

In Vitro Investigation of the Impact of Aortic Valve Stenosis Severity on Left Coronary Artery Flow

E. Gaillard

Laboratory of Biomedical Engineering,
Clinical Research Institute of Montreal,
University of Montreal,
110 Avenue des Pins Ouest,
Montreal, QC, H2W 1R7, Canada
e-mail: emmanuel.gaillard@ircm.qc.ca

D. Garcia

CRCHUM,
Research Centre,
University of Montreal Hospital,
2099 Alexandre de Seve,
Montreal, QC, H2L 2W5, Canada

L. Kadem

Laboratory of Cardiovascular Fluid Dynamics,
Concordia University,
1515 St. Catherine Street West,
Montreal, QC, H3G 1M8, Canada

P. Pibarot

Quebec Heart Institute,
Laval Hospital, Laval University,
2725 Chemin Sainte-Foy,
Sainte-Foy, QC, G1V 4G5, Canada

L.-G. Durand

Laboratory of Biomedical Engineering,
Clinical Research Institute of Montreal,
University of Montreal,
110 Avenue des Pins Ouest,
Montreal, QC, H2W 1R7, Canada

Patients with aortic valve stenosis (AS) may experience angina pectoris even if they have angiographically normal coronary arteries. Angina is associated with a marked increase in the risk of sudden death in AS patients. Only a few in vitro models describing the interaction between the left ventricular and aortic pressures, and the coronary circulation have been reported. These models were designed for specific research studies and they need to be improved or modified when other specific studies are required. Consequently, we have developed an in vitro model that is able to mimic the coronary circulation in presence of aortic stenosis. First, we have validated the model under physiological conditions. Then, we have examined and quantified the hemodynamic effects of different degrees of AS (from normal to severe AS) on the coronary flow using a model of the normal left coronary artery. In the coronary in vitro model without AS (normal valve), the amplitude and shape of coronary flow were similar to those observed in in vivo measurements obtained under physiological conditions, as described by Hozumi et al. (1998, "Noninvasive Assessment of

Significant Left Anterior Descending Coronary Artery Stenosis by Coronary Flow Velocity Reserve With Transthoracic Color Doppler Echocardiography," Circulation, 97, pp. 1557–1562). The presence of an AS induced an increase in the maximum and mean coronary flow rates (97% and 73%, respectively, for a very severe AS). Furthermore, when AS was very severe, a retrograde flow occurred during systole. This study allowed us to validate our coronary in vitro model under physiological conditions, both in the absence and presence of AS. These changes could explain the fact that even if patients have angiographically normal epicardial coronary arteries, we can observe the occurrence of angina pectoris in these patients in the presence of an AS.
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Keywords: left coronary artery, aortic valve stenosis, in vitro model

1 Introduction

Patients with aortic valve stenosis (AS) may experience angina pectoris and prevalent electrocardiogram (ECG) signs of myocardial ischemia, even if they have angiographically normal epicardial coronary arteries [1]. Angina is associated with a marked increase in the risk of sudden death in AS patients [2] and is generally relieved immediately after aortic valve replacement (AVR) [3], whereas regression of left ventricular (LV) hypertrophy may occur over the next several months to years [4]. The reduction in the coronary flow reserve (CFR), which is defined as the maximal increase in the coronary blood flow, relative to baseline flow, for a given perfusion pressure when coronary arteries are maximally dilated, is the key factor responsible for myocardial ischemia in AS outcomes [5]. However, there are remaining questions about the causes of impairment of CFR in these patients. Development of concentric LV hypertrophy in patients with AS is an adaptive response to reduce LV wall stress [6]. In relation to LV mass, total coronary blood flow 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 the limitation of CFR. This mechanism was initially believed to be the main cause of impaired CFR in AS patients until the recent study by Rajappan et al. [5]. This study, which was performed in a cohort of 20 patients with AS and normal coronary arteries, revealed that the decrease in CFR measured by positron emission tomography was related to the severity of AS rather than to LV mass. Additionally, CFR was more severely impaired in the subendocardium than in the subepicardium in patients with severe AS. In a subsequent study, the same team reported that changes in CFR after AVR were not directly related to regression of LV mass but rather depended on the change in the valve effective orifice area (EOA) achieved with AVR [7]. These recent results are in agreement with those of previous studies in AS patients, where coronary hemodynamics was correlated with valve EOA [8], transvalvular pressure gradient [8,9], and LV wall stress [10]. Consequently, extravascular compression of coronary vessels due to increased intramyocardial pressure seems to be responsible for impaired CFR, and thus myocardial ischemia in AS.

Only a few in vitro models describing the interaction between the LV and aortic pressures, and the coronary circulation have been reported [11–13], very likely because of the difficulty to mimic such a complex hemodynamic system. Undeniably, the hemodynamic features of the coronary flow are highly dependent on the transmural pressures, which themselves differ from the epicardium to the endocardium.

Thus, the purpose of this study was to develop an in vitro model that is able to mimic the coronary circulation in presence of AS in order to examine and quantify its hemodynamic effects on a normal left coronary artery.

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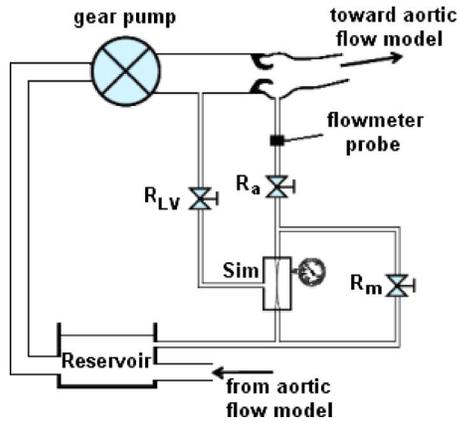


Fig. 1 Schema of the in vitro flow model

2 Methods

2.1 Experimental Model. For the purpose of this study, we modified our validated ventriculo-aortic model [14] by the addition of an in vitro coronary model based on the theoretical model described by Judd and Mates [15]. The hydraulic analog is shown in Fig. 1. The coronary flow model was made up of a soft tube connected to the left coronary ostium of the aorta, which comprises a flow probe, a valve resistance (R_a) mimicking the arteriolar resistance, and a bifurcation including a valve resistance (R_m) on one hand, and a systolic resistor simulating intramyocardial stresses (Sim) on the other hand, depending on the LV pressure. The systolic resistor was based on the model used by Sabbah and Stein [11]. The pressure surrounding the collapsible tube of the systolic resistor was transmitted from the LV and adjusted by using a valve resistance (R_{LV}). This collapsible tube was made of silicone and contributed in part to the compliance in our in vitro coronary model. The outlet of the coronary flow model was connected to the main reservoir of the in vitro aortic flow model.

2.2 Aortic Stenosis Model. To simulate AS, we designed and built a locking system to block the opening of the leaflets of a bioprosthetic aortic valve. A series of screws was inserted in the aortic wall around a 27 mm aortic Mitroflow Synergy™ PC valve and covered with a piece of elastic tube in order to protect the valve (see Fig. 2(a)). The screws were used to control the opening displacement of the valve leaflets (Fig. 2). This system allowed us to vary AS severity from 0% (EOA=2.8 cm²) to a maximum of about 90% (EOA=0.28 cm²) (this means that the valve EOA was reduced, for example, by 90%). In this paper, four different AS severities were studied as presented in Table 1: 0% mimicking a normal aortic valve (EOA=2.8 cm²), 25% mimicking a moderate AS (EOA=1.4 cm²), 50% mimicking a severe AS (EOA=0.7 cm²), and 90% mimicking a very severe AS (EOA=0.28 cm²).

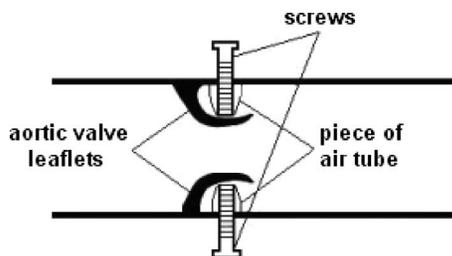


Fig. 2 Schema of the locking system of the aortic valve leaflets

Table 1 AS severity in relation to aortic valve EOA. Values of the coronary flow rate (Qc) and the left ventricular pressure (LVP) for the four different values of EOA. The variations are calculated in relation to the value obtained in the case without aortic stenosis (EOA=2.8 cm²). % systolic Qc means the percentage of mean systolic coronary flow rate in relation to the total mean coronary flow rate.

EOA (cm ²)	2.8	1.4	0.7	0.28
AS severity (%)	0 (no AS)	50 (moderate)	75 (severe)	90 (very severe)
Qc max (mL/min)	108.9	115.3	134.8	214.2
Variations (%)	0	6	24	97
Qc mean (mL/min)	56.9	61.4	61.5	98.2
Variations (%)	0	8	8	73
% systolic Qc	33.9	30.4	28	24.6
LVP max (mm Hg)	118.9	132.2	165.3	223.5
Variations (%)	0	11	39	88
LVP mean (mm Hg)	36.4	37.5	50.9	71.1
Variations (%)	0	3	40	95
Reverse flow (Yes/No)	No	No	No	Yes
Qc min (mL/min)	-	-	-	-41.6

2.3 Experimental Conditions. A Millar catheter (SPC 360S, accuracy of 0.5% full scale) was introduced downstream of the aortic valve in order to measure the aortic pressure. A second Millar catheter was directly introduced in the LV outflow track to measure the instantaneous LV pressure. The aortic flow and left coronary inflow were measured using two electromagnetic flowmeters (Carolina Medical Electronics, East Bend, NC, 600 series, internal diameter=20 mm and 4 mm, respectively, accuracy of 1% full scale). All measurements were performed simultaneously under a wide range of physiologic and pathologic conditions. The aortic flow model was first adjusted to obtain typical normal hemodynamic conditions (Stroke volume=70 ml, systolic blood pressure=120 mm Hg, and diastolic blood pressure=80 mm Hg) at 70 bpm. Then, the resistance and compliance of the coronary section were adjusted in a manner that the coronary flow waveform and its mean value were similar to the ones observed in normal subjects (without AS).

3 Results

As shown in Fig. 3, simulated aortic and LV pressures and aortic flow rate in normal conditions (without AS) were comparable to that observed in human beings [13]. In addition, the amplitude and shape of the coronary flow rate in our in vitro model without AS were similar to in vivo measurements obtained in a normal subject under physiological conditions, as described by Hozumi et al. [16]. In early systole, in this subject, a fast flow rate drop toward zero flow appeared due to the compression of the subendocardial coronary vessels (via a high intraventricular pressure). Over the rest of systole, the heart muscles were still contracted and very little flow occurred in the coronary artery. During diastole, the heart muscles were relaxed, the lumen of the intramyocardial arteries was fully opened, and the major portion of the coronary flow occurred.

In addition, the flow conditions (LV pressure and coronary flow rate) in the in vitro model with an AS (Fig. 4) were in agreement with those reported in patients [8,9]. As can be observed in Fig. 4 and in Table 1, the presence of an AS induced significant increases in the mean coronary flow rate (approximately 73% for a very severe AS), the maximum coronary flow rate (approximately 97% for a very severe AS), and the maximum LV pressure (approximately 88% for a very severe AS). Similarly, variations in EOA were inversely proportional to the variations in the mean coronary flow rate, maximum coronary flow rate, and maximum LV pressure. Furthermore, there was a huge increase in the coronary flow

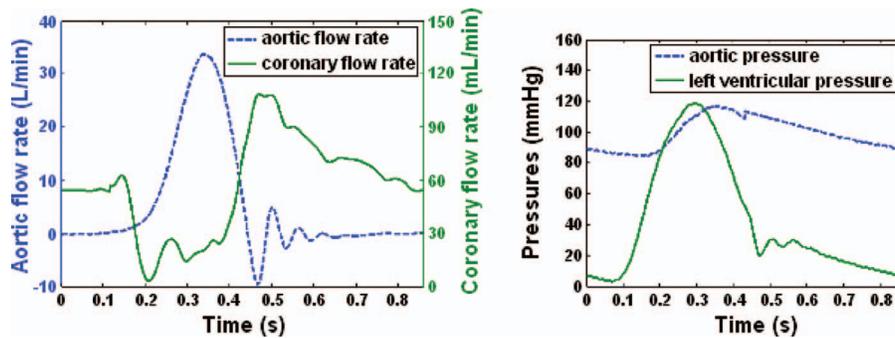


Fig. 3 On the left: aortic and coronary flow rates in normal conditions (without AS) obtained from the in vitro model (notice that scales are not the same for the aortic (L/min) and coronary (mL/min) flow rates); on the right: aortic and LV pressures in normal conditions obtained from the in vitro model

rate at the beginning of diastole. The majority of this mean coronary flow rate increase occurred during diastole (about 80% throughout diastole and 20% throughout systole). Moreover, when the AS is very severe, at the beginning of systole, the coronary flow rate became retrograde (with a minimum flow rate around -41 mL/min), as reported in previous studies [8,17,18], while it remained antegrade without AS and for other AS severities (with a minimum flow rate of about 0 mL/min in all cases). The suction produced by the so-called “Venturi effect” of the aortic flow jet was suggested to be responsible for this reverse in flow [17,19]. However, several investigators have questioned the validity of this mechanism [11,20], some arguing that the flow is not reversed in the right coronary artery [20,21]. But the fact that the compression level is not the same between the left and right sides of the heart due to the pressure difference between the two ventricles could explain that the suction is less important in the right coronary artery. In vivo, it has been shown that the presence of an AS induces an increase in the ventricular activity due to a greater demand in myocardial oxygen consumption [1]. Consequently, the mean coronary flow rate increased (via a decrease in the coronary pressure), which allowed an additional contribution of oxygen and energy to the myocardial muscles. In the presence of an AS, the percentage of the mean systolic coronary flow rate decreased with increasing AS severity, due to the marked increase in LV pressure during systole (Table 1).

4 Conclusions

This study allowed us to validate our coronary in vitro model under physiological conditions, both in the absence and presence of AS. We have shown that AS induced important modifications on the normal left coronary artery flow. The two main changes

were an increase in the maximum and mean coronary flow rates, and the occurrence of a retrograde flow during systole for a very severe AS. These changes could explain the fact that even if patients have angiographically normal epicardial coronary arteries, we can observe the occurrence of angina pectoris in these patients in the presence of an AS [1].

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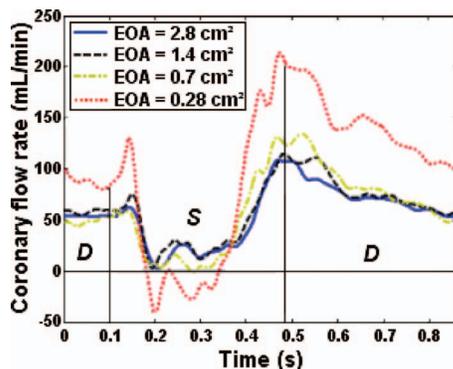


Fig. 4 Coronary flow rate for the four different AS severities obtained from the in vitro model

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