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

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Ventriculo-arterial coupling: the ventricle 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 adequate organ perfusion in different physiological (rest 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. The 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 key 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 of the arterial elastance (Ea) to the 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 unbalance between Ea and Ees as reflected by an increase or decrease in the Ea/Ees ratio may lead to heart failure.

Ventriculo-valvulo-arterial decoupling in AS: on the path to heart failure

In this this issue of the Journal, Migliore et al. (2) compared 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 cm^2): i) Severe AS and no symptoms; ii) Severe AS and symptoms: i.e. NYHA class II, angina or syncope; iii) Severe AS and heart failure symptoms: i.e. NYHA class III and IV). The main findings of this elegant study are: i) Patients with severe AS and symptoms have a 1.3-fold higher Ea/Ees ratio compared to those with asymptomatic severe AS; ii) Patients with severe AS and heart failure symptoms have a 1.8 to 2.5- fold increase in Ea/Ees compared to the 2 other 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 heart failure in AS is essentially determined by the extent of imbalance between the increase in LV hemodynamic load due to the valvular obstruction and/or concomitant arterial hypertension, on the one hand, and the capacity of the left ventricle to overcome this increase in load both at rest and during exercise, on the other hand (Figure). In patients with calcific AS, several factors may lead to an unbalance between Ea and Ees and thus to ventriculo-arterial decoupling. First, the aortic valve obstruction contributes to increase the LV afterload and thus the ventriculo-arterial decoupling. Second, patients with calcific AS are generally older and thus frequently have reduced arterial compliance and associated systolic hypertension (3). As a matter of

facts, hypertension, and particularly systolic hypertension, is highly prevalent (30-70%) in these patients (3, 4). And therefore, these patients often have increased Ea as a result of concomitant reduced arterial compliance and increased vascular resistance. Third, 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 (Figure): i) 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; ii) Impaired LV contractility due to concomitant coronary artery disease, which is also frequent in the elderly population with AS.

The 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 (Figure). Indeed, the authors measured the peripheral (brachial) arterial pressure and from these measurements they estimated the end-systolic pressure. The end-systolic pressure measured at the brachial level was assumed to be close to the LV end-systolic pressure. However, the arterial pulse waveform and amplitude are different in the brachial artery versus 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 no or minimal transvalvular pressure gradient), this is not the case in patients with severe AS in whom the peak and mean LV systolic pressure are much higher than the 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 to the severe valvular stenosis. To estimate the true total: i.e. arterial + valvular hemodynamic load that the left ventricle is facing in patients with AS, we proposed to calculate the valvulo-arterial impedance, which is the ratio of the LV peak systolic pressure to the 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. At of the difference of Ea, this parameter also includes the valvular load (i.e. the mean transvalvular gradient) and it accounts for the inter-individual variability in body size. Values of impedance > 4.5 mmHg.ml^{-1}.m^2 have been shown to provide incremental value to predict symptoms and mortality in patients with AS (6, 7). The 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, 4.5 mmHg.ml^{-1}.m^2 in the severe AS groups with heart failure, symptoms, and no symptoms, respectively. The average Ea was 3.8, 3.0, 2.8, and respectively in these groups. Hence, valvulo-arterial might be superior to Ea to discriminate patients with symptoms versus those with no symptoms and potentially to predict the occurrence of heart failure 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 reported that a low flow state defined as a stroke volume index < 35 ml/m^2 is a powerful predictor of outcomes in patients with AS both before and after aortic valve replacement (8, 9). The stroke volume index is actually a good surrogate marker of the 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 heart failure groups (i.e. 38, 34, 27 mL/m^2) that paralleled the increase in Ea/Ees (0.61, 0.81, 1.5, respectively). As expected, the group with heart failure 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/m^2. Although from a mechanistic standpoint, it may be interesting to measure Ea, Ees and Ea/Ees ratio in patients with AS, from a practical standpoint however, it may be preferable and easier to measure the 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 AS

Among the symptoms associated with AS, dyspnea is, by far, the most frequent, followed by angina, and then syncope (7). As well emphasized by the findings of Migliore et al. (2), ventriculo-arterial decoupling and ensuing decrease in stroke volume are key determinants of symptoms and heart failure in AS (Figure). 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, which makes difficult the analysis and interpretation of the association between diastolic dysfunction, E/e' and dyspnea. Interestingly, patients with heart failure symptoms (i.e., severe dyspnea: NYHA class III and IV) had markedly higher E/e' ratio compared to the 2 other 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 the coronary flow reserve, which is, in large part attributable to the LV hemodynamic load imposed by AS (10). Hence, the pathogenesis of symptoms in AS is complex and may involve serval factors including not only ventriculo-valvulo-arterial decoupling and ensuing reduction in stroke volume, but also diastolic dysfunction with increased filling pressures, and increased LV intracavitory pressure due to elevated total (valvulo+arterial) hemodynamic load (Figure).

Future Perspectives

The ventriculo-arterial coupling reflects the balance between the forces (valvular and / or arterial) opposing to 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 heart failure, 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 other causes 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 the 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 heart failure therapy plus transcatheter aortic valve replacement versus heart failure therapy alone in patients with moderate AS, depressed LV ejection fraction, and heart failure 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.

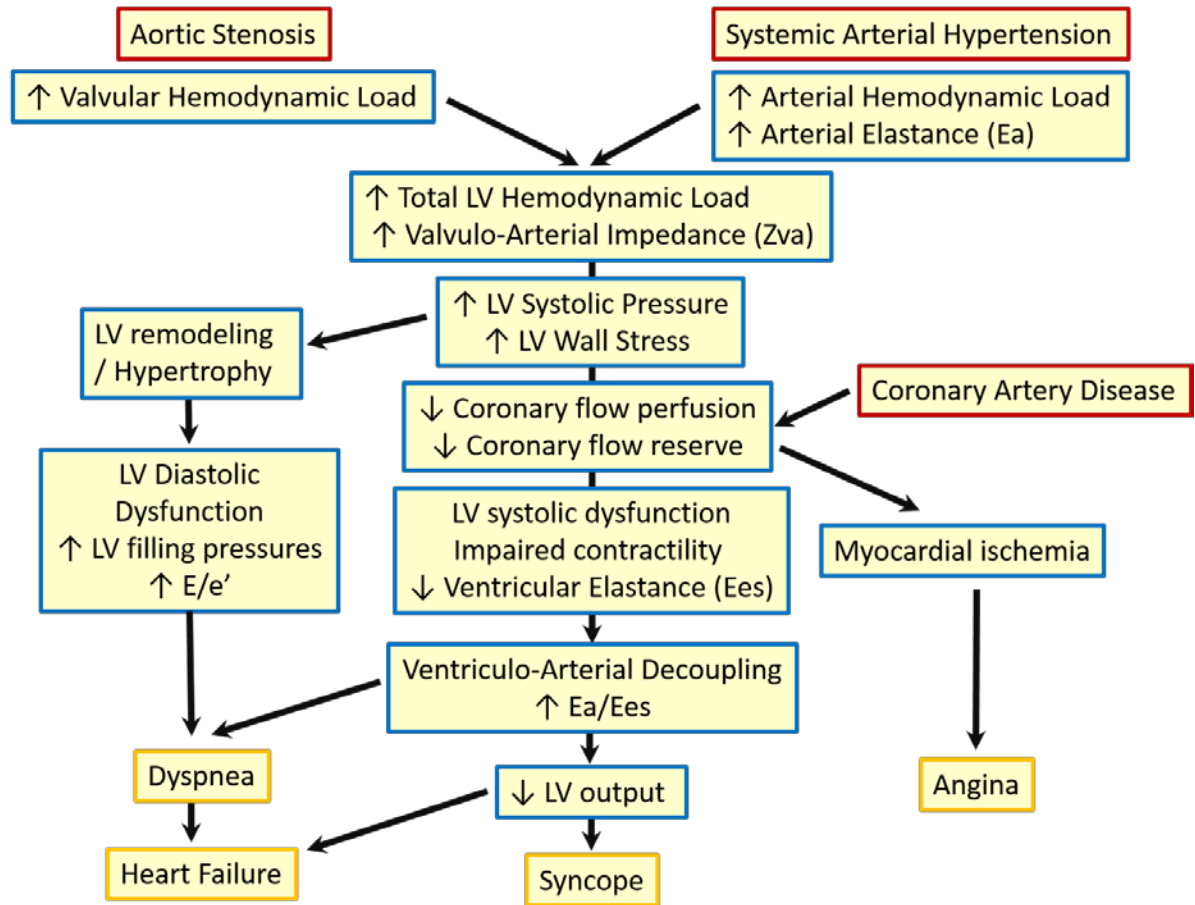**Figure:** Pathophysiology of Symptoms and Heart Failure in Aortic Stenosis

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