Independent Contribution of Left Ventricular Ejection Time to the Mean Gradient in Aortic Stenosis

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Background and aims of the study: Transvalvular mean pressure gradients (MPG) are important in the evaluation of aortic stenosis, but surprisingly they often differ in patients having similar valve effective orifice area (EOA) and stroke volume (SV). The study aim was to determine if these differences could be explained by variations in left ventricular ejection time (LVET).

Methods: A pulse duplicator system with a constant SV of 75 ml and incremental increases of LVET from 250 to 450 ms was used to measure MPG by Doppler echocardiography in three fixed stenoses (0.5, 1.0 and 1.5 cm²). The same variables were also measured at rest in 192 patients with isolated aortic stenosis (EOA <1.5 cm²) as well as during stress in a subgroup of 24 patients.

Results: In vitro, the increase in LVET produced marked decreases of MPG ranging from -40 mmHg (-45%) for the 0.5-cm² stenosis to -22 mmHg (-61%) for the 1.5-cm² stenosis. In vivo, MPG measured by Doppler correlated strongly (R² = 0.83) with the MPG predicted by the formula: MPGpred = [SV/(50×EOA×LVET)]², and on this basis the relative contributions of EOA, SV and LVET to the variance of MPG were found to be 36, 34 and 13%, respectively. During stress, the contribution of LVET to the increase in MPG was variable, but was sometimes as important as that of SV.

Conclusion: LVET may significantly and independently influence MPG in aortic stenosis. Clinically, variations of up to 15 mmHg in MPG may be observed uniquely on the basis of a change in duration of LVET, and hence the MPG cannot be used as a stand-alone parameter for serial evaluations or for comparisons of aortic stenosis severity between patients. A correction of MPG for LVET (in ms) such as MPGc = MPG×(LVET/300)² might be helpful for rendering comparisons of MPG more meaningful in patients with aortic stenosis.

The Journal of Heart Valve Disease 2002;11:615-623

The transvalvular mean pressure gradient (MPG) is one of the major criteria utilized to evaluate aortic stenosis severity by Doppler echocardiography. Also, it is well understood that patients with significant stenosis and low cardiac output will tend to have lower gradients given that the MPG is physiologically determined by two factors: (i) the effective orifice area (EOA) of the valve; and (ii) transvalvular flow. Nonetheless, it is sometimes puzzling that, given similar values of stroke volume (SV) and EOA, different patients or the same patients returning for a control examination may have quite different values of MPG. In this context, it must be remembered that transvalvular flow is determined not only by SV but also by the left ventricular systolic ejection time (LVET), which may vary quite extensively depending on heart rate, as well as due to the presence of left ventricular dysfunction, systemic hypertension or cardiac arrhythmias. In this context, it should be emphasized that many laboratories rely heavily on measurement of the MPG for the longitudinal follow up of their patients, and it is theoretically possible that a change in aortic stenosis severity could occur without necessarily having a change in mean gradient, or vice versa.

The study aim was thus to examine the importance of the contribution of LVET to MPG in the context of aortic stenosis, and to determine if the knowledge of this variable contributes to the evaluation of its severity. For this purpose, both in-vitro and in-vivo Doppler echocardiographic data were used to examine how MPG is influenced by physiological variations in LVET.

Presented at the 74th Annual Meeting of the American Heart Association, November 2001, California, USA

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Materials and methods

Theoretical background

The mean valve EOA can be written as a function of mean transvalvular flow rate \( Q_{\text{mean}} \) and MPG using a combination of the continuity equation and the modified Bernoulli equation (1,2):

\[
EOA_{\text{mean}} = \frac{Q_{\text{mean}}}{50 \sqrt{\text{MPG}}} \tag{1}
\]

Except for a small change in the constant, this equation is similar to the traditional expression of the Gorlin equation and, as previously discussed (1), it contains other small errors of transformation without important consequence for clinical evaluation. Mean transvalvular flow is the ratio of SV to LVET:

\[
Q_{\text{mean}} = \frac{SV}{LVET} \tag{2}
\]

Thus, the expression of the EOA can be written as follows:

\[
EOA_{\text{mean}} = \frac{SV}{50 \cdot LVET \cdot \sqrt{\text{MPG}}} \tag{3}
\]

and the MPG can be written under the form:

\[
\text{MPG} = \left( \frac{SV}{50 \cdot EOA_{\text{mean}} \cdot LVET} \right)^2 \tag{4}
\]

where MPG is expressed in mmHg, SV in ml, \( EOA_{\text{mean}} \) in cm\(^2\) and LVET in s. From a theoretical standpoint, it is thus apparent that, for a given SV and EOA, the MPG is inversely proportional to the LVET squared.

In vitro study

Experimental model

The pulse duplicator used in this study is shown schematically in Figure 1, and has previously been described in detail and validated (3). It is constructed of silicone, and is an anatomically shaped model of the left heart cavities and aorta. The ventricular model is activated by a pump and a hydrodynamic generator which reproduce physiological flow conditions. The blood is mimicked by using a mixture of water (60%) and glycerol (40%) (viscosity 4 cP) containing corn starch soluble particles. Pressure measurements are performed using Millar catheters (MPC 500, accuracy 0.5%). The transducers of the proximal and distal catheters are located in the left ventricle and at 5 cm downstream from the aortic valve, respectively. Transvalvular flow rate is measured with an ultrasound flowmeter (Tranonic probe 28A31; accuracy 1%). An Ultramark 9 HDI (Advanced Technologies Laboratories) equipped with a 2.25 MHz probe is used for Doppler echocardiographic measurement of flow velocity.

Experimental conditions

Two bioprosthetic valves (Medtronic Mosaic 21 and 25 mm) and three fixed stenotic orifices of varying size (three plexiglass plates with circular orifices of 0.5, 1.0 and 1.5 cm\(^2\)) were tested. In order to avoid flow regurgitation across the stenotic orifices during diastole, a bioprosthetic valve was inserted at the distal end of the aorta. All valves and stenotic orifices were tested under five LVETs (250, 300, 350, 400 and 450 ms), whilst SV (75 ml) and heart rate (65 beat/min) were held constant.

Catheter measurements of pressures and gradients were performed over 15 cardiac cycles and averaged. Using the modified Bernoulli equation and the maximum aortic jet velocity measured by continuous-wave Doppler, the Doppler-derived mean gradient was calculated as the average of the instantaneous gradients occurring during systole. Valve EOA was determined by the standard continuity equation using the SV measured by ultrasound flowmeter (the pulse duplicator model does not allow measurement of prestenotic velocities by Doppler). The measurement of transvalvular Doppler velocity was performed over five to seven cycles, and averaged.

In vivo study

Patient population

A retrospective study was carried out in 192 consecutive patients (116 males, 76 females; mean age 68 ± 13 years; range: 18 to 97 years) who underwent an echocardiographic evaluation at the Quebec Heart Institute between January 1998 and January 1999, and were considered to have either moderate (valve EOA ≤1.5 cm\(^2\) and >1.0 cm\(^2\)) or severe (EOA ≤1.0 cm\(^2\)) aortic stenosis based on the criteria recommended by the American Heart Association/American College of Cardiology (4).

Doppler echocardiography

Measurements were performed using a Sonos 2000, 2500 or 5500 ultrasound system (Hewlett Packard, Andover, MA, USA) and included the transvalvular flow velocity using continuous-wave Doppler, the left ventricular outflow tract velocity using pulsed-wave Doppler, and the left ventricular outflow tract diame-
ter, as described previously (2,5). The LVET was measured on the transvalvular flow velocity signal from the beginning of the systolic acceleration phase to the end of the deceleration phase. From these measurements, the left ventricular SV and mean transvalvular flow rate, the MPG using the modified Bernoulli equation, and the valve EOA using the standard continuity equation, were each calculated.

Stress echocardiography

A stress Doppler echocardiographic study was performed in a subgroup of 24 patients to assess the variation of LVET within a given patient under exercise conditions, and its contribution to the increase in MPG. A dobutamine infusion protocol was used in 21 patients, and a graded exercise protocol in three. The dobutamine infusion protocol was designed to obtain incremental increases in flow and a steady state at each level. This consisted of 15-min increments of 2.5 μg/kg/min up to a maximum dosage of 10 μg/kg/min, and reported values for the Doppler echocardiographic measurements were those recorded before the infusion and at maximal dosage (5). The exercise protocol consisted of a maximum ramp upright bicycle exercise test with workload increments between 15 and 35 W/min, depending on the subject’s physical condition. Patients were encouraged to exercise until exhaustion or appearance of symptoms. The test was also stopped if there was an abnormal rise or fall in blood pressure, electrocardiogram evidence of ischemia, or significant arrhythmia. Doppler echocardiographic measurements were performed with the patient sitting on the bicycle, and carried out at peak exercise, i.e. within 2 min after the cessation of maximum ramp exercise (5,6).
valve, and it therefore confirms that the magnitude of pressure recovery is minimal in this model. Given the high correlation between Doppler- and catheter-derived MPGs and the fact that MPG was only measured by Doppler in patients, the data reported hereafter are those obtained by Doppler.

**Effect of ejection time on gradient**

Figure 3A shows the variation of MPG as a function of LVET for the three fixed stenotic orifices and the two bioprosthetic valves. In all cases, MPG decreased significantly \((p < 0.001)\) as LVET was increased from 250 ms to 450 ms: -13 mmHg for the 25-mm Mosaic valve, -20 mmHg for the 21-mm Mosaic valve, -22 mmHg for the 1.5-cm² stenosis, -27 mmHg for the 1.0-cm² stenosis, and -40 mmHg for the 0.5-cm² stenosis. From these results, it became obvious that, in each case, the 200-ms increase in LVET resulted in an approximately 50% reduction in MPG.

**Effect of ejection time on EOA**

The statistical analysis showed that the values for EOA did not change significantly with increasing LVET (Fig. 3B), except in the case of the 1.5-cm² stenosis, where it increased when the LVET varied from 250 to 300 ms.

**In vivo study**

The Doppler echocardiographic data recorded in the 192 patients with aortic stenosis are shown in Table I. The LVET at rest in these patients ranged from 206 to 418 ms, and was inversely related to the heart rate \((R^2 = 0.41; p < 0.001)\). There was a significant inverse correlation \((r = -0.23; p = 0.002)\) between LVET corrected for heart rate using the formula \(\text{LVETC} = \text{LVET}/(HR/70)\) and valve EOA. This finding suggests that the aortic stenosis severity, per se, also has a significant effect on LVET.

<table>
<thead>
<tr>
<th>Pair no.</th>
<th>Patient no.</th>
<th>EOA (cm²)</th>
<th>SV (ml)</th>
<th>LVET (ms)</th>
<th>(Q_{\text{mean}}) (ml/s)</th>
<th>MPG (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>#53</td>
<td>1.21</td>
<td>93</td>
<td>290</td>
<td>321</td>
<td>28</td>
</tr>
<tr>
<td>#2</td>
<td>#27</td>
<td>1.21</td>
<td>94</td>
<td>345</td>
<td>273</td>
<td>23</td>
</tr>
<tr>
<td>#3</td>
<td>#31</td>
<td>1.01</td>
<td>90</td>
<td>315</td>
<td>286</td>
<td>32</td>
</tr>
<tr>
<td>#4</td>
<td>#45</td>
<td>1.02</td>
<td>91</td>
<td>380</td>
<td>240</td>
<td>22</td>
</tr>
<tr>
<td>#5</td>
<td>#50</td>
<td>0.71</td>
<td>54</td>
<td>295</td>
<td>183</td>
<td>38</td>
</tr>
<tr>
<td>#6</td>
<td>#69</td>
<td>0.70</td>
<td>55</td>
<td>340</td>
<td>162</td>
<td>23</td>
</tr>
</tbody>
</table>

In each pair, the patients had similar valve effective orifice areas (EOA) and stroke volume (SV), but different left ventricular ejection times (LVET).

\(Q_{\text{mean}}\): Mean transvalvular flow rate.
Figure 3: Changes in (A) mean transvalvular pressure gradient (MPG) and (B) valve effective orifice area (EOA) as a function of left ventricular ejection time (LVET) in three rigid stenotic orifices and two bioprosthetic valves.

To better illustrate the effect of LVET on individual data, the results of three actual pairs of patients selected on the basis of similar SVs and EOAs but different LVETs, are shown in Table II. In each case, MPG is systematically lower in the patient having the longer LVET, and the greatest difference is observed in the pair of patients with the most severe stenosis (pair # 3, 15 mmHg).

As expected from the theoretical background, there was an excellent correlation ($R^2 = 0.83$) between MPG measured by Doppler and MPG as theoretically predicted by Eqn. (4) (Fig. 4). Comparison of the MPG measured by Doppler with MPG predicted by Eqn. (4) is particularly valuable to analyze the independent effect of LVET from SV and valve EOA. In this context, it is interesting to note that the correlation between MPG and EOA in the same patients was only moderate ($R^2 = 0.39$; $p < 0.001$), but that it improved markedly when the SV was factored in ($R^2 = 0.70$), and even more when the LVET was introduced ($R^2 = 0.83$). Hence, the combination of SV, EOA and LVET as defined in Eqn. (4) allows an explanation of the 83% variance of MPG in these patients, thereby confirming the experimental results.

**Stress echocardiography**

The Doppler echocardiographic data in the subgroup of 24 patients who underwent stress echocardiography are shown in Table III. On average, MPG increased by 67% during the test, whilst SV increased only by 23%. This increase in SV was also associated with a concomitant 18% decrease in LVET, thus resulting in a 52% increase in mean transvalvular flow rate (since mean flow rate = SV/LVET). Because MPG is a square function of flow rate (see Eqn. (4)), a 52% increase in flow rate should theoretically have produced an increase in MPG greater than 67%. However, as is often the case in patients with moderate aortic stenosis and a semi-rigid valve, there was also a concomitant increase in EOA during stress (+22%), thus minimizing the increase in MPG that would have been expected based on the increase in flow rate.

Moreover, it should be emphasized that the directional changes in the aforementioned parameters may vary quite significantly from one patient to the other.
Hence, Figure 5 compares the values at rest and during exercise (30 W and peak exercise levels) for EOA (panel A), MPG (panel B), left ventricular SV (panel C) and LVET (panel D) in two patients, one of whom had severe stenosis (resting valve EOA = 0.8 cm²) and one who had moderate stenosis (valve EOA = 1.38 cm²). In both cases, the MPG increased significantly during exercise. However, the patient with severe stenosis had an only modest increase in SV (+7%), and in his case the increase in MPG can be mostly related to an important decrease in LVET (-31%) due to the marked acceleration in heart rate (66 to 183 beats/min) that occurred during exercise. In contrast, the patient with moderate stenosis had a lesser increase in heart rate during exercise (66 to 122 beats/min) and consequently, his LVET decreased by only 9% during exercise. Hence, in his case the increase in MPG was more related to an increase in SV (+23%) rather than to a decrease in LVET.

In the subgroup of patients who underwent stress echocardiography, there was a strong ($R^2 = 0.96$) correlation between MPG measured by Doppler and MPG predicted by Eqn. (4). However, when LVET was removed from this equation, the strength of the correlation decreased markedly: $R^2 = 0.40$. According to these results, the consideration of both valve EOA and SV explains only 40% of the variation of MPG in individual patients undergoing stress echocardiography.
The introduction of LVET into the multivariate model further improved its predictive performance to 83%, consistent with an approximately 13% contribution of LVET to the variance of MPG. Because heart rate may vary over a wide range during exercise or dobutamine infusion, the independent contribution of LVET to the change in MPG was much more important (56%) in patients undergoing stress echocardiography. The remainder of the variance of MPG (17% in the complete cohort and 4% in the subgroup undergoing stress echocardiography) was not readily explained but was likely due to other factors such as the temporal relationship between instantaneous valve EOA and instantaneous flow. Indeed, it should be remembered that, notwithstanding similar values of SV, mean EOA and LVET, the MPG could in theory vary depending on the pattern of opening of the valve and on the proportion of flow which is ejected when the valve is in a more or less open position.

Nonetheless, the present results suggested that a difference in the duration in LVET may translate clinically into a variation of up to 15 mmHg in MPG. This may be best illustrated by considering the results shown in Table II which were obtained in three different pairs of patients with similar left ventricular SVs and EOAs, but markedly different LVETs, as well as in the patient with severe stenosis illustrated in Figure 5 whose gradient increased markedly during exercise, almost uniquely on the basis of a decrease in LVET due to a marked increase in heart rate. The practical implications of these results are that many factors must be considered when interpreting a gradient (including LVET), in addition to previously recognized factors such as left ventricular function, body surface area, EOA and indexed EOA (5,9-13). In particular, if confronted with a relatively low gradient in association with a small EOA and normal left ventricular function, the case should not necessarily be dismissed as being

### Table III: Doppler echocardiographic data in 24 patients with aortic stenosis at rest and at peak stress (peak dobutamine dose, n = 21; peak exercise, n = 3).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rest (Mean ± SD range)</th>
<th>Peak stress (Mean ± SD range)</th>
<th>Relative difference* (Mean ± SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>67 ± 11 (50-97)</td>
<td>91 ± 31 (56-183)</td>
<td>+35 ± 40%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>81 ± 22 (38-122)</td>
<td>100 ± 30 (41-154)</td>
<td>+23 ± 12%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVET (ms)</td>
<td>309 ± 32 (240-370)</td>
<td>251 ± 26 (200-310)</td>
<td>-18 ± 9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean flow rate (ml/s)</td>
<td>260 ± 66 (141-414)</td>
<td>297 ± 117 (191-633)</td>
<td>+52 ± 19%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>5.28 ± 1.23 (2.77-8.05)</td>
<td>8.65 ± 2.92 (4.05-15.4)</td>
<td>+64 ± 41%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valve EOA (cm²)</td>
<td>1.07 ± 0.25 (0.67-1.45)</td>
<td>1.31 ± 0.34 (0.72-1.86)</td>
<td>+22 ± 15%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
<td>26 ± 7 (13-42)</td>
<td>44 ± 17 (16-83)</td>
<td>+67 ± 28%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Relative difference (Stress-Rest)

EOA: Effective orifice area; LVET: Left ventricular ejection time.
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mild or moderate aortic stenosis, particularly if the LVET is relatively long (>350 ms). Indeed, in such patients, the gradient may increase markedly during exercise and reveal that there is an unacceptably high burden on the left ventricle in these circumstances (Fig. 5).

Likewise, the consideration of LVET should also be useful when interpreting results in patients undergoing serial examinations for the longitudinal follow up of asymptomatic aortic stenosis or after aortic valve replacement (4). Indeed, underlying conditions such as heart rate, rhythm disturbances, left ventricular function and medication may have changed from one examination to the other, resulting in a change in MPG that is not necessarily due to a change in aortic stenosis severity or prosthetic valve function. The LVET is an easy measurement to perform, and it can easily be compared to the values observed during the previous examination. In the present authors' experience, the differences in LVET from one examination to another might be quite important and often readily explain apparent discrepancies in MPG. This observation is particularly frequent in patients who have undergone valve replacement and in whom there is often a noticeable increase in LVET between the early and late postoperative period.

The average LVET, which was 308 ± 39 ms in the present patients, can easily be measured either on-line or off-line on the aortic jet continuous-wave Doppler signal that is already collected for MPG and EOA measurement. Hence, it might be advantageous routinely to measure LVET and to correct MPG for LVET if the latter is noticeably shorter or longer than usual. In this context, the following formula could be suggested:

\[ \text{MPGc} = \text{MPG} \left( \frac{\text{LVET}}{300} \right)^2 \]  

(5)

where MPGc is the MPG corrected for LVET, assuming that the average LVET is 300 ms (the value of 300 rather than 308 was chosen for the sake of convenience). In Figure 6, the actual values of MPGc as calculated in the present patients were then compared to the values of MPG predicted from Eqn. (4), using the values of EOA and SV but now assuming a standardized LVET of 300 ms in all cases. As can be seen, the correlation (R² = 0.85) is very close to that observed in Figure 4, suggesting that the correction is successful in accounting for the effect of LVET on MPG, the remainder of the variance being due to factors other than EOA, SV and LVET. The correlation between MPGc and MPG predicted from Eqn. (4) (R² = 0.94) was even better in the subgroup of patients undergoing stress echocardiography, thus underlining the potential value of this correction when interpreting the changes in MPG during dobutamine or exercise stress tests.

In many laboratories, the follow up of aortic stenosis progression in asymptomatic patients is based solely on the consideration of MPG because this parameter is easier and more rapid to measure than valve EOA. However, several previous studies have demonstrated that the severity of the stenosis may have an effect on LVET (14-16). In general, the more severe the stenosis, the longer the LVET. Accordingly, in the present study, a significant association was found between valve EOA and LVET corrected for heart rate. These findings suggest that the patient's follow up based solely on MPG may underestimate the worsening of the stenosis because the increase in MPG due to the increased severity may be tempered by the concomitant lengthening of LVET. In this context, the correction of MPG for LVET that is proposed in Eqn. (5) may be useful to overcome this limitation - particularly in those laboratories which use MPG as their prime measure of follow up.

The impact of these findings with regard to clinical decision-making remains to be determined. Nonetheless, LVET and MPGc are simple to calculate and, from a practical standpoint, they could easily be used as adjuncts to the other Doppler echocardiographic parameters, particularly when there are apparent discrepancies in results. In this context, it must however be remembered that 17% of the variance of MPG remains unexplained. As demonstrated, the use of these parameters could also prove especially useful during stress echocardiography as it may allow better understanding and interpretation of the changes in gradient that occur during these examinations. The results of this study also raise the interesting possibility that medications targeted at decreasing the heart rate (and thus increasing LVET) could be helpful in decreasing transvalvular gradients and left ventricular systolic wall stress in patients with aortic stenosis. Further studies are necessary however to assess the potential benefits and limitations of such interventions.

Acknowledgements

These studies were supported by operating grants from the Canadian Institutes of Health Research (MOP-10929) and the Heart and Stroke Foundation of Quebec. Dr. Pibarot is a senior research scholar of the Heart and Stroke Foundation of Canada. The authors also thank Jocelyn Beauchemin, Isabelle Laforest, Jean Fuseri and Frédéric Derivaux for their technical assistance.
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