

Respective impacts of aortic stenosis and systemic hypertension on left ventricular hypertrophy

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Abstract

It has been reported that 30–40% of patients with aortic stenosis are hypertensive. In such patients, the left ventricle faces a double (i.e. valvular and vascular) pressure overload, which results in subsequent wall volume hypertrophy. From a clinical standpoint, it is difficult to separate the respective contributions of aortic stenosis and systemic hypertension to left ventricular burden and patient's symptoms and thus to predict whether valve replacement would be beneficial. The objective of this theoretical study was therefore to investigate the relative effects of valvular and vascular afterloads on left ventricular hypertrophy. We used a ventricular–valvular–vascular mathematical model in combination with the Arts' model describing the myofiber stress. Left ventricular wall volume was computed for different aortic blood pressure levels and different degrees of aortic stenosis severity. Our simulations show that the presence of concomitant systemic hypertension has a major influence on the development of left ventricular hypertrophy in patients with aortic stenosis. These results also suggest that mild-to-moderate aortic stenosis has a minor impact on left ventricular wall volume when compared with hypertension. On the other hand, when aortic stenosis is severe, wall volume increases exponentially with increasing aortic stenosis severity and the impact of aortic stenosis on left ventricular hypertrophy becomes highly significant.

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1. Introduction

The aortic valve is located between the left ventricle and the aorta and keeps blood flowing towards the peripheral system. Aortic stenosis is generally caused by a progressive calcification of the aortic valve leaflets and it is the most common cardiovascular disease after hypertension and coronary artery disease in developed countries (Tornos, 2001). It creates an obstruction to blood flow from the left ventricle to the aorta which leads to a left ventricular pressure overload. When aortic stenosis becomes severe, symptoms such as shortness of breath, chest pain, and dizziness may occur and survival

is markedly reduced (Nishimura, 2002). Concomitantly, it has been reported a prevalence of systemic hypertension of 30–40% in patients with aortic stenosis (Antonini-Canterin et al., 2003; Briand et al., 2005). When aortic stenosis coexists with hypertension, the left ventricle faces a double (valvular and vascular) pressure overload and this may adversely affect left ventricular function and patient outcome. This pressure overload results in concentric hypertrophy primarily characterized by wall thickening, as new contractile-protein units are generated in parallel to existing ones, whereas the left ventricular cavity volume generally remains unchanged. A few studies tend to show that concentric hypertrophy compensates for the increased left ventricular wall stress and helps to maintain a normal cardiac output (Grossman et al., 1975; Berkin and Ball, 2001).

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In the particular condition of coexistent valvular and vascular overloads, it is difficult to separate the effects caused by aortic stenosis from those caused by hypertension and thus to predict whether valve replacement would be beneficial. These patients represent a challenge since they may fall within the paradigm of a “symptomatic aortic stenosis,” but without having the severity criteria warranting a surgical intervention. It still remains largely unknown to which extent systemic hypertension contributes to left ventricular hypertrophy in comparison with aortic stenosis. Such an investigation is very difficult to perform in patients because of the implications of numerous mechanical, hormonal and neurogenic factors. In this study, we focused on the mechanical aspects by considering a hypothetical asymptomatic patient whose left ventricle is able to adapt to the double overload. For this purpose, we simulated the respective effects of valvular and vascular afterloads on left ventricular hypertrophy with the use of the mathematical ventricular–valvular–vascular (V^3) model (Garcia et al., 2005a) in combination with the Arts’ model describing the myofiber stress (Arts et al., 1991).

2. Methods

2.1. Mathematical V^3 model

The mathematical V^3 model (Fig. 1) has been validated in patients who underwent an aortic valve

replacement as described in details in (Garcia et al., 2005a). It consists of the combination of the time-varying elastance model for the left ventricle, the instantaneous pressure–flow relationship for the aortic valve, and the three-element Windkessel representation of the peripheral system. The left ventricular elastance model relates the left ventricular pressure (P_V) to the left ventricular cavity volume (V) decremented by V_0 (unloaded volume) as follows (Suga et al., 1973):

$$E_{\max}E_N(t/T_{E_{\max}}) = \frac{P_V(t)}{V(t) - V_0}, \tag{1}$$

where E_{\max} represents the peak elastance and $T_{E_{\max}}$ is the time to peak elastance. E_N is the normalized left ventricular elastance (Fig. 2) which has been shown to be somewhat similar in the normal or diseased human hearts despite the presence of different heart diseases (the raw data for E_N are available in (Senzaki et al., 1996)). The pressure–flow relationship in aortic stenosis relates the difference of pressure between the left ventricle and the ascending aorta ($P_V - P_A$) to the transvalvular flow rate (Q):

$$P_V(t) - P_A(t) = \frac{2\pi\rho}{\sqrt{E_LCo}} \frac{\partial Q(t)}{\partial t} + \frac{\rho}{2E_LCo^2} Q(t)^2, \tag{2}$$

where E_LCo is the valvular energy loss coefficient defined as $E_LCo = EOAA/(A - EOA)$. EOA is the effective orifice and A is the aortic cross-sectional area measured at the sinotubular junction (Garcia et al., 2003). EOA corresponds to the minimal cross-sectional area of the transvalvular flow jet (Fig. 1). Note that

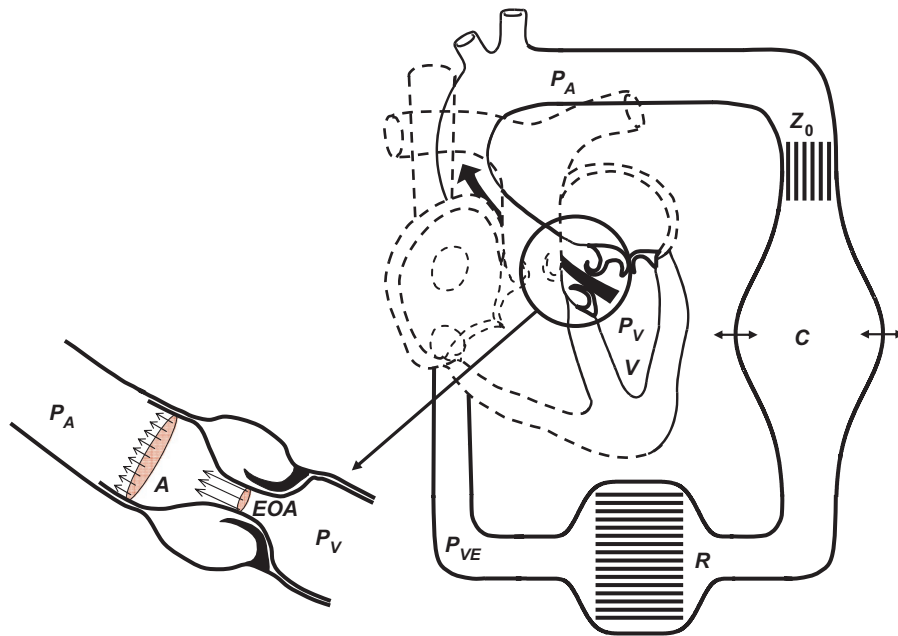


Fig. 1. Schematic representation of the V^3 model. V : left ventricular volume, P_V : left ventricular pressure, P_A : aortic pressure. See also Table 1. From (Garcia et al., 2005a), with permission.

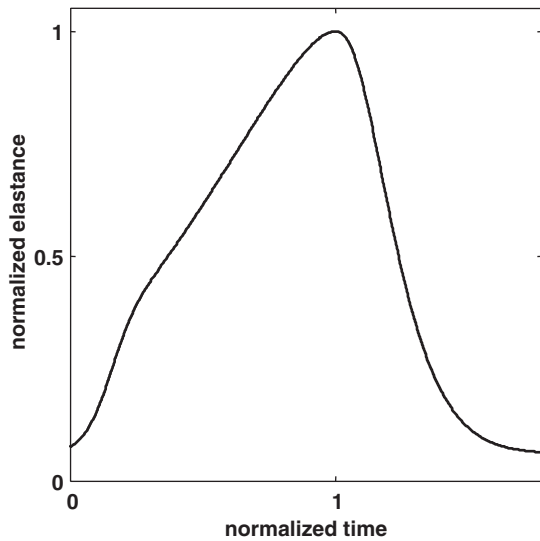


Fig. 2. Normalized left ventricular elastance as a function of normalized time (dimensionless) as measured by Senzaki et al. in patients (Senzaki et al., 1996) and included in the V^3 model.

Table 1
Cardiovascular parameters required for the resolution of the V^3 model

<i>Ventricular parameters</i>	
Left ventricular end-diastolic volume	LVEDV (150 mL)
Unloaded volume	V_0 (15 mL)
Maximal elastance	E_{\max} (adjusted for SV)
Time to maximal elastance	$T_{E_{\max}}$ (0.33 s)
<i>Vascular parameters</i>	
Aortic characteristic impedance	Z_0 (0.07 mmHg.s/mL)
Systemic vascular resistance	R (see Table 3)
Total arterial compliance	C (see Table 3)
Central venous pressure	P_{VE} (5 mmHg)
<i>Valvular parameters</i>	
Effective orifice area	EOA (see Table 2)
Aortic cross-sectional area	A (5 cm ²)

Values in brackets are typical physiologic values used for the simulations performed in this study. E_{\max} (mmHg/mL), R (mmHg.s/mL), C (mL/mmHg) and EOA (cm²) were chosen as explained in the subsection entitled “Simulations”.

when EOA tends towards A (as in the case of a normal aortic valve), E_LCo tends towards $+\infty$ and the transvalvular pressure difference is therefore zero. Eq. (2) has been validated with bioprosthetic heart valves in an in vitro model under numerous physiologic conditions (see (Garcia et al., 2005b) for details). The three-element Windkessel model is an analytical lumped model which has been proved to simulate adequately the hemodynamic characteristics of the peripheral system (Westerhof et al., 1971; Fogliardi et al., 1996). It includes three independent vascular parameters (the aortic characteristic impedance Z_0 , the systemic vascular resistance R and the total arterial compliance C , see

Fig. 1 and Table 1) and relates the aortic pressure (P_A) to the transvalvular flow rate (Q):

$$\frac{\partial P_A(t)}{\partial t} + \frac{P_A(t)}{RC} = \frac{Z_0 + R}{RC} Q(t) + Z_0 \frac{\partial Q(t)}{\partial t} + \frac{P_{VE}}{RC}, \quad (3)$$

where P_{VE} is the central venous pressure. The V^3 model is issued from the combination of the three-above-mentioned mathematical models. The resulting third-order non-linear differential equation, with the use of appropriate initial conditions, completely describes the left ventricular cavity volume for the periods of ejection and isovolumic contraction and relaxation (see (Garcia et al., 2005a) for more details). Transvalvular flow rate, left ventricular and aortic pressures are then immediately deduced as previously described (Garcia et al., 2005a). Table 1 summarizes the independent parameters necessary for solving the V^3 model.

2.2. Simulations

We performed numerical simulations using the V^3 model in order to analyze the respective effects of aortic stenosis and systemic hypertension on left ventricular hypertrophy. Aortic stenosis severity was varied from nonexistent to severe (EOA = 3.5, 1.75, 1.25, 1.0, 0.75 and 0.5 cm², Table 2), and for each degree of severity, aortic blood pressure level was progressively increased from normotensive conditions to severe hypertension (systolic/diastolic pressures = 120/80, 135/87, 150/95, 170/105 and 190/115 mmHg). For each degree of hypertension, systemic vascular resistance (R) and arterial compliance (C) were adjusted to obtain the desired systolic and diastolic aortic pressures (Table 3). Systolic and diastolic aortic pressures were chosen according to the classification of blood pressure levels of the European Hypertension Society (Zanchetti et al., 2003) (Table 2). The aortic characteristic impedance was fixed at 0.07 mmHg.s/mL according to previous estimations in patients with aortic stenosis (Garcia et al., 2005a). The maximal elastance (E_{\max}) was adjusted so that stroke volume was equal to 70 mL (normal output

Table 2
Classification of hypertension and aortic stenosis according to (Bonow et al., 1998) and (Zanchetti et al., 2003)

	Hypertension		Aortic stenosis
	Systolic	Diastolic	EOA (cm ²)
Normal	120–129	80–84	≥ 3
High normal	130–139	85–89	—
Mild	140–159	90–99	> 1.5
Moderate	160–179	100–109	1.0–1.5
Severe	≥ 180	≥ 110	≤ 1.0

Systolic and diastolic pressures are in mmHg. EOA = effective orifice area.

condition) and heart rate was fixed at 70 beats per minute. Values for E_{max} ranged between 1.6 mmHg/mL (without aortic stenosis or hypertension) to 3.2 mmHg/mL (severe aortic stenosis and severe hypertension), which is within the range previously measured in some patients (Dekker et al., 2003). Because ejection fraction is usually normal (50–60%) in adequate concentric left ventricular hypertrophy (Berkin and Ball, 2001), left ventricular end diastolic volume (LVEDV) was also held constant. Typical constant values were also chosen for unloaded volume, time to maximal elastance, central venous pressure and aortic cross-sectional area (Table 1). By way of example, Fig. 3 illustrates simulated left ventricular and aortic pressure waveforms with moderate aortic stenosis (EOA = 1 cm²) and/or moderate

hypertension (170/105 mmHg) obtained with the V³ model.

2.3. Left ventricular hypertrophy

In the case of so-called adequate hypertrophy, left ventricular systolic wall stress is maintained within normal range (Grossman et al., 1975; Berkin and Ball, 2001). Hypothesizing that myocardial muscle fiber stresses are homogeneously distributed, Arts et al. have shown that left ventricular muscle fiber stress (S_f) may be simply related to left ventricular pressure (P_V) and cavity volume to wall volume ratio (V/V_W) as follows (Arts et al., 1991; Vendelin et al., 2002):

$$P_V/S_f = \frac{1}{3} \ln(1 + V_W/V). \tag{4}$$

Rather than assuming that adequate hypertrophy maintains a constant wall stress, we assumed that it is the mean fiber stress, which is kept at normal value during one cardiac cycle. Indeed, according to recent theoretical studies, homogeneity of myofiber stress leads to high pumping efficiency and optimal mechanical load (Arts et al., 1994; Vendelin et al., 2002; Arts et al., 2005). Applying Eq. (4) with a normal left ventricular wall volume of 120 mL (Kuhl et al., 2003) and with left ventricular pressure and volume waveforms obtained under normotensive conditions without aortic stenosis, the calculated mean fiber stress is 185 mmHg. Using the

Table 3
Values for systemic vascular resistance (R) and total arterial compliance (C) used for simulating the different levels of hypertension

Blood pressure level	Systolic/diastolic pressures (mmHg)	R (mmHg s/mL)	C (mL/mmHg)
Normal	120/80	1.07	2.05
High normal	135/87	1.21	1.47
Mild	150/95	1.35	1.23
Moderate	170/105	1.53	0.98
Severe	190/115	1.71	0.83

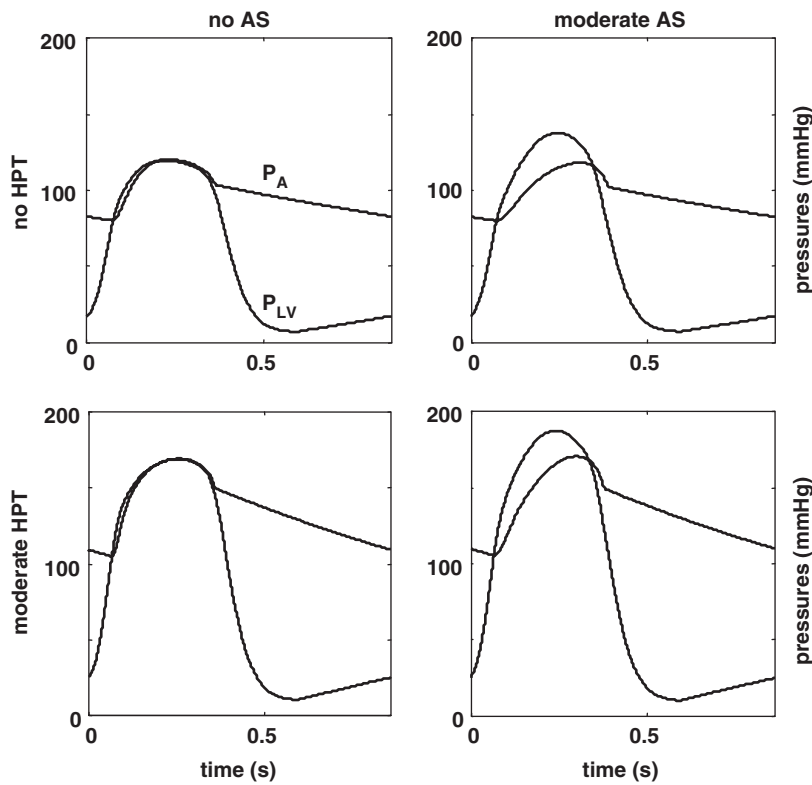


Fig. 3. Simulated left ventricular (P_V) and aortic (P_A) pressures with moderate aortic stenosis (AS) and/or moderate hypertension (HPT). Pressures are in mmHg, time in s.

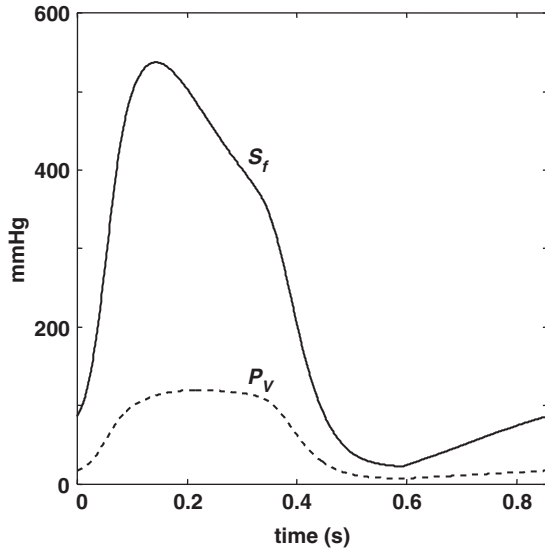


Fig. 4. Change in left ventricular pressure (P_V) and myofiber stress (S_f) during the cardiac cycle under normal conditions.

postulate that the left ventricular wall hypertrophies so that mean S_f is maintained at the normal value of 185 mmHg, we thus calculated the wall volume (V_W) for every set of simulated (P_V, V) with the use of Eq. (4). For information, Fig. 4 shows the change in left ventricular pressure (P_V) and myofiber stress (S_f) during the cardiac cycle in the normal condition.

3. Results

The simulations show that, for a given aortic stenosis severity, left ventricular wall volume increases almost linearly with increasing hypertension severity. On the other hand, left ventricular wall volume increases “exponentially” with increasing aortic stenosis severity for a given hypertension severity (Fig. 5). As shown in Fig. 5, mild or moderate aortic stenosis ($EOA > 1 \text{ cm}^2$) has little effects on hypertrophy as opposed to mild or moderate hypertension. According to our simulations (Table 4), moderate aortic stenosis ($EOA = 1.25 \text{ cm}^2$) induced an increase in left ventricular wall volume as small as 10 mL (i.e. a 8.3% increase), whereas moderate hypertension (170/105 mmHg) induced an increase of 89 mL (74%). On the other hand, very severe aortic stenosis ($EOA = 0.5 \text{ cm}^2$) has a preponderant impact on left ventricular hypertrophy (138 mL = 115% increase). To better quantify the respective impacts of aortic stenosis (AS component) and hypertension (HPT component) on left ventricular wall volume, we fitted the simulated V_W with a function of the form $V_W = \alpha(A/EOA - 1)^n + \beta(P_S/P_{ref} - 1) + 120$, where P_S is the systolic pressure (peak aortic pressure), P_{ref} is the systolic pressure in normotensive condition (120 mmHg), A is

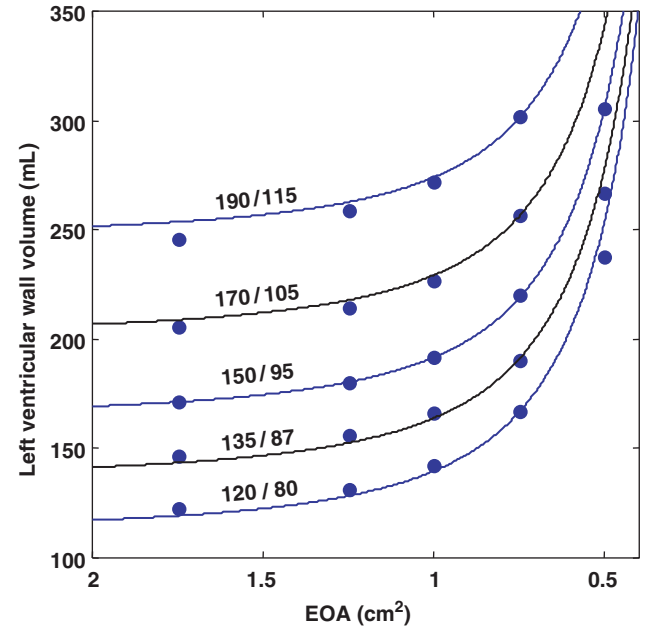


Fig. 5. Theoretical left ventricular wall volume as a function of effective orifice area (EOA) for different grades of systemic hypertension. Numbers above curves refer to systolic and diastolic aortic pressures and each dot represent one simulation. The fitting curves are issued from Eq. (5).

the aortic cross-sectional area (5 cm^2 in this study) and α , β and n are dimensionless coefficients to be determined. A minimization method gave ($r^2 = 0.989$, $N = 30$, $SEE = 9.5 \text{ mL}$, see Fig. 5):

$$V_W = \underbrace{0.781 \left(\frac{A}{EOA} - 1 \right)^{2.35}}_{\text{AS component}} + \underbrace{214 \left(\frac{P_S}{P_{ref}} - 1 \right)}_{\text{HPT component}} + 120 \quad (\text{in mL}). \quad (5)$$

Note that, according to this equation, V_W has the normal fixed value of 120 mL without aortic stenosis ($EOA = A = 5 \text{ cm}^2$) and under normotensive conditions ($P_S = 120 \text{ mmHg}$). Fig. 6 depicts the respective impacts of aortic stenosis (AS component) and systemic hypertension (HPT component) on left ventricular hypertrophy as described by Eq. (5). Note again the minor influence of mild-to-moderate aortic stenosis in comparison with that of hypertension. A very few studies have investigated the degree of left ventricular hypertrophy in patients with aortic stenosis or systemic hypertension, before and after treatment. Rajappan et al. and Tse et al. used the cardiovascular magnetic resonance (CMR) standard method for measuring left ventricular mass before and after treatment of aortic stenosis and hypertension, respectively (Rajappan et al., 2002; Tse et al., 2003). Assuming a 120 mL mean wall volume for normal left ventricle (Kuhl et al., 2003), our simulations

Table 4

Increase in left ventricular wall volume (in mL) with aortic stenosis and/or hypertension for the hypothetical cases simulated in this study

Blood pressure level	Aortic stenosis				
	No AS 3.5 cm ²	Mild 1.75 cm ²	Moderate 1.25 cm ²	Severe 0.75 cm ²	Very severe 0.5 cm ²
Normal 120/80	0	3	10	46	138
Mild 150/95	54	57	64	100	191
Moderate 170/105	89	93	100	136	227
Severe 190/115	125	128	135	171	263

The left ventricular wall volume in normal condition was fixed at 120 mL (see Section 2).

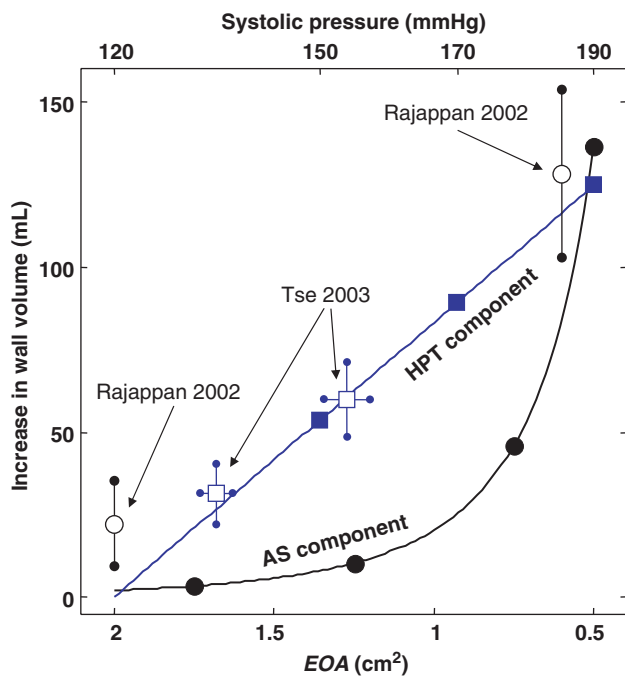


Fig. 6. Influence of aortic stenosis (AS component, circles) and systemic hypertension (HPT component, squares) on the increase in left ventricular wall volume. These curves both refer to Eq. (5) issued from the fitting of the simulated data. Open dots illustrate some clinical findings issued from patients with aortic stenosis (Rajappan et al., 2002) or systemic hypertension (Tse et al., 2003). The error bars represent the standard errors of the mean. EOA were assumed to be 0.6 (before aortic valve replacement) and 2 cm² (after aortic valve replacement) for the data issued from Rajappan et al.

are relatively consistent with the measurements reported by Rajappan et al. and Tse et al. (Fig. 6).

4. Discussion

Concentric left ventricular hypertrophy is an adaptive mechanism compensating for pressure overload mainly by an increase of the myocardial wall thickness. But ultimately, left ventricular hypertrophy may lead to the development of myocardial ischemia, symptoms (i.e. angina, shortness of breath, dizziness, syncope) and

adverse outcomes (i.e. heart failure, sudden death). To this effect, it has been demonstrated that left ventricular hypertrophy is an important independent risk factor for cardiovascular morbidity and mortality. The main findings of our numerical study are: (1) in patients with aortic stenosis, concomitant systemic hypertension may cause a marked increase in left ventricular afterload, thus leading to the development of severe concentric hypertrophy, (2) the impact of mild/moderate hypertension on left ventricular hypertrophy is much more important than that of mild/moderate aortic stenosis, (3) when the stenosis becomes severe (i.e. EOA < 0.75 cm²), its impact increases “exponentially” and may even become preponderant relatively to that of hypertension. This is consistent with the clinical observation showing that chronic isolated aortic stenosis tends to be free of cardiovascular symptoms until relatively late in the course of the disease, and that symptoms appear when EOA is on average 0.6 cm² (Braunwald, 2001). On the other hand, when significant systemic hypertension coexists, symptoms of aortic stenosis develop with larger EOA (Antonini-Canterin et al., 2003) and cumulative survival after aortic valve replacement is largely reduced (Lund et al., 2003).

4.1. Comparison with previous studies

Li et al. have previously developed a computer model to investigate the impact of aortic stenosis severity and vascular compliance and resistance on left ventricular hypertrophy (Li et al., 1997). Their results also suggest that the combination of hypertension with aortic stenosis has a major impact on the development of left ventricular hypertrophy. However, they found that the effects of mild/moderate aortic stenosis on left ventricular hypertrophy were equivalent to those of mild/moderate hypertension, which was not the case in the present study. The discrepancies between these two studies are likely due to the fact that their model included a valvular resistance based on the linear electrical Ohm’s law. This transvalvular pressure-flow model is inappropriate since it does not take account of the local and non-linear convective accelerations

(Garcia et al., 2005b). In this study, we postulated that, in the presence of pressure overload, left ventricular hypertrophy develops in order to maintain the myocardial fiber stress constant. Other studies rather used the normalization of the left ventricular wall stress to develop their numerical models (Li et al., 1997; Segers et al., 2000). However, recent theoretical studies performed by Arts et al. have shown that the homogeneous distribution of myofiber stress leads to high pumping efficiency and optimal mechanical load (Arts et al., 1994; Vendelin et al., 2002; Arts et al., 2005). Therefore, the hypothesis that left ventricular hypertrophy preserves a normal myofiber stress is likely more appropriate.

4.2. Potential clinical implications

According to current ACC/AHA guidelines, the decision to perform an aortic valve replacement should be based on two criteria: (1) diagnosis of a severe aortic stenosis ($EOA \leq 0.75 \text{ cm}^2$) and (2) presence of symptoms (Bonow et al., 1998). Unfortunately, there are often discrepancies between the severity of the stenosis and the symptomatic status. Some patients indeed become symptomatic although they have only a moderate aortic stenosis, whereas others remain asymptomatic despite the presence of a severe stenosis. Our theoretical results may explain, at least in part, these discrepancies. According to these results, a patient having a moderate aortic stenosis and concomitantly a moderate hypertension may have indeed higher left ventricular afterload and more left ventricular hypertrophy than a patient with severe aortic stenosis and normal blood pressure (Fig. 5 and Table 4). Our results may also contribute to explain why the regression of left ventricular hypertrophy varies extensively from one patient to another after aortic valve replacement. This operation corrects the valvular component of the left ventricular afterload but not its vascular component related to hypertension. Hence, patients with severe aortic stenosis and concomitant moderate hypertension may still have important left ventricular hypertrophy despite valve replacement. The contribution of hypertension to the development of left ventricular hypertrophy and symptoms in patients with aortic stenosis is often underestimated in the clinical practice whereas even mild concomitant hypertension (150/95 mmHg) could significantly speed up the course of left ventricular hypertrophy (Fig. 7). This theoretical study thus provides some evidence that hypertension, even at mild degree, is a potentially important determinant of left ventricular afterload and hypertrophy in patients with aortic stenosis. These findings have important implications given that hypertension is frequently associated with aortic stenosis. This suggests that systemic arterial pressure, and more generally vascular hemodynamics

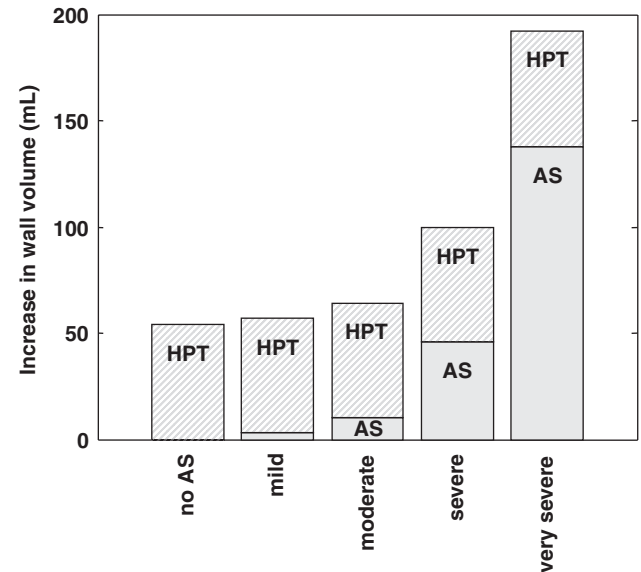


Fig. 7. Theoretical increase in left ventricular wall volume for different severities of aortic stenosis (see Table 4) with concomitant mild hypertension (150/95 mmHg). AS = aortic stenosis, HPT = hypertension.

(Briand et al., 2005), should be routinely considered when assessing the severity of aortic stenosis.

4.3. Limitations of the study

In this study, we only considered the mechanical aspects of left ventricular hypertrophy whereas it is known that numerous hormonal and neurogenic factors are also involved. A complete mathematical model of the cardiovascular system should therefore include the baroreceptor reflexes and the sympathetic and parasympathetic discharges to heart and arterioles and veins. Such a model may be useful to study the short-term cardiovascular regulation (Ursino, 1998; Ursino and Magosso, 2003). However, this type of model is complex and difficult to apply in the context of the modelization of the outcomes of chronic diseases such as aortic stenosis and systemic hypertension. Because we focused on the long-term myocardial regulation, we postulated that myofiber stresses remain within normal range as the left ventricle hypertrophies. A few studies indeed suggested that left ventricular wall stress is maintained constant in cardiac hypertrophy (Grossman et al., 1975) and this postulate is likely appropriate as long as the ventricle functions normally and can adapt to the pressure overload. In addition we hypothesized that the diastolic function was normal because the V^3 model in its present form does not include the atrium–ventricle interaction. The Frank Starling's law, by which cardiac output may be improved by modulating filling pressure, is therefore not taken into consideration in this study. Finally, because it has been reported that ejection

fraction, heart rate, and stroke volume are usually normal in adequate concentric left ventricular hypertrophy (Berkin and Ball, 2001), all the cardiovascular parameters (unloaded volume, end diastolic volume, heart rate, stroke volume) except peak elastance were fixed in the simulations. This may not be the case in some patients and more particularly in symptomatic patients with severe aortic stenosis or severe hypertension. Our simulations thus represent an ideal hypothetical left ventricle, which is able to adapt to even large overloads. Although this may appear restrictive, this method allowed to shed some light on the respective impacts of aortic stenosis and hypertension on left ventricular hypertrophy.

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