The Right Heart-Pulmonary Circulation Unit and Left Heart Valve Disease

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KEYWORDS

• Valvular heart disease • Echocardiography • Exercise • Pulmonary hypertension • Outcome

KEY POINTS

- Pulmonary hypertension (PH) is a classical pathophysiologic consequence of left-sided valvular heart disease (VHD). Aortic and mitral valve (stenosis and regurgitation) diseases are frequently accompanied by PH, especially when they are severe and symptomatic.
- In asymptomatic patients, PH is rare, although the exact prevalence is unknown and mainly stems from the severity of the VHD and the presence of diastolic dysfunction. Recently, exercise echocardiography has gained interest in depicting PH.
- In these asymptomatic patients, exercise PH is observed in about greater than 40%. Either PH at rest or during exercise is also a powerful determinant of outcome and is independently associated with reduced survival, regardless of the severity of the underlying valvular pathology.
- PH is a marker of poor prognosis; assessment of PH in VHD is crucial for risk stratification and management of patients with VHD.

INTRODUCTION

Pulmonary hypertension (PH) described in valvular heart disease (VHD) is frequent and belongs to the group 2 corresponding to PH related to left heart disease according to the new classification of PH.[1] Diagnosis of PH related to VHD is based on the following criteria: mean pulmonary arterial pressure (PAP) greater than 25 mm Hg associated with pulmonary capillary wedge pressure (PCWP) or left ventricular (LV) end-diastolic pressure greater than 15 mm Hg. The increase of LV volume or pressure in VHD induces a rise of left atrial (LA) pressure, which causes a passive backward transmission to the pulmonary venous system with subsequent increase of PH.[2] Persistent high pulmonary venous pressure can induce irreversible vasculature vasoconstriction and hyperplasia

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contributing to further increase in PH, excessive regarding PCWP.[3] At advanced stage of VHD, chronic PH contributes to increased right ventricular (RV) afterload and leads to progressive RV remodeling, including RV hypertrophy followed by RV dilatation. It leads to increased tricuspid regurgitation (TR) severity and RV dysfunction. When PH occurs in VHD, it is frequently associated with clinical symptoms (**Fig. 1**).

Echocardiography gives an estimation of systolic PAP (sPAP) and plays a key role in assessment of VHD and consequences of PH, in particular on RV function (**Table 1**). In some cases, right heart catheterization is mandatory to determine accurate value of PCWP and confirm diagnosis. Many indices have been developed for quantifying RV function, but reference standards for RV functional assessment are lacking.[4,5] The development of three-dimensional echocardiography and cardiac magnetic resonance provides a better evaluation of RV volume and geometry than conventional two-dimensional echocardiography.[2,6]

Because PH is a marker of poor prognosis, assessment of PH in VHD is crucial for risk stratification and management of patients (**Table 2**). The impact of RV function on outcomes of VHD has been underestimated for a long time,[7] whereas it is now clearly established that RV failure compromises patient outcomes in VHD.[2,8]

RESTING PULMONARY HYPERTENSION AND AORTIC STENOSIS

Prevalence of resting PH in aortic stenosis (AS) is difficult to establish because it depends on clinical profile and definition of PH. Lancellotti and colleagues[9] reported only 6% of resting PH in a series of 105 patients presenting with asymptomatic AS, whereas the prevalence of PH could range from

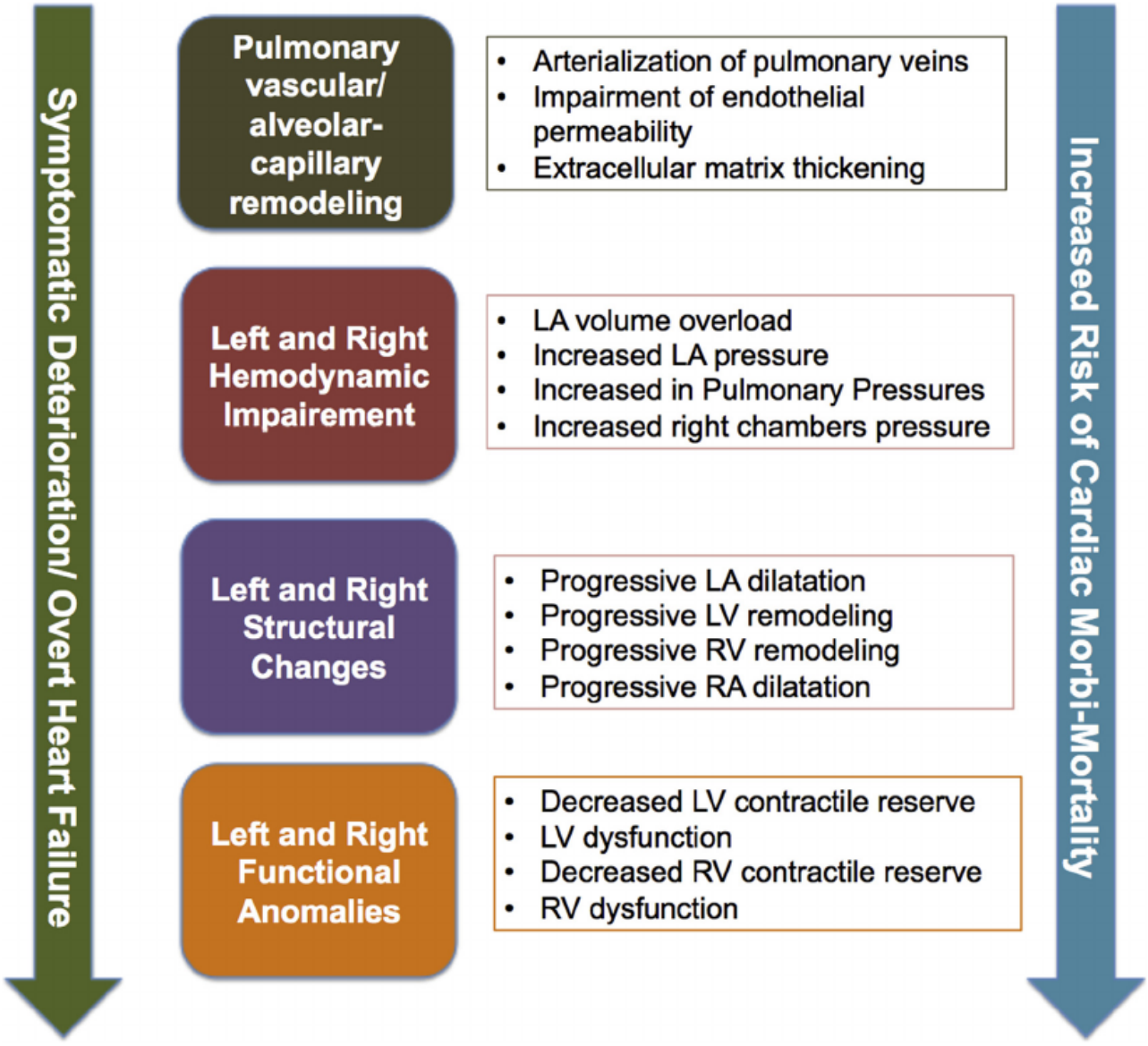

Fig. 1. Hemodynamic, structural, and functional changes induced by left-sided valvular.

Table 1
Echocardiographic features used for diagnosing pulmonary hypertension

Peak TR Velocity (sPAP)	Inferior VC	RV vs LV RA Area	Septal Wall	Pulmonary AT	Likelihood of PH
≤2.8 m/s (≤36 mm Hg)	≤2.1 cm Inspiratory collapse >50%	RV < LV RA area <18 cm^2	Normal	>105 ms	Unlikely/low
≤2.8 m/s (≤36 mm Hg)	>2.1 cm Inspiratory collapse <50%	RV ≥ LV RA area ≥18 cm^2	Flattening Abnormal septal motion	<105 ms	Intermediate
2.9–3.4 m/s (37–50 mm Hg)	≤2.1 cm Inspiratory collapse >50%	RV < LV size RA area <18 cm^2	Normal	>105 ms	
2.9–3.4 m/s (37–50 mm Hg)	>2.1 cm Inspiratory collapse <50%	RV ≥ LV RA area ≥18 cm^2	Flattening Abnormal septal motion	<105 ms	High
>3.4 m/s (>50 mm Hg)	Presence or not of supportive signs				

Other supportive signs are: pulmonary artery diameter greater than 25 mm, early diastolic pulmonary regurgitation velocity greater than 2.2 m/s.

Abbreviations: AT, acceleration time; RA, right atrial; sPAP, systolic pulmonary arterial pressure; VC, vena cava.

47% to 65% in patients with symptomatic aortic disease.[10,11] Roselli and colleagues[12] found that 74% of patients with severe AS presented with moderate (sPAP from 35 to 50 mm Hg) to severe (sPAP >50 mm Hg) PH, as assessed by echocardiography. However, the level and the severity of PH depends more on diastolic burden that the severity of AS.[10,13]

The presence of PH is a sign of advanced disease stage. It has been found that moderate to severe PH was associated with poor prognosis in cases of conservative therapy.[14] Indeed, several studies identified elevated PH at baseline as an independent predictive factor for early and late mortality after aortic valve replacement (AVR), whereas patients with normal PH at baseline presented a good prognosis.[15] Melby and colleagues[11] showed that patients with PH had a higher risk of operative mortality than without PH (5.4% vs 9.3%; $P = .02$). Interestingly, the degree/level of preoperative PH seemed to be associated with the postoperative survival rates. Roselli and colleagues[12] demonstrated that patients with severe PH (sPAP >50 mm Hg) had the worst prognosis (31% 10-year survival). Barbarsh and colleagues[16] found similar results in case of transcatheter aortic valve implantation (TAVR): severe PH at baseline is a predictive factor of mortality at 1 year after performing TAVR in a group of 415 patients with symptomatic AS. It has been demonstrated that PH may be reversible, at least partially, because remodeling of pulmonary vasculature and may decrease after AVR or TAVR,[12] in particular in patients with higher preoperative PCWP.[14] Nevertheless, persistent PH after procedure is associated with adverse outcomes.[11]

Although preoperative PH was clearly associated with early and late postoperative morbidity and mortality, actual recommendations consider resting PH as a trigger for AVR or TAVR.[17,18] Optimal timing of AVR or TAVR in asymptomatic severe AS remains challenging.[2] Therefore, PH is often associated with symptoms and its presence might suggest hidden symptoms in apparently asymptomatic patents, classically in elderly patients with limited activities.[19] In practice, AVR should be considered in patients with PH at rest if confirmed by a right heart catheterization and if the risk of intervention is perfectly weighted.[17]

RESTING PULMONARY HYPERTENSION AND PRIMARY/SECONDARY MITRAL REGURGITATION

Primary and secondary mitral regurgitation (MR) are common causes of resting PH and its prevalence depends on MR severity, clinical status, and LV systolic function.[19] Ghoreishi and colleagues[20] reported significant PH (sPAP >50 mm Hg) in 20% to 30% of patients with severe primary MR and up to 64% in symptomatic patients

			mortality after intervention				
	Asymptomatic	6%	• Resting PH not associated with reduced survival • Significant relationship between resting SPAP and outcome exists	IIa (ESC)	55%	≈2-fold increase risk of cardiac event	—
Aortic regurgitation	Asymptomatic for long	16%–24%	Increased risk of events	—	—	—	—
Mitral stenosis	Asymptomatic for long	14%–33%	3-fold increased risk of death at 10 y	IIa (ESC)	>30%	—	—
Primary MR	Symptomatic	20%–30%	>2-fold increase in risk of postoperative death	—	—	—	—
	Asymptomatic	6%–30%	2-fold increase in risk of occurrence of symptoms	IIa (ESC; AHA/ACC)	≈50%	>3-fold increase in risk of occurrence of symptoms	—
Secondary MR	Symptomatic for most	37%–62%	≈1.4-fold increase in risk of death	—	40%	>5-fold increase in risk of death, involved in the pathogenesis of acute pulmonary edema	—

Abbreviations: AHA/ACC, American Heart Association/American College of Cardiology; ESC, European Society of Cardiology; MR, mitral regurgitation; sPAP, systolic pulmonary arterial pressure.

with New York Heart Association functional class III-IV. Greater than 40% of patients presenting with secondary MR and LV dysfunction experienced moderate-severe PH.[21,22] Resting PH may be also found in MR and preserved LV function.[23]

In cases of primary MR, it has been previously demonstrated that PH at baseline was a powerful predictor of poor outcomes in terms of survival, heart failure symptoms, LV function, and LV remodeling whatever initial LV function or clinical status.[20,22,24,25] In patients with severe primary MR and preserved LV function, initial PH was associated with postoperative LV dysfunction (LV ejection fraction [LVEF] <50%). Barbieri and colleagues[24] reported in a large study that PH was a strong independent predictive factor of all-cause mortality, cardiovascular mortality, and heart failure in degenerative MR. Le Tourneau and colleagues[26] found similar results and suggested that pre-existing PH doubled the risk of postoperative mortality or heart failure after adjustment for cofactors at 8 years of follow-up. Mentias and colleagues[27] showed a greater relationship between the level of pre-existing PH and reduced postoperative survival. Previous data supported that early surgery might be beneficial in patients with PH whatever LV function or clinical status. Resting PH (sPAP >50 mm Hg) has been considered as a determinant criterion to trigger mitral valve repair in patients presenting with primary severe MR and no LV dysfunction or dilatation according to international recommendations (class IIa indication).[17]

In cases of secondary MR, similar results have been found. Resting PH was an independent predictive factor of death and congestive heart failure.[22,28] Miller and colleagues[22] reported a 30% increase of mortality in patients with PH as compared with those without PH, after adjustment for MR severity, clinical status, and LV systolic and diastolic function. Nevertheless, management of patients with secondary MR is still challenging in case of severe asymptomatic MR.[2,17]

RESTING PULMONARY HYPERTENSION AND MITRAL STENOSIS

The prevalence of PH in mitral stenosis (MS) is related to MS severity and clinical status and varies ranging from 14% to 33% for moderate PH and 5% to 9.6% for severe PH.[29,30] PH is closely associated with heart failure symptoms and recent studies confirmed the prognostic value of PH in MS.[2,31] Yang and colleagues[32] suggested that moderate and severe PH was associated with adverse outcomes in MS after adjustment of confounding factors. Similarly, Fawzy and colleagues[33] determined that severe PH (sPAP >60 mm Hg) was associated with higher risk of cardiovascular events at midterm follow-up after percutaneous balloon. Patients presenting with MS and moderate-severe PH had a three-fold increased hazard ratio of death at 10 years compared with patients with normal-moderate PH (sPAP from 35 to 44 mm Hg).[34] Death resulted in most from congestive heart failure, acute pulmonary edema, and RV heart failure.[2] PH is partially reversible after mitral valvular replacement. Parvathy and colleagues[35] explained that not only did PH decrease after surgery but its regression was in concert with improvement of RV and LV remodeling (except LA enlargement) and reduction of pulmonary vascular resistance. Pathologic changes might take longer to resolve and differ in time and in degree from relative preoperative PH.

There is no doubt that surgery or percutaneous balloon is recommended for symptomatic significant MS (valve area <1.5 cm^2).[17] However, the role of resting PH in management of mild or asymptomatic MS differed according to European and American guidelines. The American guidelines propose to refer patients for surgery or percutaneous balloon before the progression of severe PH,[36] whereas the European guidelines recommend to warrant an annual follow-up for patients presenting with symptomatic moderate MS (surface area >1.5 cm^2 and mean transmitral gradient <5 mm Hg) and to perform percutaneous balloon in selective asymptomatic patients with high risk of decompensation.[17]

RESTING PULMONARY HYPERTENSION AND AORTIC REGURGITATION

Aortic regurgitation (AR) is defined by a diastolic reflux of blood from aorta to LV. PH appears at advanced stage in natural history of AR, because LV has the ability to adapt to pressure and volume overload.[37] With time, LV volume increases and LV systolic function decreases with a decrease in LV diastolic compliance and an increase in LV filling pressure, which leads to increased sPAP.

The prevalence of PH in AR is, however, less documented. Severe PH (sPAP >60 mm Hg) was reported in 16% to 24% of patients with severe chronic AR.[38,39]

The prognostic value of resting PH is not completely elucidated. In a recent retrospective study including 506 patients with severe AR, Khandhar and colleagues[38] showed that severe PH was associated with LV dysfunction and functional MR and returned to normal in most cases after surgery. AVR was an independent predictor of

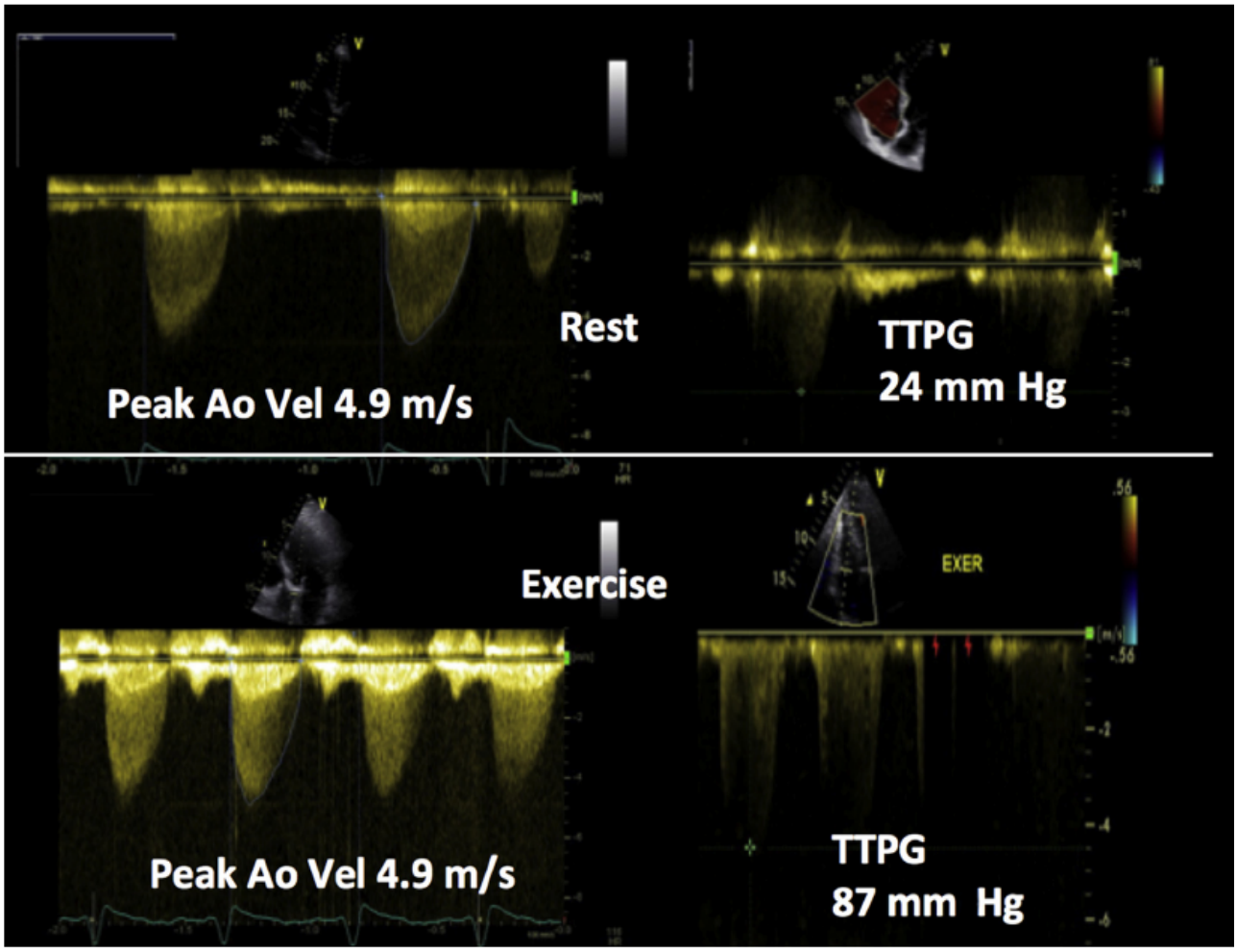

Fig. 2. Example of dynamic increase in systolic pulmonary arterial pressure during exercise in a patient with severe aortic stenosis (peak aortic jet velocity >4 m/s). Ao Vel, aortic jet velocity; TTPG, transtricuspid pressure gradient.

better survival at 5 years follow-up in patients with both severe chronic AR and severe PH. Consistently with previous data, Varadarajan and colleagues[40] described that 35% of patients with severe AR had TR greater than 2. TR was related to sPAP (PH was present in 25% of patients with TR >2, whereas only 8% in patients with mild TR). AVR in this subgroup was associated with a better 5-year survival (78% vs 42%; $P<.001$), despite higher PH.

However, PH plays a modest role in the current management of AR according to recommendations. PH in AR should be considered as a marker of limited functional capacity, which might encourage clinicians to propose AVR.[2]

EXERCISE PULMONARY HYPERTENSION AND VALVULAR HEART DISEASE

Resting PH is common in severe and symptomatic VHD and more rarely reported in asymptomatic patients (**Figs. 2** and **3**).[19] Nevertheless, patients can remain asymptomatic for a prolonged period of time at early stages of VHD and develop either exercise-related symptoms, such as dyspnea, before displaying heart failure. Symptoms at exercise are related to increased sPAP secondary to the increment of LV filling pressure in relation to advanced grade of diastolic dysfunction, severity of VHD, and RV function adaptation capacity and pulmonary vascular function.[2] Exercise echocardiography should therefore contribute to unmask patients with hidden symptoms, revealing moderate or severe VHD. It has been suggested that exercise echocardiography was a useful tool to screen exercise-induced PH (EIPH) and to identify patients with asymptomatic VHD at rest and higher risk of further worsening.[25] Previous study also suggested that the kinetic of changes of exercise PAP were a marker of adverse outcomes in VHD rather than the level of exercise PAP.[41]

It was demonstrated that exercise echocardiography improved the risk stratification in asymptomatic AS with preserved LV function.[42,43] Lancellotti and colleagues[43] found that EIPH (sPAP >60 mm Hg) was present in 55% of patients with severe AS and normal LVEF. After a

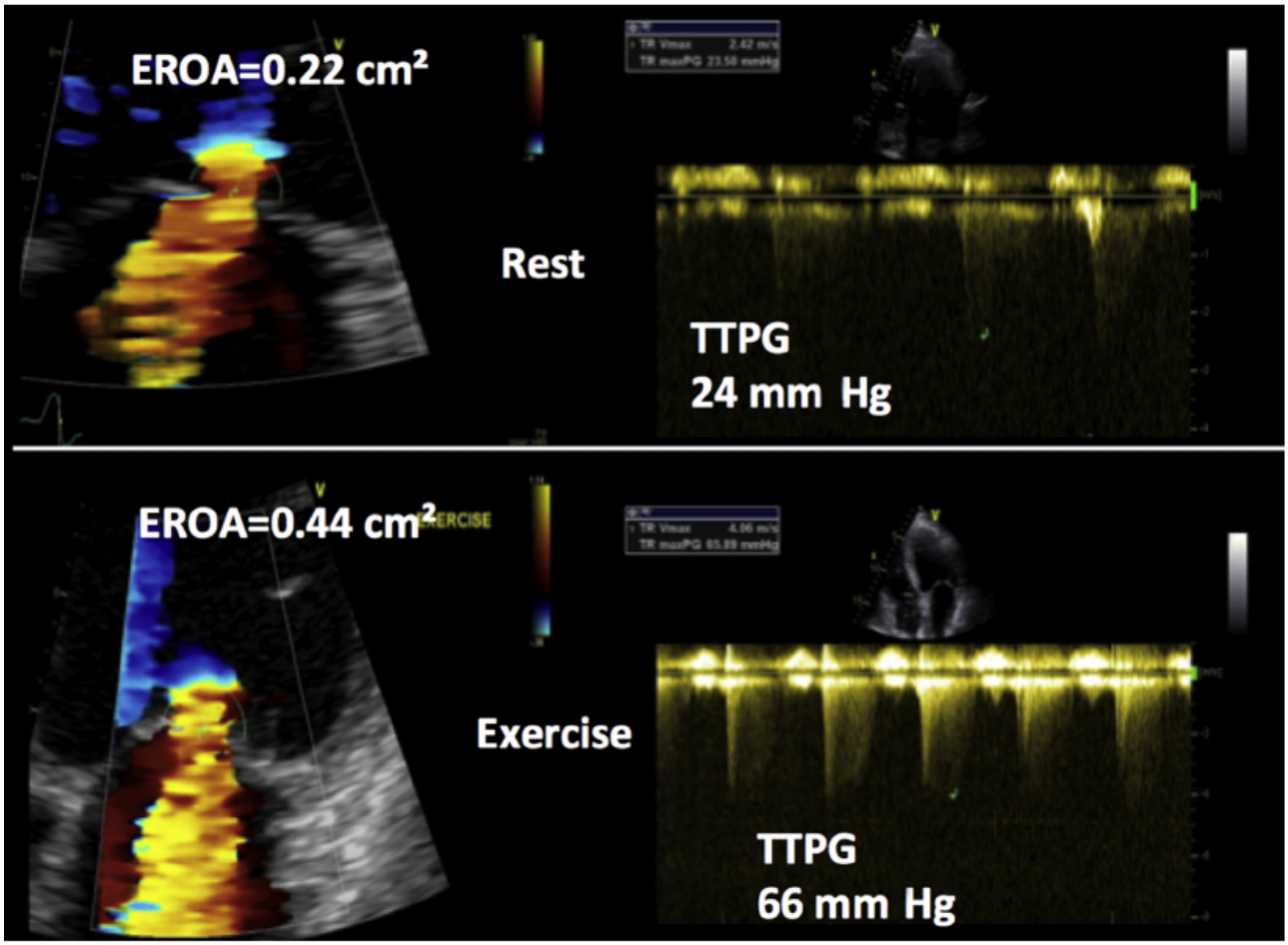

Fig. 3. Example of dynamic increase in systolic pulmonary arterial pressure and in mitral regurgitation severity during exercise in a patient with secondary mitral regurgitation and left ventricular systolic dysfunction. EROA, effective regurgitant orifice; TTPG, transtricuspid pressure gradient.

mean follow-up of 19 ± 11 months, EIPH was independently associated with a two-fold increase risk of cardiac events, even after adjustment with demographic data, resting PH, and other exercise echocardiographic parameters. EIPH should help to individualize a subgroup of high-risk patients with asymptomatic AS. Surgery might be reasonable in case of increase greater than 20 mm Hg, whereas a closer follow-up should be warranted for patients without EIPH.[2]

EIPH was more frequent in asymptomatic patients with primary MR and preserved LV function and size, than resting PH. Magne and colleagues[44] described for the first time EIPH in 78 patients with moderate and severe primary MR. Only 20% of patient with EIPH did not develop symptoms after mean follow-up 19 months. A cut-off value of 56 mm Hg for EIPH was the best predictor of symptoms. More recently, Kusunose and colleagues[45] suggested that the combination of EIPH (sPAP >54 mm Hg) and exercise-induced RV dysfunction (tricuspid annular plane systolic excursion (TAPSE) <19 mm) was a better predictor of worst outcome that EIPH alone in patients with asymptomatic degenerative MR. Exercise RV dysfunction should be taken into account with EIPH to predict outcomes in asymptomatic patients with primary MR. In addition, EIPH was a predictive factor of cardiac events after MV repair. To summarize, asymptomatic patients with primary moderate and severe MR and EIPH greater than 60 mm Hg might be referred to surgery.

The prevalence of EIPH was estimated at 40% in patients with secondary MR whatever LV function.[46] Dynamic MR and subsequent dynamic PH was a main predictive factor of worsening heart failure and mortality in patients with chronic LV dysfunction[47] and the established cutoff value for the increase in sPAP is 21 mm Hg.[48] Surgery might be recommended in patients with EIPH, exercise-induced MR, and planned coronary artery bypass. In the absence of surgical decision, a closer follow-up should be warranted.[2]

RIGHT VENTRICULAR FUNCTION AND AORTIC STENOSIS

There are limited data regarding the prevalence of RV dysfunction in AS. Galli and colleagues[49] found RV dysfunction (assessed by TAPSE

<17 mm) in 48 of 200 patients (24%) presenting with severe AS. Similarly, Koifman and colleagues[50] reported 24% of RV dysfunction in a larger study included 606 patients with severe AS undergoing TAVR.

Several mechanisms leading to RV dysfunction have been determined. As classically described in the VHD model, LV remodeling contributed to the increase of LV end-diastolic pressure and of PCWP and RV dysfunction resulted directly from increased sPAP at final stages.[51] Indeed, Galli and colleagues[49] demonstrated a main correlation between LV systolic function and RV performance, related to RV-LV interdependence, whereas sPAP was not a determinant predictor of RV function. They suggested that the increase of sPAP noticed 1 year after AVR or TAVR might be the consequence of irreversible structural damage of RV function and morphology, because significantly RV dilatation at advanced RV failure exceeded adaptive stage. Before irreversible damage, RV function and size may improve after TAVR.[50]

Data on the impact of RV function on outcomes are limited. Galli and colleagues demonstrated that a biventricular dysfunction (LVEF <50% and TAPSE <17 mm) was a main predictor of mortality in patients with severe AS independent of the strategy of treatment chosen (hazard ratio, 4.08 [1.36–12.22]; $P = .012$), whereas RV dysfunction alone was not a significant prognostic indicator. In patients with AS referred to surgical AVR, impaired RV function was a known adverse prognostic factor,[8] whereas in patients with severe AS undergoing TAVR, Koifman and colleagues[50] did not find a significant association between RV dysfunction (assessed by TAPSE <17, s' <9.5 cm/s, and fractional area change <0.35) and mortality. In contrast, Testa and colleagues[52] identified severe RV dilatation and dysfunction (TAPSE <10 mm) as independent predictors of 1-year mortality in a larger study including patients with severe AS undergoing TAVR. Several investigations emphasized the prognostic value of RV dilatation in patients with severe AS undergoing TAVR.[53,54] In addition, in patients with low flow/low gradient AS, RV function has been considered as marker of poor prognosis and should be take into account in the decision-making process.[55]

Nevertheless, whatever the method of assessment of RV function (quantitative, semiquantitative, or qualitative), RV dysfunction should be considered as a marker of poor prognosis in advanced VHD. The prognostic value and the implication of RV in the strategy management require further investigation.

RIGHT VENTRICULAR FUNCTION AND MITRAL REGURGITATION

RV impairment has been commonly observed in MR with or without LV dysfunction, in particular in patients with large regurgitation.[56] Le Tourneau and colleagues[57] reported a prevalence of 30% of RV dysfunction in patients with severe organic MR referred to surgery. In a small study including 60 patients with high-risk functional MR undergoing MitraClip, moderate and severe RV dysfunction (TAPSE <16 mm and S' <10 cm/s) was noticed in 37% of cases.[58]

RV dysfunction results from complex hemodynamic and structural changes. Downstream, chronic MR leads to LV volume overload with subsequent LV enlargement and a decrease of interventricular septal function, and upstream, induces an increase in LA pressure and with a subsequent increase in sPAP and PCWP.[5] It is speculated that RV dysfunction may be the consequence of RV pressure afterload. Nevertheless, several observations demonstrated that LV remodeling and septal function were the main determinant of RV function impairment, rather than PH.[57]

There are conflicting results regarding the prognostic value of RV function in functional MR. Isolated RV dysfunction has not been considered as a predictive factor of early and long-term mortality after surgery,[59,60] whereas biventricular dysfunction (LVEF <60% and right ventricular ejection fraction <35%) was associated with mid- and long-term poor outcome in patients with severe organic MR.[57] In a recent study including 117 patients with severe functional MR undergoing MitraClip, Kaneko and colleagues[61] demonstrated that preexisting RV dysfunction (TAPSE <16 mm) was significantly associated with all-cause mortality at 6 months follow-up despite a similar improvement of MR regardless of RV function (hazard ratio, 1.975 [1.026–3.805]; $P = .042$). Conversely, Godino and colleagues[58] reported that successful MitraClip procedure leads to a significant improvement of RV function even in patients with baseline RV dysfunction (TAPSE <16 mm and/or S' <10 cm/s). Reverse RV remodeling and reduced RV pressure overload by regression of MR and sPAP might explain its functional benefit. However, patients with baseline RV dysfunction presented more frequently with adverse events (stroke and heart failure) as compared with patients without RV dysfunction, as demonstrated by Neuss and colleagues.[62] Moreover, data are lacking regarding the prognostic value of RV dysfunction and long-term effects of persistent MR after valvulopathy correction on RV size and function.[63] Previous data showed that RV assessment should be useful

to improve management process but further investigations are required.

RIGHT VENTRICULAR FUNCTION AND MITRAL STENOSIS

RV function is frequently impaired in MS and remains an essential step in the development of clinical symptoms and in progression of the disease.[64,65] RV dysfunction may be attributed to two different mechanisms. First, RV impairment resulted from RV increased afterload and PH, caused by increased LA pressure and chronic pulmonary congestion.[7] Second, prior studies suggested that RV dysfunction was related to rheumatic involvement with subsequent myocyte necrosis, replacement by fibrosis, and calcification.[66,67] Nevertheless, PH seemed to be a determinant of RV impairment because changes in RV function depended on the degree of PH.[68]

Several studies demonstrated that RV function improved in the early period and the improvement seemed to continue at the late period after postoperative MS correction. Kumar and colleagues[69] analyzed RV strain and strain rate in 60 patients with severe MS before and after valvulopathy correction. They showed a significant increase in peak systolic global and segmental RV strain at basal, mid, and distal septum. There was no change in strain rate, because strain rate did not depend on load. They reported also a significant increase of TAPSE and RV fractional area change, whereas Tei index, s', and Isolumic acceleration were not affected by percutaneous valvuloplasty. On the contrary, Drighil and colleagues[70] suggested that Tei index and Fractional Area Change (FAC) improved immediately after Percutaneous balloon mitral valvuloplasty (PBMV) in 12 patients presenting with MS. These discordant results may be explained by the parameters used for RV function evaluation, which depended or not on load condition.[69] Nevertheless, it has been proved that the release of mitral valve obstruction by PBMV in patients in sinus rhythm led to decreased LA volume, which contributed to reduce chronic pulmonary congestion, PH, and RV afterload.[71] Pre-existing RV dysfunction did not prevent clinical improvement after PBMV.[72] Further investigations with larger populations are required to assess RV remodeling and long-term outcomes of patients with MS after percutaneous valvuloplasty.

RIGHT VENTRICULAR FUNCTION AND AORTIC REGURGITATION

Data are limited concerning RV impairment in AR. A study analyzed the consequences of LV volume overload in 40 patients with severe AR on RV diastolic function. Patients with elevated RV pressure (>30 mm Hg) were excluded. RV diastolic function was assessed by echocardiography, based on Doppler-derived indexes and RV isovolumic relaxation time. Dourvas and colleagues[73] found abnormal relaxation and RV filling along diastole related in case of severe AR and suggested that RV diastolic impairment was related to LV dilatation and ventricular interdependence. To the best our knowledge, the prognostic value of RV dysfunction in severe AR has not yet been studied.

SUMMARY

VHD is the most frequent cause of PH. Regardless of VHD type, resting PH is closely linked with clinical symptoms and poor prognosis. Even though resting PH remains a classic indication of VHD correction, a more aggressive approach might be proposed for selected patients with normal resting PAP but abnormal increase during exercise. Finally, because the left and right side of heart and lung vasculature formed a global unit, PAP, LV, and RV function are closely linked and should be considered and evaluated as a whole unit.

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