Hemodynamics at Rest and during Exercise in Combined Aortic Stenosis and Insufficiency

By Philip O. Ettinger, M.D., Martin J. Frank, M.D., and Gilbert E. Levinson, M.D.

SUMMARY
The effects of exercise in combined aortic stenosis and insufficiency were evaluated in 10 patients by pressure measurements and the measurement of forward (Q_F) and regurgitant (Q_R) flows by simultaneous upstream and downstream sampling using indocyanine green. While heart rate increased, systolic aortic valve pressure gradient (mean, 37 ± 9 mm Hg) did not change. Increased Q_F (mean, 4.54 ± 0.34 at rest and 6.89 ± 0.42 liters/min with exercise, P < 0.001) was balanced by decreased Q_R (means, 4.09 ± 1.02 and 2.33 ± 0.71 liters/min, P < 0.02), and total flow did not change significantly. Although diastolic regurgitant period declined, total diastolic seconds per minute decreased by only 6%, while calculated systemic resistance decreased by 30%. Left ventricular systolic and aortic pressures increased, while left ventricular end-diastolic pressure and diastolic aortic valve gradients were unchanged. Mean systolic aortic valve area, calculated by utilizing total valve flow, was 1.8 ± 0.3 cm² in both states.

Thus, exercise reduces regurgitant fraction in mixed aortic lesions as in pure aortic insufficiency. This observation confirms the necessity of measuring total valve flow in evaluation of mixed valve lesions. Reduced regurgitation primarily reflects an altered relationship of peripheral resistance to backflow resistance. While the stenotic valve is demonstrated to behave as a fixed stenotic orifice, the diastolic aortic orifice area cannot be calculated from the Gorlin equation as it does not account for peripheral resistance.

Additional Indexing Words:
Dye dilution  Aortic orifice area  Gorlin hydraulic equation

When patients with aortic regurgitation exercise, regurgitation is reduced and effective forward flow increases.¹ That alteration in peripheral vascular resistance influence aortic regurgitant flow is indicated clinically by the changes induced by vasoactive agents in the intensity of the regurgitant diastolic murmur.² ³ Amyl nitrite lessens the murmur primarily by decreasing peripheral resistance while methoxamine and norepinephrine increase peripheral resistance and, hence, the murmur. Pregnancy, which results in a decline in peripheral resistance, reduces the murmur,⁴ and squatting, which increases

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resistance, accentuates it. Exercise, on the other hand, alters systemic vascular resistance, heart rate, myocardial contractility, and possibly myocardial compliance, so that the reduction in regurgitant flow might be ascribed to exercise-induced vasodilatation, reduced diastolic filling time, or altered compliance of the ventricle.

Studies performed in our laboratory on patients with aortic regurgitation (AR) have demonstrated that during mild exercise the increased forward flow and diminished regurgitant flow balance, resulting in relatively constant total flow across the aortic valve. It would be likely that in mixed aortic stenosis and insufficiency exercise would also reduce regurgitation and increase effective forward flow. Forward flow in aortic stenosis, however, may be dependent in part upon the severity of stenosis. It was recently suggested that the stenotic aortic valve may not behave as a fixed obstruction and may differ in systolic orifice area during rest and exercise. The present study was designed to evaluate changes during effort in pressures, flows, resistances, and orifice areas in mixed aortic stenosis and insufficiency.

Methods

Ten adults with mixed aortic valve disease, seven men and three women, were studied while supine both at rest and during mild exercise on a bicycle ergometer during diagnostic cardiac catheterization. All were in a compensated state at the time of study, and all but one were receiving digitalis. Mitral stenosis was an associated lesion in three but was critical only in one (calculated valve areas, 0.4, 1.9, and 2.6 cm²). No patient had mitral regurgitation. All but one had regular sinus rhythm; a single patient had atrial fibrillation.

With the patient fasting and under pentobarbital and meperidine premedication, a Brockenbrough catheter was introduced into the left ventricle by the transeptal technic, and the aorta was entered with either a polyethylene catheter (PE 160; ID, 1.13 mm; length, 70 cm) introduced percutaneously through a brachial artery by the Stille-Seldinger technic or an NIH catheter (6 or 7F, 80 cm) introduced through a right brachial arteriotomy. In all instances, the aortic catheter was placed into the left ventricle and then positioned just distal to the aortic valve by pressure and fluoroscopic monitoring, and the ventricular catheter was placed near the apex of the left ventricle. A no. 17 thin-walled Cournand needle was placed in the other brachial artery.

Simultaneous pressure recordings from the left ventricle and aorta were made through the saline-filled catheters attached to Statham P 23 Cb strain gauges. The gauge deflections were made equisensitive by balancing their outputs, and recordings were made at paper speeds of 50 to 100 mm/sec on an eight-channel oscillographic recorder (Electronics for Medicine) and calibrated with a mercury manometer. The reference level for zero pressure was half way from manubrium to table top. All pressure recordings were made within 1 min of flow recordings after a steady state had been attained at rest and again after 8 to 20 min of supine bicycle exercise. The systolic and diastolic pressure gradients across the aortic valve were measured by planimetry of four successive and simultaneously recorded left ventricular and aortic pressure complexes for the patients in sinus rhythm and six complexes for the patient in atrial fibrillation. Systolic ejection period (SEP) in seconds was measured as the duration of systolic pressure gradient. Diastolic regurgitant period (DRP) was calculated by the relation:

\[
\text{DRP} = \frac{60}{(\text{heart rate})} - \text{SEP}.
\]

Systolic and diastolic seconds per minute were calculated as the products of the ejection and regurgitant periods, respectively, and the heart rate.

As an index of the pressure gradients in each minute associated with ejection and regurgitation, systolic and diastolic gradient pressure-times per minute were calculated as the products, respectively, of the mean systolic or diastolic pressure gradients and the systolic or diastolic seconds per minute. All calculations were made at rest and during exercise.

To measure flows, dilution curves were obtained using indocyanine green dye (Cardio-Green),* Gilford densitometers, Harvard infusion-withdrawal pumps, and an Electronics for Medicine recorder. Calibration was by the integrated sample technic. The 90% response time for the catheter-densitometer system was 1 sec or less for all measurements. Dye was introduced into the aortic root by continuous infusion of a 1-mg/ml solution at a constant rate of 30 to 75 ml/min. Blood was withdrawn simultaneously at a constant rate of 0.7 or 2.0

*Cardio-Green used in this study was provided by Hynson, Westcott and Dunning, Pharmaceutical Manufacturers, Baltimore, Maryland.

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ml/sec from the left ventricle and brachial artery.

During continuous indicator infusion, left ventricular and brachial arterial indicator concentrations were seen to rise to equilibrium plateaus, followed by recirculation. The equilibrium plateau indicates a steady state in which all blood free of indicator has left the vascular bed between injection and collection sites and in which the amount of indicator leaving this bed per unit of time is equal to the amount infused per unit of time. With the height of the plateau above the baseline of the arterial dilution curve as \( A_r \), and the height of the plateau above the baseline of the left ventricular dilution curve as \( A_v \), forward flow was calculated as:

\[
Q_v = \frac{\text{indicator concentration} \times \text{infusion rate} \times \text{calibration factor}}{A_v}
\]

and aortic regurgitant flow as

\[
Q_r = \frac{Q_v}{(A_r/A_v)} - 1.
\]

Total aortic valve flow, \( Q_T = Q_R + Q_F \), and the regurgitant fraction of total aortic valve flow \( Q_R/Q_T \). The range of values for \( Q_R \), \( Q_F \), and \( Q_R/Q_T \) in replicate determinations is strikingly small for the continuous infusion technic.\(^7\)\(^8\) The regurgitant fraction calculated by this method has been demonstrated to correlate well with the severity of regurgitation seen angiographically.\(^7\) At least two measurements were obtained in each state and regurgitation taken as the mean of the multiple determinations.

The systolic orifice area of the stenotic and insufficient aortic valve (AVA systolic) was calculated at rest and during exercise from the hydraulic formula of Gorlin and Gorlin\(^9\) as:

\[
\text{AVA systolic} = \frac{(HR) \times (SEP) \times (44.5) \times \sqrt{\text{systolic gradient}}}{\sqrt{V}}
\]

where HR = heart rate, SEP = systolic ejection period, and 44.5 is the gravity acceleration factor. Systemic vascular resistance was calculated as the ratio of mean aortic pressure to \( Q_F \).

A diastolic orifice area of the aortic valve was also calculated in both states by rearrangement of a formula suggested by Gorlin and associates\(^10\):

\[
\text{AVA diastolic} = \frac{Q_R}{(HR) \times (DRP) \times (44.5) \times \sqrt{\text{diastolic gradient}}}
\]

To our knowledge the applicability of the orifice equation to aortic diastole has not previously been tested. The empirical constant of 44.5 is used as suggested by Gorlin and Gorlin\(^9\) and agrees with the theoretical considerations of Rodrigo\(^11\) relating to systolic orifice hemodynamics. While the numerical value used may not apply to flow retrograde across the aortic valve, there is no reason to believe that the actual value, whatever it is, should change during exercise. Therefore, relative changes in diastolic valve area should be calculable if they occur.

All statistical analyses were made by computer using conventional statistical technics for small samples. All data are expressed as means ± standard errors (se). Probability values (\( P \)) were determined by paired \( t \)-testing (Student's \( t \)-test) of the rest and exercise data.

**Results**

All hemodynamic data are summarized in table 1. As expected, heart rate increased during exercise in every patient, from a mean of 87 ± 5 to 109 ± 5 beats/min, \( P < 0.01 \).

**Left Ventricular and Aortic Pressures**

Left ventricular systolic pressure increased in every patient but one with significant mitral stenosis (case 8, C.So.) from a mean of 156 ± 12 to 171 ± 15 mm Hg, \( P < 0.02 \). End-diastolic pressure in the left ventricle (LVEDP) was not altered by exercise. The increased ventricular systolic pressure during exercise was similar to that reported for pure aortic regurgitation by ourselves\(^1\) and by Lewis and co-workers.\(^12\) The latter noted a small exercise-induced increase in LVEDP while our previous results are similar to those noted in these patients. Aortic pressures tended to rise, with a significant increase in diastolic pressure (68 ± 6 to 77 ± 6 mm Hg, \( P < 0.05 \)) while the rise in systolic and mean pressures missed significance, using a two-tailed \( t \), at the 5% level (\( t = 2.13, P < 0.1; t = 1.95, P < 0.1 \), respectively).

**Systolic Ventriculoaortic Gradient**

Exercise resulted in no significant change in the mean aortic systolic gradient which
Summary of Hemodynamic Data

<table>
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<tr>
<th>Patient</th>
<th>HR</th>
<th>LV (mm Hg)</th>
<th>Ao (mm Hg)</th>
<th>Ao mean (mm Hg)</th>
<th>Systolic gradient (mm Hg)</th>
<th>SEP (sec)</th>
<th>Systolic pressure-time (mm Hg-sec/min)</th>
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<tr>
<td></td>
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<td>128/66</td>
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<tr>
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<td>E</td>
<td>104</td>
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<td>133/77</td>
<td>97</td>
<td>38</td>
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</table>

*Patients 4, 7, and 8 had mitral stenosis as well; this was critically small (0.4 cm²) in patient 8 but minimal in patients 4 and 7 (2.6 and 1.9 cm², respectively.)

Abbreviations: HR = heart rate; LV = left ventricular pressure, systolic/end-diastolic; Ao = aortic pressure, systolic/diastolic; SEP = systolic ejection period; DRP = diastolic regurgitant period; QF = forward flow; QR = regurgitant flow; QT = total flow; QR/QF = regurgitant fraction; AVA systolic = systolic aortic valve area; TSR = total systemic resistance; R = rest; E = exercise.

Table 1

Decreased in four patients, increased in six, and averaged 37 mm Hg at rest and 38 mm Hg during exercise. None of the other hemodynamic parameters measured was, of itself, predictive of how individual patients would respond in this regard.

Ejection and Regurgitant Periods

The mean systolic ejection period (SEP) shortened significantly during exercise from 0.25 ± 0.02 to 0.22 ± 0.02 sec, P < 0.01. Systolic ejection time per minute increased from 21.3 ± 1.1 to 23.8 ± 1.7 sec, P < 0.05. These changes are demonstrated in figure 1. Diastolic regurgitant period (DRP) shortened, but the decrease in diastolic seconds per minute, from 38.7 ± 1.0 to 36.3 ± 1.7, P < 0.05, represented a change of only 6%.

Pressure-Time per Minute

Systolic gradient pressure-time per minute, 829 ± 220 mm Hg-sec/min at rest, rose during exercise to 1,028 ± 335 mm Hg-sec/min, but this change was not statistically significant. Diastolic gradient pressure-time per minute also did not change significantly (2,466 ± 206 at rest, 2,486 ± 227 mm Hg-sec/min during exercise).

Transaortic Valve Flows

The effects of exercise upon mean forward, regurgitant, and total flows are shown in figure 2. Forward flow (QF) increased from

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<th>Diastolic pressure-time (mm Hg-sec/min)</th>
<th>$Q_T$ (liters/min)</th>
<th>$Q_R$ (liters/min)</th>
<th>$Q_T/Q_R$ (liters/min)</th>
<th>Diastolic gradient (mm Hg)</th>
<th>AYA systolic (cm²)</th>
<th>TSR (dyne-sec-cm⁻²)</th>
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<0.001 <0.05    NS  <0.001 <0.02  NS  <0.001 NS NS <0.01

4.54 ± 0.34 to 6.89 ± 0.42 liters/min, $P < 0.001$; regurgitant flow ($Q_R$) diminished from 4.09 ± 1.02 to 2.33 ± 0.71 liters/min, $P < 0.02$; and total flow ($Q_T$) did not change significantly (8.63 ± 1.05 to 9.22 ± 0.91 liters/min).

**Regurgitant Fraction**

The ratio of regurgitant to total flow, $Q_R/Q_T$, diminished significantly from a mean of 0.40 ± 0.07 at rest to 0.21 ± 0.05 during exercise. Every patient demonstrated this change, as each increased forward flow and decreased regurgitant flow (fig. 3).

**Figure 1**

*Mean systolic ejection period, systolic and diastolic seconds per minute at rest and during exercise. While changes are significant, the fall in diastolic seconds per minute during exercise is only 6%.*

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Mean forward ($\dot{Q}_F$), regurgitant ($\dot{Q}_R$), and total ($\dot{Q}_T$) transaortic valve flows at rest and during exercise. The increased forward flow was balanced by a decreased regurgitant flow so that total flow did not change.

Calculated Systolic Aortic Valve Orifice Area

The mean calculated systolic orifice area was $1.81 \pm 0.26$ cm$^2$ at rest and $1.85 \pm 0.28$ cm$^2$ during exercise, thus demonstrating that the stenotic valve behaves as a fixed outflow obstruction. This is shown in figure 4, where the individual changes in valve area with exercise are seen in the right-hand graph to be scattered randomly over a small range of differences ($\pm20\%$) from the resting values, with a mean orifice area differing by only 2% from that calculated at rest. Thus, no systematic differences were demonstrated, and the variation observed is consistent with measurement error and appropriate in magnitude since each measurement used in the calculation is subject to an estimated error of approximately 5%.

Systemic Vascular Resistance

Calculated systemic vascular resistance declined in all but one patient (V.M.); the mean for the group declined from $1,644 \pm 155$ to $1,147 \pm 63$ dyne-sec-cm$^{-5}$, $P < 0.01$.

Calculated Diastolic Aortic Valve Orifice Area

The mean calculated orifice area was $0.32 \pm 0.09$ cm$^2$ at rest and $0.20 \pm 0.07$ cm$^2$ during exercise ($P < 0.05$). An apparent decline occurred in every patient. As systolic orifice area was constant, it is unlikely that the diastolic area was variable as implied by the orifice equation. An explanation for this inconsistency lies, we believe, in the inaccuracy of assumptions underlying the applicability of the orifice equation to situations wherein fluid exits from a chamber via alternate channels.
HEMODYNAMICS IN AORTIC VALVE DISEASE

AVA = \frac{Q_T}{44.5 \times HR \times SEP \times \sqrt{\text{gradient}}}

![Graph showing changes in orifice area during exercise and rest](image)

**Figure 4**

Calculated systolic orifice areas during exercise differ unsystematically and by 20% or less of the resting value from those calculated at rest but with no mean change. The means are indicated by open circles.

pathways. A fuller discussion of this problem is presented below.

**Discussion**

Changes in the intensity of the murmur of aortic insufficiency caused by vasoactive agents and maneuvers altering peripheral vascular resistance indicate that these changes affect regurgitant flow. In these situations, myocardial contractility, heart rate, and the diastolic interval may vary. As methoxamine increases the murmur without altering contractility, a contractile increase is not essential for this change. An increase in heart rate alone by atrial pacing does not appear to influence regurgitant or total flow. Exercise represents a more complex phenomenon in which systemic resistance, heart rate, and contractility all change. Although diminution of the regurgitant fraction during exercise in pure aortic insufficiency has been shown, the cause of this change has not been fully defined, and the effect of exercise upon hemodynamics in combined insufficiency and stenosis has not been evaluated.

While the diastolic regurgitant period shortened considerably in our patients, heart rate increased so that the effective diastolic seconds/minute shortened by only 6%. The pressure-time per minute across the valve in diastole was unchanged by exercise. Therefore, it is unlikely that either the alterations in diastolic regurgitant period or any diastolic pressure variations could have accounted for the considerable reduction of regurgitant flow demonstrated. On the other hand, calculated peripheral resistance decreased by 30%. The magnitude of this change appears more likely to account for the altered regurgitant flow. Unfortunately, calculated peripheral resistance in aortic regurgitation is subject to misinterpretation, as aortic diastolic pressure is a resultant of peripheral and regurgitant runoff. Burch noted that peripheral runoff in aortic regurgitation is complex and apparently discontinuous, thus limiting the interpretation of calculated peripheral resistance. The effect of possible compliance changes in the left ventricle during diastolic regurgitation was not measured, and their contribution to altered regurgitation is unclear, although it is most likely that orifice resistance in these patients constituted the major impediment to backflow, and an altered relationship of resistances to forward and backward flows was the predominant cause of the observed change in regurgitant fraction. The decreased systemic resistance allowed greater peripheral
runoff, accompanied by an unaltered or decreased ventricular compliance or by an increased compliance smaller in relative magnitude than the fall in peripheral resistance.

Anderson and co-workers\textsuperscript{16} recently suggested that the stenotic aortic valve may not behave as a fixed obstruction during exercise. From their review of a large series of patients with aortic stenosis, with and without aortic insufficiency, they concluded that the dynamics of exercise might act to change the geometry of the aortic outflow area, requiring calculation of a different orifice constant. However, their analysis was based upon valve areas calculated from forward flow alone, as regurgitant flow was not measured. A previously reported study from our own laboratory\textsuperscript{17} indicates that the degree of aortic regurgitation in mixed valve lesions is frequently underestimated and that appreciable regurgitation occurs through many highly stenotic valves. Failure to account for this regurgitation will lead to error in calculation of orifice areas. In the present study, systolic orifice areas, calculated from forward flow measurements alone, ranged from 0.38 to 1.94 cm\(^2\) with a mean of 1.05 cm\(^2\) at rest and from 0.44 to 2.37 cm\(^2\) with a mean of 1.42 cm\(^2\) during exercise. Figure 5 shows that an apparent increase in systolic orifice area during exercise, ranging from 5\% to 80\% of the area calculated at rest, occurred in every patient. The mean difference in estimated area, amounting to an average apparent increase of 35\%, is statistically significant but physiologically meaningless. It represents, not a change in the orifice area with exercise, but a serious underestimation of the area at rest, the mean underestimate (40\%) corresponding to the neglected regurgitant fraction (mean = 0.40). That this error played a role in the study of Anderson and associates is indicated by the fact that calculated aortic orifice area was smaller in their patients with mixed lesions than in those with pure aortic stenosis, an unlikely event. When, in the present study, total flow (Q\(_T\)) was used in the orifice equation, the aortic valve area in systole was unchanged during exercise, behaving hemodynamically as a fixed orifice. These data may be interpreted as confirming the applicability of the Gorlin hydraulic formula to the systolic aortic valve area in mixed lesions during a changing state provided total systolic flow across the obstruction is known. Recently, changes in orifice geometry have been demonstrated radiographically in aortic stenosis\textsuperscript{18} during exercise. Whether such changes would be associated with a measurable change in orifice resistance is unknown. Although the present study does not preclude the possibility of such variations, it indicates

\textbf{Figure 5}

When Q\(_p\) alone was used to compute systolic aortic orifice area, all patients appeared to show an increased aperture. Calculation in this erroneous manner would have led to the conclusion that valve area increased by 35\%. The mean apparent increase is indicated by the open circle.
that they are neither appreciable in magnitude nor systematic in direct.on.

Gorlin and co-workers\textsuperscript{16} speculated that the diastolic aortic orifice area could also be calculated if diastolic gradient, regurgitant flow, and diastolic period were known. From the data available in the present study, we calculated this area making the assumption that the numerical value of the equation constant was 44.5, as in systole. (The actual value of the constant need not be known, but it must be assumed that it is not changed during exercise.) Since diastolic gradient did not change and diastolic seconds/minute decreased by only 6%, the decline in aortic regurgitant flow caused the calculated diastolic valve area to fall from a mean of $0.32 \pm 0.09$ cm$^2$ to a mean of $0.20 \pm 0.07$ cm$^2$. This apparent decrease in size was significant ($P < 0.05$) and occurred in every patient. As systolic orifice was constant, it would be more likely that diastolic valve area is similarly fixed. The explanation for this apparent inconsistency arises, we believe, from failure to consider the effects of variable diastolic peripheral runoff. The systolic pressure gradient is generated by frictional losses incurred by blood flow in transit across the stenotic aortic orifice from a ventricle with but one exit. All changes in flow, pressure, and velocity in this system must be due to changes in the force of ventricular contraction or in orifice size. In diastole, however, the aortic left ventricular gradient is only a potential pressure difference, having been established in the prior systole, and is not caused by regurgitant flow but rather is reduced by it. Pressure in the aorta is dissipated through parallel runoffs, upstream into the ventricle and downstream through the resistance vessels. Changes in peripheral resistance must alter the balance of flow even without postulating changes in aortic orifice size. Exercise, by increasing myocardial contractile force, increased aortic pressure, and the latter, accompanied by decreased systemic resistance and no change in aortic-left ventricular diastolic gradient, resulted in greater systemic flow and lessened regurgitation. It is not known how much of forward flow passes the resistance vessels in systole and how much in diastole, and it has been suggested that peripheral resistances in the upper and lower extremities may behave differently.\textsuperscript{3}

When Gorlin and associates\textsuperscript{16} experimented with the isolated hearts of patients with mixed aortic stenosis and regurgitation, his apparatus could not account for changes in peripheral resistance. The mean fall in calculated systemic resistance in this study (30%) approximated the mean fall in calculated diastolic aortic valve area (35%). We believe it unlikely that actual changes occur in diastolic valve area, but rather that the calculated changes represent an inaccuracy in the assumption that the simple orifice equation applies to situations where flow from a vessel or chamber can exit via more than one orifice. This limitation would also be expected to apply to orifice calculations in patent ductus arteriosus and in arteriovenous fistulas, lesions in which the balance of flow may similarly be changed with alterations in peripheral resistance.

While total flow across the aortic valve remained unchanged in mild exercise as compared with the resting state, the majority of these patients had regurgitant volumes of at least moderate degree and exercise was not severe. Heavier exertion might have led to progressive increments of total and forward flow and, therefore, of left ventricular work, and patients with mild aortic regurgitation might increase total flow with even mild exercise.

Since the major impediment to the calculation of true aortic valve area is lack of quantitative knowledge of $Q_{fr}$, it follows from this investigation that any error incurred by a sizable $Q_{fr}$ is maximal at rest. It may be speculated that, at certain levels of exercise, $Q_{fr}$ will decrease to a negligible level (or, at any rate, to an attainable minimum), and at this point a more correct value for aortic valve area may be approximated by calculation utilizing $Q_f$ data alone. Peripheral vasodilation with pharmacologic agents might achieve a similar end, alone or in conjunction with exercise.
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