Assessment of Aortic Valve Stenosis Severity
A New Index Based on the Energy Loss Concept

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Background—Fluid energy loss across stenotic aortic valves is influenced by factors other than the valve effective orifice area (EOA). We propose a new index that will provide a more accurate estimate of this energy loss.

Methods and Results—An experimental model was designed to measure EOA and energy loss in 2 fixed stenoses and 7 bioprosthetic valves for different flow rates and 2 different aortic sizes (25 and 38 mm). The results showed that the relationship between EOA and energy loss is influenced by both flow rate and aortic cross-sectional area ($A_A$) and that the energy loss is systematically higher (15±2%) in the large aorta. The coefficient ($EOA \times A_A$)/($A_A - EOA$) accurately predicted the energy loss in all situations ($r^2 = 0.98$). This coefficient is more closely related to the increase in left ventricular workload than EOA. To account for varying flow rates, the coefficient was indexed for body surface area in a retrospective study of 138 patients with moderate or severe aortic stenosis. The energy loss index measured by Doppler echocardiography was superior to the EOA in predicting the end points, which were defined as death or aortic valve replacement. An energy loss index $\equiv 0.52 \text{cm}^2/\text{m}^2$ was the best predictor of adverse outcomes (positive predictive value of 67%).

Conclusions—This new energy loss index has the potential to reflect the severity of aortic stenosis better than EOA. Further prospective studies are necessary to establish the relevance of this index in terms of clinical outcomes.

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Key Words: echocardiography □ hemodynamics □ valves □ stenosis

Transvalvular pressure gradients (TPG) and valve effective orifice area (EOA) are the parameters currently used for the hemodynamic evaluation of native and prosthetic heart valves.1-5 Recent studies, however, have emphasized the importance of taking into account the pressure recovery phenomenon that occurs downstream from heart valves.6-9 Indeed, often quite a difference exists between the gradient measured by Doppler echocardiography (TPGmax) and that measured by catheterization. The latter is the net pressure drop (TPGnet), ie, the gradient of pressure between the left ventricular outflow tract and the ascending aorta. The difference between TPGmax and TPGnet is called pressure recovery, and it is due to the conversion of a certain amount of kinetic energy (dynamic pressure) to potential energy (static pressure) downstream from the valve (Figure 1). Recent studies suggested that pressure recovery may be clinically relevant in patients who have moderate or severe aortic stenosis and a small aortic cross-sectional area.7,10,11 Overall, these observations suggest that the parameters presently used to assess the severity of aortic valve stenosis do not always accurately reflect the energy loss and the increased workload caused by the stenosis.

The purpose of this study was to find a Doppler echocardiographic parameter that provides a more accurate estimate of the energy loss across aortic valves and, hence, of the severity of aortic stenosis. To do this, we used an experimental model to derive Doppler and catheterization measurements for 2 stenoses and 7 bioprosthetic heart valves studied at different steady and pulsatile flow rates and for 2 different aortic cross-sectional areas. A second objective was to evaluate the performance of this new index in predicting the adverse clinical outcome of patients with aortic stenosis when compared with the currently recommended parameter for the assessment of the severity of aortic stenosis, ie, the valve EOA.5

Methods

In the equations, the following symbols, $\rho$, $P$, $V$, $A$, and $Q$, are used to indicate the density, the static pressure, the velocity, the cross-sectional area, and the flow rate, respectively. The cross-product is denoted $AB$, and the integral $\int AB$ is understood as $\int AB \, ds$. The symbols $\sigma$, $S$, and $\alpha$ denote the generalized stress function, the component of the strain tensor, and the thickness of a section, respectively. The parameter $\alpha$ is positive if the section is convex. The vector $\mathbf{N}$ denotes the outward normal to the section, and $\mathbf{I}$ and $\mathbf{II}$ are the vectors parallel to the section and the plane containing the section, respectively.

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Theoretical Background

Using the basic concepts of hydraulics, a loss of fluid energy by dissipation into heat is observed after an abrupt change in flow geometry. The energy in a fluid (due to gravity, static pressure, and motion) is often expressed in terms of total pressure. Because the contribution of gravity is negligible in the context of aortic valve flow, the energy of this flow can be defined as \( P + (0.5\rho \times V^2) \); note that \( 0.5\rho \times V^2 = 4V^2 \) when the pressure is expressed in \( \text{mm Hg} \) and the velocity in \( \text{m/s} \). The first term is the potential energy due to static pressure, and the second is the kinetic energy due to dynamic pressure. When the blood flows through an aortic valve, it is spatially accelerated from the left ventricular outflow tract to the vena contracta; then, it is decelerated within the divergence of the jet downstream from the vena contracta (Figure 1). During acceleration, a part of static pressure is converted to dynamic pressure, which is a stable and low-energy dissipation process. More precisely, the fluid energy upstream from the vena contracta is negligible. During deceleration, a certain amount of dynamic pressure is reconverted to static pressure. This process is unstable and it generates turbulence, which means that a part of the initial energy is dissipated into heat and is, therefore, irreversibly lost after the vena contracta. Thus, the energy loss between the left ventricular outflow tract and the ascending aorta can be shown as follows:

\[
E_L = (P_V - P_A) + \left( \frac{1}{2} \rho \times K \times Q^2 \right)
\]

where \( K = \frac{A_v}{A_A} \times \frac{A_A}{A_v} \)

This equation was used to determine energy loss by means of catheter pressure and flowmeter measurements. Energy loss can also be determined by Doppler echocardiography. Indeed, using equation 9 (in the Appendix), energy loss can be expressed as follows by using the flow rate (Q) and the EOA.

\[
E_L = 4V_v^2 \left( 1 - \frac{A_A}{A_V} \right)^2 = (4 \times 10^{-4}) \left( \frac{Q^2}{1 - \frac{A_A}{A_V}} \right)^2
\]

Equation 2 can also be rearranged, taking into account the unit conversion, as follows:

\[
\frac{E_O A \times A_A}{A_A - E_O A} \times \frac{Q}{50 \times \sqrt{E_L}}
\]

In Vitro Study

Description of the Model

The modular mock flow circulation model used in this study is shown in Figure 2. It was previously described in detail and validated. Blood was mimicked by using a water/glycerol solution (70%/30%) that contained cornstarch particles (ultrasound scatterers). Pressure measurements were performed using fluid-filled side-hole catheters, and flow rate was measured with an electromagnetic flowmeter. An Ultramark 9 HDI was used for Doppler velocity measurements.

Protocol: Steady Flow

All measurements were made in the same flow model, but 2 different aortic cross-sectional areas were used. The cross-sectional area of the left ventricular section \( A_v \) was 5.07 cm² (diameter, 2.54 cm). That of the first aortic section \( A_a \) was 5.07 cm² (hence, \( A_v/A_a = 1 \)). The cross-sectional area of the second section \( A_{a2} \) was 11.34 cm² (diameter, 3.80 cm; hence, \( A_v/A_{a2} = 0.45 \)). Seven aortic bioprosthetic valves (Medtronic Intact 19, 21, 23, and 25 mm; Medtronic Mosaic 21, 23, and 25 mm) and 2 stenoses (2 plexiglas plates with circular orifices of 75 and 100 mm², respectively) were tested. The ventricular pressure was adjusted to \( \approx 100 \text{ mm Hg} \). The bioprosthetic valves and stenoses were tested under flow rates of 90, 147, 203, 260, 317, 373, and 430 mL/s. The stenoses could not be tested at 373 and 430 mL/s because of an excessive increase in ventricular pressure. For each flow rate, the ventricular pressure was measured 20 mm upstream from the valve, and the aortic pressure was measured at 0.0, 2.5, 5.0, 7.5, 10, 15, 20, 30, 40, 60, 80, and
100 mm downstream from the valve. The reference point 0.0 mm corresponded to the exit of the valve ring. For each flow rate tested, the measurement of the TPG was repeated 3 times and averaged. The highest jet velocity was measured by continuous-wave Doppler. In the steady-flow experiments, the mean ventricular flow velocity was derived from the continuity equation by dividing the mean flow rate measured with the electromagnetic flowmeter by the cross-sectional area of the ventricular section.

Protocol: Pulsatile Flow
The bioprosthetic heart valves and the stenoses used for the pulsatile flow study were tested under 3 stroke volumes, 50, 60, and 70 mL, and an ejection time of 300 ms, which corresponded to mean flow rates of 166, 200, and 233 mL/s. The pulse rate was maintained at 72 beats/min. The pressure measurements were performed at the same positions as those used in steady-flow measurements. These measurements were averaged over 10 cardiac cycles. The valve parameters were computed at peak systole because the flow acceleration is negligible at this specific moment. The jet velocity was assessed by continuous-wave Doppler. The ventricular flow velocity was obtained by positioning the sample volume of the pulse-wave Doppler beam ~20 mm upstream from the valve using a sample volume of 15 mm.

Data and Statistical Analysis
The valve EOA was determined by Doppler echocardiography using the standard continuity equation and by catheter using a combination of Bernoulli and continuity equations, as previously described.14 The energy loss was measured by catheterization using equation 1 and by Doppler echocardiography using equation 2. Statistical analysis of the association of variables was performed with the Pearson correlation coefficient, and graphs were constructed with the corresponding linear regression equation.

In Vivo Study
Patients
A retrospective study was performed on 138 consecutive patients (80 men and 58 women; mean age, 67±14 years) who underwent an echocardiographic evaluation at the Quebec Heart Institute between January 1997 and June 1998 and who were considered to have moderate (valve EOA ≤1.5 cm² and >1.0 cm²) or severe (EOA ≤1.0 cm²) aortic stenosis on the basis of the criteria recommended by the American Heart Association and the American College of Cardiology.3 End points were defined as death or aortic valve replacement within 8 months after the echocardiographic evaluation. To give more clinical perspective to the study, an echocardiographic evaluation was also performed on 26 healthy subjects (21 men and 5 women; mean age, 45±11 years) with no evidence of heart disease (normal group).

Doppler Echocardiography
Measurements were performed using a Sonos 2000, 2500, or 5500 ultrasound system (Hewlett Packard) and included the transvalvular flow velocity using continuous wave Doppler, left ventricular outflow tract velocity using pulsed-wave Doppler, and left ventricular outflow tract diameter, as previously described.3 Two-dimensionally directed left ventricular M-mode dimensions and the aortic diameter at the tip of the valve leaflets were measured in the left parasternal long-axis view using the recommendations of the American Society of Echocardiography. With these measurements, we calculated left ventricular stroke volume and ejection fraction, left ventricular mass (using the corrected American Society of Echocardiography formula), peak and mean TPG (using the modified Bernoulli equation), valve EOA (using the standard continuity equation), and the energy loss coefficient (EOA×A2)/(A3−EOA). To take into account the cardiac output requirements of the patient under normal resting conditions,2 3 the EOA and the energy loss coefficient were also indexed for body surface area.

Results
In Vitro Study
Relationship Between Doppler and Catheter Measurements
A very good correlation between Doppler and catheter measurements was found both with steady and pulsatile flows for TPGmax and EOA (r²>0.97). The fitted lines were very close to the identity lines for TPGmax (slope was 0.96 under steady flow and 1.02 under pulsatile flow). For EOA, the Doppler measurements were slightly underestimated compared with the catheter measurements (slope was 0.93 under steady flow and 0.94 under pulsatile flow). The standard errors of the estimates of TPGmax and EOA were ≤3.09 mm Hg and ≤0.05 cm², respectively.

As shown in Figure 3, a very good correlation (r²>0.98) and concordance between Doppler and catheter measurements were also found for energy loss. These results confirm the validity of the theoretical assumptions used for the determination of energy loss by Doppler echocardiography. Effects of EOA and Cross-Sectional Aortic Area on Energy Loss
Figure 4 shows the relationship between energy loss and the EOA for different levels of flow rate (for clarity, only 3 flow...
rates are shown in the figure). This figure includes the data obtained by Doppler echocardiography with the small (Aa1) and the large (Aa2) aortic sections. In accordance with the theory (equation 2), the energy loss increased with increasing flow rate and decreasing valve EOA. Furthermore, for the same valve EOA and the same flow rate, the energy loss was systematically higher (15±2%) with the larger aorta.

Figure 5 shows the relationship between the energy loss and the coefficient (EOA×Aa1)/(Aa1−EOA) for different flow rates and the 2 cross-sectional aortic areas. In contrast with Figure 4, the measurements obtained with the small and the large aortic sections are on the same curves. In accordance with the theory (equation 3), the energy loss increased markedly with increasing flow rate and decreasing (EOA×Aa1)/(Aa1−EOA). It is also clear that the energy loss is determined uniquely by the (EOA×Aa1)/(Aa1−EOA) coefficient for a given flow rate. Also, the two stenoses had lower (EOA×Aa1)/(Aa1−EOA) coefficients than did bioprosthetic valves and, therefore, they resulted in greater energy loss. The small overlap observed between the normal bioprosthetic valves and the fixed stenotic orifices is due to the fact that the small porcine bioprostheses are at least mildly stenotic, although they function normally. For example, the valve EOA of the 19-mm Medtronic Intact bioprosthesis was between 0.67 and 0.90 cm², depending on flow rate, which is close to the EOA of the largest stenotic orifice: 0.64 cm².

**In Vivo Study**

Among the 138 patients included in this retrospective study, 44 (31.9%) had moderate aortic stenosis and 94 (68.1%) had severe aortic stenosis. Of these patients, 5 (3.6%) died and 60 (43.5%) underwent aortic valve replacement within 8 months after the echocardiographic evaluation.

The results of the univariate analysis of potential predictors of outcome (ie, death or aortic valve replacement) are shown in the Table. A significant (P<0.01) association existed between the outcome and patient age, peak TPG, mean TPG, valve EOA, indexed EOA, energy loss coefficient, and energy loss index. However, in the multivariate analysis (Table), the energy loss index (P<0.0001) and patient age (P=0.014) were the only independent predictors of outcome. The best predictor of outcome (sensitivity, 68%; specificity, 67%; positive predictive value, 67%) was obtained using an energy loss index ≤0.52 cm²/m². Of the 68 patients who had an energy loss index >0.52 cm²/m², 44 (65%) died or underwent aortic valve replacement within 8 months after the echocardiographic evaluation compared with 21 of 70 patients (31%) in the group of patients with an energy loss index >0.52 cm²/m² (Figure 6). All normal subjects had an energy loss index >1.35 cm²/m², and no overlap existed between these subjects and the patients with aortic stenosis.

**Discussion**

Patients who have aortic stenosis and similar aortic valve EOs may have different clinical outcomes2,16; this observation suggests that factors other than valve area may impact left ventricular workload. The noninvasive estimation of energy loss might be useful for the hemodynamic assessment of patients with aortic stenosis because it more closely reflects the amount of left ventricular energy that is lost during systole due to the obstruction created by the valve. Several investigators suggested studying the hemodynamic performance of stenotic valves by assessing energy loss.9,17–20 However, to our knowledge, this is the first study that proposes an expression of the energy loss that can be easily and accurately determined by Doppler echocardiography.

As demonstrated, the energy loss caused by an aortic valve depends not only on flow rate and valve EOA, but also on the aortic cross-sectional area. Hence, at any given flow rate, the energy loss is dependent on the coefficient (EOA×Aa1)/(Aa1−EOA) rather than EOA alone. To illustrate this concept, Figure 7 shows the variation of energy loss as a function of EOA for different aortic diameters and, thus, different values of Aa1 (left) and as a function of Aa1 given different values of EOA (right). These relationships show that in the context of severe aortic stenosis (EOA<1.0 cm²), a small decrease in EOA results in dramatic increases in energy loss (Figure 7, left). In contrast, the energy loss increases markedly when the aortic diameter increases from 15 to 30 mm; it then reaches a plateau when the aortic diameter becomes >30 mm (Figure 7, right). These results agree with those determined in the study.
of Baumgartner et al., which showed that the pressure recovery phenomenon is clinically relevant mostly in patients with an aortic diameter <30 mm.

As pointed out in previous studies, a valve EOA that is acceptable for a small, inactive patient may be unsatisfactory for a larger, physically active individual; it is therefore relevant to index the valve EOA for body surface area to take into account the cardiac output requirements of the patient under normal resting conditions. As suggested by equation 3 and confirmed by experimental in vitro data, the energy loss is essentially determined by 2 factors: the coefficient \((\text{EOA} \times \text{AA}) / (\text{AA} - \text{EOA})\) and the transvalvular flow rate, which at rest is mainly related to body size. Hence, for clinical application, the coefficient \((\text{EOA} \times \text{AA}) / (\text{AA} - \text{EOA})\) was indexed for body surface area. The resulting energy loss index, \([\left(\text{EOA} \times \text{AA}\right) / (\text{AA} - \text{EOA})]/\text{body surface area}\), is an estimate of the energy loss through the physiological system composed of the valve and the aortic root, assuming a normal transvalvular flow rate, and it allows one to compare the severity of aortic stenosis in patients with different body surface areas and different resting cardiac outputs.

Figure 8 illustrates the theoretical relationship between energy loss and this index assuming a normal cardiac index of 3.0 L \(\cdot\) min \(^{-1}\) \(\cdot\) m\(^2\) at rest, a heart rate of 65 beats/min, and a systolic ejection time of 300 ms. This relationship is analogous to the strong inverse exponential relation that we previously found between the mean TPG, either at rest or during exercise, and the valve area indexed for body surface area. However, as stated in the introduction, the TPG does not necessarily reflect the energy loss in all situations. By integrating both the valve area and the aortic cross-sectional area, the new index proposed in the present study represents an evolution in that it provides a more accurate estimation of energy loss across the valve.

![Figure 6](image-url)  
**Figure 6.** Comparison of energy loss index between patients with and without adverse clinical events (death or aortic valve replacement) and normal subjects. Dashed line represents an energy loss index of 0.52 cm\(^2\)/m\(^2\). AVR indicates aortic valve replacement.

![Figure 7](image-url)  
**Figure 7.** Variation of energy loss as a function of EOA (left) when \(A_a\) remains constant and as a function of \(A_a\) (right) when EOA remains constant. Transvalvular flow rate was assumed to be 250 mL/s. Abbreviations as in Figure 5.
The validity of this new index is also confirmed by the results of the in vivo study, which showed that the energy loss index was superior to the valve EOA in predicting adverse clinical outcomes in patients with moderate to severe aortic stenosis. In this context, it is interesting to note that the critical threshold that we found in the clinical study (Figure 6) is consistent with the theoretical relationship shown in Figure 8, whereby the energy loss increases dramatically when the energy loss index becomes <0.50 cm²/m². Therefore, an energy loss index <0.50 cm²/m² should probably be considered a critical value below which patients should be closely monitored for the appearance of symptoms.

**Limitations of the Study**

Several in vitro and in vivo studies have demonstrated that the EOA of native or prosthetic valves can increase with increasing flow rates and in varying degrees depending on valve geometry and compliance.23,24 A significant increase in the EOA of bioprosthetic valves with increasing flow was indeed observed in the present study. In contrast, previous studies suggest that minimal or no change occurs in the aortic root diameter with increasing flow.25 Consequently, an increase in valve EOA with flow rate, such as may occur during exercise, would result in an increase in the coefficient (EOA×Aa)/(Aa−EOA), meaning that relatively less energy would be lost between the left ventricle and the ascending aorta. Given the many variables involved, the changes in EOA and Aa occurring with increasing flow rates cannot be predicted from a resting parameter, and the use of the energy loss index would, therefore, not necessarily obviate the need to perform dobutamine or exercise stress tests in certain clinical situations. Nonetheless, its use during these tests should provide more accurate information. Also, the complexity of the cardiovascular system cannot be rigorously simulated in vitro.

**Conclusions**

This study proposes using a new index to estimate the severity of aortic valve stenosis. This index is more accurate than the currently used parameters to estimate work loss, and it has the advantage of being easily measurable using Doppler echocardiography. Moreover, the results of the in vivo study clearly suggest that this index is a better predictor of outcomes than the currently recommended index of severity, i.e., the valve EOA. Prospective studies are now necessary to further document the validity of this new index in the clinical situation.

**Appendix**

We sought an expression for energy loss expressed in units of pressure (mm Hg) in an aortic valve as a function of Aa, AV, VV, and VC. The energy loss was calculated using the following assumptions: flow is incompressible, the velocity profile is uniform, gravity is neglected, the acceleration terms are negligible (because measurements were performed with steady flow or pulsatile flow at peak systole), and the energy loss is negligible upstream from the vena contracta. By projecting the linear momentum equation26 on the flow direction axis using the control volume defined by the gray square in Figure 1, equation 4 is obtained.

\[
\frac{(P_{VC}\times A_{VC}) - (P_{A}\times A_{A})}{5} = -\left(\frac{\rho}{2} \left( V_{VC}^2 - V_{A}^2 \right) \right) - E_{L}
\]

The Bernoulli equation between the vena contracta and aorta follows.

\[
P_{A} - P_{VC} = \left( \frac{\rho}{2} (V_{VC}^2 - V_{A}^2) \right) - E_{L}
\]

Equations 4 and 5 can be combined to give the following equation.

\[
E_{L} = \left( \frac{\rho}{2} (V_{VC}^2 - V_{A}^2) \right) + \left( \frac{\rho}{2} X A_{A} V_{V} \right) + \left( \frac{\rho}{2} X A_{A} V_{V} \right)
\]

The continuity equation yields the following:

\[
\frac{A_{VC}}{V_{VC}} = \frac{A_{V}}{V_{V}} \quad \text{and} \quad \frac{V_{I}}{A_{A}} = \frac{V_{I}}{A_{I}} - \frac{V_{I}}{A_{A}}
\]

By using equation 7, the energy loss can be reduced to the following:

\[
E_{L} = \frac{\rho}{2} (V_{VC}^2 - V_{A}^2)
\]

This expression can be determined by transthoracic Doppler echocardiography. VVC and VA are expressed in m/s, EL is in mm Hg, and ρ is 1.03 g/cm³.

The energy loss can also be expressed by using the EOA as follows:

\[
E_{L} = 4V_{VC}^2 \left( 1 - \frac{EOA}{A_{A}} \right)^2
\]

where EOA and Aa are expressed in cm².

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**References**


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