IMPACT OF AORTIC STENOSIS ON CORONARY BLOOD FLOW

D. Garcia*, L. Kadem*, P. Pibarot** and L.G. Durand*

* Laboratory of biomedical engineering, IRCM, Montreal, Canada
** Quebec heart institute, Laval university, Quebec, Canada

Damien.Garcia@ircm.qc.ca

Abstract - Aortic stenosis is the most frequent valvular heart disease in developed countries. Development of left ventricular hypertrophy in patients with aortic stenosis is accompanied by an impaired coronary blood flow reserve. The objective of our study was to develop a theoretical model to investigate how aortic stenosis may affect the coronary blood flow and more specifically the coronary vasodilatory reserve. For this purpose, we combined the mathematical ventricular-valvular-vascular (V^3) model with the lumped model of left coronary inflow proposed by Judd and Mates. Effective orifice area was ranged from 3.5 cm^2 (no stenosis) down to 0.35 cm^2 (very severe stenosis). Normotensive conditions (120/80 mmHg) were simulated with a heart rate of 70 bpm. When the severity of aortic stenosis was increased from mild to severe (effective orifice area = 1.5 to 0.5 cm^2), mean coronary blood flow increased exponentially from 150 to 295 mL/min, whereas coronary vasodilatory reserve decreased from 3.6 to 1.2. The theoretical results were very consistent with those previously observed in patients with aortic stenosis. The V^3 model upgraded with the coronary lumped model may therefore contribute to a better understanding of the impact of aortic stenosis on left ventricular coronary circulation and may be useful to predict the development of left ventricular failure.

Introduction

Aortic stenosis (AS) refers to the narrowing of the aortic valve aperture during left ventricular (LV) ejection. AS is the most frequent valvular heart disease and the most frequent cause of valvular replacement in developed countries [1]. It is generally a senile degenerative disease caused by a progressive calcification of the valve leaflets. AS induces an obstruction to blood flow from the left ventricle to the aorta, resulting in an increase of the LV pressure overload. In presence of AS, a compensatory concentric hypertrophy of the left ventricle appears which contributes to maintain normal LV wall stess. As the blood flow passes through an AS, it forms a jet which contracts to a minimum cross-sectional area (so-called effective orifice area, *EOA*) at the level of the vena contracta (Figure 1). The coronary vasodilatory reserve or coronary flow reserve (*CVR*) is defined as the ratio of the coronary flow measured when coronary vasculature is maximally dilated to the basal coronary flow at resting level. Development of LV hypertrophy in patients with AS is accompanied by coronary microcirculatory dysfunction demonstrated by an impaired *CVR* [2]. In such patients, the reduction of *CVR* limits the ability of coronary circulation to increase its flow in order to match myocardial demand. Reduction of *CVR* thus plays a key role in the development of myocardial ischemia and the occurence of symptoms. The objective of our study was to develop a mathematical model to investigate how AS may affect the coronary blood flow and more particularly the coronary vasodilatory reserve (*CVR*). For this purpose, we combined our previously validated mathematical V^3 model [3] with the viscoelastic model of coronary inflow proposed by Judd and Mates [4;5] as described below.

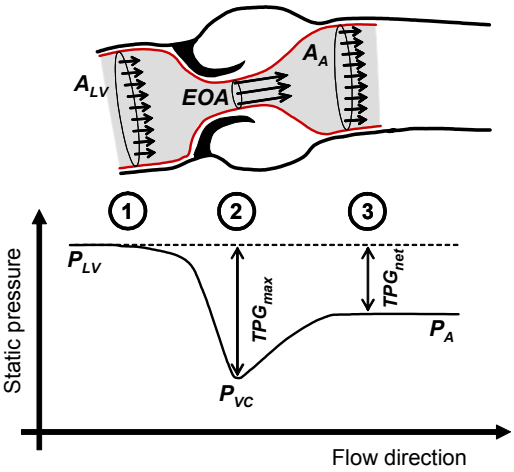

Figure 1. Schema of the flow across an AS during ejection and corresponding pressure field along the flow axis. Locations 1, 2 and 3 correspond to the detachment of the flow, the vena contracta and the reattachment of the flow to the aortic wall. *TPG* is the transvalvular pressure gradient and *EOA* is the valvular effective orifice area. P_{LV} = left ventricular pressure, P_{VC} = pressure in the vena contracta, P_A = aortic pressure, A_{LV} = cross-sectional area of the left ventricular outflow tract, A_A = aortic cross-sectional area.

Materials and Methods

To compute the impact of AS on *CVR*, three previously published mathematical models were utilized, namely the V^3 model [3], the Arts' model [6] and that of Judd and Mates [4]. The V^3 model permits to simulate LV pressure and volume (P_{LV} and V) and aortic pressure under specific cardiovascular conditions, such as aortic stenosis and hypertension. The inlet coronary pressure (P_{IC}) can also be immediately deduced, using the

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maximal transvalvular pressure gradient (TPG_{max}), as explained further. Knowing P_{LV} and V, the Arts' model provides the LV wall volume, and thus the LV wall mass, under the hypothesis that the LV hypertrophy is adequate. Because the mean coronary blood flow (CBF) is essentially proportional to LV mass, one can deduce CBF. From P_{IC} and P_{LV}, the coronary vasculature resistance (R_C) was estimated by means of the lumped model of the coronary circulation proposed by Judd and Mates. Finally, CVR was calculated from CBF and R_C. The overall numerical method is schematized in Figure 2 and each step is thoroughly described below.

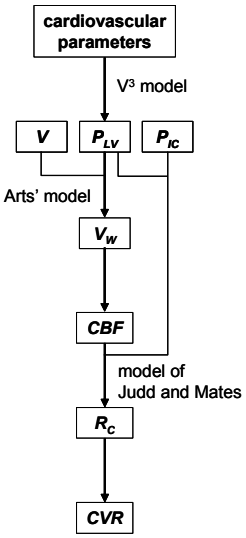

Figure 2. Diagram of the numerical method. V: LV cavity volume, P_{LV}: LV pressure, P_{IC}: inlet coronary pressure, V_W: LV wall volume, CBF: coronary blood flow, R_C: coronary resistance, CVR: coronary vasodilatory reserve.

Mathematical V^3 model. The mathematical V^3 (ventricular-valvular-vascular) model has been validated in six patients during surgery, before and after aortic valve replacement, as described in detail in [3]. Briefly, it combines 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 (Figure 3). The corresponding following equation completely describes the LV cavity volume during blood ejection under the conditions that the ventricular contractility, the arterial properties, and the aortic stenosis severity are known:

$$\frac{2\pi\rho}{\sqrt{E_L Co}}\frac{\partial^3 V(t)}{\partial t^3} = a_3(t)\frac{\partial^2 V(t)}{\partial t^2} + a_2(t)\frac{\partial V(t)}{\partial t} + a_1(t)V(t) + a_0(t)$$

where

$$a_0(t) = V_0\frac{E_{\max}}{T_{E_{\max}}}\frac{\partial E_N(\hat{t})}{\partial \hat{t}} + V_0 E_{\max}\frac{E_N(\hat{t})}{RC} + \frac{P_{VE}}{RC} \quad (1)$$

$$a_1(t) = -\frac{E_{\max}}{T_{E_{\max}}}\frac{\partial E_N(\hat{t})}{\partial \hat{t}} - E_{\max}\frac{E_N(\hat{t})}{RC}$$

$$a_2(t) = \frac{\rho}{2\,RC\,E_L Co^2}\frac{\partial V(t)}{\partial t} - \frac{Z_0 + R}{RC} - E_{\max}E_N(\hat{t})$$

$$a_3(t) = \frac{\rho}{E_L Co^2}\frac{\partial V(t)}{\partial t} - \frac{2\pi\rho}{RC\sqrt{E_L Co}} - Z_0$$

with the appropriate initial conditions:

$$V(t_0) = LVEDV \;;\; \frac{\partial V}{\partial t}(t_0) = 0 \;;\; \frac{\partial^2 V}{\partial t^2}(t_0) = 0 \quad (2)$$

ρ is the blood density. E_N is the normalized ventricular elastance relating LV pressure to $V(t)$ [7] and was shown not to vary significantly from one patient to the other [8]. Its typical waveform issued from [8] and utilized in this study is depicted in Figure 4.

Time parameters t_0 and $\hat{t}$ correspond to the onset of ejection and normalized time (t/T_{Emax}), respectively. $E_L Co$ is the valvular energy loss coefficient defined as $E_L Co = EOA\ A_A/(A_A - EOA)$ where EOA is the effective orifice and A_A is the aortic cross-sectional area [9] (Figure 1). Table 1 summarizes the ten independent cardiovascular parameters necessary for solving equation (1).

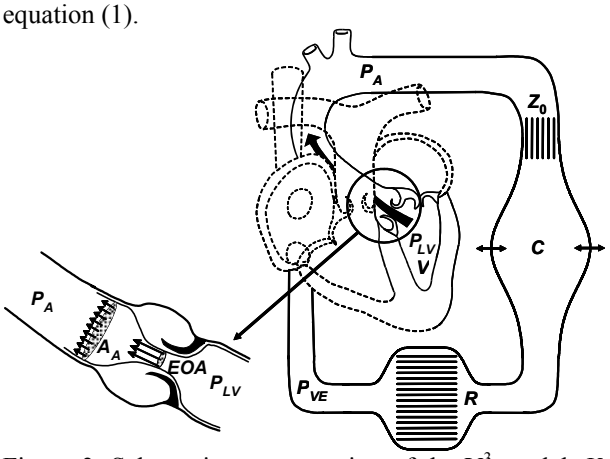

Figure 3. Schematic representation of the V^3 model. V: left ventricular volume, P_{LV}: LV pressure, P_A: aortic pressure, see also Table 1. From [3] with permission.

Table 1. Cardiovascular parameters required for the resolution of the V^3 model. Values in brackets are typical physiological values used for the simulations performed in this study. Note that the cross-sectional area of the LV outflow tract (A_{LV}) is not required for the V^3 model but for equation (3) only.

Ventricular parameters	
Left-ventricular end-diastolic volume	$LVEDV$ (150 mL)
Unloaded volume	V_0 (15 mL)
Maximal elastance	E_{max}
Time to maximal elastance	T_{Emax} (0.33 s)
LVOT cross-sectional area	A_{LV} (3.6 cm^2)
Vascular parameters	
Aortic characteristic impedance	Z_0 (= R/15)
Systemic vascular resistance	R
Total arterial compliance	C
Central venous pressure	P_{VE} (5 mmHg)
Valvular parameters	
Effective orifice area	EOA
Aortic cross-sectional area	A_A (7 cm^2)

The numerical algorithm for solving equation (1) in combination with initial conditions (2) is explained in

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detail in [3]. The transvalvular flow rate $Q(t)$ during ejection is calculated using the negative derivative of $V(t)$ and is further assumed to be zero during the rest of the cardiac cycle as no aortic valve regurgitation is considered. Knowing $V(t)$, LV and aortic pressures (P_{LV} and P_A) are then calculated as previously described [3].

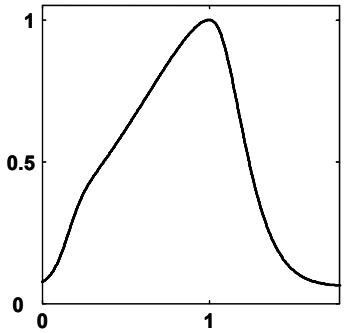

Figure 4. Normalized LV elastance as a function of normalized time (dimensionless).

For this study, *EOA* was ranged from 3.5 cm^2 (no stenosis) down to 0.35 cm^2 (very severe stenosis). Systemic vascular resistance (R) and total arterial compliance (C) were fixed at 1.1 mmHg.s/ mL and 1.8 mL/mmHg to simulate normotensive conditions (120/80 mmHg). Heart rate was 70 bpm and, for every simulation, maximal elastance (E_{max}) was adjusted so that stroke volume was 70 mL. The other required cardiovascular parameters were chosen as in Table 1. Figure 5 depicts two typical examples obtained with the V^3 model.

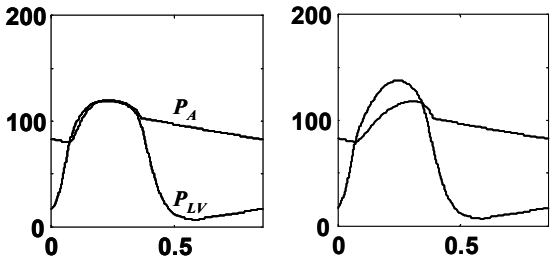

Figure 5. Simulated left ventricular (P_{LV}) and aortic (P_A) pressures without AS (left) and with moderate AS (right). Pressures are in mmHg, time in s.

Inlet coronary pressure. As the blood flow passes through an AS, it forms a jet which contracts to a minimum cross-sectional area (*EOA*) at the level of the vena contracta (location 2, Figure 1). The difference between the LV static pressure (P_{LV}, location 1, Figure 1) and the static pressure at the vena contracta (P_{VC}, location 2) is the so-called maximal transvalvular pressure gradient (TPG_{max}, Figure 1).

According to the study of Sung et al. [10], the mean and peak systolic inlet coronary pressures are similar to those measured in the transvalvular flow jet at the level of the vena contracta during LV ejection. Postulating that the equality is still valid throughout the whole ejection period, the inlet pressure in the ostium may thus be written as [11]:

$$P_{IC} = P_{LV} - TPG_{max} \quad \text{during LV ejection}$$
$$P_{IC} = P_A \quad \text{otherwise,}$$

with $$TPG_{max} = 2\pi\rho\,(1/\sqrt{EOA} - 1/\sqrt{A_{LV}})\,\partial Q/\partial t + 0.5\rho Q^2\,(1/EOA^2 - 1/A_{LV}^2), \quad (3)$$

where P_A and P_V are the aortic and LV pressures, Q is the transvalvular flow rate and A_{LV} is the cross-sectional area of the LV outflow tract (typically 3.6 cm^2). The expression relating instantaneous TPG_{max} to instantaneous transvalvular flow rate (Q) has been recently validated in 19 pigs with different grades of aortic stenosis severity [11].

Left ventricular mass. In case of so-called adequate hypertrophy, LV systolic wall stress is maintained within normal range [12;13]. Hypothesizing that myocardial muscle fiber stresses are homogeneously distributed, Arts et al. have shown that LV muscle fiber stress (σ_f) may be simply related to LV pressure (P_{LV}) and cavity volume to wall volume ratio (V/V_W) as follows [6;14]:

$$P_{LV}/\sigma_f = \frac{1}{3}\ln(1 + V/V_W) \quad (4)$$

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. Indeed, according to recent theoretical studies, homogeneity of myofiber stress leads to high pumping efficiency and optimal mechanical load [14-16]. Applying equation (4) with a normal LV wall volume of 120 mL [17;18] and with a LV pressure waveform obtained under normotensive conditions without aortic stenosis (Figure 5, left), the calculated mean fiber stress is 200 mmHg. Using the postulate that the LV wall hypertrophies so that mean σ_f = 200 mmHg, we thus calculated the wall volume (V_W) for every sets of simulated (P_{LV},V) with the use of equation (4). Figure 5 shows the comparison between LV pressure and myofiber stress in the normal conditions. LV wall mass was calculated assuming a myocardial density of 1.08 g/cm^3.

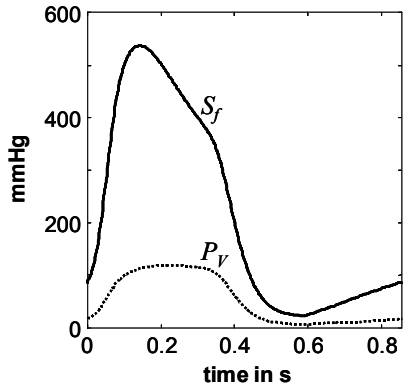

Figure 6. Comparison between left ventricular pressure (P_{LV}) and myofiber stress (S_f) under normal conditions.

Coronary blood flow. Coronary blood flow (*CBF*) is tightly coupled to myocardial oxygen demand [19;20]. Moreover, LV hypertrophy has been suggested to be a structural adaptation which aims at restoring oxygen consumption per unit mass of myocardium toward normal [21]. Thus, it can be postulated that, in patients

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with adequate LV hypertrophy, *CBF* is essentially proportional to LV mass. This has been confirmed in healthy subjects and in patients with hypertrophy cardiomyopathy [22]. The coronary blood flow at rest per gram of myocardial mass is approximately 0.75 mL/min/g [22].

Coronary vasculature resistance. Judd et al. [4;5] have shown in vivo that the relationship between the mean left coronary blood flow (*CBF*) and the inlet coronary pressure (P_{IC}) can be simply related to LV pressure (P_{LV}) as follows:

$$CBF = \frac{1}{R_C}\left(\overline{P_{IC}} - 0.5\,\overline{P_{LV}} - P_{zf}\right) \quad (5)$$

where the overline denotes the temporal mean. R_C is the basal coronary resistance and P_{zf} is the zero-flow pressure that is the inlet coronary pressure at which coronary blood flow would cease. A typical value for P_{zf} in humans is 20 mmHg [23;24]. Assuming such a value for P_{zf}, R_C can be calculated from P_{IC} and P_{LV} by means of equation (5).

Coronary vasodilatory reserve. The coronary vasodilatory reserve or coronary flow reserve (*CVR*) is defined as the ratio of the coronary flow found when coronary vasculature is maximally dilated to the basal coronary flow at resting level [25]. Maximal coronary flow is generally achieved by intracoronary administration of dipyridamole. Thus, *CVR* is expressed as:

$$CVR = \frac{CBF_{\max}}{CBF} \quad (6)$$

what can also be written as:

$$CVR = \frac{R_C}{R_{C\min}} \quad (7)$$

where $R_{C\min}$ represents the minimal resistance that is the reistance of coronary vasculature when maximally dilated. Equation (7) may be rewritten by using the expression of *CVR* in case of no aortic stenosis (CVR_{noAS}) as follows:

$$CVR = \frac{R_C}{R_{C\,\text{noAS}}} CVR_{\text{noAS}} \quad (8)$$

In healthy subjects without aortic stenosis, *CVR* is around 4 [26]. We therefore postulated that $CVR_{\text{noAS}} = 4$. Moreover, in such subjects, *CBF* is ≈ 140 mL/min [22] what gives a $R_{C\,\text{noAS}}$ value of ≈ 20 mmHg.s/mL when applying equation (5) and LV pressure waveform as that of Figure 5 (left). Therefore, *CVR* can be immediately deduced from R_C by means of equation (8).

Table 2. LV wall volume (V_W, mL), mean coronary blood flow (*CBF*, mL/min) and coronary vasodilator reserve (*CVR*) for different AS severities.

EOA	no AS	1.5 cm^2	1.0 cm^2	0.75 cm^2	0.50 cm^2
$\boldsymbol{V_W}$	180	195	220	260	380
CBF	140	150	170	205	295
CVR	4	3.6	3.0	2.3	1.2

Results

When the severity of AS was gradually increased from mild to severe (*EOA* = 1.5 to 0.5 cm^2), LV wall volume and mean coronary blood flow increased exponentially from 190 to 380 mL and from 150 to 295 mL/min, respectively, whereas *CVR* decreased from 3.6 to 1.2 (Table 2). The theoretical results are very consistent with those observed in patients [2;18].

Discussion

Clinical observations. Patients with AS may experience angina pectoris and present ECG signs suggestive of myocardial ischemia, even if they have normal epicardial coronary arteries. Angina is associated with a marked increase in the risk of sudden death in AS patients and is relieved immediately after aortic valve replacement [27], whereas regression of LV hypertrophy may occur over the next several months to years [28]. The reduction of *CVR* is the key factor responsible for myocardial ischemia in AS patients and this may contribute to the development of LV dysfunction, symptoms, and adverse outcomes [2]. There persist some uncertainties and controversies as to the causes of the impairment of *CVR* in these patients. Development of concentric LV hypertrophy in patients with AS is an adaptive response to reduce LV wall stress [12]. In relation to LV mass, total LV *CBF* increases, whereas arteriolar density is reduced. The combination of these two abnormalities is responsible for a partial exhaustion of the autoregulatory capacity of the coronary microcirculation under resting conditions, thus contributing to reduction of *CVR*. This mechanism was initially believed to be the main cause of impaired *CVR* in AS patients until the recent study of Rajappan et al. [2]. This study performed in patients with AS and with normal coronary arteries revealed that the decrease in *CVR* was related to the severity of AS and diastolic perfusion time rather than to LV mass alone. In a subsequent study, the same team reported that changes in *CVR* after aortic valve replacement were not directly related to regression of LV mass but were rather dependent upon change in valve *EOA* [29]. These recent results are in agreement with those of previous studies where coronary hemodynamics were correlated to valve *EOA* [18], transvalvular pressure gradient [18;30;31], and LV wall stress [30]. These findings suggest that extravascular compression of coronary vessels due to increased intramyocardial pressure is one of the main mechanisms responsible for impaired *CVR* and thus myocardial ischemia in AS.

Theoretical results. The present theoretical study was based mainly on the combination of the V^3 model with the lumped model of coronary circulation developed by Judd and Mates. The model of Judd and Mates shows that the mean coronary blood flow depends essentially upon the inlet coronary pressure minus the intramyocardial pressure, the latter being equal to the half of the LV pressure (see Equation 5 and [4]). Postulating that the left ventricle hypertrophies adequately in response to an overload induced by an AS, we deve-

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loped a mathematical model to predict the impact of AS severity on *CVR* in the absence of concomitant cardiovascular disease. The theoretical prediction was very consistent with the clinical observations performed by Rajappan et al. [2] in patients with pure AS. Figure 7 illustrates the comparison between the theoretical curve and their patients' data. The good agreement between the two studies tends to confirm the validity of our theoretical model. We now plan to simulate the effect of AS with concomitant systemic hypertension on *CVR* to analyze their respective clinical impact on LV failure.

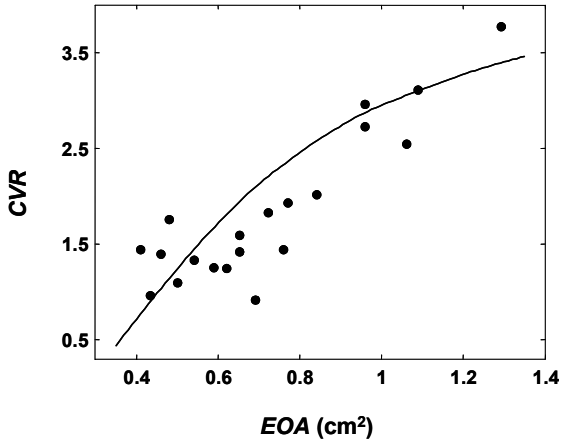

Figure 7. Comparison between the theoretical results (curve) issued from the present study and the measurements performed by Rajappan et al. in patients with AS and no concomitant cardiovascular disease [2].

Conclusion

The mathematical V^3 model upgraded with the coronary lumped model of Judd and Mates may contribute to a better understanding of the effect of aortic stenosis on left ventricular coronary circulation and may be useful to predict the development of left ventricular failure.

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