Acid-Base Status of Seriously Wounded Combat Casualties:

II. Resuscitation with Stored Blood

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STORED bank blood contains an appreciable acid load. Patients who require rapid and sustained transfusions are likely to have a pre-existing metabolic acidosis. Concern for the acid-base status of such recipients is reasonable, and several experiments indicate that the acid load of stored blood can be lethal to dogs. A number of authors have therefore proposed the routine administration of alkalinizing solutions on an empiric basis in clinical situations of extensive transfusion.

The excess acidity of stored blood is due mainly to the citric acid of the anticoagulant and the lactic acid generated during storage. Both of these organic acids are normal intermediary metabolites and are rapidly metabolized under normal conditions. The pre-existing metabolic acidosis of the recipient is also an organic acidosis which is rapidly reversed when blood volume is restored, an effect that is to be expected from the transfusion of stored blood. The impact of transfusion on the acid-base status of the recipient is therefore not a simple one of buffering and titration in a closed system, but rather a complex one involving rates of administration, rates of metabolic removal, and the changing circulatory efficiency of the recipient.

There have been only a few studies of acid-base changes during rapid and extensive transfusion in man, with contradictory conclusions.[13, 35, 60-62] Recommendations for routine alkalinization during extensive transfusion, many with specific formulas, continue to appear in recent publications,[7, 20, 33, 35, 42, 47, 51, 55, 56, 62] although some authors oppose this practice.[10, 15, 27, 43] The most recent edition of the *Manual on Preoperative and Post-operative Care* of the American College of Surgeons [20] calls for the most extensive use of bicarbonate during transfusion of any formula that we have found. None of the listed citations qualify their recommendations in terms of the clinical condition of the patient, and none defines extensive transfusion.

The present report deals with acid-base and lactate studies on a series of combat casualties during unusually rapid or prolonged transfusion with stored blood in U. S. Army hospitals in Vietnam.

Materials and Methods

The patients were U. S. Army combat personnel, 18 to 28 years old, and in good general health before injury. The studies were begun on admission to the U. S. Army 93rd Evacuation and 3rd Surgical Hospitals in South Vietnam. Most casualties were studied less than 1 hour after in-

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TABLE 1. *Acid-Base Characteristics (Mean ± 1 Standard Deviation) of Bank Blood Used in Vietnam During This Study*

Age of Stored Blood	Number of Units	H+ (nEq./l)	*p*H	P_{CO_2} (mm.Hg)	Lactate (mg./100 ml. blood
3- 4 hours	3	140	6.86	103	15
11–14 days	10	273 ± 40	6.56 ± .07	151 ± 13	92 ± 40
15–22 days	33	308 ± 37	6.51 ± .05	140 ± 22	111 ± 24

jury; none had received more than one unit of blood or one liter of electrolyte solution before study. The study period was terminated with cessation of continuous transfusion or with administration of alkalinizing solution.

Anaerobic samples of arterial blood were analyzed on Instrumentation Laboratories Model 123-S2 and 125A equipment at 37° C. Calibration was performed immediately before and after each sample run with known gas mixtures and with standard buffer solutions. Arterial blood for lactate and pyruvate measurement was immediately and thoroughly mixed with an equal volume of premeasured, iced 6% perchloric acid and centrifuged within 15 minutes. Determinations were usually performed without delay, but occasionally the supernatant was frozen and used later. An enzymatic method was used with commercially available kits (Boehringer and Sons) and a Gilford Model 300 spectrophotometer. Thirty-four resting normal combat personnel had arterial lactate levels of 6.6 ± 2.1 mg./100 ml. blood (mean ± 1 S.D., range 3.9 to 10.2 mg./100 ml.). Hematocrit was measured by microcentrifugation for 5 minutes on an aliquot of the sample for blood gas analysis. Blood buffer base was derived from the Singer-Hastings nomogram; "base deviation" signifies the difference between the observed value and the value for blood of the same hematocrit at pH 7.40, P_{CO_2} 40 mm. Hg. Rectal temperatures were taken on all patients during the period of transfusion. Significant hypothermia was observed in only one patient. The surprising lack of hypothermia can be attributed to the high ambient temperatures (often over 35° C)., to the fact that much of the blood was given to the patients when they were not anesthetized, and to the occasional use of long intravenous tubing passing through warm water baths.

Bank blood was drawn anaerobically from the intravenous tubing midway through actual transfusions and handled exactly as if it were arterial blood. Most of the blood used was in the third week of storage. No patient in this series received more than 25% of the total transfusion requirements as fresh blood and for most, all blood received was in the third week of storage. The stored blood came from U. S. military bases in the Continental United States and Japan. The anticoagulant was ACD, NIH solution A, 67.5 ml. for 450 ml. donor blood. All blood was in plastic bags.

Results

The acid-base status of the bank blood used in Vietnam during the period of study is shown in Table 1. The most marked change during storage was the accumulation of lactate. The base deficit of this blood was estimated by titration of a few units in each group: 20–25 mEq./l. for fresh blood, 28–35 mEq./l. for 10–14 day old blood, and 33–40 mEq./l. for 15–22 day old blood. Free citric acid was originally present as about 15.4 mEq./l. of blood and presumably changed very little with storage. The lactic acid levels measured in the samples were 10 to 12 mEq./l. The major portion of the excess acid load was therefore accounted for by citrate and

TABLE 2. *Casualties Transfused in the Field Contrasted with Those Not Transfused (Mean ± Standard Error)*

	Transfused		Not Transfused		
Cuff systolic blood pressure on admission (mm. Hg)	<90	>90	Unobtainable	<90	>90
Number of patients	7	28	28	101	322
Arterial pH	7.274 ± 0.050	7.365 ± 0.012	7.254 ± 0.03	7.343 + 0.01	7.405 ± 0.005
$Paco_2$ (mm. Hg)	38.5 ± 4.0	40.1 ± 1.3	34.1 ± 1.6	34.1 ± 0.8	35.0 ± 0.4
Base deviation (mEq./l.)	−9.1 ± 2	−2.4 ± 0.6	−9.6 ± 1.2	−5.4 ± 0.6	−2.1 ± 0.2
Arterial Lactate (mg/100 ml. blood)	68 ± 17	34 ± 5	64 ± 9	34 ± 3	16 ± 1
Hct.	34.7 ± 1.5	40.0 ± 1.1	34.4 ± 0.6	35 ± 0.6	39.4 ± 0.4
Patients with peripheral injury only	5/7 (71%)	15/28 (54%)	10/28 (36%)	43.6%	60.9%
Number of units transfused	5.4 ± 1.5	4.1 ± 0.4	0	0	0
Time from injury to study (hours)	3.1 ± 0.7	2.8 ± 0.6	2.4 ± 0.6	1.9 ± 0.3	1.9 ± 0.1

lactate. The high P_{CO_2} represents liberation of CO_2 from bicarbonate in buffering the acid anticoagulant and the generated lactic acid in the closed system of the blood bag. Equilibrating this blood with alveolar gas tensions raised the pH about 0.2 units.

A small group of casualties who were transfused in the field were compared with a larger non-transfused group according to blood pressure on admission (Table 2). The transfused casualties were more acidemic, but they were injured severely enough to warrant use of uncrossmatched blood in the field or in helicopters, and many had recently been severely hypotensive.

The bulk of our studies dealt with serial changes in individual patients during transfusion. These patients are divided into two groups, 17 transfused very rapidly, and 19 transfused to a large total volume in a single continuous transfusion (Table 3). The effect of the transfusion is presented in terms of acid-base status at the beginning and at the end of the transfusion period, and considered from three methods of grouping; lowest observed blood pressure during transfusion, Table 4; base deficit at the onset of transfusion, Table 5; and blood pressure at the end of the period of transfusion, Table 6.

When the data are examined according to the lowest blood pressure recorded before or during transfusion (Table 4), there was lessening or reversal of the base deficit at the end of the period of transfusion in all groups with the most marked improvement occurring in the large volume transfusion series. The only persisting mean base deficits occurred in the rapid transfusion series. The changes in mean lactate levels were inconsistent and not statistically significant. As a result there was marked increase in the blood buffer base relative to the lactate level for all groups at the end of the transfusion period.

When the results are considered according to the degree of base deficit before transfusion (Table 5), again there was no marked increase in base deficit for any sub-group and the only significant base deficits persisting after transfusion were in the rapid transfusion series. The groups with severe base deficits before treatment had the most impressive improvement, even when rapidly transfused, while those with fairly normal acid-base values had a slight worsening of base deficit and a significant increase in lactate at the end of transfusion.

The most clinically significant relationship is presented in Table 6, where groups

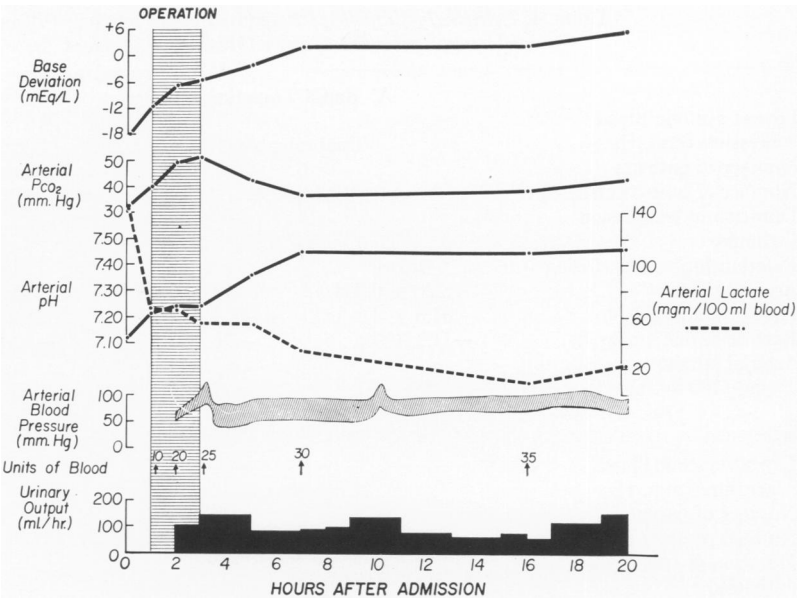

FIG. 1. Patient with multiple blast amputations and penetrating wounds in unusually severe acidemia on admission, treated with transfusion of stored blood as indicated without additional alkalinizing solutions. Lactic acidosis was rapidly reversed and a mild metabolic alkalosis was evident by 20 hours after admission.

are arranged according to blood pressure at the termination of the sampling period. The initial base deficit was corrected in patients transfused with large volumes at relatively slow rates, whether or not arterial blood pressure was restored above 90 mm. Hg. In those rapidly transfused, there was significant improvement in the base deficit when blood pressure was restored, but not when the blood pressure remained below 90 mm. Hg. Some individual patients in this last sub-group had deterioration of acid-base balance. Six of these seven patients had continuing extensive hemorrhage. Two of the three deaths during extensive transfusion occurred in this sub-group.

There were several patterns evident in the serial studies of individual patients. The patient whose data are shown in Figure 1 sustained two major blast amputations and multiple penetrating wounds. He remained untreated for over an hour and arrived in unusually severe acidemia, arterial pH 7.12, base deficit of 20 mEq./l., and a lactate level of 139.5 mg./100 ml. During rapid and prolonged transfusion, with a maximum rate of 12 units in 1 hour, he improved consistently in vital signs and urinary output, with correction of the base deficit and an almost constant fall in lactate level. Because his injuries were all in the limbs, blood loss was moderately well controlled with tourniquets, even during

TABLE 3. *Extensively Transfused Patients*

	A. Rapid Rate of Transfusion	B. Large Total Volume Continuous Transfusion
Number of patients	17	19
Mean values (±1 S.E.)	15.4 ± 1.6 units in 1.9 ± 0.2 hours	28.7 ± 2.4 units in 9.1 ± 1.0 hours
Maximum volume	28 units in 1.5 hours	66 units in 22 hours
Maximum rate	28 units in 1.5 hours	37 units in 6.5 hours
Minimum volume	6 units in 0.5 hour	19 units in 4 hours
Minimum rate	12 units in 2.75 hours	25 units in 16 hours

TABLE 4. *Extensively Transfused Patients Grouped by Lowest Blood Pressure before or during Transfusion (Mean ± 1 Standard Error)*

	A. Rapid Transfusion Series			
Lowest systolic Blood pressure (mm. Hg.)	Unobtainable		<90	
Number of patients	6		11	
Number of units transfused	17.1 ± 2.8		14.5 ± 2	
Duration of transfusion (hours)	2 ± 0.6		1.9 ± 0.2	
Relationship to transfusion	Before	After	Before	After
Arterial pH	7.228 ± 0.044	7.278 ± 0.060	7.29 ± 0.051	7.306 ± 0.033
$Paco_2$ (mm. Hg)	37.8 ± 4.1	41.5 ± 2.7	35.4 ± 2.2	44.7 ± 2.4
Base deviation (mEq./l)	−11.3 ± 2.6	−7.6 ± 2.6	−8.5 + 2.8	−3.9 ± 1.8
Arterial lactate (mg./100 ml. blood)	58 ± 10	52 ± 6	51 ± 14	53 ± 8
	B. Large Volume Transfusion Series			
Lowest systolic blood pressure (mm. Hg)	Unobtainable		<90	
Number of patients	11		8	
Number of units transfused	31.5 ± 3.8		24.8 ± 1.6	
Duration of transfusion (hours)	8.9 ± 1.4		9.3 ± 1.6	
Relationship to transfusion	Before	After	Before	After
Arterial pH	7.355 ± 0.035	7.405 ± 0.025	7.396 ± 0.023	7.37 ± 0.038
$Paco_2$ (mm. Hg)	30.6 ± 3.1	40.4 ± 2.1	36 ± 3.4	49.6 ± 5.5
Base deviation (mEq./l)	−7.8 ± 1.5	+0.2 ± 1.2	−3.2 ± 1.4	+1.4 ± 1.1
Arterial lactate (mg./100 ml. blood)	55 ± 13	48 ± 8	34 ± 6	39 ± 12

multiple simultaneous debridements. At the termination of the period of continuous transfusion, he had a mild base excess. This general pattern of response was characteristic of casualties who arrived with an established metabolic acidosis but in whom bleeding could be moderately well controlled and in whom the rate of transfusion easily exceeded the rate of blood loss.

In Figure 2, the sequence of changes in lactate, base deviation, and blood pressure are shown in two casualties in whom blood loss during operation exceeded the transfusion rate for a sustained period of time. Both began with mild base deficits and lactate elevations, which rapidly worsened during extensive and bloody debridements. When hemorrhage was controlled (restoration of blood pressure), base deficits were corrected earlier than were the elevated lactate levels.

The courses of two patients who died of exsanguination during extensive transfusion are presented in Figure 3. Both received large quantities of alkalinizing solutions (and calcium, not shown) before death. The studies in L. K. were continued after the bicarbonate was given and demonstrate the difficulty in chemically reversing the acidosis of hypoperfusion when the perfusion itself cannot be improved.

The remaining death during transfusion occurred in a patient who had perfusion restored to an essentially dead leg and who developed profound clotting abnormalities, uncontrollable generalized bleeding, anuria, and severe pulmonary insufficiency—almost certainly a prolonged course of disseminated intravascular coagulation and fibrinolysis, perhaps initiated and sustained by the dead but perfused leg. As can be seen in Figure 4 this patient died in shock but without acidemia.

Three patients died during rapid transfusions in whom initial blood samples were obtained. They were not included because

there were no follow-up studies. These patients had initial base deficits of 7, 9 and 14 milliequivalents per liter, and received 6, 9 and 11 units of blood in less than an hour. All died of exsanguination from intra-abdominal bleeding.

Two patients in this series died after cessation of transfusion, at 43 hours and 8 days after admission, with peritonitis and with gram negative bacteria recovered from blood cultures. Most of the remaining patients in this series were doing well when evacuated, but our follow-up information beyond this is poor.

Discussion

Transfusion

The present study indicates that decompensating acidemia is not to be expected during rapid and extensive transfusion in previously healthy adults who respond well. The rates of transfusion often approached or remained at one unit of blood every 5 minutes, but rarely exceeded that level for any sustained period. We found, in fact, that it was difficult to exceed that rate by the transfusion methods used, multiple intravenous portals with transfusion from plastic bags under pressure. The only

TABLE 5. *Extensively Transfused Patients Grouped by Initial Base Deficit (Mean ± 1 Standard Error)*

A. Rapid Transfusion Series

Base deficit before transfusion	Mild (−4 mEq./l. or less)		Moderate (−4 to −10 mEq./l.)		Severe (Greater than −10 mEq./l.)	
Number of patients	6		4		7	
Number of units transfused	15.7 ± 7.6		12.3 ± 4.4		17.1 ± 7.1	
Duration of transfusion (hours)	2.4 ± 0.4		1.8 ± 1.2		1.5 ± 0.6	
Relationship to transfusion	Before	After	Before	After	Before	After
Arterial pH	7.38 ± 0.05	7.32 ± 0.08	7.32 ± 0.1	7.25 ± 0.2	7.14 ± 0.14	7.30 ± 0.1
$Paco_2$ (mm. Hg)	38.9 ± 4.9	48 ± 8.8	43.3 ± 7.7	44.2 ± 5.5	32.3 ± 7.2	39.4 ± 5.4
Base deviation (mEq./l.)	−1.7 ± 2	−2.6 ± 2.5	−5.5 ± 0.9	−6.4 ± 10.9	−17 ± 6.5	−6.6 ± 5.1
Arterial lactate (mg./100 ml. blood)	25.8 ± 20	43.5 ± 10	44.5 ± 21	46.2 ± 33.5	89.3 ± 31	56.3 ± 34

B. Large Volume Transfusion Series

Base deficit before transfusion	Mild (−4 mEq./l. or less)		Moderate (−4 to −10 mEq./l.)		Severe (Greater than −10 mEq./l.)	
Number of patients	7		9		3	
Number of units transfused	28.3 ± 16.8		28.2 ± 5.3		31 ± 5.2	
Duration of transfusion (hours)	9.4 ± 7		9.4 ± 2.8		7.5 ± 0.8	
Relationship to transfusion	Before	After	Before	After	Before	After
Arterial pH	7.44 ± 0.08	7.33 ± 0.08	7.35 ± 0.06	7.44 ± 0.06	7.27 ± 0.13	7.43 ± 0.06
$Paco_2$ (mm. Hg.)	34.5 ± 11	47.9 ± 12.3	33.8 ± 10.4	39.6 ± 7.7	26.3 ± 5.3	39.3 ± 2
Base deviation (mEq./l.)	−0.9 ± 2.7	−1.3 ± 3.5	−6.1 ± 1.6	+2.4 ± 3	−13.3 ± 4	+1.3 ± 4
Arterial lactate (mg./100 ml)	35 ± 13	56 ± 31	38 ± 19	35 ± 16	74 ± 57	26 ± 11

TABLE 6. *Extensively Transfused Patients Grouped by Blood Pressure at End of Transfusion (Mean ± 1 Standard Error)*

A. Rapid Transfusion Series				
Cuff systolic blood pressure (mm. Hg)	<90		>90	
Number of patients	7		10	
Number of units transfused	17.6 ± 2.2		14 ± 2.3	
Duration of transfusion (hours)	1.9 ± 0.4		1.9 ± 0.3	
Relationship to transfusion	Before	After	Before	After
Arterial pH	7.263 ± 0.045	7.207 ± 0.045	7.272 ± 0.055	7.359 ± 0.025
$Paco_2$ (mm. Hg)	38.9 ± 3.1	45.5 ± 1.9	34.4 ± 2.6	42.2 ± 2.8
Base deviation (mEq./l.)	−9.1 ± 2.5	−9.8 ± 2.5	−9.6 ± 3	−1.9 ± 1
Arterial lactate (mg./100 ml. blood)	54 ± 16	68 ± 8	53 ± 14	40 ± 5
B. Large Volume Transfusion Series				
Cuff systolic blood pressure (mm. Hg)	<90		>90	
Number of patients	5		14	
Number of units transfused	35.2 ± 7.9		26.4 ± 1.6	
Duration of transfusion (hours)	11.4 ± 2.7		8.3 ± 1	
Relationship to transfusion	Before	After	Before	After
Arterial pH	7.33 ± 0.068	7.398 ± 0.044	7.387 ± 0.019	7.387 ± 0.025
$Paco_2$ (mm. Hg)	33.9 ± 5.5	44.2 ± 8.1	32.5 ± 2.6	44.3 ± 2.6
Base deviation (mEq./l.)	−8.1 ± 2.9	+0.3 ± 1.2	−5.2 ± 1.2	+0.5 ± 1
Arterial lactate (mg./100 ml. blood)	85 ± 29	63 ± 15	37 ± 4	40 ± 9

evidence of decompensation was noted in some patients who did not respond to transfusion by the usual clinical criteria of rising blood pressure, adequate urinary output, slowing pulse, and improved skin color and mental status. All such patients had rapid continuing blood loss and it is likely that this acidemia was due to shock at least as much as to transfusion.

Burton and Holderness [13] found that base deficits developed with rapid transfusion during hemorrhage, but cleared rapidly with restoration of the circulation. They stated that these deficits did not occur when heparinized blood was used but this was not supported by the data presented. Foote *et al.*[27] demonstrated the rapidity with which the acid load was cleared when citrated blood was used as the prime for cardiopulmonary bypass. Schweizer and Howland [60, 61] came to conclusions similar to ours in their early studies on patients undergoing extensive resections for cancer, but recently have become advocates of routine alkalinization during transfusion because of a clinical series which showed decreased mortality in patients receiving over 20 units of blood and given sodium bicarbonate.[35, 62] This series was not randomly selected and did not include concurrent controls. Age, associated disease, operative risk, causes of death, and anesthetic agents were not compared for the two groups. One hopes that operative mortality for major cancer resections is decreasing, but it is doubtful that this is due to use of bicarbonate.

The three main acidifying elements in stored blood are carbon dioxide, lactate, and citrate. Changes in the first two were studied in this series and there is indirect evidence relating to citrate conversion.

The accumulated CO_2 in a bag of blood should be rapidly excreted, but in most patients there was a higher Pa_{CO_2} after transfusion, often exceeding normal. The ventilatory response is relatively blunted in acute addition metabolic acidosis because the blood brain barrier delays entry of organic acids into the CSF but allows

immediate equilibration of P_{CO_2} resulting in a normal or even alkaline CSF.[48, 50, 57] This could not explain a higher than normal Pa_{CO_2} with a lower than normal arterial pH, however, as was observed in many of these patients. This may have been due to increased production of CO_2 during restoration of peripheral perfusion, to ventilatory depression by narcotics or anesthetic agents, or to decreased central nervous sensitivity to CO_2 or [H +] due to previous hypoperfusion.[19]

Average lactate levels after transfusion were similar to those before transfusion, both levels being well below those found in bank blood, so that the lactate administered exogenously as part of the stored blood did not markedly elevate the recipient's lactate levels. Patients whose lactate levels were very high before transfusion tended to have a significant fall in lactate even during rapid transfusion (Fig. 1), while those who began with very low levels developed marked increases during transfusion (Fig. 2). These latter patients usually underwent the major part of their blood loss during transfusion and it is impossible to separate the hyperlactatemia of shock from that due to transfusion. The initial response to rapid transfusion, then, was a tendency to approach the lactate level of the blood being infused. Subsequent changes indicate that this was not a sustained effect and that the recipient's circulatory status was the most important determinant of his blood lactate level.

Schweizer and Howland [62] reported lactate changes in 50 patients during elective operations, 23 of whom were extensively transfused. Some patients exhibited a high total lactate but low Excess Lactate, and this was most marked in those receiving the most blood. The authors interpreted this as indicating that the lactate must have been exogenous, that is, from the transfused blood, because the low Excess Lactate values indicated little anaerobic metabolism. This seems arbitrary since exactly the same picture is seen during recovery from endogenous lactic acidosis, which presumably would be most severe

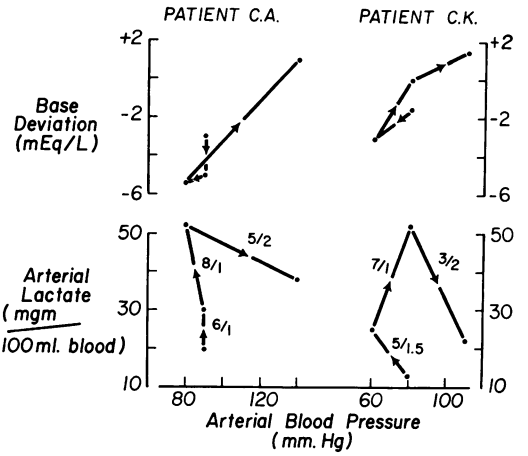

FIG. 2. Changes in arterial lactate level and base deviation in two casualties in fairly normal acid-base balance before transfusion, whose bleeding exceeded the early rate of transfusion. The fractions indicate number of units of blood transfused/number of hours between data points. The arrows indicate the sequence of changes. With restoration of blood volume (rising blood pressure), base deficits were corrected earlier and more completely than were elevated lactate levels.

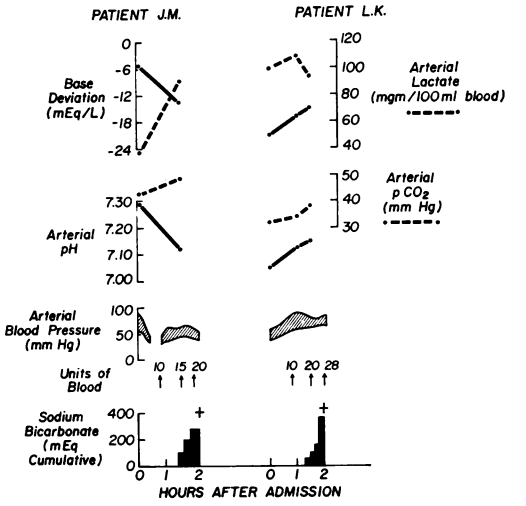

FIG. 3. Two patients who died of exsanguination during rapid transfusion. Patient L. K. illustrates the quantitative difficulty in trying to reverse the acidosis of hypoperfusion when the hypoperfusion persists.

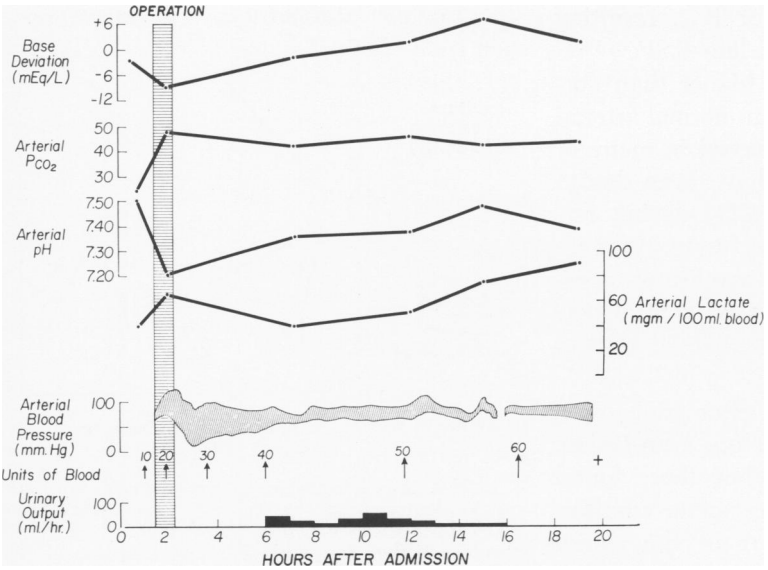

FIG. 4. Patient with a perfused but dead leg who developed anuria, pulmonary insufficiency, generalized bleeding and profound clotting abnormalities. Acidosis did not develop despite prolonged hypotension and transfusion of 60 units of blood in 16 hours. The blood lactate level rose steadily after the twelfth hour despite the use of fresh blood beyond that point.

in those requiring the most blood. In addition, it is doubtful if such precision can be attributed to the Excess Lactate measurements.[19] Since the blood lactate level in many of their patients exceeded the level reported by the authors for the bank blood used, it is doubtful that the blood transfusions caused the elevated lactate levels.

The blood level of lactate is the result of a dynamic equilibrium which can involve high rates of input and conversion, both markedly influenced by changes in perfusion. This is illustrated by the ability of normal adults to rapidly clear large infused loads of lactate,[22, 28, 30, 66] large lactate loads resulting from strenuous exercise,[23, 41, 54, 58, 70] and even infused lactate while carrying elevated blood lactate levels due to previous fluid loss or operation,[29, 31, 37] and by the marked regional differences in metabolism of lactate in viscera (consumption) contrasted with skeletal muscle (production) during hemorrhage.[3, 5, 38, 45]

Citrate levels were not measured in these patients, but the rapidly changing relationship of lactate levels to base deviation reflected the rapid metabolic conversion of the sodium citrate in the anticoagulant to available base.[43] Citrate has long been known to be rapidly metabolized, and to become toxic only at high rates of administration.[59] A number of clinical studies have documented elevated citrate levels in patients rapidly transfused or being infused with citrate solutions.[11, 12, 34, 44] More than moderate elevations were usually found only at transfusion equivalents greater than one unit every 5 minutes for a 70 Kg. recipient.

Acidosis

There may be circumstances in which severe acidemia, even if theoretically transient, should be prevented or reversed. Nahas and associates [52] and Hunt [36] both have demonstrated that the lethal effects of rapid transfusion of stored citrated blood into dogs after severe or prolonged hemorrhage can be prevented by administration of exogenous alkalinizing solution. Hunt used more clinically equivalent blood (acidified with L (+) lactic acid rather than hydrochloric acid) and found that this phenomenon occurred in animals in which ventilatory response to acidosis was deteriorating. The rates of transfusion in both studies were extremely rapid (50–

70% of blood volume in 10 minutes or less) and surpassed anything we achieved clinically even with frantic efforts by multiple teams. In both studies, calcium was as effective as alkali in preventing death.

Some of our patients did become acidemic during rapid transfusion, and more frequent sampling may have detected more severe acidemia. Most of them rapidly reversed this acidemia without administration of alkalinizing solutions, however. Those who remained in significant acidemia could be detected on clinical grounds by failure to respond satisfactorily. Continued hemorrhage was usually an obvious cause for this. Administration of alkali to some of these patients was without effect, even when the acidosis could be reversed or lessened (Fig. 3).

Abundant laboratory evidence indicates little influence on survival in hypovolemic shock when the acidemia alone is prevented or reversed.[4, 8, 53, 63] It has been difficult to demonstrate a deleterious cardiovascular effect of acidemia itself in clinical studies [17, 26] or to detect clinical benefit from exogenous reversal of the acidosis in human shock states except in circumstances where there is significant pre-existing myocardial disease.[21, 46, 64, 71] Restoration of volume without correction of the severe acidosis in patients in shock with asiatic cholera has been accomplished with saline infusions; blood pressure and pulse were restored, and serum potassium and electrocardiographic abnormalities were reversed.[14] Severe acidosis routinely occurs in exhausting exercise. Arterial pH approaches 7.1 or below and lactate levels are above 100 to 200 mg./100 ml.[2, 9, 23, 41, 48, 49, 68] Cardiovascular performance during these states is impressive despite the acidosis. There have been several reports of patients in diabetic acidosis with arterial pH's below 7.0 and base deficits exceeding 20 mEq./l. Shock was not often present, and almost all survived.[1, 6, 24, 39] Certainly in treating hemorrhagic shock, prompt restoration of the circulating blood volume is far more important than reversal of the acidosis by exogenous means.

Alkalosis

The dangers from the use of alkalinizing solutions are mainly theoretical. Unnecessary alkalinization during citrate infusions should increase the danger of hypocalcemia by increasing the binding of calcium ion by plasma proteins.[25, 67] Sudden shifts in [H+] produce sudden changes in myocardial extracellular/intracellular K+ ratios which may not be desirable.[65] Severe alkalemia will depress ventilation [40] and can induce large urinary losses of potassium.[32] Oxygen delivery by stored blood is impaired because of 2,3-DPG depletion with increased oxygen affinity.[16, 69] Alkalinization further increases the affinity of hemoglobin for oxygen and theoretically could intensify this impairment.

Bank blood is itself alkalinizing because of its sodium citrate content [43]; unnecessary additional alkali will intensify the post-transfusion alkalosis. If sodium bicarbonate is used, a large sodium load may be added to a patient who is already a candidate for pulmonary complications.[18] If the patient whose course is given in Figure 1 had been given sodium bicarbonate according to the recommendations in the *Manual on Preoperative and Post-operative Care,* he would have received from 1,250 to 2,100 mEq. of additional sodium during the first 24 hours. Using the more cautious formulas, he would have received about 313 mEq. Any amount would have been unnecessary. If THAM is used, there is a danger of immediate respiratory arrest and hypoglycemia.

Clinical Implications

The patients in this study were in unusually fine general health and were athletically conditioned before injury. Hypo-

thermia was avoided. Presumably they represent the maximum efficiency of the protective mechanisms against the occurrence and the effects of acidosis, hypovolemia, and citrate toxicity. Metabolic defenses are less efficient during hypothermia, impaired liver function, and in the newborn. Normal defenses may be overwhelmed by sustained rates of transfusion exceeding one unit every four to five minutes for an adult. Pre-existing myocardial disease may increase the dangers of any acidosis that occurs. Under any circumstances, however, it seems likely that patients responding to transfusion in a favorable manner do not require pharmacological manipulation. The need for such intervention should be based upon objective studies of the acid-base status. When the rapidly transfused patient is responding poorly and objective studies are not available, it would seem advisable to administer calcium as well as alkali because sudden alkalinization might intensify hypocalcemia and because the same circumstances which produce decompensating acidemia also reduce the ability to convert infused citrate.

Summary and Conclusions

Acid-base changes during rapid and extensive transfusion were serially studied in 36 combat casualties. Patients who responded well to transfusion easily handled the infused acid load of the stored blood and reversed pre-existing metabolic acidosis, when present. Worsening acidemia during transfusion was associated with uncontrolled hemorrhage and was likely due more to shock than to transfusion.

This population was unusually healthy before injury, hypothermia was avoided, and the rate of transfusion was not sustained above one unit every five minutes. Under those circumstances, and probably under most clinical circumstances, routine empiric administration of alkalinizing solution during rapid or sustained transfusion is not necessary. It should be considered only in patients who are not responding well, should be based upon objective measurements of acid-base status, and upon theoretical grounds, should be accompanied by cautious administration of calcium.

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