Acute Hemodynamic Effects of Red Cell Volume Reduction in Polycythemia of Cyanotic Congenital Heart Disease

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SUMMARY
Acute reduction in red cell volume (RCV) without significant alterations of blood volume in 22 patients with severe polycythemia secondary to cyanotic congenital heart disease resulted in a decrease in peripheral vascular resistance and an increase in stroke volume, systemic blood flow (SBF), and systemic oxygen transport. These changes are probably related to the decreased blood viscosity and yield shear stress associated with lower red cell concentrations. Hypervolemia in hypoxic polycythemia should be maintained in order to sustain an adequate SBF. In contrast to acute phlebotomy which may be expected to decrease blood oxygen content and SBF, the replacement of whole blood with plasma or 5% albumin is shown to result in an increased systemic blood flow and oxygen delivery.

Additional Indexing Words:
Blood viscosity Phlebotomy Cardiac output Exchange transfusion
Hematocrit Hypoxemia Plasma

In polycythemia accompanying cyanotic congenital heart disease, both the hematocrit (Hct) and the circulating whole blood volume (WBV) are increased. The hypervolemia results from an increase in red cell volume (RCV). The increase in RCV provoked by hypoxia provides an increased oxygen-carrying capacity which maintains an adequate oxygen supply to the tissues. Since studies in dogs and man suggest that at any given Hct the systemic blood flow (SBF) is greater with hypervolemia than normovolemia, the induced hypervolemia probably helps sustain a sufficient SBF despite the increased viscosity that occurs at high hematocrits. Polycythemia in cyanotic congenital heart disease, however, is often of such severity that it may become a liability and produce adverse physiologic effects. The clinical manifestations of headaches, irritability, anorexia, and dyspnea have been attributed to polycythemia. Thrombotic lesions in the lungs, kidneys, and central nervous system have been found in polycythemic patients. Postoperative hemorrhagic diathesis, possibly a result of intravascular coagulation, is also frequently observed in these individuals. These complications have been attributed to the elevated blood viscosity and intravascular red cell aggregation that accom-
Acute Hemodynamic Effects of Erythropheresis in 22 Patients with Severe Polycythemia Secondary to Cyanotic Congenital Heart Disease

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Mean: 73.5 62.0 76 72 100 100

Standard deviation: 5 4 9 9 18 18

P value by paired t test: <0.001 0.5

Abbreviations: vHct = venous hematocrit; Art. sat. = arterial oxygen saturation; \( \bar{V}O_2 \) = oxygen consumption; \( \bar{P}aR \) = mean arterial pressure; HR = heart rate; \( \bar{F}cv \) = mean central venous pressure; SVR = systemic vascular resistance; SBF = systemic blood flow; SI = stroke index; SOT = systemic oxygen transport; D-TGA = dextrotransposition of great arteries; PAH = pulmonary artery hypertension; PS = pulmonary stenosis; VSD = ventricular septal defect; L-TGA = levotransposition of great arteries; PA = pulmonary atresia; T/F = tetralogy of Fallot; TA = tricuspid atresia; A-V = atrioventricular.

Companies high red cell concentrations.\(^6\) Attempts at therapy by acute phlebotomy without volume replacement may be followed by vascular collapse and cerebrovascular accidents probably due to the sudden reduction in the blood volume and SBF. The circulatory response to reduction in RCV and fluid replacement in cyanotic polycythemic patients has not been evaluated. This investigation was, therefore, designed to determine the acute hemodynamic effects of RCV reduction and its replacement with fresh frozen plasma or 5% solution of human albumin in severe hypoxic polycythemia.

\[ WBV \text{ to be removed} = \text{weight (L/kg)} \times 0.11 \times (\text{vHct}_t - \text{vHct}_p)/\text{vHct}_t, \]

\( \text{Circulation, Volume XLII, August 1970} \)
RED CELL VOLUME REDUCTION IN POLYCYTHEMIA

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where weight (L/kg) = body volume in liters, 0.11 = assumed blood volume as fraction of body volume, vHct₁ = initial vHct, and vHct₂ = desired vHct. Demerol compound (meperidine, 25 mg, promethazine, 6.25 mg, and chlorpromazine, 6.25 mg/100 ml of mixture) in a dose of 1 ml/30 pounds was administered prior to the study (maximal dose, 2 ml).

The hematocrit was determined on central venous blood using the Adams microhematocrit centrifuge (M-90). Oxygen-carrying capacity was measured by the cyanmethemoglobin method, and blood oxygen saturation was determined by an oximeter (American Optical Corporation model no. 10840). Central venous pressure was measured via catheters placed in the superior vena cava or right atrium. Arterial and venous pressures were obtained using strain-gauge transducers, and heart rate was monitored. Oxygen consumption was measured and SBF determined in duplicate by the direct Fick principle using mixed venous (superior vena cava or right atrium) and arterial blood oxygen saturations. Arterial partial pressure of carbon dioxide (PaCO₂), oxygen (PaO₂), and pH were determined by the use of the Instrumentation Laboratory gas electrode and pH meter, respectively. The CO₂ content was calculated from PaO₂, PaCO₂, and pH using radiometer blood gas calculator.* Viscosity measurements (at 38°C) were obtained in four patients with the GDM rotational viscometer. This technic permits the measurement of shear stress as a function of shear rate at a range of 0.1 to 100 inverse seconds (sec⁻¹). The yield shear stress was extrapolated from a plot of the square roots of shear stress against the square roots of shear rate. Yield shear stress (at 38°C) was also measured in four additional subjects undergoing red cell pheresis and in whom complete hemodynamic data were not obtained. Fibrinogen determinations were done in duplicate on each blood sample obtained for viscometric studies.

Simultaneous measurements of RCV with ⁵¹Cr autologous-labeled red cells and plasma volume

*The London Co., West Lake, Ohio.
with 125I-labeled albumin were performed on eight patients by a previously described method.\textsuperscript{15} Measurements were obtained prior to and following the completion of erythropheresis. The combined dosage of the two isotopes given was proportional to the weight of the subject and was always below the recommended dose.\textsuperscript{16} In four of the 22 patients (nos. 18, 19, 20, and 22) the blood removed was replaced with a 5% solution of human albumin instead of fresh frozen plasma. All significance tests were based on the paired t statistic.

Results

The data reflecting acute hemodynamic effects of reduction of RCV and its replacement with plasma or 5% human albumin are shown in Table 1. The quantity of blood removed from the patients varied depending on the initial vHct, the subject’s weight, and the initial arterial oxygen saturation. The mean initial vHct of the entire group was reduced from 73.5\% (range, 66 to 85\%) to 62\% (range, 53 to 69\%). A concomitant reduction occurred in the oxygen-carrying capacity from 28.8 vol\% (range, 21.7 to 35.5\%) to 24.5 vol\% (range, 19.5 to 28.4\%). Simultaneous determinations of red cell and plasma volumes, obtained on eight of the patients (cases 1 to 8), revealed that following replacement of whole blood with an equal volume of plasma total blood volume had diminished slightly. Whole blood volume (WBV) decreased from

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the body by the systemic circulation (systemic oxygen transport).

**Blood Viscosity and Yield Shear Stress**

Following vHct reduction a decrease in blood viscosity occurred in all patients studied. Results from four patients (cases 2, 9, 10, and 17) who had simultaneous hemodynamic and viscometric studies before and after red cell pheresis are shown in figure 1. Blood viscosity varies inversely and nonlinearly, with shear rate. Viscosity values at shear rates of 0.1 sec\(^{-1}\) and 10 sec\(^{-1}\) were selected because these shear rates define the approximate range relevant to the blood flow in the microcirculation.

Yield shear stress is the force necessary to make the structure of static blood "yield" and thereby allow flow to begin. Since at any given temperature only one yield shear stress value exists for each blood sample, it is more convenient to direct attention to yield shear stress rather than viscosity when comparing different samples of blood. Yield shear stress, normally 0.04 ± 0.01 dyne/cm\(^2\) (mean ± standard deviation), was considerably increased at high hematocrits (fig. 2). The yield shear stress was lowered following red cell pheresis in all patients studied. Fibrinogen content, which is also known to affect yield shear stress, remained in the normal range for all samples (306 ± 40 mg%).

**Systemic Blood Flow**

The initial SBF was low (2.5 L/min/m\(^2\) or less) in seven of the 22 patients. Two of these
seven patients had clinically severe congestive heart failure. Reduction of the vHct and RCV was followed by an increase in the SBF in all patients \( (P < 0.001) \) from a mean of \( 3.2 \pm 1.3 \) L/min/m\(^2\) to \( 5.1 \pm 2.3 \) L/min/m\(^2\) (fig. 3A). For a 10\% relative reduction in the vHct there was a 38\% average increase in the SBF (fig. 4B). The increase in SBF was the result of an increase in stroke volume. Stroke index (SI) rose from a mean of \( 33 \pm 14 \) ml/beat/m\(^2\) to \( 52 \pm 23 \) ml/beat/m\(^2\) \( (P < 0.001) \); fig. 3B). Following the procedure there was no consistent or significant change in the heart rate or the rate of oxygen consumption \( (\dot{V}_{O_2}) \). In only two subjects did the heart rate vary more than 10 beats/min (table 1). There was no evidence of a relationship between the initial vHct and heart rate \( (r = 0.06) \), but \( \dot{V}_{O_2} \) tended to be lower in those with a high vHct \( (r = -0.42) \). The systemic arteriovenous \( (A-V) \) oxygen difference was reduced in all patients reflecting the increased SBF. The initial mean A-V oxygen difference of \( 4.8 \pm 1.7 \) vol \% of blood decreased to a mean of \( 3.2 \pm 1.7 \) vol \% \( (P < 0.001) \).

**Systemic Vascular Resistance**

The changes in systemic vascular resistance (SVR) following acute RCV reduction in the individual patients are shown in table 1. SVR decreased in all patients \( (P < 0.001) \) from an initial mean of \( 29 \pm 12 \) mm Hg/L/min/m\(^2\) to \( 17 \pm 7 \) following the procedure (fig. 3C). The fall in SVR correlated well with the decrease in red cell concentration. For a 10\% relative decrease in the vHct there was a 23\% average change in SVR (fig. 4A). Great variability was encountered in the arterial blood pressure response to erythropheresis. The changes in blood pressure recorded were stable over a half-hour period of observation. A decrease of 10 mm Hg or more in mean systemic arterial pressure was noted in four patients and was associated with a reduction in both systolic and diastolic pressures (table 1). Three subjects (cases 2, 9, and 16) developed mild postural hypotension lasting from 12 to 24 hours after completion of the study. Following the exchange, central venous pressure rose in 16 subjects, remained unchanged in four, and decreased in two \( (P < 0.001) \). In the two patients with clinically severe congestive heart failure, the initial high mean central venous pressure showed a further increase. In none of the patients, however, was congestive heart failure precipitated by the procedure. The reason for the rise in central venous pressure is...
not clear, but it may be due to increased venous return caused by a decrease in the venous resistance resulting from a reduction in blood viscosity. The situation may be somewhat analogous to a sudden opening of a systemic arteriovenous fistula.20

**Systemic Oxygen Transport**

Systemic oxygen transport (SOT) can be defined as the amount of oxygen delivered to the body by the systemic circulation per unit of time.21 To facilitate comparisons between individuals of different sizes, the amount of oxygen delivered per unit of time per unit of body weight is used. This expression for SOT is derived by multiplying SBF by arterial oxygen content and dividing the result by the patient's weight. Thus, SOT (ml O₂/min/kg) = SBF (L/min) × arterial oxygen content (ml O₂/L)/weight (kg). The effects of a change in the vHct on the SOT is shown in table 1 and figure 3D. An increase in oxygen delivery to the tissues occurred in 21 of the 22 patients (P < 0.001). SOT increased from a mean of 27 ± 10.6 ml/min/kg to a mean of 35.0 ± 14.0 ml/min/kg. The quantitative response in SOT to a given relative change in the vHct was rather variable among the patients. For example, for a 10% reduction in the vHct, the increase in SOT ranged from 10% to 40%, while the mean was about 20% (fig. 4C). There was no significant relationship between initial vHct and SOT at rest in patients with severe secondary polycythemia (vHct > 65%).

**Systemic Arterial Oxygen Saturation**

To illustrate the effect of red cell pheresis on the systemic arterial blood oxygen saturation in cyanotic patients, it is useful to divide the patients into two groups (fig. 5A and B). Group I consists of 17 patients with severe pulmonary stenosis (tetralogy of Fallot, tricuspid atresia with pulmonary stenosis, or transposition of the great arteries with pulmonary stenosis) or marked pulmonary vascular obstructive disease (pulmonary vascular resistance greater than one-third SVR). Group II consists of five patients with dextrotransposition of the great arteries (D-TGA) without significant pulmonary stenosis or pulmonary vascular obstruction (table 1, cases 1, 2, 4, 8, and 11). Patients in group I showed a significant drop in systemic blood arterial oxygen saturation (P < 0.001) following RCV reduction and its replacement with plasma or albumin (fig. 5A). The fall in systemic saturation was most pronounced in subjects with pulmonary atresia and least in those with tricuspid atresia. In group II (D-TGA) the systemic arterial oxygen saturation remained essentially unchanged by the procedure (fig. 5B).
Arterial Blood Gases
The changes in the $P_{AO_2}$ induced by erythropheresis are similar to those described for systemic arterial oxygen saturation. In group I patients, the mean $P_{AO_2}$ before and after pheresis was $51.6 \pm 10.2$ mm Hg and $45.2 \pm 8.3$ mm Hg, respectively ($P < 0.01$). In group II the $P_{AO_2}$ remained essentially unchanged ($45.0 \pm 9.7$ vs. $45.8 \pm 8.0$ mm Hg). There was an increase (1.5 mm Hg or more) in $P_{CO_2}$ following the procedure in 10 of the 22 patients; it remained unchanged in 10 others (in four of whom the blood was exchanged with albumin), and it was decreased in two ($P = 0.05$ from two-sided sign test). An increase in arterial pH was demonstrated in all the cases in which blood was replaced with plasma. The mean initial arterial pH of $7.33 \pm 0.06$ increased to $7.38 \pm 0.05$ ($P < 0.001$). When 5% solution of human albumin was utilized for replacement, the initial blood pH was not significantly altered ($7.35 \pm 0.05$ and $7.34 \pm 0.04$, respectively). The rise in blood pH following plasma infusion would appear to be secondary to the rise in blood CO$_2$ content which rose in all case of plasma exchange ($P < 0.001$). The mean CO$_2$ content before and after exchange transfusion with plasma was $21.0 \pm 3.1$ mm/L and $25.8 \pm 4.0$ mm/L, respectively. The infusion of 5% albumin solution was not associated with a rise in CO$_2$ content ($23.9 \pm 3.2$ mm/L vs. $24.3 \pm 2.3$ mm/L).

Clinical Findings and Side Effects
Following red cell volume reduction, subjective symptomatic improvement occurred in 15 patients. The beneficial effects most frequently cited were relief from headaches, decreased dyspnea and fatigue, increase in stamina, and improvement in appetite. No significant relationship was observed between symptomatic improvement and the magnitude of increase in SOT. No serious complications or side effects were encountered in any of the patients during or following the procedure of erythropheresis. Transient postural hypotension was noted in three patients and urticaria in two. The pH of nonbuffered fresh frozen plasma is low (6.8 to 7.1), and hyperpnea sometimes occurs on rapid infusion of plasma. A similar response follows the rapid administration of 5% human albumin solution (pH 6.9 to 7.2).

Discussion
The main purpose of this study was to delineate the acute effects of isovolumic red cell volume reduction on circulatory dynamics in patients with polycythemia secondary to cyanotic congenital heart disease under stable and controlled conditions. Red cell concentration and volume were reduced while whole blood volume (WBV) was maintained as constant as possible. Although the amount of solution infused was carefully adjusted to replace all blood withdrawn, determinations of blood volume revealed a small but definite decrease in WBV following the procedure.

The mean resting SBF and stroke volume of our patients with severe hypoxic polycythemia were comparable to those of normal individuals except when there was marked congestive heart failure. The increase in blood viscosity at high Hct levels tends to increase resistance to blood flow. However, the concomitant hypervolemia with its associated increased vascular dilatation may have the opposite effect and thus resting SBF may remain essentially normal. A significant increase in stroke volume and SBF followed RCV reduction and its replacement with an equal volume of plasma or 5% human albumin. This differs from the effect of phlebotomy without fluid replacement in normal patients and those with polycythemia vera when stroke volume and SBF are reduced. Our clinical experience has shown that acute phlebotomy in patients with hypoxic polycythemia may result in vascular collapse, cyanotic spells, cerebral vascular accidents, or seizures. These findings may be the sequelae of an acute reduction in SBF resulting from a decrease in blood volume. A controlled study using phlebotomy alone was, therefore, considered too hazardous.

An explanation for the observed increase in SBF and stroke volume is provided by the decrease in peripheral vascular resistance
resulting from the procedure (figs. 4A and 3C). Marked changes in peripheral vascular resistance and SBF were induced experimentally by Murray and co-workers by producing normovolemic Hct changes in dogs. The decrease in peripheral vascular resistance and the consequent increase in SBF induced by normovolemic reduction of the Hct may be primarily attributed to the reduction in the viscosity and yield shear stress. Elevated blood viscosity in association with polycythemia of cyanotic heart disease has been adequately documented. The effect of a reduction in vHct on the viscosity at shear rates of 0.1 and 10 sec⁻¹ in four of our patients is illustrated in figure 1. Physiologically the most significant viscosity measurements are those obtained at shear rates of 0 to 20 sec⁻¹ since these represent the changes relevant to flow in the microcirculation. Furthermore, the changes in viscosity with greater red cell concentrations are paralleled by progressive increase in the yield shear stress (fig. 2). Replogle and associates have suggested that in polycythemia the yield stress may thus represent a significant portion of the peripheral resistance to the flow of blood. We observed in vitro a sharp decrease in yield shear stress following a reduction in the vHct in four patients in whom measurements were made prior to, and following, red cell pheresis. This suggests that a reduction in viscosity and yield shear stress may be important factors in lowering the peripheral vascular resistance. Further evidence of this effect is provided by the great similarity between the hematocrit-peripheral resistance relationship obtained experimentally and the viscosity-hematocrit curves obtained by direct measurements.

In addition to the decrease in viscosity, two other factors must be considered in explaining the fall in peripheral resistance and increased SBF. These are the decreased arterial oxygen content and increased blood pH. Both are known to produce local vasodilation and increased SBF. The rise in blood pH produced by intravenous infusion of plasma probably had no effect on SBF regulation since alkalosis was not produced, and replacement with albumin caused a similar rise in SBF without any significant alterations in blood pH. Previous experiments have shown that in anemia the drop in arterial oxygen content, rather than the decrease in viscosity, primarily results in an increase of SBF. A decrease in oxygen content without any changes in blood viscosity can produce progressive rise in SBF, therefore, it seems likely that the mechanisms for decrease in peripheral resistance and increased SBF induced by erythropheresis are a reduction in the viscosity and yield shear stress and possibly a decreased arterial oxygen content. The present study demonstrates for the first time that the changes in vascular resistance and SBF induced in severe hypoxic polycythemia are similar to those previously observed in animal experiments.

Substantial acute improvement in SOT was produced by the reduction of vHct in most of our patients. As previously defined, the SOT is a measure of the amount of oxygen supplied, but not extracted by, the tissues per minute per unit of body weight. It represents the maximum amount of oxygen available to the tissues for utilization. The increase in SOT produced by erythropheresis is primarily due to the increase in SBF since oxygen-carrying capacity is always reduced and arterial oxygen saturation often declines as a result of pheresis. The maximum SOT usually occurs at the normal vHct. In hypoxic polycythemia arterial blood is desaturated, and oxygen transport is less effective relative to the vHct. The increased blood volume, however, by lowering the resistance to blood flow enough to maintain an adequate SBF, provides for more normal oxygen delivery at rest. The advantage of an increase in SOT following isovolemic RCV reduction may be in providing for a greater oxygen reserve available for tissue utilization on exercise. It should be emphasized that the improvement in oxygen delivery was shown here as an acute result of erythropheresis. How long it may persist following RCV reduction has not been determined.
In individuals with increased right ventricular outflow obstruction or pulmonary vascular resistance (group I), associated with marked secondary polycythemia, RCV reduction may produce a considerable fall in systemic arterial oxygen saturation. This is a result of the reduction in SVR, in the probable absence of a significant change in pulmonary resistance, leading to an increased right-to-left shunt via the ventricular septal defect. In patients with pulmonary atresia the fall in systemic saturation may be dramatic because the entire pulmonary blood supply is derived from the aorta. Among those with D-TGA without significant pulmonary stenosis or pulmonary vascular obstruction (group II), systemic oxygen saturation remained essentially unchanged following the procedure. The ability to maintain the blood arterial oxygen saturation in those with D-TGA may be related to increase in pulmonary blood flow and the improved mixing between the pulmonary and systemic circulations.

The replacement of whole blood with plasma was accompanied by a rise in blood CO₂ content and pH. These changes were not observed when blood was replaced with a 5% human albumin solution. The rise in pH after replacement with plasma is most likely secondary to the increased CO₂ content which in turn was attributed to the metabolism of the sodium citrate and anhydrous citric acid present in the administered plasma. (100 ml of anticoagulant contains 0.8 g of citric acid and 2.2 g of sodium citrate).

Our experience has suggested that acute RCV reduction and replacement with plasma or albumin (erythropheresis) reduced coagulation abnormalities and decreased operative mortality in severely polycythemic patients. The present study indicates that erythropheresis lowers blood viscosity and increases SBF and SOT. These effects together with the absence of any serious complications make erythropheresis preferable to acute phlebotomy (without fluid replacement) in management of patients with severely hypoxic polycythemia.

References

Acute Hemodynamic Effects of Red Cell Volume Reduction in Polycythemia of Cyanotic Congenital Heart Disease
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