The Adequacy of Subendocardial Oxygen Delivery
The Interaction of Determinants of Flow, Arterial Oxygen Content
and Myocardial Oxygen Need

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SUMMARY

The interactions of determinants of subendocardial oxygen delivery (flow and oxygen content) and oxygen demand were studied. In open chest dogs, oxygen requirements were increased with aortic stenosis and oxygen delivery reduced with normovolemic anemia. We estimated potential subendocardial flow from a Diastolic Pressure Time Index (DPTI) and oxygen demands from the Tension Time Index (TTI), and detected ischemia with endocardial (Endo) and epicardial (Epi) electrocardiograms (ECG). Subendocardial oxygen delivery per unit of TTI was significantly lowered and Endo ECGs showed ischemia (ST elevation) when Endo/Epi flow ratios (microsphere method) fell below 1.0 (P < 0.001). Ischemia occurred without anemia (Hgb > 10 g %) in severe aortic stenosis; with mild anemia (Hgb 5-10 g %) and mild aortic stenosis; and with severe anemia (Hgb < 5 g %) without aortic stenosis. Ischemic Endo ECGs occurred with mild supravalvar aortic stenosis and mild anemia despite a 63% (92 to 150 cc/100 g/min) average increase in subendocardial flow while Epi ECGs remained normal. Altered flow distributions and abnormal ECGs were always predictable from the ratio: DPTI × O₂ content (Supply)/TTI (Demand). These determinants of Supply and Demand are readily obtained from measurements of hemoglobin, saturation, and blood pressure.

Additional Indexing Words:
Microspheres  Subendocardial ischemia  Regional coronary blood flow
Anemia  Supravalvar aortic stenosis  Epicardial electrocardiogram
Endocardial electrocardiogram  Diastolic pressure time index (DPTI)  Tension time index (TTI)
DPTI × O₂ content/TTI

LEFT VENTRICULAR SUBENDOCARDIAL ISCHEMIA and infarction, in the presence of patent coronary arteries, is becoming increasingly recognized as a cause of previously unexplained cardiac failure. In the absence of coronary obstruction, these changes are likely due to a discrepancy between myocardial oxygen requirements and available subendocardial oxygen supply.

Myocardial oxygen supply is determined by the coronary blood flow and its oxygen content. Normally, there is almost complete extraction of oxygen as coronary blood passes through the myocardium, so that coronary flow must increase if elevated myocardial oxygen demands are to be met adequately. This increased flow is achieved through coronary artery dilatation (autoregulation) but can reach the subendocardial region only during diastole (intramyocardial compressive forces are greatest in the subendocardium and therefore prevent its perfusion during cardiac contraction).

When subendocardial vessels become maximally dilated, subendocardial flow will be determined by the coronary driving pressure (coronary artery diastolic pressure minus the opposition to flow offered by diastolic intramyocardial compressive forces or coronary sinus pressure) and the duration of diastole. In the absence of coronary artery obstruction, these factors are represented by the area between the aortic and left ventricular pressure curves in diastole. We have referred to this area as the diastolic pressure time index (DPTI).

While DPTI indicates potential subendocardial blood supply, the adequacy of this supply is determined by how well it meets simultaneous oxygen demands. We estimated myocardial oxygen demands

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Supported by grants from the Wilbur May fund, Beaumont Foundation, Frank W. Clark Charities and the US Public Health Service. Computing assistance was obtained from the Health Sciences Computing Facility, UCLA, sponsored by NIH special research resources grant RR-3.
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Received November 26, 1973; revision accepted for publication January 14, 1974.
ADEQUACY OF MYOCARDIAL OXYGEN DELIVERY

from the tension time index (TTI) and proposed that the ratio DPTI/TTI was an expression of the supply/demand relationship and assessed the adequacy of subendocardial oxygen delivery.

Our studies show that coronary blood flow, which is normally evenly distributed across the left ventricular myocardium, becomes redistributed away from the subendocardial muscle when the ratio DPTI/TTI falls below 0.70. To assess the significance of these changes in the flow distribution, sections of left ventricle were stained histochemically and showed ischemia, which was most severe in the subendocardium, when this muscle was relatively underperfused.

Subendocardial oxygen delivery is provided not only by coronary flow but also by the oxygen content of the blood. The amount of hemoglobin and its saturation are the primary determinants of how much oxygen is contained within arterial blood. We studied the interrelationship between anemia, which reduces oxygen delivery at all levels of coronary blood flow, and other factors (DPTI, TTI) determining the adequacy of left ventricular subendocardial oxygen supply.

Methods

Experimental Procedure and Protocol

Twenty-six mongrel dogs weighing 15-27 kg were anesthetized with 3 mg/kg morphine intramuscularly and 50 mg/kg chloralose intravenously. Supplemental chloralose was given as necessary. Ventilation was maintained with a positive pressure respirator through an endotracheal tube. Arterial oxygen tensions were maintained between 100 and 500 mm Hg, and arterial pH ranged from 7.32 to 7.48. Polyethylene catheters were passed through the femoral vessels to the right atrium and supravalvular aorta. Through a unilateral thoracotomy the left atrium was cannulated via a pulmonary vein. A unipolar platinum tipped electrode was placed into the left ventricular cavity through the right carotid artery for measurement of left ventricular pressure and for endocardial electrocardiograms. Electrodes were also sutured to the anterior surface of the left ventricle to record epicardial electrocardiograms. Changes in the ST segment more than 2 mm above or below the isoelectric point were interpreted as abnormal. All pressures were measured with strain gauge pressure transducers. The coronary sinus was cannulated through the right atrial appendage to obtain blood samples for metabolic measurements.

Statham electromagnetic flowmeter transducers (SP7515) were placed about the pulmonary artery and left anterior descending coronary artery. Phasic and mean cardiac output and coronary flow were measured with Statham electromagnetic flowmeters (SP2202).

Dogs were separated into three experimental groups:

Group 1 (Anemia): Thirteen dogs were made isovolemically anemic by withdrawing blood from the femoral artery and simultaneously replacing it with equal volumes of 6% Gentrans. The exchange of blood for dextran

was stopped intermittently and measurements of blood pressure, flow, electrocardiograms and microsphere injections were made after stabilization had occurred for five minutes.

Group 2 (Supravalvular aortic stenosis and anemia): In five dogs we placed an umbilical tape around the ascending aorta and progressively tightened it until left ventricular pressure increased an average of 35 mm above control levels. After allowing five minutes for stabilization, isovolemic anemia was induced as in group 1.

Group 3 (Supravalvular aortic stenosis without anemia): In nine dogs we progressively tightened the snare around the ascending aorta until diastolic coronary flow was reduced to less than 40% of total coronary flow (normally, 80-90% of flow is diastolic). We did not manipulate blood hemoglobin levels in these dogs.

Measurements

Cardiac output, coronary blood flow, epicardial and endocardial electrocardiograms, right and left atrial, left ventricular and supravalvular aortic blood pressures were recorded on a Hewlett-Packard multi-channel recorder (7700 series). Baseline stability of the coronary flow was assessed by occluding the anterior descending coronary artery distal to the flow meter transducer. Reactive hyperemic responses were taken after a ten second occlusion of this vessel. The flow debt was calculated as the control flow times the duration of occlusion. The payback of this debt was measured by planimetry of the area beneath the mean coronary blood flow curve from the time of restoring flow until the mean flow stabilized at or near the pre-occlusion level. The area above the pre-occlusion mean flow during reactive hyperemia was divided by the calculated flow debt and multiplied by 100 to obtain the percent hyperemic response; 100% indicates that the flow debt was repaid exactly.

Regional and total coronary flow was measured by determining the myocardial distribution of 8 to 10 micron spheres labelled with 14Ce, 8Sr and 4Sc injected into the left atrium. A reference sample was collected from a peripheral artery during each microsphere injection. At the end of the procedure the heart was removed and the left ventricular free wall divided into subendocardial, subepicardial and midmyocardial layers of approximately equal thickness. These tissue samples were placed into separate vials for counting by gamma spectrometry with a Nuclear Chicago pulse height analyzer. The total activity of each isotope was calculated by modifying the method of Rudolph and Heymann. Total and regional blood flows were calculated from the equation: \( F_c = C_h \times F_r/C_r \), where \( F_c \) is the flow to the heart, \( F_r \) is the flow in the reference sample (cc/min), \( C_h \) is the counts in the heart, and \( C_r \) is the counts in the reference sample.

Microsphere injections were made and blood samples obtained during the control period, progressive anemia, and supravalvular stenosis, and when the subendocardial epicardio-cardiogram showed ischemic patterns.

pH and pCO2 were measured by the Astrup method. Venous oxygen contents were measured directly (Lex-O-Con, Lexington Instruments Corporation) and arterial oxygen contents calculated from measurement of oxygen saturation (American Optical Oximeter), hemoglobin (cyanohemoglobin method), arterial pO2 (Radiometer pO2 Electrode) from the equation: \( O_2 \) content = 1.34 X grams hemoglobin X % saturation + 0.003 X pO2 mm Hg.

*Dextran-75, Travenol Laboratories, Inc., Morton Grove, Illinois

Circulation, Volume XLIX, May 1974
Myocardial oxygen demands were estimated from the tension time index (TTI) of Sarnoff obtained by planimetry of the area beneath the left ventricular systolic pressure curve from the onset of systole to the dicrotic notch. TTI times heart rate is TTI/min (mm Hg/sec/min).

To predict the potential supply of blood to left ventricular subendocardial muscle, we measured by planimetry the area between the aortic and left ventricular pressure curves in diastole. This area equals the diastolic pressure time index (DPTI). DPTI times heart rate is the DPTI/min (mm Hg/sec/min). We used the expression DPTI × O₂ content to estimate potential subendocardial oxygen delivery and the ratio DPTI × O₂ content/TTI to estimate the supply/demand relationship.

Calculation of total left ventricular and subendocardial oxygen consumption, delivery, and vascular resistance was made as follows: a) Left ventricular oxygen consumption (LVMVO₂) = LVBF (A-V), where LVBF is the total left ventricular blood flow measured by the microsphere method, A is the arterial oxygen content, and V is the coronary sinus oxygen content; b) Left ventricular oxygen delivery = LVBF × arterial oxygen content; where LVBF is left ventricular coronary blood flow; c) Subendocardial oxygen delivery = LV subendocardial flow (LVf) × arterial oxygen content; d) LV subendocardial vascular resistance = subendocardial driving pressure (DPTI) divided by subendocardial flow (LVf).

Results

Relationship Between Myocardial Flow Distribution and Electrocardiograms

Under control conditions the coronary blood flow was evenly distributed across the left ventricular myocardial wall and the ST segments of the epicardial and left ventricular cavity electrocardiograms were isoelectric. In all experiments (anemia, supravalvar aortic stenosis, and anemia with supravalvar aortic stenosis) in which the parity of flow across the left ventricular wall was maintained (endocardial/epicardial flow ≥ 1.0), the ST segment of the electrocardiogram from the myocardial surface and left ventricular cavity remained isoelectric.

Conversely, significant ST elevation 6.6 ± 5.2 mm, so P < 0.001) of the intracavitary electrocardiogram occurred in nine of eleven experiments when coronary blood flow became redistributed away from the subendocardial region (endocardial/epicardial flow < 1.0) (fig. 1). Although occasional changes were seen on the epicardial electrocardiogram, the average ST segment recorded from the surface of the heart did not change significantly from control values despite marked alterations in myocardial flow distribution and the occurrence of endocardial injury currents.

Relationship Between Tension Time Index and Myocardial Oxygen Consumption

The highest tension time indices were observed with supravalvar aortic stenosis (SVAS) as mean left ventricular pressure increased and systolic ejection became prolonged (P < 0.01). TTI values for anemic dogs were similar to control values. Figure 2 shows that left ventricular oxygen consumption rose as myocardial demands increased, as estimated from the tension time index. Total left ventricular oxygen consumption increased in dogs with both homogeneous (solid line) as well as uneven flow distribution (endocardial/epicardial flow < 1.0) (broken line).

Left ventricular oxygen consumption was significantly less in dogs with altered myocardial flow distribution and altered endocardial ECGs (P < 0.001) for any level of TTI (broken line).

Extrapolation of the regression line for those animals with normal flow distribution to zero tension time index represents an oxygen consumption of 2.5 cc/100 g/min for the beating nonworking heart.

Arterial-Venous Oxygen Differences

Coronary sinus oxygen saturation varied from 31-37% in control experiments. There was no significant difference in the percent extraction of oxygen with the various interventions.

The arterial coronary sinus oxygen content difference was 14 vol % in control dogs with a mean hemoglobin of 12.7 g %. With progressive anemia the A-V difference fell to 4.5 vol % (P < 0.01).

Subendocardial Oxygen Delivery

In all experiments, subendocardial oxygen delivery increased relative to myocardial oxygen demands as estimated from the tension time index (fig. 3).

The highest values for subendocardial oxygen delivery at any level of demand were observed in dogs whose coronary flow remained evenly distributed
Adequacy of Myocardial Oxygen Delivery

Left ventricular myocardial oxygen consumption (cc/100 g/min) is plotted against the tension time index (TTI). The solid line is the regression line for MVO₂ vs TTI in those instances where the subendocardial to subepicardial ratio remained normal. Y = 0.00217X + 2.54, se = 0.00119. The broken line represents the regression line in dogs with relative subendocardial underperfusion (endo/epi < 1) with an abnormal flow distribution. Y = 0.00199X + 1.26, se = 0.00047. Note: MVO₂ is significantly lower at all levels of TTI in animals with altered flow ratios.

Across the myocardium and who had normal endocardial and epicardial electrocardiograms (solid line).

Subendocardial oxygen delivery for any level of demand (TTI) was less in dogs with altered myocardial flow distribution (broken line) and abnormal electrocardiograms (elevated ST segments) (P < 0.001).

Determinants of Oxygen Delivery

In control dogs, oxygen content was 17.2 vol%. There was no direct correlation between oxygen content and electrocardiographic signs of ischemia and altered myocardial flow distribution, since these changes were seen with oxygen contents ranging from 1.5 to 17.8 vol%. Dogs developing ischemic electrocardiograms with supravalvar aortic stenosis had oxygen contents which were comparable to control values (15.9 vol%). Altered myocardial flow distribution and injury current on intracavitary electrocardiograms occurred in dogs with moderate supravalvar stenosis when they were moderately anemic (oxygen content 7.4 vol%), and in severely anemic dogs without associated supravalvar aortic stenosis when oxygen content was reduced to 4.9 vol%.

In the control period, mean total left ventricular blood flow was 82 cc/100 g/min and left ventricular-subendocardial muscle received 92 cc/100 g/min (endo/epi = 1.13). Figure 4A shows the changes in total left ventricular and subendocardial flow in experiments where coronary flow remained homogeneously distributed across the myocardium. Total left ventricular blood flow increased 46% above control levels (P < 0.05) in dogs with moderate supravalvar aortic stenosis and mild anemia (endo/epi = 1.14) and rose 30% in dogs with moderate anemia alone (hemoglobins 5-10 g%) (P < 0.05) (endo/epi = 1.07).

Although total left ventricular coronary flow exceeded control levels in all experiments where ischemic electrocardiograms were recorded from intracavitary leads (fig. 4B), the proportion of total flow delivered to the subendocardium was reduced in each instance (mean subendocardial to subepicardial flow ratio 0.70 vs 1.13 for control values). The absolute volume of flow delivered to the subendocardium in dogs with ischemia varied from 23 cc/100 g/min (severe SVAS alone) to 450 cc/100 g/min (severe anemia) (table 1). The lowest subendocardial flows were seen in dogs with severe supravalvar aortic stenosis (mean 60 cc/100 g/min). Subendocardial flows in dogs with mild supravalvar aortic stenosis and mild anemia were 63% above control values (mean 150 cc/100 g/min) and with severe anemia along (< 5 g% hemoglobin) flows also rose to a mean of 150 cc/100 g/min (P < 0.01).

Determinants of Subendocardial Blood Flow

During the control period, the coronary vascular resistance was 48 ± 11 units. This resistance was noted to decrease in all experiments (table 2). During...
Table 1

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Abbreviations: SVAS = Supravalvar aortic stenosis; A = Arterial oxygen saturation; CS = Coronary sinus oxygen saturation; DPTI = Diastolic pressure time index; TTI = Tension time index; ENDO = Subendocardial, EPI = Subepicardial; M = Mean value; SD = Standard deviation; SEM = Standard error of the mean; N = Number of observations.
the control period the coronary reactive hyperemic payback of flow debt averaged 382%. We observed a progressive reduction in the payback of the flow debt as a) the supravalvar aortic stenosis was made more severe and b) the degree of anemia was increased. The average payback of the flow debt in dogs with severe supravalvar aortic stenosis was 25% and was less than 100% in all dogs exhibiting ischemic electrocardiographic patterns and in whom moderate to severe degrees of anemia were induced with or without supravalvar aortic stenosis.

During the control period, the subendocardial driving pressure (diastolic pressure time index - DPTI) averaged 4320 mm Hg-sec/min (table 1). The lowest values for DPTI were recorded in dogs with severe supravalvar aortic stenosis (fig. 5). Although diastolic pressure remained normal in these dogs, DPTI was reduced because left ventricular diastolic pressure increased to an average of 31 mm Hg, the duration of diastole was shortened by a prolonged systolic ejection period and further reduced by the associated tachycardia (DPTI = 1767 mm Hg-sec/min).

A less severe, although significant ($P < 0.001$), reduction of DPTI occurred in dogs with mild SVAS and anemia and in dogs with severe anemia. This index was lowered in both of these groups because diastole was shortened by tachycardia and because aortic diastolic blood pressure fell as the animals became more anemic.

Correlation of Hemodynamic Indices and Flow Distribution

**DPTI/TTI**

Endocardial/epicardial flow ratios below 1.0 occurred over a variable range of DPTI/TTI ratio (fig. 6A). In dogs with severe supravalvar aortic stenosis and normal blood oxygen content, altered flow distributions occurred only when the DPTI/TTI ratio was below 0.70 as previously reported.* In dogs with anemia, with and without supravalvar aortic stenosis, however, altered flow distributions occurred with DPTI/TTI values extending to 1.4. A significant number of homogeneous flow distributions also occurred in the DPTI/TTI range of 0.7 to 1.4. There was, therefore, no correlation between DPTI/TTI and myocardial flow distribution when arterial oxygen content was reduced.

$DPTI-O_2$ Content $/TTI$

In figure 6B, subendocardial/subepicardial flow distribution is plotted against a ratio using both DPTI and oxygen content to estimate potential supply. With all interventions, the left ventricle remained homogeneously perfused with $DPTI \times O_2$ content $/TTI$ ratios ranging from 10-35. Altered flow distribution and elevated intracavitary ST segments occurred with severe anemia, severe aortic stenosis, and with moderate degrees of combined anemia and aortic stenosis whenever the ratio of these indices fell below 10 ($P < 0.01$).

![Figure 5](image)

Simultaneous recordings of aortic and left atrial pressure during control supravalvar aortic stenosis (SVAS), and anemia. The stippled area between aortic and left ventricular diastolic pressures was used to calculate diastolic pressure time index (DPTI). The tension time index (TTI) was calculated from the area beneath the left ventricular pressure curve from the point of LVEDP to the dicrotic notch on the aortic pressure recording.
ischemia occurred despite increased subendocardial flow. We conclude, therefore, that the ischemia was caused by a discrepancy between myocardial oxygen delivery and the cardiac oxygen demands. We used the tension time index (TTI) to estimate myocardial oxygen needs because this index has been shown to correlate well with changes in oxygen uptake in normal hearts\(^9\) and is readily obtained. We realize that the tension time index may not adequately estimate oxygen demand when contractility increases or heart size changes.\(^{19, 20}\) Although contractility reportedly increases with tachycardia\(^{21}\) heart size probably becomes reduced. This may explain why most studies, including ours,\(^{22}\) show that the tension time index and myocardial oxygen consumption rise in parallel over a moderate range of heart rates.\(^{20, 23, 24}\)

We assumed that the tension time index (TTI) reflected the oxygen demands of all layers of the left ventricular wall since coronary flow is evenly distributed across the myocardium in compensated hearts. Recent studies of intramyocardial tissue pO\(_2\), however, indicate that oxygen tension is lowest in the subendocardium.\(^{25}\) If this method of tissue measurement is proven valid, then both resting oxygen consumption and requirement may be highest in the subendocardium. As we did not measure tissue levels of oxygen tension, we could not make this comparison in our studies.

Our findings (fig. 2) show that the slope of the regression line describing the relationship between tension time index and myocardial oxygen consumption in hearts with a normal flow distribution had an intercept of 2.5 cc/100 g/min MVO\(_2\) when tension time index was extrapolated to zero. This finding is consistent with the observations of Monroe and French who showed that the oxygen consumption of the beating empty heart (where tension time index is zero) is 2.0 cc/100 g/min.\(^{26}\)

The calculation of myocardial oxygen consumption was made for the entire left ventricle. The coronary sinus sample used to calculate the arterio-venous difference showed that the left ventricle extracted between 63 and 78% of its delivered oxygen in all experiments. Although the coronary sinus drains blood primarily from all layers of the left ventricle, it also receives a small contribution from the right ventricle, so that changes occurring in the left ventricular subendocardial region may have been obscured.

Although the oxygen consumption of the subendocardial muscle cannot be calculated because of the above mentioned constraints imposed by coronary sinus sampling, blood flow to the subendocardium can be measured by the microsphere method and arterial oxygen content can be determined. Consequently,
subendocardial oxygen delivery can be calculated. We found that oxygen delivery to the subendocardium rose with increasing demands (TTI) in both ischemic and nonischemic hearts. The subendocardial oxygen delivery per unit of demand was, however, significantly less in dogs with ischemic electrocardiograms and altered transmural flow distribution (fig. 3). These findings indicate that oxygen delivery to the subendocardium, even though augmented, is inadequate when the homogeneity of flow cannot be maintained.

These conclusions are consistent with those of Holmberg and associates who compared the changes in coronary flow and left ventricular oxygen consumption in response to heavy exercise in patients with coronary artery disease and in subjects with normal coronary arteries. They found a significantly lower coronary flow increment relative to demand (product of blood pressure and heart rate) in patients with coronary artery disease. As a consequence of reduced oxygen delivery, cardiac oxygen consumption per unit of demand was significantly less in these patients. Two developed angina and a raised left atrial pressure following heavy exercise indicating the inadequacy of myocardial oxygen delivery and resultant ventricular failure.

When arterial blood is normally saturated, the oxygen content is determined primarily by the hemoglobin concentration. Studies of anemia show that a progressive lowering of arterial oxygen content must be accompanied by concomitant increase in coronary blood flow if myocardial oxygen demands are to be met adequately. The flow increase is a result of a decrease in vascular resistance; vascular tone is lowered (vasodilatation) and blood viscosity is reduced. We observed this sequence in normal dogs with mild anemia (5-10 g % hemoglobin) when the coronary blood flow remained evenly distributed across the left ventricular wall. Similar levels of anemia and augmented coronary flow were, however, associated with electrocardiographic signs of ischemia and relative subendocardial underperfusion in dogs whose cardiac oxygen requirements were raised by mild supravalvar aortic stenosis (SVAS). Ischemia and altered flow distributions were also seen with severe anemia (Hgb < 5 g %) despite a marked augmentation in coronary flow (up to 450 cc/100 g/min in one dog). The importance of considering the interrelationship between oxygen content and coronary blood flow was emphasized further by our studies showing the development of subendocardial ischemia without associated anemia when we raised oxygen requirements with severe supravalvar aortic stenosis in dogs with normal hemoglobin concentrations.

Under resting conditions, coronary blood flow is distributed evenly across the left ventricular wall. In order for subendocardial muscle, which is perfused primarily during diastole, to receive the same flow per gram as subepicardial muscle during a shorter time period, it must have a lower vascular resistance. If vascular tone is lowest in the subendocardium, as has been shown, we may expect maximum vasodilatation to occur earliest in this region. With maximum subendocardial vasodilatation, flow becomes pressure dependent, and oxygen delivery is determined by the diastolic driving pressure and time, and oxygen content of coronary blood. If oxygen requirements increase further, or if oxygen content is lowered, flow could be augmented to the subepicardial area (which retained vascular tone and could still dilate its vessels) but not to the subendocardium. This would result in an altered flow distribution and subendocardial ischemia. Subendocardial muscle could also be made ischemic by reducing either diastolic driving pressure or duration.

Our previous studies showed that changes in flow distribution could be predicted from a supply/demand relationship estimated from the ratio DPTI/TTI. The proportion of total coronary blood flow delivered to subendocardial muscle became reduced when this ratio fell below a critical value (0.70). In the present experiments we could use the supply/demand relationship calculated from DPTI/TTI to predict subendocardial ischemia only in those dogs whose hemoglobin and blood oxygen content was normal. When hemoglobin was reduced, altered flow distributions occurred with higher DPTI/TTI ratios. This suggests that maximum vasodilatation occurs earlier when similar stresses are placed upon the heart and blood oxygen carrying capacity is reduced. This is not surprising since considerable vasodilator reserve must be utilized under resting conditions in order to insure adequate oxygen delivery when anemia is present. Oxygen delivery is determined not only by the factors affecting flow (DPTI) but also by the oxygen content of the blood. When both factors affecting supply were taken into account and related to oxygen demands the resultant supply/demand relationship (DPTI X oxygen content/TTI) allowed us to differentiate those animals with ischemia and altered myocardial flow distributions in each instance.

When the supply/demand ratio was over 10, adequate oxygen delivery to the left ventricle was maintained. When this ratio became reduced, but remained over 10, the coronary vasodilatory reserve was expended to maintain the parity of flow in different layers. Evidence of this vasodilation is
provided by the reduced subendocardial vascular resistance and reactive hyperemic responses.8

With ratios below 10, subendocardial oxygen delivery became reduced relative to demands, flow became inhomogeneously distributed and electrocardiographic signs of ischemia developed. This ischemia was probably limited to the subendocardium since subepicardial flow continued to rise and epicardial electrocardiograms remained normal.10

Clinical Implications

The importance of considering all factors contributing to the supply/demand relationship is emphasized in all of our studies. Although arterial oxygen content was reduced progressively with anemia, subendocardial vascular resistance fell sufficiently to maintain adequate perfusion until arterial hemoglobin fell below 5 g%. Signs of ischemia and cardiac failure are reported in patients with chronic anemia when hemoglobin is reduced to this level.31 We expect the subendocardium to become ischemic with higher levels of hemoglobin if the arterial blood became unsaturated (e.g. acute or chronic pulmonary insufficiency).32 Although myocardial oxygen requirements are normal in patients with coronary disease, diastolic pressure beyond the area of obstruction is low so that considerable vasodilator reserve must be expended to insure adequate resting coronary blood flow. At this time, any reduction in arterial oxygen content would reduce subendocardial oxygen delivery and cause ischemia. This ischemia would be more severe if oxygen requirements were raised simultaneously (e.g. aortic stenosis, pacing).33, 34, 35

Since our studies were done in anesthetized normal dogs, inferences about conscious animals or man with normal and/or diseased ventricles are speculative. However, the principles set forth here should apply both clinically and experimentally in normal and hypertrophied hearts. In all probability, the actual numerical values which predict when subendocardial ischemia occurs will vary in these different circumstances, as well as others such as drug therapy and sympathetic stimulation. However, further exploration of the interrelationships referred to in this study offers the prospect of getting information useful in human disease since the measurement of aortic and left ventricular pressure and blood oxygen saturation and hemoglobin are relatively easy.

References

1. Friedberg CK, Horn H: Acute myocardial infarction not due to coronary artery occlusion. JAMA 112: 1675, 1939

Circulation, Volume XLIX, May 1974
ADEQUACY OF MYOCARDIAL OXYGEN DELIVERY

associated with increased heart rate. Circ Res 24: 725, 1969


Circulation, Volume XLIX, May 1974
The Adequacy of Subendocardial Oxygen Delivery: The Interaction of Determinants of Flow, Arterial Oxygen Content and Myocardial Oxygen Need
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Circulation. 1974;49:968-977
doi: 10.1161/01.CIR.49.5.968
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1974 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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