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Complications of massive blood transfusion with blood stored in acid solution : with emphasis on citrate toxicity as a possible hazard

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COMPLICATIONS OF MASSIVE BLOOD TRANSFUSION WITH BLOOD STORED IN ACD SOLUTION: EMPHASIS ON CITRATE TOXICITY AS A POSSIBLE HAZARD

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INTRODUCTION

This review was instigated by the challenge to explain the role of citrate in the untoward response of a patient to the administration of a large volume of stored whole blood.

In 1915 the introduction of sodium citrate anti-coagulation by Lewisohn permitted the storage of whole blood for extended periods. Prior to this time no ade-quate method of transfusion had been devised other than a direct arterial-venous anastomosis which required "rare abilities".[1] Because blood could be kept fluid with citrate and could be transported to another patient simply and impersonally it became commonly available. Recipient and donor blood was cross matched but the technique was relatively simple and poorly understood. As a result the literature of the period reports a number of complications attending blood transfusion of which many were attributed to citrate.[2,3]

In 1919 Unger[2] reporting on blood transfusion reac-tions observed that there were more reactions following transfusions with citrated blood than with unmodified blood. Drinker & Brittingham reported that after citrate transfusions febrile reactions occurred in 60 percent of cases and a chill developed in 57 percent. Unger observed febrile reactions occurring in only 10 percent and chills

in 3 percent of his patients receiving unmodified blood. The maximum transfusion quantity used in this period was 1000 ml. with citrate, while with the unmodified method measurement was inaccurate, and thus by 1921, Bernheim was calling attention to the apathy which had developed towards the reactions to citrated blood. He concluded that two definite groups of patients should not be transfused by this method: 1) those in whom there had been hemorrhage of such intensity that the extreme limits of bleeding had been reached so that the patient was so near shock that everything in the nature of additional shock must be avoided and 2) those in whom anemia, whether primary or secondary, was so severe that the patient was almost dead. He cites cases of his own that fell into these categories and died with chills and shock after receiving citrated blood.[3]

Many of the adverse effects attributed to citrate were clarified with the advances made during subsequent years. Additional blood types were identified. The rh factor was recognized as were the problems of sensitization. More accurate methods of blood typing and cross matching were developed and methods of storage and collection were improved.[4,5,6]

The development of relatively safe transfusion of stored citrated blood resulted in the use of large quan-

tities of blood during World War II. Following the war an aggressive surgical approach towards neoplasms and cardiovascular disease led to occasional use of large quantities of stored citrated blood. This was not without consequences, for with the infusion of stored citrated blood, rapidly or in massive quantities, came reports of adverse effects on the cardiovascular system.

INDICATIONS FOR BLOOD TRANSFUSION

Before considering complications of blood transfusion and particularly massive blood transfusion it is appropriate to review the indications for transfusions. Based upon the physiology of the blood some rational considerations for transfusion of blood would be:[10]

1. To maintain blood volume and prevent or treat shock.
2. To maintain the oxygen carrying capacity of the blood and prevent or treat hypoxia.
3. To promote or sustain coagulation of the blood.
4. To provide exchange transfusions in the newborn infant with erythroblastosis fetalis.
5. To maintain the circulation in extra corporal or cardiac bypass shunts.

A classic statement on the indications for the use of blood transfusion was made by Leisrink in 1872.[11] He said "transfusion is indicated in all those pathologic conditions where the blood, in quantity and quality, is so altered that it is unfit to fulfill its physiological duties".

COMPLICATIONS OF BLOOD TRANSFUSION

Acute blood loss, regardless of etiology, if of sufficient magnitude will be followed by hypovolemic shock. In operative procedures shock is usually avoided by replacing blood loss with banked whole blood.

When the amount of blood loss requiring replacement is not massive-that is amounts less than 2000 to 2500 ml.-transfusion reactions can be related to a single unit transfusion. The hazards include transmitted disease, allergic and febrile reactions, reactions due to incompatibility, reactions due to infected blood, over transfusion, air embolism, transfusion hemosiderosis and thrombophlebitis.

Diseases transmitted by blood transfusion include serum hepatitis, syphilis, malaria and brucellosis. Hepatitis is the most important problem. It is least easily detected and least amenable to therapy. Exclusion of donors with clinical jaundice or known association with a patient having the disease is the best available precaution to avoid this hazard.[12]

Febrile reactions are characterized by chills, fever, headaches and apprehension during the course of or immediately following a transfusion. Previously, many of these reactions were due to imperfectly cleansed equipment.[13,14,15] Disposable equipment has eliminated this source of diffi-

culty. Reactions of this type are still common, some of them appearing to be associated with a leukocyte agglutinin in the recipient.[16,17]

Allergic reactions of varying degrees of severity occur in 1 to 2 percent of transfusions. They are manifest by urticaria, bronchospasm, angioneurotic edema, fever and polyarthritis. Various explanations for allergic reactions have been suggested ranging from passive transfer of antibodies or antigens to transfusion of antigens to which a patient is already sensitive, ie. horse serum, penicillin, or foods.[18,19] Screening and rejection of donors who have active allergies or who have recently received injections may be helpful in reducing this hazard.[19]

Reactions resulting from red blood cell incompatibility are dangerous and may be avoided only with careful and accurate blood typing and cross matching technics. A reaction results in hemolysis of red cells and is sudden in onset. Severe pain in the lumbar region of the back, breathlessness, a feeling of constriction about the ribs, and hypotension are early symptoms with fever and signs of hemolysis developing later. Free hemoglobin in the plasma leads to hemoglobinuria and to the development of jaundice.[20,21] If the patient survives the acute hemolytic phase, renal failure may occur.[22,23] A hemorrhagic tend-

ency may develop reflected by thrombocytopenia, hypothrombinemia and hypofibrinogenemia.[24] Treatment involves supportive measures combating hypovolemia and hypoxia in the acute phase followed by careful attention to fluid and electrolyte requirements during the renal phase. The artificial kidney may have to be used.[24,25]

Administration of blood contaminated with bacteria promptly produces profound shock accompanied by hyperthermia and frequently vomiting. Contamination usually occurs at the time of collection of the blood. Organisms implicated include gram-negative psychrophils capable of multiplication at 4°C, especially members of pseudomonas, paracolon and escherichia groups. Skin staphylococci have been implicated also. This hazard is reduced by careful cleansing of the skin of donors. Braude recently described sucessful treatment with the combined use of antibiotics and the continuous intravenous administration of pressor drugs in very large doses.[26-31]

Patients with congestive heart failure or pulmonary insufficiency are especially prone to pulmonary edema and death attending injudicious administration of large volumes of blood or administration at a rapid rate.[32,33] Slow infusion of packed red cells or careful monitoring of venous pressure is necessary to prevent a sudden increase in load on the cardiovascular system.

A rare complication which is hard to demonstrate is air embolism. Animal experiments imply that a healthy adult may recover from the introduction of 200 ml. of air. However, smaller amounts have undoubtably proved fatal. Blood infusion under pressure, as with massive, rapid, transfusion is the most frequent source of air embolism although poorly supervised administration with bottles running empty may be a source.[34] Risks of air embolism have been reduced with the use of closed system plastic equipment.

Massive blood transfusion is arbitrarily defined as replacement of the blood volume of the patient within a twenty-four hour period. The administration of a massive transfusion imposes the hazards inherent in an individual transfusion as well as the hazards to cardiovascular adjustment imposed by rapid infusion of a quantity of colloid solution. In addition a massive transfusion creates additional hazards related to the average age of the blood, the anticoagulant content, the temperature of the blood, and the chemical changes which have attended storage. Special problems with compatability may arise. Crosby demonstrated that massive transfusions of Group O blood to recipients of other groups may result in an accumulation of transfused antibodies active against the red cells of the recipient, making it unsafe to transfuse the patient with blood of his own hereditary group until the foreign antibodies disappear---a period of two weeks.[35]

ANALYSIS OF ACD STORED BLOOD

The most significant complications associated with rapid transfusion of large quantities of stored citrated blood are related to induced hemorrhagic tendencies and to cardiovascular complications. If one examines the physiology of stored blood explanations of these complications become evident.

A unit of stored, citrated bank blood contains 120 ml. of acid citrate dextrose (ACD) solution and 480 ml. of donor blood. The ACD solution employed is most commonly solution B recommended by the National Institutes of Health. This solution contains 13.2 grams trisodium citrate, 4.8 grams citric acid and 14.7 grams dextrose diluted to one liter by addition of distilled water. This means each bottle of bank blood filled with 120 ml. of solution B contains the equivalent of 1.43 grams of citric acid.

During collection, up to 20 percent of the cells withdrawn are injured reducing the in-vivo life span to only 2.2 hours. With infusion 4 to 8 percent are destroyed immediately, and the remainder survive their expected normal effective life. Destruction may be expressed as 0.83 percent per day (life span of 120 days).[36] Metabolic acids accumulate as a result of continuing glycolytic activity of the red cells, and as a result the pH falls to levels of 7.1 and 6.6. The hematocrit averages 41.5

percent and plasma hemoglobin increases. Interference with cell respiration leads to electrolyte changes; extracellular potassium increases to levels as high as 25 mEq. by the fourteenth day. Sodium enters the cell in exchange for potassium. Bank blood is stored at 4°C and is frequently administered at temperatures of 8° to 10°C. Citrated blood is depleted of ionized plasma calcium with some known excess of citrate. After very brief storage it becomes deficient of platelets, shows marked decreases in antihemophilic globulin and factor V (labile factor). The oxygen disassociation curve is shifted to the left. Thus a number of unfavorable chemical and physical changes attend the storage of whole blood.[37,38]

DEFINITION OF MASSIVE BLOOD TRANSFUSION

The more serious the operation, illness or injury the greater the morbidity and mortality and of course the greater the probability of need for massive blood transfusion. In studying this problem Boyan and Howland observed that patients receiving rapid transfusion of blood greater than 5 units commonly demonstrated a deterioration of cardiac function leading at times to ventricular fibrillation or standstill. The blood pressure in such cases either showed a gradual decline to unobtainable levels or a sudden drop to zero. Patients receiving 10 or more units of bank blood commonly exhibited a tendency toward oozing from the

operative site. The incidence of these two complications encountered in a series of 253 patients were as follows: 2.4 percent receiving 5 to 10 units of stored blood had cessation of cardiac function or a hemorrhagic tendency, 16.9 percent receiving greater than 10 units had cardiac arrest and 31.5 percent demonstrated an oozing tendency. Of 130 patients receiving 10 or more units, 43 percent developed a major complication. There were 22 cases of cessation of cardiac function, 9 of which had an electrocardiographic evidence diagnostic of ventricular fibrillation and 2 diagnostic of cardiac asystole. The remaining cases did not have an electrocardiogram available.[39-41]

Howland and his group noted that the appearance of cardiac disorders seemed to parallel the speed of administration of the blood, while the incidence of bleeding tendencies paralleled the increasing volume administered. Seventy-five percent of patients in his study suffered complications during the first two hours after receiving large volumes of blood within a relatively short time. Important factors to observe with massive transfusion, as emphasized by Foote are: the nature of the blood used; the total quantity administered and the rate of administration. He observed also that when ACD blood is transfused in volumes greater than two liters "hemorrhagic diath-

esis and circulatory disturbances" may arise.[42]

Based on these considerations any blood transfusion greater than 2500 ml. within a few hours is considered a massive transfusion. When blood is to be administered abnormally fast, cardiovascular complications may be encountered with a limited quantity of whole blood. Howland noted that rapid transfusion was most commonly associated with ventricular fibrillation. Some of these patients received as much as 500 ml. of blood in less than three minutes.[43]

ETIOLOGIES OF COMPLICATIONS RESULTING FROM MASSIVE BLOOD TRANSFUSIONS

Many explanations have been advanced to explain the adverse effects of massive blood transfusion. Cardiovascular effects have been attributed to citrate intoxication,[7,44-47] depressed ionized calcium,[48,49] hyperpotassemia,[50,51] disturbed calcium potassium ratio,[51] hypothermia,[52] and acid base disturbance.[53] Blood clotting and oozing difficulties have been attributed to a deficiency of platelets, decreased ionized calcium, elevated plasma citric acid levels, fibrinolysins, decreased labile factor, hypothermia and incompatible transfusion reactions.[41] Citric acid with its capacity to bind calcium and lower pH has been a prime suspect and has received considerable emphasis as an eteologic agent. It is this "citrate

lesion"[37] that stimulated the examination considered in the remainder of this paper.

CITRIC ACID

Elevations of serum citrate have been reported to occur in man during multiple rapid transfusions of citrated blood.[44,48] Harmful effects from citrate have frequently been described but are often discounted.[44,54] The effects of citrate intoxication reported in the literature have been ascribed to decreased ionized calcium. As previously noted it is the ability of citrate to bind calcium which makes it an effective anticoagulant.

Citric acid occurs endogenously in nearly all tissues and one would expect the body to have efficient avenues of metabolism.[55] The Kreb's cycle (citric acid cycle) provides pathways for production of high enery phosphate bonds which are necessary for cell metabolism. The greatest quantity of citric acid is thought to be metabolized by muscle, through the stages of cisaconitic and isocitric acid in the presence of the enzyme aconitase.[55]

Under usual conditions serum citric acid is present at levels between 2 and 3 mg. percent.[56] Parathormone appears to influence this concentration since increased parathyroid activity increases the serum citric acid level. It is not known whether this is secondary to increased cellular activity or to a breakdown of bone tissue.[57] Thunberg demonstrated that the highest concentration of citric

acid exists in the bones (1000 mg. percent).[58] Dickens estimates that over 95% of the total citric acid of the body resides in the skeleton.[59]

The role of the liver in citric acid metabolism has been controversial. Sjostrom in 1937 demonstrated that if a citrate solution was perfused through an animal's liver, the citrate in the perfusing fluid was handled easily even though the concentration was 100 times that normal for the animal. He observed that so much of the citrate was transformed during a single passage that the level in the hepatic venous blood was near that normally found in serum. No corresponding decrease in citrate content was observed when the hindquarters of the animals were perfused.[60]

Conversely, Martensson concluded from perfusion experiments that the liver had little or no ability to destroy citrate but that the kidney had a marked ability to do so. He explained Sjostrom's results on the fact that his perfusion experiments were done on livers removed from the animals so that many of the cells had been macerated. This, he felt, released intracellular enzymes to metabolize the citric acid. His experiments avoided this possibility because the hepatic tissue was perfused in the intact animal.[55]

Support for Martensson's idea is gained from work

done by Battelli and Stern who observed that citrate was oxidized when incubated with extracts of animal organs. Oxygen appeared to affect this reaction, for the rate of disappearance of citrate varied directly with the oxygen concentration. The reaction was conversely retarded by acid.

This concept contradicted Bunker[48] who demonstrated an increased toxicity of bank blood in patients with hepatic disease. He observed that in normal adult patients receiving multiple transfusions at a rate of not more than about 500 ml. every 30 minutes there was no evidence of toxicity. Thus, with citrate infused at a rate less than 0.5 mg. per kilogram of body weight per minute the serum concentration of citrate remained below 9 mg. per 100 ml. At this level of citrate the serum ionized calcium concentration remained above 0.85mM per liter which is within the normal range. Fifteen patients with advanced liver disease receiving whole blood transfusions at about the same rate (less than 0.5 mg. citrate per minute) had higher serum citrate levels, above 9 mg. per 100 cc. In 5 of the patients the calculated ionized calcium level fell below 0.8 mM per liter. Bunker's evidence suggests that hepatic tissue plays a role in citrate metabolism but it does not necessarily pinpoint the liver as the only site of citrate metabolism.

Other substrates and enzymes may originate in liver which are necessary for the metabolism of citrate in peripheral tissues.

Howland and his co-workers [39,41] showed that in patients with abnormal liver function tests resulting from metastatic carcinoma there was no elevation of plasma citric acid levels. It may be that the metabolic disturbances associated with cirrhosis impair citric acid metabolism and account for this discrepancy. Similarly, in a series of patients undergoing hepatic lobectomy, the rate of metabolism or clearance of citric acid was the same as that in patients undergoing operations on other organs and receiving equivalent volumes of blood.

The kidney has been shown to participate actively in citrate metabolism and excretion. Amberg and McClure were first to identify citric acid as a normal excretory product in human urine.[62] Oestberg[63] later demonstrated that citrate excretion increased greatly during metabolic alkalosis and decreased during states of acidosis. Recent evidence presented by Cooke and co-workers has shown that administration of potassium to potassium-deficient animals with hypochloremic alkalosis increased citrate excretion greatly.[64] Evans has substantiated this in man showing that as potassium chloride was administered, there was a concomitant change in urine pH.[65] It would appear

from work done by Grollman et. al. with intermediates of the tri-carboxylic acid cycle that the renal mechanism is one of filtration and reabsorption without tubular secretion.[66] Earlier work done by Mortensson suggested that the epithelial cells of the renal tubule utilized circulating citric acid.[55]

Physiologically, excess citrate is believed to have its main adverse effect by lowering ionized calcium.[48] In 1916, Salant and Wise[67] observed that if citrate was given to experimental animals by vein even in comparatively small doses it produced marked symptoms resulting in death on occasion if the rate of injection were too fast. Dyspnea, convulsions, fibrillary twitching of voluntary muscles and dilatation of the pupils were observed following the administration of 70 mg. sodium citrate per kilogram. Dogs receiving a 2.5 percent solution of sodium citrate intravenously, in doses of 100 mg. per kilogram body weight, injected at the rate of 50-70 mg. per kilo., per minute had cessation of respiration, and sometimes also arrest of the heart action.

Citric acid effect on ionized serum calcium has been studied by many with variable results depending on, the rate of administration of citric acid, the circulatory status of the patient, and the acid-base balance. It is the ionized calcium in the body which appears to be

physiologically active.[56] The greatest amount (99%) of total calcium in the body is contained in the bone and less than one percent is found in the blood and extracellular fluid.[68] Fifty to 75 percent of the calcium in the blood is diffusible while the rest is bound to protein.[69] Of the diffusible calcium in the plasma, most is ionized and is physiologically active, while a small part is non-ionized but diffusible.[56] Saffran and Denstedt studied ionized calcium during the administration of citrate and observed that the restoration of ionized calcium was very rapid even with high elevations of plasma citric acid.[70] Bunker, Stetson and Coe[48] working with patients observed no essential change in ionized serum calcium with serum citrate levels to 9 mg. per 100 ml., however, in 5 patients with serum levels above 9 mg. per 100 ml., ionized serum calcium fell below 0.8 millimols per liter. From the work of Wexler,[70] Bunker et. al.[48] and Ludbrook & Wynn[71] a level of 50 mg. of citrate per 100 ml. of plasma gives in a normal person a calculated plasma ionized calcium of about 0.5 millimols per liter and may be considered undesirable. The range of toxicity, however, seems to be quite variable and is dependent on factors of time, pH and circulation. The rate of calcium mobilization is directly proportional to the lowering of serum calcium. Since bone represents the storehouse of calcium in the

body mobilization is limited by blood flow to the bone.

Likewise, acidosis is known to increase ionization while alkalosis has the opposite effect.

Adams and co-workers attempting to correlate the complications of citrated whole blood with the pharmacologic effects of citrate describe the picture of citrate intoxication as alterations of blood pressure observed several minutes prior to a rapid terminal fall. Some change in respiratory activity was usually present for several minutes before fatal intoxication occurred. Respiratory failure was never observed prior to cardiac failure. Definite tetanic contractions accompanied citrate intoxication in some of the group under local anesthesia. Eye reflexes usually became very sluggish and were at times completely absent. Blood findings were quite dramatic. The color became very dark red, "almost black", and gas analysis revealed that the oxygen was as low as three to four volumes percent. The authors found that with the administration of calcium gluconate there was rapid restoration of blood pressure and normal respiratory activity. The color of the blood returned to a bright red and gas analysis revealed a normal oxygen content. Eye reflexes, similarly, returned to a normally reactive state.[73]

Firt and Hejhal[74] observed a rise in venous pressure

with infusion of citrate, appearing much like cardiac overloading. They observed what they felt was evidence of an effect on the vascular bed as well as on the myocardium. This was characterized by prolonged increased pulmonary arterial pressures after systemic and myocardial effects had apparently disappeared. The vaso constrictive effect was observed in short, peaked wave patterns beginning in the pulmonary artery pressure records. Of course, increased pulmonary vascular resistance does not produce a rise in pulmonary artery pressure during myocardial insufficiency but the authors noted that it was so intense in some cases that pulmonary artery pressure did not fall even in known periods of insufficiency. The vaso constriction phenomenon observed, produced obvious blanching of the lung parenchyma after the intravenous administration of citrate.

Working with cats, Shafer and Crismon demonstrated a vagal blocking effect of sodium citrate occurring at the synapse between pre and post ganglionic fibers. Used in doses just in excess of that necessary to cause vagal block a direct action on heart muscle was observed as evidenced by increased venous pressure, dilatation of the heart with ineffectual contractions and decreased blood pressure in the face of a decreased peripheral resistance.[75] Love demonstrated a depression of the myocardium with a

rise or no change of blood pressure. The effect occurred after section of the vagi and after atropine, without appreciable change of heart rate.[76]

Studying the hemodynamic effects of intravenous sodium citrate, Bunker and co-workers report results on animals and human subjects in a carefully controlled series of experiments. In patients the levels of serum citrate attained were 46 to 77 mg. per 100 ml. (2.4 to 4.1 millimols per liter).[49] These levels had been reported previously in patients receiving rapid blood transfusion.[44,48] They observed circulatory depression occurring in man and dog at approximately similar blood levels, 2.5 to 4.0 millimols per liter (47 to 75 mg. per 100 ml.). Critical circulatory depression or death occurred in the dog at blood levels of 2.7 to 10 millimols (50 to 90 mg. per 100 ml.) and at rates of infusion of citrate of 10 to 15 mg. per kilogram of body weight, per minute very close to the fatal dose rates reported in early studies.[67,73,77]

Circulatory depression in man and dogs was manifested by hypotension, by variable changes in cardiac output and by narrowed pulse pressure. These changes occurred with electrocardio-graphic evidence of hypocalcemia as well. Direct evidence of cardiac depression was provided in the dog by strain gauge measurements and supported by the rise in central venous pressure and end diastolic

pressure in the left ventricle. With such increases in filling pressure one would expect an increase in cardiac output which in the cases usually fell, suggesting that cardiac depression existed.[49]

Electrocardiographic changes produced by citrate infusion have been reported frequently. Nakasone and coworkers noted prolongation of the Q-T interval, depression of T wave and depression of P wave voltage when dogs were infused with solutions of ACD solution.[78] Similarly Krautwald and Darow produced prolongation of the Q-T interval in conscious human volunteers given infusions of sodium citrate. These patients also had occasional tetany and clouding of consciousness which was relieved by the administration of calcium chloride.[79]

The ECG picture produced by citrate infusion resembles that present with hypocalcemia as studied in postoperative or idiopathic types of hypoparathyroidism. Studying the electrocardiogram in patients with hypoparathyroidism Ljung observed a prolonged Q-T interval, abnormal T waves and generally marked instability of the T wave. He remarks, however, that cardiac insufficiency is generally not present with pure hypocalcemia.[80]

DISCUSSION

Various observers have demonstrated an enhanced toxicity of citrated preserved blood compared to non-citrated

blood. Muirhead in 1942 called attention to citrate toxicity when he observed rigor, lack of elevation of blood pressure and sudden death in dogs administered concentrated plasma.[22] Likewise Ivy and co-workers[50] investigating the benefits of various blood substitutes described a greatly increased mortality in dogs given citrated pooled dogs plasma. Death was characterized by respiratory failure evidenced by apnea or sudden ventricular fibrillation, signs compatible with demonstrated citrate effects. Similarly animals transfused with pooled heparinized plasma resulted in only 3 deaths out of 50 compared to 35 deaths out of 50 animals with the citrated plasma.

Comparing citrated blood to heparinized blood Bruneau and Graham repeatedly bled and transfused dogs of one percent of their body weight at half hourly intervals. Sodium citrate was used at concentrations of 0.6 percent and heparin in concentrations of 0.085 ml. per 100 ml. of blood. The citrated group withstood nine and twenty-five hundredths bleedings before death while the heparinized dogs an average of 25.2 bleedings. Death in the citrated group was preceeded by dyspnea, convulsions or fibrillary twitchings while none of the heparinized groups showed these signs.[81]

Many authors have demonstrated the relative safety

of ACD stored blood as commonly used. In those patients in whom complications arise, citrate is frequently implicated and justifiably so considering that it has adverse effects when present in great enough quantities. A serum citrate level of 50 mg. per 100 ml. seems to be considered as the upper limits of desirability.[9,48,72] In a normal adult this corresponds to a steady rate of citrated blood infusion of about one bottle (540 ml.) every five minutes.[72] Various authors have observed that the plasma citrate level appears to rise in a direct proportion to the rate of infusion.[41,72,82] At a citrate infusion rate of 1 mg. per kilogram per minute the elevation of plasma citrate was 12.5 mg. per 100 ml. in Ludbrook & Wynns experiments.[72] Calculations based upon the data of Bunker [48,49] gives a figure of 11 mg. per 100 ml. and Howland[41,44] reported an increase of 8 mg. per 100 ml. at a similar infusion rate. It appears that high plasma citrate levels are unlikely to occur with ACD blood transfusions in normal humans.

It is an obvious fact, that patients receiving massive blood transfusions are not normal humans and that the blood administered may be less than physiologic. Other considerations exist such as the potassium concentration, hypothermia (either via the cold blood, induced or as a result of the operative procedure), shock, com-

promising disease processes, (hepatic cirrhosis, osteoporosis, hypoparathyroidism) or heart disease. Not only do many of these factors play a possible role in cardiac abnormalities themselves but many of them act as synergists to the changes effected by citrate. For example, Brown and Prasad showed in experimental animals that a rapid decrease in alveolar pCO_2 with a simultaneous, rapid increase in serum potassium level and a decrease in the ultrafilterable calcium frequently lead to ventricular fibrillation.[83]

Potassium is liberated from red blood cells during storage in ACD solution resulting in a considerable increase of potassium concentration in the plasma. Similarly, in the face of shock or stress kidney function may be depressed. At the same time epinephrine stimulation of glycogenolysis occurs liberating large amounts of potassium directly into the vena cava close to the heart. As a result the heart and myocardium is perfused with blood having an excessively high potassium concentration which may be in excess of that in the peripheral blood. LeVeen[51] demonstrated this central hyperkalemia by sampling vena caval blood. They also cite two cases of cardiac arrest during operations with massive blood transfusion in which blood potassium concentrations were 8.7 milliequivalents and 8.2 milliequivalents per liter. From their studies

of massive transfusion, they concluded that the potassium, ionized calcium ratio is the critical consideration in cardiac irregularities. Cardiac glycosides appeared to offer protection against toxic effects of hyperkalemia as previously demonstrated by Page & Heal.[77]

Boyan & Howland[52] studied esophageal temperature changes during transfusion at a point directly behind the right atrium. Significantly, they observed that a three and one-half hour expossure of the abdominal cavity to 20.5°C room temperature without significant blood replacement could lower the esophageal temperature 2.1°C. In several patients a marked lowering of temperature to levels of 27.5°C and 32°C was observed with massive blood transfusion. At these temperatures cardiac arrest occurred in two patients. Mclean and Van Tyn similarly have reported esophageal temperatures as low as 29°C during surgical procedures in which massive blood transfusions were given. The heart is the first organ to be exposed to a stream of cold blood infused into an antecubital vein. Changes in the myocardium may be considerably greater than that reflected in other body tissues. The cardiac effects of hypothermia have been well documented, although as yet not well explained. Hara and co-workers[82] studying citrate metabolism in hypothermic dogs demonstrated impaired metabolism of citrate, however, his

animals seemed to tolerate the condition without exhibiting the usual signs and symptoms of toxicity with citric acid levels up to 70 mg. per 100 ml. Potassium levels, pH and anoxia would seem to play a more important role in myocardial effects of hypothermia than does citrate per se.[43]

Under normal circumstances citric acid is rapidly metabolized and toxic reactions do not occur. If toxic sequelae occur they most frequently follow extremely rapid administration of stored ACD blood. Frequently, in such circumstances many other factors are present which interfere with the metabolism or normal physiologic response of the body to citric acid infusion. Hypothermia, induced or secondary to the blood administration itself, decreases the rate of metabolism and has a primary effect on the myocardium. Long standing liver disease especially cirrhosis with associated avitaminosis and malnutrition appears to contribute to decreased metabolism of citric acid. One possible explanation is saturation of enzyme systems. Operation, per se, as demonstrated by Drucker[85] although not interferring with citric acid metabolism does block intermediary metabolism and energy production. Patients who have hypoparathyroid disease or osteoporosis, and cannot mobilize calcium may be more prone to citrate intoxication. Children, especially the

newborn, may not have adequate stores of calcium and may demonstrate hypocalcemia with exchange transfusion. Shock, with concomitant hypoxia, also contributes to decreased metabolism. With poor circulation to bone and peripheral tissues citrate infusion is poorly tolerated probably because calcium is not mobilized.

It is likely that elevated serum citrate and hypocalcemia is less well tolerated in debilitated and cardiac patients. Hyperkalemia secondary to tissue destruction, pH change and anesthesia also play a role in the surgical patient and share with citric acid in the etiology of cardiac abnormalities with massive blood transfusion.

Most authorities continue to recommend proplylactic calcium chloride or calcium gluconate administration with massive blood transfusion. Howland and his group, however, no longer feel it is indicated. They use a blood warmer and have observed a remarkable decrease in morbidity and mortality with massive ACD blood infusion. Other authors have recommended proplylactic use of cardiac glycosides, epinephrine, and procaine infusion, however, these as yet have not been adequately demonstrated to be effective.

In avoiding the cardiovascular complications of massive whole blood transfusions precautionary measures

should include:

a) ECG monitoring of patients

b) Continuous replacement of blood loss

c) Venous pressure monitoring

d) Calcium gluconate or calcium chloride administration with blood infusion in excess of 2 liters

e) Warming of blood prior to administration if large quantities are anticipated.

One must consider any transfusion hazardous especially when modifying circumstances are present. In addition massive transfusions are prone to produce grave complications of which cardiac standstill or fibrillation are the most severe. Any transfusion which exceeds the following criteria should be considered massive and the necessary precautions should be practiced:

1) Any transfusion of greater rapidity than one unit (540 ml.) in five minutes.

2) Any transfusion during which multiple units of blood will be given such as to exceed one unit every thirty minutes up to five.

3) Any time more than five units of blood are given in a 24 hour period.

SUMMARY

Complications of blood transfusions are reviewed with emphasis on the infusion of acid-citrate-dextrose stored blood. Changes in ACD stored blood are reviewed. Massive blood transfusion is defined as to the rate and quantity of blood administration necessary to cause in-

creased morbidity or mortality. Finally citrate, its metabolism and physiology are considered. The relative safety of ACD stored blood is pointed out and those factors which may compromise its use defined.

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