

Ventriculo-Arterial Decoupling in Aortic Stenosis: When the Ventricle and the Arteries Do Not Dance on the Same Tempo

Desacoplamiento ventriculoarterial en la estenosis aórtica: cuando los ventrículos y las arterias no bailan al mismo ritmo

PHILIPPE PIBAROT^{FACC, FAHA, FESC, FASE}

VENTRICULO-ARTERIAL COUPLING: THE VENTRICLES AND THE ARTERIES NEED TO DANCE ON THE SAME TEMPO

The dynamic interaction between the heart and the systemic circulation allows the cardiovascular system to be efficient in providing adequate cardiac output and arterial pressures to ensure satisfactory organ perfusion in different physiological (resting and exercise) conditions. The cardiovascular system indeed works better when the heart and the arterial system are coupled. In other words, the ventricle and the arterial system need to dance on the same tempo. Ventriculo-arterial coupling is achieved by the continuous modulation of the arterial system compliance and resistance with respect to left ventricular (LV) systolic performance, and this physiological process is fundamental to maintain adequate LV stroke volume and cardiac output. Because LV stroke volume depends on myocardial contractility and loading conditions, i.e. preload and afterload, both myocardial, valvular, and arterial dysfunction can lead to ventriculo-arterial decoupling with resulting decrease in stroke volume, cardiac output, and organ perfusion.

Ventriculo-arterial coupling can be defined as the ratio between arterial elastance (Ea) and ventricular elastance (Ees) measured on the LV pressure-volume loop. (1) This ratio is useful to evaluate the mechanical efficiency of the cardiovascular system and the interaction between cardiac performance and systemic vascular function. An imbalance between Ea and Ees, as reflected by an increase or decrease in the Ea/Ees ratio, may lead to heart failure (HF).

VENTRICULO-VALVULO-ARTERIAL DECOUPLING IN AORTIC STENOSIS: THE PATHWAY TO HEART FAILURE

In this issue of the Journal, Migliore et al. (2) com-

pared Ea, Ees, and the Ea/Ees ratio estimated non-invasively by Doppler-echocardiography between 3 groups of patients with severe aortic stenosis (AS; defined as an aortic valve area < 1.0 cm²): 1) asymptomatic severe AS; 2) symptomatic severe AS (NYHA class II angina or syncope) and 3) severe AS with HF symptoms (NYHA class III and IV dyspnea). The main findings of this elegant study are: a) in patients with symptomatic severe AS, the Ea/Ees ratio is 1.3-fold higher than in patients with asymptomatic severe AS, and b) in patients with severe AS and HF symptoms Ea/Ees is 1.8 to 2.5 higher than in the other two groups. Hence, the presence and severity of symptoms in this series of patients with severe AS was associated with a gradual worsening of ventriculo-arterial decoupling.

The pathophysiology of HF in AS is essentially determined, on the one hand, by the extent of imbalance between the increase in LV hemodynamic load due to valvular obstruction and/or concomitant arterial hypertension, and on the other hand, by the capacity of the left ventricle to overcome this increase in load both at rest and during exercise (Figure 1). In patients with calcific AS, several factors may lead to imbalance between Ea and Ees and thus to ventriculo-arterial decoupling. Firstly, aortic valve obstruction contributes to increase LV afterload and thus ventriculo-arterial decoupling. Secondly, patients with calcific AS are generally older and thus frequently have reduced arterial compliance and associated systolic hypertension. (3) As a matter of fact, hypertension, and particularly systolic hypertension, is highly prevalent (30-70%) in these patients. (3, 4) Therefore, these patients often have increased Ea as a result of concomitant reduced arterial compliance and increased vascular resistance.

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Address for reprints: Dr. Philippe Pibarot, Institut Universitaire de Cardiologie et de Pneumologie de Québec, 2725 Chemin Sainte-Foy, Québec, Québec, Canada, G1V-4G5. e-mail: philippe.pibarot@med.ulaval.ca

Institut Universitaire de Cardiologie et de Pneumologie de Québec / Québec Heart & Lung Institute, Department of Medicine, Laval University, Québec, Canada.

^{FACC} Fellow of the American College of Cardiology

^{FAHA} Fellow of the American Heart Association

^{FESC} Fellow of the European Society of Cardiology

^{FASE} Fellow of the American Society of Echocardiography

Thirdly, Ees is often reduced in AS patients, thus further contributing to the increase in Ea/Ees ratio and ventriculo-arterial decoupling. The main factors responsible for the decline in Ees in AS are (see Figure 1): 1) LV afterload mismatch and associated decrease in myocardial contractility related to the disproportionate increase in LV afterload (resulting from AS and frequent concomitant hypertension) relative to LV performance, and 2) impaired LV contractility due to concomitant coronary artery disease, which is also frequent in the elderly population with AS.

Ea as calculated in the study of Migliore et al. (2) includes the arterial component of the hemodynamic load but not the valvular load, which is important in patients with severe AS (see Figure 1). Indeed, the authors measured the peripheral (brachial) arterial pressure and from these measurements they estimated end-systolic pressure assuming it to be close to the end-systolic pressure measured at the brachial level. However, the arterial pulse waveform and amplitude are different in the brachial artery than in the ascending aorta. (5) Furthermore, although the systolic pressure in the ascending aorta is similar to that in the left ventricle in subjects with a normal aortic valve (and thus with negligible transvalvular pressure gradient), this is not the case in patients with severe AS in whom peak and mean LV systolic pressures are much higher than aortic systolic pressures. Hence, in these patients, the end-systolic arterial pressure and the Ea calculated from this pressure grossly underestimate the total LV hemodynamic load as they only reflect the arterial load but not the hemodynamic burden related with the severity of valvular stenosis. To estimate the true total load: i.e. arterial + valvular hemodynamic load that the left ventricle is facing in patients with AS, we have proposed the calculation of valvulo-arterial impedance, which is the ratio between LV peak systolic pressure and stroke volume index. (3, 6) The LV systolic pressure is estimated by adding the mean transvalvular gradient to the systolic blood (brachial) pressure. The rationale for using the stroke volume index rather than the unindexed stroke volume is that a small-size subject may have a much smaller stroke volume than a large-size subject but nonetheless similar arterial and LV pressures. The valvulo-arterial impedance represents the valvular and arterial factors that oppose ventricular ejection by absorption of the mechanical energy developed by the left ventricle. Different from Ea, this parameter also includes valvular load (expressed as mean transvalvular gradient) and it accounts for inter-individual variability in body size. Values of impedance >4.5 mmHg.ml⁻¹.m² have been shown to provide incremental value to predict symptoms and mortality in patients with AS. (6, 7) Valvulo-arterial impedance was not calculated in the study of Migliore et al., (2) but from the data provided in the tables, it is possible to estimate that the average values of this parameter are around: 5.9, 5.1 and 4.5 mmHg.ml⁻¹.m² in the severe AS groups with HF, symptomatic and asymptomatic, respectively. Average

Ea was 3.8, 3.0 and 2.8, respectively, in these groups. Hence, valvulo-arterial impedance might be superior to Ea to discriminate symptomatic from asymptomatic patients and potentially to predict the occurrence of HF and adverse events.

The stroke volume index is another simple Doppler-echocardiographic parameter that may be used to enhance risk stratification in AS. Several studies and meta-analyses have reported that a low flow state defined as a stroke volume index <35 ml/m² is a powerful predictor of outcomes in patients with AS both before as after aortic valve replacement. (8, 9) The stroke volume index is actually a good surrogate marker of ventriculo-arterial coupling and of the overall performance of the cardiovascular system. In the study of Migliore et al. (2) there was a graded decrease in stroke volume index in the asymptomatic, symptomatic, and HF groups of 38, 34, 27 mL/m², respectively, that paralleled the increase in Ea/Ees (0.61, 0.81, 1.5, respectively). As expected, the group with HF symptoms was the worst in terms of ventriculo-arterial decoupling and accordingly, this group was in low flow state with a stroke volume index well below the lower normal value of 35 mL/m². Although from a mechanistic standpoint, it may be interesting to measure Ea, Ees and Ea/Ees ratio in patients with AS, from a practical viewpoint however, it may be preferable and easier to measure valvulo-arterial impedance, i.e. a marker of the true total LV hemodynamic load, and the stroke volume index, i.e. a downstream marker of ventriculo-arterial decoupling.

PATHOGENESIS OF SYMPTOMS IN AORTIC STENOSIS

Among the symptoms associated with AS, dyspnea is, by far, the most frequent, followed by angina, and then syncope (7). As emphasized by the findings of Migliore et al., (2) ventriculo-arterial decoupling and the ensuing decrease in stroke volume are key determinants of symptoms and HF in AS (see Figure 1). To this effect, Harada et al. previously reported that higher valvulo-arterial impedance and lower stroke volume index, but not parameters of stenosis severity were strongly associated with the presence of syncope in AS. (7) On the other hand, higher E/e' reflecting elevated LV filling pressures was the strongest determinant of the occurrence of dyspnea, although valvulo-arterial impedance and stroke volume index were also associated with this type of symptom. In the study of Migliore et al., (2) the E/e' ratio was not significantly higher in patients with symptoms versus those with no symptoms. However, the group of patients with symptoms in this study was quite heterogeneous and included patients with mild dyspnea (NYHA class II) as well as patients with angina and those with syncope, hampering the analysis and interpretation of the association between diastolic dysfunction, E/e' and dyspnea. Interestingly, patients with HF symptoms (i.e., severe dyspnea: NYHA class III and IV) had markedly higher E/e' ratio compared with the other two groups. Although this was not obvious in the study of Migliore et al., (2) the

development of LV diastolic dysfunction certainly has an important role in the pathogenesis of symptoms in AS. There are few studies on the determinants of angina in patients with severe AS. Some studies suggest that the pathogenesis of angina in patients with severe AS and angiographically normal coronary arteries is related to the exhaustion of the coronary flow reserve, which is, largely attributable to the LV hemodynamic load imposed by AS. (10) Hence, the pathogenesis of symptoms in AS is complex and may involve several factors including not only ventriculo-valvulo-arterial decoupling and the ensuing reduction in stroke volume, but also diastolic dysfunction with increased filling pressures and increased LV intracavitary pressure due to elevated total (valvular+arterial) hemodynamic load (see Figure 1).

FUTURE PERSPECTIVES

Ventriculo-arterial coupling reflects the balance between the forces (valvular and / or arterial) opposing LV ejection versus the mechanical efficiency of the left ventricle. For patients with ventriculo-arterial decoupling due to severe AS who present with symptoms or HF, it is imperative to consider aortic valve replacement. However, further studies are needed to determine if asymptomatic patients with severe AS and preserved LV ejection fraction having evidence of ventriculo-arterial decoupling would benefit from early “prophylactic” valve replacement versus watchful waiting strategy. Furthermore, although ventriculo-

arterial decoupling is, of course, more likely to occur in patients with severe AS, this phenomenon may also be observed in patients with moderate AS and LV systolic dysfunction due to causes other than AS. In such case, Ea is moderately increased and Ees is markedly decreased due to ischemic or non-ischemic cardiomyopathy. To this effect, we recently hypothesized that correction of such moderate AS in this context would improve ventriculo-arterial coupling and thus the LV function and outcome of these patients. To test this hypothesis, we designed the TAVR-UNLOAD randomized trial (<https://clinicaltrials.gov/ct2/show/NCT02661451>) that compares HF therapy plus transcatheter aortic valve replacement versus HF therapy alone in patients with moderate AS, depressed LV ejection fraction, and HF symptoms. Hopefully, this strategy will help to “re-couple” the left ventricle, the aortic valve, and the arterial system and thereby improve the longevity and quality of life of these patients.

Conflicts of interest

None declared.

(See authors’ conflicts of interest forms in the website/Supplementary material).

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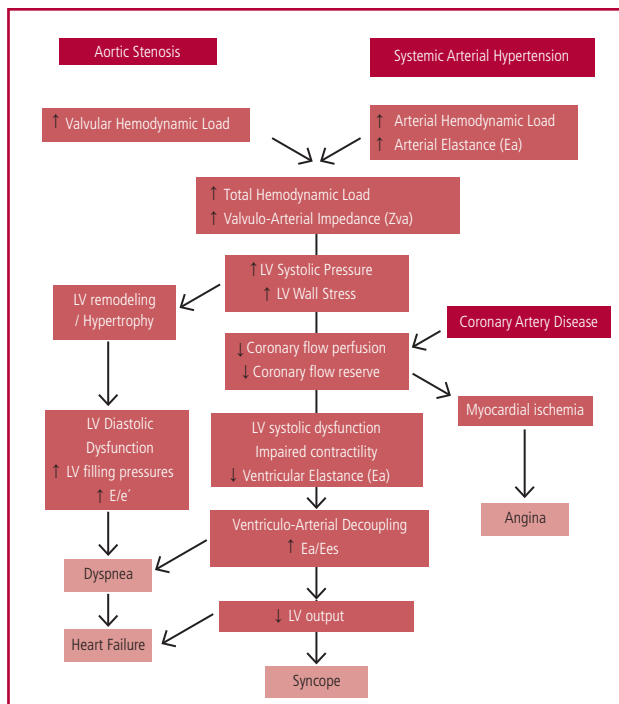


Fig. 1. Pathophysiology of symptoms and heart failure in aortic stenosis