Oxygen Consumption in Subepicardial and Subendocardial Regions of the Canine Left Ventricle

The Effect of Experimental Acute Valvular Aortic Stenosis

J. Vinten-Johansen and Harvey R. Weiss

SUMMARY

Moderate and severe levels of experimental valvular aortic stenosis (VAS) were produced in anesthetized, open-chest dogs to determine the effects of VAS on subepicardial (EPI) and subendocardial (ENDO) blood flow, \(O_2\) extraction, and \(O_2\) consumption (\(MVO_2\)). Regional flow was determined by microspheres, and \(O_2\) saturation and extraction were analyzed by a three-wavelength absorbance microspectrophotometric method. Left ventricular pressure-volume work increased by 49% in moderate and 135% in severe VAS. The ENDO:EPI flow ratio averaged 1.21 \(\pm\) 0.09 in controls and decreased to 0.90 \(\pm\) 0.16 in moderate and 0.89 \(\pm\) 0.09 in severe VAS, and coronary flow increased by 40% and 58%, respectively. \(O_2\) extraction increased with both moderate and severe VAS, with extraction being higher in the ENDO than the EPI. \(MVO_2\) increased more in severe VAS than in moderate VAS. The ENDO:EPI \(MVO_2\) ratios fell to 1.10 (moderate) and to 0.84 (severe) from 1.44 in controls. We conclude that the \(O_2\) supply and consequently the \(MVO_2\) became limited in the ENDO relative to that in the EPI by simultaneous limitation of the \(O_2\) extraction reserve and the blood flow to this region during the increased \(O_2\) requirements imposed by experimentally induced VAS.


THE adequacy of subendocardial oxygenation represents a fine balance between the \(O_2\) supplied by coronary flow and \(O_2\) content and the \(O_2\) required to meet ambient myocardial needs. In normally functioning hearts, the \(O_2\) extraction reserves are low, and it is lower in the subendocardium (Weiss et al., 1978), so coronary blood flow offers the greater flexibility in altering \(O_2\) supply. The subendocardium is particularly vulnerable to \(O_2\) supply and demand imbalances (Hoffman and Buckberg, 1976; Weiss, 1974). Blood flow has an approximately equal distribution transmurally, but the subendocardium becomes underperfused relative to the subepicardium when perfusion pressure is decreased in various ways or when the coronary artery is occluded to varying degrees (Hoffman and Buckberg, 1976). Relative subendocardial underperfusion and a possible imbalance in subendocardial \(O_2\) supply relative to the demands have been found to occur in coronary stenosis or experimental occlusion, arteriovenous fistula (Buckberg et al., 1972; Hoffman and Buckberg, 1976), and aortic valvular insufficiency (Vinten-Johansen and Weiss, 1978).

The hemodynamic circumstances generated by valvular aortic stenosis (VAS) (left ventricular hypertension, normal or subnormal aortic pressures, and prolonged systolic period) may jeopardize the adequacy of subendocardial \(O_2\) supply at a time when the left ventricular hypertension imposes greater \(O_2\) requirements. Consequently, the \(O_2\) supply and demand status may be perturbed, a situation which may be responsible for the frequent presentation of angina pectoris in patients with valvular stenosis (Fallen et al., 1967).

We were interested in determining the \(O_2\) consumption and supply in the subepicardial and subendocardial regions of the left ventricular free wall during experimentally induced VAS to determine, for the first time, the adequacy of regional \(O_2\) supply in this condition. We employed a recently developed three-wavelength microspectrophotometric technique to quantitate the \(O_2\) saturation of blood contained within small diameter (20- to 100-\(\mu\)m) arteries and veins in quick-frozen myocardium (Sinha et al., 1975; Sinha et al., 1977; Weiss and Sinha, 1978). With this technique, the \(O_2\) extraction determined on a regional basis, when combined with regional blood flow information provided by the microsphere technique, allowed us to determine regional \(O_2\) consumption by the Fick principle in relation to the myocardium's functional state (Weiss et al., 1978).

Methods

Twenty-four mongrel dogs of both sexes between 18 and 34 kg (mean 20.9 kg) in weight were anesthetized with sodium pentobarbital (30 mg/kg, iv)
and thoracotomized midsternally. Artificial ventilation with room air was maintained with a Harvard respiratory pump, and positive end-expiratory pressure was adjusted between 2 and 4 cm water. Ventilatory frequency and volume were adjusted to maintain end-tidal CO₂ constant. A pericardial cradle was formed. Catheters were placed via the femoral artery into the aortic arch, at least 2 cm into the coronary sinus, into the left ventricular cavity through the apical dimple, and into the left atrium. The aortic arch and left ventricular catheters were connected to Statham pressure transducers. A precalibrated electromagnetic flow probe was fitted around the root of the aorta and connected to a Biotronex Laboratory, Inc., pulse logic flowmeter (model BL-610) to measure instantaneous stroke volumes. A proximal segment of the left anterior descending (LAD) branch of the left coronary artery was fitted with an electromagnetic flow probe for the measurement of phasic coronary blood flow. All pressures and flows were recorded on Beckman type R-411 recorders. Electrodes were secured on the right atrial appendage to maintain heart rate constant at 150 beats/min.

An obstructive balloon catheter, fashioned from a no. 8 French balloon catheter with a semipliable retainer cage built around the balloon portion, was inserted into the brachiocephalic trunk, manipulated into the left ventricle, and maintained uninflated and without effect until the experimental run. After completion of surgery, an interval of 30 minutes was allowed for the dog to stabilize.

The dogs were divided into two major groups: 12 served only as controls, and in 12 an experimental valvular stenosis was made by filling the balloon with varying amounts of saline and securing it at the level of the aortic valves proximal to the coronary ostia. Moderate and severe degrees of VAS were produced, with six dogs in each class. For both degrees of severity of VAS, each dog served as its own paired control. Because of the freezing and cutting of the heart involved in microspectrophotometric analysis, paired samples could not be obtained. Therefore, a pure control group was required for comparison of regional O₂ blood saturation, O₂ extraction, and MVO₂ with the two degrees of severity of VAS. In addition, measurements in paired control states were obtained in the VAS groups to demonstrate homogeneity prior to stenotic intervention, and to determine percent changes in some hemodynamic parameters.

For the pure control group and the paired control state in the VAS groups, the following hemodynamic parameters were obtained: left ventricular pressure, aortic pressure, maximal left ventricular dP/dt, instantaneous stroke volume, and mean and phasic coronary blood flow. Arterial and coronary sinus blood samples were withdrawn anaerobically into preheparinized syringes. These were analyzed for PO₂, PCO₂, and pH with a blood gas analyzer (Instrumentation Laboratory model 113) and for percent saturation of hemoglobin by a CO-oximeter. Blood concentration of hemoglobin was assessed by a Fisher hemophotometer. Blood withdrawal for a microsphere reference sample from the femoral-aortic catheter was begun at a constant rate (10 ml/min). Thirty seconds after reference sampling was initiated, either ¹¹³Ce- or ⁸⁵Sr-labeled microspheres, 15 ± 3 μm in diameter, were injected into the left atrial catheter in a bolus and flushed with 3 ml of saline. The reference sampling continued for a total of 2 minutes. In the control dogs, the heart was fibrillated at this point. The heart then was excised rapidly below the atriocentric ring and immersed in liquid nitrogen-cooled liquid propane. The time between fibrillation and freezing was only 10–15 seconds.

In the VAS dogs, after the paired control state measurements had been taken, the left ventricular balloon was withdrawn to the level of the aortic valves (below the coronary ostia) and filled with saline to partially obstruct left ventricular outflow. Inadvertent obstruction of the coronary ostia or supravalvular placement of the balloon was prevented by palpation of the balloon placement and by observing immediate decreases in mean coronary blood flow and cardiac function. After 30 minutes of stable VAS (VAS-30), blood pressures and flows were measured, and samples were taken, the second set of microspheres injected and sampled, and the heart fibrillated, excised, and quick-frozen.

Immediately adjacent duplicate transmural samples of the left ventricular free wall, approximately 1 cm in diameter, were cut from the apex and base areas with a band saw in a -20°C cold room. Samples were prepared for analysis of regional microsphere distribution and for microspectrophotometric analysis as described previously (Weiss and Sinha, 1978). Each transmural sample was divided into equal thirds, and the mid-myocardial portion was discarded. Briefly, 30-μm thick frozen tissue sections were cut on a cold rotary microtome in a -25°C cold box. Each section was then transferred to a precooled slide, covered with degassed silicone oil, and rapidly transferred to the microspectrophotometer's cold stage. Arteries and veins, 20–150 μm in diameter, were located and absorbance at 560, 523, and 506 nm obtained to give O₂ saturation of the blood contained within the vessels. Five arteries and five veins were analyzed in each region in each apical and basal tissue sample.

Regional oxygen extraction (ml O₂/100 ml blood) was calculated as the arteriovenous difference multiplied by the hemoglobin concentration times the maximal O₂ combining capacity of 1.36 ml O₂/g hemoglobin. The O₂ consumption for a given region was determined by the product of O₂ extraction and regional blood flow (Weiss et al., 1978). Overall left ventricular MVO₂ (arterial minus coronary sinus O₂ content × LAD flow) is also reported for cross-comparison in all groups and to demonstrate changes in MVO₂ with VAS by the more classical
method of MVO₂ determination.

The severity of VAS was assessed by the ratio of the systolic aortic-left ventricular pressure gradient to the left ventricular peak systolic pressure. When multiplied by 100, this ratio actually represents the percentage of the left ventricular systolic pressure that is involved in the systolic transvalvular pressure gradient. A pressure ratio less than or equal to 45% represented moderate degrees of VAS; ratios greater than 45% represented severe VAS. Mean left ventricular pressures and transvalvular pressure gradients also are reported for each group.

For all groups, the following data were calculated from the original records: the integrated left ventricular systolic pressure (the tension-time index of Sarnoff et al., 1958, or the systolic pressure-time index of Hoffman and Buckberg, 1978) measured by planimetry and averaged for five consecutive cardiac cycles; the mean left ventricular systolic pressure determined by dividing the integrated systolic pressure by the duration of systole; the total stroke volume determined by planimetry of the systolic ejection record. The stroke volumes were divided by animal weight and multiplied by heart rate to obtain the cardiac output normalized for animal weight. Mean left ventricular pressure-volume work per kilogram body weight per minute (LVW/kg) was calculated as the product of mean left ventricular systolic pressure and mean stroke volume per kilogram per minute. This is actually minute work (power), but the designation of pressure-volume work has been retained.

In the VAS groups, differences between paired control states and VAS-30 were analyzed by paired t-analysis, whereas control vs. VAS-30 differences were studied by analysis of variance with post hoc testing done with the Student-Newman-Keuls procedure. Regional flow, vessel saturation, and O₂ consumption were analyzed by multifactorial analysis of variance (Winer, 1971). Values cited are means ± standard error of the mean. Significance was accepted at the P < 0.05 level.

Results

The hemodynamic data are presented in Table 1. In moderate VAS, in which a mean of 37.5 ± 2% stenosis was produced, left ventricular pressure increased significantly by 37% above the paired control. There was a mean transvalvular pressure gradient of 60 mm Hg. In severe VAS, a mean of 52.4 ± 3% stenosis was produced. Left ventricular peak systolic pressure increased significantly by a mean of 46%. A mean transvalvular pressure gradient of 104 mm Hg was produced. The systolic pressure-time index per minute increased significantly by 54% in moderate and by 67% in severe VAS above the respective paired controls. The maximum dp/dt was not changed with moderate VAS but did sustain a slight decrease in severe VAS. The LVW/kg increased significantly by 45% in moderate and by 95% in severe VAS from paired controls. Increases in LVW/Kg above controls and paired controls were due primarily to the greater left ventricular pressures produced by the valvular obstruction, since cardiac outputs did not change significantly. Mean left ventricular end-diastolic pressure increased only modestly with both degrees of severity of VAS.

Group values for mean coronary blood flow measured by the LAD flow probe are presented in Table 2. Mean flows increased by an average of 40% and 50% above paired controls with moderate and severe VAS, respectively. The reactive hyperemic responses to 20-second occlusions of the LAD were reduced or nearly absent, particularly in the more severe degrees relative to those in the corresponding paired controls. Phasic flow remained predominantly diastolic and did not differ from that in controls, averaging 73% of control diastolic flow for all dogs. Similar increases were seen in myocardial

Table 1  Blood Pressure, Cardiac Output, and Left Ventricular Pressure-Volume Work Parameters for Control Group and the Paired Control and VAS-30 States for Moderate and Severe Degrees of VAS

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 12)</th>
<th>Paired control</th>
<th>VAS-30</th>
<th>Paired control</th>
<th>VAS-30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular systolic pressure (mm Hg)</td>
<td>116 ± 6</td>
<td>115 ± 6</td>
<td>118 ± 11</td>
<td>135 ± 7</td>
<td>197 ± 10</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
<td>8 ± 3</td>
<td>3 ± 1</td>
<td>16 ± 2</td>
</tr>
<tr>
<td>Aortic systolic pressure (mm Hg)</td>
<td>117 ± 6</td>
<td>113 ± 6</td>
<td>98 ± 7</td>
<td>134 ± 7</td>
<td>93 ± 6</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>98 ± 5</td>
<td>94 ± 6</td>
<td>81 ± 8</td>
<td>127 ± 8</td>
<td>72 ± 4</td>
</tr>
<tr>
<td>Aortic end-diastolic pressure (mm Hg)</td>
<td>89 ± 5</td>
<td>84 ± 5</td>
<td>73 ± 9</td>
<td>117 ± 5</td>
<td>62 ± 5</td>
</tr>
<tr>
<td>Systolic pressure time index (mm Hg/sec per min)</td>
<td>2330 ± 172</td>
<td>2273 ± 110</td>
<td>3473 ± 184</td>
<td>2600 ± 106</td>
<td>4352 ± 278</td>
</tr>
<tr>
<td>Maximum dp/dt (mm Hg/sec)</td>
<td>1787 ± 102</td>
<td>2424 ± 396</td>
<td>2423 ± 560</td>
<td>2853 ± 303</td>
<td>2500 ± 345</td>
</tr>
<tr>
<td>Cardiac output/kg (ml/kg per min)</td>
<td>35.0 ± 2.1</td>
<td>49.0 ± 11.9</td>
<td>53.0 ± 13.0</td>
<td>38.0 ± 4.5</td>
<td>32.0 ± 10.6</td>
</tr>
<tr>
<td>LVW/kg</td>
<td>4.11 ± 0.28</td>
<td>4.07 ± 0.89</td>
<td>5.89 ± 0.87</td>
<td>4.99 ± 0.84</td>
<td>9.66 ± 2.04</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SE.
TABLE 2

Overall Left Ventricular Coronary Blood Flow, Arterial and Coronary Sinus \( O_2 \) Saturation, and \( O_2 \) Consumption Data for Control and VAS Groups

<table>
<thead>
<tr>
<th></th>
<th>Moderate (n = 6)</th>
<th>Severe (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n = 12)</td>
<td>Paired control</td>
</tr>
<tr>
<td>Arterial % saturation</td>
<td>86.0 ± 2.0</td>
<td>90.0 ± 2.3</td>
</tr>
<tr>
<td>Coronary sinus % saturation</td>
<td>27.6 ± 3.0</td>
<td>27.1 ± 2.0</td>
</tr>
<tr>
<td>Mean LAD flow (ml/min)</td>
<td>22.0 ± 3.5</td>
<td>24.0 ± 6.1</td>
</tr>
<tr>
<td>Overall ventricular ( MVO_2 ) (ml ( O_2 )/min)</td>
<td>2.51 ± 0.3</td>
<td>3.0 ± 0.6</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SE.

flow measured by microspheres (Fig. 1). The ENDO:EPI flow ratio was 1.21 ± 0.03 in pure controls and did not differ significantly from flow ratios in paired controls. The flow ratio dropped significantly to 0.90 ± 0.16 with moderate VAS and to 0.89 ± 0.09 with severe VAS. Hence, the subendocardial region became underperfused relative to the subepicardium with both degrees of severity of VAS.

Arterial saturations determined by combining data from CO-oximetry and microspectrophotometric analysis averaged approximately 90% in all groups. No regional differences were observed, nor was there a relation between vessel size and arterial \( O_2 \) saturation in any group. Coronary sinus oxygen saturations (Table 2) were lower with both degrees of severity of VAS relative to controls, as were venous saturations determined by microspectrophotometric analysis. Regional venous saturations were significantly lower in the subendocardium than in the subepicardium in all three groups and decreased in both regions of the myocardium with moderate and severe VAS (Fig. 2). Oxygen extractions determined by both methods showed increases with both moderate and severe VAS. Average \( O_2 \) extraction determined microspectrophotometrically was significantly greater than controls in severe VAS. Regionally, \( O_2 \) extractions were significantly greater in the subendocardium than in the subepicardium of each group (Fig. 2). It is interesting to note that there was no further increase in subendocardial \( O_2 \) extraction in severe compared to moderate VAS.

The overall \( O_2 \) consumption determined by LAD flow and arteriocoronary sinus extractions are shown in Table 2, and regional \( O_2 \) consumptions determined by microspectrophotometric and microsphere information are shown in Figure 2. Oxygen consumptions determined by both methods show that \( MVO_2 \) increased with VAS, more so with severe VAS than with moderate VAS. These increases in

![Figure 1](http://circres.ahajournals.org/)

**Figure 1** Regional coronary blood flows in ml/min per 100 g of tissue determined by radioactive microsphere distribution. Shown are means ± SE.

![Figure 2](http://circres.ahajournals.org/)

**Figure 2** Regional venous saturation (%), \( O_2 \) extraction (ml \( O_2 \)/100 ml blood), and \( MVO_2 \) (ml \( O_2 \)/min per 100 g tissue).
MVO₂ were supported by increases in O₂ extraction and blood flow. On a regional basis, MVO₂ in the subendocardium was significantly greater than in the subepicardium in controls, giving an ENDO: EPI consumption ratio of 1.44. The greater subendocardial consumption was related primarily to the greater amount of O₂ extracted in this region. With moderate VAS, subepicardial MVO₂ increased proportionately more than did subendocardial MVO₂ so that the ENDO:EPI MVO₂ ratio dropped to 1.10, indicating that the consumptions now were nearly equal in both regions. In severe VAS, this proportional disparity was more aggravated, with the ENDO:EPI MVO₂ ratio dropping significantly to 0.84. Although extraction of O₂ increased in both regions with both severities of VAS, it was not enough to preserve the regional proportionality of MVO₂ seen in the controls.

Discussion

The theory and limitation of the three-wave-length absorbance microspectrophotometric technique used in this study have been discussed in detail previously (Sinha et al., 1975; Sinha et al., 1977; Weiss and Sinha, 1978). As long as the heart is frozen within 15–30 seconds, there is no change in O₂ saturation due to diffusion of O₂ from measured arteries or veins (Weiss and Sinha, 1978). Fibrillation halts flow, by reducing the driving pressure, within 1–2 seconds. There will be less blood movement than in the contracting ventricle, and this will preserve O₂ saturation in the vessels we observe in the state existing prior to fibrillation (Weiss et al., 1978). Since we are looking at larger vessels, it does not matter what change in the diffusion rate for O₂ occurs at the capillary level after fibrillation as long as flow does not occur. The accuracy in measuring regional coronary blood flow with microspheres using the reference sample method has also been reviewed (Buckberg et al., 1971). Recommended precautions were observed to ensure a low error. The error in measurement of regional O₂ consumption by combining information obtained by microspectrophotometric analysis and microspheres is ± 8.7% in the canine gracilis muscle and is expected to be similar in the heart (Weiss et al., 1978). Values for O₂ consumption in heart obtained by the two methods used in this study were shown to compare favorably (Vinten-Johansen and Weiss, 1978).

Our results show that O₂ consumption increases with increasing severity of VAS. This corroborates evidence reported by Blumenthal et al. (1982) in which acute valvular stenosis produced by an umbrella-type obstructive device caused MVO₂ to increase. The augmented MVO₂ seen with varying degrees of VAS may be caused by the greater pressures generated by the left ventricle per se (Sarnoff et al., 1958; Sonnenblick et al., 1968) or by increased generated wall stress resulting from both increased left ventricular pressures and dilation. Left ventricular dilation was visually evident during VAS and was suggested by the moderately elevated end-diastolic pressures. Left ventricular dilation in valvular stenosis and pressure overload have been reported by others (Dodge, 1974; Sasayama et al., 1976). It is not clear what role changes in contractility played in VAS, since our estimate of changes in contractile function (dP/dt) is afterload dependent and therefore may not reflect myocardial contractile function in pressure load conditions (Mason, 1969).

Increased coronary blood flow provided much of the increased O₂ needed by the myocardium during VAS. The regional blood flow increased modestly in moderate and considerably more in severe degrees of VAS. However, the subendocardium became underperfused relative to the subepicardium with moderate and severe VAS. These discrepancies in regional flow distribution were due to the alterations that VAS imposes on a number of factors which govern perfusion of the inner region. First, the simultaneously increased O₂ demands and modestly decreased diastolic perfusion pressures created by VAS, resulting in vasodilation, may have encroached preferentially upon subendocardial vasodilator reserve. It has been shown that, normally, the subendocardium has a lower vasodilatory reserve than does the subepicardium (Guyton et al., 1977; Rouleau et al., 1976). It is clear that vasodilation occurred during VAS because coronary flow increased despite moderate decreases in aortic diastolic pressure, and reactive hyperemic responses to transient coronary occlusion were reduced with moderate VAS and were nearly absent in severe VAS. Preferential encroachment on the available subendocardial vasodilator reserve would compromise this region's ability to augment blood supply in relative proportion to that in the subepicardium.

Second, since the subendocardium is perfused primarily during diastole, the reduced diastolic period seen in our experiments may have decreased the quantity of diastolic blood flow, particularly if the subendocardial vasodilator reserve was compromised. The systolic extravascular forces which increase with myocardial depth (Baird et al., 1970) and offer impedance to subendocardial blood flow are augmented in VAS. However, flow to the subendocardium is limited primarily to diastole so the augmented extravascular compression probably does not contribute significantly to the disparities in subendocardial flow.

During VAS, arterial-coronary sinus O₂ extraction was elevated in this study in agreement with results obtained by Blumenthal et al. (1982) using an inverted umbrella-type catheter. On a regional basis, venous O₂ saturation fell and O₂ extraction increased in both the subepicardium and subendocardium. Thus, the heart appears to use not only its ability to increase flow but also its ability to extract O₂ to meet its increased metabolic needs in
VAS. It appeared, however, that subendocardial $O_2$ extraction may have reached an apparent physiological limit of approximately 14.6 ml $O_2$/100 ml blood during VAS since $O_2$ extraction did not further increase in the subendocardium from moderate to severe VAS. An apparent limitation of subendocardial $O_2$ extraction at approximately the same value of $O_2/100$ ml of blood was reported to occur in aortic valvular insufficiency (Vinten-Johansen and Weiss, 1978) in which the subendocardium was relatively underperfused. When the ability of the subendocardium to extract $O_2$ is exhausted, $MVO_2$ becomes flow dependent and will decrease with inadequate flow.

In control hearts, the subendocardial $O_2$ consumption was found to be greater than that in the subepicardium. The greater subendocardial $O_2$ consumption in these control hearts was permitted primarily by greater $O_2$ extraction. Regional differences in $MVO_2$ were also found in previous studies by us (Weiss et al., 1978) and by others (Holtz et al., 1977). Greater subendocardial $O_2$ consumption may be related to several factors, including the greater wall tension and degree of shortening in this region. Spotnitz et al. (1966) have shown that sarcomere lengths are greater in the subendocardial region than in the subepicardium, and this may indicate greater tension and possibly greater systolic shortening in this region. Yoran et al. (1973) showed that end-diastolic sarcomere lengths were shorter in the subendocardium than in the subepicardium until a filling pressure of 20 mm Hg was obtained, whereupon subendocardial sarcomere lengths were greater. Differences in results obtained by these two groups may be related to differences in transmural electron photomicrographic sampling sites. Transmural stress analysis reported by Sterter et al. (1970) showed that radial stress (pressure) at both end diastole and end systole was greater in the subendocardium than the subepicardial region. It is possible, therefore, that the transmural gradient in wall stress and shortening may be responsible for the observed transmural differences in $MVO_2$.

In the hearts subjected to moderate and severe degrees of VAS, both myocardial shortening and wall stress should have increased in a directionally similar, if not proportional, manner. Under conditions of adequate $O_2$ supply, $MVO_2$ should have increased proportionally in the subepicardial and subendocardial regions. However, the failure of subendocardial $O_2$ consumption to increase proportionately to that of the subepicardium may represent a failure of blood flow or $O_2$ extraction, or both, to increase sufficiently to meet ambient subendocardial needs fully.

From these data, it appears that the $O_2$ supply becomes limited in the subendocardial region relative to that in the subepicardium. The $O_2$ supply and consumption status, which may be assessed by arterial $O_2$ content $\times$ flow/$O_2$ consumption, was lower in the subendocardium than in the subepicardium in all three groups, in agreement with results in control dogs reported by Weiss et al. (1978). The $O_2$ supply/consumption status becomes more precarious by falling to 1.34 with moderate VAS and to 1.29 with severe VAS from a control level of 1.44. Furthermore, a marked decrease in ENDO:EPI $MVO_2$ and the subendocardial oxygen supply and consumption status may imply that the subendocardium may not be adequately supplied with $O_2$ to support the workload in this region.

Significant differences may exist in the hemodynamic and morphological adaptation between acute and chronic pressure load conditions, so care must be exercised when extrapolating results found in the acute model to chronic situations. First, in acute VAS and other pressure load conditions, left ventricular wall stress is augmented by increased pressure or diameter, or both, which may contribute to increased $MVO_2$. In chronic pressure loading, left ventricular adaptation includes wall thickening (concentric hypertrophy) and decreasing diameter, and a consequent return to normal wall stress (Sawayama et al., 1976). A normal wall stress also has been found in patients with long-standing compensated VAS (Fallen et al., 1967). Second, the open pericardium in our preparation may have allowed a greater dilation of the left ventricle (and a greater wall tension) than would have occurred with a closed pericardium. Third, capillary density may be diminished in the pressure-hypertrophied heart due to a failure in capillary proliferation relative to increases in muscle mass, and this may reduce myocardial blood flow per unit mass in hypertrophic hearts, but not in the acutely pressure-loaded heart. It is possible that the $O_2$ supply and demand balance in chronic pressure overload may differ considerably from that found in the acute situation.

A relative imbalance in the $O_2$ supply and demand in the subendocardium as we have shown with two degrees of severity of VAS may be responsible for the accumulation of myocardial lactate in the coronary sinus effluent in dogs (Shea et al., 1962) and man (Fallen et al., 1967) and for the preferential increase in the lactate:pyruvate ratio in the subendocardium in canine hearts (Griggs et al., 1973). In VAS, subendocardial ischemia resulting from $O_2$ supply and demand imbalances is suggested by the high incidence of angina pectoris (Fallen et al., 1967). The presence of normal coronary arteries suggests that these symptoms of subendocardial ischemia are related solely to the hemodynamic consequences of the valvular obstruction rather than to other factors, i.e., coronary artery disease.

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