Myocardial Blood Flow and Its Distribution in Anesthetized Polycythemic Dogs

ADRIANTA SURJADHANA, JACQUES ROULEAU, LAWRENCE BOERBOOM, AND JULIEN I.E. HOFFMAN

SUMMARY Decreased cardiac output, coronary blood flow, and systemic oxygen transport in polycythemia are attributed to increased blood viscosity and regarded as potentially harmful. We studied the effects of isovolemic polycythemia on these variables as well as on myocardial oxygen consumption and regional myocardial blood flow in 31 anesthetized dogs, seven with cannulated left main coronary arteries. Measurements were made at rest, during hypoxemia or adenosine infusions, and with aortic stenosis, pacing, or an aorto-atrial fistula. When hematocrit increased from 42\% to 66\%, it reduced cardiac output by 36\% and systemic oxygen transport by 8\%; with hypoxemia, cardiac output rose in polycythemic dogs. Normoxemic polycythemia decreased myocardial blood flow by 46\% and increased mean coronary resistance by 54\%, slightly decreased myocardial oxygen transport and consumption, and did not alter coronary sinus oxygen tension or myocardial oxygen extraction. Cardiac stress, hypoxemia, and adenosine infusion lowered coronary resistance in polycythemic dogs. Left ventricular myocardial oxygen transport was dependent on pressure work and not on arterial oxygen content or hematocrit. With maximal coronary vasodilation, coronary vascular resistance at hematocrits of 66\% was 1.5 times that at 42\%. Polycythemia per se did not alter the even distribution of flows across the left ventricular wall, but subendocardial underperfusion began at higher perfusion pressures in polycythemic than in normocytic dogs. We conclude that autoregulation plays a role in regulating flows and oxygen transport in polycythemia. With maximal coronary vasodilation, however, the increased viscosity of polycythemic blood could be an important factor reducing the amount of myocardial blood flow and oxygen transport.

THE EFFECTS of polycythemia on the circulation depend in part on whether there is an associated increase in blood volume which is usually elevated in most forms of polycythemia in man. Because of the raised blood volume, cardiac output is usually increased, unless there is heart failure. Systemic oxygen transport (cardiac output times arterial oxygen content) is therefore increased above normal when arterial oxygen saturation is normal and may be normal or only moderately reduced when there is arterial hypoxemia.

In experimental animals it is possible to keep blood volume constant when inducing polycythemia, thereby demonstrating the effects of the raised hematocrit per se. With high hematocrits, systemic oxygen transport decreases because cardiac output is decreased more than arterial oxygen-carrying capacity is increased. The fall in output has been attributed to the increased viscosity of polycythemic blood, and the reduced systemic oxygen transport has been regarded as actually or potentially endangering the supply of oxygen to tissues. Some support for these hypotheses in man has come from studies in children with cyanotic heart disease in whom an isovolemic reduction of hematocrit caused an increase in cardiac output and systemic oxygen transport. However, demonstration of the inadequacy of the oxygen supply in polycythemia has not been well documented. In polycythemic dogs or people, increased blood viscosity does not prevent the cardiac output from rising with exercise so that autoregulatory responses need not be abolished by polycythemia.

Less attention has been paid to the effects of polycythemia on coronary blood flow. There was a reduced coronary blood flow to the left ventricle when polycythemia was produced in dogs, and similar findings in people living at high altitude were reported by Moret et al., the coronary vascular bed therefore seems to respond like the whole body when there is polycythemia. No studies of regional myocardial blood flow have been done in polycythemia, yet there is reason to think that high hematocrits might play a part in producing myocardial ischemia. Children with cyanotic heart disease may have subendocardial hemorrhages, necrosis, or fibrosis at autopsy, so that the possibility of subendocardial ischemia caused by polycythemia must be considered.

Because of the occurrence of polycythemia in many diseases and because of the physiological importance of understanding the control of oxygen
delivery in polycythemia, we designed studies of dogs with acute isovolemic polycythemia. We measured cardiac output and total and regional myocardial blood flows, as well as systemic and left ventricular myocardial oxygen transport. These measurements were made at rest and after stressing the circulation by producing hypoxemia or altering cardiac work by pacing, aortic stenosis, or an aortoatrial fistula, and also after infusing adenosine to abolish autoregulation.

Methods

Thirty-one dogs weighing 25–35 kg were anesthetized with sodium pentobarbital, 30 mg/kg, iv, and given small supplemental doses as needed. They were ventilated via a cuffed endotracheal tube by a Harvard respirator with room air and either added oxygen to maintain normal arterial oxygen tensions or nitrogen to produce hypoxemia. We opened the thorax in the 5th left intercostal space, incised the pericardium, and supported the heart in a pericardial cradle. Two end-hole catheters were inserted into the left atrium through its appendage, one to measure pressure and one to inject microspheres. The coronary sinus was cannulated to obtain blood samples and measure its pressure. Pressures in the left ventricle were measured with a catheter tip manometer (Bio-Tek Instruments) inserted through the left atrium and mitral valve, and aortic pressures were measured by a catheter advanced into the ascending aorta from the left femoral artery. Pulmonary arterial pressures were measured with a side-hole catheter inserted directly into the main pulmonary artery. All pressures, except for those from the catheter tip manometer, were measured with Statham P23Db transducers and the tracings were recorded on a Beckman 12 channel Dynograph pen recorder. Large polyvinyl catheters were placed in a femoral and a jugular vein for infusing and withdrawing blood, and a catheter was placed in the right femoral artery to obtain reference samples during microsphere injection.

In seven of these dogs we placed a modified Gregg cannula in the left main coronary artery via the subclavian artery. The cannula received blood from a pressurized bottle and this bottle, in turn, was filled from the dog’s carotid artery by a Sarns roller pump; the bottle was kept in a water bath at 37°C. Pressure in the coronary artery was measured via a tube that passed inside the cannula to its tip. Phasic and mean flows in the circumflex or left anterior descending coronary artery were recorded with an electromagnetic flowmeter (Narco Biosystems). A thread was placed distal to the transducer to obtain periodic occlusion zeros and to test reactive hyperemia. Lead II of the electrocardiogram also was recorded.

Total and regional myocardial blood flows were measured with $9 \pm 1$ (SD) $\mu$m in diameter microspheres labeled with $^{125}$I, $^{14}$Ce, $^{85}$Sr, or $^{46}$Sc (3M Company). Microspheres were injected into the left atrium except that, in the dogs with the Gregg cannula, they were injected into the tubing leading to the cannula. The microspheres were suspended in saline to which Tween 80 had been added to a concentration of less than 0.05% to reduce aggregation. The vial was then placed on a Vortex mixer just before injection to ensure uniform suspension; microscopic examination of samples from the vial revealed no aggregates. For the left atrial injection, we injected about $3 \times 10^5$ microspheres with 15–20 ml of warmed blood over 15–20 seconds and collected reference samples for 2 minutes with a Holter pump at a steady rate of 11–12 ml/min. In the dogs with the Gregg cannula, we injected about $3 \times 10^6$ microspheres with 15 ml of warmed blood over 15–20 seconds and collected a reference sample at a rate of 11–12 ml/min from a side arm of the cannula that was about 40 cm from the point of injection and separated from it by two mixing chambers.

At the end of the experiment, the dogs were killed with potassium chloride or sodium pentobarbital. The heart was removed and placed in 10% formalin for 5–7 days, after which it was cut into atria, right and left ventricular free walls, and ventricular septum. The left ventricular free wall and septum were cut into three segments from apex to base, and each segment was cut into four layers of about equal thickness from endocardium to epicardium or, for the septum, from left to right ventricular sides. The right ventricle was also cut into three segments from apex to base, and each segment was divided into inner and outer layers of equal thickness. The individual layers were then cut into small pieces, placed in vials, and their gamma emissions were counted for 1 minute in a well scintillation counter with a sodium iodide crystal. We used a multichannel pulse height analyzer with variable regions of interest (Nuclear-Chicago), according to the methods described by Heymann et al. The counts per minute of the tissues and blood samples were then run on an IBM 360 computer to determine flows, flows per gram, and cardiac outputs. The percentage of total counts of each isotope in the region of interest and the counting efficiency were related to the height of the tissues in the vial, and corrections were included for these in the program.

Flow to any cardiac region (ml/min) was computed as $Cr \times Fa/Ca$, where $Cr$ and $Ca$ are the counts per minute in the cardiac regions and blood reference samples, respectively, and $Fa$ is the rate of withdrawal of the reference sample (ml/min). For any region of the heart, the flows in component pieces were added and the total was divided by the total weight of the pieces to give the average flow per gram in that region. Cardiac output was calculated as $Ci \times Fa/Ca$, where $Ci$ is the total counts per minute injected into the left atrium.

Donor blood, collected from one or two dogs 1 day before or on the day of study, was centrifuged (International Equipment Co.), and the dogs were given heparin (500 IU/kg). Polycythemia was achieved by infusing 1000–1500 ml of packed red
cells (hematocrit 85-90) into the dogs while the same amount of whole blood was withdrawn over 30-40 minutes. Hematocrits were determined on arterial samples by the microhematocrit method (International Equipment Co.); no correction was made for trapped plasma. Like Gregg and Wiggers, we observed that the spleen was very distended after transfusion and that we could maintain higher hematocrits after acute splenectomy; this was done, therefore, on all except the first six dogs. Arterial pH, PO₂, and PCO₂ were measured with a Radiometer blood gas analyzer at 37°C; in some dogs this was done also for coronary sinus blood. The oxygen contents of arterial and coronary sinus samples were measured by the Lex-O₂-Con (Lexington Instrument Corp.). Part of the same sample was exposed to room air for 20 minutes in a tonometer and analyzed for oxygen capacity. Blood oxygen saturation was then calculated by correcting for dissolved oxygen.

In six splenectomized dogs we measured blood volume before and after exchange transfusion. We labeled the dogs' own red cells with nonradioactive cesium, injected the cells, and sampled them after 10 and 20 minutes. The cell dilution was detected by fluorescence excitation and the blood volume was calculated by extrapolating back to zero time. No correction was made for differences between large vessel and whole-body hematocrits.

Statistical tests were done by unpaired t-tests, linear regression, and correlation and multiple linear regression. Values are reported as mean ± standard error unless otherwise specified.

Experimental Protocol

We studied 31 dogs, 24 without and 7 with a Gregg cannula. In 10 of the uncannulated dogs, we studied those with normal hematocrits and then gave an exchange transfusion to raise the hematocrit; arterial oxygen tension was kept normal. In eight other uncannulated dogs, we did not make control measurements with normal hematocrits but made the first measurements with polycythemia; in four dogs with normal hematocrits, polycythemia was not produced, and two dogs with polycythemia were not studied unstressed. Thus, in total, there were 14 dogs with normal hematocrits and 18 unstressed polycythemic dogs with normal arterial oxygen tensions. Eighteen polycythemic dogs were then studied during stress. We made 16 measurements with hypoxemia in which arterial oxygen tensions varied from 20-60 torr, seven measurements while pacing the atria between 200 and 250 beats/min, and eight measurements in which an aortic-right atrial fistula was produced. We also induced supravalvar aortic stenosis with peak systolic gradients ranging from 75 to 220 mm Hg by placing an umbilical tape around the ascending aorta and made eight measurements; one of these was in a dog with a fistula. Three uncannulated dogs were studied with normal hematocrits before and after hypoxemia, and five measurements were made with arterial oxygen tensions between 20 and 50 torr. Before each intervention, arterial blood gases and pH were checked and corrected if needed. After the microsphere injection, we sampled arterial and coronary sinus blood to measure blood oxygen content and capacity, gases, and pH. In another seven dogs we produced polycythemia and then inserted a Gregg cannula into the left main coronary artery. While left ventricular systolic pressure was kept constant, we reduced perfusion pressure in the coronary artery and measured flows at 21 different DPTIc:SPTI ratios (see below). In three of these cannulated dogs, we infused adenosine into the perfusion line (1.22 mg/min) until reactive hyperemia was abolished and flow measurements were made at six different DPTIc: SPTI ratios.

Calculations

Myocardial oxygen demand was estimated from the tension time index (TTI) of Sarnoff et al obtained by multiplying the mean left ventricular pressure by cycle length and subtracting from it the mean left atrial pressure multiplied by diastolic duration. Mean pressures were measured by electrical damping. We prefer to call this index the systolic pressure time index (SPTI) rather than TTI because tension is not measured. SPTI multiplied by heart rate gives SPTI per minute (mm Hg × sec/min). The area between the aortic and left ventricular pressures in diastole was calculated by multiplying the difference between mean aortic and left ventricular diastolic pressures by diastolic duration; we termed this the diastolic pressure time index or DPTI. Multiplying DPTI by heart rate gave DPTI per minute (mm Hg × sec/min), an index of pressure and time available each minute for coronary perfusion in diastole. In the cannulated dogs, DPTI was calculated similarly, except that coronary arterial pressure at the tip of the cannula replaced aortic pressure; the index was termed DPTIc. The ratio DPTIc:SPTI or DPTIc:SPTI is used to predict subendocardial blood flow, and when either of these ratios is multiplied by arterial oxygen content (CaO₂), it should predict the balance of myocardial oxygen supply and demand.

Systemic oxygen transport (ml/min per kg) is the product of cardiac output (liters/min per kg) and arterial oxygen content (ml/liter), and left ventricular oxygen transport (ml/min per 100 g) is the product of left ventricular flow (liters/min per 100 g) and arterial oxygen content (ml/liter). Left ventricular myocardial oxygen consumption (ml/min per 100 g) is the product of left ventricular flow (liters/min per 100 g) and arterio-coronary sinus difference of oxygen content (ml/liter). The percentage of oxygen extraction is the difference in oxygen content of arterial and coronary sinus blood divided by arterial oxygen content and multiplied by 100.

Systemic vascular resistance (mm Hg/liter per min per kg) was calculated by dividing mean aortic pressure (mm Hg) by cardiac output (liters/min per
kg) and pulmonary vascular resistance (mm Hg/liter per min per kg) by dividing the difference between mean pulmonary arterial and left arterial pressures (mm Hg) by cardiac output (liters/min per kg). Mean coronary vascular resistance (mm Hg/liter per min per 100 g) was calculated by dividing the mean difference between aortic or coronary arterial pressure and coronary sinus pressure by left ventricular flow (liters/min per 100 g). Minimal coronary vascular resistance (mm Hg/liter per min per 100 g) was calculated from peak diastolic coronary flow during reactive hyperemia and corresponding aortic or coronary pressures. These flows were computed from mean and phasic flows recorded with the flowmeter on a branch of the coronary artery, and then the mean flows were calibrated from the simultaneous microsphere measurements; this calibration was then used for the phasic flow tracings. In this way there was no need to calibrate the flowmeter at the end of the experiment, thereby risking errors due to changes in calibration throughout the experiment. Coronary vascular reserve (reactive hyperemic response) was estimated for each intervention by occluding a branch of the coronary artery for 15 seconds, measuring the peak diastolic flow, and comparing it to the peak diastolic flow before occlusion.

Results

Systemic Measurements

The 18 polycythemic dogs had hematocrits of 66 ± 1.3% (mean ± se) compared to 42 ± 1.7 for the 14 controls. There was no significant change in blood volume after the exchange transfusion in the six dogs in which it was measured; the mean difference was -1.47%, with a range of +12 to -20%. In dogs with normal arterial oxygen saturations, the cardiac output decreased significantly as hematocrit increased (Fig. 1). Since the heart rate did not change significantly with polycythemia (162 ± 8.2 in controls and 152 ± 6.1 beats/min in polycythemic dogs), the decreased cardiac output was due to a fall in stroke volume. Cardiac output increased in the polycythemic dogs during hypoxemia, particularly when arterial oxygen tensions were under 30 torr, and in one dog during adenosine infusion. Mean arterial pressure fell significantly (P < 0.05) from 128 ± 6.4 mm Hg in controls to 105 ± 5.6 mm Hg with polycythemia. Systemic vascular resistance did not change up to a hematocrit of 68%, and it averaged 1593 ± 89 mm Hg/liter per min per kg. For hematocrits of 68–74%, the resistance rose significantly (r = 0.61, P < 0.05) with a slope of 396 mm Hg × liter/min per kg for each 1% increase in hematocrit. Systemic vascular resistances in the polycythemic dogs did not change with mild hypoxemia (arterial oxygen tensions 47–67 torr) but fell from an average of 2359 to 1031 mm Hg/liter per min per kg (P < 0.05) with severe hypoxemia (arterial oxygen tensions, 17–34 torr) especially when the resistances were high before hypoxia was induced. Pulmonary arterial pressure was 15 ± 0.6 mm Hg with normocytosis and was similar with polycythemia. Pulmonary vascular resistance (Y) rise with hematocrit (X); the correlation coefficient was slightly higher for the logarithm of Y (r = 0.64) than for a linear relationship (r = 0.57). The regression equation was log_{10} Y = 0.0089 ± 0.0025 X + 1.7225, where the term in parentheses is the standard deviation of the slope. This relationship was not altered by hypoxemia even though pulmonary arterial pressures rose to 18 ± 1.4 mm Hg. A change in hematocrit from 42% to 66% caused an average change in pulmonary vascular resistance from 125 to 204 mm Hg/liter per min per kg.

In dogs with normal arterial oxygen saturations, systemic oxygen transport was lower with polycythemia than with normocytosis and, when plotted against hematocrit (Fig. 1), gave a roughly inverted U-shaped curve with its peak in the hematocrit range of 45–55%. When the polycythemic dogs were made hypoxic, although cardiac output increased, the systemic oxygen transport was lower than in the polycythemic dogs with normal arterial oxygen saturations.

Myocardial Measurements

The ratios of myocardial blood flows per 100 g in the left and right ventricular free walls were 1.78 in normocytic dogs, 1.60 during polycythemia, and 1.39 for polycythemic dogs with hypoxemia. Myocardial blood flows per 100 g were similar in the left ventricular free wall and the septum in all experiments, and only data from the left ventricular free wall will be discussed further.

The control dogs had a left ventricular flow of 90 ± 7.2 ml/min per 100 g and, in polycythemic dogs with normal arterial oxygen saturations, left ventricular flow decreased linearly as hematocrit increased (Fig. 2). A negative linear correlation was also found between left ventricular flow and arterial
oxygen content \( (r = -0.79, P < 0.01) \). When hypoxemia was added to polycythemia, left ventricular flow increased from 49 ± 4.2 to 111 ± 25 ml/min per 100 g, and this rise was proportionately greater than the rise in cardiac output \( (P < 0.01) \); furthermore, with mild hypoxemia, there was an increase in left ventricular flow but no change in cardiac output. When data from hypoxemic dogs were included, left ventricular flow no longer correlated with hematocrit but showed a hyperbolic relationship to arterial oxygen content (Fig. 3); there was a linear correlation between the logarithm of left ventricular flow and arterial oxygen content, with \( r = -0.84 \). In polycythemic dogs, pacing and aortic stenosis increased left ventricular flow by 31% and 84%, respectively, and also increased SPTI and myocardial oxygen consumption (Table 1). When there was an aorto-atrial fistula, left ventricular flow in the polycythemic dogs was initially maintained but decreased when the fistula was so large that perfusion pressure decreased markedly.

Left ventricular oxygen transport fell slightly \( (0.05 < P < 0.10) \) when hematocrit was increased in dogs with normal arterial oxygen saturations; there was no convincing inverted U-shaped curve relating hematocrit and oxygen transport (Fig. 4). There was no significant relationship of left ventricular oxygen transport to hematocrit under 68%, but 7 of 11 dogs with hematocrits of 68–74% had lower values for left ventricular oxygen transport than had any of the other dogs. The hematocrits of these low and high oxygen transport groups were, respectively, 70.5 ± 1.03 and 70.8 ± 0.97%, and were not significantly different \( (P > 0.5) \). However, the low oxygen transport group when compared to the high oxygen transport group had significantly lower values for myocardial oxygen consumption \( (6.7 ± 0.43 \text{ vs. } 10.6 ± 0.64 \text{ ml/min per 100 g, } P < 0.01) \) and significantly lower values for SPTI \( (2814 ± 291 \text{ vs. } 3887 ± 248 \text{ mm Hg × sec/min, } P < 0.01) \). At any SPTI, the left ventricular flow was much lower with polycythemia than with normocytemia (Fig. 5, left panel), but left ventricular transport for a given SPTI was similar in polycy-
themic and normocytic dogs (Fig. 5, right panel). Left ventricular oxygen transport was also related to myocardial oxygen demand as estimated by SPTI and to measured myocardial oxygen consumption for the polycythemic dogs with pacing, aortic stenosis, and fistula and was not related to the increased hematocrit. When there was hypoxemia, the polycythemic dogs increased their left ventricular flows. With mild hypoxemia, this increase in flow compensated for the fall in arterial oxygen content so that left ventricular oxygen transport was not decreased, but with severe hypoxemia, compensation was incomplete and left ventricular oxygen transport was below normal.

The variables affecting left ventricular flow and oxygen transport were assessed further by multiple linear regression analysis (forward method). The logarithm of left ventricular flow for all the studies \((n = 76)\) was predominantly related to arterial

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{SPTI} \quad \text{mm Hg} \cdot \text{sec} \cdot \text{min}^{-1}
\]

\[
\text{LV Flow} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]

\[
\text{LV Oxygen Transport} \quad (\text{ml} \cdot \text{min}^{-1} \cdot \text{100 g}^{-1})
\]
Coronary blood flow in polycythemia/Surfadhan et al.

Coronary blood flow in polycythemia/Surfadhan et al.

Mean coronary vascular resistance (Y) in mm Hg/liter per min per kg increased as hematocrit (X) rose (Fig. 6). As in the pulmonary bed, a curvilinear relationship gave a slightly higher correlation coefficient than did the linear relationship (r = 0.79 and 0.76, respectively); in addition, it made the variance of Y homogeneous over the range of X values. The equation was log Y = 0.0096 ± 0.0013 X + 2.7227. A change in hematocrit from 42% to 66% caused an average increase in coronary vascular resistance from 1336 to 2271 mm Hg/liter per min per 100 g. To determine how much coronary vascular resistance (log Y) was related to hematocrit (X1) in the absence of changes in myocardial oxygen demand as assessed by SPTI (X2), we calculated the multiple linear regression relating these three variables for the normoxic, unstressed dogs. The equation was: log10 Y = 0.009626X1 - 0.0000000932X2 + 2.7232, with r = 0.806 (P < 0.01). The coefficient for SPTI was not significant and was of small magnitude. This lack of significant influence of SPTI on coronary vascular resistance was confirmed by examining the relationship of these two variables in the 11 dogs with hematocrits of 68–74%; the correlation between them was not significant (r = 0.31, P > 0.20). In the polycythemic dogs, mean coronary resistance was lowest with severe hypoxemia when it was similar to the values found during adenosine infusion (Table 1). After temporary occlusion of a branch of the left coronary artery, there was reactive hyperemia in all the polycythemic dogs without stress; however, no reactive hyperemia was noted in some of the polycythemic dogs with severe hypoxemia or a large fistula. The minimal diastolic resistance at peak reactive hyperemia (Y) was significantly related to hematocrit (X) by log10 Y = 0.0076 ± 0.0020X + 2.1168 (Fig. 6). The minimal resistances at hematocrits of 42% and 66%, respectively, 273 and 415 mm Hg/liter per mm per 100 g.

As the hematocrit rose there was a linear increase in arterial oxygen content in dogs with normal oxygen tensions, with r = 0.937. Oxygen saturations were similar in normocytic and polycytemic dogs. Arterial-coronary sinus oxygen difference of oxygen content increased from a mean of 13.2 ml/dl in controls to 19.7 ml/dl with polycythemia; however, the coefficient of oxygen extraction did not change (Fig. 2). Coronary sinus oxygen tension fell as low as 18 torr in a few dogs at high hematocrits, but the change for all the dogs was not significant. The arteriovenous oxygen difference, coronary sinus oxygen content, and coefficient of oxygen extraction were not significantly altered in the polycythemic dogs with pacing or aortic stenosis (Table 1). With severe hypoxemia and a large fistula, however, the coronary sinus oxygen content and tension fell and the coefficient of oxygen extraction rose to 80–90%.

Left ventricular oxygen consumption was reduced in polycythemia, and its fall correlated well with the fall in SPTI (r = 0.64, P < 0.01) and the decrease in left ventricular flow (r = 0.75, P < 0.01). Left ventricular oxygen consumption also changed linearly as demand (SPTI) was increased by pacing or stenosis or decreased by a fistula, (r = 0.64, P < 0.01). However, no correlation was noted in dogs with polycythemia and hypoxemia among left ventricular flow, oxygen consumption, and SPTI. When all data were examined by multiple linear regression analysis, left ventricular oxygen consumption was significantly correlated with SPTI (r = 0.69) and the correlation was not significantly increased by including hematocrit or arterial oxygen content.

Regional Left Ventricular Measurements

Polycythemia reduced both DPTI and SPTI proportionately in the unstressed and hypoxemic dogs so the DPTI:SPTI did not change from control values. As expected, the ratio fell markedly with
both aortic stenosis and the fistula \((P < 0.01)\) but not with pacing. Pacing reduced the proportion of flow in diastole only slightly from 82% to 67%, but it produced a marked increase of 167% in absolute systolic flow when the mean heart rate was 230 beats/min. Although left ventricular flow increased 105% with supravalvar aortic stenosis, the proportion of flow in diastole fell by 38%, diastolic time decreased by 15%, and ejection time was prolonged. With large fistulas, there was a marked fall in aortic diastolic pressure and a 33% decrease in the proportion of diastolic flow. The myocardial oxygen supply-demand ratio \((\text{DPTI} \times \text{CaO}_2: \text{SPTI})\) rose with polycythemia and was reduced slightly by pacing and markedly by stenosis, fistula, or hypoxemia \((P < 0.01)\).

With polycythemia, although left ventricular flows were reduced, the subendocardial-subepicardial flow ratio (inner-outer flow ratio) did not change from control values and was unchanged with the imposed stresses except the fistulas. When the inner-outer flow ratios were plotted against the DPTI:SPTI ratio (Fig. 7, left panel) most of the points fell within the normal range determined in our laboratory. However, when the inner-outer ratio was plotted against the myocardial oxygen supply-demand ratio (Fig. 7, right panel), some polycythemic dogs with fistulas and stenosis had myocardial oxygen supply-demand ratios above the critical value of 10, yet had inner-outer flow ratios below the lower limit of normal for anesthetized dogs; these are the five points below and to the right of the normal range. With hypoxemia, the polycythemic dogs had inner-outer ratios of about 0.8 or more, even with low DPTI \times \text{CaO}_2:SPTI ratios, whereas the normocytic dogs at similar low ratios of DPTI \times \text{CaO}_2:SPTI had inner-outer ratios of about 1.2. This can be seen in Figure 7 (right panel) in which most of the data points for hypoxemic dogs fell to the left of and above the normal curve.

**Cannulated Polycythemic Dogs**

The hematocrit values of the cannulated dogs were 70 ± 1.0%, slightly higher than in the uncannulated dogs, but they had similar arterial oxygen contents because of the slightly lower arterial oxygen saturations in the cannulated dogs. In two dogs we varied coronary arterial pressure over a wide range while keeping the left ventricular pressure constant, and demonstrated that, during a stable state, left ventricular flow, as judged by the flowmeter readings on the circumflex coronary artery, remained constant over DPTIc:SPTI ratios ranging from 0.60 to 1.02. With lower ratios there was a progressive fall in the flowmeter readings. In Figure 8 we plotted the pressure ratios against inner-outer flow ratios for 21 measurements in polycythemiac dogs. When these polycythemic dogs were compared to normocytic dogs studied previously, the polycythemic dogs began to show a decrease in inner-outer flow ratios at a higher DPTIc:SPTI ratio (as well as a higher DPTI \times \text{CaO}_2:SPTI ratio) than did the normocytic dogs. For dogs with normal hematocrits, the point of departure from even distribution of flow across the wall was at a

---

**Figure 7** Flow ratios per 100 g of left ventricular subendocardial muscle (inner) to subepicardial muscle (outer) measured by microspheres is plotted against DPTI:SPTI (left panel) and DPTI \times \text{CaO}_2:SPTI ratios (right panel) for various interventions. The black lines represent the normal range found in our laboratory. The area between the parallel black lines separates the graph into three zones. The zone between the lines indicates the normal relationship of the inner-outer flow ratio to the myocardial supply-demand ratios. The zone below and to the right of the lower line indicates flow ratios that are too low for the corresponding supply-demand ratios. The zone above and to the left of the upper line indicates flow ratios that are higher than expected for the corresponding supply-demand ratios. The data points with the fistula, aortic stenosis, and pacing are in polycythemic dogs with normal oxygen tensions.
inner / outer since there may be differences between viscosities diac output and hematocrit to be predicted exactly, vitro viscometry data allow the relationship of car-
suggested that this decrease in output can be ex-
plained by the known curvilinear rise in blood vis-
cosity as hematocrit increases, based on data from
in vitro viscometry. However, it is doubtful if in
vitro viscometry data allow the relationship of car-
diac output and hematocrit to be predicted exactly,
since there may be differences between viscosities measured in vitro and in vivo. At any hematocrit,

**Discussion**

**Systemic Vascular Bed**

A major factor in the cardiac output response to polycythemia is blood volume. In our experiments there was no significant change in blood volume in the six dogs in which it was measured. Furthermore, the similarity of our results and those obtained in other studies when blood volume was known to be constant leads us to believe that changes in blood volume played no part in our results.

We confirmed that at a constant blood volume there is a roughly linear decrease of cardiac output as hematocrit increases. Castle and Jandl have suggested that this decrease in output can be explained by the known curvilinear rise in blood viscosity as hematocrit increases, based on data from in vitro viscometry. However, it is doubtful if in vitro viscometry data allow the relationship of cardiac output and hematocrit to be predicted exactly, since there may be differences between viscosities measured in vitro and in vivo. At any hematocrit, viscosity is largely a function of shear rate, which varies in different vascular beds and vessels of different caliber. It is also affected by anomalous viscosity and inertial pressure losses. To evaluate the magnitude of the effect of increased hematocrit on vascular resistance it is necessary to use vascular beds in which vascular tone is unlikely to change during the experiments. The pulmonary vascular bed has been used for this purpose, and at a hematocrit of 70%, the pulmonary vascular resistance has been found to be about 1.5-2 times that at a hematocrit of 40-45%. Our results for pulmonary vascular resistance were similar.

Levy and Share performed maximally dilated vessels of the dog hindlimb with blood of different hematocrits and viscosities and noted an increase of about 50% in vascular resistance when hematocrit was raised from 48% to 74%, either when perfusing pressure was 80 mm Hg or when flow rate was 100-200 ml/min (their Fig. 2). Djojosugito et al. reported similar results.

The fact that increased blood viscosity in normocytic polycythemia is associated with a reduced cardiac output at rest does not mean that at times of increased demand there cannot be decreases of vascular tone or increases in tissue oxygen supply. The increased peripheral vascular resistance in polycythemia can be lowered by exercise in dogs and man, and could be lowered by hypoxemia and adenosine infusions in our experiments. Furthermore, since tissue oxygen transport in polycythemia can be increased during exercise, the reduced systemic oxygen transport that is found with polycythemia at rest may not be disadvantageous to tissue oxygen supply, as some workers have suggested. Murray et al., for example, speculated that the reduced oxygen delivery to tissues in polycythemia might tend to dilate vessels and attenuate the increase in resistance that would be due to the raised viscosity. However, this implies that there was a reduced supply of oxygen below tissue needs for
which there is little evidence. Replogle and Merrill\textsuperscript{10} did observe that with polycythemia there was a decreased systemic oxygen transport and that, at times, excess lactate was produced; they therefore concluded that polycythemia reduced tissue perfusion enough to produce anaerobiosis. However, in their study there was only mild polycythemia (hematocrit 60\%) and the arteriovenous difference of oxygen content was 7.15 ml/dl, so that the mixed venous oxygen saturation can be calculated as about 72\%. It is difficult to believe that generalized anaerobiosis would occur with so much venous oxygen still available. Furthermore, with polycythemia, in their study, there was a fall in body oxygen consumption, so that in fact the decrease in systemic oxygen transport matched the decrease in oxygen consumption.

If autoregulation is still possible, there is no reason why tissue hypoxia should occur in polycythemia and, in fact, not all the dogs studied by Replogle and Merrill\textsuperscript{10} produced excess lactate. Furthermore, Thorling and Erslerv\textsuperscript{33} produced tissue pockets in rats and measured the oxygen tension in them at different hematocrits; at high hematocrits the tissue oxygen tensions were normal. This response to polycythemia is probably part of a more fundamental regulation of tissue oxygen transport that has been shown in many ways. For example, in normocytic dogs, Shepherd et al.\textsuperscript{34} did a series of studies to show that cardiac output was regulated partly by the peripheral vascular beds. Although the degree of autoregulatory control of blood flow was highly variable from dog to dog, oxygen delivery to tissues was constant. They stressed that oxygen extraction could also be important in delivering enough oxygen to tissues. A similar observation was made by Weisse et al.\textsuperscript{11} who showed that in polycythemia a decreased systemic oxygen transport was not necessarily disadvantageous to tissue oxygen uptake.

Finally, it is important to note that, although the inverted U-shaped curve relating systemic oxygen transport to hematocrit is also found when blood volume is increased, the actual oxygen transport is higher at each hematocrit than when blood volume is normal.\textsuperscript{1} There is thus even less reason to think that when blood volume is increased the reduced oxygen transport at high hematocrits limits tissue oxygen use, a view supported by the lack of anaerobic metabolism in patients with polycythemia vera.\textsuperscript{4, 5}

**Coronary Vascular Bed**

The polycythemic dogs with normal arterial oxygen saturations had lower total and left ventricular blood flows and higher coronary vascular resistances, as noted by others in dogs\textsuperscript{9, 13, 14} and man.\textsuperscript{15} In our studies, the rise in coronary vascular resistance as hematocrit increased was not related to changes in myocardial oxygen demand or consumption, so that it probably was due either to the increase in viscosity or to the increased arterial oxygen content that paralleled the rise in hematocrit.

We can estimate the magnitude of the increase of in vivo viscosity in these polycythemic dogs from examining the changes of resistance in vascular beds that do not undergo autoregulatory changes of tone. When hematocrit increased from an average of 42–66\%, there was a 1.63-fold increase of pulmonary vascular resistance and a 1.53-fold increase of coronary vascular resistance when the coronary vessels were maximally dilated by reactive hyperemia or adenosine infusion. In the autoregulated coronary vessels, the comparable increase in resistance was 1.70-fold. By analysis of covariance, the slopes relating the logarithm of resistance to hematocrit for pulmonary, coronary, and maximal coronary resistances were not significantly different ($P > 0.5$). This similarity of logarithmic slopes supports the similarity of resistance ratios at hematocrits of 42\% and 66\%. Since there would have been lower shear rates and thus higher in vivo viscosities with the lower coronary flows when autoregulation was intact than with the higher flows of maximal coronary vasodilation, it is possible that there might even have been some autoregulatory vasodilation that helped to minimize the reduction of coronary blood flow induced by a raised viscosity. However, our data are too variable to demonstrate this with certainty, and an alternative explanation is that, even in polycythemic dogs, the lowest shear rates were high enough not to affect viscosity.\textsuperscript{9}

In the normoxic dogs, left ventricular oxygen transport was related to myocardial oxygen demand and not to hematocrit; myocardial oxygen extraction and coronary sinus oxygen tension did not change as hematocrit increased, in keeping with previous reports.\textsuperscript{9} There was thus no evidence that the increased blood viscosity caused myocardial ischemia at this time. Even though, in a few dogs, the coronary sinus oxygen tension was as low as 18 torr, this is still well above the level at which myocardial ischemia occurs. Furthermore, with polycythemia there was no rise of left atrial pressure so that there was no evidence of gross myocardial dysfunction. Finally, well-marked reactive hyperemia and normal inner-outer ratios in the normoxic unstressed dogs indicated good vasomotor reserve in all layers of the left ventricle.

The fact that in these polycythemic dogs the changes of coronary flow and resistance seemed to be related to viscosity with little evidence for autoregulatory changes is probably fortuitous. The arterial oxygen content increased 1.57-fold when the average hematocrit rose from 42\% to 66\%, and this almost balanced the decrease in coronary flow due to a similar increase in hematocrit and viscous resistance. Therefore, there was no need for major autoregulatory changes of vascular geometry to maintain left ventricular oxygen transport, although it is likely that variations in viscosity or oxygen need were compensated for by autoregula-
Coronary Blood Flow in Polycythemia

Coronary Blood Flow in Polycythemia/Surjadhana et al. 629

The decrease in left ventricular oxygen transport when hematocrit was below 20%.

That autoregulation is still working even in polycythemic dogs, they had maximal vasodilation and pressure dependency in subendocardial vessels at higher-than-normal pressure ratios. This occurred because the increased oxygen-carrying capacity at a hematocrit of 66% in our experiments was only 1.50 times greater than normal and the viscosity due to polycythemia increased slightly more than that. Furthermore, when perfusing pressure was reduced in the Gregg cannula, there might have been reduced shear rates and even higher viscosities. (This conclusion is supported by Levy and Share who noted that the relative viscosity of blood perfusing maximally dilated vessels of the dog's hindlimb was greater at low than high perfusing pressures.) As a result, autoregulation was lost at higher pressure ratios than in dogs with normal hematocrits.

In the uncannulated dogs, the data points from the polycythemic dogs fell in the normal range in the figure relating the DPTIc:SPTI ratio to the inner-outer flow ratio (Fig. 7, left panel). If the arterial oxygen content rose without a change in blood viscosity, then a normal left ventricular oxygen transport could occur at lower than normal coronary pressures and flows; therefore, the DPTIc:SPTI ratio at which maximal subendocardial vasodilation occurred should be lower in polycythemic than in normocytic dogs, and the experimental data points should be to the left of the lower portion of the normal range. Their absence from this region of the graph implies that the increased viscosity due to polycythemia decreased subendocardial oxygen transport at higher pressure ratios than in normocytic dogs. That this reasoning is correct is shown by Figure 7, right panel. When the pressure ratios were multiplied by arterial oxygen content to give an estimate of the balance of myocardial oxygen supply and demand of the left ventricle, some of the data points from the polycythemic dogs fell to the right of the normal range relating DPTIc × CaO=SPTI to inner-outlet flow ratio. These findings were also consistent with the...
Clinical Implications and Conclusions

Care is needed in extending our findings to clinical situations, since only the aspect of increased red cell mass (hematocrit) was studied in acutely induced normovolemic polycythemia. Moret et al. 15 and Balke 20 have shown that people with increased hematocrits function well at high altitudes. We showed that, as long as perfusion pressure is normal, hematocrit values up to 74% did not alter blood flow distribution across the myocardial wall. Thus, subendocardial hypoxemia is unlikely to occur at rest in normoxic polycythemic patients with normal coronary arteries.

The decreased cardiac output and systemic oxygen transport in polycythemia in these studies were probably due to increased viscosity but did not limit oxygen supply to tissues, and both could be increased when metabolic needs caused peripheral vasodilation. Furthermore, even in polycythemia, autoregulation is retained in the heart, as shown by the constancy of myocardial oxygen transport and its relation only to myocardial oxygen demand regardless of hematocrit. This fits in with the idea that there is a tissue autoregulatory mechanism for oxygen. 34,39 The mechanism of this autoregulation still is not clear; it could be either a direct effect of oxygen on the vessels or an indirect effect via vasodilatory metabolites like adenosine, as suggested by Berne. 40

However, when maximal coronary vasodilation is reached (and this occurs earlier in subendocardial vessels than in subepicardial vessels), the raised viscosity of polycythemic blood could decrease flow enough to outweigh the effect of the high arterial oxygen content, and a reduced subendocardial oxygen supply would occur. This may happen in polycythemia with stenotic coronary arteries or with severe stresses, especially when accompanied by arterial hypoxemia.

Acknowledgments

We thank Elizabeth Shapkin, Bruce Payne, and Roger Cheitlin for their technical assistance, Lesley Williams for expert electronic assistance, Elizabeth Dornbusch and her staff for performing the blood gas analyses, and Susan Axelrod for the preparation of this manuscript. Dr. John Murray gave us helpful advice about the conduct of these experiments and Dr. Leon Kaufman provided advice and assistance in the fluorescent excitation analysis.

References

40. Berne RM: Regulation of coronary blood flow. Physiol Rev 44: 1-29, 1964
Myocardial blood flow and its distribution in anesthetized polycythemic dogs.
A Surjadhana, J Rouleau, L Boerboom and J I Hoffman

Circ Res. 1978;43:619-631
doi: 10.1161/01.RES.43.4.619

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circres.ahajournals.org/content/43/4/619.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in
Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the
Editorial Office. Once the online version of the published article for which permission is being requested is
located, click Request Permissions in the middle column of the Web page under Services. Further information
about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/