The Hemodynamic Effects of Potassium Infusion in Dogs

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The hemodynamic effects of K infusion were studied in 8 normal and 5 reserpine-treated dogs, anesthetized with nitrous oxide-oxygen and paralyzed with succinyldicholine. Infusion rates of K were chosen to equal or exceed those obtained with rapid, massive transfusions of banked blood. Arterial blood K levels were correlated with changes in hemodynamic parameters.

Normal animals were more resistant to deleterious changes in cardiac output, total peripheral resistance, mean transit time, heart rate, mean arterial pressure, stroke volume, and left ventricular work, although the difference was statistically significant only with the first three parameters. Reserpine treated animals survived much higher serum K concentrations than did normals. All normal dogs died in ventricular fibrillation, all reserpinized dogs in asystole.

Release of catecholamines seems at first to protect against the deleterious circulatory effects of moderate elevations of K; then, in combination with K, to hasten death when K increases further. The adverse effects in normal dogs were apparent usually only at K concentrations greater than those seen in clinical transfusions. The possibility of interaction of hyperkalemia with other events occurring during massive transfusions is discussed.

DURING the storage of blood for transfusion, potassium is lost from red cells, with resultant increasing plasma concentrations. It has been asserted [1-4] and discounted [5,6] that K may therefore cause some of the circulatory disasters occurring during rapid massive transfusion. In order to enlarge the meager store of information on the hemodynamic effects of rapid increments of serum K, we infused KCl into 13 dogs at rates equalling or exceeding those occurring during rapid transfusion. Five of these dogs were pretreated with reserpine, in order to study the effects of partial depletion of catecholamines on the hemodynamic response to acute hyperkalemia.

Methods

Thirteen mongrel dogs weighing from 15 to 45 kg. were used. Five dogs were given 0.1 mg./kg. reserpine intraperitoneally 24 and 48 hours prior to the experiment. This regimen is known to deplete catecholamines from the dog's heart,[7] but not necessarily from the adrenals or brain.[8] Anesthesia was induced with 12.5 or 25 mg./kg. thiopental intravenously, the smaller amount being used in reserpine-treated animals. An endotracheal tube was introduced under direct vision. Intermittent positive pressure ventilation was maintained with a Harvard nonrebreathing animal respirator * using a 2:1 nitrous oxide oxygen mixture. Rate and tidal volume were adjusted to maintain an arterial *p*H of 7.40–7.45, as measured with a Beckman glass *p*H electrode. Fifteen to thirty minutes after injection of thiopental, when the animal showed signs of emergence, succinyldicholine 15–20 mg./kg. was injected intravenously. The neuromuscular block thus obtained was of 2–3 hours duration, during which time the animal was prepared. A second injection of succinyldicholine 15–20 mg./kg. was given thirty minutes before control measurements of cardiovascular function were made and 2–3 hours after the first injection. One femoral artery was cannulated for systemic blood pressure measurements, while the contralateral artery

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* No. 607 Harvard Apparatus Co., Inc., Dover, Massachusetts.

was used for withdrawing blood samples. A no. 9 Cournand catheter was advanced blindly from the right jugular vein to the right ventricle. The contour of the pressure curve was used to verify the presence of the catheter in the ventricle. The left carotid artery was cannulated for continuous withdrawal of blood during cardiac output determinations. Lead 2 of the electrocardiogram was recorded. A Brodie-Walton arch strain gauge was sutured to the right ventricle of 2 of the normal dogs ten days prior to study. The complete data from these dogs were excluded from statistical analysis, since the trauma of operation and the presence of the strain gauge had altered the cardiovascular system.

Pressures were measured with Statham P23Db strain gauges. Mean arterial pressure was obtained by electrical damping. All cardiovascular parameters were recorded on an eight channel direct-writing Offner oscillograph.

KCl, 2 mEq./liter, was infused by a Harvard Infusion Pump (no. 600–950) via a polyethylene catheter (Intracath) inserted percutaneously into a brachiocephalic vein. Infusion rates ranged initially from 0.007 to 0.022 mEq./kg./minute and were doubled every thirty minutes. Peak infusion rates ranged from 0.046 to 0.134 mEq./kg./minute. The infusion was continued until the animal died. Cardiac output determinations were performed every fifteen minutes. Blood samples were routinely obtained after each cardiac output determination and shortly before death. Serum K concentration was determined by means of a Coleman Junior flame photometer.

Cardiac output was determined by the Stewart-Hamilton method, using indocyanine green dye † as indicator. The dye was injected directly into the right ventricle with a calibrated syringe, while blood was continuously withdrawn from the left carotid artery by a Harvard infusion-withdrawal pump (no. 600–900) and passed through a Gilford cuvette photodensitometer. The output of the densitometer was recorded on the oscillograph and cardiac output calculated in the usual manner after extrapolation of the down curve on semilogarhythmic paper and correction for the dead space of the catheter. The blood was reinfused into the dog after each determination. Calibration of the densitometer was performed after each study, with serial dilutions of the dye with the dog's own blood. Blood withdrawn for calibration was replaced by an equivalent amount of dextran in normal saline.

Heart rate was calculated over a 30-second period. Stroke volume was obtained by dividing the cardiac output by the heart rate. Mean transit time was calculated by the method described by Etsten.[9] Total peripheral resistance was calculated by the method of Aperia: [10]

$$\text{TPR (dyne-sec. cm}^{-5}) = \frac{1332 \times \overline{AP}}{\text{CO ml./sec.}}.$$

Left ventricular work was calculated according to the formula: LVW (kg.M/minute) = 0.0135 × CO (liters/minute) × AP.

In order to correlate the percentage changes in the cardiovascular parameters with the corresponding serum K value, the data were analyzed using a BIMD06 Program [11] on an IBM 7090 digital computer. This provided a thorough regression and correlation analysis. In addition, two types of data transformation were performed on each K value—square and $\log_{10}$. A regression and correlation analysis was performed on each of the newly generated sets of data. Thus, three basic regression equations were obtained: $y = a + bx$, $y = a + bx^2$, and $y = a + b \log_{10} x$. The smallest mean of the squares of deviation about the regression was used to determine which equation fit each set of data best (for example, cardiac output in normal and reserpine-treated animals). Two times the square root of this number was used as the 95 per cent confidence limits of each regression equation. T values determined the significance of each equation. Equations were considered significant at the 0.05 per cent level. A null hypothesis was used to determine any significant difference between the slopes of the two lines within each parameter: is

$$b_N - b_R \pm 2\sqrt{(SE_{b_N})^2 + (SE_{b_R})^2} \geq 0?$$

b_N = regression coefficient in normal dogs

b_R = regression in reserpine treated dogs

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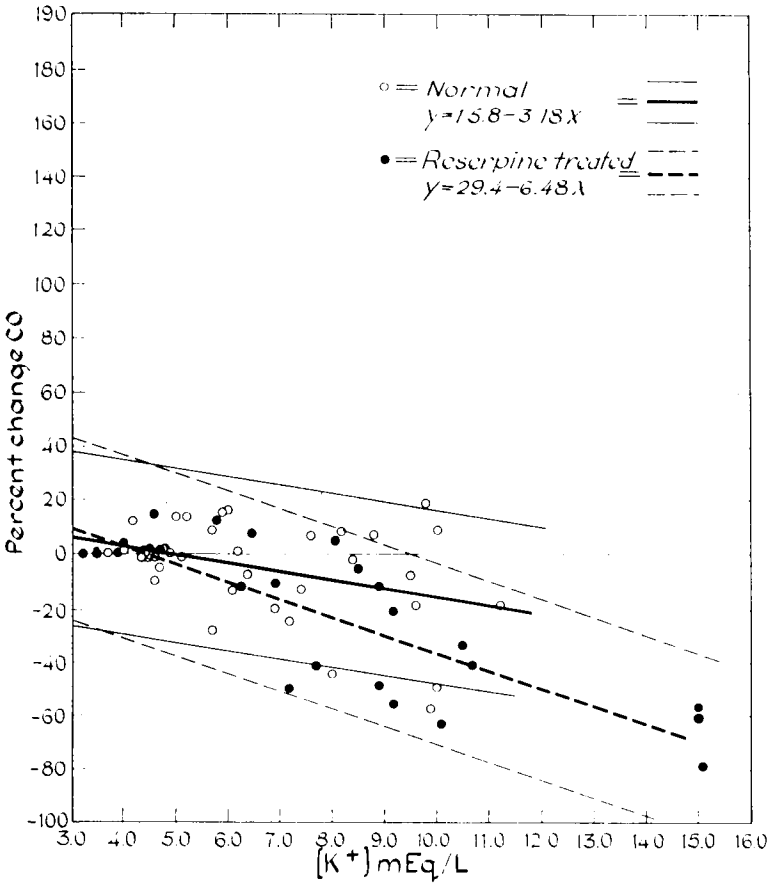

FIG. 1. The concentration of K in the serum is plotted against the percentage change in cardiac output. Data transformation of K—none. The light lines parallel to the corresponding heavy center lines represent the 95 per cent confidence limits. The difference between the slopes of the two regression lines is significant.

SE_{b_N} = standard error of the regression coefficient in normal dogs

SE_{b_R} = standard error of the regression coefficient in reserpine treated dogs.

If the value of the formula was greater than zero, the difference between regression coefficients was considered significant at the 0.05 per cent level. All other statistical computations were performed using standard methods.

Results

Electrocardiogram. The classic electrocardiographic changes of acute and chronic hyperkalemia have been reported extensively elsewhere.[12, 13] Our results confirm these findings and need not be repeated here.

Myocardial Contractile Force (MCF). In the two dogs with chronically implanted Brodie-Walton strain gauges there was no change in MCF until the terminal stages of the experiment, when all cardiovascular functions deteriorated rapidly.

Cardiac Output. Figure 1 shows the regression lines and equations for the changes in cardiac output with increasing serum K levels. Cardiac output decreased significantly in both groups of animals. ($P < 0.025$ for normal dogs, < 0.001 for reserpine-treated dogs). The decline in cardiac output was significantly more rapid in the reserpine-treated dogs than in the normal animals.

Stroke Volume. There was no significant change in stroke volume in normal dogs, but a highly significant decline in the reserpine-treated animals. ($P < 0.001$). In spite of the large difference between the two groups of animals, there was no significant difference between the regression coefficients.

Heart Rate and Mean Arterial Pressure. Both of these parameters declined in the normal and reserpine-treated animals ($P < 0.05$,

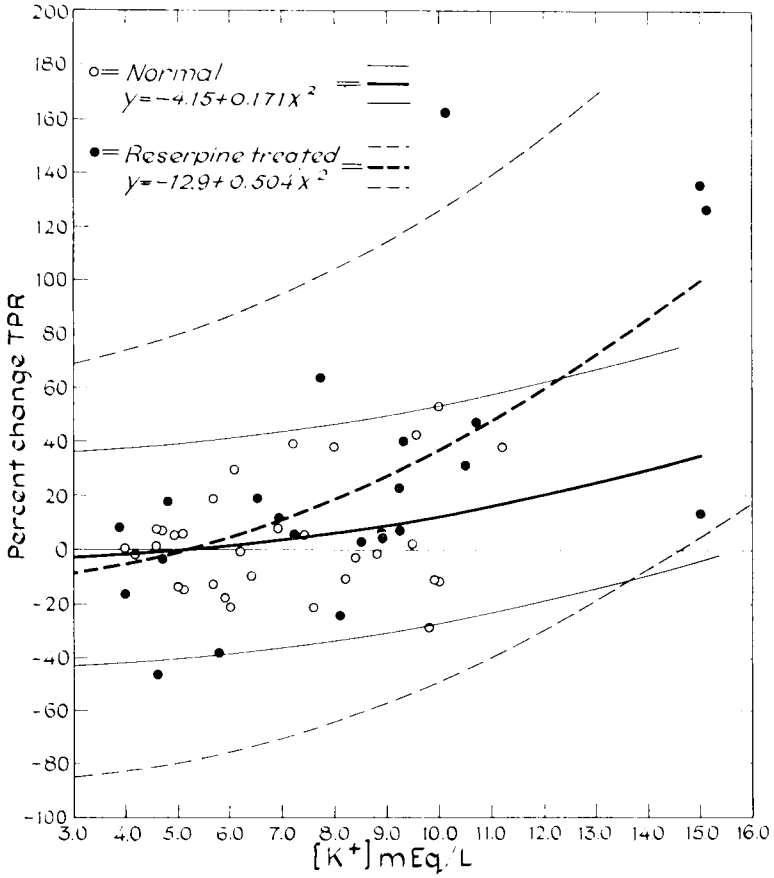

FIG. 2. See figure 1. (K^+) versus total peripheral resistance. Data transformation of K—square (note the parabolic regression lines). The difference between regression slopes is significant.

$< 0.001, < 0.05, < 0.05$), although the decrease in mean arterial pressure in each group was statistically barely significant. ($t = 2.0968$, $N = 32$, $t = 2.0682$, $N = 27$). This mirrors the fact that some normal animals maintained a good arterial pressure until just before death, and that the reserpine-treated animals entered the experiment with a low mean arterial pressure. The differences between the slopes were not significant.

Total Peripheral Resistance. TPR did not change significantly in the normal dogs, but did increase rapidly in the reserpine-treated animals ($P < 0.001$) (fig. 2). The difference was significant.

Mean Transit Time. Hyperkalemia caused a significant increase in mean transit time in both groups (fig. 3). ($P < 0.001$). In the reserpinized animals it increased more rapidly, the difference being significant.

Left Ventricular Work. LVW decreased in both normal and reserpine treated animals (fig. 4). ($P < 0.001$). The difference in decline was not significant, although the reserpine-treated animals showed a more rapid decline.

Even though five of the seven parameters showed a statistically significant change in the normal dogs, the changes, except for left ventricular work, were relatively minor—0.47 — 3.17 per cent for each mEq./liter rise in serum K; that is, if the serum concentration of K changed from 4 to 10 mEq./liter, the change in parameters would be only 2.82 — 19.02 per cent. In four of the eight normal dogs, the cardiovascular parameters were either well maintained or, in the case of pressures, actually increased.

Ventricular fibrillation was the terminal event in all normal dogs at a serum K level of 9.79 ± 0.78 mEq. liter. Reserpine-treated dogs all died in asystole at a mean serum K

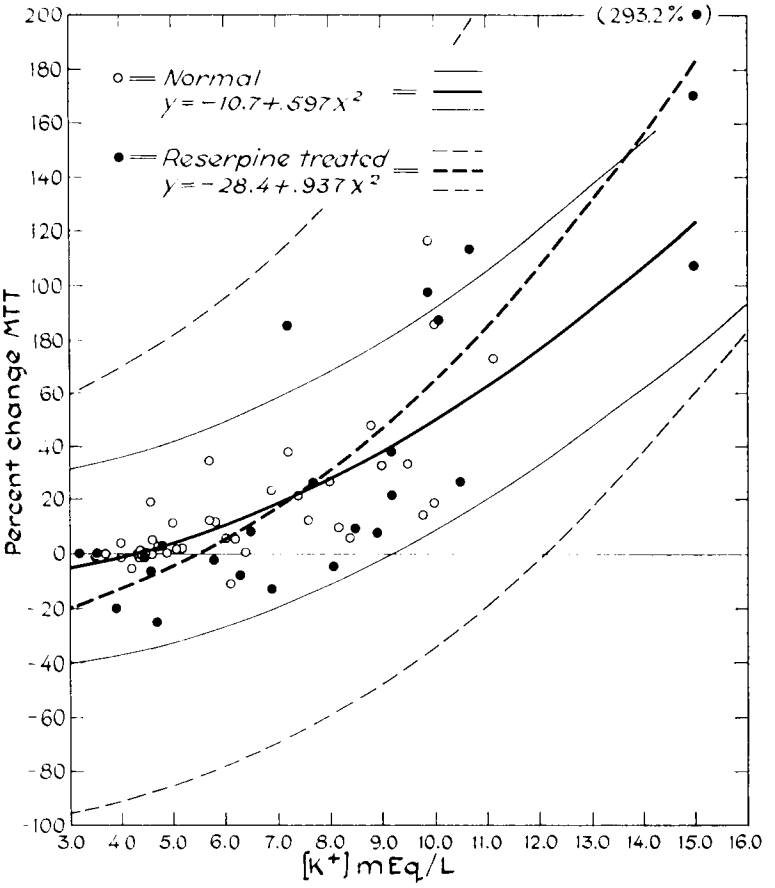

FIG. 3. See figure 1. (K^+) versus mean transit time. Data transformation of K—square (note the parabolic regression lines). The difference between regression slopes is significant.

level of 15.00 ± 2.25 mEq./liter. The difference in K levels at death between the two groups is significant ($t = 5.188$, $P < 0.01$). The chi-square value calculated from a fourfold contingency table shows a significant difference in the mechanism of death in the two groups of animals ($\chi^2 = 8.506$, $P < 0.005$).

Discussion

Our results can be explained by the hypothesis that a release of catecholamines accompanies acutely elevated serum levels of K, and that the catecholamines and K each modifies the pure cardiovascular action of the other. The stability of MCF during the K infusion, a phenomenon also noted by others,[14] may reflect a balancing of the negative inotropic actions of K by the positive inotropic actions of catecholamines. The greater changes in cardiovascular parameters in the reserpine-treated animals (decreased cardiac output and stroke volume and increased mean transit time and total peripheral resistance) suggest a protective role of the catecholamines against the effects of K.

Although we did not measure serum catecholamines, the evidence for their release during elevation of serum K levels is strong. Houssay [15] observed an increase in blood pressure following intra-arterial injection of KCl into the cat and pointed out the disparity between the depressant action of K on the isolated heart [16] and the stimulating effects in the intact animal. Several other authors confirmed Houssay's results and attempted to define the mechanism.[17-21] They noted that the pressor response could be abolished by adrenalectomy and attributed it to the release of epinephrine by the adrenal glands.

The effect of increased K on the peripheral circulation has been extensively studied in isolated organs and perfused limbs. The size

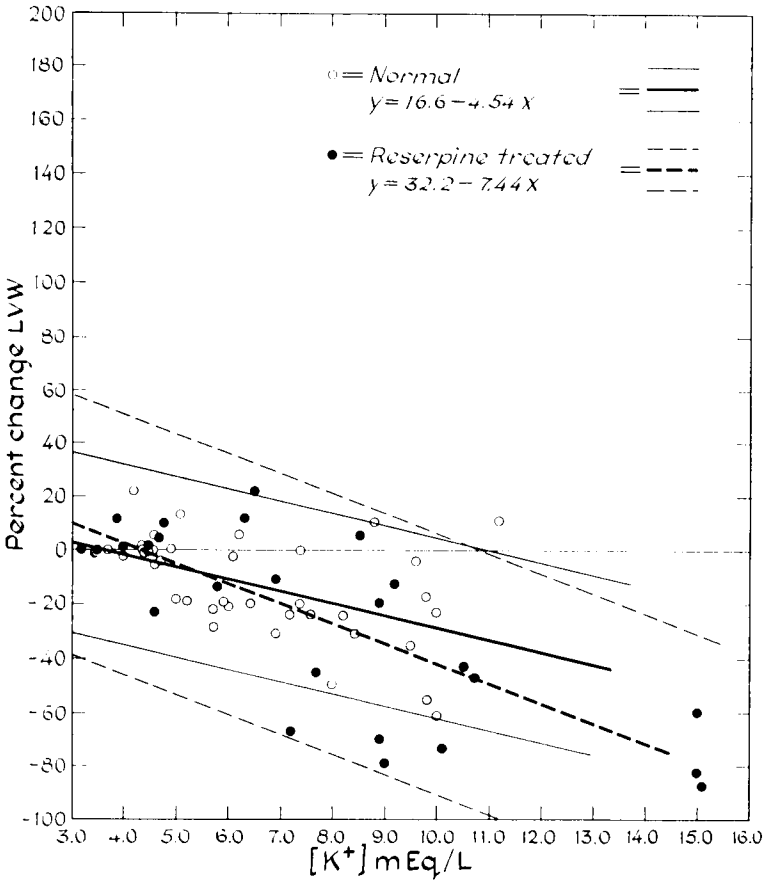

FIG. 4. See figure 1. (K^+) versus left ventricular work. Data transformation of K—none. The difference between regression slopes is not significant.

of individual doses,[22, 23] the tonicity of K in the infusion,[24, 25] the serum level of K obtained,[26–28] the speed of injection,[12] or the region or species studied have all been implicated in determining the effect of excess K. Generally, small doses or serum levels in the range of 4–8 mEq./liter cause vasodilation, while larger doses or concentrations of K greater than 8 mEq./liter cause vasoconstriction. These direct effects of K on blood vessels may in turn be modified by epinephrine. Waugh [29] noted a dual effect of K on isolated vascular smooth muscle strips: a previously contractile-inducing amount of injected K exerted a relaxing effect on the arterial segment perfused with low K solution when the muscle was contracted by epinephrine.

Thus it appears that while the release of catecholamines does modify the effects of infused K, and K modifies the effects of the released catecholamines, the precise role of each in the present study is impossible to define.

The partial cardiovascular protection afforded by the release of catecholamines in the present studies persisted to about 10 mEq./liter of K, a level at which ventricular fibrillation occurred in the normal dogs. Others have not found this consistent death by fibrillation.[2, 3, 14, 30] The differences in results may be explained by our use of hypertonic KCl solutions. Ventricular fibrillation has been reported to occur more regularly with the infusion of these solutions.[30] (We used a hypertonic solution in order to keep the total infused volume from becoming inordinately large and affecting cardiovascular dynamics.)

The mechanism of ventricular fibrillation with increased K levels in the present studies is not clear. However, it appears that potassium-induced ventricular fibrillation is facili-

tated by excess epinephrine and *vice versa*.[31-33] Epinephrine-induced ventricular arrhythmias have been prevented by using drugs and techniques which prevent increases in serum K.[34] In the present studies, we prevented potassium-induced ventricular fibrillation by using a drug which decreases the stores of endogenous catecholamines.

Results of our studies cannot be directly extrapolated to the clinical problems of massive blood transfusions, but they can be used as a basis for discussion. Hyperkalemia has been indicted as a cause of cardiac arrest during rapid transfusions.[1-4] Seven day old banked blood contains 12 mEq./liter of potassium, 14 day old blood 24 mEq./liter, and 21 day old blood 32 mEq./liter.[35] At the rather rapid rate of 500 ml. of blood every five minutes in a 70-kg. man, this would amount to infusion rates of 0.017, 0.034, and 0.046 mEq./kg./minute, respectively. Schweizer and Howland[5] and Bunker *et al.*[6] noted that the administration of large volumes of banked blood did not result in appreciable increases in serum K. However, observations by the former group were apparently made in patients receiving blood less than seven days old[36] and thus presumably low in plasma K.[36] Furthermore, the absence of elevations in serum K does not preclude the possibility of clinical harm, since LeVeen[1] noted that during infusion of KCl in dogs, normal serum levels of K were maintained until just before death. In the present studies, although we were able to achieve step-wise increases in serum K, serious cardiovascular impairment occurred only at elevations in serum K considerably in excess of those which have been reported to occur during clinical transfusions.

In spite of this tolerance to hyperkalemia, it is probable that increased serum K may interact with other events occurring during massive transfusions—hypovolemia, hypotension, hypocalcemia, hypothermia, and acidosis. LeVeen[2,3] has pointed out that only one-third the usual lethal amount of K is required to produce cardiac arrest in dogs with acute, compensated hypovolemia. In isolated guinea pig atria, excess K in the bath potentiates the negative inotropic action of decreased calcium ion.[37] During respiratory acidosis, hyperkalemia may[38] or may not[39] be present. Scribner *et al.*[38] believed that there was less tolerance to hyperkalemia at normal blood *p*H than during respiratory acidosis. Young *et al.*[40] indicated that K toxicity was aggrevated by an acute decrease in P_{CO_2}, but that this was not solely due to changes in *p*H. LeVeen *et al.*[41] found that acidifying the perfusing solution of turtle hearts did not accentuate the myocardial depressant properties of hyperkalemia. However, he also found no decrease in contractility even with a *p*H as low as 6.2, and only a moderate decrease with a *p*H of 4.3. This is at variance with results obtained with mammalian hearts. Further research is obviously needed to define and to clarify these problems.

Summary

In order to examine the role of acute hyperkalemia, such as might occur during rapid massive transfusions of banked blood, the hemodynamic effects of graded infusions of K were studied in 8 normal and 5 reserpine-treated dogs, anesthetized with nitrous oxide-oxygen and paralyzed with succinyldicholine. Serum K levels were correlated with changes in cardiovascular parameters.

In normal dogs, cardiac output, left ventricular work, heart rate, and mean arterial pressure decreased at high levels of K. The last two parameters showed great variability, being well maintained in some animals until just before death. Right ventricular myocardial contractile force, stroke volume, and total peripheral resistance showed no significant change, and mean transit time increased.

Reserpine-treated animals showed a more rapid deterioration of cardiovascular function, which was statistically significant only with cardiac output, total peripheral resistance, and mean transit time, but also striking with stroke volume. However, these dogs survived much higher serum concentrations of K than did the normals (15.0 versus 9.8 mEq./liter). Moreover, all normal dogs died in ventricular fibrillation, all reserpine-treated dogs in asystole.

The deleterious effects of acute hyperkalemia were evident only at levels of serum K or infusion rates far exceeding those reported during transfusions. Of interest is the apparent protective role of catecholamine release against the direct negative inotropic effects of K. De-

pletion of myocardial catecholamines by reserpine, although allowing an earlier and more rapid deterioration of hemodynamic function, permits the animal to survive higher concentrations of K. One can speculate whether hyperkelamia and high levels of catecholamines acted in combination to kill our normal animals.

Although our results do not indicate a clinically significant role of hyperkalemia by itself in massive transfusions, the interaction of moderate hyperkalemia with other metabolic changes occurring concomitantly must be considered in explaining the cardiovascular events occurring during transfusions.

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MUSCLE PAIN Nondepolarizing muscle relaxants have been used prior to succinylcholine in order to prevent muscle fibrillation and pain. In patients given gallamine prior to succinylcholine, fibrillations and muscle pains were significantly reduced as compared to control groups in which succinylcholine alone was used. (*Kreuscher, H., and others: Influence of Gallamine on Fibrillations and Muscle Pain after Succinylcholine, Der Anaesthesist 14: 1 (Jan.) 1965.*)

NEWBORN RESPIRATION Various degrees of asphyxia develop during labor and delivery, yet recovery is usually rapid after birth but depends upon the prompt establishment of pulmonary function. Under normal circumstances, the lungs expand almost completely within the first few breaths and the function of the lung is comparable in its homeostatic mechanism to that of the adult. The basic control of respiration in the newborn infant appears to be the same as that of the adult. The duration of apnea that can be tolerated with preservation of functional integrity of the newborn is not definitely established. However, observations in lower primates tend to suggest that the duration of successfully tolerated apnea may not be significantly prolonged in comparison to adults. (*James, L. S., and Adamsons, K., Jr.: Respiratory Physiology of the Fetus and Newborn Infant, New Engl. J. Med. 271: 1352 (Dec. 24) 1964) and 271: 1403 (Dec. 31) 1964.*)