvements in the 6MWT though not a surety for increased survival still offer significant value as a tool for monitoring treatment success.[24,25]

An improvement in the 6MWT offers better morbidity/mortality outcomes in addition to a better quality of life.[25]

Conclusion

This study's findings indicate that worse outcomes may await HF patients with concurrent PH. Thus, continuous monitoring of their exercise tolerance capacity using the 6MWT is of significant clinical benefit as part of their overall management, especially as the 6MWT is an inexpensive, reproducible tool that can afford clinicians a better opportunity as regards monitoring and managing their patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Balloon Valvuloplasty as Percutaneous Intervention for Pulmonary Stenosis: Experience from a Tertiary Care Center

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Abstract

Background: To assess immediate and intermediate outcomes of percutaneous balloon pulmonary valvuloplasty (BPV) in children and adults. **Materials and Methods:** This retrospective, single-center study included patients who had undergone balloon valvuloplasty for the treatment of moderate to severe pulmonary stenosis at a tertiary care center in India between May 2011 and July 2018. Clinical profile, echocardiographic details, procedural details, complications, short term, and intermediate results were assessed. **Results:** A total of 43 patients were assessed. The mean age of the study population was 13.87 ± 11.71 years. Of them, 21 (48.8%) patients were men and 30 (69.8%) patients were children/adolescents. Single-balloon technique was used in all the cases. Balloon/annulus ratio was 1.28 ± 0.04. Immediate procedural success (Group 1) and partial procedural success (Group 2) were achieved in 26 (60.5%) and 17 (39.5%) patients, respectively. The right ventricular systolic pressure reduced from 117.70 ± 31.77 mmHg to 53.56 ± 13.29 mmHg postprocedure ($P < 0.001$). Peak-to-peak transvalvular gradient reduced from 102.81 ± 31.66 mmHg to 35.56 ± 12.47 mmHg postprocedure ($P < 0.001$). Intermediate follow-up was conducted for 2.61 ± 0.75 years (range: 2–4 years). At intermediate follow-up, peak-to-peak instantaneous gradient was 27.21 ± 5.80 mmHg. Restenosis, moderate, and severe pulmonary regurgitation were reported in 2 (7.1%), 4 (14.3%), and 2 (7.1%) patients, respectively. **Conclusion:** Percutaneous BPV is a safe and efficacious procedure for the treatment of moderate to severe pulmonary valve stenosis in children and adults. The procedure had excellent immediate and intermediate follow-up results.

Keywords: Balloon valvuloplasty, congenital heart disease, echocardiography, pulmonary regurgitation, pulmonary valve stenosis, pulmonary valve

Introduction

Pulmonary valve stenosis is one of the most prevalent congenital heart defects accountable for 5%–10% of all congenital heart diseases.[1,2] It has an incidence of 0.6–0.8 per 1000 live births.[3] Surgical valvotomy using the Brock method in 1948 was the first effort to treat pulmonary valve obstruction. However, this was an invasive procedure.[4] In 1982, Kan *et al*.[5] introduced a safer non-invasive procedure to relieve pulmonary obstruction by inflation of a balloon catheter assembled across the stenotic pulmonary valve.[6] Since then

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balloon pulmonary valvuloplasty (BPV) is considered the treatment of choice for pulmonary valve stenosis irrespective of age or valvular morphology.[7]

In this study, we retrospectively assessed the outcomes with BPV as a percutaneous therapy for pulmonary valve stenosis at a tertiary care center in India over a period of 8 years. In this study, we report immediate and intermediate follow-up results. Furthermore, this study analyzes the information regarding balloon/annulus ratio, balloon dilatation techniques, and various types of balloons.

Materials and Methods

Study design and patient population

This was a retrospective, single-center study of patients who had undergone balloon valvuloplasty for the treatment of moderate to severe pulmonary stenosis at a tertiary care center in India. During the period between May 2011 and July 2018, a total of 43 patients were identified and enrolled in the study. Patients were taken for BPV based on echocardiographic findings of peak instantaneous gradient >60 mmHg or mean gradient >40 mmHg in asymptomatic patients and peak instantaneous gradient >50 mmHg or mean gradient >30 mmHg in symptomatic patients. Patients with pulmonary regurgitation of mild or grade II severity were eligible to undergo BPV and were included in the study. None of the patients had pulmonary regurgitation of moderate or severe degree on color Doppler. Patients who had atrial septal defect (ASD) and patent foramen ovale were also included in the study. The exclusion criteria were patients who had undergone balloon valvuloplasty as palliative treatment for cyanosis or ventricular septal defect. The study was retrospective in nature; therefore, Institutional Ethics Committee approval was not obtained for the procedure. Written informed consent for the procedure and data release was obtained from all patients before the procedure.

Data collection

All patients underwent an electrocardiogram, chest X-ray, and 2D echocardiography with color Doppler after analysis of symptoms and clinical characteristics. A retrospective analysis of baseline characteristics, hemodynamics, complications, and follow-up was performed. Twenty-eight (65.1%) patients were followed up for >2 years. The severity of pulmonary valve stenosis was quantified by continuous-wave Doppler. Maximum instantaneous gradient was calculated with the help of Bernoulli's equation using maximum velocity obtained. The presence and severity of pulmonary regurgitation were assessed by color Doppler after analysis of the regurgitant jet and its width at the origin.

Study procedure

Antibiotic prophylaxis was given before the start of the procedure. The procedure was done under local anesthesia in adults and adolescents while general anesthesia was given to children. The femoral vein access was obtained in all patients. In addition, femoral arterial access was obtained for hemodynamic monitoring. Unfractionated heparin was administered to maintain activated clotting time >250 s.

Right heart catheterization was routinely performed in all patients. The right ventriculogram was taken in lateral projection using a pigtail catheter to measure pulmonary annulus size in diastole at leaflet hinge points and to rule out infundibular obstruction [Figure 1]. Peak-to-peak systolic gradient was measured between the right ventricle (RV) and pulmonary artery using an end-hole catheter. The stenosed pulmonary valve was crossed with a 0.035 "guidewire and then exchanged with a 0.035" stiff guide wire of 260 cm length with the help of an end-hole catheter. After the measurement of the transvalvular gradient, appropriately sized balloon was selected depending on pulmonary annular size. The size of the balloons used for valvuloplasty was 1.2–1.4 times the pulmonary annulus size with a standard balloon size being 1.25 times greater than the annulus size. Higher balloon sizes were reserved for unyielding pulmonary valves which had suboptimal results with lower balloon sizes. Different types of balloons were utilized for valvuloplasty depending on patient subset, operator choice, and availability. Different balloons used for valvuloplasty were namely Tyshak Mini (NuMed, Hopkinton, NY), Z-Med (NuMed, Hopkinton, NY), Admiral Xtreme (Medtronic, Minneapolis, MN), Andratec (Koblenz, Germany) and Inoue balloon (Toray Industries, Japan) [Figure 2]. Inoue balloon was advanced over a 0.025 "coiled wire whilst the rest of the balloons were advanced over a 0.035" 260 cm extra stiff guide wire (Cook Amplatz) [Figure 3]. The balloon was positioned midway over the stenotic pulmonary valve and inflated with dilute contrast till the disappearance of the waist. Following dilation and removal of the balloon, the transvalvular gradient was measured again. In addition, the right ventriculogram was done to assess the severity of pulmonary regurgitation and any evidence of infundibular obstruction. Further dilation with balloon or upsizing of the balloon was done after the assessment of transvalvular gradient.

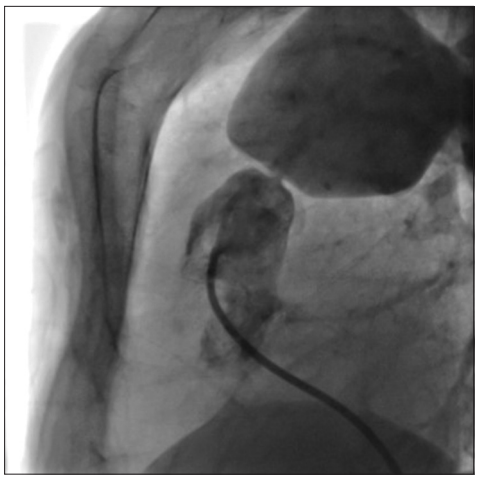


Figure 1: Classic doming pulmonary valve stenosis

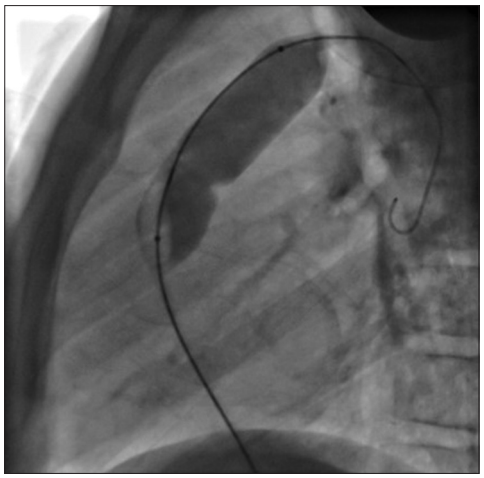


Figure 2: Centering of waist of balloon over stenotic pulmonary valve during inflation

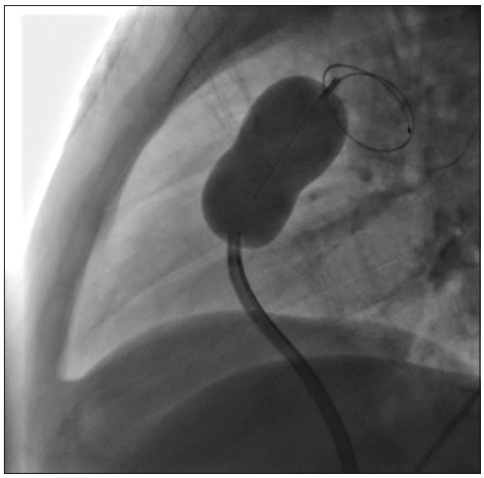


Figure 3: Balloon valvuloplasty using Inoue balloon

After the procedure, the sheath was removed and hemostasis was achieved. Patients were shifted to intensive care unit and were observed closely. Transthoracic echocardiography was done before discharge and at follow-up. Patients who had suboptimal results with postprocedure peak to peak systolic gradient >36 mmHg were prescribed oral beta-blocker therapy.

Study definitions

Procedural success was defined as fall in peak-to-peak systolic gradient between the RV and pulmonary artery immediate postprocedure to a value <36 mmHg. Partial procedural success was defined in cases in which peak-to-peak systolic gradient did not decrease to <36 mmHg immediately postprocedure and there was reduction in gradient during follow-up to a value <36 mmHg. Pulmonary valve restenosis was defined as re-elevation of peak instantaneous gradient on echocardiography to >50 mmHg after initial successful reduction in transvalvular gradient to <36 mmHg.[8,9]

Statistical analysis

Continuous variables were expressed as means with standard deviations and categorical variables as counts and percentages. Continuous variables were compared with Student's *t*-test. A $P \leq 0.05$ was considered statistically significant. All data were processed using the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA) program version 15.0.

Ethical statement

The study was retrospective in nature; therefore, Institutional Ethics Committee approval was not obtained for the procedure. Written informed consent for the procedure and data release was obtained from all patients prior to the procedure.

Results

Baseline characteristics

A total of 43 patients underwent balloon valvuloplasty for pulmonary valve stenosis. The patient age was 13.87 ± 11.71 years (range: 6 months–52 years). There was an almost equal distribution of men and women; 21 (48.8%) men and 22 (51.2%) women. The study predominantly involved (n = 30, 69.8%) children and adolescents. Of the study group, most (n = 40, 93.0%) had exercise intolerance. Three patients had a history of presyncope/syncope. Cyanosis was present in two cases as a result of reversal of shunt across ASD. The most frequently observed anomalies were ASD (n = 4, 9.3%) and facial dysmorphism (n = 3, 7.0%). Down syndrome was observed in 1 patient (2.3%). None of the cases in the study had Noonan syndrome while 1 patient had dysplastic pulmonary valve stenosis. The right ventricular systolic dysfunction was present in 4. The baseline characteristics and associated anomalies are shown in Table 1.

Balloon characteristics

Balloon/annulus ratio was 1.28 ± 0.04 mm. Single-balloon technique was followed in all the cases. Tyshak mini and Inoue were the most commonly used balloons in 28 (65.1%) and 10 (23.2%) cases, respectively. Single inflation was sufficient in majority (n = 28, 65.1%) while double and triple inflations were required in 8 (18.6%) and 2 (4.7%) cases, respectively. Balloons were stepped up in size in 7 cases (16.2%). The balloon characteristics are demonstrated in Table 2.

Immediate results

Right ventricular systolic pressure was reduced from 117.70 ± 31.77 mmHg to 53.56 ± 13.29 mmHg postprocedure. Pulmonary artery systolic pressure increased from 14.65 ± 1.90 mmHg to 17.79 ± 1.99 mmHg postprocedure. Peak-to-peak transvalvular gradient reduced from 102.81 ± 31.66 mmHg to 35.56 ± 12.47 mmHg postprocedure. Procedural success was achieved in 26 (60.5%) cases whilst partial procedural success was achieved in 17 (39.5%) cases. Moderate pulmonary regurgitation occurred in 4 cases while infundibular obstruction was observed in 8 cases. Depending on whether peak-to-peak transvalvular gradient fell to a value less than or more than 36 mmHg postprocedure, patients were retrospectively divided into two groups: Group 1 with

Table 1: Baseline characteristics of study population

Characteristics	*n*=43, *n* (%)
Age, (mean±SD, years)	13.87 ± 11.71
Male	21 (48.8)
Female	22 (51.2)
Children/adolescents	30 (69.8)
Adults	13 (30.2)
Symptoms	
Exercise intolerance	40 (93.0)
Syncope/presyncope	3 (7.0)
Cyanosis	2 (4.7)
Right heart failure	1 (2.33)
Associations	
Atrial septal defect	4 (9.3)
Right ventricle dysfunction	4 (9.3)
Facial dysmorphism	3 (7.0)
Patent ductus arteriosus	1 (2.33)
Mental retardation	1 (2.33)
Deafness	1 (2.33)
Down syndrome	1 (2.33)
Noonan syndrome	0

SD: Standard deviation

Table 2: Balloon characteristics

Parameter	*n*=43
Balloon characteristics	
Balloon size (mean±SD, mm)	18.86 ± 4.67
Pulmonary annulus mean±SD, mm)	14.79 ± 3.69
Balloon/annulus ratio, (mean±SD)	1.28 ± 0.04
Balloon dilation characteristics	
Single-balloon technique	
Admiral	6 (13.09)
Tyshak mini	28 (65.1)
Z med II	2 (4.7)
Andratec	4 (9.3)
Inoue	10 (23.2)
Step-up balloons	7 (16.2)
Number of inflations	
Single	28 (65.1)
Double	8 (18.6)
Triple	2 (4.7)

SD: Standard deviation

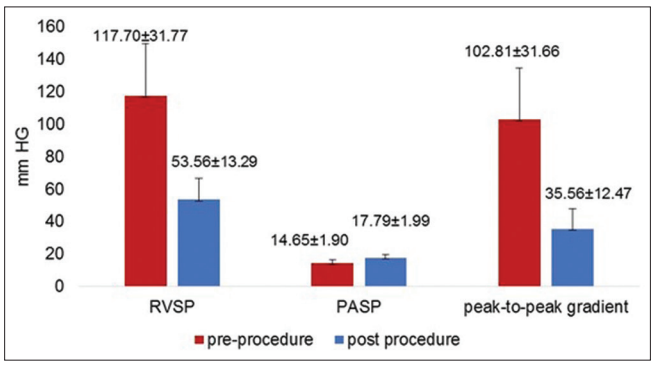


Figure 4: Immediate procedural results

complete procedural success (*n* = 26) and Group 2 with partial procedural success (*n* = 17). The immediate procedural results are illustrated in Figure 4.

Age was 12.16 ± 10.39 and 16.47 ± 13.38 (*P* = 0.243) for Group 1 and Group 2, respectively. Balloon/annulus ratio was 1.28 ± 0.04 and 1.27 ± 0.03 (*P* = 0.347) for Group 1 and Group 2, respectively. The preprocedure right ventricular systolic pressure was 98.96 ± 19.10 mmHg in Group 1 and 146.35 ± 25.26 mmHg in Group 2 (*P* < 0.001). Postprocedure right ventricular systolic pressure was 44.62 ± 7.86 mmHg in Group 1 and 67.24 ± 6.19 mmHg in Group 2 (*P* < 0.001). Preprocedure peak to peak gradient was 84.12 ± 18.96 mmHg in Group 1 and 131.41 ± 25.14 mmHg in Group 2 (*P* < 0.001). Postprocedure peak-to-peak gradient was 26.92 ± 5.98 mmHg in Group 1 and 48.76 ± 6.77 mmHg in Group 2 (*P* < 0.001). The procedural results are shown in Table 3 and Figures 5a and b.

Intermediate follow-up results

An analysis of patients with at least 2 years' follow-up was available for 28 (65.1%) patients with a mean follow-up period of 2.61 ± 0.75 years. At this follow–up, the right ventricular systolic pressure was 40.2 ± 6.4 mmHg and peak instantaneous gradient was 27.21 ± 5.8 mmHg. Restenosis was reported in 2 (7.1%) patients. Moderate pulmonary regurgitation was seen in 4 (14.3%) patients, while severe pulmonary regurgitation was seen in 2 (7.1%) patients. The intermediate follow-up results are given in Table 4.

Discussion

Transcatheter BPV is an established procedure for relief of pulmonary stenosis. In the current study, BPV could be performed in all the cases. There was an effective fall in transvalvular gradient to <36 mmHg in majority of patients which translated into immediate procedural success rate in 26 (60.5%) patients. Partial procedural success was achieved in 17 (39.5%) patients. These outcomes adequately demonstrate the efficacy of this technique in children, adolescents, and adults.

Immediate procedural success was 60.5% in our study. This fits within the range of 54%–87.1% suggested by previous authors.[4,7,10,11] Hatem *et al.*[4] and Lanjewar *et al.*[12] reported that patients unable to obtain immediate success had a greater severity of pulmonary stenosis highlighted by a significantly greater pulmonary transvalvular gradient and right ventricular systolic pressure than those who achieved immediate success. This observation is reflected in our study for parameters such as right ventricular systolic pressure (98.96 ± 19.10 mmHg vs. 146.35 ± 25.26 mmHg) and peak-to-peak pulmonary transvalvular gradient (84.12 ± 18.96 mmHg vs. 131.41 ± 25.14 mmHg) for the immediate and partially successful groups, respectively. No significant difference between the two groups in terms of age, sex, balloon/annulus ratio, and degree of reduction in the pulmonary transvalvular gradient was observed. Despite suboptimal initial results in patients of the partial procedural success group, the further reduction in transvalvular gradient

Table 3: Procedural results

Parameter	Group 1 (*n*=26)	Group 2 (*n*=17)	*P*
Age (mean±SD, years)	12.16 ± 10.39	16.47 ± 13.38	0.243
Balloon/annulus ratio (mean±SD, mm)	1.28 ± 0.04	1.27 ± 0.03	0.347
Preprocedure right ventricular systolic pressure (mean±SD, mmHg)	98.96 ± 19.10	146.35 ± 25.26	<0.001
Postprocedure right ventricular systolic pressure (mean±SD, mmHg)	44.62 ± 7.86	67.24 ± 6.19	<0.001
Preprocedure pulmonary artery systolic pressure (mean±SD, mmHg)	14.46 ± 1.86	14.94 ± 1.98	0.425
Postprocedure pulmonary artery systolic pressure (mean±SD, mmHg)	17.35 ± 2.13	18.47 ± 1.59	0.070
Preprocedure peak to peak gradient (mean±SD, mmHg)	84.12 ± 18.96	131.41 ± 25.14	<0.001
Postprocedure peak to peak gradient (mean±SD, mmHg)	26.92 ± 5.98	48.76 ± 6.77	<0.001

SD: Standard deviation

Table 4: Intermediate follow up results

Parameter	*n*=28
Follow up period (mean±SD, years)	2.61±0.75
Number of patients available for follow up period >2 years	28 (65.1)
Right ventricular systolic pressure, before procedure (mean±SD, mmHg)	120.89±31.37
Right ventricular systolic pressure, after procedure (mean±SD, mmHg)	55.46±14.23
Right ventricular systolic pressure, at follow up - echo derived (mean±SD, mmHg)	40.2±6.4
Peak to peak gradient, before procedure (mean±SD, mmHg)	106.36±30.88
Peak to peak gradient, after procedure (mean±SD, mmHg)	37.39±13.57
Peak instantaneous gradient, at follow up - echo derived (mean±SD, mmHg)	27.21±5.80
Restenosis, *n* (%)	2 (7.1)
Moderate pulmonary regurgitation, *n* (%)	4 (14.3)
Severe pulmonary regurgitation, *n* (%)	2 (7.1)

SD: Standard deviation

to <36 mmHg was attained with beta-blocker therapy during the intermediate follow-up period. Notwithstanding, this observation in intermediate follow-up, it implies that earlier intervention in natural history of severe pulmonary stenosis would result in lower residual gradient with consequent beneficial effects on the right ventricular hypertrophy.

It is a common occurrence for hypertrophied infundibular muscles to go into spasm after BPV. Numerous studies have reported this complication.[13-17] The consequence of this complication is a significant residual gradient despite adequate dilatation of the pulmonary valve. Hence, if only immediate results are considered, outcomes may be skewed by this complication. However, this is not a permanent complication as infundibular obstruction gradually regresses within the follow-up period. Secondary infundibular hypertrophy may contribute to the obstruction present postvalvuloplasty but it resolves after relief of obstruction. This process of regression is a dynamic process and may rapidly regress on the administration of oral beta-blockers.[10,13,14]

Numerous modern approaches to BPV implement a single- or double-balloon technique. Double-balloon technique may be used in the case of larger annular size. It maintains continuous blood flow eliminating chances of hypotension. However, the pitfall of double or triple balloons includes additional venous access, prolonged procedural time, stretch-induced injury to vessels, balloon slippage and more frequent injury to the pulmonary valve.[18,19] We were comfortable with singe-balloon technique in our patients and all the procedures utilized single-balloon technique. In addition, we found the sequential balloon technique very useful whilst dealing with a number of patients. The technique is very useful during procedures involving very severe stenosis or presence of RV dysfunction when there is transient hypotension during catheter advancement or balloon dilation. In such cases, rapid catheter manipulation and rapid balloon inflation-deflation are desirable. We used short and small diameter low profile balloons for initial valve dilation so as to get better control of hemodynamics while final valvuloplasty was done by larger diameter balloons.

A variety of balloons were utilized for the procedure depending on patient subset, operator choice, and availability. Among these, the most important factor was the availability of different balloons. In the initial years of the study period, Tyshak and Admiral Balloons were easily available while Andratec balloons were available in the later period. Inoue balloons were used especially in the presence of larger pulmonary annulus size in adults. These balloons conferred several advantages over other balloons. Flexible, short, and self-positioning characters of these balloons minimize injury to the RV outflow tract and main pulmonary artery. Adjustable inflation permits stepwise dilation reducing the risk of over-dilation of the pulmonary valve.[11,17,20] Further, short inflation-deflation cycle of approximately 5S takes care of hemodynamic compromise during inflation.

Twenty-eight patients were analyzed for the intermediate results of the balloon valvuloplasty. These patients were followed up for 2–4 years. Successful relief of obstruction was sustained in majority of the patients in intermediate period. Restenosis was seen in only 2 cases (1 at 2 years and the other at 3 years of follow-up). In 1 of these cases of restenosis, partial relief of obstruction with residual gradient was seen immediately postprocedure. Risk factors for recurrence identified in a study of 36 cases were balloon/pulmonary valve annulus ratio <1.2 and immediate postvalvuloplasty gradient >30 mmHg.[21] Dysplastic pulmonary valves and pulmonary valve hypoplasia did not seem to have any influence on recurrence in this study. In addition

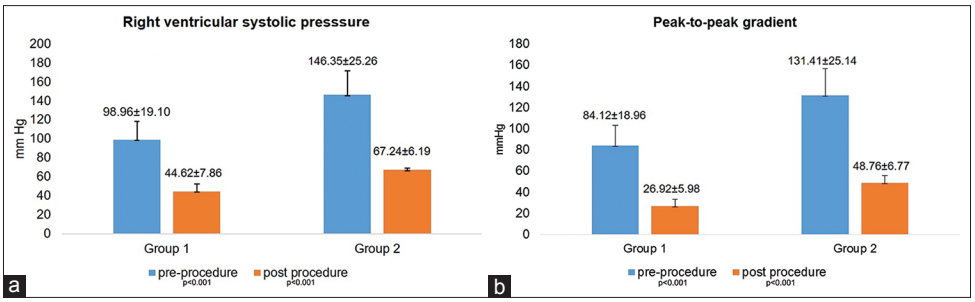


Figure 5: (a) Right ventricular systolic pressure pre and post procedure. (b) Peak-to-peak gradient pre and post procedure

to these two factors large multi-institutional valvuloplasty and angioplasty of congenital anomalies (VACA) registry also found earlier study year, small valve annulus, and postsurgical or complex pulmonary stenosis as predictive factors for restenosis.[9] Depending on these studies and our experience, it can be concluded that larger balloons should be used to reduce valvular gradient to <36 mmHg for longer-lasting results. However, the use of larger balloons for valvuloplasty comes at the price of more chances of pulmonary regurgitation in the long term. Although mild pulmonary regurgitation was seen in as many as 23 patients, hemodynamically significant pulmonary regurgitation was found in follow-up in 6 patients. Among them, 2 patients had severe pulmonary regurgitation at the end of 4 years of follow-up. However, there was no significant volume overload or systolic dysfunction of RV. These cases will require further follow-up for any adverse consequences in future. The prevalence of pulmonary regurgitation has been reported to be 40%–90% in literature which roughly corresponds to our study.[8,22-25] Majority of the cases in these studies did not require valve replacement due to the absence of volume overload except few exceptions.[22] Berman *et al*.[23] suggested young age, higher degrees of obstruction, large balloon/annulus ratio, use of noncompliant balloons, and low postdilatation peak-to-peak systolic pressure gradient as factors contributing to the development of pulmonary regurgitation. Another study of 68 cases found that use of larger balloon with balloon/annulus ratio >1.3:1 was associated with the development of pulmonary regurgitation at follow-up.[23] Depending on these experiences Rao *et al*. recommend a balloon/annulus ratio of 1.2–1.25 instead of previously recommended 1.2–1.4 ratio as optimal choice for balloon selection for achieving adequate relief of obstruction with least incidence of significant pulmonary regurgitation at follow-up.[6]

Complications in our study were limited to 27 cases of acute pulmonary regurgitation, 8 cases of infundibular obstruction, 2 cases of vasovagal syncope and only 1 case of femoral vein thrombosis. Hatem *et al*.[4] reported complications of dissection of the inferior vena cava, 2 cases of convulsions during balloon inflation, two cases of atrial fibrillation, one case of rupture of tricuspid valvular apparatus and 1 case of cardiac arrest. Similarly, Amoozgar *et al*.[3] reported 2 cases of cardiac arrest and 1 case each of detachment of the cover of the hydrophilic catheter, mild pericardial effusion, sepsis, supraventricular tachycardia, and umbilical vein dissection. Further acute pulmonary regurgitation not requiring surgical management is a common occurrence.[10] BPV is a safe, effective, and less invasive alternative in comparison to surgical valvotomy. Significant residual gradient after valvuloplasty recedes gradually with regression of infundibular hypertrophy over time. Less than moderate pulmonary regurgitation develops in most cases, but rarely requires surgical treatment. The incidence of restenosis is truly low.

Study limitations

The first limitation of our study is retrospective collection of data. The second limitation is the small study population size.

Conclusion

Percutaneous BPV is a safe and efficacious procedure for the treatment of moderate to severe pulmonary valve stenosis in children/adolescents and adults. The procedure yielded excellent immediate and intermediate follow-up results.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Preoperative and Perioperative Predictors of Right Ventricular Failure after Left Ventricular Assist Device Implantation

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Abstract

Background: Right ventricular (RV) failure is a serious adverse event for patients with left ventricular assist devices (LVADs). Here, we seek to identify the risk factors which may predict the development of RV failure (RVF). **Methods and Results:** Forty-two patients were implanted with LVADs (32 HeartWare® ventricular assist device and 10 Thoratec® HeartMate II) between March 2013 and April 2014 at the Ege University Medical School, Izmir, Turkey. Baseline clinical, demographic, and laboratory information were measured and patients prospectively fallowed after surgery. Endpoint was defined RVF development for patients. Before surgery, hemodynamic parameters, electrocardiographic findings, standard echocardiographic measurements, and medications were recorded. Multivariate regression analysis showed that the presence of ascites, prealbumin <14 mg/dl, bilirubin >1.5 mg/dl, RV diameter >3.2 cm, RV-fractional area change (FAC) <24%, right atrial area (RAA) >28 cm,^{2} and RV-myocardial performance index >0.35 were the strongest predictors of RVF after LVAD implantation. **Conclusions:** RAA and RV-FAC are easily obtained and should be evaluated in potential LVAD patients. Risk assessment systems should also take into account the presence of ascites and low prealbumin levels which are not currently incorporated into any risk models. Validation of the relative importance of all of these parameters requires further investigation.

Keywords: Left ventricular assist device, patient outcomes, right ventricular failure, risk factors

Introduction

Right ventricular failure (RVF) is an important cause of the morbidity and mortality that develops in patients with left ventricular assist devices (LVADs). RVF prolongs stay in the intensive care unit, increases 30-day mortality, and decreases the transplantation bridging rates.[1,2] INTERMACS has defined RVF as a condition leading to low cardiac output, high central venous pressure (CVP), low left ventricle filling pressure, and requires inotrope infusions for longer than 14 days or ECMO or right ventricular assist devices (RVAD).[3]

The incidence of RVF after LVAD implantation varies from 6 to 44% according to recent studies. This large variability is due to differences in definitions of RVF and the patient populations of the studies.[4] Some authors defined RVF only as a condition of need RVAD,[5-7] and some others especially INTERMACS defined RVF as a condition leading to low cardiac output, high CVP, low left ventricle filling pressure,

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and requires inotrope infusions or need for RVAD. Based on riquirement of inotrope time, RVF has been classified by INTERMACS as mild (within 7 days), modarate (7-14 days) and severe (>14 days or need for RVAD). The complex pathophysiology of RVF makes it difficult to predict the patients who are susceptible to developing this condition. The structure of the right ventricular (RV) myocardium and pathologies of the pulmonary vascular bed may contribute to the formation of RVF. Perioperative factors such as myocardial stunning, ischemia, infarction, and arrhythmias can also lead to RVF. Finally, with mechanical circulatory support, the sudden septal displacement which occurs during the emptying of the left ventricle as well as the increase in preload may contribute to the deterioration of right ventricle.[1,8] The purpose of this study was to identify the clinical, laboratory, hemodynamic, and echocardiographic risk factors that may predict the development of RVF in end-stage heart failure patients requiring LVADs.

Materials and Methods

Patient population

Fifty patients were initially enrolled in this prospective study. Bleeding is a known risk factor for RVF and so patients who underwent revision due to bleeding after LVAD implantation were excluded. The forty-two remaining patients were implanted with LVADs between March 2013 and April 2014. The HeartWare® ventricular assist device (HVAD, HeartWare Inc., Framingham, MA) was implanted in 32 (76%) of the patients, while the HeartMate II (HM2, Thoratec Corp., Pleasanton, CA) was implanted in 10 (24%) patients.

In this study, RVF was defined as the need for inotropes for more than 14 days and/or need for RVAD implantation. To identify the risk factors for RVF after LVAD implantation, baseline values were collected for the patients' clinical, demographic, and laboratory information. Immediately before surgery, patient hemodynamic parameters, electrocardiographic findings, and medications were also recorded. Finally, the Michigan RV risk score (vasopressor need: 4 points, aspartate aminotransferase [AST] >80:2 points, total bilirubin >2:2.5 points, creatinine >2.3:3 points) and Lietz–Miller risk score (thrombocyte <148000:7 points, albumin <3.3:5 points, INR >1.1:4 points, vasodilator treatment: 4 points, mean pulmonary artery pressure [PAP] <25 mmHg: 3 points, AST >45:2 points, Htc <34%:2 points, BUN >51:2 points, no need for IV inotropes: 2 points) were calculated for all patients. For the analysis, patients were divided into ischemic and nonischemic groups according to the etiology of their heart failure and also were categorized into INTERMACS groups (1/2, 3/4, and 5–7).

Echocardiographic measurements

Before surgery, all patients underwent transthoracic echocardiography to obtain standard echocardiographic measurements (VIVID 7 PRO, GE, M4S probe, 1.5–4.3 MHz). The RV fractional area change (RV-FAC), the right atrial area (RAA), RV outflow tract (RVOT), the proximal (RVOT1, diastole and systole) and distal (RVOT2) diameters, the RVOT fractional shortening (RVOT-FS), the RV diameters (RVD1, RVD2, RVD3), the tricuspid regurgitation velocity, and the systolic PA*P* values were calculated according to the guidelines of the American Society of Electrocardiography. The ratio of the RV diameter to the left ventricular diameter (LV diameter) was measured with two-dimensional measurements in apical and parasternal slices separately (RV/LV ratio apical, RV/LV ratio parasternal). The RV myocardial performance index (MRI) was calculated in all cases using the pulsed wave Doppler technique.[9] The parasternal short-axis slice was measured at the aortic valve level and the anterior wall of the RVOT. The systolic displacement of the RVOT was measured using the M-mod technique (RVOT-SE).[10]

Statistical analysis

All variables were expressed as percentages or mean ± standard deviation. All continuous variables were compared with the Mann–Whitney U test and categorical variables were compared with the Chi-square or Fisher's exact test. Logistic regression analyses were performed for the variables that were significantly associated with RVF. ROC curve analyses were performed to identify the cutoff values, diagnostic sensitivity, and specificity of the variables significantly associated with the development of RVF. $P < 0.05$ was considered statistically significant and all analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, USA).

Ethical statement

This scientific research was initiated with the desicion of Ege Univercity Faculty of Medicine Clinical Research Board dated 19/03/2013 and numbered 13-2.2/1.

Results

RVF occurred in 7 (16.7%) patients during follow-up. One patient required an RVAD and the six others required more than 14 days of inotropes. The preoperative baseline characteristics and comorbidity conditions of the patients in both the groups are shown in Table 1 with no significant differences observed between RVF and non-RVF patients. Ischemic etiology was noted in 57% ($n = 24$) of the patients and 43% ($n = 18$) were nonischemic, with no significant association between etiology and RVF. There was, however, a significant association between a low INTERMACS class (class 1 and 2) and the development of RVF ($P = 0.017$).

The hemodynamic parameters in Table 2 show patients who developed RVF had significantly lower systolic and diastolic blood pressures. Although RVF occurred more often in patients who required inotropes the difference was not statistically significant ($P = 0.063$). In addition, ascites was identified in seven patients before surgery and 4 (57%) of those patients developed RVF. Despite the small sample size, there was a significant association between the presence of ascites and RVF ($P = 0.009$). The analysis of the preoperative medication data showed that there were no significant differences in the

Table 1: Basal characteristics and comorbidity conditions

Baseline characteristics	All patients (N_{total}=42), *n* (%)	RVF (N_{total}=7), *n* (%)	Non-RVF (N_{total}=35), *n* (%)	*P*
Age (years)	50.2 ± 12.4	50.1 ± 15.4	50.2 ± 11.9	0.774
Male	39 (93)	7 (100)	32 (91)	1.000
BMI (m^2)	1.7 ± 0.1	1.8±0.1	1.7 ± 0.1	0.223
BSA (kg/m^2)	24.5 ± 3.3	24.1 ± 2.7	24.6 ± 3.4	0.698
Etiology				
Ischemic	24 (57)	3 (43)	21 (60)	0.438
Non-ischemic	18 (43)	4 (57)	14 (40)	
Diabetes	13 (31)	3 (43)	10 (29)	0.657
Hypertension	18 (43)	2 (29)	16 (46)	0.679
Hyperlipidemia	16 (38)	2 (29)	14 (40)	0.690
COPD	5 (12)	0 (0)	5 (14)	0.569
Liver disease	2 (5)	1 (14)	1 (3)	0.309
Prior sternotomy	7 (17)	0 (0)	7 (20)	0.326
Cerebrovascular disease	5 (12)	0 (0)	5 (14)	0.569
Peripheral artery disease	2 (5)	0 (0)	2 (6)	1.000
Device type				
HVAD	32 (76)	5 (71)	27 (77)	1.000
HMII	10 (24)	2 (29)	8 (23)	
Intermacs				
1/2	8 (19)	4 (57)	4 (11)	0.017*
3/4	34 (81)	3 (43)	31 (89)	

**p* value<0,05, RVF: Right ventricular failure, BMI: Body mass index, BSA: Body surface area, COPD: Chronic obstructive pulmonary disease, HVAD: HeartWare® ventricular assist device, HMII: HeartMate II

Table 2: The association of blood pressure, heart rate, need for inotropes and presence of ascites with right ventricular failure

Hemodynamic parameters	All patients (N_{total}=42)	RVF (N_{total}=7)	Non-RVF (N_{total}=35)	*P*
Systolic blood pressure (mmHg)	94 ± 10	85 ± 5	96 ± 10	0.002*
Diastolic blood pressure (mmHg)	59 ± 7	52 ± 8	60 ± 7	0.032*
Heart rate (beat/min)	81 ± 13	85 ± 17	81 ± 13	0.685
Intravenous inotropes, *n* (%)				
+	11 (26)	4 (57)	7 (20)	0.063
–	31 (74)	3 (43)	28 (80)	
Ascites, *n* (%)				
+	7 (17)	4 (57)	3 (9)	0.009*
–	35 (83)	3 (43)	32 (91)	

**p* value<0,05, RVF: Right ventricular failure

patients with and without RVF for all medications except for angiotensin-converting enzyme inhibitors (ACE-I). All 15 patients using ACE-I did not develop RVF which was significantly different from the 7 of 27 (25.9%) of patients not using ACE-I who later developed RVF (P = 0.038).

Preoperative right heart catheterization (RHC) showed no significant differences between the patients with and without RVF except in the case of mean right atrial pressure (RAP). Patients who developed RVF had significantly higher RAP (15 ± 6 vs. 9 ± 4 mmHg, P = 0.039). There were generally no differences in the biochemical laboratory results [Table 3]. Patients with RVF tended to have lower leukocytes and albumin levels but the differences were not statistically significant. The mean prealbumin levels were significantly lower for the patients with RVF (P = 0.003). RVF patients also had significantly higher bilirubin and NT-proBNP levels (P = 0.008 and P = 0.041, respectively).

The results of current RV risk assessment methods are in Table 4. The Michigan RV Risk score showed a significant association between a high-risk assessment and eventual development of RVF (P = 0.02). However for this cohort, the Lietz–Miller Risk Assessment was not successful in identifying which patients were at high risk and eventually developed RVF (P = 0.203). Echocardiographic measurements [Table 5] showed that RVF was associated with an overall larger right ventricle as RV diameter, RAA, tricuspid annular diameter, and the ratio of the right to left ventricle were all significantly higher for patients with RVF. As expected, patients with RVF also showed many signs of deteriorated heart condition as they had significantly worse ejection fraction, tricuspid

Table 3: Association between biochemical laboratory results and right ventricular failure

Biochemical laboratory results	All patients (*n*=42)	RVF (*n*=7)	Non-RVF (*n*=35)	*P*
Hb (g/dl)	12.6 ± 1.7	12.2 ± 1.8	12.7 ± 1.7	0.380
Htc (%)	38.2 ± 4	37.1 ± 4.3	38.4 ± 4	0.353
Leukocyte (K/mm^3)	7 ± 2	6 ± 1	8 ± 2	0.052
Platelet (K/mm^3)	240 ± 84	250 ± 105	239 ± 80	0.566
INR	1.2 ± 0.2	1.2 ± 0.1	1.2 ± 0.2	0.313
BUN (mg/dl)	55 ± 34	66 ± 58	53 ± 28	0.457
Creatinine (mg/dl)	1.07 ± 0.2	1.02 ± 0.4	1.08 ± 0.2	0.589
Uric acid (mg/dl)	6.4 ± 1.9	5.8 ± 1.3	6.5 ± 2	0.489
Sodium (mEq/l)	134 ± 5	133 ± 4	134 ± 5	0.624
Albumin (g/dl)	4 ± 0.5	3.6 ± 0.4	4.1 ± 0.5	0.063
Prealbumin (mg/dl)	18 ± 7	11 ± 3	19 ± 7	0.003*
AST (IU/l)	31 ± 22	50 ± 43	27 ± 12	0.146
ALT (IU/l)	36 ± 41	57 ± 78	32 ± 30	0.468
LDH (IU/l)	245 ± 77	250 ± 70	244 ± 80	0.826
Bilirubin (mg/dl)	1.8 ± 2.1	3.5 ± 3.2	1.5 ± 1.7	0.008*
NT-proBNP (pg/ml)	6045 ± 6660	9237 ± 6882	5406 ± 6527	0.041*

**p* value<0,05 is significant, RVF: Right ventricular failure, Hb: Hemoglobin, Htc: Hematocrit, INR: International normalized ratio, BUN: Blood urea nitrogen, AST: Aspartate transaminase, ALT: Alanine transaminase, LDH: Lactate dehytrogenase, NT-proBNP: N-terminal prohormone brain natriuretic peptide

Table 4: Association between clinical risk scores and right ventricular failure

RV risk scores	All patients (*n*=42), *n* (%)	RVF (*n*=7), *n* (%)	Non-RVF (*n*=35), *n* (%)	*P*
Michigan RV risk score				
Low/medium	33 (79)	3 (43)	30 (86)	0.02*
High	9 (21)	4 (57)	5 (14)	
Lietz-Miller risk score				
Low	33 (79)	4 (57)	29 (83)	0.203
Medium	8 (19)	3 (43)	5 (14)	
High/very high	1 (2)	0 (0)	1 (3)	

**p* value<0,05, RV: Right ventricle

regurgitation, RV-FAC, tricuspid annular plane systolic excursion (TAPSE), and RV- MRI. Despite the changes in the RV, often patients with and without RVF did not show any significant differences in their left ventricle echocardiographic measurements.

Results of the multiple logistic regression analyses of risk factors for RVF are in Table 6. The presence of ascites, prealbumin <14 mg/dl, total bilirubin >1.5 mg/dl, RV diameter >3.2 cm, RV-FAC <24%, RAA >28 cm², and RV-MPI >0.35 were the strongest predictors of RVF. The ROC curves in Figure 1 show the specificity and sensitivity of pre-albumin, RV-FAC, RAA, and RV-MPI for predicting the development of RVF.

Discussion

The results of our study show that baseline characteristics or comorbidity conditions were not significantly associated with the development of RVF in patients undergoing LVAD placement. Previous studies have suggested that RVF develops more frequently in female patients and those with nonischemic etiology, smaller BSAs, or advanced age.[11-13] However, in a study of 197 patients, Matthews *et al*.[14] reported that there were no significant differences in those baseline characteristics similar to the results of this analysis. Furthermore, a large meta-analysis published in last years reported that female gender is an independent predictor of early RVF.[15] A low INTERMACS class has been previously reported as a risk factor for RVF,[16] which is understandable since a lower classification indicates the patient has poor cardiac reserves and systemic circulation. In this cohort, there was also a significant association between low (1/2) INTERMACS class and RVF. In contrast, patients with INTERMACS class 3/4 had a relatively low risk of developing RVF. There was also no significant difference in RVF between groups with and without inotrope use. This may suggest earlier LVAD implantation, before the patient status deteriorates to INTERMACS class 1/2, has the potential to improve morbidity and mortality.

The association between ascites and RVF has not been analyzed previously and the presence of ascites is not considered in any current RVF risk score system. As there was a significant association between the presence of ascites and RVF, it is recommended to include this condition, which should be simple to evaluate in a new risk score system. Univariate analysis showed RVF developed significantly less often

Table 5: Association of echocardiographic measurements and right ventricular failure

Echocardiographic measurements	All patients (*n*=42)	RVF (*n*=7)	Non-RVF (*n*=35)	*P*
LA diameter (cm)	4.7 ± 0.5	4.6 ± 0.3	4.7 ± 0.6	0.932
LVESD (cm)	6.2 ± 0.7	6.2 ± 0.9	6.2 ± 0.7	0.933
LVEDD (cm)	6.7 ± 0.7	6.6 ± 0.9	6.7 ± 0.7	0.543
RV diameter (cm)	2.7 ± 0.6	3.4 ± 0.6	2.6 ± 0.5	0.004*
LVEDV (ml)	258 ± 83	232 ± 81	263 ± 83	0.447
LVESV (ml)	212 ± 67	198 ± 61	215 ± 68	0.698
EF (% modified Simpson)	17 ± 5	13 ± 4	18 ± 5	0.032*
Mitral regurgitation (mild to severe), *n* (%)	19 (45)	3 (43)	16 (46)	1.000
Tricuspid regurgitation (mild to severe), *n* (%)	18 (43)	6 (86)	12 (34)	0.031*
Pulmonary regurgitation (mild to severe), *n* (%)	3 (7)	1 (14)	2 (6)	0.430
RV-FAC	29 ± 7	20 ± 3	31 ± 6	<0.001*
RAA (cm^2)	24.2 ± 5.8	29.8 ± 3.3	23.1 ± 5.5	0.004*
RVOT-FS	18 ± 8	12 ± 7	19 ± 7	0.018*
Tricuspit annular diameter (cm)	4.7 ± 0.6	5.4 ± 0.2	4.6 ± 0.6	0.005*
TRV (m/sn)	2.9 ± 0.6	2.9 ± 0.7	2.9 ± 0.6	0.986
SPAP (mmHg)	50 ± 16	50 ± 15	50 ± 16	0.879
TAPSE (mm)	15.3 ± 3.2	12.8 ± 1.8	15.8 ± 3.2	0.019*
RVSm (cm/sn)	8.4 ± 2.3	6.5 ± 1.6	8.8 ± 2.2	0.021*
RVOT-SE (mm)	7.3 ± 2.1	4.1 ± 0.6	7.9 ± 1.7	<0.001*
RV-MPI	0.31 ± 0.14	0.51 ± 0.21	0.27 ± 0.09	0.007*
RV/LV ratio (apical)	0.55 ± 0.13	0.66 ± 0.14	0.53 ± 0.12	0.036*
RV/LV ratio (parasternal)	0.41 ± 0.11	0.52 ± 015	0.39 ± 0.09	0.049*

**p* value<0,05, LV: Left ventricle, RVF: Right ventricular failure, LA: Left atrium, LVESD: LV end systolic diameter, LVEDD: LV end diastolic diameter, RV: Right ventricle, LVEDV: LV end diastolic volume, LVESV: LV end systolic volume, EF: Ejection fraction, RV-FAC: RV fractional area change, RAA: Right atrial area, RVOT-FS: Right ventricular outflow tract fractional shortening, TRV: Tricuspid regurgitation velocity, SPAP: Systolic pulmonary artery pressure, TAPSE: Tricuspid annular plane systolic excursion, RVSm: RV peak systolic velocity, RVOT-SE: Right ventricular outflow tract systolic displacement, RV-MPI: RV myocardial performance index

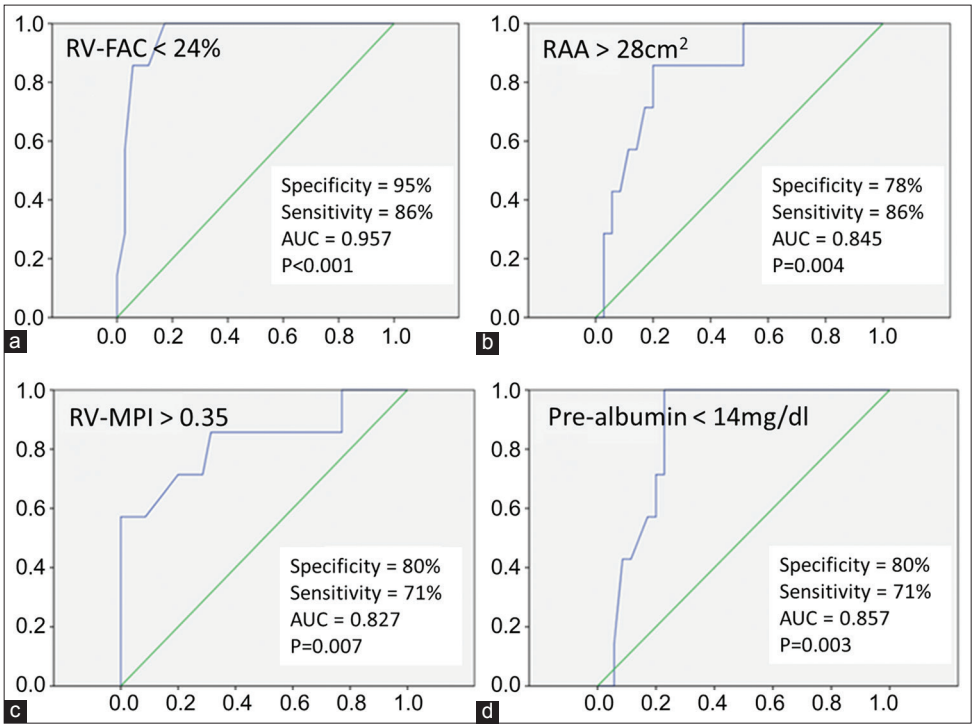


Figure 1: ROC Curves of (a) RV-FAC, (b) RAA, (c) RV-MPI, and (d) prealbumin. Sensitivity is plotted on the vertical axis while 1-Specificity is plotted on the horizontal axis. ROC = Receiver operating characteristic; AUC = Area under the curve; RV-FAC = Right ventricle fractional area change; RAA = Right atrial area; RV-MPI = Right ventricle myocardial performance index

Table 6: Multivariate regression analysis of right ventricular failure risk factors

Risk factors for RVF	*P*	OR	95% CI
Ascites	0.006	14.2	2.1-95.8
Prealbumin <14 mg/dl	0.014	10	1.5-62.7
Bilirubin >1.5 mg/dl	0.018	15	1.5-140.9
RV >3.2 cm	0.003	19.3	2.7-135.1
RV-FAC <24%	<0.001	99	7.7-1271.9
RAA >28 cm²	0.009	20.2	2.1-193.9
RV-MPI >0.35	0.014	10	1.5-62.7

RVF: Right ventricular failure, RV: Right ventricle, RV-FAC: RV fractional area change, RAA: Right atrial area, RV-MPI: RV myocardial performance index, OR: Odds ratio, CI: Confidence interval

in patients using ACE-I. However, in the multiple logistic regression analysis, it was determined that the difference was due to the patients' INTERMACS class and ACE-I use was not an independent significant risk factor of RVF.

Postoperative right heart catheterization revealed a statistically significant association between high RAP and RVF, which has similarly been reported in previous studies.[14,16,17] In this cohort, the other catheter measurements were not associated with the development of RVF as pulmonary artery pressures were not significantly different between the two groups. However, Fukamachi *et al*.[12] previously reported that a low mean PA*P* values can be a risk factor for RVF. Alnsasra *et al*.[18] reported that elevated diastolic pulmonary gradient is associated with RVF. Dandel *et al*. reported in their study including 475 patients that elevated CVP is an independent predictor of postoperative RVF.[19] Wang *et al*.[5] also reported that elevated CVP/pulmonary capillary wedge pressure ratio levels have a relation between postoperative RVF. Because of the many underlying mechanisms of RVF development, differences in the patients could lead to these conflicting results.

Although laboratory measurements such as AST, bilirubin, and creatinine can indicate end organ damage, changes in these markers are not specific to RVF. In this study, there was no correlation between most of the laboratory measurements and the development of RVF [Table 3]. However, prealbumin was significantly lower in patients with RVF and prealbumin values of <14 mg/dl predicted RVF with 80% specificity and 71% sensitivity. Prealbumin could serve as a sensitive and early indicator for RV dysfunction since it is a negative acute phase reactant and has a short half-life as previously described.[20] RVF patients also had significantly higher levels of bilirubin which concurs with other reports.[21,22] Previous studies have identified associations between RVF and increased AST, creatinine, and NT-proBNP levels.[12,13,23]

As expected, preoperative echocardiographic data revealed that there was a significant increase in size and decrease in function of the RV in patients who later developed RVF. This is consistent with previous literature where there was increased right heart size based on RV/LV ratio and tricuspid annulus diameter in patients with RVF.[23-26] Similarly, right heart function was diminished for those patients as measured by tricuspid regurgitation, TAPSE, RV-FAC, and RVOT-SE.[10,16,27,28] While previous work has shown that RVOT-SE is predictive of decreased RV function, this study revealed a correlation between RVOT-SE and RVF development after LVAD implantation.

Study limitations

Limitation of this study are that patient data were collected from a single center and site-specific practices may have had an effect on the results. For example, at this institution, patients are often implanted with an LVAD earlier to prevent development of end organ damage. This is supported by the much lower percentage of INTERMACS class 1 and 2 patients receiving the device (19% of cohort) compared to other studies. Because of this earlier implantation practice, it is possible our results did not show significant associations between RVF and certain laboratory measures of end organ damage. In addition, the smaller sample size may have limited our statistical analysis. While the univariate analysis revealed a significant association between RVOT-SE and RVF, this significance was not shown with multiple logistic regression analyses. To better determine if variables such as RVOT-SE are risk factors, larger patient groups should be considered.

Conclusions

Several hemodynamic, biochemical laboratory, and echocardiographic measurements were significantly associated with the development of RVF in this prospective single-center study. Multivariate regression analysis showed that the presence of ascites, pre-albumin <14 mg/dl, bilirubin >1.5 mg/dl, RV diameter >3.2 cm, RV-FAC <24%, RAA >28 cm^2, and RV-MPI >0.35 were the strongest predictors of RVF after LVAD implantation. These findings suggest that RAA and RV-FAC, which are easily measured with standard transthoracic echocardiography, should be evaluated in patients with plans for LVAD implantation. Similarly, risk assessment systems should take into account the presence of ascites and low prealbumin levels. Validation of the relative importance of all of these parameters requires further investigation. In this study, the risk for developing RVF was also significantly lower in INTERMACS class 3/4 patients compared to the class 1/2 cohort. This has influenced this institution's LVAD implantation strategies as we believe that earlier LVAD implantation might provide significant morbidity and mortality benefits.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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