THE PROBLEM OF CARDIAC COLLAPSE ASSOCIATED WITH THE MASSIVE TRANSFUSION OF CITRATED BLOOD

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IN RECENT YEARS there has been a great deal of discussion concerning the hazards associated with the administration of massive amounts of citrated blood. With the increase in magnitude of cancer and cardiovascular surgery the administration of ten to thirty units of blood is no longer a rarity, and with these volumes many complications, particularly cardiac, have occurred. It is not proposed to discuss the well-known complications resulting from human error in typing, labelling, and administering citrated blood. These and other types of reactions are well understood and have been frequently covered in the many excellent articles and texts that have been published. Discussion will be limited to those aspects about which there is still a large measure of ignorance and disagreement, namely, citrate intoxication, ionized calcium deficiency, potassium excess, cardiac hypothermia, and the roles that it is suspected they may play in producing cardiac asystole or ventricular fibrillation, which are the two serious cardiac complications of rapid, massive citrated blood transfusion usually reported.

Citrate intoxication was one of the first problems associated with transfusion to be studied. As citric acid combines with calcium to form a diffusible but poorly ionized complex, much of the calcium bound to citrate is thus rendered biologically inactive, at least as far as it is concerned in the function of cardiac muscle, skeletal muscle, and blood clotting. Calcium must be present in an ionized form to perform these functions.¹ Because citrate is rapidly utilized under normal conditions it has been regarded as a perfectly safe anticoagulant for blood and the danger of citric acid intoxication resulting from transfusion of blood has been thought in the past to be negligible. There is now good evidence that with the massive amounts of blood now used, and the speed with which it must often be administered, and with the increasing number of patients with liver disease undergoing surgery, citrate concentrations may often rise to toxic levels. It is now well recognized that tremendous increases in citrate concentrations can occur during exchange transfusions in erythroblastotic infants; tetany and deaths have been reported.²

Bunker³ reported that there is no serious accumulation of citrate when the rate of transfusion in adults without liver disease does not exceed 500 ml. every thirty minutes; however, when the rate was doubled, about half of the patients without liver disease and all of those with liver disease had serum citrate levels of about 9 mg. per 100 ml. This rate is frequently exceeded today, and 500 ml. in five minutes is not uncommon in certain centres. It has been stated¹ that serum

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citrate levels below 25 mg. per cent will not seriously depress the level of ionized calcium. In Bunker's³ series there were several cases with levels in excess of 25 mg. per cent. There is an increased danger of reaching excessive blood citrate levels in the presence of liver disease, hypotension, hypothermia, and metabolic diseases involving disturbances of calcium metabolism.

No direct toxic effect of citrate has been shown. Presumably then the ill-effects are all due to the decreased amount of ionized calcium. Ludbrook and Wynn⁴ reported four cases of citrate intoxication with one death. In their investigation they found that citrate infusion at the rate of 1 mg. per kilogram per minute resulted in a plasma citrate level of 12.5 mg. per cent. They state that a level of 90 mg. per cent is undesirable and in a normal adult corresponds to a steady rate of citrated blood infusion of about 540 ml. per five minutes, a rate occasionally achieved. It appeared that except with excessively rapid rates of infusion some defect in plasma clearance of citrate is necessary to produce dangerous levels. Liver disease, anuria, hypothermia, impairment of liver circulation, or high abdominal aortic clamping may so impair citrate clearance that toxicity becomes a real danger. The recognition of citrate intoxication is difficult. Hypotension may be both the cause for and the effect of rapid massive transfusion. Electrocardiographic changes seen with hypocalcemia may be due to many other factors also, such as hypothermia or hypokalemia. Muscle twitching or convulsions are unlikely under anaesthesia. Excessive oozing is more likely due to blood replacement with stored blood than to the citrate.

Howland and his group⁵ established normal citrate values in man. They also demonstrated lengthening of the Q.T. interval with large amounts of citrate and found good correlation between the rate of infusion and plasma citrate levels, but did not observe any ill-effects. These same workers⁶ reviewed 266 cases, 114 of whom received calcium during massive transfusion while the remaining 152 cases did not. Those cases receiving calcium had a higher mortality rate than those not receiving calcium. They believe that the cardiovascular effects from excess calcium are more dangerous than those from hypocalcemia and do not advise its use, a view that is certainly contrary to past and most present practice and teaching.

There is no unanimity of opinion concerning the value of or need for calcium when administering citrated blood, but it does appear that we now have some knowledge of when citrate intoxication may occur. Excessively rapid massive transfusion, the presence of anything interfering with plasma clearance of citrate such as liver or kidney disease, interference with liver or kidney blood flow, hypothermia, high aortic clamping, and diseases in which calcium is not freely mobilized; these all predispose to this danger and should make one at least consider the need for calcium. The usual dose advised is 1 gram of calcium for each 1,000 ml. of citrated blood transfused, but this dose can only be a guess, as one never knows what the level of ionized calcium is.

The next problem, which has been neglected until recent years, is the possibility of potassium intoxication resulting from the rapid transfusion of large amounts of stored blood. Again Howland and co-workers⁶ believe that there is little direct evidence in man for the incrimination of hyperkalemia as the cause of the cardiac

difficulties that often occur with massive transfusion. They state that the evidence is indirect and is based mainly on the fact that plasma potassium levels increase progressively with the age of the stored blood. The potassium content increases at the rate of approximately 1 mEq./L. per day. This possible massive administration of potassium has been put forward as another argument for the need of calcium during the transfusion to prevent a disturbance of the calcium/potassium ratio⁷.

Howland's⁶ study of calcium and potassium levels in five patients receiving blood at rapid rates failed to demonstrate any potassium levels out of the normal range. Calcium levels were only slightly below normal in three cases and these tended to rise despite further administration of blood. These workers further failed to observe any pressure response from calcium administration. Bunker,³ in his study of citrate intoxication, did not observe any elevation of the serum potassium above normal. Howland⁶ argues that even if bank blood containing 10 to 25 mEq. of potassium in each litre of plasma is given at the rate of 500 ml. per five minutes, an extremely rapid rate, the total dosage would be 0.6 to 1.6 mEq./L. per minute of potassium infusion, which is below the 1.8 mEq./L. per minute danger level for a 70-kg. man. From a great deal of experience obtained using potassium to produce cardiac arrest during open heart surgery it has been found that the average concentration of potassium required is about 200 mEq./L., which is never approached by bank blood.

Taking a completely opposite view is LeVeen,⁷ who believes that it is the disturbed calcium/potassium ratio resulting from citrate infusion that is responsible for the cardiac difficulties encountered. In his series he estimated that one-third of the cardiac arrests were due to transfusion and that these patients received an average of 77.7 mEq. of potassium. He also states that the level of potassium in the peripheral blood does not mirror the level in the large veins leading to the heart. He points out that during surgery and the hypotension of haemorrhagic shock there are other sources of potassium; primarily adrenalin, which is released in greater quantities during haemorrhagic shock and which causes the release of potassium from the liver because, as glucose is released, so also is potassium. Because isoproterenol and levarterenol are less active in this respect he recommends their use in preference to adrenaline. LeVeen also believes that the toxicity of potassium is increased in shock, hypoxia, and hypercarbia. He further states that digitalis and calcium will effectively counteract excess potassium, that calcium can be used liberally when the potassium levels are high, and that even in the digitalized patient calcium can be used safely if one is sure the potassium level is high. Unfortunately it is usually impossible clinically to know whether the potassium level is high or the calcium level low, and there is much evidence, as Howland⁶ states, that an excess of calcium can be just as dangerous as an excess of potassium, especially in the digitalized patient.

It would appear that there is considerable argument for both approaches, but nothing to prove either. Certainly there is nothing to guide a clinician in a given situation unless he possesses laboratory facilities superior to those available to the average anaesthetist. Therefore, in the present state of our knowledge, neither calcium deficiency nor potassium excess is likely except in unusual

circumstances; and few of us are ever in a position to know which, if either, factor is or is not present in any given case. Prophylaxis is then really only guess-work and may well do more harm than good.

A new approach may well be the answer to cardiac collapse associated with massive transfusion and may in itself lend more importance to the effect of relatively slight changes in potassium and calcium levels; this is the effect of cardiac hypothermia, which occurs with a rapid transfusion of massive amounts of refrigerated citrated blood. Boyan⁸ has recently investigated the occurrence of cardiac hypothermia during this type of transfusion. Rapid transfusion of refrigerated blood at 4° C. will reduce body temperature by perfusion and the first organ exposed to the cold blood is the heart. These workers measured oesophageal temperatures behind the atria and found that in general there was less than 1.5 centigrade degrees change in the oesophageal temperature until after 1,800 ml. of blood had been administered. They state that this generalization has to be correlated with body mass, speed of transfusion, temperature of stored blood, the length of time body cavities are open, and the room temperature. During haemorrhage with loss of blood the body also loses heat. Boyan reported several cases of oesophageal temperatures in the region of 30° C. They were able to correlate these temperature falls with the amount of blood transfused and the electrocardiographic changes. They also treated several cases using a blood warmer and were impressed with the minor temperature changes, the absence of electrocardiographic changes, and the improved appearance of these patients as compared with those who became hypothermic. It has been recognized for a long time that, with induced hypothermia, temperatures below 28° C. are dangerous because of the increased incidence of ventricular fibrillation. McLean⁹ has recently observed ventricular fibrillation in patients made hypothermic by the transfusion of cold bank blood. This is an event that can easily occur in the infant, who tends to become hypothermic during anaesthesia. Smith¹⁰ reported work in dogs that showed that more dogs survived a rapid massive transfusion of cold blood given by artery than when given by vein. When given by artery the blood circulates and is warmed, buffered, and citrate removed, and the temperature in the right side of the heart rarely drops over 2 or 3 degrees centigrade. When a similar transfusion is given by vein the cold acid citrated blood reaches the heart virtually unmixed and there is a precipitous fall in temperature in the right side of the heart, with fibrillation. It is well known that acid citrated blood in large amounts is more toxic than equal amounts of heparinized blood at the same temperature.

The lowering of body temperature not only affects resting and action potentials of cardiac muscle and conduction but also interferes with the movement of ions across the cardiac muscle membranes. Other factors that may play an important role in this aspect of hypothermia are pH and pCO₂ changes.¹¹ Acidosis is a regular accompaniment of severe haemorrhagic shock and it must undoubtedly play a role. Citrated blood is an acid substance with a pH range of 6.6 to 7.1 and massive amounts of it in the presence of hypovolemia and hypotension could contribute greatly to an aggravation of the metabolic acidosis. With an inadequate circulation through the lungs one could also expect excessive blood and tissue

CO₂ levels. With metabolic acidosis there is depletion of the bicarbonate buffer system and this is accompanied by a decrease in the blood's ability to carry carbon dioxide from tissues to the lung. Thrower (12), who has studied this problem of acidosis, suggests that death and shock may be due to a decrease in the ability of the blood to carry carbon dioxide, which leads to a build-up of acid cellular products, carbon dioxide narcosis, and death. These workers have demonstrated that acidosis is accompanied by a decrease in ventricular contractile force, cardiac output, and the arterial blood pressure; that there is a decrease in the response of the myocardium and vascular system to the injection of vaso-pressors; and that all of these derangements are corrected with the correction of the acidosis. We should give thought to the more frequent use of intravenous bicarbonate to correct this metabolic acidosis.

Apparently little, if any, work has been published on acid-base disturbances following massive citrate transfusion in man. A review of the literature failed to reveal any significant studies concerning this aspect of the problem. Litwin¹³ reported a study of the metabolic alkalosis that follows massive citrate transfusion, but little attention was given to the immediate metabolic acidosis that occurs other than to mention its occurrence and that the alkalosis that follows transfusion commences several hours later, reaching its peak on the third day. This alkalosis had a beneficial effect in correcting the metabolic acidosis of haemorrhagic hypotension.

Boue,¹⁴ in studying the effect of citrated blood on the isolated dog heart, found a decrease in rate and a negative inotropic effect with final standstill. These effects commenced at a pH of 7.2 with arrest at pH 6.8 to 7.0. Calcium would not correct this, but buffering the blood with THAM resulted in improvement, and with a normal calcium level would restore normal cardiac function.

Boyan and Howland⁸ have remarked that a possible common factor resulting in cardiac difficulties during massive citrated blood replacement is hypothermia of the heart. This hypothermia alone is unlikely to be dangerous, but with the possibility of calcium and potassium disturbances, low pH, pCO₂ excess, tissue hypoxia from severe hypotension, then the hypothermia could well be the determining factor in the production of cardiac asystole or ventricular fibrillation. The addition of the metabolic acidosis caused by the citrate and the tissue hypoxia could be an additional aggravating factor. Therefore, it would appear that on the basis of the present evidence we must give consideration to all of these many factors when we find it necessary to transfuse massive amounts of refrigerated, stored citrated blood rapidly.

ADDENDUM. Since this paper was submitted for publication, John P. Bunker *et al.* have published a study entitled "The Hemodynamic Effects of Intravenously Administered Sodium Citrate" (*New England Journal of Medicine* 266 (8): 372-378, Feb. 22, 1962). These workers studied the effects in dogs and man and demonstrated for the first time in man moderate to severe cardiac depression at serum citrate levels that have been reported to occur during rapid transfusion in man. They found circulatory depression at levels of 50-75 mg. per 100 ml., which levels they state can be achieved by infusion of multiple units of citrated blood

at the rate of one unit every three or four minutes to a patient weighing 70 kg. They reported that calcium chloride, digitalis, and to a lesser degree epinephrine were effective in protecting the heart against citrate intoxication.

They also suggest that the patient with poor cardiac function or the patient in haemorrhagic shock, may exhibit less tolerance to high citrate levels, and that the effects of other factors such as hyperkalaemia, increased hydrogen ion concentration, and anaesthesia may share with citric acid an additive effect on the aetiology of circulatory disaster.

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