Changes in vascular tone and pressure gradients have been established as important factors in the control of regional blood flow, but the influence of varied physical states of the perfusing blood is less clear. In a hemodynamic evaluation of shock, Seligman indicated that enhanced blood viscosity promoted the onset of irreversibility, presumably through an effect on flow. More recently Richardson assigned a major role to viscosity in the development of a diminished cardiac output during acute normovolemic polycythemia.

A judgment as to whether coronary flow is modified by increasing red cell mass acutely may be obtainable by determining the relation between the flow-dependent oxygen consumption of the left ventricle and its performance. Although there appears to be no single, dominant regulator of myocardial oxygen uptake, certain hemodynamic parameters, such as arterial pressure and pressure work of the left heart when rapidly altered, are usually associated with acute changes in oxygen uptake. These and other relevant factors have been determined in order to assess the consequences of increasing red cell mass in patients with chronic anemia and in a group of normal dogs. Supplementary information on the effects of hypervolemia with dextran, and on the effects of introducing methemoglobin-bearing red cells to minimize the effects of increased arterial oxygen content, has been obtained.

Methods

In an attempt to enhance the influence of blood viscosity upon coronary flow, out of proportion to that of arterial blood oxygen content, we studied a group of seven subjects with chronic anemia from blood loss for which transfusion was therapeutically indicated. They received, via a systemic vein, 800 ml of freshly prepared, warmed, packed red blood cells over a 45-minute period. Although citrate was used as an anticoagulant for blood collection, removal of plasma from the transfused cells presumably prevented important changes in the recipients' blood calcium. In addition, plasma potassium concentrations in the patients were not altered after red cell transfusion so that ion leakage from erythrocytes was not a problem. One subject developed urticaria and fever during transfusion and was excluded from the study.

Hemodynamic measurements were made before, and thirty minutes after, the infusion, when heart rate and arterial pressure were constant to within a range of 5% from the beginning to the end of coronary flow determination. Systemic arterial pressures were obtained from an indwelling needle in the brachial artery, and together with pulmonary artery and capillary pressures, were recorded with Sanborn electromanometers and polyviso. Coronary blood flow was measured by the nitrous oxide desaturation technic. Cardiac outputs were determined by the Fick method, blood gases by the method of Van Slyke, and the volume of packed erythrocytes by the method of Wintrobe.

To evaluate the nonspecific effect of expanding intravascular volume, a volume of 6% dextran sulfate in saline, equal to the red cell infusions, was infused over 45 minutes in a group of four subjects with normal hematocrits who were considered to have normal cardiovascular systems. The postinfusion study was done thirty minutes later. While studies on patients with anemia would have been preferable, dextran or whole blood would have substantially altered hematocrits and obscured the study of volume effects.

Because the response of the myocardium during
anemia may not be representative of the normal, a third study was done using a group of six normal, intact, anesthetized male dogs, weighing between 19 and 26 kg.* All animals were anesthetized with morphine sulfate 3 mg/kg and pentobarbital sodium 12 mg/kg and respirations were regulated by a phasic respiratory pump. Bilateral cervical vagotomy was performed in all but two animals (no. 1 and no. 2, table 3). Following the control study, about 600 ml of warmed, packed red cells, freshly prepared from heparinized blood, were transfused over thirty minutes. Prior or simultaneous removal of the recipients' whole blood to maintain normovolemia was not done because when attempted earlier, a stable hemodynamic state was difficult to achieve. Thirty minutes after the transfusion was complete, measurements of coronary flow and left heart functions were repeated. Left ventricular pressure and its first derivative were obtained by the method of Reeves from a cannula inserted through the right carotid artery. Arterial pressures were registered from the ascending aorta. Pressures were sensed through a Statham P23Db strain-gauge manometer and were recorded photographically on a multichannel oscilloscopic recorder. Left ventricular end-diastolic pressure was subtracted from the mean arterial pressure in calculations of left heart work. Although the change of hematocrit in these experiments increased blood specific gravity, this factor was omitted from the calculation of left heart work because the increment would have been small, i.e., in the order of approximately 2%. To detect and measure possible cardiac ischemia as evidenced by excess lactate production, blood samples were taken for myocardial arteriovenous differences of lactate and pyruvate. Two arterial and coronary sinus samples were taken five minutes apart in the control period, at the end of transfusion, and 30 minutes after transfusion. Experiments were extended to intact dogs to determine whether the effect on coronary flow could be made more evident by transfusing red cells without increasing the oxygen-carrying capacity. In view of the arterial desaturation induced by the subsequent experimental procedure the control study prior to transfusion was performed with the animal inspiring 10% oxygen to approximate the arterial desaturation present when methemoglobin-containing red cells were transfused. Then 600 ml of methemoglobin-containing red cells which had been freshly prepared by incubation with 360 mg of sodium nitrite followed by three saline washes, were infused into a systemic vein. Thirty minutes after infusion with a relatively constant arterial oxygen saturation as described elsewhere, the coronary flow was redetermined. Although an in vivo method for the estimation of the comparative viscosity of hypoxic and methemoglobin red cells is not available, it is assumed they are not dissimilar. Comparable arterial oxygen saturations in the control and transfusion studies were achieved in three of five animals and it is these that are reported. Although alveolar oxygen tensions were undoubtedly different during hypoxia and methemoglobin transfusion, this would not prevent a comparison of coronary flow in the two situations. The myocardial arteriovenous oxygen differences and oxygen content of blood from the coronary sinus were nearly identical in studies of both hypoxia and methemoglobin. The latter would appear to be a major factor in determining coronary flow and presumably reflects the oxygen tension of cardiac tissue. Additional support for this conclusion was obtained from this group by the finding of a similarly altered relationship of oxygen uptake and hemodynamic activity as was observed in the animals transfused with normal red cells.

**Results**

The six patients with anemia all had elevated coronary blood flows at rest (table 1) which greatly minimized the tendency to decreased oxygen delivery because of a reduced oxygen-carrying capacity. In contrast to the elevated oxygen usage per 100 g of left ventricle per minute, in another high output state, this parameter at 7.3 ml was below the normal value in the presence of a high cardiac output and left ventricular work. When compared with values from 16 resting normal subjects having a mean of 8.8 ml, myocardial oxygen usage was significantly reduced ($P < 0.001$). The lowest and highest hematocrits were associated respectively, with the largest and least deviation of oxygen usage from normal.

Thirty minutes after completion of the packed red cell transfusion, when pressure and heart rate were relatively constant, the coronary blood flow in the group of anemic patients was reduced by 49 ml/100 g per min (table 1), whereas duplicate flows in another group of normal subjects have shown no significant difference. A 50% increment in myocardial oxygen extraction, approximating

---

*Normal subjects and the anemic patients restored to normality were not studied in view of the risks of donor blood use.

Circulation Research, Volume XIII, August 1969
TABLE 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Body surface area (m²)</th>
<th>Myocardial Blood Flow (ml/100g/min)</th>
<th>Coronary O₂ Utilization (vol%</th>
<th>Arterial O₂ Saturation (%)</th>
<th>Left ventricular Work (kgm/m²/min)</th>
<th>Heart rate (BPM)</th>
<th>Oxygen usage (ml/kg/min)</th>
<th>Hct (%)</th>
<th>Heart rate (BPM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ME, 44, F</td>
<td>1.36</td>
<td>44</td>
<td>1.15</td>
<td>4.52</td>
<td>88.9</td>
<td>12.5</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>3.16</td>
</tr>
<tr>
<td>LT, 49, M</td>
<td>2.26</td>
<td>5.30</td>
<td>2.4</td>
<td>6.38</td>
<td>94.5</td>
<td>26.8</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>3.16</td>
</tr>
<tr>
<td>MH, 38, F</td>
<td>1.49</td>
<td>7.71</td>
<td>4.54</td>
<td>98.9</td>
<td>27.8</td>
<td>8.05</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>3.16</td>
</tr>
<tr>
<td>EL, 42, M</td>
<td>1.74</td>
<td>7.82</td>
<td>4.54</td>
<td>98.8</td>
<td>27.8</td>
<td>8.05</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>3.16</td>
</tr>
<tr>
<td>HI, 41, M</td>
<td>1.68</td>
<td>7.31</td>
<td>4.81</td>
<td>95.4</td>
<td>21.3</td>
<td>8.05</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>3.16</td>
</tr>
<tr>
<td>EG, 41, M</td>
<td>1.08</td>
<td>7.32</td>
<td>4.54</td>
<td>94.2</td>
<td>21.3</td>
<td>8.05</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>3.16</td>
</tr>
</tbody>
</table>

*Control values.
†After red cell transfusion.
EED CELL MASS AND MYOCARDIAL BLOOD FLOW

175

the rise in hematocrit, maintained oxygen uptake at the associated hemodynamic level. However, in

The influence of an expansion of intravascular volume per se upon myocardial blood flow was limited. The increase of

TABLE 2

Effects of Dextran Infusion in Normal Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Body surface area</th>
<th>Myocardial Blood flow</th>
<th>O2 usage</th>
<th>Coronary A-V O2 difference</th>
<th>Arterial</th>
<th>Mean press.</th>
<th>Het.</th>
<th>Cardiac index</th>
<th>Heart rate</th>
<th>Left ventricular Work</th>
<th>Oxygen usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB, 40, P</td>
<td>1.4</td>
<td>78* 9.8</td>
<td>12.6</td>
<td>98.3</td>
<td>99</td>
<td>42</td>
<td>3.82</td>
<td>80</td>
<td>4.72</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>SS, 37, M</td>
<td>1.7</td>
<td>67</td>
<td>11.0</td>
<td>10.3</td>
<td>97</td>
<td>101</td>
<td>4.55</td>
<td>76</td>
<td>5.40</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>JL, 44, M</td>
<td>1.8</td>
<td>81</td>
<td>8.7</td>
<td>10.4</td>
<td>96</td>
<td>88</td>
<td>3.95</td>
<td>74</td>
<td>3.56</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>FC, 35, M</td>
<td>1.6</td>
<td>82</td>
<td>8.0</td>
<td>10.6</td>
<td>94</td>
<td>92</td>
<td>4.72</td>
<td>82</td>
<td>4.70</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>79±1</td>
<td>9.1</td>
<td>11.0</td>
<td>95.1</td>
<td>98</td>
<td>43</td>
<td>3.58</td>
<td>73</td>
<td>3.12</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>SD of mean</td>
<td>3.1</td>
<td>0.3</td>
<td>0.5</td>
<td>1.5</td>
<td>4</td>
<td>0</td>
<td>0.4</td>
<td>0.02</td>
<td>0.26</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

*p value <0.01

*Control values
†Comparison with red cell transfusion response for significance.

Discussion appears to be the acute hypertensive. Such

Although one cannot conclude that hypervolemia would enhance oxygen consumption in anemia, an expanded intravascular

Although dextran infusion in subjects with anemia might have been more appropriate for comparison with the red cell studies, further reduction of the hematocrit, already substantially low, might have introduced variables unrelated to the acute hypertensive. Such dilution appears to be the acute hypertensive. Such
### TABLE 3

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Blood flow ml/100g/min</th>
<th>O: usage vol %</th>
<th>A-V O: difference</th>
<th>Sinus O: content</th>
<th>O: sat. %</th>
<th>Mean press. mm Hg</th>
<th>Hct</th>
<th>Cardiac output liters/min</th>
<th>Heart rate /min</th>
<th>Left ventricular Work kg-m/ln</th>
<th>Oxygen usage ml/100g/min</th>
<th>T.T.I.‡ mm Hg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62*</td>
<td>8.6</td>
<td>13.9</td>
<td>6.6</td>
<td>90</td>
<td>88</td>
<td>48</td>
<td>1.8</td>
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<tr>
<td>2</td>
<td>69</td>
<td>10.1</td>
<td>14.7</td>
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<td>95</td>
<td>92</td>
<td>45</td>
<td>2.15</td>
<td>112</td>
<td>2.56</td>
<td>.259</td>
<td>2,163</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>13.0</td>
<td>14.5</td>
<td>5.8</td>
<td>98</td>
<td>102</td>
<td>47</td>
<td>2.32</td>
<td>170</td>
<td>3.15</td>
<td>.242</td>
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<tr>
<td>4</td>
<td>102</td>
<td>12.0</td>
<td>12.6</td>
<td>7.0</td>
<td>97</td>
<td>94</td>
<td>45</td>
<td>1.90</td>
<td>165</td>
<td>2.28</td>
<td>.117</td>
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<tr>
<td>5</td>
<td>120</td>
<td>12.8</td>
<td>10.7</td>
<td>5.9</td>
<td>94</td>
<td>96</td>
<td>40</td>
<td>2.10</td>
<td>172</td>
<td>2.54</td>
<td>.198</td>
<td>3,480</td>
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<tr>
<td>6</td>
<td>99</td>
<td>12.4</td>
<td>12.9</td>
<td>3.4</td>
<td>92</td>
<td>104</td>
<td>40</td>
<td>1.73</td>
<td>108</td>
<td>2.30</td>
<td>.186</td>
<td>2,360</td>
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</tbody>
</table>

Mean 90 ± 7* 11.65 13.22 5.5 96 96 44 2.00 131 2.47 2.17 2.670
sd of ±.8 ±4 ±6 ±1.3 ±3 ±1.4 ±1 ±19 ±.18 ± .014 ± .396
mean 64 ± 41§ 10.32§ 16.23§ 8.1 96 118§ 56§ 1.78 136 2.65 2.02§ 3.277§
±.9 ±5 ±8 ±1.4 ±4 ±1.6 ±2 ±20 ±.23 ±.016 ± .470

**Methemoglobin Transfusion Group ($)**

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Blood flow ml/100g/min</th>
<th>O: usage vol %</th>
<th>A-V O: difference</th>
<th>Sinus O: content</th>
<th>O: sat. %</th>
<th>Mean press. mm Hg</th>
<th>Hct</th>
<th>Cardiac output liters/min</th>
<th>Heart rate /min</th>
<th>Left ventricular Work kg-m/ln</th>
<th>Oxygen usage ml/100g/min</th>
<th>T.T.I.‡ mm Hg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>105*</td>
<td>11.6</td>
<td>11.0</td>
<td>1.8</td>
<td>61</td>
<td>108</td>
<td>44</td>
<td>1.60</td>
<td>117</td>
<td>2.35</td>
<td>.200</td>
<td>2,640</td>
</tr>
<tr>
<td>10</td>
<td>89†</td>
<td>10.2</td>
<td>11.5</td>
<td>1.2</td>
<td>59</td>
<td>112</td>
<td>60</td>
<td>1.85</td>
<td>141</td>
<td>2.82</td>
<td>.276</td>
<td>3,310</td>
</tr>
</tbody>
</table>

*Control study.
†Post-transfusion study.
‡T.T.I. represents time tension index.
§Statistically significant change at P < 0.05 in paired tests.
lar volume is assumed not to account for the diminished coronary flow after red cell transfusion.

While the response to sedimented red cells in anemic subjects may not be characteristic of the normal heart, and because studies of normal subjects were precluded, the findings in the intact anesthetized dog are of special interest. Except for animals no. 1 and no. 2 (table 3), all were vagotomized; this did not appear to alter the qualitative response to transfusion. Peak pressure changes occurred by the end of the transfusion (fig. 1) but coronary flow studies were performed 30 minutes later when heart rate and arterial pressure varied less than 8% from the beginning to the end of the flow determination.

A 32% mean decrease in coronary flow (table 3) was not associated with sufficient increase of oxygen extraction to maintain oxygen uptake, which declined significantly. Coronary venous oxygen, reflecting tissue $O_2$ tension, and an important regulator of coronary flow\textsuperscript{10} was not altered appreciably. Unlike the results in transfused anemic subjects, cardiac output did not rise but tended to diminish. Mean arterial pressure consistently rose so that left heart work was increased in five of six animals. The ratio of left ventricular work to oxygen uptake increased significantly for the group. Other parameters having an important relationship to myocardial uptake of oxygen were also elevated. The time-tension index rose consistently, as did the left ventricular pressure-time area. In agreement with earlier transfusion studies in the closed and open-chest dog, a variable but usually small elevation of left ventricular end-diastolic pressure\textsuperscript{18} was consistently associated with accelerated isometric contraction, higher

---

**FIGURE 1**

Left ventricular pressure and excess lactate response to red cell transfusion. Connected points at top represent excess lactate values (determined in four animals of the group) at six-minute intervals. Tracings of aortic and left ventricular pressures from one animal are presented. The mean values for durations of pressures in the group of six dogs are listed below for each of the three experimental periods.
systolic pressure, and prolonged ventricular systole. Thirteen minutes after transfusion these alterations were still significantly above control values (fig. 1). As implied by the data on left ventricular performance, the reduced oxygen uptake was not associated with evidence of ischemia. The production of excess lactate, known to increase during mechanical limitation of coronary flow was not altered (fig. 1), which would also seem to exclude micro-embolic phenomena.

The attempt to minimize the compensatory influence of increased oxygen carrying capacity and extraction by the infusion of methemoglobin containing red cells did not essentially alter the relationships cited above (table 3). A smaller reduction in coronary flow occurred, attended by an unchanged oxygen extraction, and left ventricular work was maintained.

Since the manifestations of enhanced ventricular activity were associated with a decreased myocardial blood flow and oxygen consumption, the postulated role of viscosity was examined to explain the limitation of coronary flow. As indicated in figure 2, a close correlation exists between per cent change in hematocrit and the relative decrease in coronary flow ($R = 0.93; P < 0.01$). This relationship was not established in the human subjects, presumably due to variables related to chronic anemia.

Discussion

Transfusion of sedimented erythrocytes was found to evoke a similar effect on coronary flow in anemic human subjects and in normocytic anesthetized dogs. Despite a greater arterial oxygen carrying capacity of arterial blood, the myocardial uptake of oxy-
gen diminished as a consequence of the decreased coronary blood flow. It is postulated that this represents the influence of a highly viscous red cell mass upon regional blood flow, analogous to findings for the total circulation.2

Neither the experiments in anemic subjects nor those in normal animals reveal a hemodynamic parameter other than viscosity that would account for the changes in oxygen uptake by the myocardium. Several of the factors known to enhance oxygen usage in the myocardium are present during acute hypervolemia. Elevation in arterial pressure, left ventricular pressure work, and time-tension index would generally be considered adequate stimuli.8 In addition, the presence of elevated filling pressure, accelerated isometric ventricular contraction, and prolonged ventricular systole would tend to enhance the rate of myocardial oxygen consumption. These left ventricular hemodynamic changes agree qualitatively with results in other studies of red cell infusion which also demonstrated a greater left ventricular volume.14 Expectation of a modest increment in myocardial oxygen consumption is based upon the present observations on the effect of dextran infusion and upon findings during whole blood transfusion in open-chest preparations.8 The fact that the ventricular parameters mentioned above were not diminished, supports the postulated role of blood viscosity in explaining the coronary flow response.

While a constrictor effect of the red cell mass on coronary vessels or an unusual metabolic effect on left ventricular tissue is not excluded as an explanation for the diminished oxygen uptake, these are unlikely responses. Although these findings may not apply to normal man, or to patients with chronic erythrocytosis, their presence in two distinctive situations suggest a more widely applicable consequence.

The finding that myocardial function may not correlate closely with oxygen uptake has been observed in other circumstances. Perfusion of the canine heart with lactate reduced oxygen usage and did not change the index of cardiac effort, the product of heart rate and arterial pressure.16 Similarly in man and dog, lipemia reduced the Qp without affecting left ventricular performance.13, 10 Furthermore, during marked arterial hypoxia, the ratio of left heart work/coronary oxygen consumption rises,20 so that in some circumstances a relative decline in oxygen usage may occur without evidence of diminished cardiac function.

Whether a subnormal left ventricular oxygen consumption actually obtained in the patients with anemia, may be questioned in view of a lesser reliability of the nitrous oxide method at high flow rates. The observation that oxygen uptake remained the same when flow levels were substantially reduced by red cell transfusion tends to support the validity of the control flow study. It would appear then that the oxygen carrying capacity is reduced chronically and in excess of the vasodilating capacity of the coronary vessels.21 However, such relative limitation of flow may be secondary to an altered oxidative metabolism in the cardiac tissue of anemic subjects, because diminished enzyme activities have been found in studies of iron deficiency.22 It is noteworthy that a reduction in cerebral oxygen uptake has also been observed in patients with chronic anemia without detectable impairment of brain function or increase of oxygen extraction.23

Whether an increased red cell mass is clinically and hemodynamically disadvantageous, despite the increased oxygen carrying capacity it provides, remains open to question. These studies have revealed no cardiac handicap, but the effects of chronic erythrocytosis are unknown. The modest elevations of hematocrit found in some subjects with coronary disease have led to suggestion of therapeutic phlebotomy.24 This suggestion is based on the assumption that, in the presence of a reduced coronary vessel lumen diameter, red cells may contribute to a critical lowering of coronary flow through an effect on viscosity. However, the potential therapeutic benefit may be affected by a diminished arterial oxygen content and myocardial oxygen extraction.

Circulation Research. Volume XIII, August 1968
Summary

The role of red cell mass in the regulation of coronary blood flow and myocardial oxygen consumption has been examined after acute transfusion of sedimented red cells. Patients with substantial blood-loss anemia had a lower than normal left ventricular oxygen uptake, despite a high myocardial blood flow at rest. A 50% rise of hematocrit reduced coronary flow markedly. Although systemic arterial pressure, cardiac output, and left heart work rose, myocardial oxygen consumption was unchanged.

Red cell transfusion of normovolemic dogs resulted in a decrease of both myocardial flow and oxygen uptake associated with an elevation of time-tension index and left ventricular work, accelerated isometric contraction and prolonged systole. There was no evidence of ischemia or change of left ventricular hemodynamic parameters that would account for the reduced myocardial blood flow and oxygen uptake. These findings, in the presence of an increased oxygen carrying capacity and extraction, would appear to be related principally to enhanced blood viscosity.

Acknowledgment

The authors wish to extend their appreciation for the technical assistance of Mr. Henry A. Oldewurtel, Miss Margaret Reese, and Miss Muriel Rosen.

References

Myocardial Blood Flow and Oxygen Uptake During Acute Red Cell Volume Increments
Timothy J. Regan, Martin J. Frank, Patrick H. Lehan, James G. Galante and Harper K. Hellem

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