

# Analytical modeling of the instantaneous pressure gradient across the aortic valve

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## Abstract

Aortic stenosis is the most frequent valvular heart disease. The mean systolic value of the transvalvular pressure gradient (TPG) is commonly utilized during clinical examination to evaluate its severity and it can be determined either by cardiac catheterization or by Doppler echocardiography. TPG is highly time-dependent over systole and is known to depend upon the transvalvular flow rate, the effective orifice area (EOA) of the aortic valve and the cross-sectional area of the ascending aorta. However it is still unclear how these parameters modify the TPG waveform. We thus derived a simple analytical model from the energy loss concept to describe the instantaneous TPG across the aortic valve during systole. This theoretical model was validated with orifice plates and bioprosthetic heart valves in an in vitro aortic flow model. Instantaneous TPG was measured by catheter and its waveform was compared with the one determined from the transvalvular flow rate, the valvular EOA and the aortic cross-sectional area, using the derived equation. Our results showed a very good concordance between the measured and predicted instantaneous TPG. The analytical model proposed and validated in this study provides a comprehensive description of the aortic valve hemodynamics that can be used to accurately predict the instantaneous transvalvular pressure gradient in native and bioprosthetic aortic valves. The consideration of this model suggests that: (1) TPG waveform is exclusively dependent upon transvalvular flow rate and flow geometry, (2) the frequently applied simplified Bernoulli equation may overestimate mean TPG by more than 30% and (3) the measurement of ejection time by cardiac catheterization may underestimate the actual ejection time, especially in patients with mild/moderate aortic stenosis and low cardiac output.

*Keywords:* Aortic stenosis; Heart valve; Pressure gradient; Energy loss; Analytical modeling

## 1. Introduction

Aortic stenosis is the most common valvular heart disease in developed countries. It is often a gradually progressive degenerative disease which results in the calcification of the aortic valve leaflets. This causes an obstruction to blood flow from the left ventricle to the aorta which leads to an increase in the left ventricular afterload (Shavelle and Otto, 2000). Once the patient

becomes symptomatic, prognosis is poor if the aortic valve is not replaced (Ross and Braunwald, 1968). A few parameters can be used to evaluate the severity of valvular dysfunction and determine the optimal timing for surgery. The two mostly used parameters are the transvalvular pressure gradient (TPG) and the effective orifice area (EOA) (Shavelle and Otto, 2000). Their mean systolic values can be estimated either by catheterization or by Doppler echocardiography (Baumgartner et al., 1999; Bonow et al., 1998; Shavelle and Otto, 2000). Although EOA can be assumed relatively constant throughout systole in non severely calcified aortic stenoses (Arsenault et al., 1998; Beauchesne et al.,

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2003), TPG is highly time-dependent. An explicit physiological model relating instantaneous TPG to the transvalvular flow rate and EOA is still unavailable.

Clark (1978) was the first to give a detailed description of the instantaneous TPG across the aortic valve. He studied the relative contribution of the local and convective inertia components from a theoretical formulation, which was then validated by animal experimentations. However, the proposed equation included an integral term which requires some knowledge about the flow jet geometry and which makes difficult its clinical application. Recently, Bermejo et al. (2002) used an unsteady Bernoulli equation to investigate the diagnostic implications of negative TPG during late ejection. Again their equation contained an anatomical integral which cannot be calculated a priori. A few other models were also proposed to characterize the TPG through prosthetic heart valves (Graen et al., 1999; Fiore et al., 2002) but still they contain implicit parameters. Hence, to date, no explicit model of the TPG has ever been proposed. The objective of our study was therefore to develop an analytical expression of the instantaneous TPG. Such a theoretical model would improve the comprehension of the transvalvular hemodynamics and would be of great clinical interest.

## 2. Methods

The flow pattern across an aortic stenosis can be compared to the one occurring in orifice plates used as differential-pressure flow metering devices (Ward-Smith, 1980). As the flow passes through a stenotic valve, a jet is produced (cf. Fig. 1). The flow accelerates from some distance upstream from the stenosis in the left ventricular outflow tract (location 1 in Fig. 1) as far downstream as the vena contracta (location 2). The vena contracta corresponds to the location where the cross-sectional area of the jet is minimal. This area is named the EOA. During convective acceleration, static pressure is converted into kinetic energy which is a stable process with virtually no energy loss (Miller, 1990). Beyond the vena contracta, the fluid decelerates as the area occupied by the flow increases to fill the cross-section of the ascending aorta. The jet is rapidly lost in a region of turbulent mixing which involves significant fluid energy dissipation. In this region, the pressure increases until it reaches a maximum at the location where the reattachment of the flow occurs (location 3). The difference between the ventricular pressure and the recovered aortic pressure is the so-called net transvalvular pressure gradient or  $TPG_{net}$  (Baumgartner et al., 1999). We develop hereafter an expression of the instantaneous  $TPG_{net}$  as a function of the transvalvular flow rate  $Q$  and the EOA from the energy loss concept. We suppose that the valve opens and closes rapidly and that its EOA

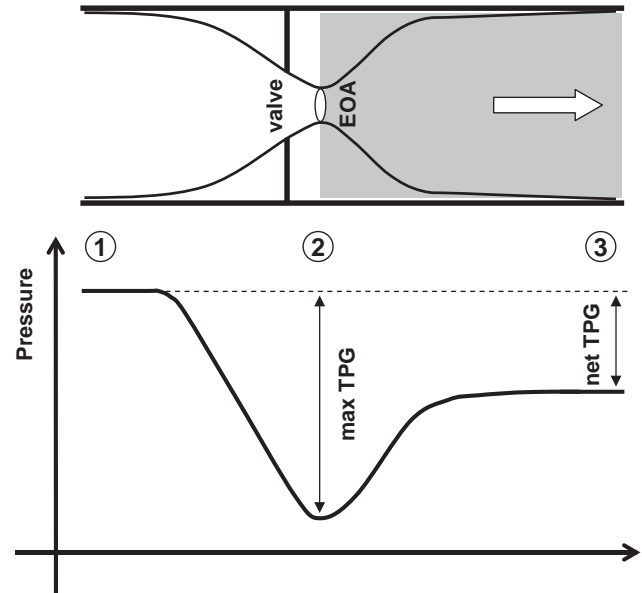


Fig. 1. Schema of the flow across an aortic valve during systole and corresponding pressure field. Locations 1, 2 and 3 correspond to the detachment of the flow, the vena contracta and the reattachment of the flow respectively. TPG is the transvalvular pressure gradient and EOA is the valvular effective orifice area.

remains constant during systole. We also assume that the flow velocity profile is flat throughout the region of interest (i.e. from location 1 to location 3 in Fig. 1). Systole is defined as the period where the transvalvular flow rate  $Q$  is  $>0$ .

### 2.1. Derivation of the energy loss

As above-mentioned, the blood decelerates between the vena contracta (location 2) and the ascending aorta (location 3) which induces an energy loss  $E_L$ . Neglecting the effects of gravitation, the generalized Bernoulli equation used along a streamline linking location 2 with location 3, for an incompressible fluid, is written as

$$P_2 - P_3 = \frac{1}{2}\rho(V_3^2 - V_2^2) + \rho \int_2^3 \frac{\partial V}{\partial t} dl + E_L, \quad (1)$$

where  $P$ ,  $V$ , and  $\rho$  are the pressure, the velocity and the density of the fluid respectively. Coordinate  $l$  is the curvilinear coordinate along the streamline. For a control volume  $\Omega$  that is fixed and nondeforming and whose boundary is  $\Gamma$ , the Newton's second law of motion applied to an incompressible fluid is (Munson et al., 1994):

$$\rho \int_{\Omega} \frac{\partial \vec{V}}{\partial t} d\Omega + \rho \int_{\Gamma} \vec{V} \vec{V} \cdot \vec{n} d\Gamma = \sum \vec{F}, \quad (2)$$

where  $\vec{V}$  is the fluid velocity vector,  $\vec{n}$  is the outward pointing normal to the surface and  $\vec{F}$  are the body and surface forces that act on what is contained in the

control volume. We assume in our study that the action of gravity and shear forces due to the wall are negligible. The only forces acting on the fluid within the control volume defined by the grey area (cf. Fig. 1), in the flow direction axis, are therefore reduced to the inlet and outlet pressure forces. Because velocity profiles are flat in locations 2 and 3, projection of Eq. (2) applied to the latter control volume on the flow direction axis yields

$$\rho \int_{\Omega} \frac{\partial V}{\partial t} d\Omega - \rho V_2^2 \text{EOA} + \rho V_3^2 A_3 = (P_2 - P_3)A_3, \quad (3)$$

where EOA is the effective orifice area and  $A_3$  is the aortic cross-sectional area. From Eqs. (1) and (3), we can get the energy loss:

$$E_L = \rho \left( \frac{1}{A_3} \int_{\Omega} \frac{\partial V}{\partial t} d\Omega - \int_2^3 \frac{\partial V}{\partial t} dl \right) + \frac{1}{2} \rho \left( V_2^2 + V_3^2 - \frac{2\text{EOA}}{A_3} V_2^2 \right). \quad (4)$$

According to the conservation of mass, the transvalvular flow rate  $Q$  can be written as  $Q = \text{EOA} V_2 = A_3 V_3 = A(l) V(l)$ , where  $A(l)$  is the cross-sectional area occupied by the through-flow at the location  $l$ . One can also write  $d\Omega = A(l) dl$ . If we further assume that  $A(l)$  is time-independent, Eq (4) yields

$$E_L = \rho \frac{\partial Q}{\partial t} \left( \frac{L_{23}}{A_3} - \int_2^3 \frac{1}{A(l)} dl \right) + \frac{1}{2} \rho Q^2 \left( \frac{1}{\text{EOA}} - \frac{1}{A_3} \right)^2, \quad (5)$$

where  $L_{23}$  is the distance separating the vena contracta from the reattachment location. Time integration of Eq. (5) over systole eliminates the time derivative of  $Q$  which leads to

$$\overline{E_L} = \frac{1}{2} \rho \overline{Q^2} \left( \frac{1}{\text{EOA}} - \frac{1}{A_3} \right)^2, \quad (6)$$

where the overline denotes the systolic mean. We have previously shown that what we called the energy loss index, derived from Eq. (6), reflects the severity of aortic stenosis better than EOA in patients (Garcia et al., 2000).

## 2.2. Derivation of the net pressure gradient

Recalling that no energy loss occurs between left ventricular outflow tract (LVOT, location 1 in Fig. 1) and the vena contracta (location 2), similarly to Eq. (1), the generalized Bernoulli equation used along a streamline linking location 1 with location 3 yields the net transvalvular pressure gradient

$$\text{TPG}_{\text{net}} = P_1 - P_3 = \frac{1}{2} \rho (V_3^2 - V_1^2) + \rho \int_1^3 \frac{\partial V}{\partial t} dl + E_L. \quad (7)$$

For simplicity we assume that LVOT and aortic cross-sectional areas are equal so that  $V_1 = V_3$  and we note  $A = A_1 = A_3$ . Dynamic pressure gradient  $1/2\rho(V_3^2 - V_1^2)$  is therefore eliminated. Then, if the expression of  $E_L$  given by Eq. (5) is substituted in Eq. (7), we obtain

$$\text{TPG}_{\text{net}} = \rho \frac{\partial Q}{\partial t} \left( \int_1^2 \frac{1}{A(l)} dl + \frac{L_{23}}{A} \right) + \frac{1}{2} \rho Q^2 \left( \frac{1}{\text{EOA}} - \frac{1}{A} \right)^2. \quad (8)$$

Note that the mean  $\text{TPG}_{\text{net}}$  is equal to the mean  $E_L$  and is written as

$$\overline{\text{TPG}_{\text{net}}} = \overline{E_L} = \frac{1}{2} \rho \overline{Q^2} \left( \frac{1}{\text{EOA}} - \frac{1}{A} \right)^2. \quad (9)$$

We define the parameter  $\lambda$ , homogeneous to a length, as follows:

$$\frac{1}{\lambda} = \int_1^2 \frac{1}{A(l)} dl + \frac{L_{23}}{A} \quad (10)$$

so that Eq. (8) is reduced to

$$\text{TPG}_{\text{net}} = \rho \frac{1}{\lambda} \frac{\partial Q}{\partial t} + \frac{1}{2} \rho Q^2 \left( \frac{1}{\text{EOA}} - \frac{1}{A} \right)^2. \quad (11)$$

According to Eq. (10), one can note that when EOA converges towards zero,  $1/\lambda$  tends towards  $+\infty$ . On the contrary, when the stenosis becomes less and less severe, converging towards a no-stenosis case, location 3, that is location where reattachment of the flow jet occurs (Fig. 1), tends towards location 1. If  $\text{EOA}/A = 1$  (no stenosis) then locations 1, 2 and 3 are superimposed and  $1/\lambda$  thus equals zero. Length  $L_{23}$ , and more generally the flow geometry between locations 2 and 3, depend mainly on EOA and  $A$  so that it is meaningful to write  $1/\lambda$  as a function of only EOA and  $A$ . A dimensional analysis leads to

$$\frac{\sqrt{A}}{\lambda} = f \left( \frac{\text{EOA}}{A} \right). \quad (12)$$

A simple monotonous function  $f$  fitting the two latter criteria is the following:

$$\frac{\sqrt{A}}{\lambda} = \alpha \left( \frac{A}{\text{EOA}} - 1 \right)^{\beta}, \quad (13)$$

where  $\alpha$  and  $\beta$  are  $> 0$ . Consequently, from Eqs. (11) and (13), the expression of  $\text{TPG}_{\text{net}}$  becomes

$$\text{TPG}_{\text{net}} = \rho \alpha \frac{1}{\sqrt{A}} \frac{\partial Q}{\partial t} \left( \frac{A}{\text{EOA}} - 1 \right)^{\beta} + \frac{1}{2} \rho Q^2 \left( \frac{1}{\text{EOA}} - \frac{1}{A} \right)^2, \quad (14)$$

where  $\alpha$  and  $\beta$  are two constants to be evaluated. Because it is difficult to calculate  $\alpha$  and  $\beta$  from an analytical development, we determined these constants from in vitro experiments as described in the next section.

### 3. Results

#### 3.1. In vitro experiments with orifice plates: determination of the 2 constants

The mock flow circulation model used in the in vitro study was mainly made up of a reservoir, a stenotic orifice plate, a compliant aortic chamber and a valve resistance. The flow was provided by a computer-controlled DC motor coupled to a gear pump (Vi-CORR, Viking Pump). The left ventricular outflow tract and the aorta were both circular and rigid (cross-sectional area = 800 mm<sup>2</sup>). The compliant chamber was located immediately downstream of the proximal rigid aorta. The fluid was composed of  $\frac{2}{3}$  of water and  $\frac{1}{3}$  of glycerol so that its density (1.08 kg/L) and viscosity (3.5 cP) were similar to that of blood under high shear rate. The flow rate was measured by an electromagnetic flowmeter (Cliniflow II, Carolina Medical Electronics) and the ventricular and aortic pressures with Millar catheters under a sampling frequency of 300 Hz. For each experiment, 10 cycles were recorded during a steady-state regime and the average was used to calculate the hemodynamic parameters.

Six circular (geometric orifice areas = 60, 80, 120, 190, 250 and 320 mm<sup>2</sup>) and 3 triangular (80, 110 and 155 mm<sup>2</sup>) rigid flat sharp-edged orifice plates were tested under 7 pulsatile flow rates (cardiac outputs from 3 to 7 L/min). The duration of the cardiac cycle and of the systole were maintained at  $857 \pm 0$  and  $341 \pm 27$  ms, respectively (70 bpm with a 40% systolic period). The left ventricular pressure was measured 2 cm upstream from the stenotic orifice. The aortic pressure was measured in the rigid aortic section 15 cm downstream of the stenotic orifice where the pressure was totally recovered. The EOA was determined using the following expression issued from Eq. (9).

$$EOA = \frac{1}{A} + \sqrt{\frac{2 \text{TPG}_{\text{net}}}{\rho Q^2}}^{-1} \quad (15)$$

The constants  $\alpha$  and  $\beta$  were evaluated from a linear regression using the logarithmic form of Eq. (14) and the in vitro results. The values of  $\alpha$  and  $\beta$  were 5.65 and 0.54, respectively ( $r^2=0.84$ ,  $n=82$ ,  $SEE=0.114$ ). For simplicity  $\beta$  was rounded at 0.5. A second minimization method thus provided  $\alpha=6.28 \approx 2\pi$  ( $r^2=0.84$ ,  $SEE=0.116$ ). Finally Eq. (14) becomes

$$\text{TPG}_{\text{net}} = 2\pi\rho \frac{\partial Q}{\partial t} \sqrt{\frac{1}{EOA} - \frac{1}{A}} + \frac{1}{2}\rho Q^2 \left(\frac{1}{EOA} - \frac{1}{A}\right)^2 \quad (16)$$

It should be noted that the resulting  $\alpha$  value of  $2\pi$  is likely a coincidence and has no particular physical meaning. Only a complete analytical demonstration could clarify this point. The total relative error

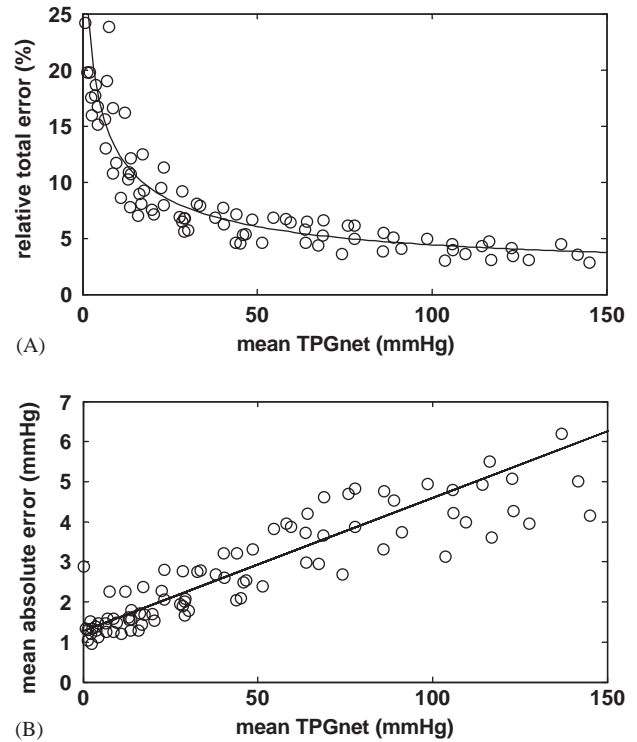


Fig. 2. Total relative error (panel A) and mean absolute error (panel B) between measured instantaneous net (TPG<sub>net</sub>) and estimated instantaneous TPG<sub>net</sub> as a function of the mean TPG<sub>net</sub> measured by catheter in rigid orifice plates ( $n=82$ ).

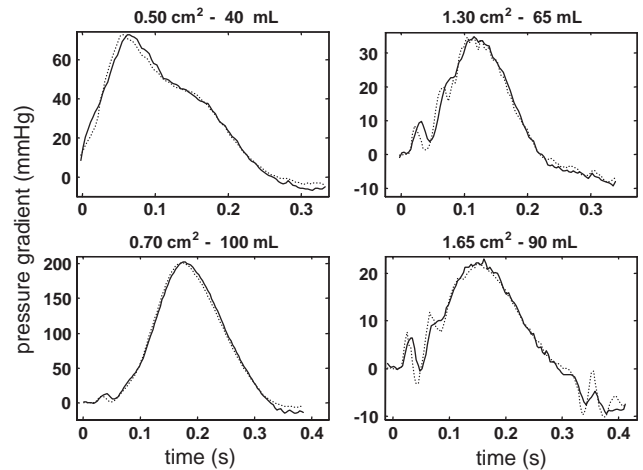


Fig. 3. Four examples showing the comparison between estimated (solid lines) and measured (dotted lines) instantaneous TPG<sub>net</sub> in rigid orifice plates. Titles refer to EOA and stroke volume.

between the measured instantaneous TPG<sub>net</sub> and the one estimated from Eq. (16) was calculated as  $|\text{TPG}_{\text{measured}} - \text{TPG}_{\text{estimated}}| \div |\text{TPG}_{\text{measured}}| \times 100$ , where  $|\dots|$  represents the vectorial 1-norm. The mean absolute

error was calculated as  $|\text{TPG}_{\text{measured}} - \text{TPG}_{\text{estimated}}| / N$ , where  $N$  represents the vector length. The total relative error was less than 6% (Fig. 2A) when the mean  $\text{TPG}_{\text{net}}$  was greater than 50 mmHg (6.66 kPa). When the mean  $\text{TPG}_{\text{net}}$  was less than 20 mmHg (2.66 kPa), it was greater than 10%. Nevertheless the mean absolute error remained around 1.5 mmHg which is of the order of the experimental measurement errors (Fig. 2B). Overall, estimated instantaneous  $\text{TPG}_{\text{net}}$  were very similar to the corresponding measured instantaneous  $\text{TPG}_{\text{net}}$  (Fig. 3). This confirms the validity of Eq. (16) with orifice plates.

3.2. In vitro experiments with bioprostheses

The present theoretical model has been derived from analytical and experimental studies applied to rigid orifice plates. To test whether Eq. (16) is also applicable to native aortic valves and bioprostheses, a second in vitro study was performed with four bioprostheses (Medtronic Mosaic 19, 21, 23 and 25 mm) tested at different flow rates (cardiac outputs from 1.4 to 7.6 L/min). In each experimental condition, systolic flow and pressure waveforms were very similar to those observed in humans (Fig. 4). The protocol was similar to the previous one, except that EOA was also determined by Doppler echocardiography using the continuity equation and assuming a flat velocity profile at the vena contracta. Hence Doppler  $\text{EOA} = \bar{Q} / \bar{V}_2$ , where  $\bar{Q}$  is the mean systolic transvalvular flow rate calculated from the flowmeter and  $\bar{V}_2$  is the mean systolic velocity at the vena contracta measured by continuous-wave Doppler. Instantaneous  $\text{TPG}_{\text{net}}$ , estimated from calculated EOA and the transvalvular flow rate  $Q$  provided by the flowmeter using Eq. (16), was compared with instantaneous  $\text{TPG}_{\text{net}}$  measured by catheter. There was no significant difference in the predicted  $\text{TPG}_{\text{net}}$  calculated using either catheter EOA (Eq. 15), or Doppler EOA. The relative and absolute errors between estimated and measured instantaneous  $\text{TPG}_{\text{net}}$  were greater than those

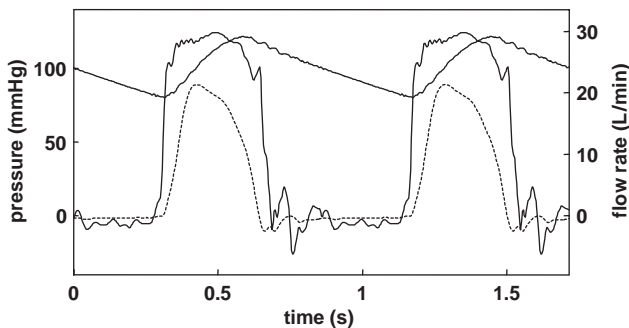


Fig. 4. Typical waveforms of the left ventricular and aortic pressures (solid lines) and of the flow rate (dotted line) obtained with a Medtronic Mosaic 21 mm inserted in the in vitro model (cardiac output = 5 L/min, 70 bpm).

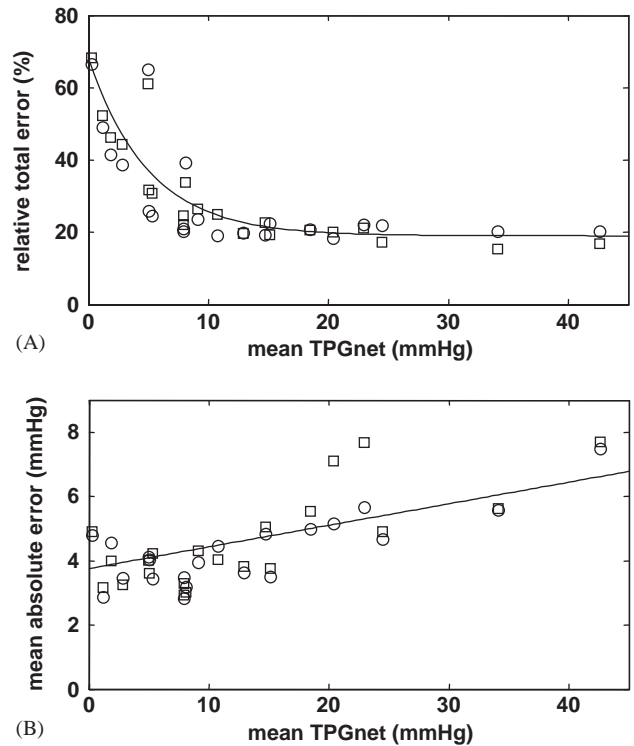


Fig. 5. Total relative error (panel A) and mean absolute error (panel B) between measured instantaneous  $\text{TPG}_{\text{net}}$  and estimated instantaneous  $\text{TPG}_{\text{net}}$  as a function of the mean  $\text{TPG}_{\text{net}}$  measured by catheter in bioprostheses ( $n = 42$ ). The EOA used to estimate  $\text{TPG}_{\text{net}}$  was estimated either by catheter (circles) or by Doppler (squares).

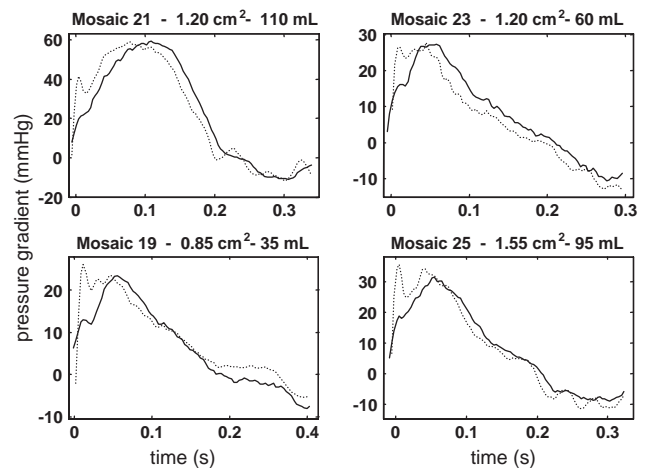


Fig. 6. Four examples showing the comparison between estimated (solid lines) and measured (dotted lines) instantaneous  $\text{TPG}_{\text{net}}$  in bioprostheses. Titles refer to EOA and stroke volume. Note that the Medtronic Mosaic 23 mm at a low cardiac output has a similar EOA as the Medtronic Mosaic 21 at a higher output. Indeed, EOA may increase with increasing flow rate in flexible valves such as the bioprostheses.

observed with the orifice plates (Figs. 5A and B). Nonetheless, Eq. (16) predicted accurately instantaneous  $\text{TPG}_{\text{net}}$  (Fig. 6).



### 3.3. Neglecting dynamic pressure gradient: mean $TPG_{net}$ versus mean energy loss

In the present analytical modeling, we postulated that the LVOT and aortic cross-sectional areas are equal so that the dynamic pressure gradient between LVOT and ascending aorta was eliminated and mean energy loss and mean  $TPG_{net}$  thus became equal (see Eqs. (7) and (9)). If the aortic cross-sectional area of the LVOT is different from that of the ascending aorta (i.e.  $A_1 \neq A_3$ ), which may often be the case in patients with aortic stenosis, the dynamic pressure gradient  $1/2\rho(V_3^2 - V_1^2)$  in Eq. (7) may not always be neglected. Therefore, it should be added into the expression of  $TPG_{net}$  given by Eq. (8). The subsequent Eq. (9) then results in the following equation:

$$\overline{TPG_{net}} = \frac{1}{2}\rho\overline{Q^2} \left[ \left( \frac{1}{EOA} - \frac{1}{A_3} \right)^2 + \left( \frac{1}{A_3^2} - \frac{1}{A_1^2} \right) \right], \quad (17)$$

where  $A_1$  and  $A_3$  are the LVOT and aortic areas, respectively. In order to assess the relative contribution of the dynamic pressure gradient in the calculation of  $TPG_{net}$ , we calculated the relative error between mean  $TPG_{net}$  and mean  $E_L$  in 185 patients with moderate or severe aortic stenosis using Eqs. (6) and (17) as follows:

$$\text{relative error} = \left| \frac{1}{A_3^2} - \frac{1}{A_1^2} \right| \div \left( \frac{1}{EOA} - \frac{1}{A_3} \right)^2. \quad (18)$$

The 185 patients underwent an echocardiographic evaluation at the Quebec Heart Institute. Measurements included left ventricular stroke volume, LVOT diameter, EOA and aortic diameter at the sinotubular junction (Garcia et al., 2003) from which we calculated the relative error defined by Eq. (18). The relative error between mean  $TPG_{net}$  and mean  $E_L$  was on average 8%. It was <10% in 79% (146/185) of patients and among the patients with a severe aortic stenosis ( $EOA < 1 \text{ cm}^2$ ), this error was <10% in 97% (126/130) of patients. Although the relative error increases with increasing EOA, it should be mentioned that for any EOA the absolute error remained very low ( $\leq 5 \text{ mmHg}$  for a cardiac output of 6 L/min) compared to the mean systolic ventricular pressure ( $> 90 \text{ mmHg}$ ). One can therefore conclude that the clinical contribution of the dynamic pressure gradient in the determination of  $TPG_{net}$  is negligible in most of the patients.

### 3.4. $TPG_{net}$ as a function of flow rate and energy loss coefficient

In a previous study (Garcia et al., 2000), we defined from Eq. (6) the energy loss coefficient for an aortic

stenosis as

$$E_L Co = \frac{EOA A_3}{A_3 - EOA}, \quad (19)$$

where  $A_3$  is the aortic cross-sectional area measured at the sinotubular junction. In a second study (Garcia et al., 2003; Levine and Schwammenthal, 2003), we demonstrated that the  $E_L Co$ , in fact, represents the “recovered EOA”, which is, by analogy to the recovered aortic pressure, an expression of EOA that takes into account the pressure recovery occurring downstream of the stenosis. From both a physiological and a clinical standpoints, the  $E_L Co$ , i.e. the recovered EOA, is more meaningful than the EOA because it better predicts the actual energy loss caused by the stenosis and thus the clinical outcomes (Garcia et al., 2000, 2003; Levine and Schwammenthal, 2003). Using the  $E_L Co$  formulation,  $TPG_{net}$  as well as its mean value can also be expressed as

$$TPG_{net} = 2\pi\rho \frac{\partial Q}{\partial t} \frac{1}{\sqrt{E_L Co}} + \frac{1}{2}\rho \frac{Q^2}{E_L Co^2}, \quad (20a)$$

and

$$\overline{TPG_{net}} = \frac{1}{2}\rho \frac{\overline{Q^2}}{E_L Co^2}. \quad (20b)$$

This shows that the net pressure gradient across the aortic valve and its mean systolic value are exclusively dependent upon the flow rate and the energy loss coefficient.

## 4. Discussion

Many studies used a theoretical approach to improve the understanding of the hemodynamics in native or prosthetic aortic heart valves and more particularly the behaviour of  $TPG_{net}$  (Baumgartner et al., 1999; Bermejo et al., 2002; Clark, 1978; Fiore et al., 2002; Graen et al., 1999; Laskey et al., 1995). However, the previous models of instantaneous  $TPG_{net}$  include parameters which can only be deduced a posteriori (Bermejo et al., 2002; Clark, 1978; Fiore et al., 2002; Graen et al., 1999; Laskey et al., 1995). As opposed to these previous models, Eq. (16) can be used to predict instantaneous  $TPG_{net}$  from transvalvular flow rate, EOA and aortic cross-sectional area, which could be of clinical interest. Indeed, because these parameters can easily be obtained by Doppler echocardiography assuming flat velocity profiles at LVOT and constant EOA (Beauchesne et al., 2003; Garcia et al., 2000), instantaneous  $TPG_{net}$  might therefore be estimated non invasively in patients. This would allow to analyze the instantaneous  $TPG$ -flow relationship, which could provide new insights into the unsteady fluid dynamics of the aortic valve and its implication for the clinical assessment of aortic stenosis severity. Further in vivo studies using simultaneous

Doppler and catheter measurements should be performed to further investigate this aspect. More importantly, our model provides a comprehensive description of the aortic valve hemodynamics, which may have several important clinical implications that are presented and discussed below.

#### 4.1. $TPG_{net}$ is not intrinsically dependent upon the systemic arterial system

It is clear from Eqs. (20a,b) that  $TPG_{net}(t)$  and mean  $TPG_{net}$  are exclusively dependent upon  $Q(t)$  or mean  $Q^2$  and  $E_L Co$ . These results are in disagreement with those of two previous studies (Laskey et al., 1995; Razzolini et al., 1999), in which the authors concluded that transvalvular hemodynamics in patients with aortic stenosis also depends on the properties and the pressure of the systemic arterial system. In fact, the arterial properties do not directly influence the transvalvular dynamics but may modify  $Q(t)$ , mean  $Q^2$  or  $E_L Co$  which, in turn, has an effect on  $TPG_{net}$ . The equations proposed and validated in the present study could thus be useful to develop a more comprehensive numerical model to investigate the ventricular-valvular-arterial interaction.

#### 4.2. Overestimation of the $TPG_{net}$ in the simplified Bernoulli equation

The simplified Bernoulli equation is applied to estimate the maximal transvalvular pressure gradient (Fig. 1) during Doppler echocardiography. Using this method, TPG is calculated from the velocity at the contracta as  $1/2\rho\overline{V_2^2}$ . Under the assumption of flat velocity profile and constant EOA over systole, it is equal to  $1/2\rho\overline{Q^2}/EOA^2$ . When confronting this equation to Eq. (9), it appears that the relative overestimation of  $TPG_{net}$  resulting from the utilization of the simplified Bernoulli equation is

$$\text{relative error} = \frac{1}{(1 - EOA/A)^2} - 1, \quad (21)$$

which increases with increasing  $EOA/A$ . In the aforementioned 185 patients (see Section 3.3),  $EOA/A$  ranged from 0.04 to 0.29 (mean  $\pm$  standard deviation =  $0.12 \pm 0.04$ ). For these patients, according to Eq. (21), the overestimation of the  $TPG_{net}$  due to the use of the simplified Bernoulli equation would be on average  $29\% \pm 14\%$ . Because  $TPG_{net}$  better reflects the impact of the aortic stenosis on the left ventricular function than the maximal TPG (Baumgartner et al., 1999; Garcia et al., 2003), the simplified Bernoulli equation is not appropriate in patients with a relatively small aorta.

#### 4.3. Clinical implications of negative $TPG_{net}$ on the estimation of ejection time

In the clinical setting, the estimation of the aortic valve EOA by catheterization using the Gorlin formula requires the determination of the systolic ejection period. During cardiac catheterization, ejection time is measured as the time between the first and second crossovers of left and aortic pressure tracings (Shavelle and Otto, 2000). Therefore, because  $TPG_{net}$  becomes negative during late ejection, the ejection period measured by catheter may be significantly lower than the actual ejection period (Fig. 7), which may introduce an important source of error in the calculation of the catheter-derived mean transvalvular flow rate and valve EOA (Bermejo et al., 2002). Using Eq. (20a), it is possible to determine which conditions are prerequisite to have significant negative  $TPG_{net}$  during systole. For this purpose it is convenient to analyze its dimensionless form. The dimensionless time is noted as  $\hat{t} = t/Te$  where  $Te$  is the actual ejection time that is the period where  $Q > 0$ . If we now consider the normalized systolic flow rate  $\hat{Q}(\hat{t})$  defined between 0 and 1 so that  $\int_0^1 \hat{Q}(\hat{t})d\hat{t} = 1$ , the flow rate  $Q(t)$  can thus be expressed as

$$Q(t) = \frac{SV}{Te} \hat{Q}(\hat{t}), \quad (22)$$

where  $SV$  is the stroke volume. By including Eq. (22) in Eq. (20a), one can derive the dimensionless form of  $TPG_{net}$ :

$$TPG_{net} \hat{G} = \frac{\partial \hat{Q}}{\partial \hat{t}} + \frac{1}{4\pi} \frac{SV}{E_L Co^{3/2}} \hat{Q}^2, \quad (23)$$

where  $TPG_{net} \hat{G} = \frac{Te^2 \sqrt{E_L Co}}{\rho SV} TPG_{net}$ .

The normalized time when  $TPG_{net}$  becomes negative is noted  $\hat{t}_{TPG < 0}$ . It is equal to the catheter ejection time normalized to the actual ejection time (Fig. 7). Consequently  $\hat{t}_{TPG < 0}$  is the solution of the following equation:

$$\frac{\partial \hat{Q}}{\partial \hat{t}} \Big|_{\hat{t}_{TPG < 0}} + \frac{1}{4\pi} \frac{SV}{E_L Co^{3/2}} \hat{Q}^2(\hat{t}_{TPG < 0}) = 0. \quad (24)$$

The shape of the dimensionless flow rate  $\hat{Q}(\hat{t})$  may vary significantly from one patient to the other. However, if we assume that the flow waveform has a sine shape to facilitate the resolution of Eq. (24),  $\hat{Q}(\hat{t})$  can be written:

$$\hat{Q}(\hat{t}) = \frac{\pi}{2} \sin(\pi \hat{t}). \quad (25)$$

Eq. (24) can therefore be reduced to a simple quadratic equation whose one solution corresponds to  $\hat{t}_{TPG < 0}$ :

$$\hat{t}_{TPG < 0} = \frac{1}{\pi} \arccos\left(\frac{1}{\Pi} - \sqrt{\frac{1}{\Pi^2} + 1}\right), \text{ where } \Pi = \frac{SV}{4\pi E_L Co^{3/2}}. \quad (26)$$

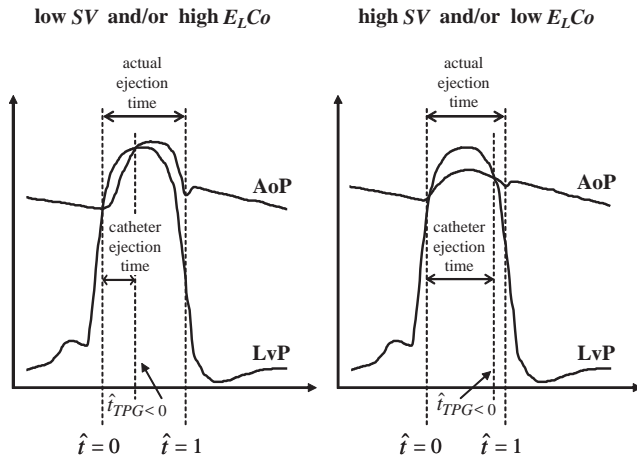


Fig. 7. Definition of the catheter ejection period as measured from left ventricular (LvP) and aortic (AoP) pressure tracings. Time  $\hat{t}_{TPG<0}$  corresponds to the normalized time when TPG becomes negative during systole. When  $SV$  is low and/or  $E_LCo$  is high, the catheter-derived ejection time markedly underestimates the actual ejection time (left panel). On the other hand, in presence of high  $SV$  and/or low  $E_LCo$ , the catheter ejection time converges towards the actual ejection time (right panel).

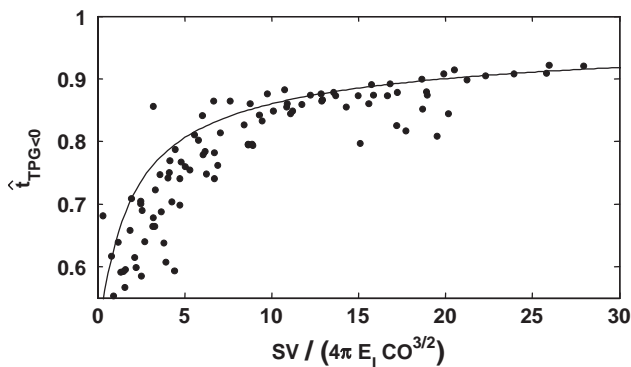


Fig. 8. Normalized time  $\hat{t}_{TPG<0}$  measured with the orifice plates and the bioprostheses as a function of the dimensionless parameter  $SV/(4\pi E_LCo^{3/2})$ , where  $SV$  is the stroke volume and  $E_LCo$  is the valvular energy loss coefficient. The curve represents the theoretical relation given by Eq. (26). Note that  $\hat{t}_{TPG<0}$  is equal to the ratio: catheter ejection time/actual ejection time.

It should be noted that according to this equation: (1)  $\hat{t}_{TPG<0}$  converges towards 0.5 if  $\Pi$  converges towards 0 (i.e. if  $SV \rightarrow 0$  and/or  $E_LCo \rightarrow \infty$ ) and (2)  $\hat{t}_{TPG<0}$  converges towards 1 if  $\Pi$  tends towards  $+\infty$  (i.e. if  $SV \rightarrow +\infty$  and/or  $E_LCo \rightarrow 0$ ). The catheter ejection time normalized to the actual ejection time (i.e.  $\hat{t}_{TPG<0}$ ) and the dimensionless  $\Pi$  parameter were calculated using the data obtained from in vitro experiments performed in orifice plates and bioprostheses. There is strong agreement between these experimental data and the theoretical relationship given by Eq. (26) (Fig. 8). It can thus be concluded that the relative error between

catheter ejection time and actual ejection time is mostly dependent on the  $SV/E_LCo^{3/2}$  ratio, and this error may be important in mild/moderate stenosis with low cardiac output (Figs. 7 and 8). For example, the application of Eq. (26) to the data obtained in the 185 patients mentioned in Section 3.3 suggests that the catheter ejection time would underestimate the actual ejection time by  $20\% \pm 4\%$ . Further clinical studies are necessary to determine the impact of this error on the calculation of the catheter-derived EOA and on the resulting assessment of aortic stenosis severity.

## 5. Limitations of the study

The derivation of the analytical expression of the  $TPG_{net}$  in this study necessitated a few essential hypotheses: (1) flat velocity profiles in the through-flow, (2) fixed flow geometry throughout systole and (3) equality of LVOT and ascending aorta cross-sectional areas. However, because the transvalvular flow is not rectilinear nor axisymmetric, irregular velocity profiles have been reported both in LVOT and in ascending aorta (Haugen et al., 2002; Segadal and Matre, 1987). Moreover, it is known that the aortic diameter changes during systole due to the visco-elastic properties of the arterial wall (Lansac et al., 2002). We also postulated that EOA is constant throughout ejection. Whereas this hypothesis is adequate in normal and mildly or moderately stenotic aortic valves as well as in bioprosthetic valves, it has been reported that the EOA may vary during ejection in patients with severe aortic stenosis, and particularly in those with severely calcified valves (Arsenault et al., 1998; Beauchesne et al., 2003). Finally a more complete model should include the LVOT area to take into account the dynamic pressure gradient. However, as mentioned in Section 3.3, its relative contribution can be neglected in patients with aortic stenosis. Hence, further studies are necessary to evaluate the applicability and accuracy of the model in patients with various degrees of aortic stenosis and/or valve leaflet calcification.

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