STATE-OF-THE-ART PAPER

Pulmonary Hypertension in Valvular Disease

A Comprehensive Review on Pathophysiology to Therapy From the HAVEC Group

Julien Magne, PhD,* Philippe Pibarot, DVM, PhD,† Partho P. Sengupta, MD, PhD,‡ Erwan Donal, MD, PhD,§ Raphael Rosenhek, MD, PhD,‖ Patrizio Lancellotti, MD, PhD¶#

ABSTRACT

Pulmonary hypertension (PH) is a classic pathophysiological consequence of left-sided valvular heart disease (VHD). However, as opposed to other forms of PH, there are relatively few published data on the prevalence, impact on outcome, and management of PH with VHD. The objective of this paper is to present a systematic review of PH in patients with VHD. PH is found in 15% to 60% of patients with VHD and is more frequent among symptomatic patients. PH is associated with higher risk of cardiac events under conservative management, during valve replacement or repair procedures, and even following successful corrective procedures. In addition to its usefulness in assessing the presence and severity of VHD, Doppler echocardiography is a key tool in diagnosis of PH and assessment of its repercussion on right ventricular function. Assessment of pulmonary arterial pressure during exercise stress echocardiography may provide additional prognostic information beyond resting evaluation. Cardiac magnetic resonance is also useful for assessing right ventricular geometry and function, which provide additional prognostic information in patients with VHD and PH. (J Am Coll Cardiol Img 2015;8:83–99) © 2015 by the American College of Cardiology Foundation.

Pulmonary hypertension (PH) related to left heart disease represents group 2 of the new clinical classification of PH (1), and subgroup 2.3 is specifically dedicated to valvular heart disease (VHD). VHD is a frequent etiology of PH, which may result from multiple mechanisms such as an increase in pulmonary vascular resistance, pulmonary blood flow, or pulmonary venous pressure. The chronic rise in pulmonary arterial pressure (PAP) often leads to right ventricular (RV) pressure overload and subsequent RV failure. When present, PH is a marker of poor outcome in VHD. Assessment of the presence and severity of PH thus has an important role in the risk stratification and therapeutic management of VHD.

In this paper, we review all relevant studies reporting mechanism, prevalence, and impact on outcomes of PH in patients with left-sided VHD. The final selection of discussed studies was based on the authors' consensus regarding robustness of data, sample size, and quality of methodology.

DEFINITION

Definitive diagnosis of PH related to VHD is based on the following criteria: mean PAP ≥25 mm Hg (2)

From the *Cardiology Department, CHU Dupuytren and INSERM 1094, Faculté de Médecine de Limoges, Limoges, France; †Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec City, Québec, Canada; ‡Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York; §Cardiologie–CHU Rennes and LTSI-INSERM U 1099, Université Rennes-1, Rennes, France; ‖Department of Cardiology, Medical University of Vienna, Vienna, Austria; ¶University of Liège Hospital, GIGA Cardiovascular Sciences, Department of Cardiology, Heart Valve Clinic, CHU Sart Tilman, Liège, Belgium; and #GVM Care and Research, Bologna, Italy. All authors have reported that they have no relationships relevant to the content of this paper to disclose.

**ABBREVIATIONS
AND ACRONYMS**

AR = aortic regurgitation

AS = aortic stenosis

AVR = aortic valve
replacement

LA = left atrial/atrium

LV = left ventricular/ventricle

MR = mitral regurgitation

MS = mitral stenosis

PAP = pulmonary arterial
pressure

PCWP = pulmonary capillary
wedge pressure

PH = pulmonary hypertension

RA = right atrial

RV = right ventricular/ventricle

TR = tricuspid regurgitation

VHD = valvular heart disease

together with an abnormally high pulmonary capillary wedge pressure (PCWP) >15 mm Hg or left ventricular (LV) end-diastolic pressure >18 mm Hg in the context of significant VHD. When pulmonary venous congestion is the main determinant of PH, PH is named isolated post-capillary PH or pulmonary venous hypertension. In this case, the transpulmonary pressure gradient is <7 to 10 mm Hg and the pulmonary vascular resistance is <1.5 Wood Units. In the more advanced stage of the disease, combined post-capillary and pre-capillary PH can be observed (PCWP >15 mm Hg and trans-pulmonary pressure gradient ≥7 to 10 mm Hg or pulmonary vascular resistance >1.5 Wood Units) (3). This form of PH is considered "out of proportion" to the LV filling pressure and results from a mixed pathophysiology (passive venous transmission, reversible pulmonary arterial vasoconstriction, fixed pulmonary vascular remodeling).

PATHOPHYSIOLOGY

An increase in LV filling pressure and left atrial (LA) pressure leads to a passive rise in backward pressure of the pulmonary vein (**Figure 1**). Persistently elevated pulmonary venous pressure can favor fragmentation of the structure and result in "alveolar-capillary stress failure," accompanied by capillary leakage and acute alveolar edema. This acute phase is completely reversible, but long-term persistence of high pulmonary venous pressure may induce some degree of irreversible remodeling of the alveolar-capillary membrane, with excessive deposition of type IV collagen. In addition, chronic elevated pulmonary venous pressure progressively and passively increases PAP and concomitantly produces pathological changes in pulmonary veins (**Figure 1**) and arteries, leading to increased pulmonary vascular resistance (3). The pathophysiology of PH in VHD thus involves progressive structural alteration of the pulmonary vascular bed mediated by the potent vasoconstrictor endothelin-1 (4). An increase in pulmonary-arterial vasoconstriction and systolic PAP results into RV dilation and hypertrophy. The RV failure is associated with tricuspid annulus dilation and an increase in tricuspid regurgitation severity, which further acerbates RV dysfunction. At the decompensated phase, systolic PAP can decrease despite the increase in pulmonary vascular resistance, due to the fall in RV stroke volume related to advanced RV failure.

After treatment, the reversibility of PH depends on the type, severity, and chronicity of VHD, as well as the underlying pathophysiological adaptations. For instance, in mitral stenosis (MS), a rapid decrease in PAP is observed after relief of the stenosis, whereas a longer time could be required in other VHDs, especially when PH is linked to volume overload, as in mitral regurgitation (MR).

DIAGNOSTIC WORK-UP

Distinctive clinical signs and symptoms of left-sided VHD PH are orthopnea and paroxysmal nocturnal dyspnea, which are generally not features of other types of PH (5). However, patients can remain asymptomatic for a long time, which often delays the diagnosis. Signs of RV failure, such as peripheral edema, ascites, and syncope, are frequently observed at an advanced stage of the disease. Clinical tests frequently reveal findings suggestive of left-sided VHD PH: presence of significant VHD; pulmonary vascular congestion, pleural effusion, or pulmonary edema on chest x-ray or computed tomography; and LV/LA hypertrophy on electrocardiogram.

Although current European guidelines state that Doppler echocardiography does not measure PAP but gives only an estimate of it and that right heart catheterization is mandatory for the confirmation of a PH diagnosis, echocardiography remains key for the differential diagnosis and evaluation of consequences of PH and has a central role in the assessment of VHD. Furthermore, in this specific clinical setting and in the likely diagnosis of PH using echocardiography (**Table 1**), the requirement of invasive measurement of PAP could be debated. Nuclear imaging has little use in this setting except to rule out ischemic heart disease, detect viable myocardium, and evaluate ventricular function. Similar information can be obtained with cardiac magnetic resonance, the main role of which is to evaluate the consequences/causes of VHD. In some cases, invasive hemodynamic evaluation with right heart catheterization is required to confirm the diagnosis because echocardiography often underestimates the systolic PAP and does not provide an accurate assessment of PCWP (or mean PAP).

RESTING ECHOCARDIOGRAPHY. In patients with confirmed or suspected PH, echocardiography is helpful for: 1) detection of increased right chamber pressure; 2) evaluation of RV changes as a consequence of increased afterload; 3) assessment of LV size and function; and 4) measurement of systolic PAP.

PH can be reasonably excluded when the following parameters are within the normal range or absent (**Table 1**, **Figure 2**) (6-8): LV and RV size and function
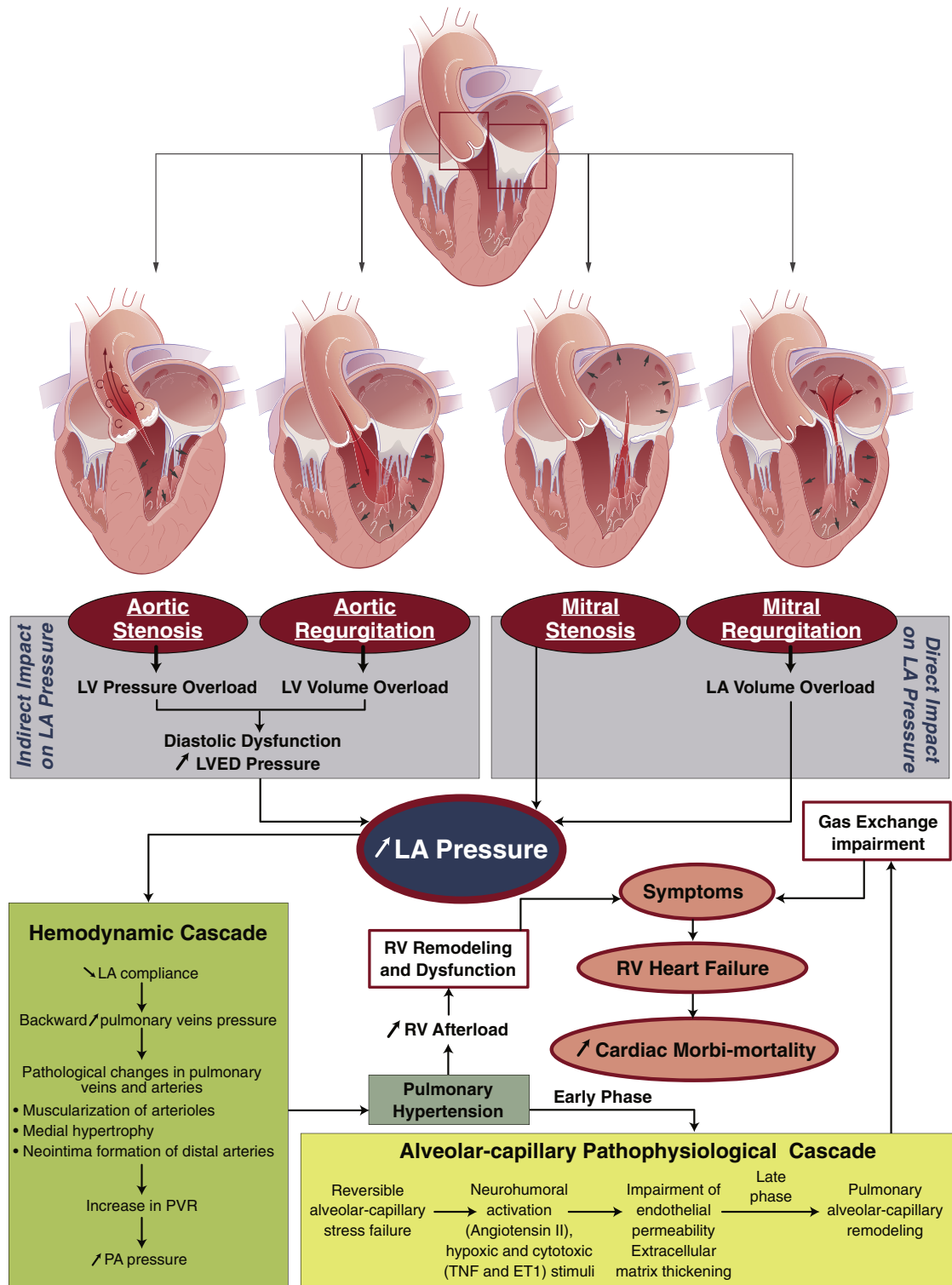
FIGURE 1 Mechanisms and Pathophysiology of PH in Patients With VHD

ET1 = endothelin-1; LA = left atrium; LV = left ventricle; LVED = left ventricular end-diastolic; PVR = pulmonary vascular resistance; PA = pulmonary arterial; PH = pulmonary hypertension; RV = right ventricle; TNF = tumor necrosis factor; VHD = valvular heart disease.

TABLE 1 Echocardiographic Features Diagnosing PH According to TR Peak Velocity and Complementary Supportive Signs of PH

sPAP Assessment		Supportive Echocardiographic Signs				
Peak TR Velocity	Estimated sPAP	Inferior VC	RV vs. LV	Septal Wall	Pulmonary AT	Presence of PH
≤2.8 m/s	≤36 mm Hg	Normal (≤2 cm) Normal inspiratory collapse (>>50%)	RV size < LV size	Normal	>100 ms	Unlikely (Class I, LOE: B)
≤2.8 m/s	≤36 mm Hg	Discordant findings				Low probability*
≤2.8 m/s	≤36 mm Hg	Dilated (>2 cm) Inspiratory collapse <50%	RV size ≥ LV size	Bowing; motion abnormalities	<100 ms	Possible (Class IIa, LOE: C)
2.9–3.4 m/s	37–50 mm Hg	Normal (≤2 cm) Normal inspiratory collapse (>>50%)	RV size < LV size	Normal	>100 ms	Possible (Class IIa, LOE: C)
2.9–3.4 m/s	37–50 mm Hg	Dilated (>2 cm) Inspiratory collapse <50%	RV size ≥ LV size	Bowing; motion abnormalities	<100 ms	High probability*
>3.4 m/s	>50 mm Hg					Likely (Class I, LOE: B)

*Indicates the lack of such a level of probabilities reported in the current guidelines (1). Reproduced with permission of the European Respiratory Society (7).

AT = acceleration time; LOE = Level of Evidence; LV = left ventricle; PH = pulmonary hypertension; RV = right ventricle; sPAP = systolic pulmonary arterial pressure; TR = tricuspid regurgitation; VC = vena cava.
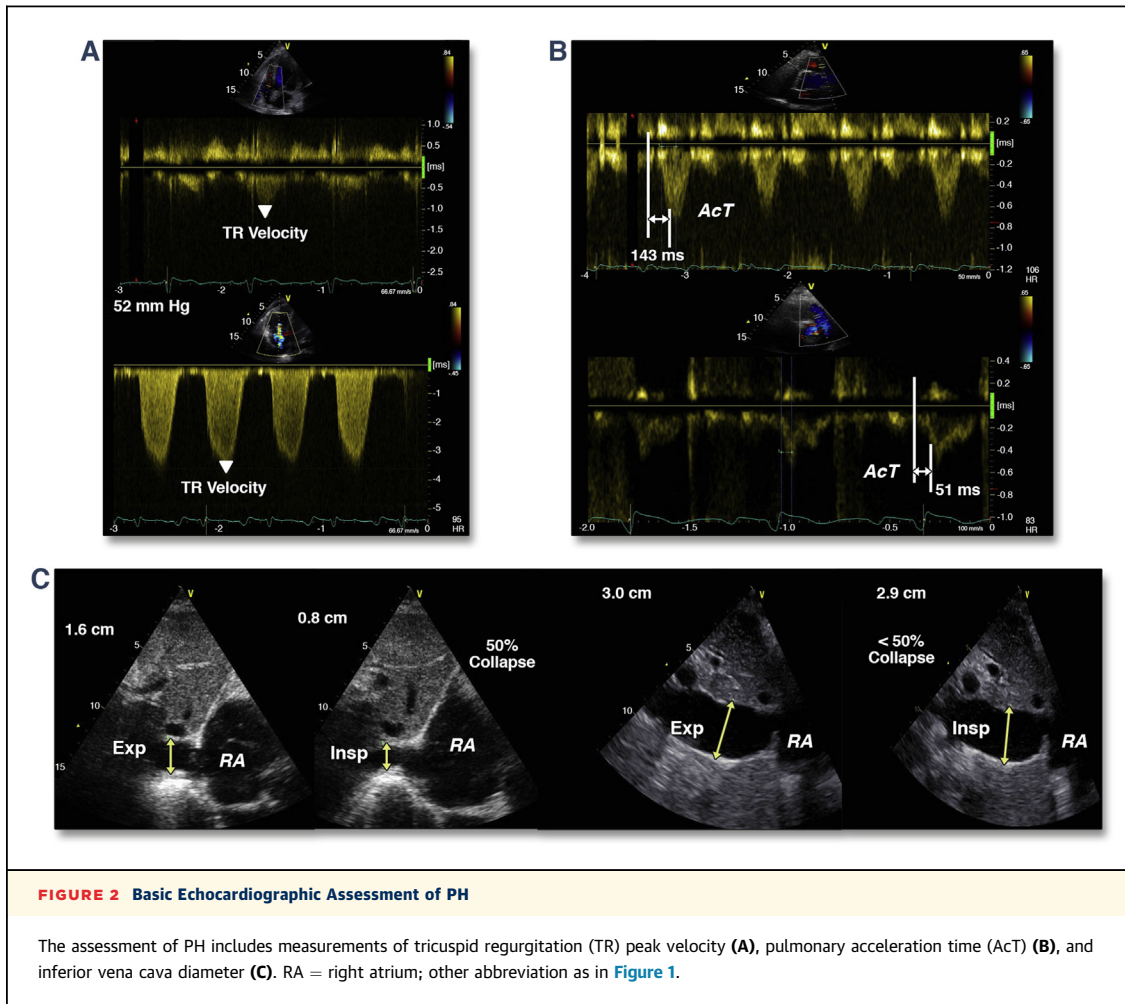
(including wall motion), intracardiac shunt, pericardial effusion, tricuspid regurgitation (TR) jet velocity (i.e., <2.8 m/s), inferior vena cava diameter (i.e., <2.1 cm), and pulmonary acceleration time (i.e., >100 ms). Nevertheless, if at least 1 of these parameters is found to be abnormal, or if several of these parameters are close to normal reference values, current expert consensus recommends performing a more advanced echocardiographic examination, including more quantitative assessment of cardiac hemodynamics and chamber sizes and function (**Figure 3**).

In patients with VHD, although there are overt limitations in some patients pertaining to the inability to detect TR and accurately measure its peak velocity, the most commonly used technique to estimate systolic PAP remains the direct measurement of peak TR jet velocity, which, according to the simplified Bernoulli equation (peak gradient $= 4v^2$), provides the derived RV systolic pressure. The systolic PAP is the sum of RV + right atrial (RA) pressures. The RA pressure may be derived from the inferior vena cava diameter and its changes during the respiratory cycle (6,7). Based upon the measurement of peak TR jet velocity and some basic echocardiographic features of PH, the following algorithm has been suggested to identify PH (**Table 1**): for a given RA pressure assumed at 5 mm Hg, systolic PAP ≤36 mm Hg = PH unlikely; systolic PAP >50 mm Hg = likely (Class I, Level of Evidence: B); and systolic PAP ≤36 mm Hg but with obvious echocardiographic signs of PH or systolic PAP 37 to 50 mm Hg = possible (Class IIa, Level of Evidence: C). In practice, it is reasonable to consider a systolic PAP ≥36 mm Hg (TR ≥2.8 m/s + RA pressure) as an appropriate threshold for PH. This should be lower in elderly patients and obese patients (6) because resting

physiological range of TR velocity–derived systolic PAP highly depends on these conditions. Of note, the estimation of systolic PAP using TR jet velocity is not appropriate for very severe/massive TR.

Despite all overt limitations, measurement of systolic PAP using Doppler echocardiography remains highly reproducible and, more importantly, closely associated with outcome.
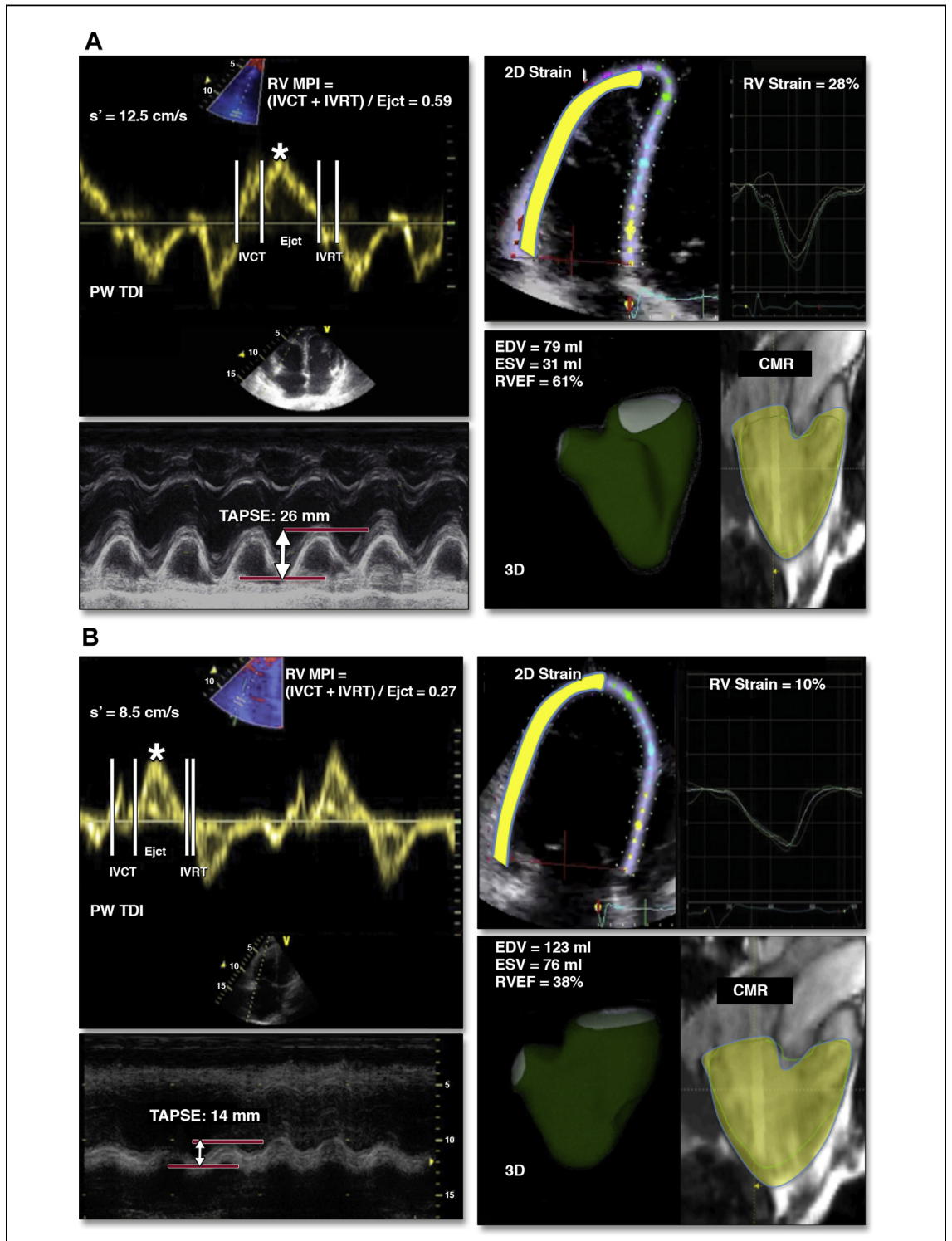
EXERCISE STRESS ECHOCARDIOGRAPHY. During exercise and secondary to the increase in oxygen demand, cardiac output increases more than 3- to 4-fold. The pulmonary vascular bed is a low-resistance high-compliance system. To accommodate the increase in flow and volume, the pulmonary vascular bed has the ability to recruit and distend pulmonary arterial vessels, leading to a drop in pulmonary vascular resistance and a moderate increase in PAP in response to an important increase in cardiac output (9). The magnitude of increase in systolic PAP during exercise depends on the ability to successfully recruit the pulmonary vasculature to accommodate increased blood flow with exercise, contribution of the reduction in cross-sectional area of the pulmonary circulation, reduction in pulmonary vascular compliance, increase in LA pressure in relation to the severity of diastolic dysfunction and VHD severity, and RV function adaptation. In VHD, systolic PAP at exercise does not simply reflect the increase in cardiac output, but development of exercise PH may be seen as an accurate marker of early, subclinical, and silent consequences of the disease. Indeed, exercise PH is frequently observed in asymptomatic patients with advanced age, more severe VHD, elevated resting and exercise LV filling pressures, and enlarged LA. Although asymptomatic at rest, patients

FIGURE 2 Basic Echocardiographic Assessment of PH

The assessment of PH includes measurements of tricuspid regurgitation (TR) peak velocity **(A)**, pulmonary acceleration time (AcT) **(B)**, and inferior vena cava diameter **(C)**. RA = right atrium; other abbreviation as in **Figure 1**.

with VHD and exercise PH often develop exertion dyspnea and became rapidly symptomatic during follow-up. Conversely, exercise systolic PAP provides useful information on individual patient outcome (10,11). Nonetheless, elevated exercise systolic PAP (i.e., >60 mm Hg) should be cautiously interpreted in regard to patient age, exercise workload, and cardiac output. Rather than peak exercise systolic PAP, the kinetic of exercise-induced changes in PAP, throughout the exercise test, seems to provide the most valuable information regarding pulmonary vascular function adaptation (12). Indeed, whereas progressive increase in PAP during exercise with end-stage development of exercise PH should not necessarily be labeled as abnormal, early and steep increases in PAP of >60 mm Hg at the first stages of exercise followed by a plateau may diagnose advanced disease (13). The former may be seen as a "normal" adaptation to exercise because healthy subjects may regularly exceed 60 mm Hg during exercise (14). The latter, however, is more frequently associated with exercise

RV dysfunction and occurrence of symptoms during the test.

SPECIFIC ISSUES. RV assessment. Owing to its accessibility, rapidity of acquisition, and cost, echocardiography is the first-line imaging modality to evaluate the RV. Nevertheless, cardiac magnetic resonance is now considered the gold standard for RV assessment. The basic evaluation of RV geometry should include the measurement of RV cavity dimensions and volumes and RV wall thickness, as well as the identification of wall morphological abnormalities. The simplest method used in clinical practice to screen for RV dilation is the measurement of RV end-diastolic and end-systolic areas and linear dimensions (RV basal and mid-cavity diameters and RV outflow tract proximal and distal diameters) using single echocardiographic planes (**Table 2**) (15). Measurement of RV wall thickness may help to identify hypertrophy. The normal RV has a wall thickness of <5 mm, as measured from the subcostal or parasternal long-axis views or corresponding cardiac magnetic resonance slices.

FIGURE 3   Advanced Echocardiographic Assessment of RV Function

Healthy patient **(A)** and patient with pulmonary hypertension secondary to left-sided mitral valve disease **(B)**. CMR = cardiac magnetic resonance; EDV = end-diastolic volume; ESV = end-systolic volume; IVCT = isovolumic contraction time; IVRT = isovolumic relaxation time; MPI = myocardial performance index; PW = pulsed wave; RVEF = right ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging; other abbreviation as in **Figure 1**.

The LV eccentricity index (i.e., the ratio of the LV anteroposterior to septolateral diameters in short-axis view), measured just slightly above the papillary muscles, is one of the parameters that can be used to detect changes in RV shape, providing quantitative assessment of septal flattening. In normal states, the LV eccentricity index is 1, both in systole and diastole.

By echocardiography, RV function can be evaluated using multiple parameters, among which the fractional area change, tricuspid annular systolic plane, and peak systolic tricuspid annular velocity are the most common (**Table 2**, **Figures 3A and 3B**). Three-dimensional (3D) echocardiography-derived RV ejection fraction is a global measure of RV systolic performance, which incorporates the contributions of both radial and longitudinal fibers, as well as the outflow tract. Accurate volume analysis independent of RV size and shape, without foreshortened views and geometric assumptions, ensures the superiority of real-time 3D echocardiography for RV size and function assessment over the conventional echocardiographic methods. Good correlation between real-time 3D and cardiac magnetic resonance imaging for calculating RV volumes and ejection fraction has been reported, and RV volumes calculated from 3D echocardiography have shown significantly better agreement and lower intraobserver and interobserver variability than 2D echocardiography. Real-time 3D echocardiography quantitation of RV end-diastolic volume was recently demonstrated to be feasible and superior to 2D in the subset of patients with primary PH. The capability to complement RV assessment with geometric data on tricuspid valve tenting in TR secondary to PH confirms the unique value of real-time 3D echocardiography to comprehensively evaluate patients with PH (16). Nevertheless, the inability to cooperate for breath-holding, arrhythmias, the larger footprint and size of matrix-array transducers, dependence on optimal acoustic quality, and need for specific training are among the drawbacks of 3D echocardiography. Currently, limited data are available regarding normal reference values for RV volumes and ejection fraction using real-time 3D echocardiography. In addition, 3D echocardiography tends to slightly underestimate RV volumes compared with cardiac magnetic resonance, despite similar RV ejection fraction estimation between the 2 methods (17).

For adequate measurement of RV volumes with cardiac magnetic resonance, the following features should be taken into account: correct identification of the tricuspid and pulmonary valve planes, correct delineation of endocardial borders in the heavily trabeculated apical segments, and correct definition of RV apex.

TABLE 2 Summary of Doppler Echocardiographic Parameters and Criteria Used for the Identification of RV Dilation and Dysfunction

	Threshold for Abnormal Value	Limitations
RV basal diameter	>41 mm	Dependent on probe rotation
RV mid-cavity diameter	>35 mm	Dependent on probe rotation; no validated reference point
RV base-to-apex diameter	>86 mm	Identification of the apical point; dependent on probe rotation
RV free wall thickness (subcostal or PSLA view)	>5 mm	Endocardial border delineation (trabeculations)
LV eccentricity index	>1	
Fractional area change	<35%	Endocardial border delineation
TAPSE	<17 mm	Dependent on alignment with RV free wall; less accurate in case of free TR
Peak S′-wave velocity of the tricuspid annulus	<9.5 cm/s	Dependent on alignment with RV free wall; less accurate in case of free TR
Myocardial performance index	PW Doppler <0.43, PW TDI <0.54	Angle dependent
RV free wall longitudinal strain	<−20%	Dependent on image quality (angle dependency of TDI)
3D echocardiography		
RV ejection fraction	<44%	Dependent on image quality; endocardial border delineation
RV end-diastolic volume	>87 (M) or 74 (F) ml/m^2	
RV end-systolic volume	>44 (M) or 36 (F) ml/m^2	

Reference ranges are derived from the Recommendations on Chamber Quantification published jointly by the American Society of Echocardiography and the European Association of Cardiovascular Imaging (8).

3D = 3-dimensional; F = female threshold; M = male threshold; PSLA = parasternal long axis; PW = pulsed wave; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging; TR = tricuspid regurgitation; other abbreviations as in **Table 1**.

TR assessment. Secondary TR is common in patients with left-sided VHD. It is characterized by structurally normal leaflets and is due to annular dilation and/or leaflet tethering (18). TR severity assessment requires the integration of multiple qualitative and quantitative parameters often derived from 2D/3D transthoracic Doppler echocardiography. Large coaptation defects or tricuspid valve flails indicate severe TR. A peak tricuspid E-wave velocity >1 m/s by pulsed-wave Doppler in the absence of tricuspid stenosis or systolic hepatic flow reversal is also suggestive of severe TR. A vena contracta width of >7 mm and/or a proximal isovelocity surface area radius of >9 mm at a Nyquist limit of 28 cm/s (effective regurgitant orifice area of >40 mm^2 and regurgitant volume greater >45 ml) indicate severe TR. Conventionally, a significant tricuspid annular dilation by 2D echocardiography is defined by a diastolic diameter in a 4-chamber view of ≥40 mm or >21 mm/m^2. Significant leaflet tethering is suggested by a coaptation distance of >8 mm in a 4-chamber view in mid-systole. Three-dimensional echocardiography can overcome the common limitations of 2D examinations. Actually, the regurgitant orifice shape, as well as that of the tricuspid annulus, is not circular but

elliptical. With 3D echocardiography, the actual geometry of the flow convergence and the tricuspid annulus can be evaluated without any geometric assumptions. To date, data derived from 3D echocardiography are still limited. When the imaging quality is poor, cardiac magnetic resonance can be used to evaluate the severity of TR.

AORTIC STENOSIS

PREVALENCE. The prevalence of PH varies considerably over studies (19-24), according to patient selection criteria and the threshold used to define PH (Table 3). Resting PH has been reported echocardiographically in up to 15% to 30% (>19% mild: >10% to 45% moderately elevated systolic PAP 30 to 50 mm Hg; 15% to 30% severe: systolic PAP >50 mm Hg; and 19% very severe: systolic PAP >60 mm Hg) of patients with symptomatic aortic stenosis (AS) (22). In a catheterization-based study (n = 2,185; various degrees of AS; unpublished data) (Figure 4), 23% of patients had mild PH (mean PAP >25 mm Hg), 8.9% moderate PH (mean PAP >35 mm Hg), and 4.8% severe PH (mean PAP >45 mm Hg). Its prevalence, however, was as low as 6% in "truly" asymptomatic

patients (11). In this latter group, the impact of severe AS and associated LV diastolic function (25) is generally well counterbalanced by LA compliance and/or pulmonary vascular compliance/resistance.

IMPACT ON OUTCOME. The most frequent features of PH in patients with AS are impaired LV function, concomitant MR, and increased LV end-diastolic pressure (26). The degree of PH is mainly related to the diastolic burden (i.e., LV end-diastolic pressure, LA size, and compliance), whereas it is weakly correlated with the extent of systolic dysfunction and not to the AS severity.

When conservatively treated, moderately elevated or worse systolic PAP is a marker of poor outcome (26-28). Nonetheless, evidence of impaired outcome of patients with PH receiving aortic valve replacement (AVR) is weaker. Melby et al. (24) reported a graded relationship between the levels of pre-operative systolic PAP and reduced post-operative survival, regardless of age, LV ejection fraction, symptoms, diabetes, or renal failure. These results contrasted with data from Cam et al. (27), showing no independent impact of pre-operative mean PAP on post-operative survival. Nevertheless, early

TABLE 3 Summary of the Prevalence and Prognostic and Therapeutic Implications of Patients With PH and VHD

VHD	Condition	Overall prevalence of PH*	Impact of PH on Outcome	ACC/AHA Patient Class	ACC/AHA	ESC	(Ref. #)
					Guidelines for Surgery		
Aortic stenosis	Rest	15%–30%	Controversial; ≈2-fold increase of 1 year in mortality after intervention	—	None	None	(20,21,24,27,84)
	Exercise	55%	≈2-fold increase in risk of cardiac event in asymptomatic patients	—	None	None	(11)
Mitral stenosis	Rest	>40%	Event-free survival: 77% at 10 years and 41% at 15 yrs	—	None	Class IIa, LOE: C	(36,40)
	Exercise	79%		Stage B	Mitral valve area >1.5 cm² and pulmonary arterial wedge pressure during exercise >25 mm Hg: Class IIb, LOE: C*	None	(43)
Aortic regurgitation	Rest	>25%	Controversial	—	None	None	(45,46)
	Exercise			—	None	None	
Primary MR	Rest	20%–30% and 6%–30% in asymptomatic patients; <20% in asymptomatic patients with preserved LVEF	>2-fold increase in risk of post-operative death	Stage C1	Class IIa, LOE: B	Class IIa, LOE: C	(48,52)
	Exercise	≈50%	>3-fold increase in risk of occurrence of symptoms	—	None	Class IIb, LOE: C	(10,54)
Secondary MR	Rest	37%–62%	≈1.4-fold increase in risk of death	—	None	None	(51,57,59,85)
	Exercise	40%	>3-fold increase of cardiac event; >5-fold increase in risk of death; involved in pathogenesis of acute pulmonary edema	—	None	None	(64,66,67)

*PH was defined as systolic PAP >50 mm Hg at rest and >60 mm Hg during exercise.

ACC/AHA = American College of Cardiology/American Heart Association; ESC = European Society of Cardiology; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; VHD = valvular heart disease; other abbreviations as in Table 1.

improvement in mean PAP following surgery was predictive of outcome.

Severe PH mainly affects in-hospital survival and morbidity, whereas 5-year survival is affected similarly by any degree of PH (24). In transcatheter aortic valve implantation registries, severe PH (systolic PAP >60 mm Hg) is also a powerful predictor of 1-year mortality (**Table 3**) (29). Interestingly, PH is reversible, at least partially, in most patients after AVR or transcatheter aortic valve implantation, which may lead to a more favorable long-term outcome (28). Such an improvement seems greater in patients with higher pre-operative PCWP (27). The frequent retrospective design of all of these studies explain the lack of the precise cause of death being available, and the mechanisms leading to post-operative fatal events in patients with PH remain unclear. Nonetheless, a high rate of atrial fibrillation, stroke, and renal failure have been post-operatively observed in these patients. Limited data are available in patients with asymptomatic AS. However, when present, PH may reflect an already advanced disease process (30).

MANAGEMENT OF AS AND PH AT REST. In the recent European Society of Cardiology (ESC) (31) and American College of Cardiology/American Heart Association (32) guidelines, AVR was recommended as a Class I indication in patients with severe AS and symptoms at rest or exercise and/or LV dysfunction (LV ejection fraction <50%). Although peri-operative morbidity and mortality increase significantly in the presence of PH, this factor is not considered a trigger for AVR. However, when present, PH is often associated with symptoms that are frequently underreported or subtle, especially in elderly subjects. The average reported survival of patients with symptomatic AS is <2 years. Hence, the presence of PH in apparently asymptomatic patients should raise suspicion about hidden symptoms and might represent an additional incentive for early selective surgery; however, further investigation will be required.

RISK STRATIFICATION IN AS: THE ROLE OF EXERCISE PH. Exercise stress echocardiography is very useful in patients with AS (33). The prognostic value of exercise-induced changes in the mean aortic pressure gradient has been demonstrated in 2 studies (34,35), and an increase of >20 mm Hg is a ESC Class IIb indication for surgery in asymptomatic patients with preserved LV ejection fraction. Some studies also showed that assessment of systolic PAP during exercise provides incremental prognostic value beyond that obtained from the exercise changes in transvalvular gradient. Exercise PH (systolic PAP >60 mm Hg) is more frequent than resting PH (55%
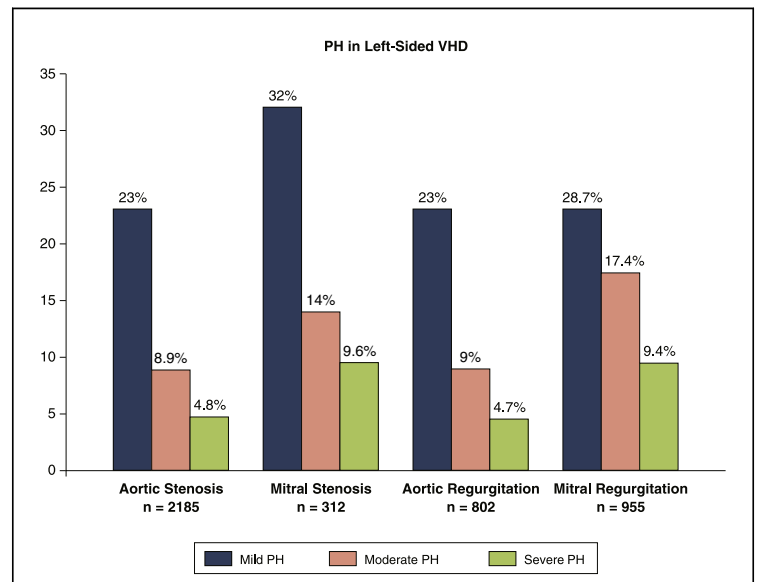

FIGURE 4 **Prevalence of Mild, Moderate, and Severe PH According to Left-Sided VHD**

The presence and severity of PH was derived from right heart cardiac catheterization and the measurement of mean pulmonary arterial pressure (mPAP). Mild, moderate, and severe PH were defined as mPAP >25 mm Hg, 35 mm Hg, and 45 mm Hg, respectively. Abbreviations as in **Figure 1**.

vs. 6%, respectively) and is mainly determined by male sex, resting systolic PAP, and exercise LV parameters of diastolic burden (i.e., LV end-diastolic volume, LA area, and e′-wave velocity) (11). In the study of Lancellotti et al. (11), exercise PH was associated with an alarming rate of cardiac death (12%) and reduced overall cardiac event-free survival in patients with asymptomatic severe AS. Exercise PH doubled the risk of cardiac events in these patients (**Figure 5A**) and had an incremental prognostic value beyond AS severity parameters (i.e., peak aortic jet velocity <4 m/s). Patients with exercise PH require a closer follow-up to rapidly identify the onset of symptoms. When peak aortic jet velocity is >4 m/s and exercise PH is observed, patients might be referred for elective AVR. Conversely, in the absence of exercise PH, patients can be followed up safely.

MITRAL STENOSIS

PREVALENCE. MS, when moderate to severe, is generally associated with a variable degree of PH (**Table 3**). The exact prevalence of moderate (14% to 33%) and severe (5.0% to 9.6%) PH varies widely according to studies, the spectrum of MS severities, and symptomatic status (36–38). Derived from cardiac catheterization (n = 312; various degrees of MS; unpublished data) (**Figure 3**), 32% of patients had mild
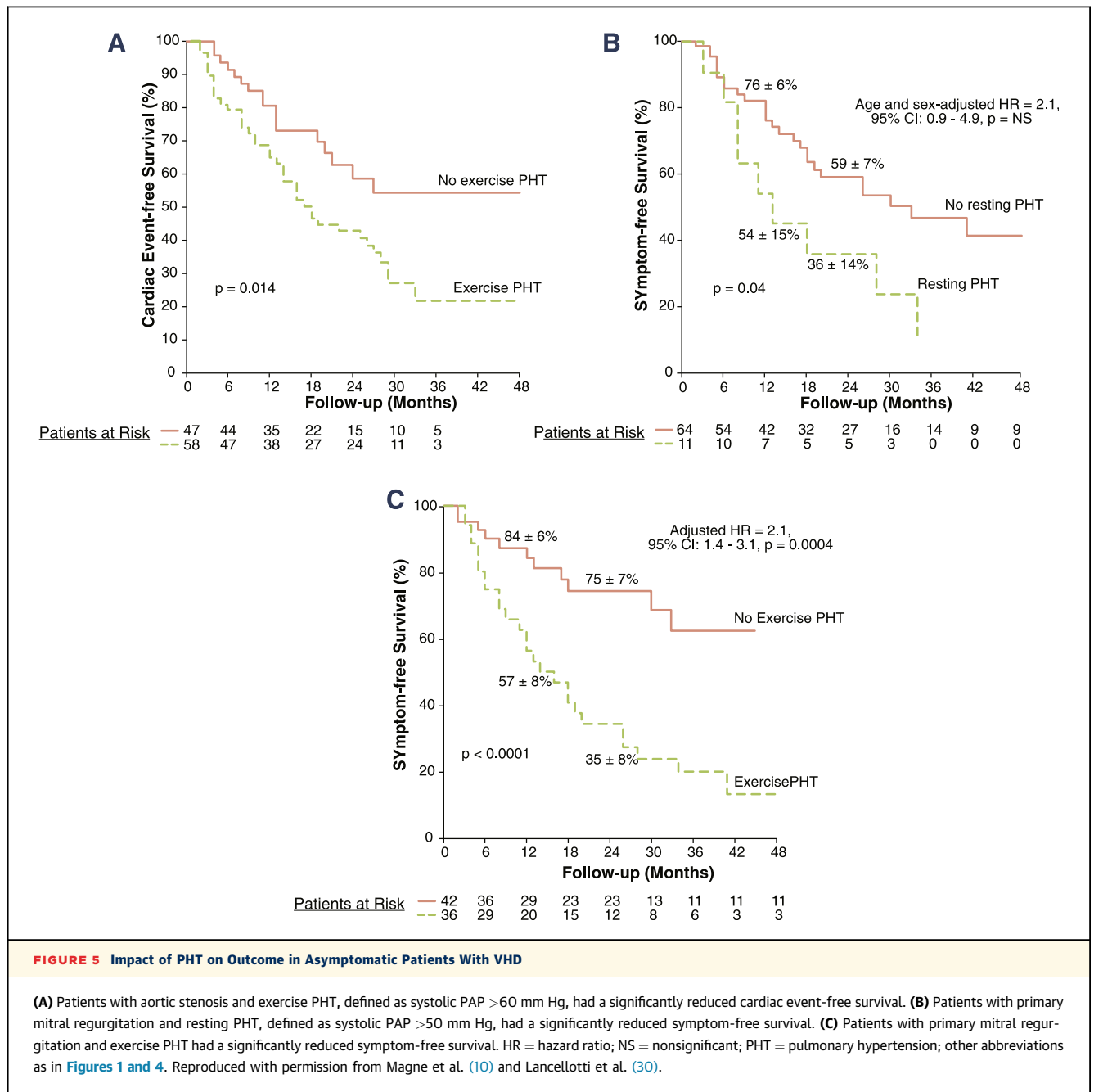
FIGURE 5 **Impact of PHT on Outcome in Asymptomatic Patients With VHD**

(A) Patients with aortic stenosis and exercise PHT, defined as systolic PAP >60 mm Hg, had a significantly reduced cardiac event-free survival. **(B)** Patients with primary mitral regurgitation and resting PHT, defined as systolic PAP >50 mm Hg, had a significantly reduced symptom-free survival. **(C)** Patients with primary mitral regurgitation and exercise PHT had a significantly reduced symptom-free survival. HR = hazard ratio; NS = nonsignificant; PHT = pulmonary hypertension; other abbreviations as in **Figures 1 and 4**. Reproduced with permission from Magne et al. (10) and Lancellotti et al. (30).

PH (mean PAP >25 mm Hg), 14% moderate PH (mean PAP >35 mm Hg), and 9.6% severe PH (mean PAP >45 mm Hg).

IMPACT ON OUTCOME. The natural history of patients with untreated MS was defined from studies in the 1960s. Due to the strong association with symptoms, the presence of PH in patients with MS is associated with markedly worse outcomes. However, limited data are available from modern series. In 2005, Maoqin et al. (39) reported that patients with MS and

very severe PH (systolic PAP >80 mm Hg) had significantly higher New York Heart Association (NYHA) functional class both before and after percutaneous balloon mitral valvuloplasty. In addition, these patients displayed a trend for higher cardiovascular event rate during follow-up. Similarly, from a cohort of 531 patients referred for percutaneous balloon mitral valvuloplasty, 15% had severe PH (systolic PAP >60 mm Hg), and these patients exhibited a significantly reduced long-term cardiac event-free survival

compared with those with normal systolic PAP (40). Overall, once symptomatic patients develop severe PH, their mean survival drops to <3 years (41). Congestive heart failure, acute pulmonary edema, and RV heart failure are the predominant causes of death.

EXERCISE SYSTOLIC PAP IN MS. In patients with MS, exercise is often accompanied by a rise in LA pressure, transmitral mean pressure gradient, and systolic PAP in response to increased heart rate and flow. Furthermore, a low atrial compliance may exacerbate the exercise-induced increase in systolic PAP. Patients with low atrial compliance and exercise PH often have reduced flow and as a consequence, the MS severity may be underestimated (42). In a study by Brochet et al. (43), asymptomatic patients with MS who stopped exercise because of dyspnea exhibited a significantly higher and more rapid increase in the mean transmitral pressure gradient and systolic PAP at low levels of exercise than did patients without symptoms. An increase in systolic PAP of ≥90% in the early stages of the exercise test (i.e., at an exercise load of 60 W) was associated with a >2-fold higher rate of exercise dyspnea or mitral valve intervention during follow-up. Conversely, peak exercise systolic PAP, even when >60 mm Hg, did not discriminate patients with versus without exercise-limiting symptoms. Hence, the evaluation of the kinetics of exercise-induced changes in systolic PAP may provide incremental information to predict symptoms and prognosis in MS (13).

MANAGEMENT OF PATIENTS WITH MS. Current European and American guidelines (31,32) recommend percutaneous balloon mitral valvuloplasty or surgery for all patients with symptomatic significant MS (valve area <1.5 cm²). In contrast, symptomatic patients with mild MS (mean transmitral pressure gradient of <5 mm Hg and valve area of >1.5 cm²) should be followed up on an annual basis but do not require further evaluation in the initial work-up. Resting PH has a modest role in the management of patients with MS. In the European guidelines, percutaneous balloon mitral valvuloplasty should be considered (Class IIa) in asymptomatic patients without unfavorable clinical characteristics and high risk of hemodynamic decompensation (i.e., systolic PAP >50 mm Hg at rest). In the American recommendations, it is also preferable to intervene before the development of very severe PH because those patients with near systemic pulmonary pressure show reduced RV function and persistent PH following percutaneous balloon mitral valvuloplasty or mitral valve surgery. Percutaneous balloon mitral valvuloplasty is also advised for asymptomatic patients with

moderate or severe MS and exercise percutaneous balloon mitral valvuloplasty >25 mm Hg. Early work in the percutaneous balloon mitral valvuloplasty era showed that PAP fell following percutaneous balloon mitral valvuloplasty, in concert with the reduction in mitral valve gradient and pulmonary vascular resistance (44). Return to normal or near normal levels of systolic PAP is expected in most patients. Interestingly, after treatment, the baseline endothelin 1 concentration has been shown to be an independent predictor of a decrease in PAP following percutaneous balloon mitral valvuloplasty at 6 months following mitral valve surgery (4). Following percutaneous balloon mitral valvuloplasty, surveillance is necessary for mitral valve restenosis with the redevelopment of PH.

AORTIC REGURGITATION

PREVALENCE. In aortic regurgitation (AR), PH has been less studied. Prior studies have reported a prevalence of PH defined as a systolic PAP >40 mm Hg in 27% (45) or >60 mm Hg in 24% (46) of patients with severe chronic AR (**Table 3**). In our catheterization-based study (n = 802; various degrees of AR) (**Figure 4**), 23% of patients had mild PH (mean PAP of >25 mm Hg), 9% moderate PH (mean PAP of >35 mm Hg), and 4.7% severe PH (mean PAP of >45 mm Hg).

IMPACT ON OUTCOME AND MANAGEMENT. There are very few data in the literature regarding the impact of PH in patients with chronic AR. In the small series of Naidoo et al. (46), post-operative patients with PH did not have significantly different rates of post-operative death, complications, or NYHA functional class. In contrast, systolic PAP >40 mm Hg was associated with reduced survival at 1 and 4 years following AVR in other series (45). More recently, a single-center retrospective study of 506 patients with severe AR demonstrated that severe PH (systolic PAP >60 mm Hg) was present in approximately 16% of patients and was associated with LV enlargement and dysfunction and with ensuing AR. Multivariable analysis with propensity score adjustment showed an independent association between AVR and survival in patients with both severe AR and severe PH during 5 years of follow-up (47). AVR was associated with a 3% operative mortality rate in patients with severe PH, and systolic PAP dropped to near normal values in the vast majority of patients following surgery. In the current guidelines, AVR for AR is not recommended based on the sole presence of PH. However, in patients with borderline LV dimension values, PH should dictate a careful search for limited functional

capacity and might represent a further incentive for AVR.

PRIMARY MR

PREVALENCE. In MR, PH has been largely documented (Table 3, Figure 4). Owing to the relationship reported between MR grade (48), regurgitant volume or effective regurgitant orifice area, and systolic PAP (10,49,50), the rate of PH varies according to MR severity. In severe MR, moderate/severe PH was noted in 17%/23% to 32% of patients, with a higher prevalence according to symptomatic status and the presence of LV systolic dysfunction (systolic PAP >50 mm Hg in 64% of NYHA functional class III to IV) (51). In asymptomatic primary MR, the concomitant presence of significant MR and PH is relatively rare. The prevalence of PH accounts for approximately 6% to 30% in asymptomatic patients (48,52,53) and does not exceed 20% when LV ejection fraction is preserved (10,54).

IMPACT ON OUTCOME. In primary MR with preserved LV ejection fraction, pre-existing PH is associated with post-operative LV systolic dysfunction (LV ejection fraction <50%) (53). Although the decline in LV ejection fraction is more pronounced in those with severe PH (systolic PAP >60 mm Hg), the drop in LV systolic function also occurs in moderately elevated systolic PAP (30 to 49 mm Hg). Barbieri et al. (52) reported a reduced 5-year survival rate (63 ± 5% vs. 86 ± 2%) and an increase in the incidence of heart failure during follow-up in patients with PH compared with those without PH. At 8 years, only 58% of patients with a systolic PAP >50 mm Hg were alive (48). After adjustment for cofactors, the presence of PH independently multiplied by 2 the risk of death or occurrence of heart failure. Despite a significant decrease in PAP, without normalization, mainly in patients with severe and moderate PH (51), patients with severe MR and PH had significantly reduced post-operative survival compared with those without PH. Similar results were reported by Le Tourneau et al. (48), who showed a rate of post-operative survival approximately divided by 2 at the 8-year follow-up (Table 3) in patients with pre-operative PH. In addition, the proportion of patients having persisting symptoms following surgery is more important among patients with pre-operative PH. A surgical series found consistent results and showed a graded relationship between increased systolic PAP and reduced post-operative survival (51). Based on these results, the investigators of the Mitral Regurgitation International Database (52) suggested that early intervention might be beneficial in patients

with PH, regardless of symptoms or LV functional status. Such a strategy was further supported by other data showing that the prognosis of patients with severe MR and PH is markedly improved when surgery is performed early (<3 months after the index examination) in the course of the disease (i.e., compared with the conservative approach) (52). In this series, the vast majority of deaths were from cardiovascular causes and were related to congestive heart failure.

In asymptomatic patients with preserved LV ejection fraction, Magne et al. (10) found that patients with PH had a significantly lower symptom-free survival (Figure 5B) (i.e., only one-third of these patients remained free of symptoms at the 2-year follow-up). As in the study of Kusunose et al. (54), this relationship was no longer significant after adjustment for age and sex.

EXERCISE PH IN PRIMARY MR. In opposition to resting PH, exercise PH is more prevalent in asymptomatic patients with primary MR and no LV dysfunction/dilation (ejection fraction <60%/end-systolic diameter <40 to 45 mm). In these patients, exercise PH has been associated with significantly lower symptom-free survival (at 2 years 75 ± 7% vs. 35 ± 8%; p < 0.0001) (Table 3, Figure 5C). The presence of exercise PH multiplied by 2.1 the risk of developing symptoms during follow-up. At the 3-year follow-up, only 20% of the patients with exercise PH at baseline remained free of symptoms and at 2 years, whereas 75% of the patients without exercise PH remained free of symptoms. These data were recently confirmed in a comparable cohort of 196 patients (54). Exercise systolic PAP was an independent predictor of the need for mitral valve surgery. Compared with patients without exercise PH/RV dysfunction, patients with 1 of these 2 exercise conditions had intermediate outcomes. Conversely, exercise PH (systolic PAP ≥54 mm Hg) in conjunction with exercise RV dysfunction identified patients with worse outcomes. Pre-operative baseline exercise PH also negatively impacts post-operative outcome, with a higher rate of cardiac events (55). Furthermore, pre-operative exercise PH is associated with significantly reduced post-operative event-free survival, including a higher rate of late atrial fibrillation and cardiac-related hospitalization (55).

MANAGEMENT OF PRIMARY MR AND PH. In the European and American guidelines regarding the management of asymptomatic patients with severe primary MR, no LV dysfunction/dilation and resting PH (systolic PAP >50 mm Hg), mitral valve repair is a Class IIa indication (Level of Evidence: B or C). Repair

can also be considered in high-volume centers in cases of isolated exercise PH (systolic PAP >60 mm Hg; ESC Class IIb, Level of Evidence: C) (Table 3). Otherwise, very close follow-up in a dedicated heart valve clinic (56) is recommended.

SECONDARY MITRAL REGURGITATION

PREVALENCE. Overall, the prevalence of PH in patients with LV systolic dysfunction and secondary MR is approximately 40% (37% moderately elevated systolic PAP and 22% to 38% severe) (57-59). PH can also be found in patients with preserved LV ejection fraction and secondary MR (59). Of note, secondary MR is a major determinant of elevated systolic PAP in both conditions (Table 3) (60).

IMPACT ON OUTCOME. In patients with LV dysfunction, PH is associated with an increased risk of congestive heart failure and mortality (61,62). In a large cohort of patients undergoing mitral valve surgery (N = 873) for various etiologies of MR, including functional MR in 31% of cases, Ghoreishi et al. (51) found that PH was associated with worse post-operative outcomes (Table 3). In the study of Agricola et al. (63), systolic PAP was also an independent determinant of heart failure or death.

The recent study by Miller et al. (59) confirmed these data. The researchers identified 2 cohorts of patients with secondary MR with or without PH (systolic PAP >45 mm Hg) matched for age, sex, LV ejection fraction, severity of MR, and year of examination. PH was independently associated with reduced survival after adjustment for clinical variables, including symptomatic status, MR severity, and LV systolic and diastolic functions, carrying an excess mortality rate of >30% (Table 3).

EXERCISE PH IN SECONDARY MR. Exercise-induced increase in systolic PAP can occur in patients with secondary MR regardless of whether the LV systolic function is preserved or not. It often parallels the increase in MR severity and LV filling pressures as evaluated by E/e′ (64-66). When dynamic MR and exercise PH are concomitant, worsening heart failure, worsening pulmonary edema, and increased mortality rate are potential complications. The optimal cut point for predicting an increase in the number of future cardiac events was a 21-mm Hg increase in systolic PAP. During exercise, the abrupt increase in MR severity, even if mild, may exceed the level of LA compliance and pulmonary vascular recruitment and lead to PH. Although initially benign with no significant consequences, such a phenomenon, when repetitive, can progressively lead to LA dilation, increased LV filling pressures, atrial fibrillation, RV

dysfunction, low-level exercise dyspnea, and finally resting symptoms. In addition, this phenomenon is involved in the pathogenesis of acute pulmonary edema (67) and is associated with reduced survival, regardless of the resting severity of MR.

MANAGEMENT AND RISK STRATIFICATION. The European guidelines recommend surgery as a Class I indication in patients with severe secondary MR (effective regurgitant orifice >20 mm² and/or regurgitant volume >30 ml) undergoing coronary artery bypass graft. In the presence of moderate secondary MR, the indication for valve surgery at the time of coronary artery bypass grafting is a Class IIa indication. However, because secondary MR is dynamic by nature, exercise stress echocardiography is highly recommended in patients with moderate MR (68). In these patients, a large increase in MR associated with PH and dyspnea on exercise stress echocardiography are further incentives to combined valve and coronary artery bypass grafting surgeries. In the absence of planned surgical revascularization, close follow-up is mandatory, and other mitral valve treatments may be discussed. Conversely, in patients with moderate secondary MR and no exercise PH, a medical strategy should be followed.

Although controversial in terms of outcome benefit, the goal of surgical treatment is to reduce MR, prevent its recurrence, and promote LV reverse remodeling. Restricting annuloplasty may be less effective in patients with severe mitral valve deformation, with a higher risk of residual MR after surgery, which can limit the post-operative improvement in systolic PAP. In addition, the insertion of a small rigid ring to achieve a very restrictive annuloplasty may create some degree of post-operative MS (69), with both resting and exercise hemodynamic consequences (70), such as PH. Following restrictive mitral valve annuloplasty for secondary MR, PH is associated with adverse cardiac events (71). On the other hand, the risk of prosthesis-related complications following mitral valve replacement is not null and should be carefully assessed pre-operatively. Following mitral valve replacement, prosthesis-patient mismatch may occur and may be associated with an increased risk of post-operative PH (72) and reduced survival (73). Because secondary MR is mainly a ventricular disease, surgical strategies solely targeting the mitral valve may provide suboptimal and inconsistent results. The randomized controlled trial performed by the Cardiothoracic Surgical Trials Network (74) showed no significant difference in LV reverse remodeling or survival at 12 months between patients randomly assigned to undergo mitral valve repair or mitral valve replacement for ischemic MR.

EMERGING CONCEPTS: BIOMARKERS

Previous studies (75,76) have demonstrated that plasma B-type natriuretic peptide (BNP) activation may be a surrogate marker of adverse LA and LV remodeling. In several studies, BNP levels were correlated with systolic PAP at rest or during exercise (76–79). Overall, BNP evaluation may serve to identify patients who are susceptible to developing PH.

Pim-1 is a proto-oncogene encoding a serine/threonine protein kinase that is minimally expressed in healthy cells but is implicated in cardiac remodeling, along with systemic vascular smooth muscle cell (SMC) proliferation. Recent studies have demonstrated that Pim-1 activation in systemic vascular SMCs enhances nuclear factor of activated T cells (NFAT) activity in PH (80). NFAT activation is not restricted to SMCs but is also found in circulating T cells of patients with PH. Although NFAT activation in T cells is involved in numerous physiological and pathological processes, such as inflammation, the activation of NFAT through Pim-1 is specific to PA remodeling, suggesting that circulating Pim-1 levels might represent a good biomarker for PH. In support of this hypothesis, it was recently reported that circulating levels of Pim-1 appropriately discriminated proliferative PH from control subjects and was an independent predictor of mortality in patients with PH (81).

RV failure is the major cause of morbidity and mortality in PH. There are very few studies about the prevalence and impact of RV dysfunction on outcomes in patients with VHD. However, a recent study reported that exercise RV dysfunction is associated with worse prognosis in these patients (54). The myocyte enhancer factor 2–microRNA-208 axis seemed to drive the decompensation of RV function in pre-capillary PH in recent unpublished data. Similar mechanisms may be involved in the development of RV dysfunction in VHD-related PH, mainly when MR is present. Preliminary data also implicate microRNA-126, a pro-angiogenic microRNA, in RV failure. These findings open a new window on the mechanisms that drive RV failure in PH and VHD, which could be explored in biomarkers (microRNA-208 and microRNA-126 levels) and therapeutic research programs.

DISEASE-TARGETED THERAPY

The European guidelines (1) state that there is currently no specific therapy for PH related to left heart disease. Any medical treatment that plays a role in the decrease in LV end-diastolic pressure may potentially lower PAP, although no evidence is available in the setting of VHD. The classic recommended treatment for primary PH targeting the pulmonary vasculature and RV ejection impedance was investigated in PH due to left heart disease, but the results of these studies were not satisfactory.

Regarding therapeutic management of PH related to VHD, guidelines recommend (Class I, Level of Evidence: C) optimizing the treatment of the underlying VHD. PH is markedly more prevalent in patients with severe VHD and in those with surgical indication. In addition, PH itself is a trigger for surgery in MR and MS. Consequently, the first-line therapeutic target in these patients is to remove the valvular burden.

The systolic PAP may decrease following AVR (82), mitral valve replacement (83), or percutaneous balloon mitral valvuloplasty. Nevertheless, following mitral valve replacement, the presence of prosthesis-patient mismatch precluded normalization of systolic PAP and was associated with a high rate of post-operative PH (83), which was an independent determinant of chronic heart failure–related post-operative hospitalization (72) and mortality (73). Overall, following VHD interventions, any post-operative residual hemodynamic alteration limiting reduction in LA pressure may potentially delay improvement in PAP and symptoms or even, in some cases, participate to maintain the presence of PH.

CONCLUSIONS

The presence of PH in left-sided VHD is frequent and of high prognostic significance. The assessment of PH is crucial in these patients, more particularly in the absence of overt symptoms because there are important implications with regard to risk stratification and management. Nevertheless, owing to relatively limited data derived from a large cohort of patients with VHD, the place of PH in current guidelines remains limited, except in primary MR.

The role of exercise stress echocardiography and evaluation of exercise PH is gaining interest. Exercise PH is likely helpful in identifying patients with advanced risk of rapid and frequent development of symptoms who may require and benefit from early intervention. There is no specific treatment for patients with PH related to VHD, and therapeutic management only targets the underlying disease. In addition, further data are needed to confirm the real prevalence and impact on outcome of PH in asymptomatic left-sided VHD.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Patrizio Lancellotti, Department of Cardiology, University of Liège Hospital, CHU du Sart Tilman, 4000 Liège, Belgium. E-mail: plancellotti@chu.ulg.ac.be OR Dr. Philippe Pibarot, Institut Universitaire de Cardiologie et de Pneumologie de Québec, 2725 Chemin Sainte-Foy, Québec City, Québec, Canada, G1V-4G5. E-mail: philippe.pibarot@med.ulaval.ca.

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