1957

Electrocardiographic and serum electrolyte changes occurring during exchange transfusions

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ELECTROCARDIOGRAPHIC AND SERUM ELECTROLYTE CHANGES OCCURRING DURING EXCHANGE TRANSFUSIONS

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Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

April 1, 1957

Omaha, Nebraska

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INTRODUCTION

Since the discovery of the Rh blood factor in 1941 tremendous advances have been made in the understanding of the entity known as erythroblastosis fetalis and in its management. Exchange transfusion, the present accepted treatment for those severely affected by this condition, has been used only for the past decade. Although the exchange transfusion has done much to reduce the mortality and morbidity of erythroblastosis fetalis, it is by no means an innocuous procedure. The exchange, in which most of the infant's blood volume is replaced by citrated (or heparinized) donor blood, can and does place many physiologic stresses upon the infant. Relatively few detailed studies have been reported concerning electrocardio-graphic and serum electrolyte changes occurring during exchange transfusions and often parallel studies of the two aspects have not been made on the same group of patients. This paper reports a study made upon nine infants with erythroblastosis fetalis subjected to exchange transfusion in which special attention was directed toward the effect of the transfusion upon the electrocardiographic tracings and upon the serum electrolytes.

HISTORICAL REVIEW

The first reported attempt to completely replace the blood volume of an infant was made by Hart (1) in 1925 on an erythroblastotic child, in which he injected 335 cc. of donor blood into the saphenous vein and withdrew 300 cc. through the anterior fontanelle. Although the child recovered he did not report any further trials with the procedure. It was not until 1944, after the discovery of the Rh factor and more was understood about blood groups and the etiology of erythroblastosis, that further attempts were made to replace the total blood volume of the affected infant as a means of treatment for the disease. Weiner and associates (2) in 1944 successfully attempted an exchange transfusion on a Mongolian idiot. Encouraged by this success they began using the procedure on erythroblastotic babies (3). Wallerstein was another early advocate of the exchange transfusion, performing his first in 1946(4,5).

Since these early attempts the technique of the exchange transfusion has been improved greatly. In general two types of procedures are used today. One is the method advocated by Weiner (6) in which blood is simultaneously injected via a cannula into the saphenous vein and withdrawn from the radial artery. The other method, as advocated by Diamond (7), utilizes the umbilical vein, in which blood is alternately withdrawn and injected through the same polyethylene tubing. Most workers use citrated donor blood, but recently

the use of heparinized blood has been advocated by Pew (8) to avoid the danger of hypocalcemia. By either method a large percentage of the infant's circulating blood volume is replaced by donor blood. Estimately an average newborn infant's blood volume at 250 ml., a transfusion of 500 ml. replaces 82-86 percent of the patient's blood volume, whereas a transfusion of 1000 ml. (four times the infant's blood volume) replaces 96 percent of the blood (7,9). These figures are roughly true for either method of transfusion (9).

Investigators early recognized the possibility of electrolyte changes accompanying exchange transfusions. Wallerstein (5) was the first to advocate the administration of calcium gluconate during the procedure to counteract the effect of the citrate in the donor blood. Citrate by forming an unionized complex with calcium can thereby lower the ionized fraction of serum calcium (which is the portion that is physiologically active) to potentially dangerous levels. At one time some workers gave the calcium only after the transfusion was completed, but now most advocate its administration periodically (generally 0.1 gm. for each 100 ml. infused) during the procedure to guard against hypocalcemia (6,7 and 10).

Potassium is another electrolyte which must be considered. It has long been known that the plasma potassium level tends to gradually rise the longer donated blood is stored because of the escape of potassium from the erythrocytes. Miller and associates (11) tested the plasma potassium concentrations of several bottles of donor blood which had been stored for variable periods of time.

Those stored less than five days had potassium concentrations ranging from 5-8 meq./l.; those for 5-10 days, 6-13 meq./l.; those for 11-15 days, 8-14 meq./l.; and those stored for 16-20 days, 10-18 meq./l. The question must always arise whether an erythroblastotic infant can handle this extra load of potassium. Often it has been the most severely affected infants who have been given the older units of blood, these often being more readily available for immediate use. It has been shown repeatedly that calcium and potassium are somewhat antagonistic in their effects on the body's physiology (12,13), so that a combination of hypocalcemia and hyperpotassemia as might occur during an exchange transfusion could prove to be especially dangerous.

Because of the meager clinical signs which accompany all but the more severe electrolyte imbalances, the electrocardiograph can be a great aid in detecting these imbalances. The recording of the electrical activity of the heart will often be an early clue to the presence of electrolytic disturbance. Thus it would seem worthwhile to review briefly the ECG changes which have been reported with abnormalities of the serum calcium and potassium concentrations.

The main effect of calcium upon the ECG tracing is noted in the duration of the Q-T interval, which is the measure of the duration of the electrical systole of the heart. The Q-T interval normally varies inversely with the heart rate so that in measuring its duration some sort of correction must be made for the heart rate at the given time. Also it should be noted that the Q-T interval adjusts gradually rather than instantaneously to changes in

the heart rate (14). The most widely used formula for adjusting the Q-T for the heart rate is that devised by Bazett (15): $Q\text{-}T_c$ (or K) = Q-T/ c, in which $Q\text{-}T_c$ is the corrected Q-T interval and c is the length of an individual cycle in seconds. Ashman and Hull (14) have modified Bazett's formula as follows: $Q\text{-}T_c$= Q-T/ log10(c + .07). They maintain that this formula is more accurate than Bazett's formula, which gives values too low for males and too low for females when the heart rate is rapid.

In hypocalcemia the major effect noted is a lengthening of the Q-T interval (16,17,18 and 19), this lengthening occurring in the S-T segment (19,20,21 and 22). White and Mudd (17) noted no other conditions which prolonged the Q-T except for those which produced prolonged QRS complexes, such as premature ventricular contractions and bundle branch block. In general the degree of lengthening of the Q-T parallels the degree of lowering of the ionized calcium (21), but Wofford and Ernstene (18) have pointed out that there is no mathematical relationship between the degree of prolongation of the Q-T and the level of the serum calcium, also that some cases of hypocalcemia did not have prolonged Q-T intervals. Reports of the effects of hypocalcemia on the T wave are not consistent. Ernstene and Proudfit (19) report that it is not altered whereas Bellet (22) states it may become inverted. Lepeschkin (23) in his review of the U wave and its significance states that if a U wave is normally present it will become lower or disappear with lowered serum calcium.

In hypercalcemia a slight shortening of the Q-T interval may be noted (20,21). Merrill (20) states this change is too small to be useful. It has been noted also that the T wave may be followed by a prominent U wave (22,23).

One of the earliest signs of hyperkalemia is a narrowing of the base of the T wave, producing a "tent-shaped" wave (13). The T wave also may increase somewhat in amplitude (20,22). Bellet (22), who compared ECG changes with the level of potassium in the serum, noted these changes at levels of 6-9 meq./l. With higher concentrations of potassium (e.g. 10-13 meq./l.) the QRS complex widens with associated irregular ventricular rhythm appearing. With very high concentrations (e.g. 14-18 meq./l.) there is a slow idioventricular rhythm with wide QRS complexes. Other changes which have been noted with hyperkalemia are sinus pauses (22) and prolonged P-R interval with decreased amplitude of the P wave (20).

In hypokalemia the pattern is somewhat more variable. The T wave becomes lowered or inverted and the U wave appears and becomes more prominent with decreasing potassium concentration (19,20,22 and 23). Both Ernstene and Proudfit (19) and Merrill (20) state that the Q-T interval is prolonged independent of the U wave, whereas Lepeschkin (23) claims that the Q-T is not prolonged but only seems so because the U wave is often mistaken for the T wave. Bellet (22) points out the difficulty in measuring the true Q-T interval because of the bizarre waves seen in hypopotassemia. With a rapid heart rate the P wave may appear to be more prominent because of the

superposition of the preceding U wave (22). Supraventricular arrhythmias are apt to occur (22). There may be some depression of the S-T segment (19,20 and 22), with no prolongation of the segment according to Ernstene and Proudfit (19) or with prolongation according to Bellet (22).

There have been three reports giving detailed descriptions of electrocardiographic tracings taken on infants receiving exchange transfusions. Fürman, Hellerstein and Startzman (24) took serial tracings on six infants during the procedures. In all of these infants signs of hypocalcemia developed (no calcium was injected until the end of the transfusion). Four of them showed marked fine muscle tremors, detectable clinically in only one, which made measurement of the Q-T intervals impossible. The other two demonstrated marked prolongation of the Q-T interval with slight decrease in the amplitude of the T waves in leads I and aVL. No changes were noted in the P-R interval, QRS complexes or the electrical position of the heart. After the termination of the transfusions, when the calcium gluconate was injected, there was a marked reversal in the appearance of the ECG tracings. The muscle tremors disappeared and the Q-T interval returned to normal in the ones in which it could be measured before and after. In all the infants there was a consistent reduction of the heart rate, ranging from 24-34 beats per minute, with injection of the calcium. In four of the six patients T waves that had been upright in I and aVL before the transfusion were isoelectric or inverted after the calcium was given.

Gustafson (25) reported on electrocardiographic tracings taken on eight infants receiving exchange transfusions, these infants receiving 0.2 gm. of calcium gluconate with each 100 ml. of infused blood, or when indicated by the ECG. He noted that gross muscle tremors appeared after every 100 to 150 ml. of infusion which disappeared promptly after calcium administration. He also noted that while in the healthier babies the tremors were accompanied by fussing and crying, the more severely involved babies did not demonstrate these clinical signs, although the ECG tracings still showed the need for calcium and improvement following its administration. Injection of calcium slowed the heart rate. In most of the patients the Q-T interval could not be measured accurately because of the muscle tremors or because the T was isoelectric. In instances where it could be measured no prolongation was noted. No consistent variation in the heart rate was noted with injection or withdrawal of blood, nor did rapid injection of blood produce any ECG changes. However with rapid injections the babies fussed more. No significant difference was noted between the tracings taken before and ten minutes after the procedures.

Joos, Yu and Miller (26) took ECG tracings on ten newborn infants receiving exchange transfusions, the infants receiving 0.1 gm. calcium gluconate per 100 ml. of blood. They noted the heart rate to decrease with calcium injection in 22 instances and rise in 8. No consistent changes in heart rate were observed with any other phase of the procedure, e.g. injection or withdrawal of

blood. There was definite lengthening of the S-T segment at some time in all the cases except one. This lengthening appeared before the muscle tremors. The injection of calcium gluconate shortened the Q-T interval by shortening the S-T segment. No significant changes were observed in the T wave, although calcium administration usually produced transient lowering of the T. The T wave was consistently taller with injection than with withdrawal of blood. Two infants developed arrhythmias--partial A-V block--which were relieved by calcium injection.

Several investigators have checked serum electrolyte concentrations on samples of blood taken at various intervals during exchange transfusions. These have shown no significant change in the serum sodium concentration (26,27 and 28). All calcium measurements were for total serum calcium, since unfortunately no laboratory test is available for directly measuring the level of the ionized calcium. Total serum calcium measurements showed normal or elevated levels, even though electrocardiographic tracings taken simultaneously showed signs of hypocalcemia (24, 25 and 26).

Some infants have been found to have somewhat elevated potassium levels prior to the start of the exchange transfusion (26,27, 29 and 11). As has been previously pointed out, many infants receive hyperkalemic donor blood, and the older the donor blood the higher its potassium concentration in the plasma is apt to be. Many but not all of the infants which have been studied for serum electrolytes could compensate well for the larger load of potassium infused.

Miller and associates (11,29) noted that among the eight patients they studied four started with normal potassium concentrations and received normokalemic donor blood; these all exhibited no change during the procedure. Four others received hyperkalemic blood. Two of these started with normal levels but ended with elevated concentrations and a third started with a somewhat elevated level which rose slightly during the procedure. Of the ten cases reported by Joos, Yu and Miller (26) two developed increased potassium concentrations during the exchange, both of these receiving hyperkalemic blood and one starting with an elevated potassium level. In these cases the only ECG evidence of potassium toxicity was an increase in the amplitude of the T wave. Bolande, Traisman and Philipsborn (28) reported 23 cases of which four received normokalemic blood and all did well. Of the 19 which received hyperkalemic blood, 12 did well but seven suffered cardiac arrest and/or death during the procedure or afterward (two deaths were thought not to be related to the procedure itself). They felt that the rate of infusion of the hyperkalemic blood might be an important factor in how well the infant tolerates it.

Ames, Syllm and Rapoport (30) point out the possibility of citrate toxicity independent of its effect on the serum calcium. Wexler and associates (31) have shown that erythroblastotic babies had somewhat impaired (but still capable) ability to remove citrate from the blood. The temperature of the infused blood is also a factor which many investigators consider important, contending

that the donor blood should be allowed to warm somewhat before its infusion. Thus it is apparent that there are many factors to be considered when performing an exchange transfusion. The infant's physiology potentially may be disturbed by any or all of these factors. The infant has great capacities for adjusting to these disturbances, but such is not invariably so.

MATERIALS AND METHODS

This study was conducted on nine newborn infants who received exchange transfusions for treatment of erythroblastosis fetalis produced by Rh incompatibility. Seven of the procedures were conducted at Children's Memorial Hospital, one at Bishop Clarkson Memorial Hospital and one at Nebraska Methodist Hospital. Table I (p. 14) gives some of the basic information concerning each case. All the infants were of mature size, their birth weights ranging from 2530 to 4000 grams.. The age at which the exchange transfusion was performed varied from $2\frac{1}{2}$ to 54 hours after birth. Only Case I received one unit (or less than 500 ml.) of blood, the rest receiving two units (or close to 1000 ml.). None of the donor blood used had been stored in excess of four days (Table III, p. 15). The amount of blood transfused ranged from 390 ml. to 960 ml. In general 0.1 gm. of calcium gluconate (0.2 gm. in Case IV) was injected intravenously for every 100 ml. of infused blood, with some variations from this general pattern.

Table II gives some of the preliminary laboratory data obtained on the infants. All reacted positively to the direct Coombs' test and all had elevated serum bilirubin values. Most of them had increased numbers of normoblasts seen in the peripheral blood.

Blood samples were taken from each unit of donor blood. Samples were also taken from each patient at the start of the exchange and just prior to each injection of calcium gluconate (or following each 100 ml. injected if the calcium injection was delayed). The blood

samples were kept refrigerated during the procedure. Immediately following the transfusion the samples were centrifuged and the plasma or serum drawn off to avoid contamination of the electrolyte concentrations by erythrocyte hemolysis. The serum electrolyte determinations were made by the personnel of the University of Nebraska Hospital Laboratory. Sodium and potassium concentrations were determined by the use of the flame spectrophotometer (32). Total serum calcium concentrations were made by oxalate precipitation of the calcium followed by titration of the oxalate (Clark and Collip, 33).

An electrocardiographic tracing was taken on each infant immediately before and after the exchange transfusion, recording the six standard limb leads. During the transfusion one of the leads was recorded periodically, always before and after each injection of calcium gluconate and also at variable intervals between the calcium injections. The limb lead which showed the most prominent T wave was the one usually chosen to use during the transfusion and most often was either lead III or I. $Q\text{-}T_c$ intervals were calculated from the average measured Q-T intervals in a given tracing according to Ashman and Hull's modification of Bazett's formula (14): $Q\text{-}T_c = Q\text{-}T / \log 10(c + 0.07)$, in which the normal value for $Q\text{-}T_c$ in males and children is given as 0.375 second and "c" refers to the length of an individual cycle in seconds. Ashman and Hull give the upper limits of normal for $Q\text{-}T_c$ for children as 0.405 second.

TABLE I

General Information

Case No.	No. of Siblings	Birth Weight (gms.)	Age at Time of Exchange (hrs.)	Time for Exchange (min.)	Blood Transfused (ml.)	Blood Withdrawn (ml.)
I	2	2640	27	106	390	320
II	3	3300	4½	140	915	930
III	6	4000	2½	140	895	930
IV	1	3400	2½	64	690	720
V	1	3360	54	145	790	770
VI	3	2910	3½	100	880	870
VII	2	3520	5½	94	925	940
VIII	5	2760	6	112	705	730
IX	4	2530	15	96	960	936

TABLE II

Laboratory Data

Case No.	Direct Coombs' Test	RBC's Before Exchange (mill./cmm.)	RBC's After Exchange (mill./cmm.)	Serum Bilirubin Before Exchange 1 min. (mg. %)	Total	Nucleated RBC's (/cmm.)
I	Pos.	4.08	4.61	Jaundiced		2,700
II	Pos.	6.15	3.68	0.26	2.20	900
III	Pos.	6.77	4.65	0.46	2.8	-
IV	Pos.	5.45	4.17	3.10 *	4.4 *	9,100
V	Pos.	2.46	5.24	9.6	32.1	51,000
VI	Pos.	4.05	4.75		2.5	4,100
VII	Pos.	3.32	3.19	1.44	18.4	31,100
VIII	Pos.	3.83	3.74	0.65	12.4	52,000
IX	Pos.	2.97	3.68	13.2	29.5	202,000

* Values obtained on day following transfusion.

TABLE III

Plasma Electrolyte Levels of Units of Donor Blood
Used in Exchange Transfusions

Case No.	Donor Bottle	Age (Days)	Sodium (meq./l.)	Potassium (meq./l.)	Calcium (meq./l.)
I	A	Fresh	165	4.3	4.5
II	A	2	-	-	3.4
	B	2	136	5.4	3.7
III	A	4	134	10.7	3.9
	B	4	134	7.4	3.9
IV	A	1	154	9.3	4.6
	B	1	-	-	-
V	A	4	138	8.8	4.4
	B	4	152	13.0	3.1
VI	A	1	170	5.5	4.3
	B	1	142	4.9	-
VII	A	1	154	4.3	2.8
	B	1	152	4.6	3.0
VIII	A	2	148	5.1	4.1
	B	2	148	6.0	4.5
IX	A	2	146	8.2	4.5
	B	1	142	5.3	3.6

RESULTS AND DISCUSSION

All of the infants survived the transfusions and were in satisfactory condition at the close of the procedure. Case II developed a brief period of cyanosis precipitated by vomiting and possible aspiration, but this was rectified rapidly by suction and oxygen administration. No other untoward events of any significance occurred during the transfusions. One infant (Case IV) subsequently died of a cause unrelated to the erythroblastosis and exchange transfusion (meconium ileus with perforation of bowel). A few of the infants required small simple blood transfusions later in their hospitalization or at subsequent hospitalizations to correct anemia, but none of them received a second complete exchange transfusion. No complete follow-up information is available as to whether any of the infants sustained cerebral damage, but no such signs were evident at the time the patients were dismissed from the hospital.

Serum Electrolytes.

1. Donor Blood. Table III (p. 15) lists the plasma electrolyte values of the units of blood used in the exchange transfusions. The ranges of normal for these electrolytes for the UNH Laboratory are as follows: sodium 133-152 meq./l., potassium 3.7-5.6 meq./l. and calcium 4.5-5.5 meq./l. (9-11 mg. %). The plasma sodium levels were variable with no particular significance being placed upon these variations. Seven of the seventeen units exhibited elevated potassium

concentrations, but only two of these were above 10 meq./l. It is noted that all four units which had been stored four days had elevated potassium levels, and even one of the day old units (Case IV) had a plasma potassium of 9.3 meq./l. While most of these potassium elevations were not enough to cause any great concern, they do point out the rapidity with which plasma potassium may rise in stored donor blood and the value of using as fresh a unit as possible.. The calcium concentrations were at the lower limits of normal or below. These low levels may be only apparent, possibly because of the high citrate concentration interfering with the complete precipitation of calcium as oxalate in the laboratory determination.

2. Serum Sodium. There were no significant fluctuations or abnormalities of the serum sodium concentrations in the nine infants, either before or during the exchange transfusions. Serum sodium levels at the start of the procedures varied from 136 to 154 meq./l. Sodium concentrations at the time of withdrawal of the last blood samples, usually close to or at the end of the exchange, varied from 134 to 150 meq./l. The greatest differential between the concentration at the beginning and the end of the procedure for any one individual was 8 meq./l., an insignificant difference.

3. Serum Potassium. As has been mentioned earlier, elevated serum potassium concentrations may occur not only during the course of an exchange transfusion due to the administration of hyperkalemic donor blood but may be present at the onset of the exchange. Potassium levels on the nine infants at the beginning of the exchange transfusions

varied from 3.6 to 6.1 meq./l. Only one (Case II) had an elevated potassium concentration (6.1), the next highest value being 4.9 meq./l. That one elevation may not have been valid, since the next sample was recorded as 5.2 meq./l. and at no time during the remainder of the exchange did the serum potassium rise above 5.5. Possibly hemolysis of erythrocytes in that particular blood sample accounted for the high value. A few isolated samples from some of the other patients were found to have elevated potas ium concentrations, whereas the samples taken before and after these particular samples had considerably lower values. These also probably represent abnormally high potassium levels produced by erythrocyte hemolysis in the specimens.

Disregarding the few isolated specimens just mentioned, none of the infants developed hyperkalemia during the transfusions. Cases III, IV and V, all of whom received units of blood with moderately elevated potassium concentrations in the plasma (see Table III), began with potassium values of 3.8, 3.8 and 4.9 meq./l. and ended with values of 4.3, 4.2 and 4.2 meq./l. respectively. These are insignificant changes. For the whole group the range of serum potassium concentration at the time of the taking of the last blood sample was 3.6 to 5.4 meq./l., all within the normal limits. One patient (Case I) developed hypokalemic levels of 3.1 and 3.2 meq./l. midway through the procedure, but the concentration rose to 3.7 by the end. An explanation for these low concentrations is not readily apparent. No electrocardiographic signs of hypokalemia appeared during this period.

4. Serum Calcium. Levels of serum calcium during the exchange transfusions are depicted for each infant in Graphs A through J. These values are for total serum calcium and unfortunately do not measure the physiologically active fraction--the ionized calcium. As one might expect with periodic injections of calcium gluconate, the total calcium concentration gradually rose in each of the infants during the procedure. Serum calcium concentrations at the onset of the transfusions varied from 4 to 5.8 meq./l (8 to 11.7 mg. %), this range being a little wider than the reported normal range. The levels at the time of withdrawal of the last blood samples varied from 5.4 meq./l. (in the infant receiving only one unit of blood) to 7.4 meq./l. The increase in serum calcium in Case I was 1 meq./l., whereas the increase in the rest varied from 1.1 to 2.5 meq./l. (2.2 to 5 mg. %). The one infant (Case IV) which received 0.2 gm. of calcium gluconate per injection had the most rapid rise in calcium, the concentration rising 2.3 meq./l following 700 ml. transfusion and seven injections. Case VII, while having its concentration rise a slightly greater amount of 2.5 meq./l., received ten injections in 900 ml. transfusion.

Since the total serum calcium does not measure the ionizable portion, it is of no value in evaluating the presence or absence of a hypocalcemic effect upon the infant's physiology (indications of the presence of hypocalcemia in the presence of these rising total serum calcium concentrations will be discussed later). However it is of interest to observe the degree of rise in the total calcium produced by the periodic calcium gluconate injections.

Electrocardiographic Tracings.

1. Heart Rate. The fluctuations in heart rate for each infant during the exchanges are depicted in Graphs A through J. The rates at the beginning of each transfusion varied from 110 to 145 beats per minute. One hundred beats per minute was the slowest rate recorded by any of the infants during the procedure and 190 the most rapid. No changes were noted in the rates taken during injection of blood as compared to withdrawal of blood.

Typically the heart rate would gradually rise as citrated blood was injected and then abruptly fall with the injection of calcium gluconate. Out of a total of 67 injections of calcium, 47 were accompanied by a decrease in heart rate, 38 of these being drops of 10 or more beats per minute and some being drops of as much as 40 to 70 beats per minute. Ten injections produced no change in the heart rate and ten were accompanied by increases in the heart rate, all of a minor degree. In some of the patients (e.g. Cases III and V, Graphs C and E) the response of the heart rate to calcium was quite dramatic while in others (e.g. Cases IV, VI and IX, Graphs D, F and J) the response was minimal.

In one instance (Case VI, Graph F) the heart rate fell to the abnormally low level of 100 beats per minute and calcium injection increased the rate to 120. Oberst (10) has pointed out that both abnormally high and low heart rates may be indications of the need for calcium gluconate. Apparently the former is much more common.

Another generality which might be observed from these heart rate curves is the tendency for the rate to stabilize during the

course of the procedure. During the first few hundred ml. of infusion the rate often climbed to quite high levels--180 to 190 beats per minute--and the drop in rate following calcium gluconate injection was large. Later in many instances the heart rate response to calcium was considerably less and the average heart rate gradually decreased. Cases II, V and IX (Graphs B, E and J) show variations of this general stabilizing tendency.

Although typically a rise in the heart rate to 160 or more beats per minute indicates the need for calcium injection and administration of same will produce a fall in the rate, this is not always true. One cannot depend upon this as being an infalliable sign to indicate the need of the infant for additional calcium; this is clearly shown by some of these heart rate curves. Case IX (Graph J) depicts this especially well. Initially the typical drop in heart rate with calcium injection was noted. Then during a 300 ml. period in which no calcium was given the heart rate did not rise but rather gradually decreased to 120 per minute. When calcium was finally given there was a small increase in the rate to 130, and subsequent calcium injections in this patient were accompanied by very minor changes in the heart rate. Other findings (see Q-T Interval) during this 300 ml. period indicated that the patient was hypocalcemic in spite of the lack of heart rate response.

2. Q-T Interval. The calculated Q-T_c intervals on each of the infants are also depicted on Graphs A through J. Often the Q-T interval could not be measured, either because the T wave was

isoelectric or because the T wave was obscured by muscle tremors or other extraneous factors. Any small shifts in the T wave vector during the course of the procedure could possibly produce an apparent change in the length of the T wave (thereby affecting the measured Q-T) as noted upon a single lead tracing, as taken during the procedures, whereas if several lead tracings were available one could be certain whether any such change were real or apparent. In these cases there was a generally rapid heart rate and wide variations in the heart rate, both factors which possibly decrease the accuracy of the formula for calculating $Q\text{-}T_c$. In view of the above mentioned factors the calculated $Q\text{-}T_c$ intervals as depicted in Graphs A through J can be considered as only rough approximations of what was happening to the electrical systole of the heart.

Almost all of the infants manifested prolonged $Q\text{-}T_c$ intervals at some time during the exchange transfusions (upper limit of normal for children is 0.405 second). Only in Case IV (Graph D), in which 0.2 gm. of calcium gluconate was given in each injection, was the $Q\text{-}T_c$ well below the upper limit of normal. No lower limit of normal has been defined for the $Q\text{-}T_c$ interval, but the values in this patient were consistently below the so-called normal value of 0.375 second (Ashman and Hull, 14). Thus there is a suggestion that this infant might have been exhibiting hypercalcemia. At least in this patient it appears that the administration of 0.2 gm. of calcium gluconate per 100 ml. of citrated blood was a larger dose than necessary to counteract the hypocalcemic effect of the citrated donor blood.

On the other hand, giving 0.1 gm. of calcium gluconate per 100 ml. did not prevent the other infants from developing prolonged Q-T_c intervals, Case V (Graph E) being the only possible exception. In that patient, when the Q-T interval could be measured, it remained below 0.40 second except for one occasion early in the transfusion. Case VI (Graph F) had a persistently prolonged Q-T_c interval throughout the times it could be measured in spite of periodic calcium injections. Most of the rest of the infants had Q-T_c intervals which fluctuated above and below the upper limit of normal, in general staying near that level. It is interesting to note that in the series of ECG tracings reported by Gustafson (25), in which the infants received 0.2 gm. of calcium gluconate per 100 ml. of infused blood, no prolongation of the Q-T interval was noted, whereas in the study of Joos, Yu and Miller (26), in which 0.1 gm. was injected per 100 ml., all but one case had some prolongation of the Q-T interval, findings somewhat similar to those observed in this group of patients.

Usually the injection of calcium gluconate would shorten the Q-T_c interval whether or not it had previously been prolonged. Of the 47 injections of calcium in which Q-T intervals could be measured before and after injections, the interval shortened in 34 cases, lengthened in 3 (each only 0.01 second--an insignificant change) and showed no change in 10 cases. Thus it would seem that the lengthening of the Q-T intervals was produced by lowered ionized serum calcium which was rectified by the administration of calcium

gluconate, even though the total serum calcium levels were gradually rising during the transfusions. The prolongation of the Q-T occurred in the S-T segment, as has been previously reported as being a sign of hypocalcemia.

Case IX (Graph J) reveals what can happen if calcium is not injected with every 100 ml. of blood. During the 300 ml. period in which no calcium gluconate was given the $Q\text{-}T_c$ rose to and remained at a significantly prolonged level--0.46 second. Subsequent injections of calcium shortened the interval but were not sufficient to bring it below 0.40 second. It has already been mentioned that in this patient the heart rate was no help in indicating the need for calcium. Nor did the infant become excessively irritable during the 300 ml. period when no calcium was given.

3. T Wave. No consistent T wave changes were observed during the transfusions. In two cases (II and V) there was inversion of the T wave beginning shortly after the start of the procedure. In Case II the inversion persisted to the end so that there was an almost 180° shift in the T wave vector, being $\nearrow 90°$ at the beginning and -85° at the end. In case V the inversion persisted until the last third of the exchange, at which time the T wave became isoelectric and at times even slightly upright. In both cases the T wave became deeper and more pointed during each 100 ml. of infusion and temporarily returned closer to the base line following each calcium injection. In one other infant (Case IV) there was no shift in the T wave vector between tracings before and after the transfusion but

there was a similar fluctuation in the amplitude of the T wave before and after calcium injections. (Since only one lead was being followed in each case during the transfusion, one cannot be certain whether these temporary fluctuations in height or depth of the T wave represented decrease in amplitude of the wave or a shift in its vector). No significant changes or abnormalities of the T wave were noted in the other six cases.

An explanation for these T wave changes is not readily available. Bellet (22) has reported that T wave inversion can occur with hypocalcemia. Furman (24) reported some of his patients as having inversion or lowering of the T wave at the completion of the transfusion. Joos (26) has reported lowering of the T wave immediately following calcium injection. Nevertheless it is difficult to relate the T wave changes noted in Cases II and V directly to hypocalcemia. If Q-T prolongation is a valid sign of hypocalcemia, then one might expect these T changes to be more evident in some of the other patients in which the Q-T was more prolonged. The fluctuations in amplitude of the T wave with the calcium injection, however, would seem to have some relationship to the serum calcium concentration.

Inversion of the T wave could be a generalized ischemic effect. Case II did have a brief period of cyanosis following an episode of vomiting, but the T wave inversion appeared before this episode and did not significantly change at the time of the cyanosis. If the T wave inversion were due to ischemia, then it would be hard to explain why each injection of calcium would lessen this inversion.

4. Other Electrocardiographic Findings. Irritability of the infant has often been used as a criterion for the need for calcium administration during an exchange transfusion. This irritability manifests itself upon the ECG by the appearance of irregularities in the base line produced by the electrical activity of muscle tremors. Sometimes these tremors are noticeable on the ECG before one can clinically observe them in the patient. In approximately one-third of the instances immediately prior to calcium injection these muscle tremors could be seen, only to disappear upon giving the calcium. The tremors were more apt to be seen at those times in which the heart rate was high (160-180 beats per minute) prior to calcium administration and slowed considerably immediately following the injection of calcium. Since muscle activity normally produces an increase in the heart rate, this correlation is not surprising. However on several occasions the pattern of high heart rates being slowed considerably with calcium injection was seen in the absence of muscle tremors, so one cannot attribute the heart rate fluctuations entirely to the presence or absence of muscle tremors.

Only a few other scattered findings were noted on the tracings. No arrhythmias developed. No significant changes occurred in the P wave, P-R interval or QRS complex. Two infants (Cases II and VII) exhibited decreases in amplitude of the QRS complx with no change in vector direction. In Case II the decrease occurred immediately following the period of cyanosis and in the other the decrease occurred

gradually. A U wave was present both before and during the exchange transfusion in Case IV and was not altered by the procedure or the calcium injections.

TABLE A
Case I

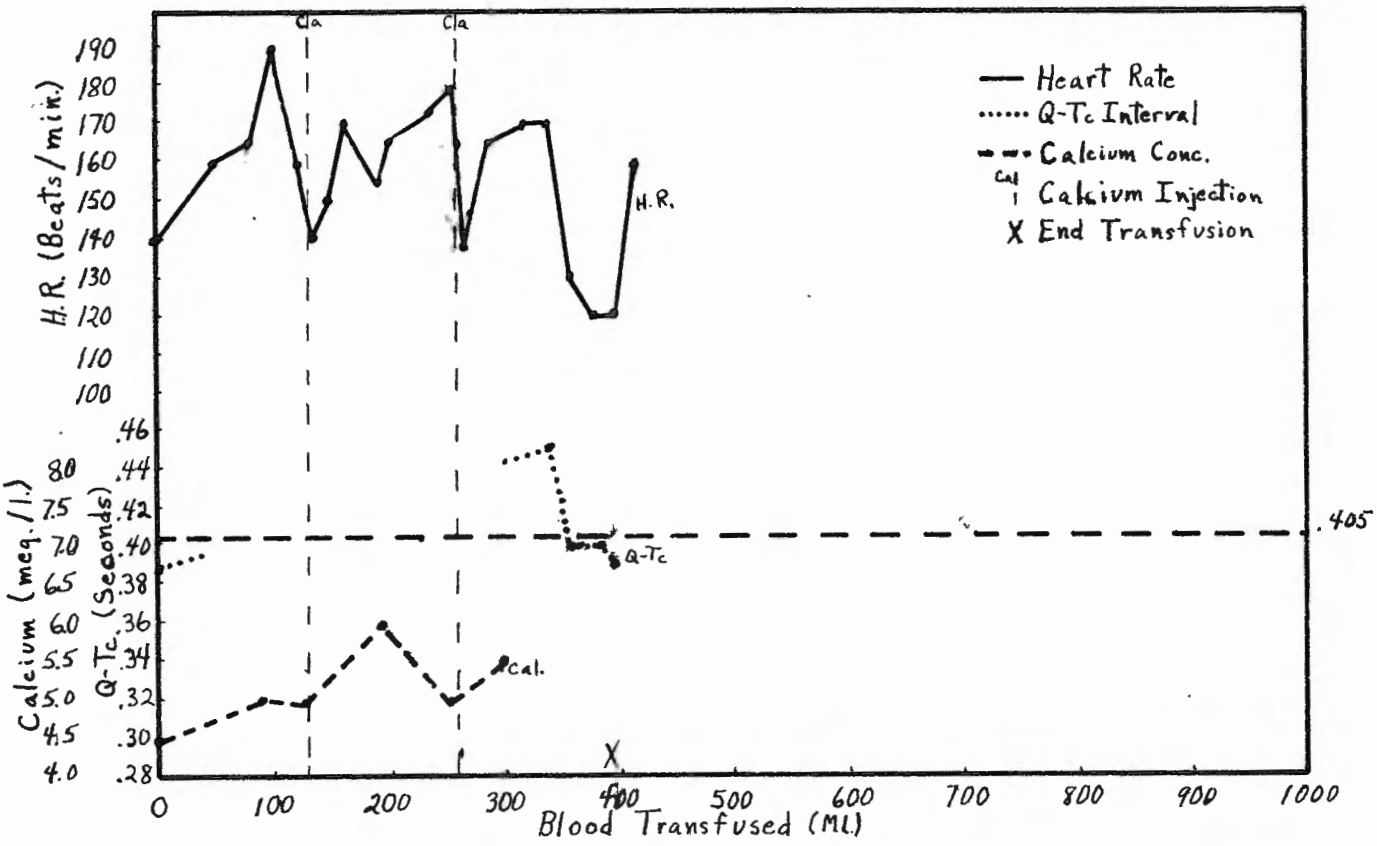


TABLE B
Case II

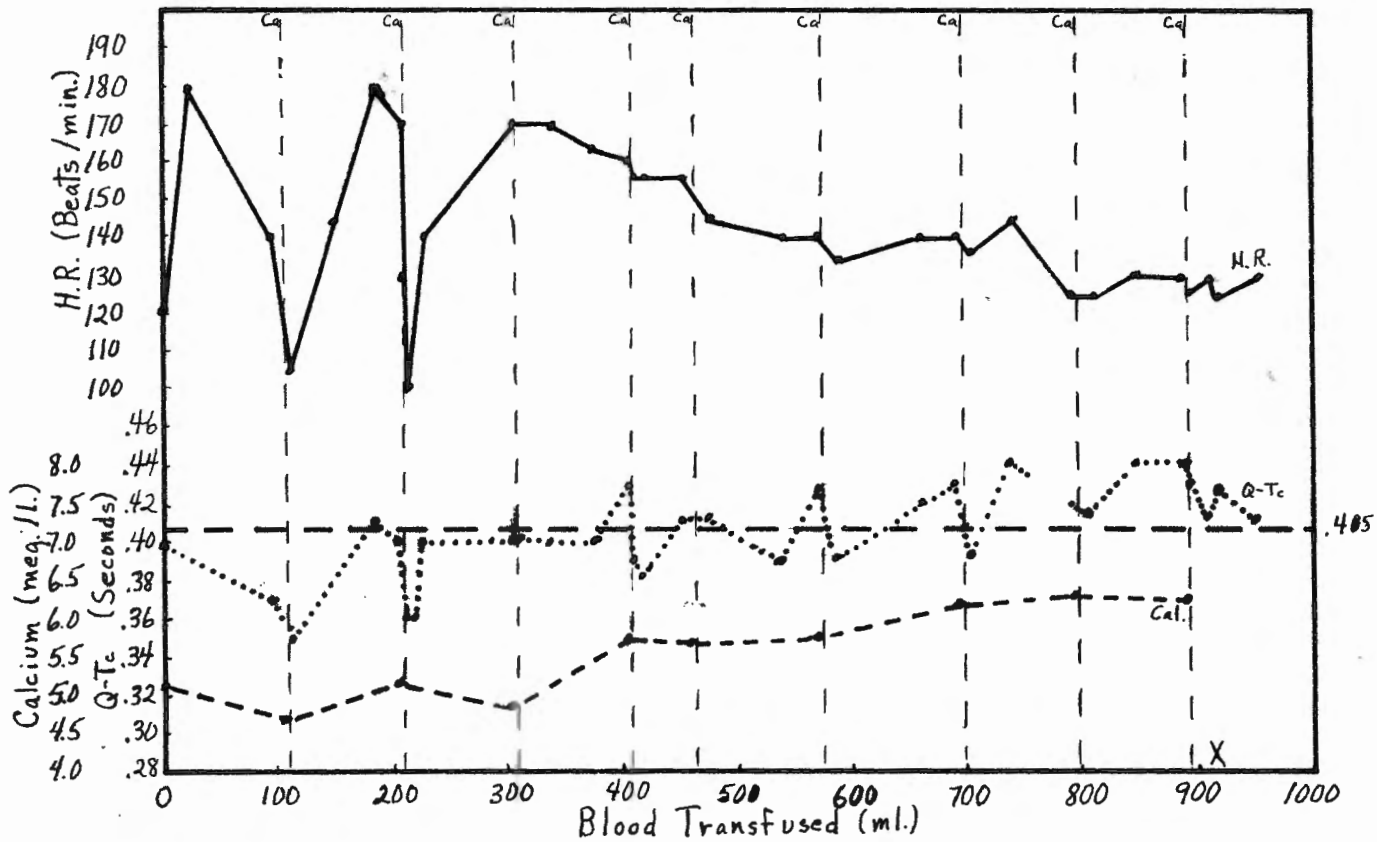


TABLE C
Case III

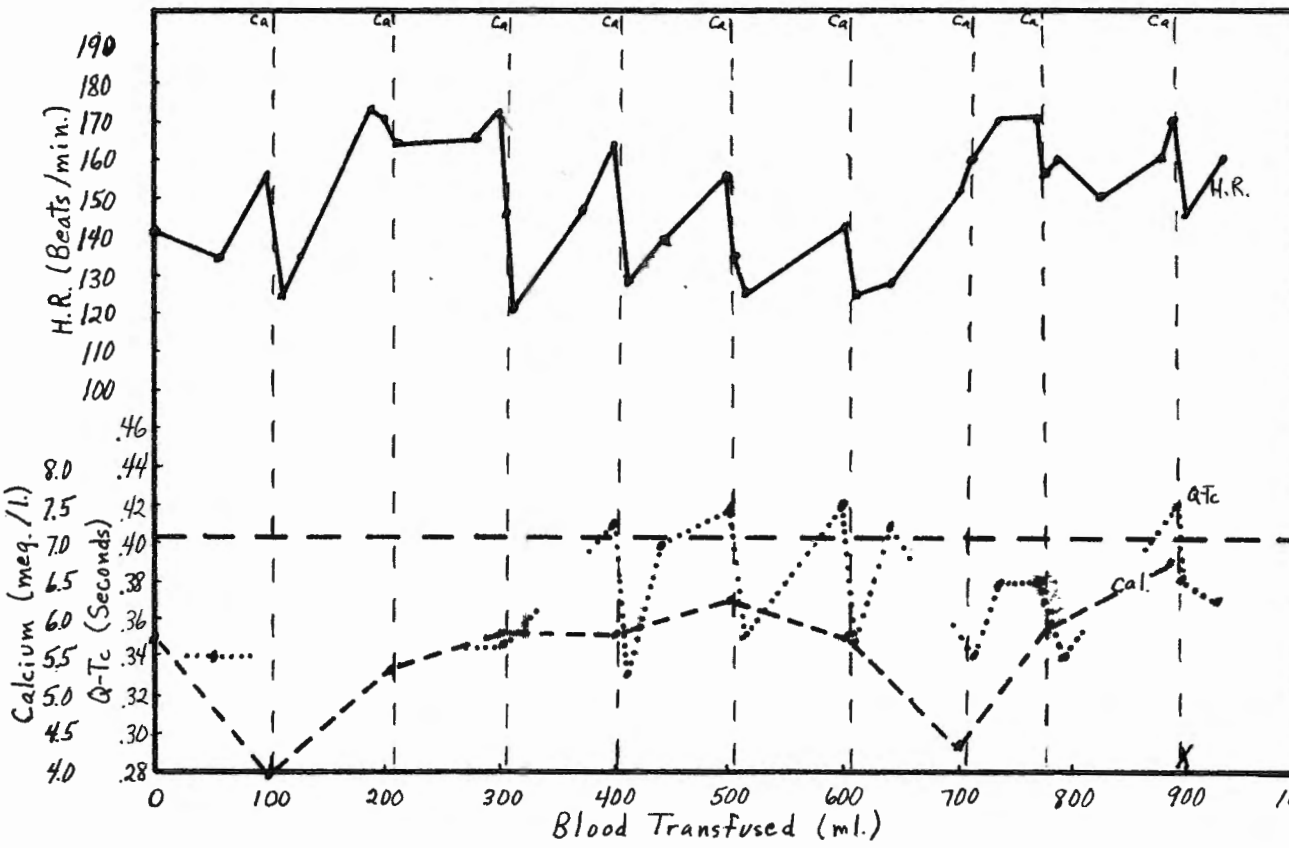


TABLE D
Case IV

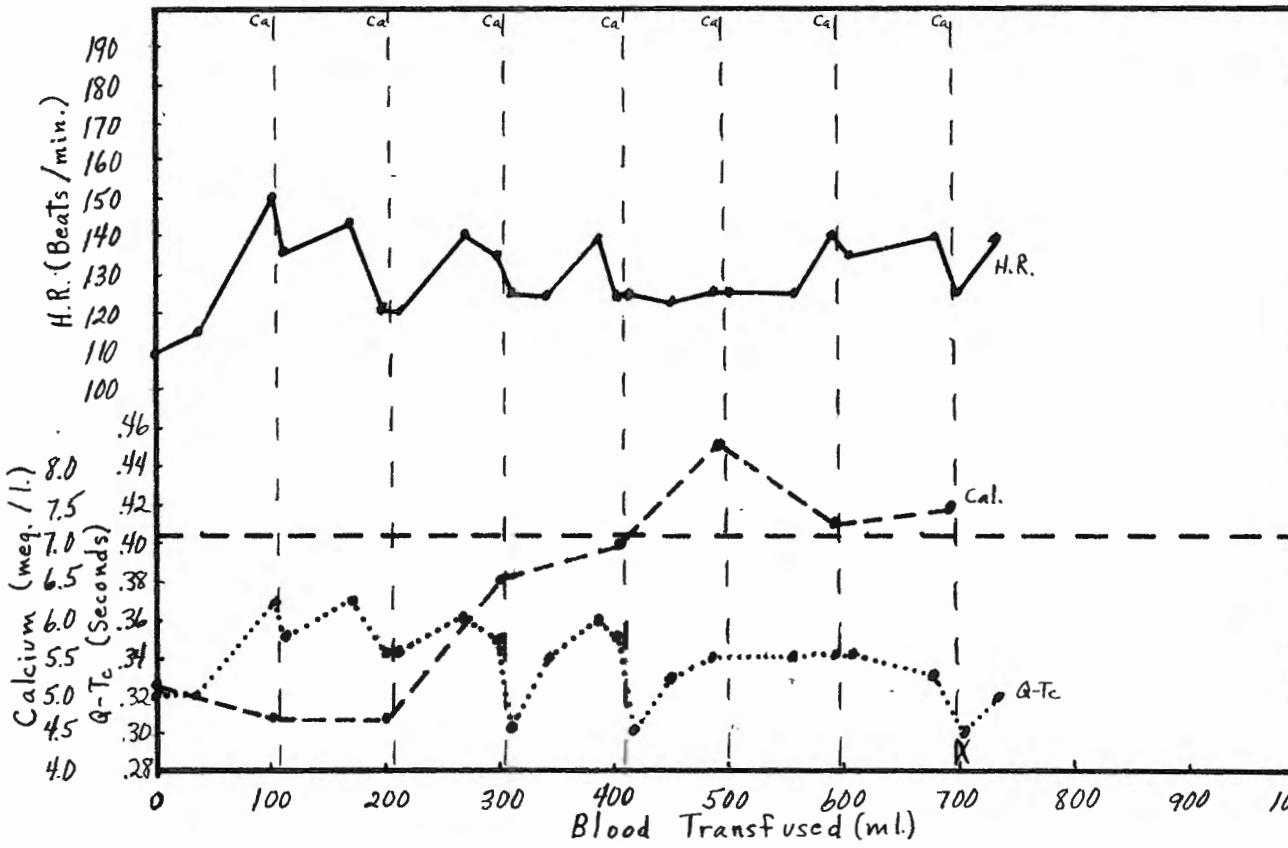


TABLE E
Case V

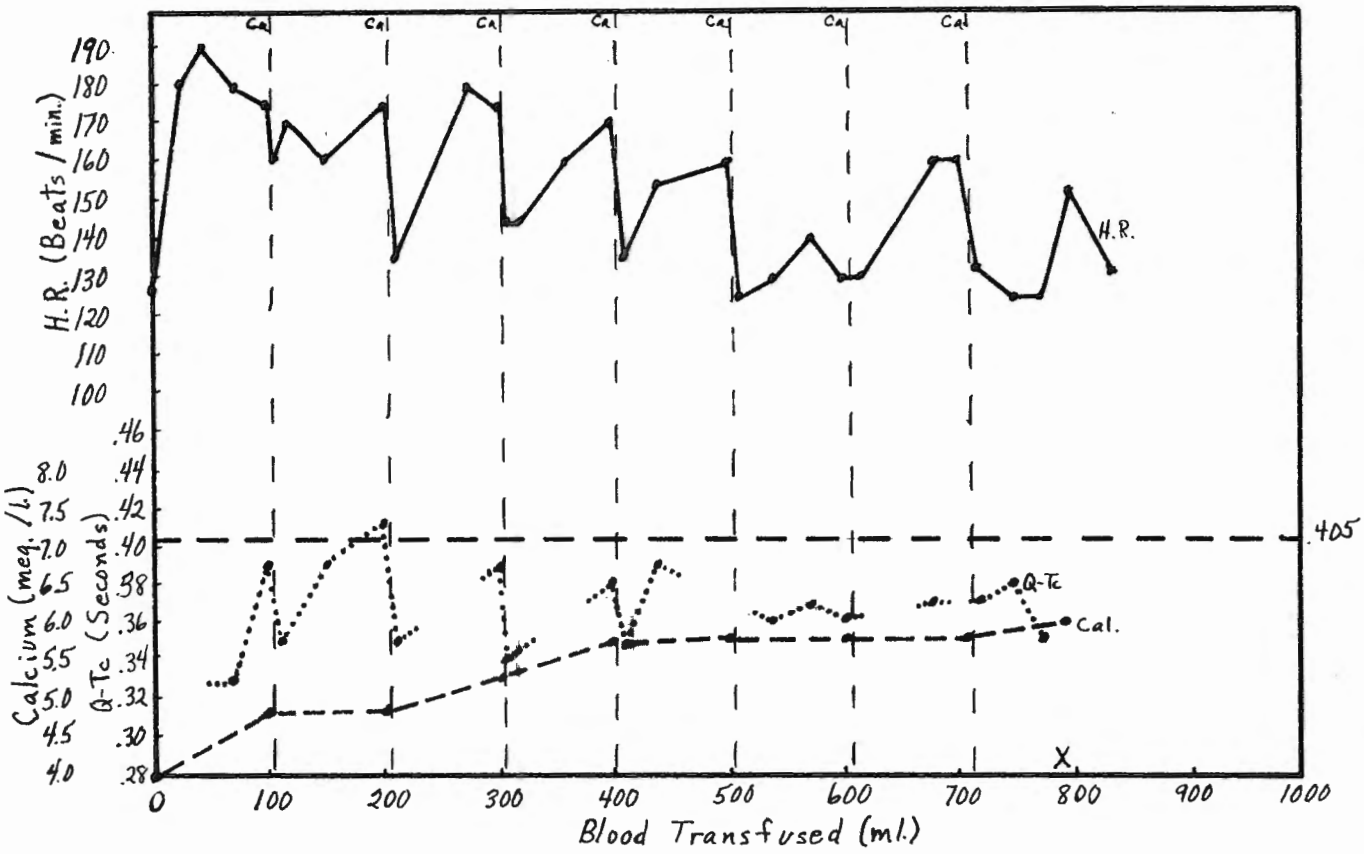


TABLE F
Case VI

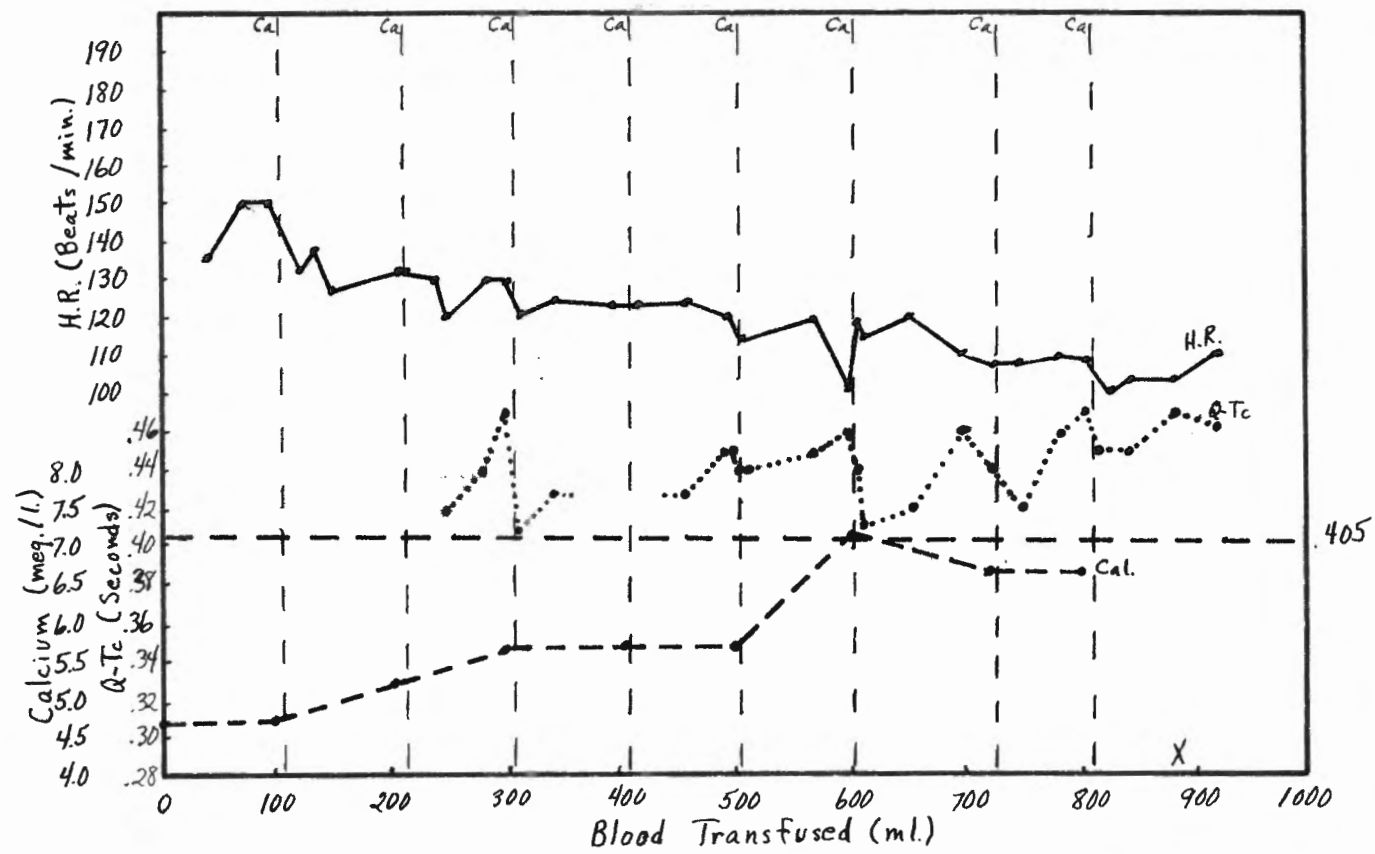


TABLE G
Case VII

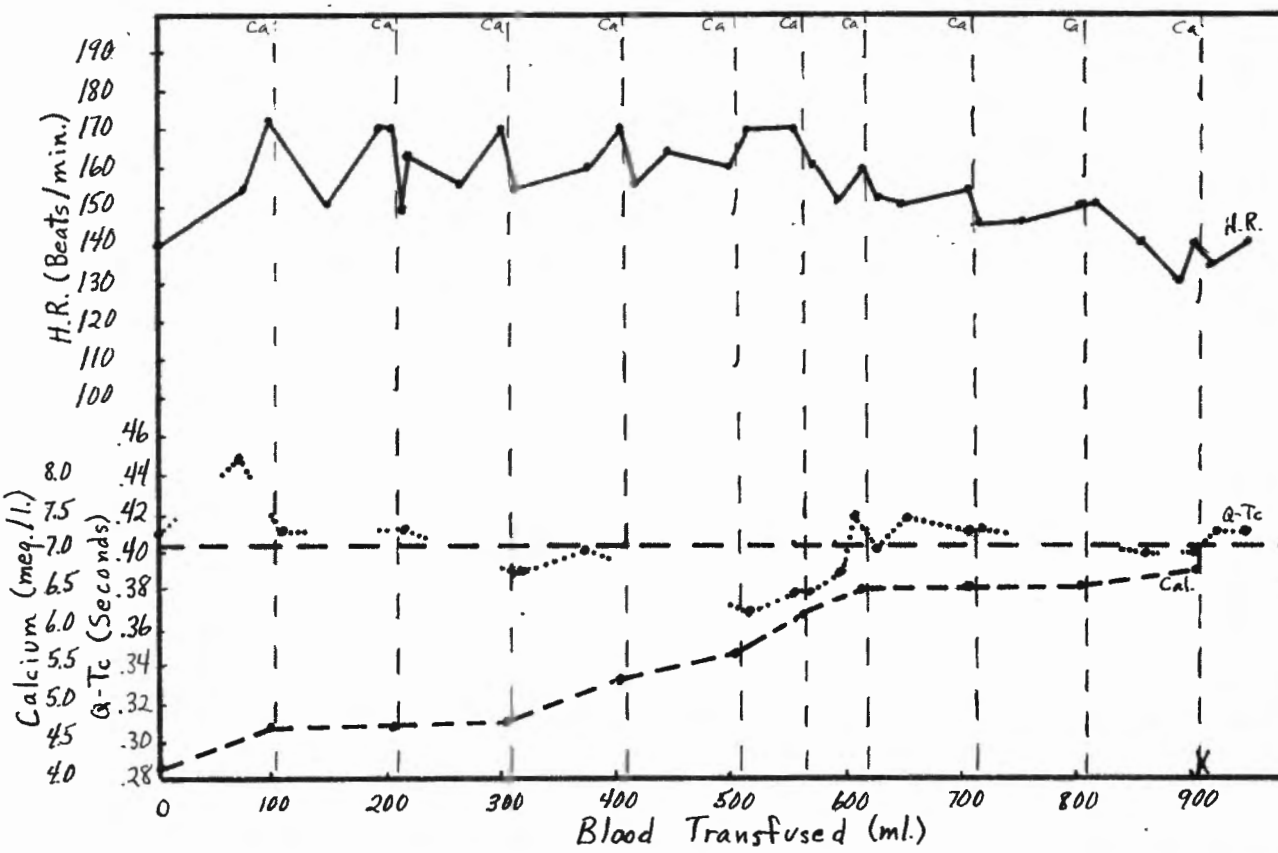


TABLE H
Case VIII

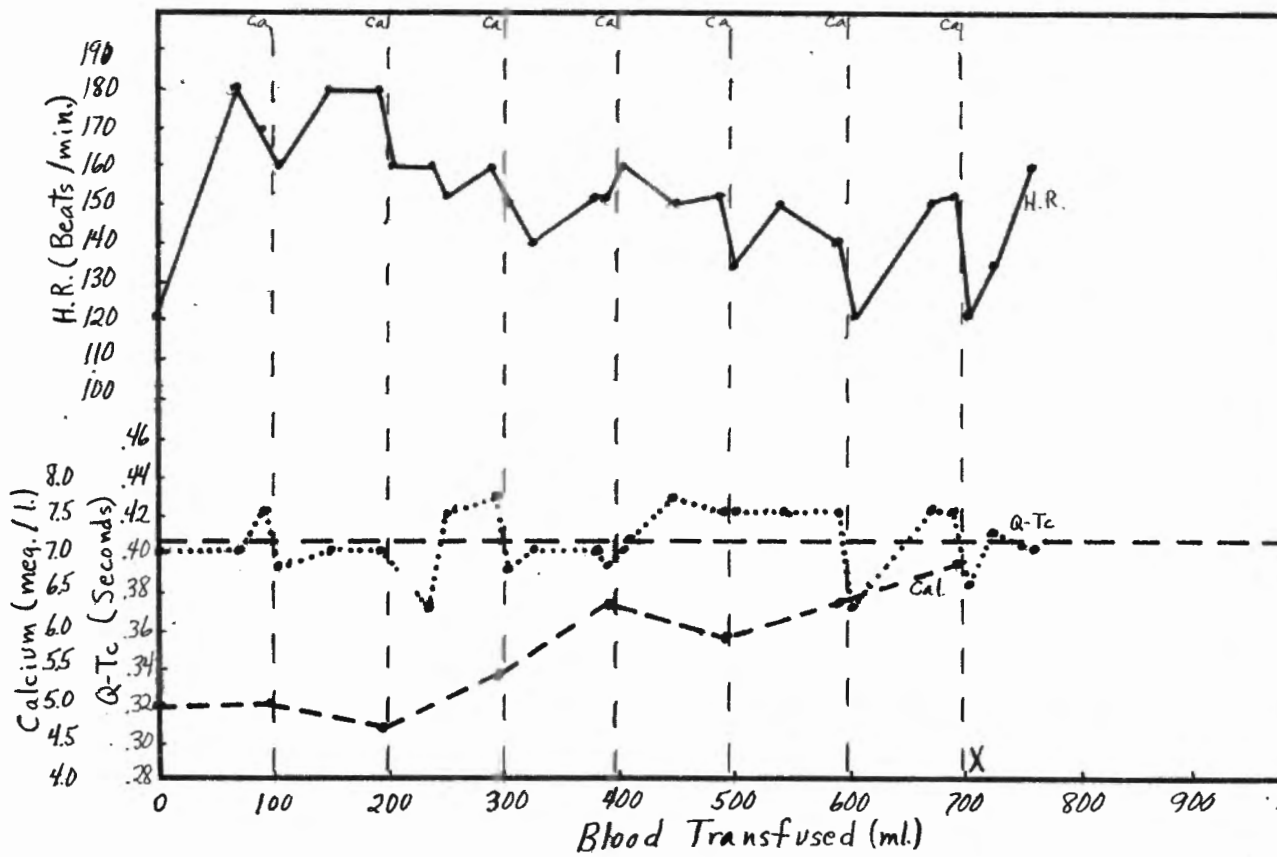
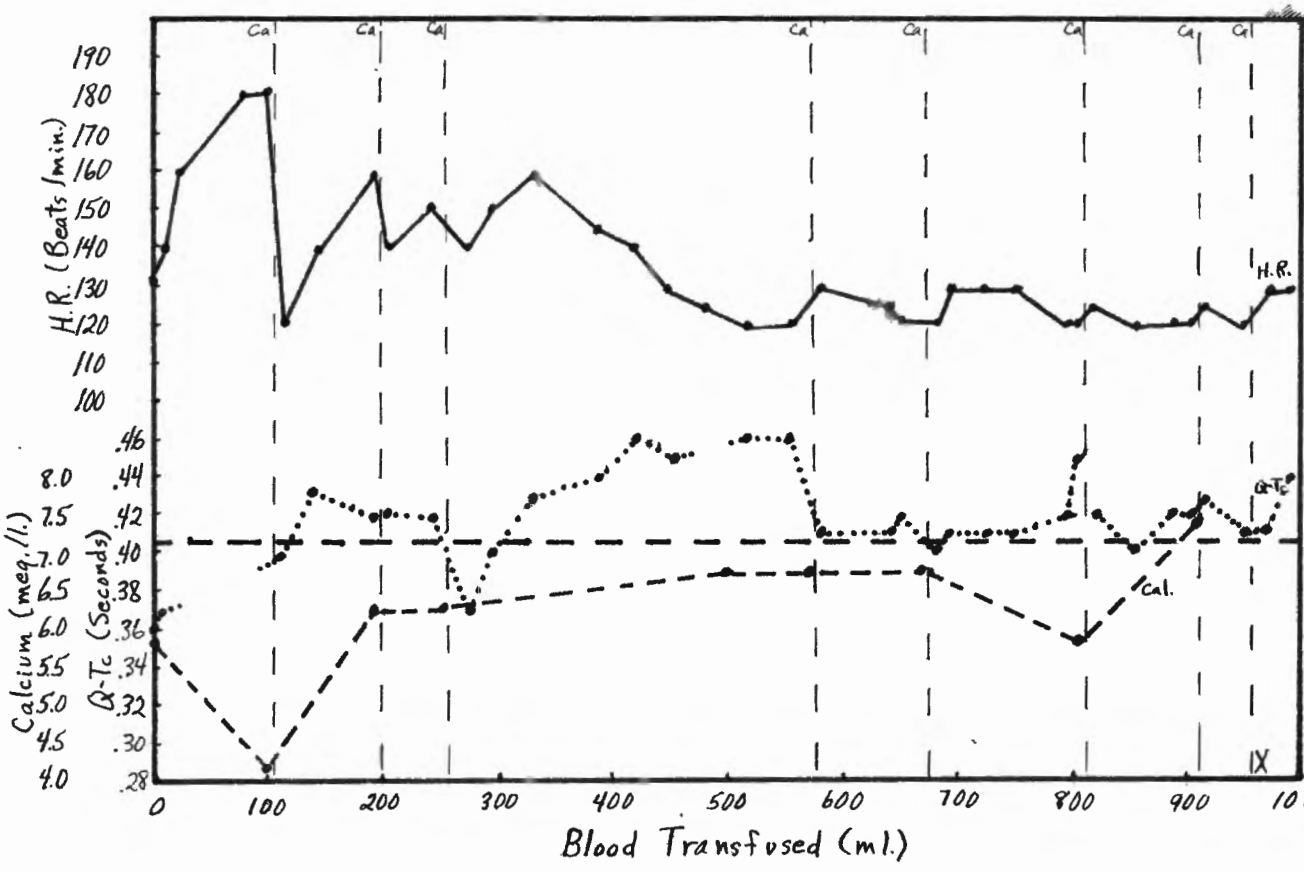


TABLE J
Case IX



SUMMARY

Complete exchange transfusion has been an accepted method of treatment of erythroblastosis fetalis for the past decade. With the wealth of experience now available concerning this procedure, the dangers involved have been reduced considerably. However the exchange transfusion, in which most of the infant's blood is replaced by donor blood, is by no means innocuous. The citrate in the donor blood combines with ionized calcium in the infant's blood and thereby tends to produce hypocalcemia. It has been recommended that periodic intravenous injections of calcium gluconate (usually 0.1 gm. per 100 ml. of infused blood) be given to counteract this effect. Another possible source of danger is hyperkalemia. Some erythroblastotic infants have elevated serum potassium concentrations before treatment. As citrated blood is stored its plasma potassium level gradually rises, sometimes to as much as 15-20 meq./l. If old blood is given to the infant there is a large potassium load which he must attempt to handle.

Previous studies on ECG tracings taken during exchange transfusions have shown signs of hypocalcemia (prolonged Q-T interval, muscle tremors, rapid heart rate) which were reversed by the administration of calcium gluconate. Studies made on serum electrolytes during the transfusions have revealed no significant changes in serum sodium concentrations. Total serum calcium remained normal

or somewhat elevated in the presence of ECG evidence of hypocalcemia. Many of the infants who received hyperkalemic blood were able to handle the extra load of potassium and remain normokalemic, but some could not and developed moderately elevated serum potassium concentrations.

The material reported in this paper was obtained from nine infants with erythroblastosis on an Rh incompatibility basis who were treated with exchange transfusion a few hours after birth. All but one of the infants received two units of citrated blood in the procedure and all the units were less than five days old. Blood samples were taken from each donor bottle, from each patient at the start of the transfusion and prior to each injection of calcium gluconate. Sodium, potassium and calcium concentrations were determined on these samples. A six-lead ECG tracing was taken on each infant before and after the transfusion and one lead was recorded periodically during the procedure.

All the infants survived the transfusions in satisfactory condition although one died several days later of an unrelated cause. No repeat exchanges were done but some of the patients eventually needed additional simple transfusions for the correction of anemia.

Serum sodium concentrations remained stable and within normal limits. Hyperpotassemia did not develop in any of the patients, even though several of them received donor blood with mild to moderate elevation of the plasma potassium (highest donor plasma

concentration was 13.0 meq./l.). The total serum calcium concentration gradually rose in all of the patients, the total increase varying from 1 to 2.5 meq./l. These rises occurred in the face of other evidence indicating the presence of at least intermittent hypocalcemia.

Usually the heart rate would gradually increase as citrated blood was transfused, sometimes to abnormally high rates (160-190 beats per minute). With the administration of calcium gluconate there would then be a prompt but temporary decrease in the rate. Rarely calcium injection might also cause an abnormally low heart rate to increase. When present, the rising heart rate was a helpful guide for the need for calcium. Some patients showed marked responses of the heart rate to calcium, others only minimal changes. There were enough instances in which the typical heart rate responses did not occur to indicate that one cannot follow that alone as a criterion for need for calcium. There was also noted a tendency for the heart rate to stabilize somewhat as the transfusion progressed.

The one infant who received 0.2 gm. of calcium gluconate per 100 ml. of blood exhibited short Q-T intervals on the ECG tracings; in fact they might have been indicative of the presence of hypercalcemia. All the other patients, who received 0.1 gm. of calcium gluconate per injection, had at one or more times during the transfusion prolonged $Q\text{-}T_c$ intervals. On most occasions injection of the calcium shortened the interval, but not always to within normal limits. The prolongation of the Q-T occurred in the S-T segment.

The presence of muscle tremors and irritability of the patient was sometimes an indication for the need for calcium administration. Prolongation of the Q-T occurred more often than the appearance of the muscle tremors. The typical rise in heart rate followed by sharp decrease with calcium administration was apt to be present with the muscle tremors. The tremors disappeared promptly with the injection of calcium. The presence of muscle tremors appears to be an even less dependable criterion for the need for calcium than is the rise in heart rate.

Other electrocardiographic findings were minor and scattered. In two cases there was an inversion of the T wave, and in these two plus one other case the amplitude of the T wave diminished with each calcium injection.

CONCLUSIONS

1. This is a report of a study made on nine erythroblastotic infants (Rh incompatibility) who were treated with exchange transfusion within a few hours after birth. Serial electrocardiographic tracings were taken during the transfusions and periodic blood samples were saved for the determination of electrolyte concentrations.

2. No significant alterations were noted in either the serum sodium or potassium concentrations. No rise in serum potassium developed in any of the patients, even in those who received donor blood (none older than four days) containing mild to moderate plasma potassium elevation.

3. Total serum calcium levels rose gradually during the procedures and were of no value in following what was happening to the ionized fraction--that portion which is physiologically active.

4. The heart rate of the infant was a helpful but not infallable aid in determining the need for calcium administration. Usually it would rise as citrated blood was given and then temporarily fall immediately following the injection of calcium gluconate. There was considerable variability of the degree of heart rate response to calcium between individuals and also within the same individual.

5. All but one infant developed prolonged $Q\text{-}T_c$ intervals on one or more occasions during the transfusions, the prolongation occurring in the S-T segment. The one exception was an infant who received 0.2 gm. of calcium gluconate per injection and had short $Q\text{-}T_c$ intervals, possibly indicative of hypercalcemia. All the others received 0.1 gm. of calcium gluconate per injection. Although this was not enough to prevent some prolongation of the $Q\text{-}T_c$, in the majority of instances it kept it near the upper limit of normal even when prolonged.

6. The presence of muscle tremors as noted by irregularities of the base line in the ECG tracing was another indication of hypocalcemia. These did not appear as often as either the heart rate or Q-T changes.

7. In performing exchange transfusions, one should use as fresh a unit of donor blood as possible to avoid any chance of the development of hyperkalemia. To guard against the development of citrate-induced hypocalcemia, at least 0.1 gm. of calcium gluconate should be given per 100 ml. of transfused blood, and more may be necessary. No one clinical sign or combination of signs are reli-able enough to always indicate the presence of hypocalcemia while still mild; therefore the recommendation is made for periodic injec-tion of calcium regardless of the absence of clinical signs indi-cating its need.

ACKNOWLEDGMENTS

I wish to thank my advisor, Dr. Carol Angle, for her aid in the preparation of this thesis. I extend my appreciation also to Dr. Byron Obsert and the other members of the Children's Memorial Hospital Staff who graciously provided the clinical material for this study and to the personnel of the University of Nebraska Hospital Laboratory who spent many hours performing the serum electrolyte determinations.

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