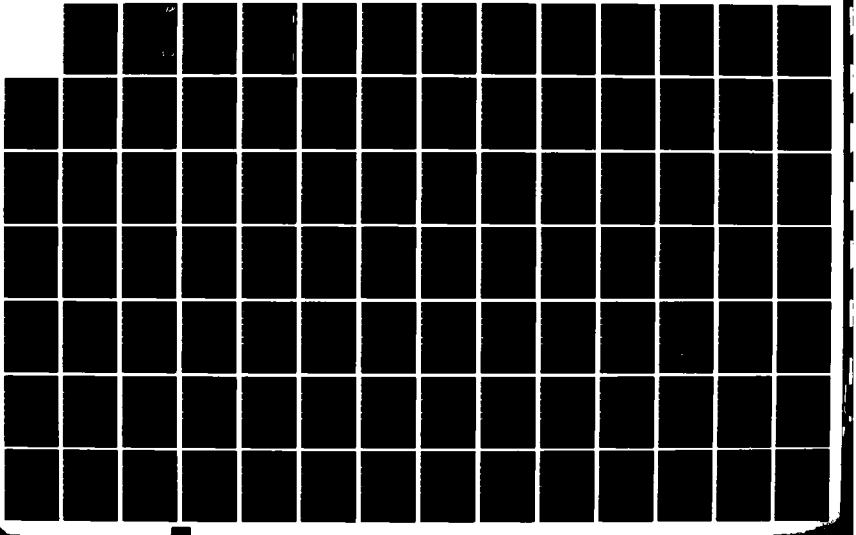
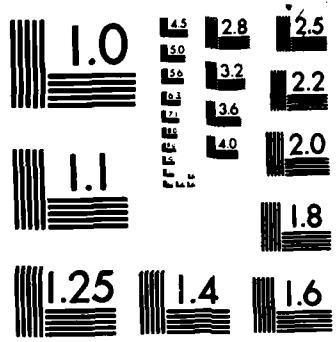
AD-A140 403 BLOOD TRANSFUSION THERAPY IN PATIENTS WITH HEART DISEASE(U) BOSTON UNIV MA SCHOOL OF MEDICINE C R VALERI 07 APR 82 BUSM-82-05 N00014-79-C-0168 1/2

UNCLASSIFIED F/G 6/5 NL





OFFICE OF NAVAL RESEARCH

CONTRACT N00014-79-C-0168

TECHNICAL REPORT NO. 82-05

BLOOD TRANSFUSION THERAPY IN PATIENTS WITH HEART DISEASE

by

C. R. VALERI

NAVAL BLOOD RESEARCH LABORATORY
BOSTON UNIVERSITY SCHOOL OF MEDICINE
615 ALBANY ST.
BOSTON, MA 02118

7 April 1982

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)*

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER NBRL, BUSM 82-05	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE *(and Subtitle)* BLOOD TRANSFUSION THERAPY IN PATIENTS WITH HEART DISEASE		5. TYPE OF REPORT & PERIOD COVERED Technical Report 6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) C. Robert Valeri		8. CONTRACT OR GRANT NUMBER(s) N00014-79-C-0168
9. PERFORMING ORGANIZATION NAME AND ADDRESS Naval Blood Research Laboratory Boston University School of Medicine 615 Albany St., Boston, MA 02118		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS Naval Medical Research and Development Command Bethesda, Maryland 20014		12. REPORT DATE 7 April 1982 13. NUMBER OF PAGES 84
14. MONITORING AGENCY NAME & ADDRESS *(if different from Controlling Office)* Bureau of Medicine and Surgery Department of the Navy Washington, D. C. 20372		15. SECURITY CLASS. *(of this report)* UNCLASSIFIED 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT *(of this Report)*

Approved for public release and sale. Distribution unlimited.

17. DISTRIBUTION STATEMENT *(of the abstract entered in Block 20, if different from Report)*

18. SUPPLEMENTARY NOTES

19. KEY WORDS *(Continue on reverse side if necessary and identify by block number)*

Blood Transfusion	Anemia
Heart Disease	Cardiorespiratory function
Red Blood Cells	Extracorporeal bypass
Rejuvenation	Platelets

20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

The oxygen transport function of preserved red cells transfused to anemic patients who have heart disease is critical. Patients with heart disease should be given red cells with normal 2,3 DPG and normal affinity for oxygen instead of low 2,3 DPG red cells. Our studies suggest that red cells with high 2,3 DPG (150 to 200% of normal) and low affinity for oxygen are the best form of transfusion therapy for anemic patients, especially those with congestive heart failure. It may even prove useful to use 2,3 DPG-enriched red cells in patients with patchy myocardial ischemia and,

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE
S/N 0102-LF-014-6601

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE *(When Data Entered)*

at any rate, it can do no harm. High 2,3 DPG red blood cells also are recommended in patients with right-to-left cardiac shunts and pulmonary shunts, provided that the inspired ambient oxygen tension is adequate to maintain an arterial pO_2 tension of greater than 40 mm Hg.

Blood products utilized during extracorporeal bypass surgery should ensure optimum oxygen delivery to tissue and maintain or restore normal hemostasis, and red cells with 250% to 300% of normal 2,3 DPG and low affinity for oxygen given in combination with crystalloid solution will do this. Red cells with elevated 2,3 DPG levels do ensure optimum delivery of oxygen to tissue, especially during hypothermia, although it cannot be stated definitely whether or not they reduce myocardial damage.

A postoperative bleeding diathesis following cardiopulmonary bypass due to a decrease in platelet number and to abnormalities of platelet function should be treated with platelet transfusions. Although a bleeding diathesis as a result of dilutional coagulopathies is rare, severe dilutional coagulopathies should be treated with fresh frozen plasma. However, routine use of fresh frozen plasma following cardiopulmonary bypass is not recommended.

Introduction

Of the various complications that might affect the clinical course of patients suffering from various types of heart disease, anemia is one of the most serious. This is because the most prominent manifestations of anemia involve cardiorespiratory function. Thus, the relation between the two must be understood to adequately treat these patients.

When the cardiac patient requires surgery, especially an operation involving the heart itself, almost always with the use of heart-lung devices, an enormous stress is placed on the heart even though global cardiac function may be normal or almost so. We will discuss in this chapter the indications for red cell transfusions in anemic patients with heart disease both in the presence and absence of congestive failure. In particular, we will discuss the effects of the quality of the transfused red blood cells in the treatment of the cardiac patient, and the indications for specific blood products, i.e., the use of red blood cells, platelets, and plasma, in treating patients during extracorporeal bypass at normothermic and hypothermic temperatures.

Indications for blood transfusions and recipient's state of health

The recipient's state of health determines which blood products are indicated. Patients who are undergoing cardiopulmonary bypass surgery for coronary artery disease but are in otherwise good health will not require the same transfusion therapy as patients with valvular heart disease who have congestive heart failure and hepatosplenomegaly. In these latter patients, the severity of the heart disease, and the presence of pulmonary congestion, hepatosplenomegaly, bone marrow abnormalities, or renal disease, must be considered in the use of transfusion therapy.

In the anemic patient with heart disease, assessment of blood volume is of primary importance. Chronic congestive heart failure is known to cause increases in blood volume in general,[1] but the determination must be made at the time that the patient presents with anemia whether he has hypovolemia, normovolemia or hypervolemia associated with the red cell volume deficit. An accurate assessment of a deficit in red cell volume cannot always be made from the patient's hematocrit value. Plasma volume usually is increased in congestive heart failure. Moreover, certain drugs may reduce plasma volume and raise the hematocrit level, and splenomegaly will further reduce the peripheral venous hematocrit value. An increase in plasma volume may be secondary to retention of salt and water by the kidneys.

The clinical assessment that transfusion therapy is necessary is based on the finding of a reduced hematocrit or hemoglobin level in the

peripheral venous blood. The peripheral venous hematocrit reflects the red cell volume, the plasma volume, and the size of the spleen.[2-8] In the presence of splenomegaly, there is an increase in plasma volume and a reduction in red cell volume due to sequestration of red cells in the spleen. Transfusion therapy should not be initiated merely to correct a low hematocrit level or hemoglobin concentration; rather, an evaluation should first be made of the patient's clinical status and laboratory data. Hypovolemia in general can be diagnosed clinically by postural changes in blood pressure and pulse rate.

Chronic Anemia

Chronic anemia may develop 1) after a large hemorrhage without adequate blood replacement, 2) after repeated undetected small losses of blood, perhaps accompanied by nutritional iron deficiency, 3) as a result of bone marrow depression, or 4) any combination of these.

Compensatory mechanisms in anemia

The cardiorespiratory compensations in chronic anemia are well known and include increased respiratory volume, increased cardiac output, decreased oxygen affinity of red cells, and changes in blood volume. The first detected change is an increase in respiratory minute

volume out of proportion to the body's metabolic requirements, which results in an increase in the alveolar air oxygen tension available for saturating the hemoglobin in the pulmonary capillaries, and compensates to some extent for the fall in blood oxygen-combining power induced by anemia. This causes a slight degree of respiratory alkalosis, and may result in a reduction in cerebral blood flow although the increase in cardiac output that occurs in anemia usually compensates for this reduction.

The cardiac output begins to increase when the blood hemoglobin concentration falls to between 8 and 10 grams per 100 ml (Fig 1).[9-12] FIG 1 At hemoglobin levels of 5 gm/dl, the increase in cardiac output is substantial. Since the body's total oxygen consumption remains normal or close to it, the systemic arterio-venous oxygen difference is smaller than expected. The mechanism that underlies the rise in cardiac output is not completely understood, although widespread vasodilation occurs as shown by a marked decrease in total peripheral resistance. The vasodilation is not the same throughout the body and indeed may be absent in skin and kidneys.

A third compensatory mechanism that increases the oxygen delivery to tissues is a change in the oxygen dissociation curve.[12,13] Red blood cells with a low affinity for oxygen produce an accelerated unloading of oxygen to the tissues. This change in the curve results from an increase in red blood cell 2,3 DPG, owing to a change in erythrocyte carbohydrate metabolism.[14-18]

Yet another compensatory mechanism in chronic anemia is an increase

in plasma volume such that the total blood volume may be normal or even increased despite a low red blood cell mass. The increased plasma volume may be due to retention of salt by anemic patients,[19] but the phenomenon as a whole is not understood. At any rate, the increase in blood volume found in chronic anemia prevents the development of oligemic anemia such as occurs in trauma,[20] a disorder in which the plasma volume remains so low that the hematocrit percentage is normal despite the decreased red blood cell mass.

Aggravation of symptoms by anemia in cardiac patients

Anemia is known to aggravate cardiac disorders in a variety of ways. Anemia induces an increase in cardiac work, and attacks of angina pectoris due to coronary atherosclerosis are made worse and more frequent by the development of anemia. The occurrence of pain may be due to an increase in cardiac muscle work without a corresponding increase in coronary blood flow in regions with rigid, narrowed arteries or with inadequate circulation due to blockage. (This is to be distinguished from the myocardial infarction that may occur when massive hemorrhage produces shock.)

In chronic congestive heart failure there is myocardial insufficiency. The heart muscle is inefficient, with a low ratio of work done-to-energy consumed. Digitalis, which increases muscle work in the failing heart, also increases cardiac muscle efficiency. Anemia, pregnancy, fever, hyperthyroidism, and drugs such as epinephrine and aminophylline, as well as some other factors, increase the work of the cardiac muscle without increasing its efficiency. This in time will aggravate myocardial

insufficiency. Whether the symptoms of cardiac failure are due to cardiac strain or produced by excessive salt retention, the symptoms improve when the anemia is cured.

Treatment of chronic anemia in cardiac patients

There may be differences in the mode of treatment among various patients with heart disease aggravated by chronic anemia. In some cases it might be appropriate simply to stop any bleeding and to treat the anemia medicinally. However, in most cases blood transfusions are required, and then the question is the quantity and kind of blood products. Since all blood products must be given by vein, the effects of large intravenous infusions also must be considered.

The "overloaded" circulation

Over a century ago in Germany, a common diagnosis in man was "beer-drinkers heart", the theory being that these individuals had drunk so much beer as to have "overloaded their circulation", and the "overloaded circulation" caused massive cardiac hypertrophy and ultimately death.

When the work of the heart was finally calculated, it was found to be:

$$W = 0 \times \text{Mean BP} + \frac{wV^2}{2g}$$

where W is work, O is output of a ventricle, mean BP is self-evident, w is the weight of blood, V is the velocity of blood in the aorta, and g is the gravitational constant. Thus, the volume of circulating blood is not a factor. The effects of an intravenous infusion on cardiac work are negligible. When the cardiac output is 4.0 liters per minute, an intravenous infusion at a rate of 20 ml per minute will increase it to 4.020 liters, a change so insignificant as to be noteworthy only to academicians.

When intravenous infusions are given, sodium chloride may accumulate locally, particularly in collagen, which makes up 60% of the lung. Cohnheim and Lichtheim[21] in 1877 studied the development of pulmonary edema in rabbits given isotonic saline solution intravenously, and found that pulmonary edema developed only after the animals received half their body weight of solution within 30 minutes, obviously a far greater dose than patients would receive. To produce pulmonary edema in dogs in this way, the amount of solution equal to the body weight of the animal must be infused within 30 minutes. The physiology of man being different from that of rodents and canines, in normal persons an intravenous infusion of 1500 ml of isotonic saline solution given within a 10- to 30-minute period causes no detectable changes in the lungs.[22] In patients with moderate or severe congestive heart failure, a dose of 1500 ml within 30 minutes may cause a decrease in vital capacity and the appearance of a few rales.[22] There is no reason to expect that blood transfusions in the usual volume would have any adverse effects

on cardiopulmonary function because of "overload".

Although this theory would appear to be refuted by the substantial accumulation of data from intensive care units devoted to the resuscitation of patients with severe trauma, many of the patients studied were given human serum albumin solution, which is known to decrease cardiac inotropic function[23] and to increase pulmonary capillary permeability. Much of the infused material never reached the left ventricle, making conclusions based on relations between pulmonary artery pressures and left ventricle work invalid. Moreover, when whole blood was used, no mention was made of the fact that stored plasma also increases pulmonary capillary permeability,[24] nor was the quality of the transfused red blood cells defined, even though it is known that cells with low 2,3 DPG levels may adversely affect cardiac function.[25,26] Further, studies have shown that some patients who do not receive intravenous fluids during operations have exactly the same pulmonary vascular changes as those who do receive infusions.[27] In reality, there is nothing in clinical or experimental medicine to substantiate the concept of "overload".

Discounting "overload" as an objection to transfusion therapy in cardiac patients, other factors should be considered. The first pertains to the liquid component of the blood, and the second pertains to the quality of the red blood cells. As regards the first, mention has already been made of the finding that serum albumin solution and week-old plasma

increase pulmonary capillary permeability.[24,28,29] In view of the tendency toward pulmonary edema in heart disease, it is important to avoid anything that might exacerbate this tendency, including plasma and albumin solution. The observation that stored whole blood depresses the metabolism of skeletal muscle suggests that a similar depression might also occur in cardiac muscle,[30,31] although there are no conclusive data on this.

In addition to the accumulation of inimical substances in the plasma of blood during liquid storage, some erythrocyte changes that occur during storage may produce adverse effects. After approximately 5 days of storage in CPD anticoagulant, the red blood cell 2,3 DPG level falls markedly,[25,32-34] and the hemoglobin oxygen dissociation curve is so changed as to impair the unloading of oxygen in the tissues. Published studies have shown the adverse effects of perfusing various tissues with red blood cells that have low 2,3 DPG levels, whether as a direct result of a lack of oxygen or due to some other metabolic change, and present evidence to show that low 2,3 DPG blood should not be given to cardiac patients.[25] What the anemic cardiac patient needs is washed plasma-free red blood cells suspended in as little salt solution as possible, and with 2,3 DPG levels that are normal or increased.

Patients with congestive heart failure accompanied by chronic anemia usually suffer "high output" failure and relative renal insufficiency. Whether or not the patient has congestive heart failure, a hemoglobin concentration of 10 g% or less should be treated with red blood cells to provide oxygen carrying and oxygen delivery capabilities. The transfused

red cells should have posttransfusion survival values of at least 70%, and red cell oxygen transport should be normal or improved to ensure optimum oxygen delivery to the tissues, especially to the myocardium. Once the anemia is treated and the delivery of oxygen to the heart is improved, it is possible that myocardial function may be improved or restored to normal.

The volume and composition of the fluid administered to patients in chronic congestive failure may influence the symptoms of underlying cardiopulmonary insufficiency. Acute phlebotomy followed by the infusion of red cell concentrates might be effective in the treatment of acute hypervolemia in anemic patients with chronic congestive heart failure.

Treatment of anemic patients with heart disease

Red cell concentrates are the treatment of choice for anemic patients with chronic congestive heart failure. Usually a volume of 100 to 150 ml of sodium chloride solution is used to dilute the red blood cell concentrates to ensure adequate flow.[35] When unwashed red blood cell concentrates that still contain some plasma are transfused, a smaller volume of sodium chloride is recommended. When the unwashed red blood cell concentrate has a hematocrit value of 80 V%, a volume of 10 to 15 ml of isotonic saline may be used to dilute the red cell concentrate for adequate flow through an ultrapore filter. The flow of washed liquid-stored or previously frozen red blood cell concentrates is satisfactory when the hematocrit value is greater than 90 V% at the

time of transfusion.[36] Ultrapore filters (40 micron or less) are recommended for the administration of blood products to patients with heart and lung disease in order to remove as much of the micro-aggregate material as possible.[25,37,38] Patients with chronic congestive heart failure subjected to acute hemorrhage or operative shock may be treated with crystalloid and colloid solutions together with red blood cell concentrates.[39-45] Because of the increased pulmonary capillary permeability in patients with chronic congestive failure, 25 to 50 grams of salt-poor albumin and 5% albumin solution may be advisable. Although it is true that albumin solutions remove the problem of posttransfusion hepatitis, one cannot ignore the potential adverse effects of albumin on myocardial function,[23] pulmonary function,[28,29] clotting system,[46-48] renal function,[49,50] and the immunologic state[51] of the recipient.

Acute hypovolemic shock in a patient with congestive heart failure can be treated with fresh frozen plasma, but there are potential hazards associated with such treatment, i.e., the risk of allergic reactions[52] and posttransfusion hepatitis.[53-56] Acute hemorrhagic shock in patients with chronic congestive heart failure should not be treated with large volumes of isotonic crystalloid solution and hypertonic sodium chloride, because the salt in these solutions is retained by the patient, producing excessive edema especially in the lungs. Red blood cells produce an increase in red cell volume followed by a prompt and satisfactory increase in plasma.[20] They do not themselves have an oncotic effect in vitro, but they do produce an in vivo increase in plasma volume, apparently by

the mobilization of interstitial albumin when closed capillaries are re-opened and perfused.

How does one determine if red blood cells have normal oxygen transport function? For normal individuals with normal adult hemoglobin, the red cell oxygen transport function is determined from temperature and from red cell 2,3 DPG, ATP, pH, and pCO_2 levels.[25,34,57] These factors affect the red cell affinity for oxygen which is usually reported as the partial pressure of oxygen (mm Hg) needed to saturate 50% of the hemoglobin at pH 7.4 and a pCO_2 of 40 mm Hg. An increase in red cell 2,3 DPG usually is seen in patients with anemic hypoxia, hypoxic hypoxia, or stagnant hypoxia.[13,25,57] Red blood cells with increased 2,3 DPG have a decreased affinity for oxygen, and this facilitates the unloading of oxygen in the tissues.

Red cell 2,3 DPG is usually increased as a pathophysiological adaptation to anemic hypoxia, hypoxic hypoxia, or stagnant hypoxia.[12,57] The increase in red cell 2,3 DPG that occurs during anemic hypoxia allows for a decrease in red cell volume by about one-third before cardiac output increases to compensate for the decrease in the number of red cells (Fig 1). In a normovolemic anemic individual, cardiac output increases in response to a reduction in hemoglobin concentration to less than 10 g%. An increase in red cell 2,3 DPG from 0.9 moles DPG per mole of hemoglobin (13 uM/g Hb) to 1.5 moles of DPG per mole of hemoglobin (22 uM/g Hb) usually is observed in normothermic patients with anemic hypoxia.[12,57] Cardiac output does not increase until the red cell volume is decreased by greater than one-third and until the

2,3 DPG has risen to 1-1/2 to 2 times normal and the red cells have improved their oxygen delivery capacity (Fig 1).

Patients with coronary artery disease with or without cardiomegaly usually have normal red cell volume and normal red cell oxygen transport function.[1,13] When the patient has valvular heart disease or myocardiopathy with cardiomegaly, he may have normal or increased red cell and plasma volumes and red cells with normal or only slightly elevated 2,3 DPG levels.[20] Patients with heart disease and congestive heart failure usually have red cells with 150% of normal 2,3 DPG levels and improved oxygen transport function.[13,25,57] Cyanotic heart disease with right-to-left shunts produces arterial hypoxemia, and these patients usually have red cells with 150 to 200% of normal 2,3 DPG levels.[58,59] The oxygen transport function of the preserved red cells transfused to patients with heart disease with or without congestive heart failure should be similar to that of the recipient's own red blood cells.[60]

To ensure acceptable posttransfusion survival values and normal or slightly increased 2,3 DPG levels, the red cell concentrates should be prepared from the unit of whole blood within 6 to 8 hours of collection. When the hematocrit value of the red cell concentrate is 80 V%, the unit can be stored at 4 C for 3 to 5 days with near normal 2,3 DPG levels. As a matter of f ing storage of blood in CPD or CPDA-1 for 24 to 48 hours at 4 s an increase in the red cell 2,3 DPG level (Figs 2-5).[61-63] The increase in red cell 2,3 DPG occurring in red cell concentrates during the 24- to 48-hour period of 4 C storage represents a form of "cold rejuvenation". During the first 10 days of storage at

FIGS 2-5

4 C, red cell 2,3 DPG is maintained better in stored red cell concentrates than in stored whole blood (Figs 2-4).

The anticoagulant in which the red cell concentrate or whole blood is stored affects the maintenance of red cell 2,3 DPG. The citrate in the anticoagulant causes the red cell pH to rise, and this increase is intensified as the red cells are stored in the anticoagulant at 4 C.[63] Glycolysis is stimulated by an increase in pH, and glycolysis in the presence of phosphate in the anticoagulant causes synthesis of 2,3 DPG during the first 24 to 48 hours of 4 C storage. Thereafter, the 2,3 DPG level begins to fall, and after 2 weeks of storage in CPD or CPDA-1 is reduced to about 10% of normal.[25] Red cells with 10% of normal 2,3 DPG levels, increased oxygen affinity and low P_{50} values have been shown to adversely affect cerebral and myocardial function under certain circumstances.[25] When the 2,3 DPG level is 70% of normal or less, the red cells have an increased affinity for oxygen.

Preservation of red cells with normal or low affinity for oxygen

The red cell 2,3 DPG level and thus oxygen transport function is better maintained during the first 3 to 5 days of 4 C storage when CPD or CPDA-1 is used as the anticoagulant and when the unit is stored as a red cell concentrate rather than as whole blood. After liquid storage at 4 C for 3 to 5 days in CPD or CPDA-1 anticoagulant,[34] red blood cells can be frozen to ensure maintenance of 2,3 DPG (non-rejuvenated). Alternatively, a biochemical modification process can be employed to increase or restore the 2,3 DPG levels of indated and outdated red blood

cells after storage at 4 C in CPD or CPDA-1 (rejuvenated).[25,63-68] Rejuvenated red cells must be washed before transfusion whether or not they are subsequently frozen to remove the rejuvenation solution.[63] Red cells frozen with 40% W/V glycerol at -80 C or with 20% W/V glycerol at -150 C are washed before transfusion to remove the glycerol, whether or not they have been rejuvenated.[69,70]

Rejuvenation of indated red blood cells increases 2,3 DPG levels to 250% of normal, and biochemical treatment can increase the 2,3 DPG level of outdated red cells to 150% of normal (Figs 6-8). Biochemically treated red blood cells have been stored in the frozen state for at least 4 years, with satisfactory posttransfusion results.[63,67] FIGS 6-8

Rapid infusion of red blood cell concentrates in patients with cardiopulmonary insufficiency

A study was made to evaluate the safety of infusing red cells at a rapid rate to elderly patients with cardiopulmonary insufficiency.[66] Eleven such patients (mean age 70; range 66-83) each was administered a pool of from 4 to 10 units of washed previously frozen red cells with a hematocrit of 70 V% within 60 minutes through a 40 micron or 170 micron blood filter. These red blood cells had been stored at 4 C for 22 to 28 days, biochemically treated to increase 2,3 DPG to 150% of normal and ATP to 175% of normal and to improve oxygen transport function, and frozen with 40% W/V glycerol at -80 C (Fig 9). After frozen storage at -80 C, the red cells were thawed and washed and stored in the final wash solution at 4 C for 24 hours. On the day of transfusion, the washed red cells FIG 9

were concentrated by centrifugation to remove the supernatant solution. Four to 10 units were pooled and were transfused rapidly as a pool to these elderly patients. The rapid infusion of these red cells with improved oxygen transport function improved cardiopulmonary symptoms and produced no adverse effects, contrary to the apprehension that cardiopulmonary insufficiency might be aggravated.

Comparisons of red blood cells with low 2,3 DPG and high affinity for oxygen to red blood cells with normal 2,3 DPG and normal affinity for oxygen

A number of studies have been made to compare the therapeutic effectiveness of red cells having low 2,3 DPG and high affinity for oxygen (stored blood) with red cells having normal 2,3 DPG and normal affinity for oxygen (fresh blood).[25,71]

In a study by Collins and Stechenberg, rodents were exchanged with either stored blood (low 2,3 DPG) or fresh blood (normal 2,3 DPG).[72] After the exchange transfusion, the rodent's red cell volume was adjusted to either a normal or a decreased level and hemorrhagic shock was produced. The rodents with a decreased red cell volume and a hematocrit of 22 V% exhibited significantly increased mortality after the transfusion of stored blood (low red cell 2,3 DPG and high affinity for oxygen) than after transfusion of fresh blood (normal red cell 2,3 DPG and normal affinity for oxygen). This study in rodents which involved a combination of reduced red cell volume and red cells with low 2,3 DPG and increased affinity for oxygen represented a simulation of the clinical condition of

resuscitation of massively injured individuals with large volumes of stored blood, in which condition the patients usually are anemic and have in their circulation donor red cells with low 2,3 DPG and high affinity for oxygen.

Malmberg and his associates[73] also have exchange-transfused rodents prior to inducing hemorrhagic shock. Following exchange transfusions of red cells with low 2,3 DPG and high affinity for oxygen or red cells with normal 2,3 DPG and normal affinity for oxygen, the red cell volume was normal with a hematocrit value of 40 V%. Oxygen consumption and cardiac output were significantly lower and mortality was significantly greater in the rodents treated with red cells with low 2,3 DPG and high affinity for oxygen.

It is noteworthy that in both the Malmberg study[73] and the Collins and Stechenberg study,[72] higher mortality rates were seen when low 2,3 DPG red cells were used, even though in one study nonanemic rodents were exchange-transfused and in the other study anemic rodents were used, and there has been no explanation for these discrepancies.

Woodson and co-workers[74,75] found that rodents exchange-transfused with red cells with normal 2,3 DPG and normal affinity for oxygen showed only minimal changes in cerebral and coronary blood flow as long as their red cell volumes were normal. On the other hand, when red cells with low 2,3 DPG and high affinity for oxygen were used in the exchange transfusions and the red cell volumes were normal, cerebral and coronary blood flow was doubled. In some rodents with a red cell volume reduced to a hematocrit value of 22 V%, the exchange transfusion with red cells

with low 2,3 DPG and increased affinity for oxygen caused the cerebral blood flow to triple and the coronary blood flow to quadruple. The increases in coronary and cerebral blood flow could not be attributed either to an increase in cardiac work or to hypercapnia. The combination of anemia and red cells with low 2,3 DPG and high affinity for oxygen produced an increase in cerebral and coronary blood flow to compensate for a decreased tissue oxygen tension. Patients who are not able to compensate for a reduced red cell volume and impaired oxygen transport function by increasing cerebral and coronary blood flow, could suffer impairment of myocardial and cerebral function.

In a study by Holsinger and associates,[26] red blood cells depleted of 2,3 DPG were infused into the circumflex coronary artery of a dog with an anterior infarct that had been induced by occlusion of the left anterior descending artery. During the infusion of red cells with low 2,3 DPG and high oxygen affinity, the left ventricular end-diastolic pressure increased and ST segment elevation occurred. These investigators contend that even though this was a pilot study, it provided direct evidence that preserved red cells with low 2,3 DPG and high affinity for oxygen produce myocardial ischemia when coronary blood flow is kept constant.

When Woodson and co-workers[76,77] perfused red cells with low 2,3 DPG levels and increased oxygen affinity at a normal but fixed cerebral blood flow to an isolated dog brain, they observed decreased cerebral oxygen consumption, decreased jugular venous pO_2 tension, and abnormalities of the electroencephalogram. Subsequent perfusion with red cells with normal 2,3 DPG levels and normal affinity for oxygen resulted in

restoration to normal of cerebral oxygen consumption, jugular venous pO_2, and electroencephalogram.

These numerous studies in both rodents and dogs indicate that in the presence of normal vasomotor function of the coronary and cerebral blood, there usually are no adverse effects from red cells with low 2,3 DPG levels and increased affinity for oxygen. However, when there is impairment in vasomotor function of cerebral and coronary blood vessels, these red cells may produce an impairment in cerebral and myocardial function. From these findings, it is reasonable to assume that patients with heart disease should not be administered red blood cells with low 2,3 DPG levels and increased affinity for oxygen.

Comparisons of red blood cells with low 2,3 DPG and high affinity for oxygen and red blood cells with elevated 2,3 DPG and low affinity for oxygen

In a study by Rice and his associates[78] in which baboons in hemorrhagic shock were resuscitated with red cells with either high or low 2,3 DPG levels, the red cells with 150% of normal 2,3 DPG restored oxygen consumption and hemodynamic measurements at lower cardiac output than did red cells with only 10% of normal 2,3 DPG.

Moores and associates[79] compared perfusions of pig red blood cells with low 2,3 DPG and high affinity for oxygen and pig red blood cells with slightly elevated 2,3 DPG and low affinity for oxygen, and found that when the hemoglobin concentration was 10 g%, the low 2,3 DPG red cells decreased the stroke volume significantly during extracorporeal

bypass at normothermic temperature.

Apstein and co-workers[80] studied the perfusion of isolated rabbit hearts with human red cells having 10% of normal 2,3 DPG or 150% of normal 2,3 DPG at normothermic and hypothermic temperatures. These investigators noted that at both 30 C and 37 C, the high 2,3 DPG red blood cells produced a greater improvement in oxygen consumption and myocardial function under basal conditions and after stimulation with isoproterenol. In this study, coronary blood flow was maintained at a constant rate to simulate conditions of fixed coronary blood flow.

Comparisons of red cells with normal to slightly reduced 2,3 DPG and normal affinity for oxygen and red cells with 120 to 150% of normal 2,3 DPG and low affinity for oxygen

Pantely and associates[81] used intravenous infusions of a solution containing pyruvate, phosphate and dihydroxyacetone, in dogs to increase the red cell 2,3 DPG levels to 120% of normal and improve oxygen delivery by increasing the P_{50} value by 2 to 3 mm Hg. Although these investigators observed no significant changes in the size of induced myocardial infarction, they did see changes in the volume of the vascular bed of the coronary circulation, and they offer the speculation that red cells with high 2,3 DPG and low affinity for oxygen may increase oxygen delivery to ischemic myocardium when flow is restricted.

Dennis and associates[82] studied patients coming off cardiopulmonary bypass, 11 of whom had been given 6 units of rejuvenated previously frozen washed red blood cells with 150% of normal 2,3 DPG, and 11 patients of

whom had received 6 units of nonrejuvenated liquid-stored nonwashed red blood cells with 70% of normal 2,3 DPG. Immediately following cardio-pulmonary bypass, the patients who received rejuvenated previously frozen washed red blood cells had P_{50} values of 31.6 mm Hg, whereas the patients who received nonrejuvenated liquid-stored nonwashed red blood cells had values of 28.3 mm Hg ($p < 0.05$) (Fig 10). Oxygen consumption values were 135 and 106 ml/minute/m^2 respectively ($p < 0.05$). Mixed venous oxygen tensions were similar in the two groups, but the arteriovenous content difference was higher in the group who received the rejuvenated red blood cells ($p < 0.05$). Fluid load produced a significantly greater increase in cardiac indices at comparable filling pressures in patients who received rejuvenated red blood cells than in the patients who received nonrejuvenated red blood cells (Fig 11). It has been suggested that the improved cardiac output may have been due to the fact that the rejuvenated red blood cells were washed before transfusion and washing removes citrate, whereas the nonwashed nonrejuvenated red cells contained citrate which may have decreased ionized calcium or impaired myocardial function.

FIG 10

FIG 11

It is true that large infusions of blood products containing citrate might decrease the blood level of ionized calcium and adversely affect myocardial function. To test the theory of citrate involvement, Krausz and co-workers[83] subsequently studied nonwashed and washed red blood cells with low 2,3 DPG levels and washed red blood cells with 150% of normal 2,3 DPG. The patients in this study, who were undergoing elective resection of abdominal aneurysms and who were hypothermic with

a body temperature of 35 C throughout the study, were given transfusions of: (a) 4.5 units of washed liquid-stored red blood cells with 10% of normal 2,3 DPG; (b) 4.5 units of nonwashed liquid-stored red blood cells with 10% of normal 2,3 DPG; or (c) 4.5 units of washed previously frozen red blood cells with 150% of normal 2,3 DPG. Blood ionized calcium levels 6 hours postoperatively were not significantly different among the patients in the three groups, even though the nonwashed liquid-stored red cells contained citrate. This may have been due to the relatively small volumes of blood products which were administered and the intervals between transfusion and measurement. Neither were there any significant differences in myocardial function between the washed and nonwashed red blood cell products.

An unexpected observation in this group of elective patients was the 2.2 C fall in intraoperative body temperature to levels below 34 C in some patients. This fall in temperature was accompanied by a 4.9 torr decrease ($p < 0.001$) in in vivo P_{50} in the patients who received nonwashed and washed liquid-stored red blood cell concentrates. A comparable fall in temperature in the patients who received high 2,3 DPG red blood cells was accompanied by an insignificant change in in vivo P_{50}, and in these patients a normal affinity state was maintained during surgery despite the fall in body temperature (Fig 12). Although there did not appear to be any improvement in myocardial function associated with the red blood cells with high 2,3 DPG levels, these patients did exhibit higher in vivo P_{50} values during hypothermia at 35 C, indicating that the red cell 2,3 DPG attenuated the red cell increased affinity for

FIG 12

oxygen which occurs at decreased body temperatures.

More recently Jalonen and associates[84] reported that in the immediate reperfusion period during cardiopulmonary bypass, red blood cells with 150% of normal 2,3 DPG levels and improved oxygen delivery led to a decrease in anaerobic metabolism and lactate production by the heart, without enhancement of cardiac output.

None of these studies show unequivocally that red cells with 150% of normal 2,3 DPG are greatly superior to red blood cells with normal 2,3 DPG levels. The data do suggest, however, that red blood cells with 150% of normal 2,3 DPG may be useful in patients with localized myocardial ischemia. Moreover, there have been no adverse effects associated with the use of high 2,3 DPG red blood cells, and in consideration of the possible beneficial effects, more clinical studies are indicated.

Comparisons of red blood cells with normal to slightly reduced 2,3 DPG and normal affinity for oxygen and red blood cells with 250 to 300% of normal 2,3 DPG and low affinity for oxygen

A number of factors affect the oxygen affinity of red blood cells, including red cell pH, pCO_2 and 2,3 DPG and ATP levels, and temperature.[25,57,85-89] Hypothermia is known to increase the oxygen affinity of red blood cells, and in vitro studies made at the Naval Blood Research Laboratory demonstrated that biochemically modified human red cells with increased 2,3 DPG (150% and 250% of normal) exhibited significantly less affinity for oxygen at 24 C than did red cells with 70% of normal 2,3 DPG. At

15 C, significant attenuation of affinity was associated with the transfusion of red cells with 250% of normal 2,3 DPG but not with red cells having 150% of normal 2,3 DPG (Figs 13 and 14).[87,88,90] FIG 13 FIG 14

In a study in which isolated fibrillating dog hearts were perfused at 24 C alternately with human red blood cells with 80% of normal 2,3 DPG (nonrejuvenated) and 300% of normal 2,3 DPG (rejuvenated), significantly greater oxygen consumption, higher coronary sinus partial pressures of oxygen and carbon dioxide, higher in vitro P_{50} values, and lower arterial and coronary sinus lactate levels were seen with the rejuvenated red blood cells.[90] The data from this study suggest that high 2,3 DPG red cells might protect myocardial tissue in patients undergoing hypothermic cardiac operations.

Human red blood cells with 150% of normal 2,3 DPG also have been perfused through extracorporeal circuits at normothermic temperatures for 3 hours. The red blood cells had been biochemically modified after they had reached their outdating period to increase the red cell 2,3 DPG and ATP levels to 150% of normal prior to freezing. The red cells were frozen with 40% W/V glycerol and stored at -80 C, thawed, washed, and stored at 4 C for as long as 3 days prior to use in the extracorporeal circulation.[91] These red blood cells had excellent posttransfusion survival and improved oxygen transport function, and produced only minimal hemolysis.[91] In another study, nonrejuvenated human red blood cells with 80% of normal 2,3 DPG and indated-rejuvenated red cells with 250% of normal 2,3 DPG were perfused in combination with a cardioplegic solution through a pump oxygenator at a hypothermic temperature of 15 C for 3 hours. The

red cells were stored at 4 C for 7 days, biochemically treated, frozen with 40% W/V glycerol and stored at -80 C, thawed, washed, and stored at 4 C for 24 hours prior to perfusion through the extracorporeal circuit. Both the nonrejuvenated and the indated-rejuvenated red cells had excellent viability and minimal hemolysis, with no sign of bacterial contamination, the red blood cells with 80% of normal had normal oxygen transport function, and the red blood cells with 250% of normal 2,3 DPG had improved oxygen transport function (Figs 15-17). FIGS 15-17

In an attempt to protect the myocardium during cardiac surgery, physicians have used local and systemic hypothermia, cardioplegic arrest, and intermittent perfusion of the coronary circulation with cardioplegic solutions with or without blood, although controversy as to the most effective approach still exists.[92-100] Myocardial oxygen consumption is reduced during hypothermia, whether because the need for and availability of oxygen is reduced, the distribution of blood flow is abnormal, or the consumption of oxygen by the myocardium is impaired.

Intermittent perfusion of cold cardioplegic solutions through the coronary circulation is a widely used method of protecting the myocardium during cardiac surgery. Cardioplegic solutions have been quite effective, but because they are asanguinuous they carry very little oxygen and therefore may not provide enough oxygen for the myocardium. For this reason, it has been suggested that a combination of red blood cells and cardioplegic solution might be more effective.[101] The expected benefit of additional oxygen delivery to the myocardium expected from a

combination of red blood cells and cardioplegic solution might be offset by an increase in red cell affinity for oxygen occurring during hypothermia which impairs the release of oxygen to tissues. Oxygen release may be hindered further by an elevated pH and a reduced pCO_2, occurring with hypothermia. It has been shown that high 2,3 DPG red cells will attenuate a hypothermia-induced increase in oxygen affinity.[87,88,90]

In a prospective randomized study in humans, the Naval Blood Research Laboratory is studying the comparative effects on myocardial function of the infusions of red blood cells with 80% of normal 2,3 DPG in a cardioplegic solution, red blood cells with 250% of normal 2,3 DPG in a cardioplegic solution, and a cardioplegic solution alone. Two units of washed previously frozen red cells with 80% or 250% of normal 2,3 DPG were diluted with a cardioplegic solution in a separate extracorporeal circuit, and were perfused intermittently in the coronary circulation.

Post-operative ischemia was observed in one of eight patients who received cardioplegic solution alone, in two of eight patients who received a combination of red blood cells with 80% of normal 2,3 DPG and cardioplegic solution, and in two of eight patients who received a combination of red blood cells with 250% of normal 2,3 DPG and cardioplegic solution. No myocardial infarcts were seen in the group receiving cardioplegic solution alone, whereas in each of the two groups receiving red blood cells and cardioplegic solution, two patients suffered myocardial infarcts.

A quantitative creatine phosphokinase (CPK) MB assay showed preoperative CPK levels of 8-18 units for the three groups. Immediately upon cessation of bypass, the levels were 18-32 units, and 24 hours later similar levels were seen in all three groups, with a mean of

56 ± 51 units.

All 24 patients survived surgery, did well clinically, and were discharged from the hospital in an improved condition. Computer analysis of the data has not been completed. If evaluation of oxygen transport and biochemical data reveal no differences among groups, the study will be terminated.

Although red cells with elevated 2,3 DPG levels do decrease the affinity for oxygen that occurs with hypothermia, there are no definitive signs that the intermittent perfusion of these red cells with cardioplegic solution in the coronary circulation of the hypothermic heart has any beneficial effect.

Red cells with high 2,3 DPG and low affinity for oxygen in patients with arterial hypoxemia

It is important in studying the beneficial effects of 2,3 DPG-enriched red blood cells that potential contraindications also be considered. For instance, are there some instances in which decreased affinity for oxygen associated with high 2,3 DPG red blood cells might impair oxygenation of the red blood cells in the lungs? It is important that the effects of red cell affinity on arterial oxygen content and oxygen tension in hypoxemia be understood.[102-109] A decreased red cell affinity for oxygen will improve arterial hypoxemia due to cyanotic heart disease with right-to-left anatomic shunts or ventilation-perfusion abnormalities with pulmonary shunting (Fig 18).[110-112] In patients with cardiac right-to-left shunts and pulmonary shunting, arterial pO_2 tension, mixed venous pO_2 tension, FIG 18

and coronary sinus pO_2 tension will increase if the red cell affinity for oxygen is decreased, provided that the inspired ambient oxygen tension is adequate to maintain an arterial pO_2 tension of greater than 40 mm Hg, and in these patients red blood cells with 150 to 200% of normal 2,3 DPG and low affinity for oxygen are indicated.[63,112] Proctor and associates[113-115] have reported clinical improvement in patients with severe pulmonary insufficiency following the transfusion of human red cells with elevated 2,3 DPG levels.

Blood products for cardiac surgery

Today there is an increased requirement for blood products for cardiac surgery in which extracorporeal bypass is utilized.[116,117] Blood products are given to provide optimum oxygen to the tissues, especially to the heart and brain, for maintenance or restoration of normal hemostasis, and for optimum protection against infection. The patient's state of health and the length of cardiopulmonary bypass determine which blood products are required, whether oncotic, clotting, and opsonic proteins, platelets, or red cells; the cardiopulmonary bypass procedure may adversely affect the viability and function of these blood components. Abnormalities in blood coagulation[118-131] and hemolysis of red cells[132,133] may occur during bypass surgery. The heparin used to anticoagulate the patient's blood during bypass and the citrate used in the anticoagulant in which the blood product is stored both may adversely affect platelet function.[134-136] Moreover, hypothermia[137,138] and anesthesia[139] may affect the hemostatic mechanism; drugs such as aspirin[140] may affect platelet function, and

heparin per se[141-144] may produce thrombocytopenia.

The bleeding diathesis during and following extracorporeal bypass surgery is a complicated process which may be affected in any number of ways, e.g., the failure of the surgeon to suture severed blood vessels, by the length of the bypass procedure, the failure to neutralize administered heparin, the excessive administration of protamine sulfate, a decrease in level of clotting proteins, a reduction in platelet number and abnormalities of platelet function, disseminated intravascular coagulation, or by fibrinolysis.

Potential risks associated with donor blood products such as post-transfusion hepatitis and isoimmunization can be reduced by collecting blood from the patient prior to elective surgery, by collecting intra-operative blood from the patient during surgery and shed blood after surgery from thoracic drainage sites.[25,145-151] It is recommended though that shed blood be washed prior to reinfusion to prevent disseminated intravascular coagulation and a bleeding diathesis.[152]

Hemodilution with crystalloid-colloid solutions to produce acute normovolemic anemia has been utilized during cardiopulmonary bypass operations to minimize or eliminate the need for blood products.[153-167] Reports that moderate hemodilution produces no deleterious effects[168-170] are encouraging, though not substantiated by physiologic data.

Albumin also has been utilized during extracorporeal bypass for the purpose of maintaining plasma oncotic pressure so as to minimize the accumulation of edema fluid in the tissue. Although albumin has also been shown to protect platelet function during cardiopulmonary

bypass,[171] its disadvantages appear to outweigh its advantages. Albumin has been shown to adversely affect the heart,[23] lung,[28,29] kidney,[49,50] immunologic system,[51] and clotting function.[46-48] Mannitol reportedly reduces myocardial edema during cardiopulmonary bypass surgery,[172] whereas the colloid solution, plasma protein fraction, is not recommended because it may produce severe hypotension during extracorporeal bypass.[173-179]

Numerous blood substitutes and blood products have been used to prime the extracorporeal circuit: crystalloid solutions, colloid solutions, and blood products, osmotic diuretic agents such as mannitol, and buffer solutions such as bicarbonate. The pump may be primed with crystalloid-colloid solutions and hemodilution, crystalloid-colloid solutions and washed previously frozen red cells alone[180] or in combination with liquid-stored blood products,[181] crystalloid-colloid solutions in combination with liquid-stored red blood cell concentrates or stored whole blood, or crystalloid-colloid solutions in combination with fresh whole blood.

Numerous studies have shown no differences in platelet counts or platelet function, white cell count, clotting measurements, oxygen transport, microaggregates, red cell function, hemodynamics, pulmonary function, blood products used, or fluid balance, whether a membrane or bubble oxygenator was utilized during extracorporeal bypass.[182-190] It may very well be true that there are no differences with these two types of oxygenators; nevertheless, studies should be made to evaluate the sensitivity of the measurements used. Other factors associated with the surgery also may be involved which have a greater effect on blood

trauma than the oxygenator. Cardiotomy suction produces far more trauma to blood than does the membrane or the bubble oxygenator, and suction damage can easily mask any difference between oxygenators.[191,192]

Coagulation tests, platelet counts, and platelet function tests during and after cardiopulmonary bypass surgery

Plasma coagulation protein levels usually are decreased during extracorporeal bypass. Coagulation factor levels about 30% of normal usually are adequate for all factors, except for Factor V which shows adequate hemostasis at levels of 10-15%.[137] Abnormal bleeding following cardiopulmonary bypass generally is not due to reductions in the levels or function of coagulation factors.[130,131,137] Moreover, factors such as excessive anticoagulation with heparin, excessive neutralization with protamine sulfate, qualitative defects in the polymerization of fibrin, increased fibrinolytic activity, or the effects of fibrin-fibrinogen degradation products on coagulation do not usually produce bleeding following cardiopulmonary bypass.[126,130,131,137]

Postoperative hemorrhage in patients undergoing cardiopulmonary bypass may be due to defective platelet plug formation related to abnormalities of platelet function.[193-199] The degree of impairment in platelet function is usually proportional to the duration of bypass and to the level of hypothermia.[137] The prostaglandin compounds, PGE_1 and PGI_2, have been utilized during extracorporeal bypass to maintain platelet number and function.[200-202] The platelet dysfunction is rapidly reversible in most patients, although clinical bleeding will

occur in patients with a persistent functional platelet defect. The standardized template bleeding time detects patients at risk of serious postoperative bleeding.[137,194] Platelet concentrate transfusions are indicated to treat a bleeding diathesis in a patient with a platelet count below 50,000/ul, as well as for patients with a bleeding diathesis and a bleeding time of greater than 20 minutes when the platelet count exceeds 100,000/ul. Bleeding time is a better indicator of the need for platelet transfusion than the platelet count itself, and measurements of both platelet count and bleeding time should be made in patients who fail to stop bleeding after cardiopulmonary bypass surgery. No currently available preoperative laboratory test of hemostatic function can accurately predict coagulopathies resulting from cardiopulmonary bypass.[130]

Blood products recommended during and after cardiopulmonary bypass surgery

Red blood cell concentrates with normal or improved oxygen transport function have been shown to provide the best results in patients undergoing cardiopulmonary bypass, and should be used instead of fresh whole blood or stored whole blood. Red blood cell concentrates stored in the liquid state at 4 C for 3 to 5 days with hematocrit values of 80 V% usually have normal 2,3 DPG levels, and liquid-stored red blood cells can be biochemically treated to elevate 2,3 DPG. Red cells with elevated 2,3 DPG levels attenuate the increased red cell affinity for oxygen that occurs during hypothermia and provide higher oxygen tension in the tissues. Whether or not the tissues utilize the increased oxygen has not yet been determined. Nevertheless, we believe that the safest course to follow

for patients undergoing cardiopulmonary bypass surgery is to use red cells with high 2,3 DPG levels and decreased oxygen affinity. Crystalloid solutions, not colloid solutions such as albumin and plasma protein fraction, are recommended as the volume expander for the pump prime.

Platelet transfusions should not be administered during extracorporeal bypass. However, platelet transfusions should be used to treat the bleeding diathesis after bypass associated with a significant thrombocytopenia (less than 50,000 platelets/ul) or with bleeding accompanied by a prolonged bleeding time and a platelet count of 100,000 or greater per ul. Six to 8 units of fresh platelets should be administered. When it is necessary to administer preserved platelets, it is important that the circulation and function of these platelets are known.[203-212] Data have shown that platelets stored at 22 ± 2 C have impaired function and require periods of time in the circulation to restore function.[25,213] Platelets stored at 4 C for 24 hours have been shown to have better function than platelets stored at room temperature (22 ± 2 C) for 24 hours.[214-216] No studies have yet been made in patients undergoing cardiopulmonary bypass to measure the function of platelet concentrates stored at room temperature (22 ± 2 C) for 5 days.[217-219] Patients with clinical bleeding and severe dilutional coagulopathies are best treated with 4 to 6 units of fresh frozen plasma, although there are no indications for the routine use of fresh frozen plasma during extracorporeal bypass surgery.[220,221]

Stored whole blood and plasma stored at 4 C have recently been

shown to give rise to impairment in oxygen consumption by isolated skeletal muscle,[30,31] and increased pulmonary permeability,[24] and therefore are not recommended during cardiopulmonary bypass surgery. As regards the use of plasma opsonic protein, this is still in the speculative stage.[222-227]

Summary

The oxygen transport function of preserved red cells transfused to anemic patients who have heart disease is critical. Patients with heart disease should be given red cells with normal 2,3 DPG and normal affinity for oxygen instead of low 2,3 DPG red cells. Our studies suggest that red cells with high 2,3 DPG (150 to 200% of normal) and low affinity for oxygen are the best form of transfusion therapy for anemic patients, especially those with congestive heart failure. It may even prove useful to use 2,3 DPG-enriched red cells in patients with patchy myocardial ischemia and, at any rate, it can do no harm. High 2,3 DPG red blood cells also are recommended in patients with right-to-left cardiac shunts and pulmonary shunts, provided that the inspired ambient oxygen tension is adequate to maintain an arterial pO_2 tension of greater than 40 mm Hg.

Blood products utilized during extracorporeal bypass surgery should ensure optimum oxygen delivery to tissue and maintain or restore normal hemostasis, and red cells with 250% to 300% of normal 2,3 DPG and low affinity for oxygen given in combination with crystalloid solution will do this. Red cells with elevated 2,3 DPG levels do ensure optimum delivery of oxygen to tissue, especially during hypothermia, although it cannot be stated definitely whether or not they reduce myocardial damage.

A postoperative bleeding diathesis following cardiopulmonary bypass due to a decrease in platelet number and to abnormalities of platelet function should be treated with platelet transfusions. Although a bleeding diathesis as a result of dilutional coagulopathies is rare,

severe dilutional coagulopathies should be treated with fresh frozen plasma. However, routine use of fresh frozen plasma following cardiopulmonary bypass is not recommended.

Acknowledgments

The author acknowledges the helpful suggestions of Dr. Mark D. Altschule, the editorial assistance of Cynthia A. Valeri, and the secretarial assistance of Marilyn Leavy, in the preparation of this manuscript.

Fig 1 -- The effect of anemia on cardiac index and red cell 2,3 DPG level. (Reproduced with permission from Finch CA and Lenfant C, N Engl J Med 1972; 286:412).

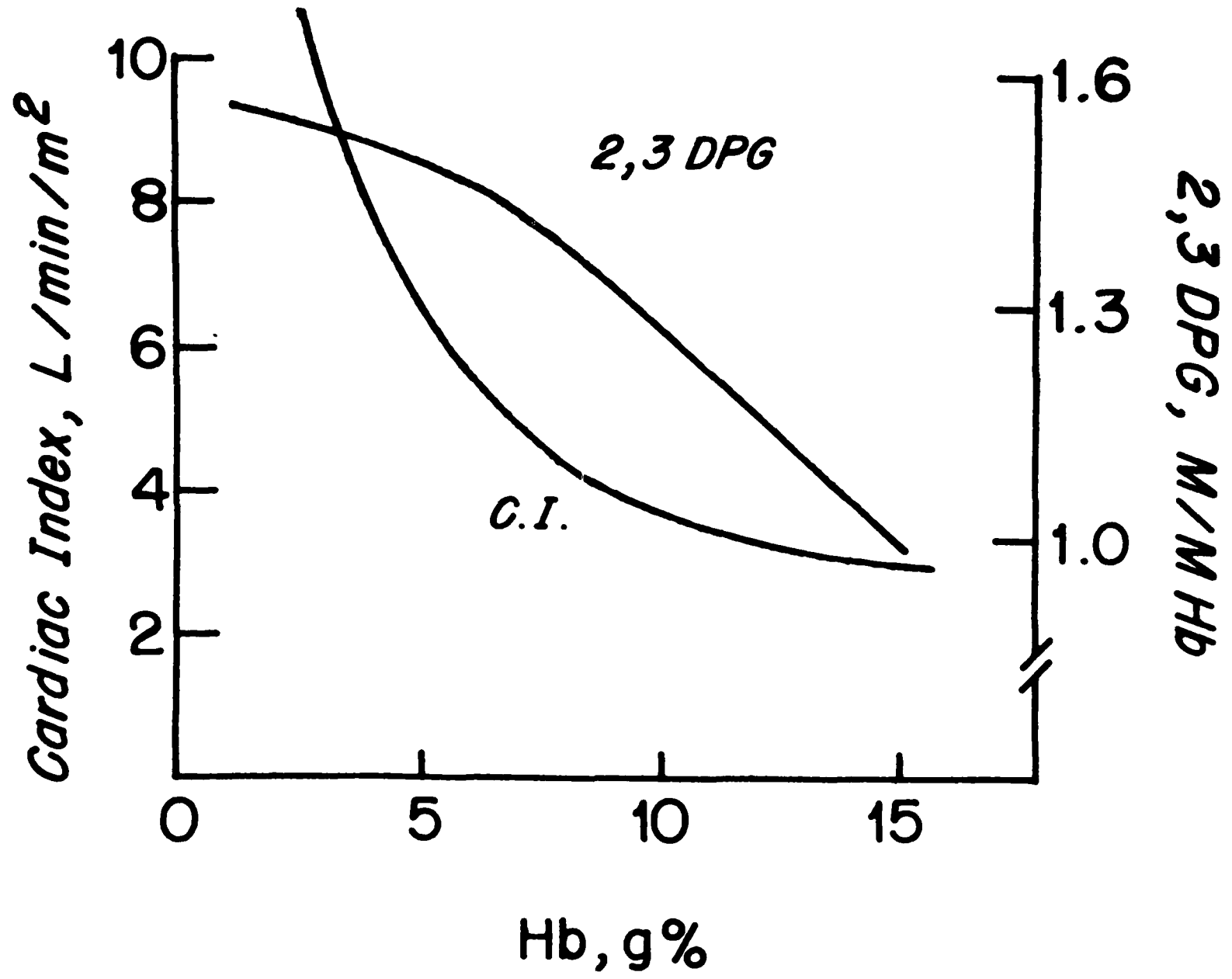

Cardiac Index, L/min/m²
10
8
6
4
2
0
5
10
15
Hb, g%
2,3 DPG
C.I.
1.6
1.3
1.0
2,3 DPG, M/M Hb

Fig 2 -- The 2,3 DPG levels in red blood cells stored at 4 C in citrate-phosphate-dextrose as whole blood with a hematocrit value of 40 V%, or as a red blood cell concentrate with a hematocrit value of 70-80 V% or of greater than 90 V%. Neither the whole blood nor the red blood cell concentrate was mixed during liquid storage at 4 C. (Reproduced with permission from Valeri CR, Surgical Rounds 1981;4:41).

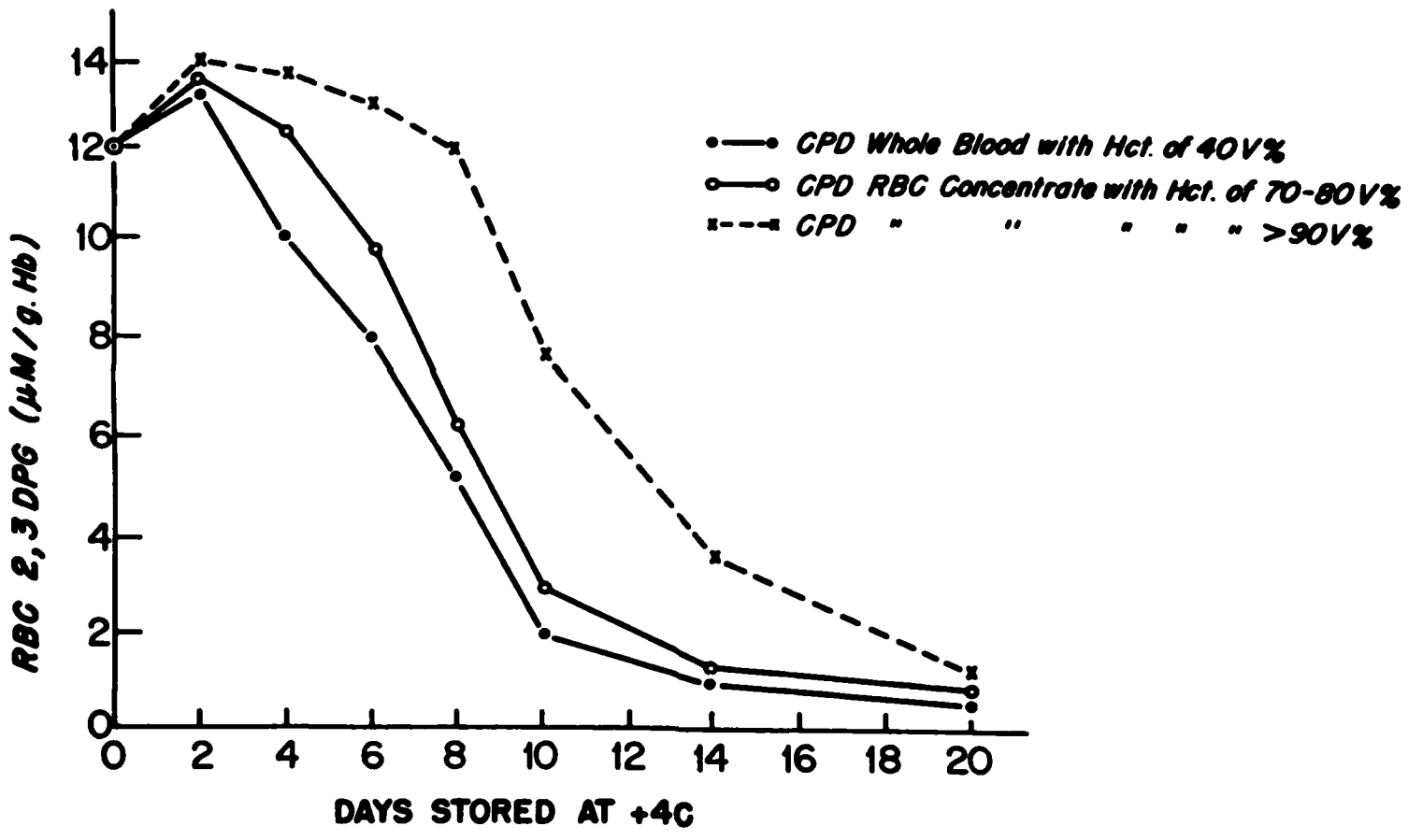

RBC 2,3 DPG (μM/g. Hb)
14
12
10
8
6
4
2
0
0
2
4
6
8
10
12
14
16
18
20
DAYS STORED AT +4C
CPD Whole Blood with Hct. of 40V%
CPD RBC Concentrate with Hct. of 70-80V%
CPD " " " " " >90V%

Fig 3 -- The 2,3 DPG levels in red blood cells after storage in CPDA-1 at 4 C as whole blood or as a red blood cell concentrate with a hematocrit value of 70 V%.

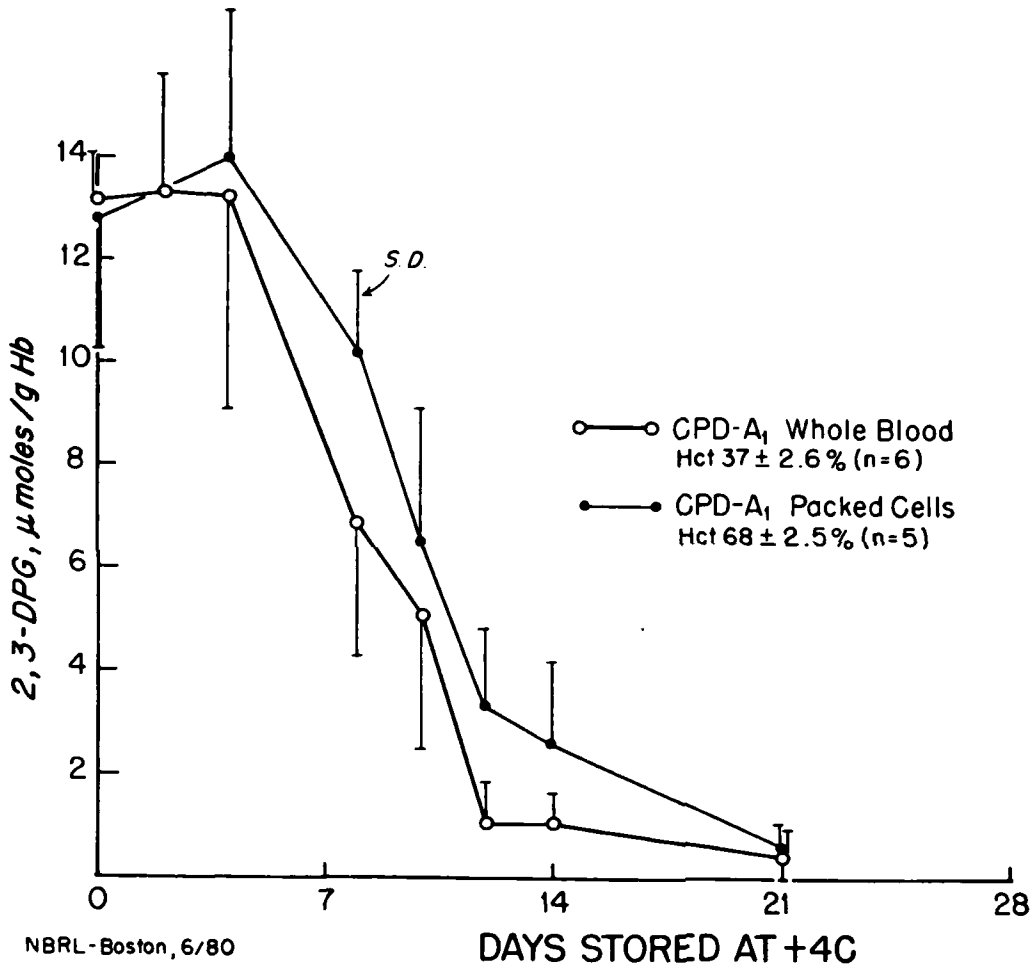

2,3-DPG, μmoles/g Hb
14
12
10
8
6
4
2
0
7
14
21
28
S.D.
CPD-A1 Whole Blood
Hct 37 ± 2.6% (n=6)
CPD-A1 Packed Cells
Hct 68 ± 2.5% (n=5)
NBRL-Boston, 6/80
DAYS STORED AT +4C

Fig 4 -- The 2,3 DPG levels of red cell concentrates stored at 4 C in CPD, CPDA-1, CPDA-2 or CPDA-3 (Reproduced with permission from Valeri CR, Crit Rev Clin Lab Sci, in press).

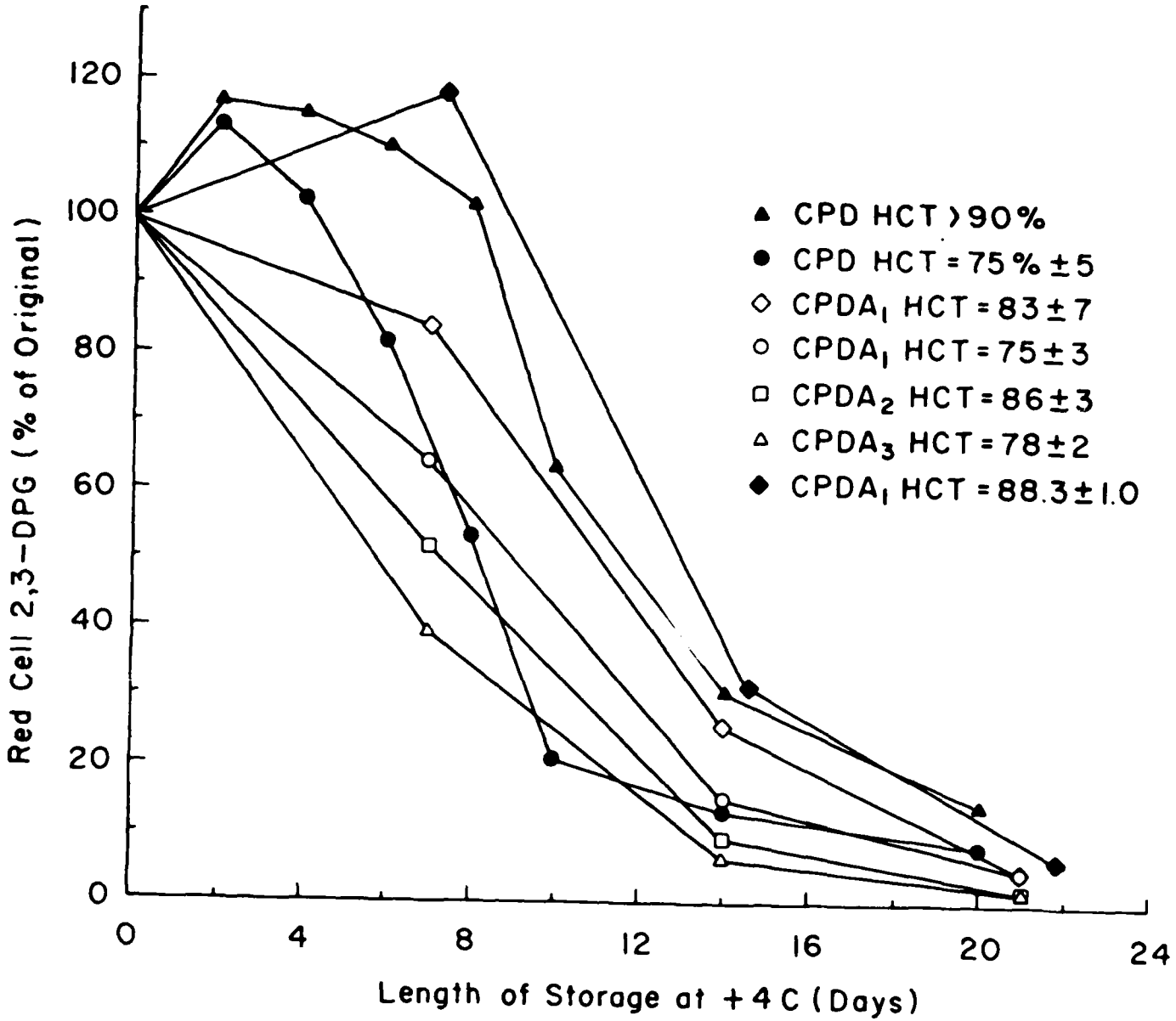

120
100
80
60
40
20
0
Red Cell 2,3-DPG (% of Original)
0
4
8
12
16
20
24
Length of Storage at +4 C (Days)
▲ CPD HCT > 90%
● CPD HCT = 75% ±5
◇ CPDA1 HCT = 83 ± 7
○ CPDA1 HCT = 75 ± 3
□ CPDA2 HCT = 86 ± 3
△ CPDA3 HCT = 78 ± 2
◆ CPDA1 HCT = 88.3 ± 1.0

Fig 5 -- The ATP and 2,3 DPG levels in red cell concentrates after storage as whole blood in ACD, CPD, ACD-supplemented with 0.5 mM adenine, or CPD supplemented with 0.25, 0.50, and 0.75 mM adenine. (Reproduced with permission from Hogman CF, Akerblom O, Arturson G, deVerdier C, Kreuger A, and Westman M. In: Greenwalt TJ and Jamieson GA, eds. The Human Red Cell In Vitro. New York: Grune & Stratton, 1974:221).

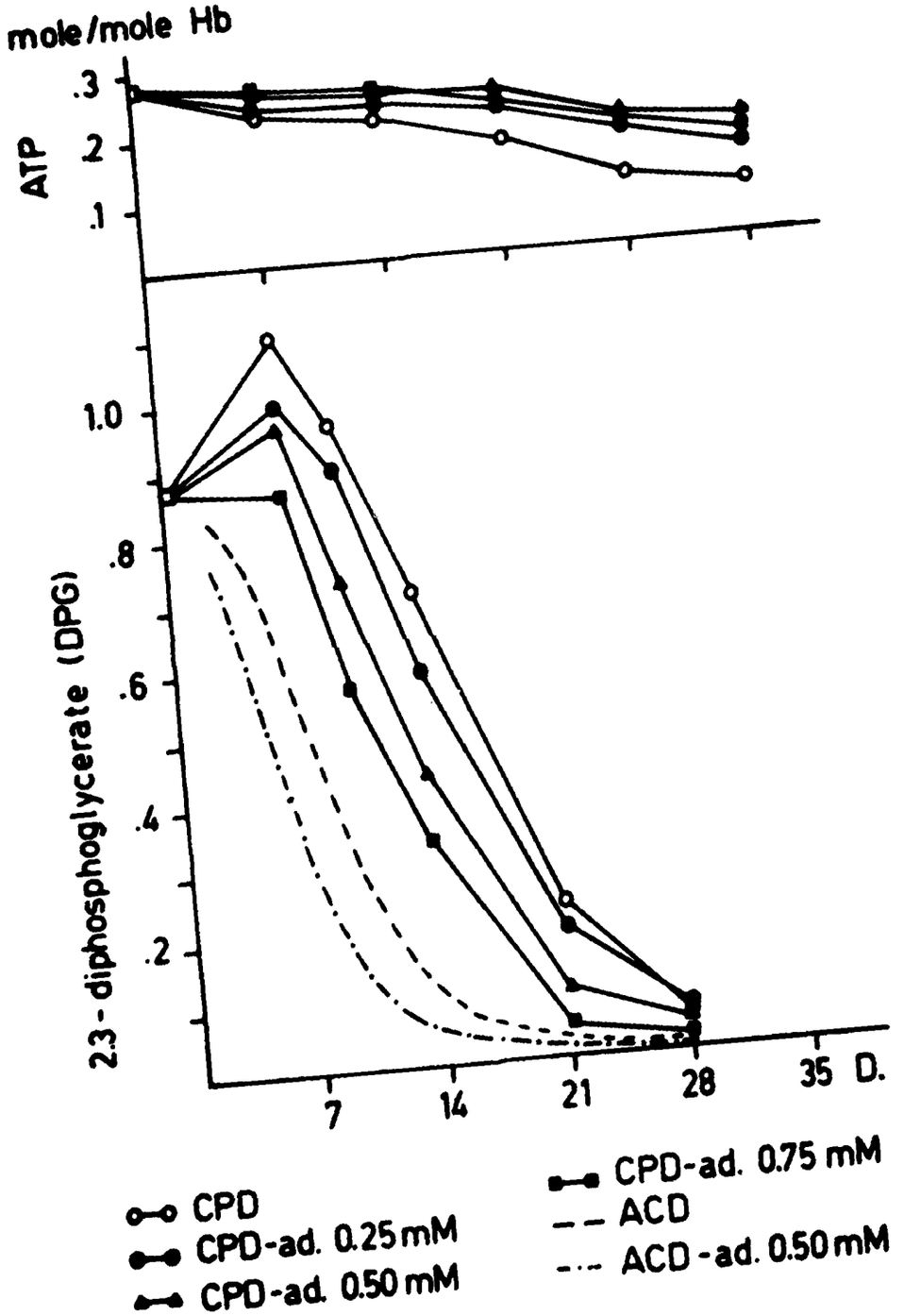

mole/mole Hb
ATP
.3
.2
.1
1.0
.8
.6
.4
.2
2.3-diphosphoglycerate (DPG)
7
14
21
28
35 D.
CPD
CPD-ad. 0.25 mM
CPD-ad. 0.50 mM
CPD-ad. 0.75 mM
ACD
ACD-ad. 0.50 mM

Fig 6 -- Red cell 2,3 DPG and ATP levels, and P_{50} values for red blood cell concentrates with hematocrits of 80 $\pm$ 5 V%, stored at 4 C in CPD for 6 to 8 days or for 25 days, biochemically treated with PIPA or FRES, frozen with 40% W/V glycerol in the original polyvinylchloride collection bag at -80 C, thawed, and washed. (Reproduced with permission from Valeri CR, Crit Rev Clin Lab Sci, CRC Press, in press).

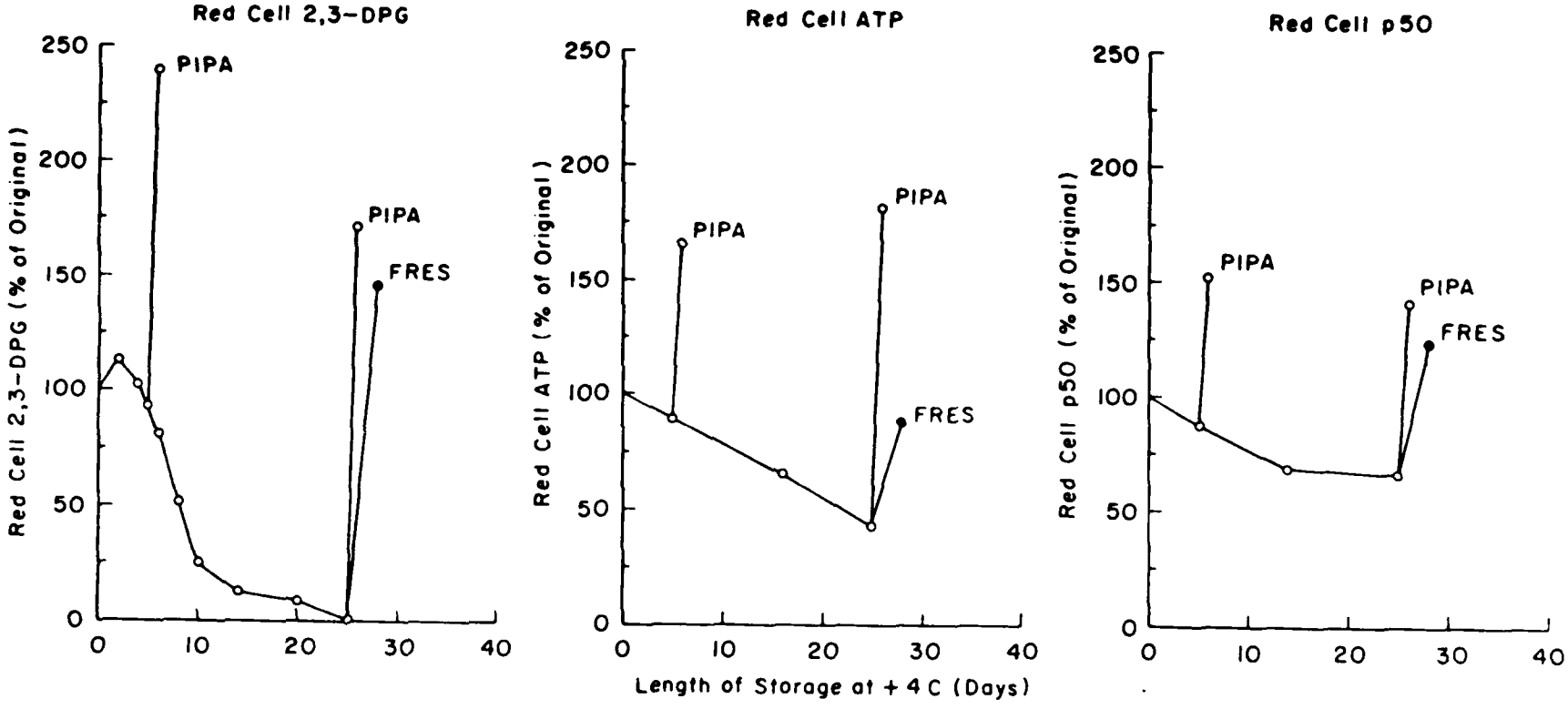

Red Cell 2,3-DPG
Red Cell 2,3-DPG (% of Original)
PIPA
PIPA
FRES
Red Cell ATP
Red Cell ATP (% of Original)
PIPA
PIPA
FRES
Red Cell p50
Red Cell p50 (% of Original)
PIPA
PIPA
FRES
0
50
100
150
200
250
0
10
20
30
40
Length of Storage at + 4 C (Days)

Fig 7 -- Red cell 2,3 DPG and ATP levels, and P_{50} values for red blood cell concentrates with hematocrits of 80 ± 5 V%, stored at 4 C in CPDA-1 for 35 days, biochemically treated with PIPA or FRES, frozen with 40% W/V glycerol in the original polyvinylchloride collection bag at -80 C, thawed, and washed. (Reproduced with permission from Valeri CR, Crit Rev Clin Lab Sci, CRC Press, in press).

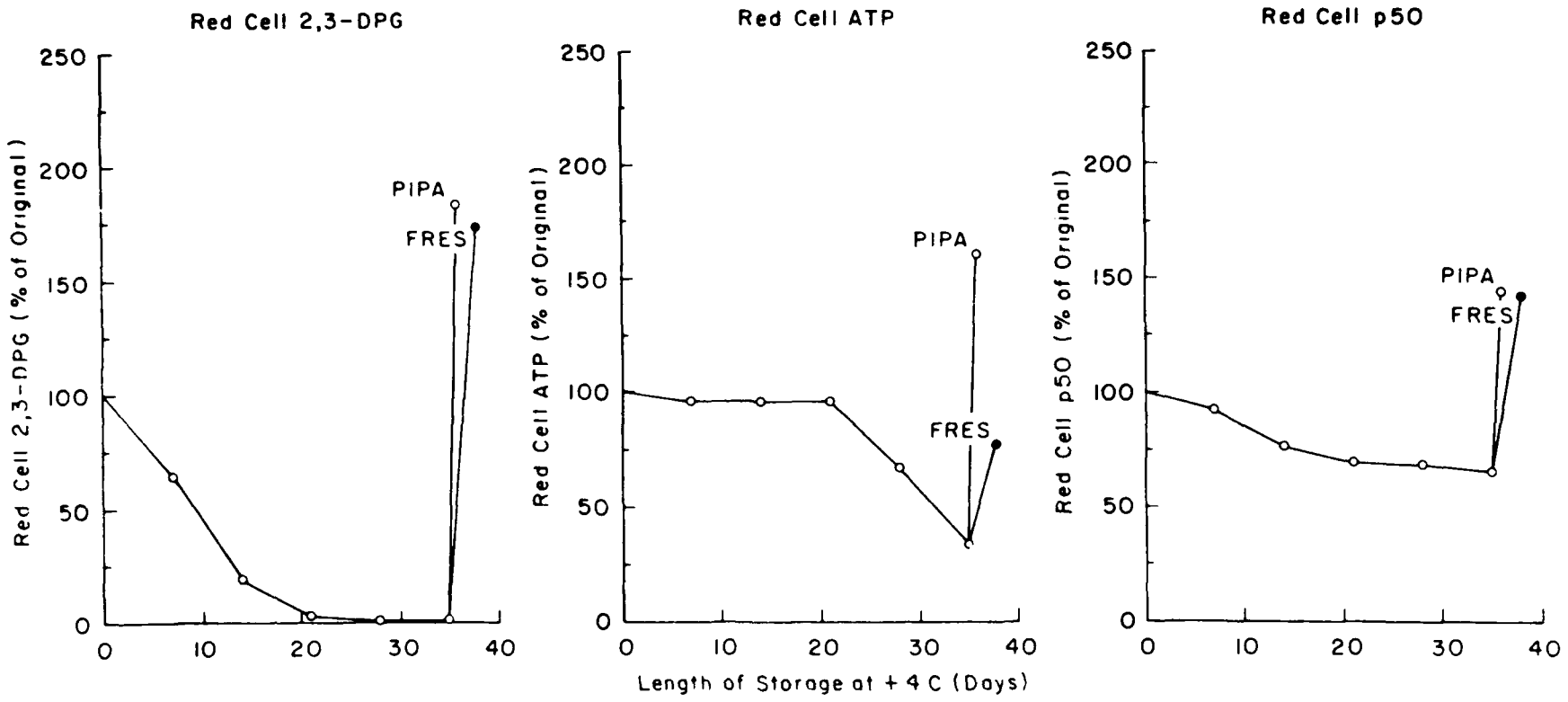

Red Cell 2,3-DPG
Red Cell 2,3-DPG (% of Original)
250
200
150
100
50
0
PIPA
FRES
0
10
20
30
40
Red Cell ATP
Red Cell ATP (% of Original)
250
200
150
100
50
0
PIPA
FRES
0
10
20
30
40
Length of Storage at + 4 C (Days)
Red Cell p50
Red Cell p50 (% of Original)
250
200
150
100
50
0
PIPA
FRES
0
10
20
30
40

Fig 8 -- Freeze-thaw-wash recovery in vitro, ^{51}Cr 24-hour posttransfusion survival, index of therapeutic effectiveness and length of storage at 4 C, of red blood cell concentrates (hematocrit value of 80 $\pm$ 5 V%) collected in CPD or CPDA-1, biochemically modified with PIPA or FRES, frozen with 40% W/V glycerol in the primary collection bag and stored at -80 C, washed in the Haemonetics Blood Processor 115 or the IBM Blood Processor 2991, and stored at 4 C for 24 hours in the final wash solution of 0.9% NaCl-0.2% glucose-40 mg% inorganic phosphorus (pH 6.8) or 0.9% NaCl-0.2% glucose (pH 5.0). (Reproduced with permission from Valeri CR, Crit Rev Clin Lab Sci, CRC Press, in press).

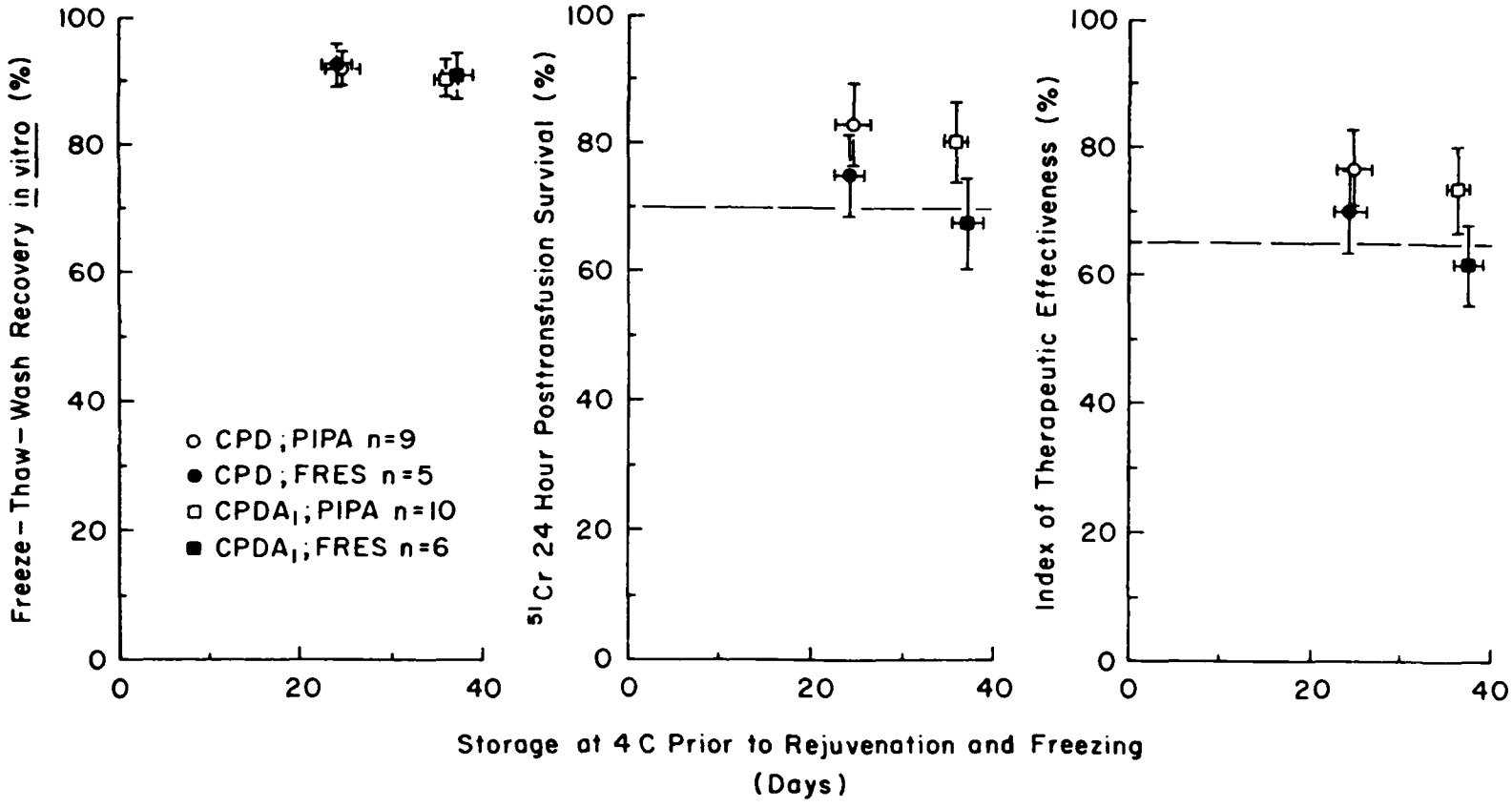
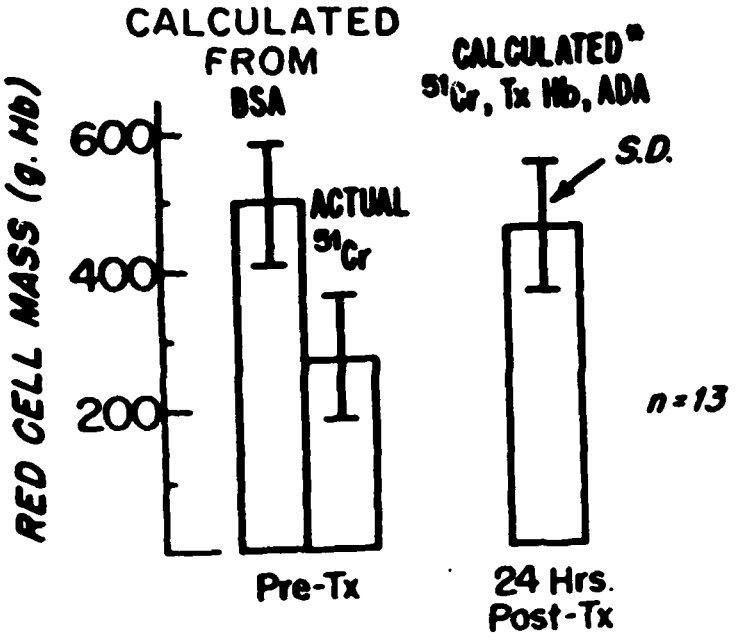
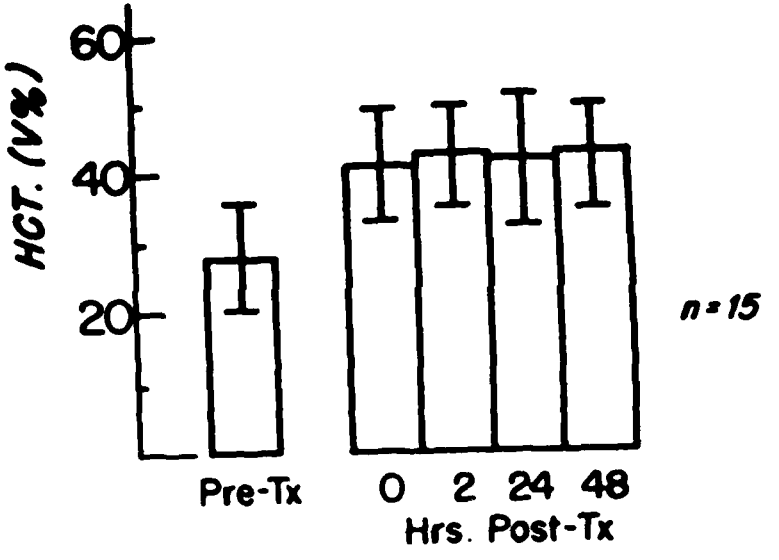
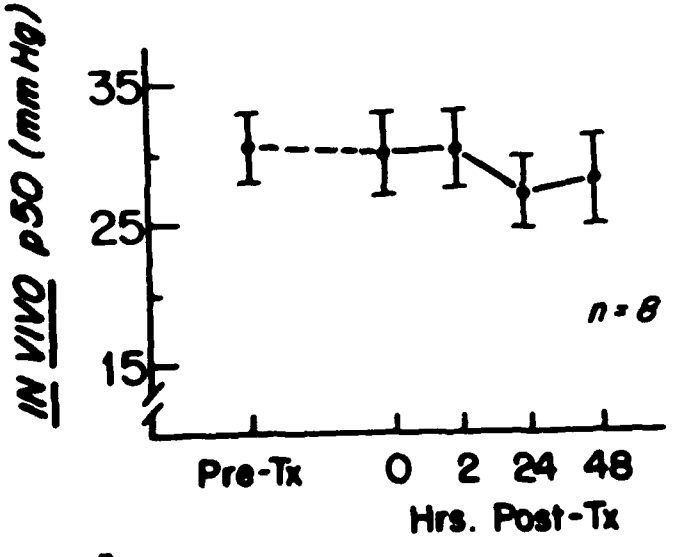
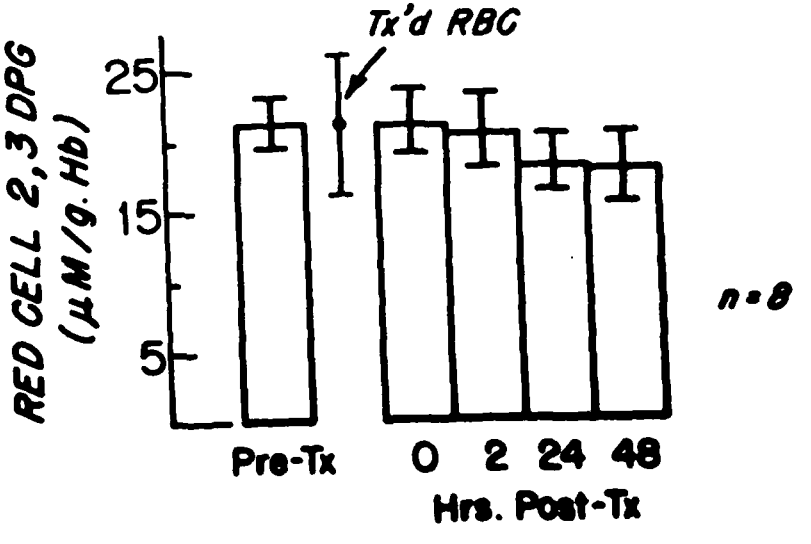

Freeze-Thaw-Wash Recovery in vitro (%)
51Cr 24 Hour Posttransfusion Survival (%)
Index of Therapeutic Effectiveness (%)
100
80
60
40
20
0
0
20
40
○ CPD; PIPA n=9
● CPD; FRES n=5
□ CPDA1; PIPA n=10
■ CPDA1; FRES n=6
Storage at 4 C Prior to Rejuvenation and Freezing
(Days)

Fig 9 -- Theoretical red blood cell mass and ^{51}Cr-measured red blood cell mass in the recipient prior to and 24 hours after the transfusions. The in vivo P_{50} value, hematocrit, and red cell 2,3 DPG level are reported prior to and following the transfusions of red cells with 150% of normal 2,3 DPG. The red cell mass 24 hours after transfusion is the sum of the red cell mass of the recipient prior to transfusion and the donor red cell mass in the circulation 24 hours after transfusion which is the product of the red cell mass of donor hemoglobin transfused multiplied by the 24-hour posttransfusion survival measured by the automated differential agglutination (ADA) procedure. (Reproduced with permission from Valeri CR, Zaroulis CG, Vecchione JJ, et al. Transfusion 1980;20:269).









* ^{51}Cr RCM + Tx'd Hb x % ADA Survival

Fig 10 -- Transfusions of 2,3 DPG-enriched red blood cells resulted in higher levels of 2,3 DPG and plasma inorganic phosphorus and an increased in vivo P_{50} value. Oxygen consumption was increased in patients given red blood cells high in 2,3 DPG in the period immediately after cardiopulmonary bypass. Both the cardiac index and arteriovenous oxygen content difference were elevated at this time. (Reproduced with permission from Dennis RC, Hechtman HB, Berger RL, Vito L, Weisel RD, and Valeri CR, Ann Thorac Surg 1978;26:20).

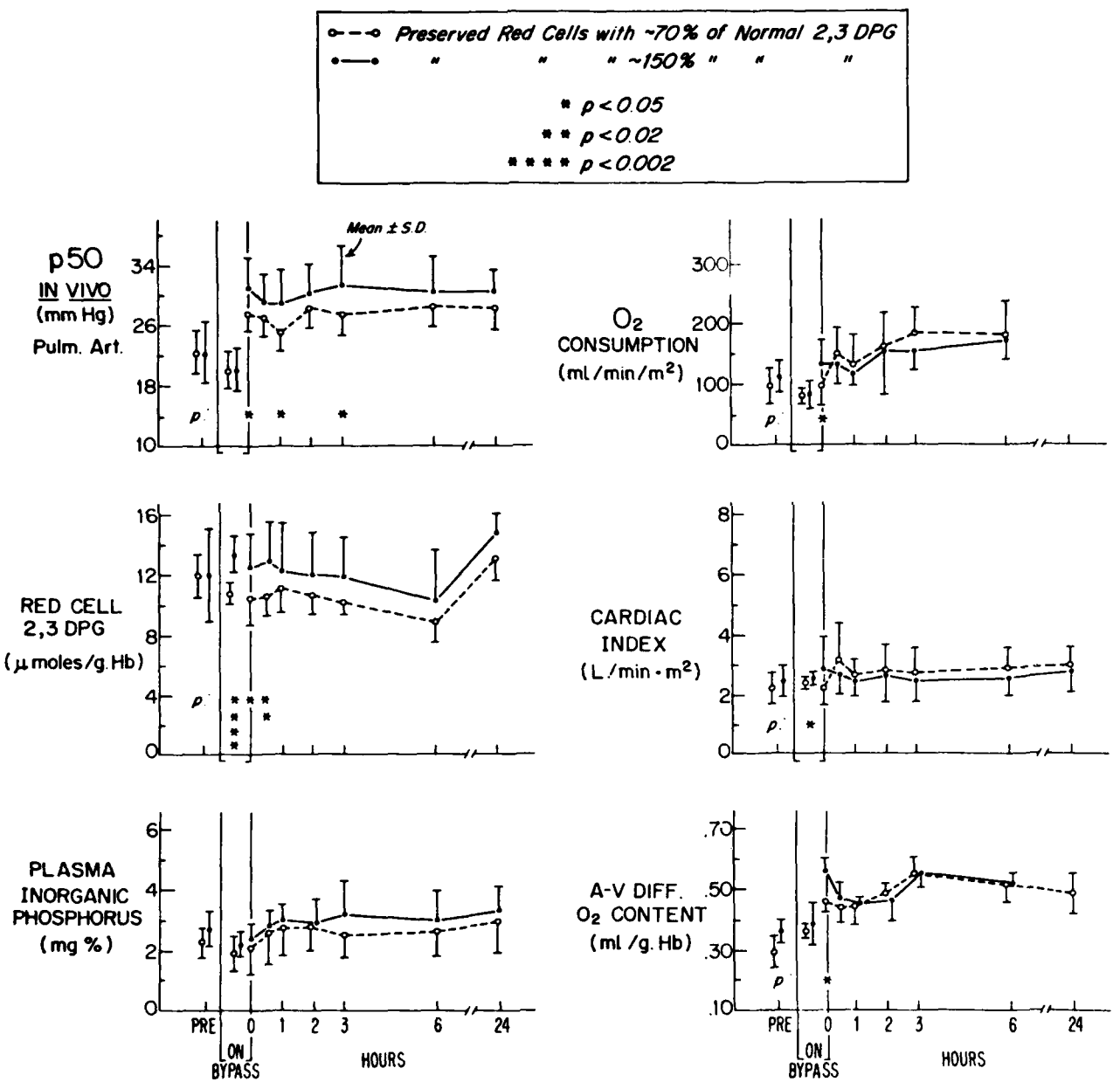
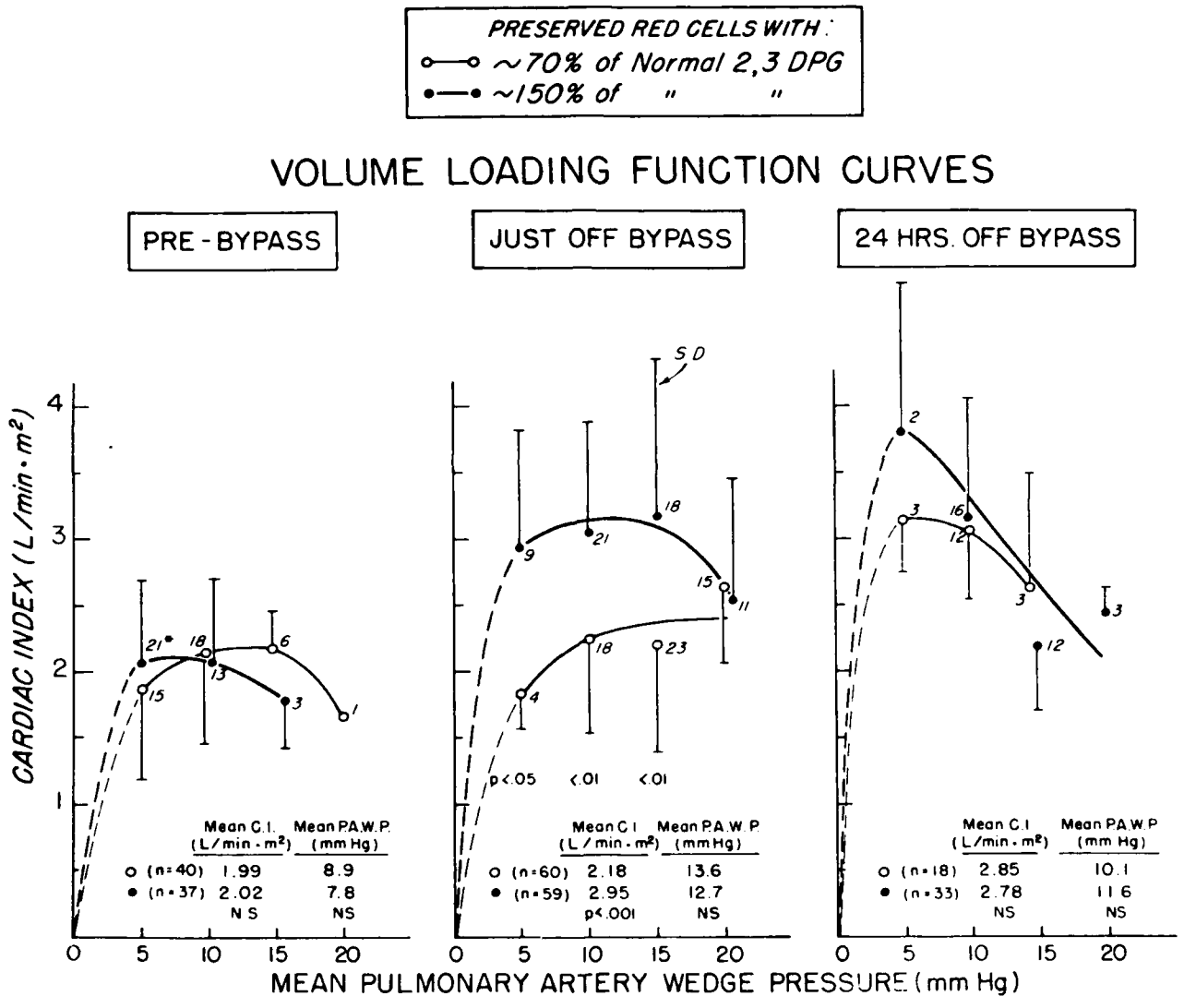
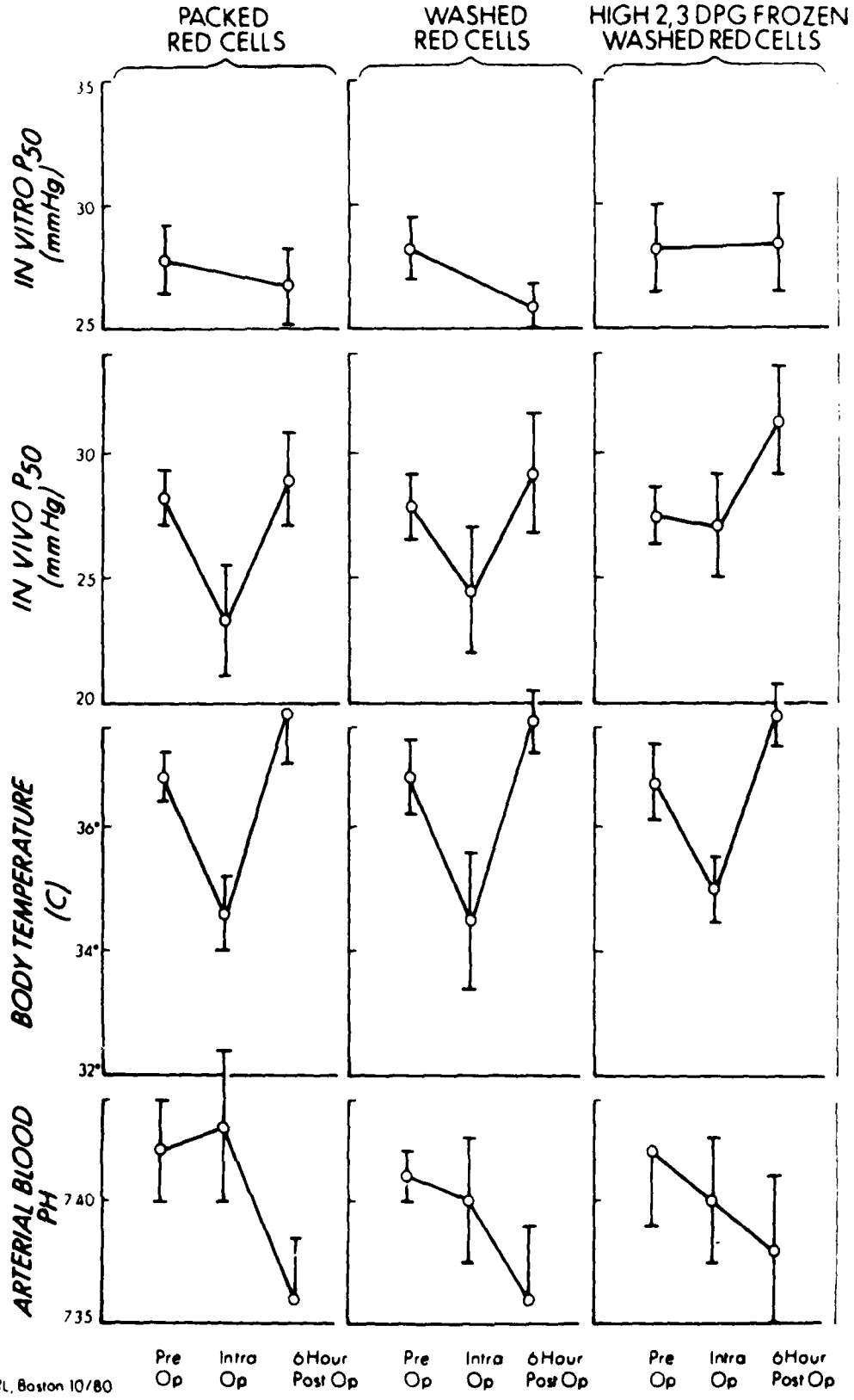

Preserved Red Cells with ~70% of Normal 2,3 DPG
" " " ~150% " " "
* p<0.05
** p<0.02
**** p<0.002
p50
IN VIVO
(mm Hg)
Pulm. Art.
Mean ± S.D.
O2 CONSUMPTION
(ml/min/m²)
RED CELL
2,3 DPG
(μ moles/g. Hb)
CARDIAC
INDEX
(L/min·m²)
PLASMA
INORGANIC
PHOSPHORUS
(mg %)
A-V DIFF.
O2 CONTENT
(ml/g. Hb)
PRE
ON BYPASS
HOURS

Fig 11 -- Cardiac output and the filling pressure of the left ventricle associated with volume loading prior to, immediately following, and 24 hours after cardiopulmonary bypass. During extracorporeal bypass for coronary artery bypass surgery, these patients with coronary artery disease received red blood cells with either 70% or 150% of normal 2,3 DPG levels. (Reproduced with permission from Dennis RC, Hechtman HB, Berger RL, Vito L, Weisel RD, and Valeri CR, Ann Thorac Surg 1978;26:22).



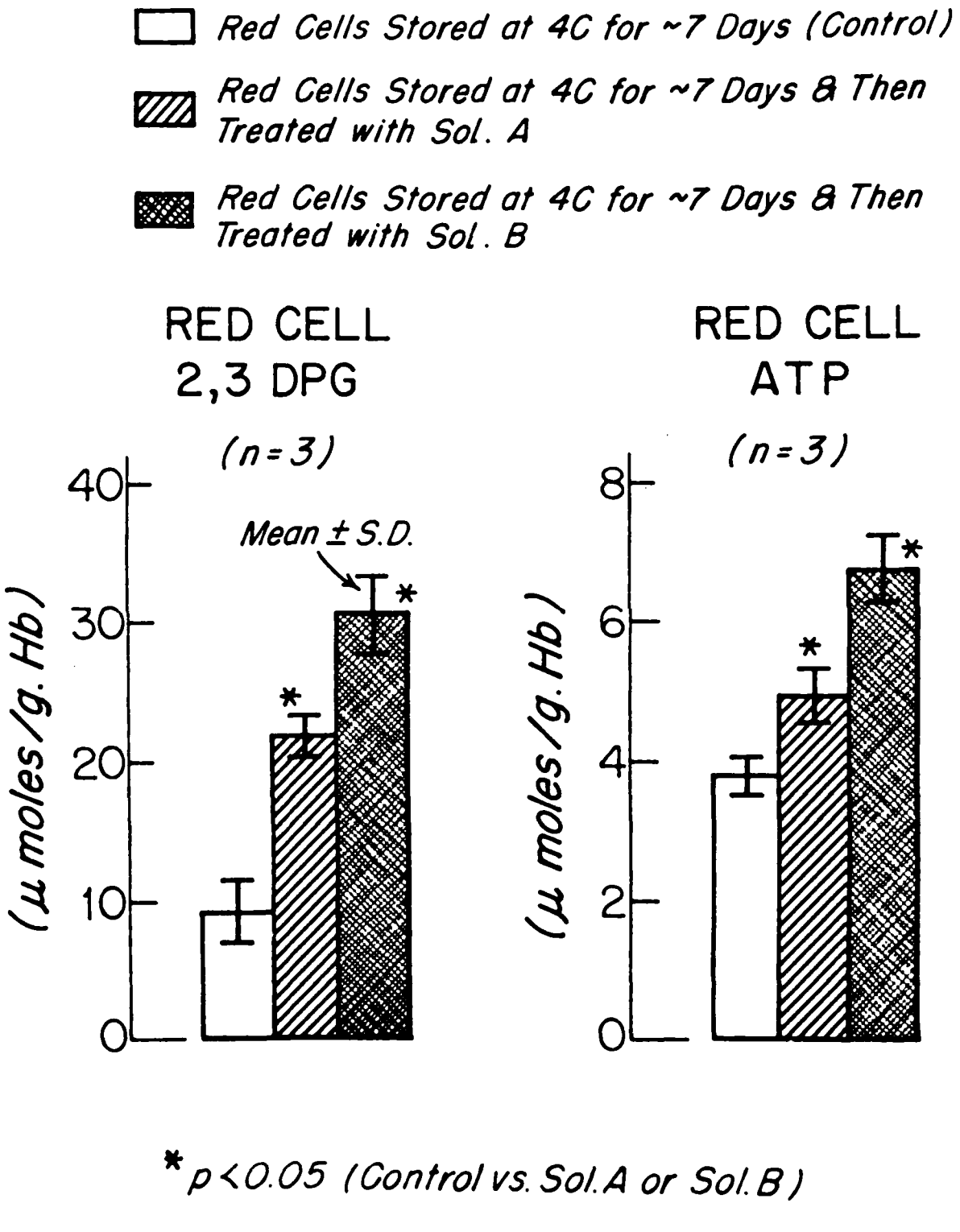
* No. of Observations at each Range of Wedge Pressure

Fig 12 -- In vitro P_{50} decreased significantly 6 hours after surgery for abdominal aneurysm resection in the patients who received nonwashed liquid-stored red cell concentrates ($p < 0.005$) and washed liquid-stored red cell concentrates ($p < 0.001$), but not in patients who received washed previously frozen red cells with 150% of normal 2,3 DPG levels. Intraoperatively body temperature decreased by more than 2.0 C in the three groups of patients ($p < 0.001$). This was followed by falls of in vivo P_{50} in the patients who received nonwashed packed red cells ($p < 0.001$) and washed red cells ($p < 0.05$), while there was no change in the patients who received washed previously frozen red cells with 150% of normal 2,3 DPG. The postoperative rise in body temperature and fall in pH in the three groups of patients was accompanied by a significant elevation of the in vivo P_{50} above preoperative values in the patients who received high 2,3 DPG red cells ($p < 0.001$). (Reproduced with permission from Krausz MM, Dennis RC, Utsunomiya T, et al, Ann Surg 1981;194:620).



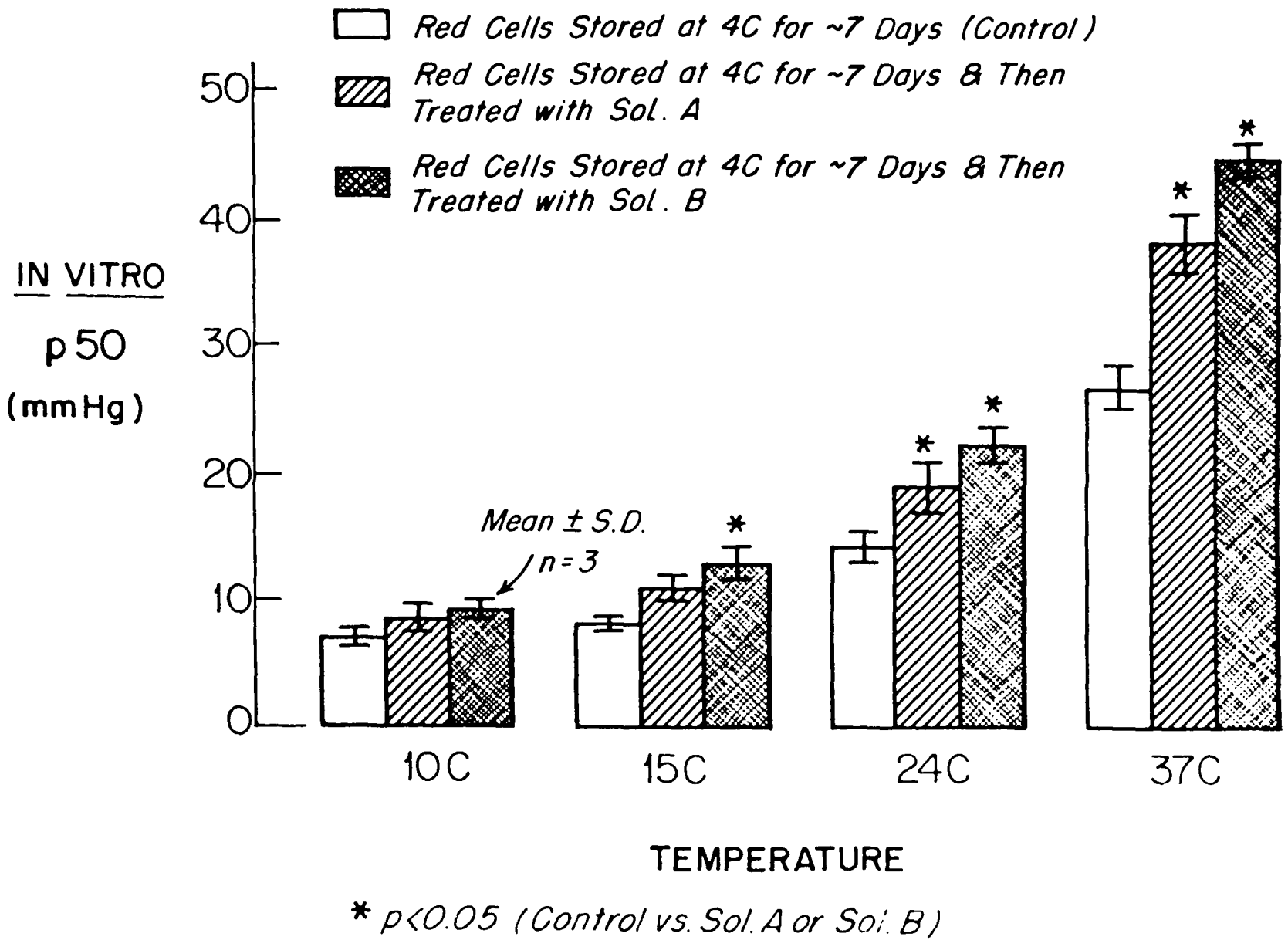
NBRL, Boston 10/80

Fig13 -- Red cell 2,3 DPG and ATP levels in non-rejuvenated and rejuvenated red blood cells after cryopreservation. Three units of red blood cells were stored in CPD at 4 C for about 7 days and then pooled. The 3-unit pool was divided into three equal portions: 1 portion was not rejuvenated (70% normal 2,3 DPG); 1 portion was rejuvenated with PIGPA Solution A (150% normal 2,3 DPG); and the third portion was rejuvenated with PIGPA Solution B (250% normal 2,3 DPG). Each portion was glycerolized to a final concentration of 40% W/V glycerol and then divided into three 130 ml aliquots. Each of the nine aliquots was frozen separately and stored at -80 C, thawed, and washed prior to study. (Reproduced with permission from Valeri CR, Yarnoz M, Vecchione JJ, et al, Ann Thorac Surg 1980;30:531).



* $p < 0.05$ (Control vs. Sol. A or Sol. B)

Fig 14 -- The P_{50} values of washed previously frozen red blood cells with 70% of normal, 150% of normal, or 250% of normal 2,3 DPG, measured at 10 C, 15 C, 24 C, and 37 C. (Reproduced with permission from Valeri CR, Yarnoz M, Vecchione JJ, et al, Ann Thorac Surg 1980;30:531).



* $p<0.05$ (Control vs. Sol. A or Sol. B)

Fig 15 -- The freeze-thaw-wash recovery, ^{51}Cr 24-hour posttransfusion survival, and index of therapeutic effectiveness (ITE) of red blood cells with 80% or 250% of normal 2,3 DPG after small aliquot (10 ml) autotransfusions with or without prior in vitro perfusion in a cardioplegic solution at 15 C. Aliquots from 5 units with 250% of normal 2,3 DPG were autotransfused without prior perfusion. Three other units with 250% of normal 2,3 DPG were perfused in vitro for 3 hours, and an aliquot from each unit was labeled with ^{51}Cr and autotransfused. Two units with 80% of normal 2,3 DPG were perfused in vitro for 3 hours, and an aliquot from each unit was labeled with ^{51}Cr and autotransfused. (Reproduced with permission from Valeri CR, Crit Rev Clin Lab Sci, CRC Press, in press).

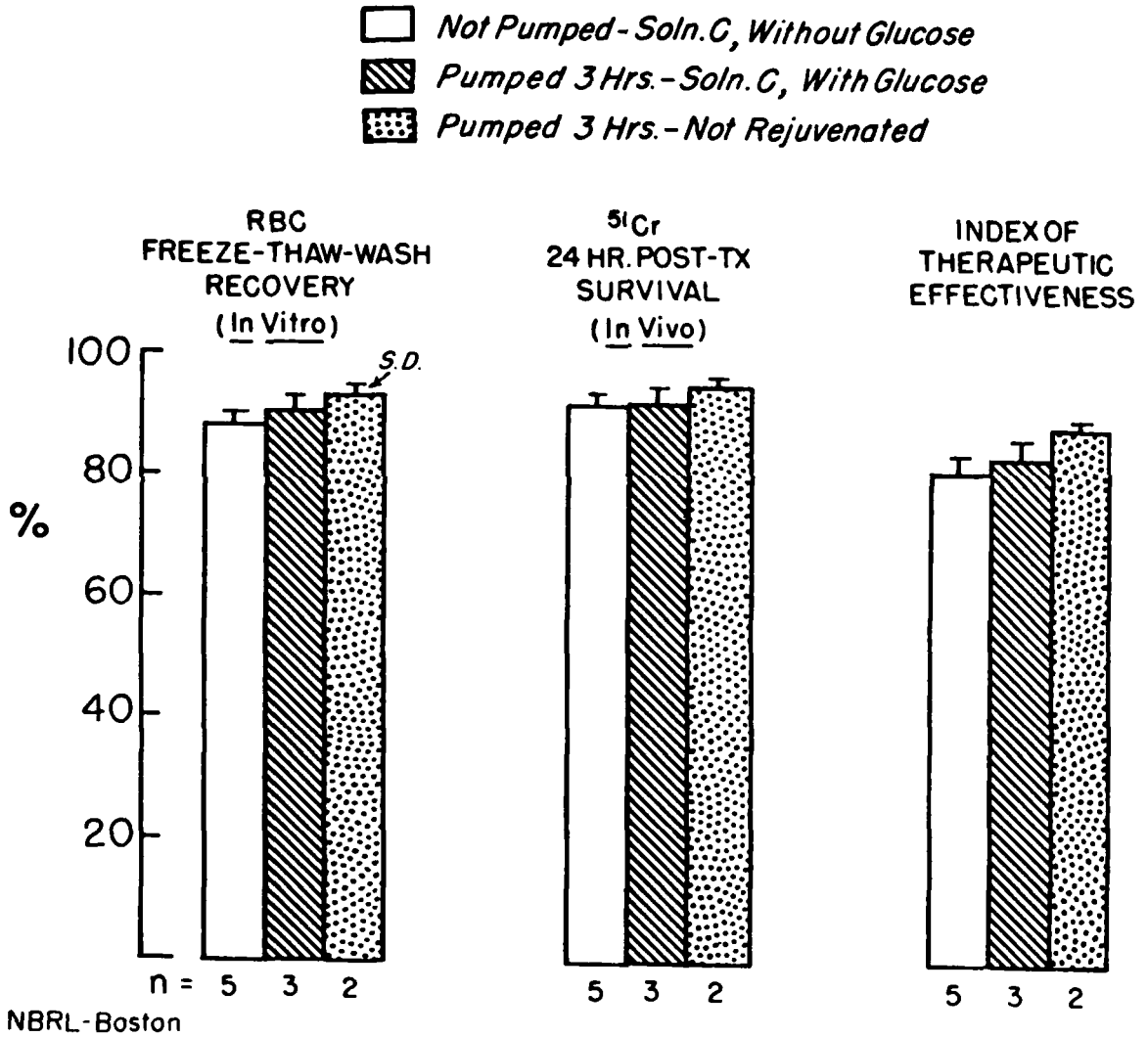

Not Pumped - Soln. C, Without Glucose
Pumped 3 Hrs. - Soln. C, With Glucose
Pumped 3 Hrs. - Not Rejuvenated
RBC FREEZE-THAW-WASH RECOVERY (In Vitro)
51Cr 24 HR. POST-TX SURVIVAL (In Vivo)
INDEX OF THERAPEUTIC EFFECTIVENESS
100
80
60
40
20
%
S.D.
n = 5 3 2
5 3 2
5 3 2
NBRL - Boston

Fig 16 -- Red blood cell 2,3 DPG, ATP, in vitro P_{50}, extracellular osmolality, and sodium ion and potassium ion of red blood cells with 80% of normal or 250% of normal 2,3 DPG perfused in vitro in a cardioplegic solution at 37 C, 22 C or 15 C. (Reproduced with permission from Valeri CR, Crit Rev Clin Lab Sci, CRC Press, in press).

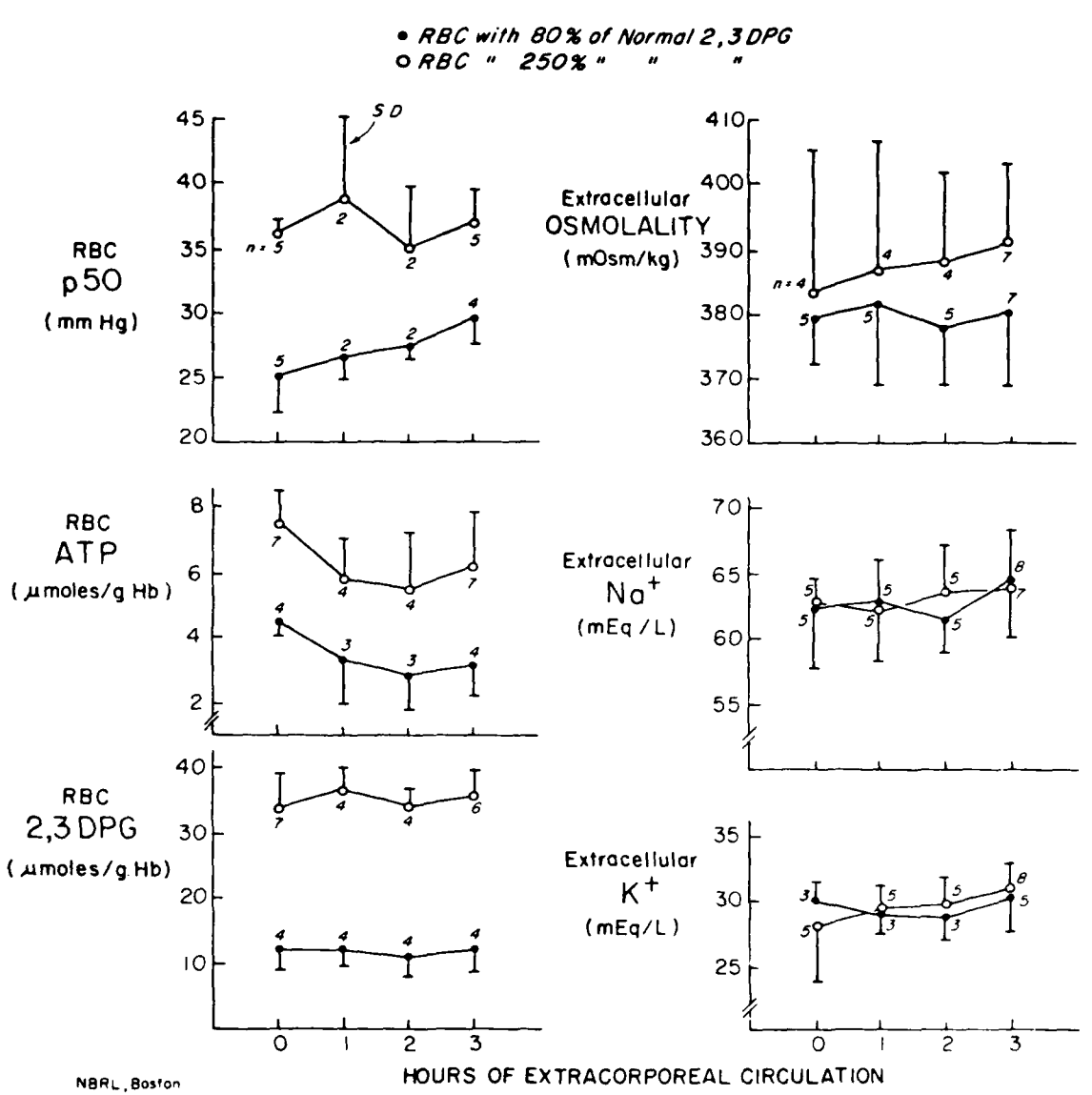
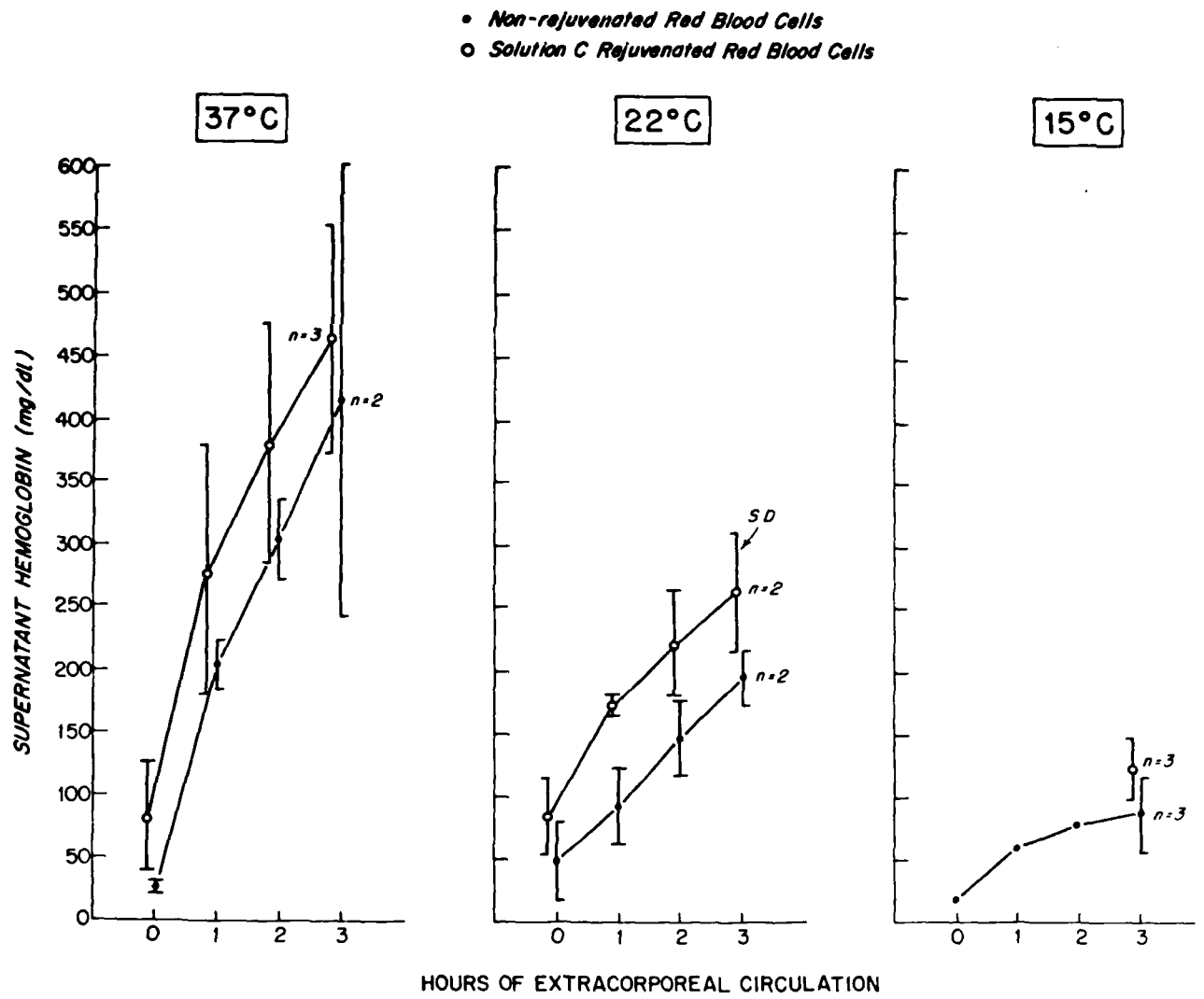
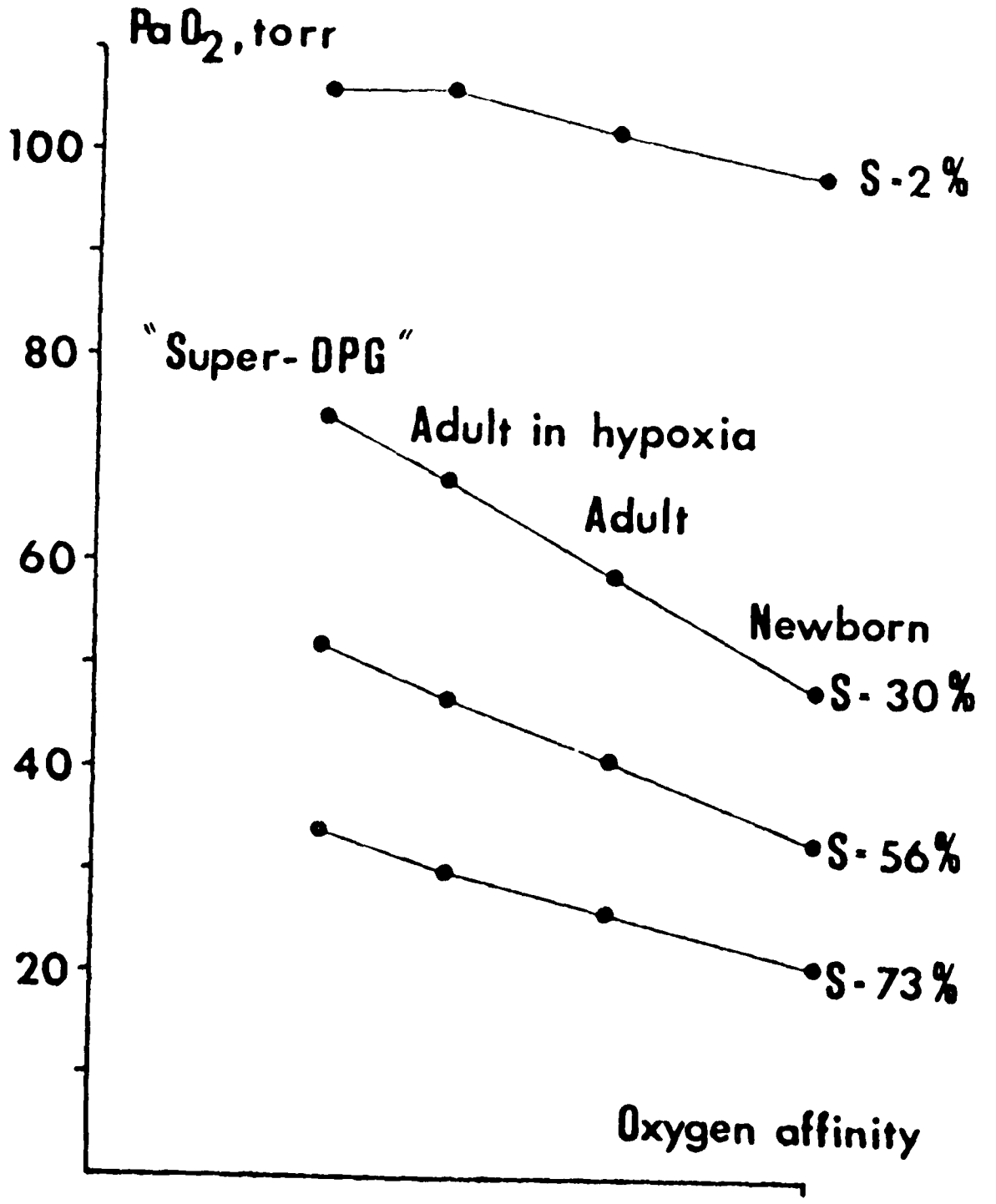

• RBC with 80% of Normal 2,3 DPG
○ RBC " 250% " " "
RBC p50 (mm Hg)
SD
n=5
Extracellular OSMOLALITY (mOsm/kg)
n=4
RBC ATP (μmoles/g Hb)
Extracellular Na+ (mEq/L)
RBC 2,3 DPG (μmoles/g Hb)
Extracellular K+ (mEq/L)
HOURS OF EXTRACORPOREAL CIRCULATION
NBRL, Boston

Fig 17 -- The supernatant hemoglobin of red blood cells with 80% of normal 2,3 DPG or 250% of normal 2,3 DPG perfused in vitro for 3 hours in a cardioplegic solution at 37 C, 22 C and 15 C. (Reproduced with permission from Valeri CR, Crit Rev Clin Lab Sci, CRC Press, in press).



NBRL, Boston Ma, 1/80

Fig 18 -- The relation between PaO_2 and blood oxygen affinity at various levels of right to left shunt (S). The calculations were based on the following data. pH = 7.40, $PaCO_2$ = 40 torr, temperature 37 C, hemoglobin concentration = 15 gm/100 ml. The pulmonary arteriovenous difference of oxygen was 4 ml/100 ml. The oxygen tension at 50% saturation at normal acid-base state and temperature: newborn = 22, adult = 27, adult adapted to hypoxia = 32 and "Super-DPG" blood = 37 torr. (Reproduced with permission from Settergren G, Soderlund S, Eklop AC, Crit Care Med 1982;10:17).


PaO2, torr
100
80
60
40
20
S-2%
"Super-DPG"
Adult in hypoxia
Adult
Newborn
S-30%
S-56%
S-73%
Oxygen affinity

REFERENCES

1. Samet P, Fritts HW Jr, Fishman AP, Cournand A. The blood volume in heart disease. Medicine 1957;36:211-35.

2. Rothschild MA, Bauman A, Yalow RS, Berson SA. Effect of splenomegaly on blood volume. J Appl Physiol 1954;6:701-06.

3. Fudenberg H, Baldini M, Mahoney JP, Dameshek W. The body hematocrit/venous hematocrit ratio and the "splenic reservoir". Blood 1961; 17:71-82.

4. Piomelli S, Nathan DG, Cummins JF, Gardner FH. The relationship of total red cell volume to total body water in octogenarian males. Blood 1962;19:89-98.

5. Loria A, Sanchez-Medal L, Kauffer N, Quintanar E. Relationship between body hematocrit and venous hematocrit in normal, splenomegalic, and anemic states. J Lab Clin Med 1962;60:396-408.

6. Huber H, Lewis SM, Szur L. The influence of anaemia, polycythaemia and splenomegaly on the relationship between venous hematocrit and red cell volume. Brit J Haemat 1964;10:567-75.

7. Bowdler AJ. Blood volume studies in patients with splenomegaly. Transfusion 1970;10:171-81.

8. Hess CE, Ayers CR, Sandusky WR, Carpenter MA, Wetzel RA, Mohler DN. Mechanisms of dilutional anemia in massive splenomegaly. Blood 1976; 47:629-44.

9. Blumgart HL, Altschule MD. Clinical significance of cardiac and respiratory adjustments in chronic anemia. Blood 1948;3:329-48.

10. Duke M, Herbert VD, Abelmann WH. Hemodynamic effects of blood transfusion in chronic anemia. N Engl J Med 1964;271:975-80.

11. Bhatia ML, Manchanda SC, Roy SB. Coronary haemodynamic studies in chronic severe anaemia. Brit Heart J 1969;31:365-74.

12. Finch CA, Lenfant C. Oxygen transport in man. N Engl J Med 1972; 286:407-15.

13. Valeri CR, Zaroulis CG, Fortier NL. Peripheral red cells as a functional biopsy to determine tissue oxygen tension. In: IV Annual Alfred Benzon Symposium. Copenhagen: Munksgaard, 1971:650-75.

14. Benesch R, Benesch RE. The effect of organic phosphates from human erythrocytes on the allosteric properties of hemoglobin. Biochem Biophys Res Commun 1967;26:162-67.

15. Benesch R, Benesch RE, Yu CI. Reciprocal binding of oxygen and diphosphoglycerate by human hemoglobin. Proc Nat Acad Sci USA 1968; 59:526-32.

16. Benesch R, Benesch RE. Intracellular organic phosphates as regulators of oxygen release by haemoglobin. Nature (London) 1969;221:618-22.

17. Chanutin A, Curnish RR. Effect of organic and inorganic phosphates on the oxygen equilibrium of human erythrocytes. Arch Biochem 1967; 121:96-102.

18. Chanutin A, Hermann E. The interaction of organic and inorganic phosphates with hemoglobin. Arch Biochem 1969;131:180-84.

19. Strauss MB, Fox HJ. Anemia and water retention. Amer J Med Sci 1940;200:454-62.

20. Valeri CR, Altschule MD. The Hypovolemic Anemia of Trauma. The Missing Blood Syndrome. Boca Raton: CRC Press, Inc., 1981.

21. Cohnheim J, Lichtheim L. Ueber hydrämie und hydrämisches oedem. Archiv für pathologische Anatomie 1877;69:106-43.

22. Caughey JL, Cournand A, Chamberlain FL. Intravenous saline infusion as a clinical test for right-heart and left-heart failure. Trans Assoc Amer Physicians 1937;52:250-58.

23. Dahn MS, Lucas CE, Ledgerwood AM, Higgins RF. Negative inotropic effect of albumin resuscitation for shock. Surgery 1979;86:235-41.

24. Mayer JE, Kersten TE, Humphrey EW. Effects of transfusion of emboli and aged plasma on pulmonary capillary permeability. J Thorac Cardiovasc Surg 1981;82:358-64.

25. Valeri CR. Blood Banking and the Use of Frozen Blood Products. Boca Raton: CRC Press, Inc., 1976.

26. Holsinger JW, Salhany JM, Eliot RS. Physiologic observations on the effect of impaired blood oxygen release on the myocardium. Adv Cardiol 1973;9:81-88.

27. DeAngelis J, Chang P, Kaplan JH, et al. Hemodynamic changes during prostatectomy in cardiac patients. Crit Care Med 1982;10:38-40.

28. Lucas CE, Weaver D, Higgins RF, Ledgerwood AM, Johnson SD, Bouwman DL. Effects of albumin versus non-albumin resuscitation on plasma volume and renal excretory function. J Trauma 1978;18:564-70.

29. Lucas CE, Ledgerwood AM, Higgins RF. Impaired salt and water excretion after albumin resuscitation for hypovolemic shock. Surgery 1979; 86:544-49.

30. Yhap EO, Wright CB, Popovic NA, Alix EC. Decreased oxygen uptake with stored blood in the isolated hindlimb. J Appl Physiol 1975;38:882-85.

31. Ross BK, Hlastala MP. Increased hemoglobin-oxygen affinity does not decrease skeletal muscle oxygen consumption. J Appl Physiol: Respirat Environ Exercise Physiol 1981;51:864-70.

32. Valtis DJ, Kennedy AC. The causes and prevention of defective function of stored red blood cells after transfusion. Glasgow Med J 1953; 34:521-43.

33. Valtis DJ, Kennedy AC. Defective gas-transport function of stored red blood cells. Lancet 1954;1:119-25.

34. Valeri CR. Viability and function of preserved red cells. N Engl J Med 1971;284:81-88.

35. Reiss RF, Katz AJ. Microaggregate content and flow rates of packed red blood cells. Transfusion 1977;17:484-88.

36. Umlas J. Washed hyperpacked frozen and shelf red blood cells. Transfusion 1975;15:111-15.

37. Marshall BE, Wurzel HA, Neufeld GR, et al. Effects of Fenwal 4C2423 transfusion microfilter on microaggregates and other constituents of stored blood. Transfusion 1978;18:38-45.

38. Cullen DJ, Kunsman J, Caldera D, Dennis RC, Valeri CR. Comparative evaluation of new fine-screen filters: Effects on blood flow rate and microaggregate removal. Anesthesiology 1980;53:3-8.

39. Demling RH, Manohar M, Will JA. Response of the pulmonary microcirculation to fluid loading after hemorrhagic shock and resuscitation. Surgery 1980;87:552-59.

40. Hauser CJ, Shoemaker WC, Turpin I, Goldberg SJ. Oxygen transport responses to colloids and crystalloids in critically ill surgical patients. Surg Gynecol Obstet 1980;150:811-16.

41. Moss GS, Lowe RJ, Jilek J, Levine HD. Colloid or crystalloid in the resuscitation of hemorrhagic shock: A controlled clinical trial. Surgery 1981;89:434-38.

42. Peters RM, Hargens AR. Protein vs electrolytes and all of the Starling forces. Arch Surg 1981;116:1293-98.

43. Sheldon GF, Watkins GM, Glover JL, Greenburg AG, Friedman BA. Panel: Present use of blood and blood products. J Trauma 1981;21:1005-12.

44. Shackford SR, Virgilio RW, Peters RM. Whole blood versus packed-cell transfusions. A physiologic comparison. Ann Surg 1981;193:337-40.

45. Puri VK, Paidipaty B, White L. Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. Crit Care Med 1981;9:833-37.

46. Johnson SD, Lucas CE, Gerrick SJ, Ledgerwood AM, Higgins RF. Altered coagulation after albumin supplements for treatment of oligemic shock. Arch Surg 1979;114:379-83.

47. Lucas CE, Bouwman DL, Ledgerwood AM, Higgins R. Differential serum protein changes following supplemental albumin resuscitation for hypovolemic shock. J Trauma 1980;20:47-51.

48. Lucas CE, Ledgerwood AM. Clinical significance of altered coagulation tests after massive transfusion for trauma. Amer Surgeon 1981;47:125-30.

49. Annest SJ, Scovill WA, Blumenstock FA, et al. Increased creatinine clearance following cryoprecipitate infusion in trauma and surgical patients with decreased renal function. J Trauma 1980;20:726-32.

50. Lucas CE, Ledgerwood AM, Higgins RF. Glomerulotubular sodium dynamics after supplemental albumin resuscitation. Amer Surgeon 1981;47:204-07.

51. Faillace DF, Ledgerwood AM, Lucas CE, Kithier K, Higgins RF. Immunoglobulin changes after varied resuscitation regimens. J Trauma 1982; 22:1-5.

52. O'Connor PC, Erskine JG, Pringle TH. Pulmonary oedema after transfusion with fresh frozen plasma. Brit Med J 1981;282:379-80.

53. Finkelstein SN, Sapolsky HM. Controlling post-transfusion hepatitis: A proposal to publicize hepatitis rates of transfusion facilities. Amer J Law Med 1979;5:1-9.

54. Tabor E, Gerety RJ. Non-A, non-B hepatitis: New findings and prospects for prevention. Transfusion 1979;19:669-74.

55. Tabor E, Hoofnagle JH, Smallwood LA, et al. Studies of donors who transmit posttransfusion hepatitis. Transfusion 1979;19:725-31.

56. Holland PV, Bancroft W, Zimmerman H. Post-transfusion viral hepatitis and the TTVS. N Engl J Med 1981;304:1033-35.

57. Valeri CR. Oxygen transport function of preserved red cells. In: Garby L, ed. Clinics in Haematology, Anaemia and Hypoxia, Vol. 3, No. 3, October 1974, pp 649-88.

58. Rosenthal A, Mentzer WC, Eisenstein EB, Nathan DG, Nelson NM, Madas AS. The role of red blood cell phosphates in adaptation to congenital heart disease. Pediatrics 1971;47:537-47.

59. Oski FA, Gottlieb AJ, Delivoria-Papadopoulos M, Miller WW. Red cell 2,3 diphosphoglycerate levels in subjects with chronic hypoxemia. N Engl J Med 1969;280:1165-66.

60. Metcalfe J, Dhindsa DS, Edwards MJ, Mourdjinis A. Decreased affinity of blood for oxygen in patients with low output heart failure. Circ Res 1969;25:47-51.

61. Valeri CR. Optimal use of blood products in the treatment of hemorrhagic shock. Surg Rounds 1981;4:38-46.

62. Högman CF, Åkerblom O, Arturson G, deVerdier C, Kreuger A, Westman M. Experience with new preservatives: summary of the experiences in Sweden. In: Greenwalt TJ, Jamieson GA, eds. The Human Red Cell In Vitro. New York: Grune & Stratton, 1974:217-54.

63. Valeri CR. Use of rejuvenation solutions in blood preservation. Crit Rev Clin Lab Sci. In press.

64. Valeri CR, Zaroulis CG. Rejuvenation and freezing of outdated stored human red cells. N Engl J Med 1972;287:1307-13.

65. Valeri CR. Metabolic regeneration of depleted erythrocytes and their frozen storage. In: Greenwalt TJ, Jamieson GA, eds. The Human Red Cell In Vitro. New York: Grune & Stratton, 1974:281-321.

66. Valeri CR, Zaroulis CG, Vecchione JJ, et al. Therapeutic effectiveness and safety of outdated human red blood cells rejuvenated to improve oxygen transport function, frozen for about 1.5 years at -80 C, washed, and stored at 4 C for 24 hours prior to rapid infusion. Transfusion 1980;20:263-76.

67. Valeri CR, Zaroulis CG, Vecchione JJ, et al. Therapeutic effectiveness and safety of outdated human red blood cells rejuvenated to restore oxygen transport function to normal, frozen for 3 to 4 years at -80 C, washed, and stored at 4 C for 24 hours prior to rapid infusion. Transfusion 1980;20:159-70.

68. Valeri CR, Valeri DA, Gray A, Melaragno A, Dennis RC, Emerson CP. Red blood cell concentrates stored at 4 C for 35 days in CPDA-1, CPDA-2, or CPDA-3 anticoagulant-preservative, biochemically modified, and frozen and stored in the polyvinylchloride plastic primary collection bag with 40% W/V glycerol at -80 C. Transfusion (in press).

69. Valeri CR. Factors influencing the 24-hour posttransfusion survival and the oxygen transport function of previously frozen red cells preserved with 40 per cent W/V glycerol and frozen at -80 C. Transfusion 1974;14:1-15.

70. Valeri CR. Simplification of the methods for adding and removing glycerol during freeze-preservation of human red blood cells with the high or low glycerol methods: Biochemical modification prior to freezing. Transfusion 1975;15:195-218.

71. International Forum. What is the clinical importance of alterations of the hemoglobin oxygen affinity in preserved blood--especially as produced by variations of red cell 2,3 DPG content? Vox Sang 1978; 34:111-27.

72. Collins JA, Stechenberg L. The effects of the concentration and function of hemoglobin on the survival of rats after hemorrhage. Surgery 1979;85:412-18.

73. Malmberg PO, Hlastala MP, Woodson RD. Effect of increased blood-oxygen transport in hemorrhagic shock. J Appl Physiol: Respirat Environ Exercise Physiol 1979;47:889-95.

74. Woodson RD. Functional consequences of altered blood oxygen affinity. Acta Biol Med Ger (in press).

75. Woodson RD, Auerbach S. Effect of increased oxygen affinity and anemia on cardiac output and its distribution. J Appl Physiol: Respirat Environ Exercise Physiol (in press).

76. Woodson RD, Costello DJ, Gilboe DD. Increased blood O_2 affinity decreases brain O_2 consumption. Clin Res 1979;27:405A.

77. Woodson RD, Fitzpatrick JH Jr, Costello DJ, Gilboe DD. Increased blood oxygen affinity decreases canine brain oxygen consumption. J Lab Clin Med (in press).

78. Rice CL, Herman CM, Kiesow LA, Homer LD, John DA. Benefits from improved oxygen delivery of blood in shock therapy. J Surg Res 1975; 19:193-98.

79. Moores WY, Walliford DC, Crum JD, Neville JR, Weiskopf RB, Dembitsky WP. Alteration of myocardial function resulting from changes in hemoglobin oxygen affinity. Circulation 1978;58:225 Suppl II.

80. Apstein CS, Dennis R, Vecchione JJ, Frazer J, Valeri CR. Improved cardiac function during coronary perfusion with low oxyhemoglobin affinity human red blood cells. Amer J Cardiol 1980;45:479.

81. Pantely GA, Oyama AA, Metcalfe J, Lawson MS, Welch JE. Improvement in the relationship between flow to ischemic myocardium and the extent of necrosis with glycolytic intermediates that decrease blood oxygen affinity in dogs. Circ Res 1981;49:395-404.

82. Dennis RC, Hechtman HB, Berger RL, Vito L, Weisel RD, Valeri CR. Transfusion of 2,3 DPG-enriched red blood cells to improve cardiac function. Ann Thorac Surg 1978;26:19-26.

83. Krausz MM, Dennis RC, Utsunomiya T, et al. Cardiopulmonary function following transfusion of three red blood cell products in elective abdominal aortic aneurysmectomy. Ann Surg 1981;194:616-24.

84. Jalonen J, Rajamaki A, Laaksonen V, Inberg MV. The effects of elevated red blood cell 2,3-diphosphoglycerate concentration on myocardial oxygenation and metabolism during cardiopulmonary bypass. J Thorac Cardiovasc Surg 1980;79:748-54.

85. Kelman GR, Nunns JF. Nomograms for correction of blood PO_2, pH and base excess for time and temperature. J Appl Physiol 1966;21:1484-90.

86. Bergman NA. Temperature coefficients PCO_2 and PO_2 in blood with varying acid base states. J Appl Physiol 1968;24:225-32.

87. Benesch RE, Benesch R, Yu CI. The oxygenation of hemoglobin in the presence of 2,3-diphosphoglycerate. Effect of temperature, pH, ionic strength and hemoglobin concentration. Biochem 1969;8:2567-71.

88. Hlastala MP, Woodson RD, Wranne R. Influence of temperature on hemoglobin ligand interaction in whole blood. J Appl Physiol 1977;43: 545-50.

89. Riley JB, Snyder JE. A technique for extrapolation of analyzed values of blood pH, pCO_2 and pO_2 to hypothermic states. Am Sect 1977;9:86-94.

90. Valeri CR, Yarnoz M, Vecchione JJ, et al. Improved oxygen delivery to the myocardium during hypothermia by perfusion with 2,3 DPG-enriched red blood cells. Ann Thorac Surg 1980;30:527-35.

91. Valeri CR, Vecchione JJ, Pivacek LE, Lowrie GB, Austin RM, Emerson CP. Viability and function of outdated human red blood cells after biochemical modification to improve oxygen transport function, freezing, thawing, washing, postthaw storage at 4 C, perfusion in vitro through a bubble oxygenator, and autotransfusion. Transfusion 1980;20:39-46.

92. Follette DM, Mulder DG, Maloney JV Jr, Buckberg GD. Advantages of blood cardioplegia over continuous coronary perfusion or intermittent ischemia - an experimental and clinical study. J Thorac Cardiovasc Surg 1978;76:604-19.

93. Follette DM, Steed DL, Foglia R, Fey K, Buckberg GD. Advantages of intermittent blood cardioplegia over intermittent ischemia during prolonged hypothermic aortic clamping. Circulation 1978;I-200-09.

94. Gay wA, Ebert PA. Functional, metabolic and morphologic effect of potassium-induced cardioplegia. Surgery 1973;74:284-90.

95. Gharagozloo BA, Bulkley BH, Hutchins GM, et al. Potassium-induced cardioplegia during normothermic cardiac arrest. J Thorac Cardiovasc Surg 1979;77:602-07.

96. Goldstein SM, Nelson RL, McConnell DH, Buckberg GD. Cardiac arrest after aortic cross clamping. Effects of conventional ischemic vs. pharmacologic techniques on myocardial supply/demand balance. Surg Forum 1975;26:271-73.

97. Harlan BJ, Ross D, MacManus O, Knight R, Luber J, Starr A. Cardioplegic solutions for myocardial preservation. Analyses of hypothermic arrest, potassium arrest, and procaine arrest. Circulation 1978; 58:I-114-18.

98. Roe BB, Hutchinson JC, Fishman NH, Ullyot DJ, Smith DL. Myocardial protection with cold, ischemic potassium-induced cardioplegia. J Thorac Cardiovasc Surg 1977;73:366-74.

99. Weisel RD, Goldman BS, Lipton IH, Teasdale S, Mickle D, Baird RJ. Optimal myocardial protection. Surgery 1978;84:812-21.

100. Wright RN, Levitsky S, Holland C, Feinberg H. Beneficial effects of potassium cardioplegia during intermittent aortic cross-clamping and reperfusion. J Surg Res 1978;24:201-09.

101. Buckberg GD. A proposed "solution" to the cardioplegic controversy. J Thorac Cardiovasc Surg 1979;77:803-15.

102. Thews G. Implications to physiology and pathology of oxygen diffusion at the capillary level. In: Shade JP, McMenemy WH, eds. Selective vulnerability of the brain. Oxford: Blackwell Scientific, 1963:27-35.

103. Turek Z, Kreuzer F, Hoofd LJC. Advantage or disadvantage of a decrease of blood oxygen affinity for tissue oxygen supply at hypoxia. A theoretical study comparing man and rat. Pflügers Arch 1973;342:185-97.

104. Bakker JC, Gortmaker GC, Vrolijk ACM, Offerijns FGJ. The influence of the position of the oxygen dissociation curve on oxygen-dependent functions of the isolated perfused rat liver. I. Studies at different levels of hypoxic hypoxia. Pflügers Arch 1976;362:21-31.

105. Bakker JC, Gortmaker GC, Offerijns FGJ. The influence of the position of the oxygen dissociation curve on oxygen-dependent functions of the isolated perfused rat liver. Pflügers Arch 1976;366:45-52.

106. Aberman A. Crossover PO_2, a measure of the variable effect of increased P_{50} on mixed venous PO_2. Amer Rev Resp Dis 1977;115:173-75.

107. Frans A, Turek Z, Yokota H, Kreuzer F. Effect of variations in blood hydrogen ion concentration on pulmonary gas exchange of artificially ventilated dogs. Pflügers Arch 1979;380:35-39.

108. Rossoff L, Zeldin R, Hew E, Aberman A. Changes in blood P_{50}. Effects on oxygen delivery when arterial hypoxemia is due to shunting. Chest 1980;77:142-46.

109. Turek Z, Kreuzer F. Effect of shifts of the O_2 dissociation curve upon alveolar-arterial O_2 gradients in computer models of the lung with ventilation-perfusion mismatching. Resp Physiol 1981;45:133-39.

110. Litwin SB, Skogen WF, Laver MB. Effect of sodium ortho-iodobenzoate on oxygen transport and erythropoiesis in hypoxemic dogs with a right-to-left cardiac shunt. Surgery 1977;81:633-39.

111. Litwin SB, Rosenthal A, Skogen WF, Laver MB. Long-term studies of hemoglobin-oxygen affinity in hypoxemic dogs with a right-to-left cardiac shunt. J Surg Res 1980;28:118-23.

112. Settergren G, Soderlund S, Eklof AC. Blood oxygen tension and oxyhemoglobin saturation in hypoxemia due to right to left shunt or low inspired oxygen concentration. Crit Care Med 1982;10:15-18.

113. Proctor HJ, Parker JC, Fry J, Johnson G Jr. Treatment of severe hypoxia with red cells high in 2,3 diphosphoglycerate. J Trauma 1973;13:340-45.

114. Proctor HJ, Fry J. Increased 2,3 DPG: usefulness during hypoxia. J Surg Res 1974;16:569-74.

115. Proctor HJ, Fry J, Lennon D. Pharmacologic increases in erythrocyte 2,3 diphosphoglycerate for therapeutic benefit. J Trauma 1974;14: 127-33.

116. Roche JK, Stengle JM. Open-heart surgery and the demand for blood. J Amer Med Assn 1973;225:1516-21.

117. Yeh T Jr, Shelton L, Yeh TJ. Blood loss and bank blood requirement in coronary bypass surgery. Ann Thorac Surg 1978;26:11-16.

118. Salzman EW. Blood platelets and extracorporeal circulation. Transfusion 1963;3:274-77.

119. Woods JE, Kirklin JW, Owen CA Jr, Thompson JH Jr, Taswell HF. Effect of bypass surgery on coagulation-sensitive clotting factors. Mayo Clin Proc 1967;42:724-35.

120. Gralnick HR, Fischer RD. The hemostatic response to open-heart operations. J Thorac Cardiovasc Surg 1971;61:909-15.

121. Signori EE, Penner JA, Kahn DR. Coagulation defects and bleeding in open-heart surgery. Ann Thorac Surg 1969;8:521-29.

122. Bachmann F, McKenna R, Cole ER, Najafi H. The hemostatic mechanism after open-heart surgery. I. Studies on plasma coagulation factors and fibrinolysis in 512 patients after extracorporeal circulation. J Thorac Cardiovasc Surg 1975;70:76-85.

123. Bick RL. Alterations of hemostasis associated with cardiopulmonary bypass: Pathophysiology, prevention, diagnosis, and management. Semin Thromb Hemostasis 1976;3:59-82.

124. Davey FR, Parker FB. Delayed hemostatic changes following cardiopulmonary bypass. Amer J Med Sci 1976;271:171-78.

125. Mason RG, Mohammad SF, Chuang HYK, Richardson PD. The adhesion of platelets to subendothelium, collagen and artificial surfaces. Semin Thromb Hemostasis 1976;3:98-116.

126. Umlas J. Fibrinolysis and disseminated intravascular coagulation in open heart surgery. Transfusion 1976;16:460-63.

127. Moriau M, Masure R, Hurlet A, et al. Haemostasis disorders in open heart surgery with extracorporeal circulation. Vox Sang 1977;32:41-51.

128. Foster ED, Spector JI, Talarico L, et al. Polybrene neutralization as a means of monitoring heparin therapy for extracorporeal circulation. Ann Thorac Surg 1977;23:514-19.

129. Abbott WM, Warnock DF, Austen WG. The relationship of heparin source to the incidence of delayed hemorrhage. J Surg Res 1977;22:593-97.

130. Marengo-Rowe AJ, Lambert CJ, Leveson JE, et al. The evaluation of hemorrhage in cardiac patients who have undergone extracorporeal circulation. Transfusion 1979;19:426-33.

131. Milam JD, Austin SF, Martin RF, Keats AS, Cooley DA. Alteration of coagulation and selected clinical chemistry parameters in patients undergoing open heart surgery without transfusions. Amer J Clin Pathol 1981;76:155-62.

132. Awad JA, Fortin B, Bernier JP, Leclerc R. Red blood cell survival after perfusion with a membrane oxygenator. Amer J Surg 1974;127: 535-40.

133. Tabak C, Eugene J, Stemmer EA. Erythrocyte survival following extracorporeal circulation. A question of membrane versus bubble oxygenator. J Thorac Cardiovasc Surg 1981;81:30-33.

134. Wallace HW, Brooks H, Stein TP, Zimmerman NJ. The contribution of anticoagulants to platelet dysfunction with extracorporeal circulation. J Thorac Cardiovasc Surg 1976;72:735-41.

135. Perkins HA, Rolfs MR, Hymas PG. Platelet loss on exposure of citrated blood to various foreign surfaces. Transfusion 1975;15:87-95.

136. Heiden D, Mielke CH Jr, Rodvien R. Impairment by heparin of primary haemostasis and platelet (^{14}C) 5-hydroxytryptamine release. Brit J Haematol 1977;36:427-36.

137. Harker LA, Malpass TW, Branson HE, Hessel EA II, Slichter SJ. Mechanism of abnormal bleeding in patients undergoing cardiopulmonary bypass: Acquired transient platelet dysfunction associated with selective -granule release. Blood 1980;56:824-34.

138. Pivorun EB, Sinnamon WB. Blood coagulation studies in normothermic, hibernating, and aroused Spermophilus franklini. Cryobiology 1981; 18:515-20.

139. Dalsgaard-Nielsen J, Risbo A, Simmelkjaer P, Gormsen J. Impaired platelet aggregation and increased bleeding time during general anaesthesia with halothane. Brit J Anaesth 1981;53:1039-42.

140. Kitchen L, Erichson RB, Sideropoulos H. Effect of drug-induced platelet dysfunction on surgical bleeding. Amer J Surg 1982;143:215-17.

141. Gollub S, Ulin AW. Heparin-induced thrombocytopenia in man. J Lab Clin Med 1962;59:430-35.

142. Babcock RB, Dumper CW, Scharfman WB. Heparin-induced immune thrombocytopenia. N Engl J Med 1976;295:237-41.

143. Wessler S, Gitel SN. Heparin: New concepts relevant to clinical use. Blood 1979;53:525-44.

144. Kapsch D, Silver D. Heparin-induced thrombocytopenia with thrombosis and hemorrhage. Arch Surg 1981;116:1423-27.

145. Lubin J, Greenberg JJ, Yahr WZ, Haynes JL, Paul E. The use of autologous blood in open-heart surgery. Transfusion 1974;14:602-07.

146. Duncan SE, Klebanoff G, Rogers W. A clinical experience with intraoperative autotransfusion. Ann Surg 1974;180:296-304.

147. Silver H. Banked and fresh autologous blood in cardiopulmonary bypass surgery. Transfusion 1975;15:600-03.

148. Kaplan JA, Cannarella C, Jones EL, Kutner MH, Hatcher CR Jr, Dunbar RW. Autologous blood transfusion during cardiac surgery. A re-evaluation of three methods. J Thorac Cardiovasc Surg 1977;74:4-10.

149. Schaff HV, Hauer J, Gardner TJ, et al. Routine use of autotransfusion following cardiac surgery: Experience in 700 patients. Ann Thorac Surg 1979;27:493-99.

150. Thurer RL, Lytle BW, Cosgrove DM, Loop FD. Autotransfusion following cardiac operations: A randomized, prospective study. Ann Thorac Surg 1979;27:500-07.

151. Cordell AR, Lavender SW. An appraisal of blood salvage techniques in vascular and cardiac operations. Ann Thorac Surg 1981;31:421-25.

152. Kingsley JR, Valeri CR, Peters H, Cole BC, Fouty WJ, Herman CM. Citrate anticoagulation and on-line cell washing in intraoperative autotransfusion in the baboon. Surg Forum 1973;24:258-60.

153. Varat MA, Adolph RJ, Fowler NO. Cardiovascular effects of anemia. Amer Heart J 1972·83:415-26.

154. Yoshikawa H, Powell WJ, Bland JHL, Lowenstein E. Effect of acute anemia on experimental myocardial ischemia. Amer J Cardiol 1973; 32:670-78.

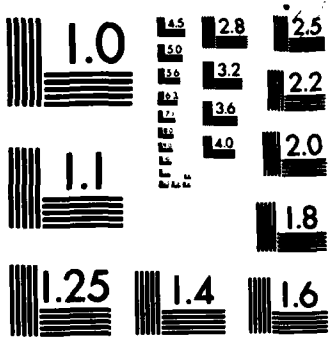
155. Buckberg G, Brazier J. Coronary blood flow and cardiac function during hemodilution. In: Messmer K, Schmid-Schönbein H, eds. Intentional Hemodilution. New York: Karger, 1975, Biblthca haemat., No. 41, 173-189.

156. Sunder-Plassmann L, Kessler M, Jesch F, Dieterle R, Messmer K. Acute normovolemic hemodilution. Changes in tissue oxygen supply and hemoglobin-oxygen affinity. In: Messmer K, Schmid-Schonbein H, eds. Intentional Hemodilution. New York: Karger, 1975, Biblthca haemat., No. 41, 44-53.

157. Kessler M, Messmer K. Tissue oxygenation during hemodilution. In: Messmer K, Schmid-Schönbein H, eds. Intentional Hemodilution. New York: Karger, 1975, Biblthca haemat., No. 41, 16-33.

AD-A140 403 BLOOD TRANSFUSION THERAPY IN PATIENTS WITH HEART DISEASE(U) BOSTON UNIV MA SCHOOL OF MEDICINE C R VALERI 07 APR 82 BUSM-82-05 N00014-79-C-0168 2/2

UNCLASSIFIED F/G 6/5 NL



MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A

158. Laks H, Handin RI, Martin V, Pilon RN. The effects of acute normovolemic hemodilution on coagulation and blood utilization in major surgery. J Surg Res 1976;20:225-30.

159. Wright CJ. The effects of severe progressive hemodilution on regional blood flow and oxygen consumption. Surgery 1976;79:229-305.

160. Messmer K, Kessler M, Sunder-Plassmann L. Hemorheologic effects of intentional hemodilution. In: Current Topics in Critical Care Medicine. Basel: Karger, 1976, 130-39.

161. Geha AS. Coronary and cardiovascular dynamics and oxygen availability during acute normovolemic anemia. Surgery 1976;80:47-53.

162. Hagl S, Heimisch W, Meisner H, Erben R, Baum M, Mendler N. The effect of hemodilution on regional myocardial function in the presence of coronary stenosis. Basic Res Cardiol 1977;72:344-64.

163. Gustafsson L, Appelgren L, Myrvold HE. Flow improvement after defibrinogenation. J Surg Res 1977;22:113-17.

164. Lucas SK, Kanter KR, Schaff HV, Elmer EB, Glower DD, Gardner TJ. Reduced oxygen extraction during reperfusion: a consequence of global ischemic arrest. J Surg Res 1980;28:434-41.

165. LeVeen HH, Ip M, Ahmed N, et al. Lowering blood viscosity to overcome vascular resistance. Surg Gynecol Obstet 1980;150:139-49.

166. Milligan DW, Tooke JE, Davies JA. Effect of venesection on calf blood flow in polycythaemia. Brit Med J 1982;284:619-20.

167. Rose D, Coutsoftides T. Intraoperative normovolemic hemodilution. J Surg Res 1981;31:375-81.

168. Zubiate P, Kay JH, Mendez AM, Krohn BG, Hochman R, Dunne EF. Coronary artery surgery, a new technique with use of little blood, if any. J Thorac Cardiovasc Surg 1974;68:263-67.

169. Laks H, Pilon R, Anderson W, MacCallum JR, O'Connor NE. Intraoperative prebleeding in man: Effect of colloid hemodilution on blood volume, lung water, hemodynamics and oxygen transport. Surgery 1975;78:130-37.

170. Cohn LH, Fosberg AM, Anderson WP, Collins JJ. The effects of phlebotomy, hemodilution and autologous transfusion on systemic oxygenation and whole blood utilization in open heart surgery. Chest 1975;63:283-87.

171. Addonizio VP Jr, Macarak EJ, Nicolaou KC, Edmunds LH Jr, Colman RW. Effects of prostacyclin and albumin on platelet loss during in vitro simulation of extracorporeal circulation. Blood 1979;53:1033-42.

172. Leaf A, Willerson JT, Powell JW Jr, Guiney TE, Stark JJ, Sanders CA. Improvement in myocardial function and coronary blood flow in ischemic myocardium after mannitol. J Clin Invest 1972;51:2989-98.

173. Harrison GA, Torda TA, Schiff P. Hypotensive effects of stable plasma protein solution (S.P.P.S.), a preliminary communication. Med J Aust 1971;2:1308-09.

174. Bland JHL, Laver MB, Lowenstein E. Hypotension due to 5 per cent plasma protein fractions. N Engl J Med 1972;286:109.

175. Bland JHL, Laver MB, Lowenstein E. Vasodilator effect of commercial 5 percent plasma protein fraction solutions. J Amer Med Assn 1973; 224:1721-24.

176. Alving BM, Hojima Y, Pisano JJ, et al. Hypotension associated with pre-kallikrein activator (Hageman-factor fragments) in plasma protein fraction. N Engl J Med 1978;299:66-70.

177. Izaka K, Tsutsui E, Mima Y, Hasegawa E. A bradykinin-like substance in heat-treated human plasma protein solution. Transfusion 1974;14: 242-48.

178. Izaka K, Morichi S, Fujita Y, Hasegawa E. A kininogen-like substance in unheated human plasma proteins. Transfusion 1975;15:46-53.

179. Combridge BS, Wesley ED. Plasma protein fraction: The disappearance of kinin from the solution on storage. Transfusion 1979;19:599-600.

180. Umlas J, Sakhuja R. The effect on blood coagulation of the exclusive use of transfusions of frozen red cells during and after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1975;70:519-23.

181. Valeri CR, Bougas JA, Talarico L, Emerson CP, Didimizio T, Pivacek L. Behavior of previously frozen erythrocytes used during open-heart surgery. Transfusion 1970;10:238-46.

182. Lee WH, Krumhaar D, Derry G, et al. Comparison of the effects of membrane and non-membrane oxygenators in the biochemical and biophysical characteristics of blood. Surg Forum 1961;12:200-02.

183. Reed CC, Romagnoli A, Taylor DE, Clark DK. Particulate matter in bubble oxygenators. J Thorac Cardiovasc Surg 1974;68:971-74.

184. Solis RT, Kennedy PS, Beall AC Jr, Noon GP, DeBakey ME. Cardiopulmonary bypass. Microembolization and platelet aggregation. Circulation 1975;52:103-08.

185. Liddicoat JE, Bekassy SM, Beall AC Jr, Glaeser DH, DeBakey ME. Membrane vs bubble oxygenator: Clinical comparison. Ann Surg 1975; 181:747-53.

186. Wright JS, Fisk GC, Torda TA, Stacey RB, Hicks RG. Some advantages of the membrane oxygenator for open-heart surgery. J Thorac Cardiovasc Surg 1975;69:884-90.

187. Byrick RJ, Nobel WH. Postperfusion lung syndrome. Comparison of Travenol bubble and membrane oxygenators. J Thorac Cardiovasc Surg 1978;76:685-95.

188. Peirce EC. The membrane versus bubble oxygenator controversy. Ann Thorac Surg 1980;29:497-99.

189. Sade RM, Bartles DM, Dearing JP, Campbell LJ, Loadholt CB. A prospective randomized study of membrane vs bubble oxygenators in children. Ann Thorac Surg 1980;29:502-11.

190. Trumbull HR, Howe J, Mottl K, Nicoloff DM. A comparison of the effects of membrane and bubble oxygenators on platelet counts and platelet size in elective cardiac operations. Ann Thorac Surg 1980;30:52-57.

191. Siderys H, Herod GT, Halbrook H, et al. A comparison of membrane and bubble oxygenation as used in cardiopulmonary bypass in patients. The importance of pericardial blood as a source of hemolysis. J Thorac Cardiovasc Surg 1975;69:708-12.

192. deJong JCF, tenDuis HJ, Smit Sibinga CT, Wildevuur CRH. Hematologic aspects of cardiotomy suction in cardiac operations. J Thorac Cardiovasc Surg 1980;79:227-36.

193. McKenna R, Bachmann F, Whittaker B, Gilson JR, Weinberg M Jr. The hemostatic mechanism after open-heart surgery. II. Frequency of abnormal platelet functions during and after extracorporeal circulation. J Thorac Cardiovasc Surg 1975;70:298-308.

194. Umlas J. In vivo platelet function following cardiopulmonary bypass. Transfusion 1975;15:596-99.

195. Hennessy VL Jr, Hicks RE, Niewiarowski S, Edmunds LH Jr, Colman RW. Function of human platelets during extracorporeal circulation. Amer J Physiol 1977;232:H622-68.

196. Beurling-Harbury C, Galvan CA. Acquired decrease in platelet secretory ADP associated with increased postoperative bleeding in post-cardiopulmonary bypass patients and in patients with severe valvular heart disease. Blood 1978;52:13-23.

197. Friedenberg WR, Myers WO, Plotka ED, et al. Platelet dysfunction associated with cardiopulmonary bypass. Ann Thorac Surg 1978;25: 298-305.

198. Addonizio VP Jr, Smith JB, Guiod LR, Strauss JF III, Colman RW, Edmunds LH Jr. Thromboxane synthesis and platelet protein release during simulated extracorporeal circulation blood 1979;54:371-76.

199. Moore EE, Dunn EL, Breslich DJ, Galloway WB. Platelet abnormalities associated with massive autotransfusion. J Trauma 1980;20:1052-56.

200. Addonizio VP Jr, Strauss JF III, Macarak EJ, Colman RW, Edmunds LH Jr. Preservation of platelet number and function with prostaglandin E_1 during total cardiopulmonary bypass in rhesus monkeys. Surgery 1978; 83:619-25.

201. Stibbe J, Ong GL, Ten Hoor F, et al. Influence of prostaglandin E_1 on platelet decrease in the heart-lung machine. Haemostasis 1973/74;2: 294-303.

202. Malpass TW, Hanson SR, Savage B, Hessel EA II, Harker LA. Prevention of acquired transient defect in platelet plug formation by infused prostacyclin. Blood 1981;57:736-40.

203. Becker GA, Tuccelli M, Kunicki T, Chalos MK, Aster RH. Studies of platelet concentrates stored at 22 C and 4 C. Transfusion 1973;13: 61-68.

204. Filip DJ, Aster RH. Relative hemostatic effectiveness of human platelets stored at 4° and 22°C. J Lab Clin Med 1978;91:618-24.

205. Holme S, Vaidja K, Murphy S. Platelet storage at 22 C: Effect of type of agitation on morphology, viability and function in vitro. Blood 1978;52:425-35.

206. Kahn RA, Johnson RK, Heaton WAL. Effects of prolonged room temperature holding of whole blood intended for preparation of components. Transfusion 1979;19:539-41.

207. Kahn RA, Staggs SD, Miller WV, Heaton WA. Recovery, lifespan, and function of CPD-adenine (CPDA-1) platelet concentrates stored for up to 72 hours at 4 C. Transfusion 1980;20:498-503.

208. Scott EP, Slichter SJ. Viability and function of platelet concentrates stored in CPD-adenine (CPDA-1). Transfusion 1980;20:489-97.

209. Bolin RB, Cheney BA, Simpliciano OA, Peck CC. In vitro evaluation of platelets stored in CPD-adenine formulations. Transfusion 1980; 20:409-18

210. Moroff G, Chang CH. Aggregation response of human platelets stored at 22 C as platelet-rich plasma. Transfusion 1979;19:704-18.

211. DiMinno G, Silver MJ, Murphy S. Stored human platelets retain full aggregation potential in response to pairs of aggregating agents. Blood 1982;59:563-68.

212. Lazarus HM, Herzig RH, Warm SE, Fishman DJ. Transfusion experience with platelet concentrates stored for 24 to 72 hours at 22 C. Importance of storage time. Transfusion 1982;22:39-43.

213. Rao AK, Niewiarowski S, Murphy S. Acquired granular pool defect in stored platelets. Blood 1981;57:203-08.

214. Lee EL, Azar HA, Kasnic G Jr. Ultrastructure of human platelets processed for transfusion under standard blood bank conditions. Transfusion 1979;19:732-37.

215. Valeri CR. Hemostatic effectiveness of liquid-preserved and previously frozen human platelets. N Engl J Med 1974;290:353-58.

216. Valeri CR. Circulation and hemostatic effectiveness of platelets stored at 4 C or 22 C: Studies in aspirin-treated normal volunteers. Transfusion 1976;16:20-23.

217. Barber R, Grode G, Buchholz DH. Five-day platelet storage: morphological, functional and chemical assessment. Transfusion 1981;21:638.

218. Murphy S, Holme S. Storage of platelets for five days in two containers - value of paired studies. Transfusion 1981;21:637.

219. Murphy S, Simon T. Characteristics of prolonged platelet storage in a new container. Transfusion 1981;21:637.

220. International Forum. What is the factual basis, in theory and clinical practice, for the use of fresh frozen plasma? Vox Sang 1978;35:426-35.

221. Wolff G. Fresh frozen plasma: Effects and side effects. In: Collins JA, ed. Surgical Hemotherapy. New York: Karger, 1980, Biblthca haemat., No. 46, 189-206.

222. McCullough J, Carter SJ, Quie PG. Preservation of opsonic activity against Staphylococcus aureus and Escherichia coli in bank blood. J Lab Clin Med 1972;79:886-92.

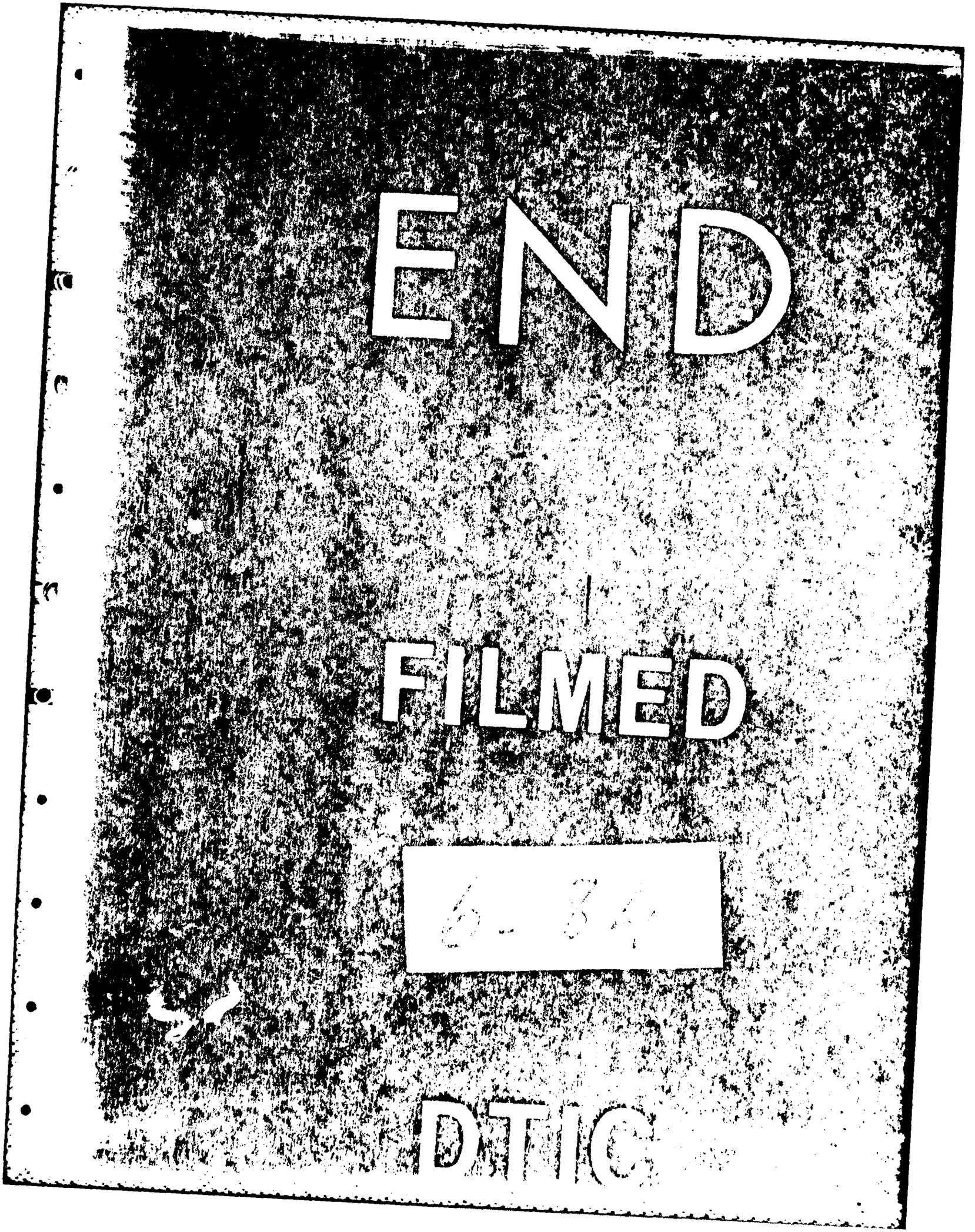
223. McClellan MA, Alexander JW. The opsonic activity of stored blood. Transfusion 1977;17:227-32.

224. Beiting CV, Kozak KJ, Dreffer RL, Stinnett JD, Alexander JW. Whole blood vs. packed red cells for resuscitation of hemorrhagic shock: An examination of host defense parameters in dogs. Surgery 1978; 84:194-200.

225. Alexander JW. Hemotherapy and antibacterial defense mechanisms. In: Collins JA, ed. Surgical Hemotherapy. New York: Karger, 1980, Biblthca haemat., No. 46, 26-36.

226. Saba TM, Jaffe E. Plasma fibronectin (opsonic glycoprotein): Its synthesis by vascular endothelial cells and role in cardiopulmonary integrity after trauma as related to reticuloendothelial function. Amer J Med 1980;68:577-94.

227. Saba TM. Disturbances in plasma and cell surface fibronectin: Relationship to altered vascular permeability and host defense. J Trauma 1981;21:679-84.


END
FILMED
DTIC