Effects of Acidosis on Cardiovascular Function in Surgical Patients *

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SEVERE uncompensated acidosis occurs not infrequently at one time or another during the operation [2, 24, 40] or convalescence [3, 9, 41] of surgical patients. In the presence of uncontrolled diabetes or renal disease, acidosis may play a prominent part in the picture. Because of the widely known narcotizing effects of an increase in the hydrogen ion concentration,[7, 13] this situation is considered to be very serious and to be responsible for failure of the cardiovascular system.[40] Although patients have been known to withstand acute severe hypercapnea for periods of several hours resulting in arterial pH values below 6.9, others die promptly if some degree of hypoxia accompanies the acidiotic state.[9] Diabetics in severe ketosis may not survive even though the recorded aterial blood pH remains depressed only slightly below normal.[42] Therefore, it is essential in evaluating the functional effects of profound acidosis to consider not only the actual blood pH but also the metabolic derangements responsible for the abnormal increase of the hydrogen ion concentration.

It is the purpose of this paper to present a correlation of the cardiac output and other hemodynamic values with determination of the blood gas and acid-base balance in 104 patients. By comparing the response of the circulation in those people who were acidiotic with those who had no acidosis during the operative procedure and the convalescent period, one is lead to the conclusion that in respiratory acidosis a reduction of the arterial blood pH to nearly 7.1 is required significantly to impair the cardiac output in man. On the other hand, a lesser degree of metabolic acidosis with pH values above 7.2 may well cause serious circulatory disturbances, especially in the presence of hypoxia or ketosis. Three parallel series of experiments, in which animals were rendered acidotic by various means, support the view that an elevation per se of the hydrogen ion concentration in the body fluids at a given value is of less serious import to the circulation if uncomplicated than if it reflects a metabolic need or disorder.

Methods

In patients and in animals the cardiac output was determined by the dye dilution method,[11, 30] using indocyanine green.[20] The central venous pressure was measured by a saline manometer connected to a venous catheter with its tip in the superior vena cava. Blood for analysis and for recording dye concentrations during cardiac output measurements was drawn through a Rochester plastic needle in an artery. This cannula was used also for recording the mean arterial blood pressure. The total peripheral resistance was calculated by the formula of Green: [27]

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$$\text{Total peripheral resistance (dyne-sec./cm.}^{-5}\text{)} = \frac{\text{Mean Art. BP (mm. Hg)} \times 1{,}332}{\text{C.O. (cm.}^3\text{/sec.)}}$$

In the animal experiments, in addition to the dye dilution curves, a chronically implanted electromagnetic flow meter of Olmsted's design [44] was employed to measure the cardiac output. Placed at the base of the aorta eight to 10 days prior to the experiments, this recorded all left heart output exclusive of the coronary bed.

Blood samples taken from the arterial cannula were analyzed for oxygen, carbon dioxide content and oxygen capacity by the method of Van Slyke and Neill.[56] The blood pH was determined with a Cambridge glass electrode pH meter and corrected to body temperature. From these data and the hematocrit the whole blood buffer base and pCO_2 were calculated from the nomogram of Singer and Hastings.[53] In a given set of circumstances, a reduction of the buffer base valve below normal reflects an accumulation of fixed acids in the plasma. This indicates the presence of metabolic acidosis. For convenience, we refer to the deficit of buffer base as "fixed acid excess." In the graphs this value is expressed in milli-equivalents per liter.

Experimental Observations

Procedure. Healthy mongrel dogs weighing 8 to 12 kilograms were used to observe the alterations in circulatory dynamics caused by acidosis. The acidosis itself was induced in three ways: 1) the administration of respiratory mixtures containing various concentrations of CO_2; 2) the infusion of 0.15 N HCl; and 3) by rendering the dog hypoxic with respiratory gas mixtures containing 6.0, 4.0 and 2.0 per cent oxygen. In contrast to the first and second methods by which acid was added to the extracellular fluid, the third method produced a form of metabolic acidosis in which the hydrogen ion concentration was increased as the production of fixed acids as anaerobic glycolysis took place.

The animals were lightly anesthetized with pentothal. An endotracheal tube was put in place through the larynx and connected to a respirator capable of delivering any desired gas mixture from a Douglas bag by intermittent positive pressure. Succinyl choline was administered intramuscularly to prevent hyperpnea. The femoral vein and artery were cannulated. The tip of the venous catheter was made to lie within the superior vena cava to facilitate the measurement of central venous pressure and for the injection of dye. All of the animals were somewhat overbreathed on a mixture of gas containing 2.0 to 4.0 per cent CO_2 and 20 per cent oxygen in nitrogen to insure that respiratory alkalosis did not occur. The CO_2 concentration of the gas mixture was chosen to insure that the arterial blood pH remained in the range from 7.35 to 7.45 throughout the control period of 30 minutes. When dye curves were used for determining cardiac output, not less than two were made to determine the value at any stage of the experiment. Employment of the electromagnetic flow meter made it possible to average many more consecutive readings. An arterial blood sample was obtained for analysis at each stage of the experiment.

Hypercapnic acidosis of varying degrees was induced in 16 animals by the introduction into the respirator of gas mixtures containing carbon dioxide in concentrations varying from 5.0 to 30 per cent. The experimental periods of acidosis lasted not less than 15 minutes, and the majority lasted an hour. Because the animals deteriorated at pH values below 7.1, seldom were more than two sets of observations taken from an individual animal. The hemodynamic readings were made at frequent intervals. The values obtained, after they and the arterial blood pH had stabilized, were averaged. To make the observations of one dog comparable with those

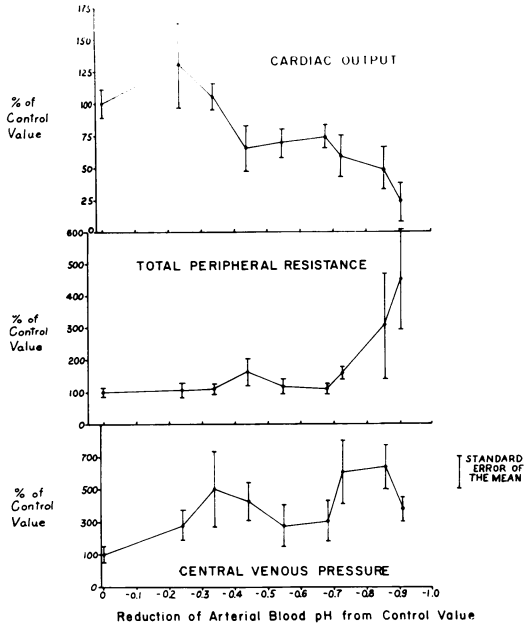

FIG. 1. The circulatory response to acidosis experimentally induced in animals by respiratory mixtures containing various concentrations of carbon dioxide. Note that a profound reduction in cardiac output occurred only after the arterial blood pH had fallen below 7.0. Also note the lack of change in peripheral resistance until the pH was below 6.7.

of another they were expressed as a percentage of the control measurements.

The experiments on the effects of hyperchloremic acidosis were conducted in a similar fashion on 18 animals. During the intravenous infusion of 0.15 N HCl the rate was varied to produced the desired arterial pH value. When a reasonably stabile pH had been attained, two or more hemodynamic measurements were made and averaged.

The production of a stable situation during the severe hypoxia induced with respiratory gas mixtures ranging from 10 to 2.0 per cent oxygen and 3.0 per cent carbon dioxide in nitrogen proved impossible. A series of 12 experiments were carried out. As the arterial oxygen content and the pH began to decline, frequent hemodynamic measurements were made. Those of cardiac output were best accomplished with the electromagnetic flow meter because of its ability to follow the frequent variations which occurred under these conditions. The arterial blood pH was checked at 2-minute intervals. All the hemodynamic values obtained, as the pH fell each 0.1 unit, were averaged to give a mean value. These were then expressed as a percentage of the control for each individual dog, representing a value for each degree of uncompensated acidosis.

Results

With their standard errors the mean values of the cardiac output, the total peripheral resistance, and the central venous pressure at each arterial pH level are given for each of the three series of experiments in Figures 1, 2, and 3. In the presence of both hypercapnia and hyperchloremic acidosis a significant fall of the cardiac output below the control value took place only when the arterial blood pH fell below 7.1.

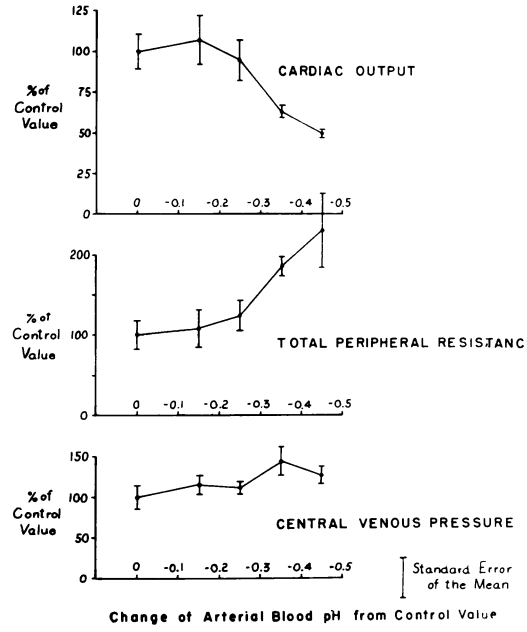

FIG. 2. The circulatory response to acidosis experimentally induced in animals by varied rates of 0.15 N HCl infusion. Although sudden death from acute heart failure often occurred, little circulatory response took place until the pH was below 7.1.

As indicated in Figure 1, the peripheral resistance (arterial BP/C.O.) only rose significantly when the pH had fallen to 6.8. On the other hand, the venous pressure attained a value nearly 300 per cent of the control when the pH was 7.2.

During the infusion of HCl (Fig. 2), the blood pressure varied but little and the peripheral resistance was inversely proportional to the cardiac output as the arterial pH declined below 7.1. In contrast to the situation in hypercapnic acidosis the venous pressure was elevated only slightly even in the presence of severe acidosis.

The animals subjected to hypoxia presented a different picture, as shown in Figure 3, from those with either hypercapnia or hyperchloremia. Little significant hemodynamic change took place unless the arterial oxygen saturation fell below 60 per cent. When the blood oxygen saturation was reduced below this a rise of both arterial and venous blood pressure occurred with an increase of cardiac output. Subsequently, when the arterial oxygen content fell below 35 per cent saturation and acidosis began to appear, there was a moderate decrease in the cardiac output and an increase of the peripheral resistance. As acidosis developed further and the arterial pH declined below 7.1 a significant reduction in cardiac output occurred associated with a further increase in the peripheral resistance to more than 200 per cent of the control value and a marked rise in the venous pressure to 328 per cent of the control. As the arterial pH dropped to near 7.0, the cardiac output progressively decreased in each of the hypoxic experiments. There were considerable fluctuations of both cardiac output and blood pressure, often terminating in sudden death from acute heart failure.

Although some degree of equilibration in arterial blood pH and the hemodynamic status of the animal could be attained with both CO_2 and HCl administration, sudden heart failure took place during HCl infu-

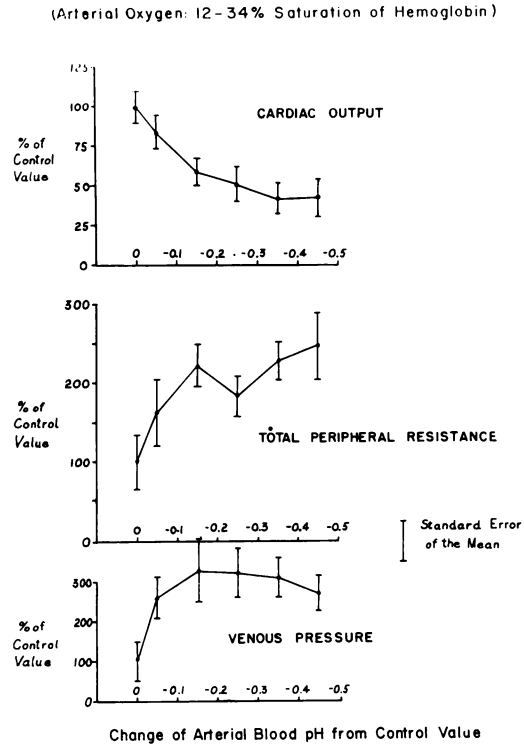

FIG. 3. The circulatory response observed as metabolic acidosis developed in animals made severely hypoxic by respiratory mixtures containing less than 6 per cent oxygen. Note the immediate decrease of cardiac output and elevation of total peripheral resistance after a minor degree of acidosis develops.

sions at pH values below 7.0. This was not so true with the hypercapnic animals which usually withstood pH levels as low as 6.6. However, all of these animals with CO_2 intoxication died within the ensuing 24 hours if the acidosis lasted for more than 20 to 30 minutes.

It is further noteworthy that, whereas the blood inorganic phosphate level more than doubled in all of the animals of each group which were severely acidotic, the blood lactate level declined or rose only slightly in the animals subjected to hypercapnia and hyperchloremia. The hypoxic animals were quite different in this regard, exhibiting a marked elevation of the lactate to concentrations between 300 and 400 per cent of the controls.

TABLE 1. *Type and Incidence of Acidosis in 104 Surgical Patients*

	Type of Acidosis					
	Hypercapnic	Hypoxic	Combined Hypoxia and Hypercapnia	Low Cardiac Output	Diabetic	Totals
Abdominal and thoracic operations						
No acidosis (Art. pH 7.34+)	—	—	—	—	—	22
Moderate acidosis (Art. pH 7.34–7.29)	13	4	0	2	0	19
Severe acidosis (Art. pH 7.29–)	4	2	2	0	2	10
Cardiac operations						
No acidosis (Art. pH 7.34+)	—	—	—	—	—	24
Moderate acidosis (Art. pH 7.34–7.29)	8	3	0	3	0	14
Severe acidosis (Art. pH 7.29–)	3	1	6	5	0	15
						104

Clinical Observations

Procedure. Patients for these studies were selected from the general and thoracic surgical services of the Cleveland Metropolitan General Hospital. Although an attempt was made to obtain a representative group of major operations, the series is weighted by the tendency to select the more seriously ill patients for observations. Of the 168 patients in whom the alterations of the blood gases and electrolytes occasioned by major surgical procedures were examined, there were 110 in whom adequate data were available for analysis of the circulatory response as well. Of these, six patients were eliminated because of known hypovolemia from bleeding or dehydration. Among the 104 patients presented in this study 14 had abdominal operations. These included: three gastrectomies, two combined-abdominal perineal resections of the rectum, three partial colectomies, and four cholecystectomies. Two patients with severe diabetic acidosis are presented with this group. One underwent drainage of an inguinal abscess and the other was treated for cellulitis of the foot and leg. Thirty-seven thoracic cases were studied exclusive of patients who had cardiac operations. Thirty-one had pulmonary resections for the treatment of tuberculosis, carcinoma, and chronic lung abscess. In addition, there were two pleural decortications, three esophagectomies, and a variety of other intrathoracic procedures.

Of the 53 cardiac operations all but eight were open procedures for the correction of acquired and congenital lesions. The others included five mitral commissurotomies, two pericardiectomies, and one drainage of a pericardial abscess.

The circulatory and blood chemical observations previously outlined were obtained by introducing a plastic catheter into the anticubital vein so that its tip lay in the superior vena cava. Dye was injected through it for measurement of the cardiac output. The central venous pressure was determined with a manometer containing isotonic saline solution, the baseline being

placed at the estimated level of the right atrium. Often this catheter remained in place for several days, being kept open by a slow drip of 5.0 per cent dextrose in water. The same catheter was also used for the administration of anesthetic agents and intravenous solutions. An arterial cannula, usually a "Rochester needle," was inserted into the radial artery. By means of this cannula, arterial blood was drawn through a Waters densitometer * at a constant rate for recording dye dilution curves. Samples of blood were also obtained by this route. After each use an injection of 3.0 ml. of sterile isotonic saline containing a 1 : 1,000 dilution of heparin made it possible to keep these arterial cannulae in use several days. Luer-lock stopcocks were used and held in place by sutures and adhesive tape. No vascular complications other than one instance of phlebitis have resulted from these procedures.

* Manufactured by the Waters Corporation, Rochester, Minnesota, Model Xc-100A.

Preoperative observations were made with patients lying quietly in bed. No sedation was used for the tests. In 38 of the cases, most of which were about to undergo cardiac operations, the preoperative test was done very early on the morning of the operation. However, these had all previously been examined by cardiac catheterization so that comparative hemodynamic data obtained under reasonably basal conditions were available. After the control observations, circulatory tests and arterial blood chemical determinations were made in the following order: 1) induction of anesthesia or tracheal intubation; 2) early in the operations after the chest or abdomen had been opened; 3) as the dissection or resection was being completed; 4) when the patient was awakening and the endotracheal tube was being removed; 5) at three to four hours postoperatively; 6) on the first postoperative day; and 7) on various days thereafter up to and including the seventh day. Occa-

TABLE 2. *Circulatory Dynamics of Surgical Patients with Uncomplicated Recovery and no Acidosis*

	Arterial Blood Chemistry				Circulatory Dynamics			
	pH	Buffer Base mEq/L.	O_2 % Sat.	pCO_2	Cardiac Index L./M².⁄ min.	Tot. Per. Resistance Dyne-sec./cm.$^{-5}$	Venous Pressure Cm. H_2O	Remarks
22 Patients major thoracic and abdominal operations. Group A								
Preoperative	7.42±.01	46±0.9	92±3%		2.62±.19	1,750	4.7±1.1	Uneventful convalescence. Recovery
Late operation	7.41±.01	46±0.7	91±3%		2.01±.21	2,112	14.8±2.8	
Extubation	7.41±.02	45±1.1	89±4%		3.03±.32	1,452	6.4±1.9	
Postop. 3 hours	7.40±.01	45±0.6	88±2%		2.56±.22	1,909	6.0±1.9	
1 day	7.42±.02	47±0.7	86±3%		2.78±.24	1,851	3.9±0.9	
7 days	7.41±.01	47±0.9	92±2%		3.16±.29	1,783	4.9±1.3	
24 Patients cardiac operations. Group B								
Preoperative	7.40±.01	44±0.5	89±4%		2.01±.14	2,311	5.4±.6	Uneventful convalescence. Recovery
Operation	7.44±.01	43±0.5	92±2%		2.02±.21	2,273	15.8±2.2	
Extubation	7.43±.02	43±0.7	89±3%		2.75±.29	1,709	11.3±2.3	
Postop. 2–4 hours	7.38±.01	43±0.7	89±3%		2.35±.51	1,966	8.8±1.3	
1 day	7.42±.01	45±0.6	85±3%		2.31±.14	2,095	7.7±1.0	
1 week	7.42±.01	46±0.8	91±3%		2.85±.18	1,670	9.9±1.4	

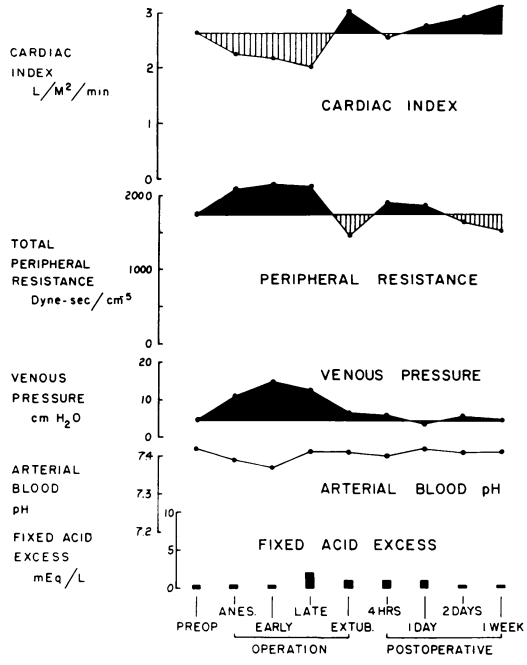

FIG. 4. The normal circulatory response in 22 patients who underwent pulmonary and abdominal operations without acidosis or complications. For standard errors of the means see Table 2, Group A.

sional later observations were made depending upon the patient's progress.

Results

For comparative purposes the patients are separated into two groups dependent upon whether they had cardiac or other operations. Futher, they are grouped according to the degree of acidosis as indicated by the arterial blood analyses. In Table 1 are presented the number of patients who fell into each group. All patients whose arterial pH never fell below 7.34 were considered to have been free of acidosis and are listed as *No Acidosis.* Twenty-two pulmonary and abdominal and 24 cardiac patients were in this category. Those patients who at any time during or after their operations exhibited arterial blood pH values between 7.34 and 7.29 and whose increase of fixed acids in whole arterial blood did not exceed 5 mEq/L. were classed as *Mild Acidosis.* Of these there were a total of 33. Any patient whose arterial blood pH fell below 7.29 was placed in the group listed as *Severe Acidosis.* In the class of "severe acidosis" were a total of 25 patients. These included 15 who underwent cardiac operations. Among the ten patients with noncardiac disease were two who had severe diabetic acidosis.

In Table 2 are presented the data on the cardiovascular dynamics of patients who had uneventful recoveries from operations and who did not show acidosis at any time before or after the operation. These patients are divided according to whether they underwent a cardiac or another operation. The means of cardiac indices (cardiac output/surface area M^2), the total peripheral resistances, and the venous pressures accompanied by the standard errors of these means indicate the pattern of normal circulatory response to surgery. They serve as a baseline for comparison with the hemodynamic observations in any patient who may have become acidiotic at a given time during his surgical course. For convenience these data are also shown in graphic form in Figures 4 and 5.

Starting with a mean preoperative cardiac index of 2.62 L./M.²/min., the patients with presumably normal hearts, who underwent uneventful abdominal and chest operations, showed a significant decrease in cardiac output during the induction of anesthesia and the operation to a mean index value of 2.01 L./M.²/min. This was accompanied by an increase of the total peripheral vascular resistance and a marked elevation of the central venous pressure to a mean value of 14.8 cm. H_2O. The latter is partly accounted for by the fact that the chest was opened in 68 per cent of this group. Upon awakening, with coughing and removal of the endotracheal tube, the cardiac output rose sharply to a value slightly above the preoperative mean. In the first two postoperative days the cardiac index remained not significantly different from that found preoperatively. However, by the seventh day the mean index was

elevated significantly to 3.16 L./M.²/min. Throughout the whole course the arterial blood pressure changed but little, and the calculated total peripheral resistance, therefore, varied inversely as the cardiac output. Except for the values during the periods of anesthesia and surgery the means of the venous pressures were not significantly different from the observed preoperative values. Although it was the rule to observe slight oxygen desaturation in the first two or three postoperative days, especially among patients who had undergone subtotal pulmonary resections, there was no significant alteration of either the arterial blood pH or the whole blood buffer base in these cases.

In the group of 24 cardiac patients who were operated upon and who recovered without complications and without acidosis the pattern is similar. Starting with a lower preoperative mean cardiac index of 2.01 L./M.²/min., there was no significant alteration of the output or total peripheral resistance during the anesthesia and operation. The venous pressure, however, rose to a mean of 15.8 cm. H_2O, again related in part to opening the chest. In the entire postoperative period the cardiac output was above the preoperative value. There was a marked elevation of the mean index to 2.75 L./M.²/min. upon awakening from anesthesia, and on the seventh day it was 2.85 L./M.²/min. The venous pressure during the first week tended to remain at levels above that found preoperatively. Except for a slight depression of the arterial blood pH to 7.38 from 7.43 during the early hours postoperatively and a tendency to exhibit a slight reduction in the oxygen saturation to a mean of 85 per cent in the first day or two, there was little alteration in the blood chemistries of this group of cardiac patients.

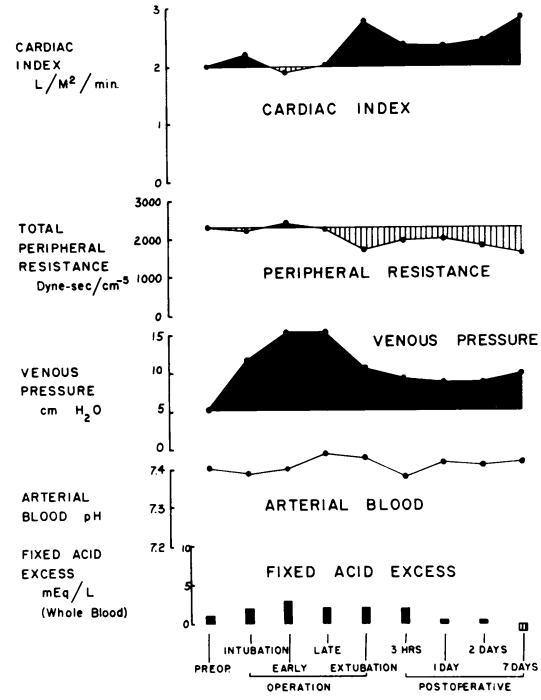

FIG. 5. The normal circulatory response in 24 patients who underwent cardiac operations (21 open) without acidosis or complications. For standard error of the means see Table 2, Group B.

Mild Acidosis

Three types of acidosis occurred among the 33 patients who developed mild acidosis with arterial pH values down to 7.30. These were due to: 1) hypercapnia; 2) hypoxia; and 3) low cardiac output. Hypercapnia, with arterial blood pCO_2 values ranging from 52 to 61 mm. Hg. occurred in 13 of the patients who underwent thoracic or abdominal procedures and in eight of those who had cardiac operations. In every instance this took place either during the operation or within the first few hours thereafter. Analysis of the circulatory dynamics showed no difference between this group at the time when the mild acidosis was present and that group consisting of patients who did not become acidotic. All of these patients recovered.

Hypoxia was responsible for the development of mild acidosis in four noncardiac and three cardiac operations. In one of the cardiac operations inadequate respiration during the latter part of the procedure led to a reduction in the arterial

TABLE 3. *Severe Hypercapnic Acidosis—Circulatory Dynamics*

Case No.	Name	Age	Sex	Time	Arterial Blood Chemistry: pH	Buffer Base mEq/L.	O_2 % Sat.	pCO_2	Circulatory Dynamics: Cardiac Index L./M.²/min.	Tot. Per. Resistance Dyne-sec./cm.⁻⁵	Venous Pressure Cm. H_2O	Remarks
1	H. J.	38	M	Preoperative	7.39	45	93		2.35	1,803	3	Inadequate ventilation. Recovery
	Pneumonectomy			Early operation	*7.19*	41	90	60	*1.67*	2,507	10	
				Late operation	*7.12*	37	78	64	*0.97*	4,154	9	
	(Fig.)			End operation	7.30	40	91	40	1.30	3,500	8	
				Postop. 4 hours	7.33	42	91	39	1.53	3,008	1	
				1 day	7.38	44	93		1.93	2,456	5	
				7 days	7.41	46	93		2.54	1,523	3	
2	S. P.	43	M	Preoperative	7.37	45	86		2.76	1,839	4	Inadequate ventilation. Recovery
	Excision pulmonary cyst			Early operation	7.21	42	85	59	2.13	2,142	16	
				Late operation	*7.08*	39	82	81	*1.83*	3,621	18	
				Extubate	7.31	42	90	41	2.14	2,206	7	
				Postop. 4 hours	7.38	42	87		2.21	2,172	8	
				1 day	7.40	46	85		2.81	1,803	5	
3	E. H.	33	M	Preoperative	—	—	—	—	4.43	1,975	4	Inadequate ventilation. Recovery
	Lobectomy			Early operation	*7.29*	46	84	55	*3.30*	2,431	12	
				Late operation	*7.24*	41	80	52	*2.75*	2,602	15	
				Extubate	7.30	42	91	46	5.08	1,647	7	
				Postop. 1 day	7.45	47	86		4.27	1,885	6	
4	J. L.	51	M	Preoperative	7.42	48	92		2.87	2,246	3	Inadequate ventilation. Recovery
	Lobectomy			Operation	*7.27*	45	89	57	*2.03*	2,731	8	
				Extubation	*7.23*	43	85	59	*2.24*	2,672	4	
				Postop. 4 hours	7.40	48	94		2.57	2,239	4	
				2 days	7.40	47	90		3.12	2,101	3	
5	H. M.	34	M	Preoperative	7.41	47	89		1.54	2,292	6	Pneumonitis and depressed respiration. Tracheostomy. Subsequently developed severe pneumonitis. Death, 11 days
	Mitral valvuloplasty open			Extubated	7.37	47	88		1.26	2,788	15	
				Postop. 3 hours	*7.20*	41	83	58	*1.64*	2,771	5	
				1 day	7.42	47	87		1.29	3,317	11	

TABLE 3.—(*Continued*)

Case No.	Name	Age	Sex	Time	Arterial Blood Chemistry				Circulatory Dynamics			Remarks
					pH	Buffer Base mEq/L.	O_2 % Sat.	pCO_2	Cardiac Index L./M.²/min.	Tot. Per. Resistance Dyne-sec./cm.⁻⁵	Venous Pressure Cm. H_2O	
6	R. E.	34	M	Preoperative	7.39	49	72		2.34	1,588	14	Inadequate ventilation
	Repair tetralogy open			Late operation	7.38	43	85		2.32	1,295	24	Recovery
				Extubate	*7.21*	41	87	55	2.81	1,318	17	
				Postop. 4 hours	7.40	44	91		1.83	2,184	11	
				1 day	7.40	46	89		2.43	1,644	7	
7	R. M.	16	F	Preoperative	7.36	47	85		2.13	1,673	6	Inadequate ventilation.
	Mitral valvulo-plasty open			Late operation	*7.18*	41	89	64	*2.01*	1,701	15	Recovery
				Extubate	7.33	42	91		2.83	1,435	7	
				Postop. 4 hours	7.38	41	88		1.96	2,349	9	

oxygen saturation to 65 per cent with an increase of the pCO_2 to 52 mm. Hg. Hypoxia uncomplicated by hypercapnea occurred in the other six patients as the result of transient atelectasis postoperatively. The arterial blood oxygen saturation fell for a few hours to values ranging from 65 to 78 per cent. Although the arterial blood pCO_2 remained at the upper limits of normal, a mild uncompensated acidosis occurred due to reductions of the buffer base from 3 to 5 mEq/L. below the calculated normal range for these patients. In each of four thoracic and abdominal patients the cardiac index was somewhat above that which would have been expected or that which was determined after the hypoxia had been corrected. In the three patients who developed hypoxia and mild acidosis during or after cardiac operations there was no significant variation of the cardiac index from those whose arterial blood pH remained in the normal range. However, under these conditions the venous pressure tended to rise 3.0 to 5.0 cm. above the expected values.

Among the group of five patients who developed mild acidosis postoperatively, apparently due to low cardiac output, were two patients who underwent noncardiac chest procedures. The first, T. S., a 66-year-old man, after esophagectomy, failed to return his cardiac output to his preoperative value (Index 2.78 L./M.²/min.). In fact, for the first two days his cardiac index remained at 1.49 and 1.33 L./M.²/min. This was accompanied by a slight decrease of blood pressure, but the total peripheral resistance increased by 56 and 58 per cent. Whereas, the arterial blood remained saturated at 90 per cent or more postoperatively and the pCO_2 remained near 45 mm. Hg, the buffer base value fell from 48 mEq/L. immediately after operation to 43 mEq/L. two days later with a pH of 7.32. This man continued to do well and gradually raised his cardiac output by the fifth day (Index 2.28 L./M.²/min.).

TABLE 4. *Severe Hypoxic Acidosis—Circulatory Dynamics*

Case No.	Name	Age	Sex	Time	Arterial Blood Chemistry				Circulatory Dynamics			Remarks
					pH	Buffer Base mEq/L.	O_2 % Sat.	pCO_2	Cardiac Index L./M.²/min.	Tot. Per. Resistance Dyne-sec./cm.$^{-5}$	Venous Pressure Cm. H_2O	
8	J. W.	45	M	Preoperative	7.37	43	94		2.42	1,474	2	Inadequate ventilation. Recovery
	Gastrectomy and vagotomy			Early operation	*7.24*	39	60	45	*4.76*	828	13	
				Late operation	7.36	41	60		3.93	852	6	
				Postop. 4 hours	7.32	40	88	35	3.45	1,506	4	
				7 days	7.41	46	94		4.04	1,023	5	
9	A. P.	51	M	Preoperative	7.38	47	92		1.93	1,723	3	Pneumonitis, atelectasis. Inadequate respiratory exchange. Recovery
	Exploratory thoracotomy. Non-resectable carcinoma			Operation	7.36	44	91		1.69	2,421	8	
				Extubation	7.40	46	91		1.91	2,182	7	
				Postop. 1 day	7.37	42	82	35	1.44	3,684	4	
				2 days	*7.22*	38	52	48	*1.21*	2,891	6	
				3 days	7.41	44	88		1.94	2,493	3	
				6 days	7.40	46	90		2.73	1,987	2	
10	E. W.	55	F	Preoperative	7.41	44	93		1.24	4,715	16	Moderate hypertension preoperatively. Pneumonitis. Inadequate respiratory exchange. Death, 22 hours
	Mitral valvuloplasty open			Postop. 3 hours	7.34	38	88		1.25	3,585	21	
				6 hours	7.39	36	81		1.39	3,713	11	
				20 hours	*7.24*	31	52	26	0.72	6,164	26	

However, he developed a mediastinal infection with pneumonia and died suddenly on the seventh day. A similar situation was encountered in the case of J. P., a 74-year-old man who underwent a pneumonectomy for cavitating carcinoma. He, too, had an output of only 56 per cent of his basal value on the third day postoperatively by which time he had developed a mild metabolic acidosis with a pH of 7.31 despite normal oxygenation and pCO_2 values of the arterial blood. Eight days later he died when pneumonitis developed on the side opposite to the operation. Each of these patients exhibited marked coronary atherosclerosis and myocardial fibrosis at autopsy, probably accounting for their low cardiac outputs.

Three cardiac patients who had low postoperative outputs (49 to 65 per cent of their preoperative basal values) for two or three days all looked worried, pale, and had thin thready pulses. In each case the arterial pH and buffer bases which had been normal at the termination of the procedure fell slightly to values ranging from 7.30 to 7.33 and 41 to 43, respectively. In each case the lungs functioned well and the arterial pCO_2 and oxygen saturation remained within the normal limits. As their cardiac outputs returned to or above the basal values, these patients appeared to be doing well. All three satisfactorily recovered.

Severe Acidosis

There were 25 patients altogether who exhibited arterial blood pH values below 7.29. Of these, 15 were in the group who had undergone cardiac operations and nine who had either thoracic or abdominal procedures. One of the latter was suffering from severe diabetic acidosis. Also included is another patient with severe diabetic acidosis and cellulitis of one foot and leg who never actually underwent an operation. The pertinent observations on the blood chemical and circulatory dynamics of each

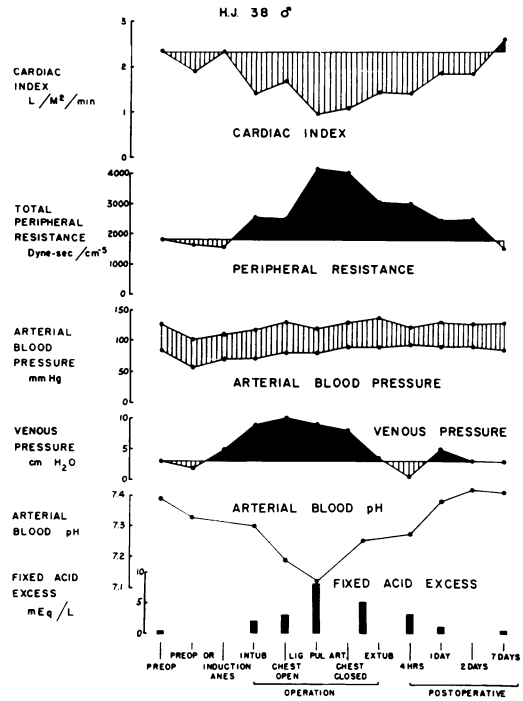

FIG. 6. An example of hypercapnic acidosis with a severe reduction in cardiac output occurring during anesthesia due to inadequate ventilation. Not also that there is a moderate metabolic acidosis present despite adequate oxygenation of the blood. Probably this is due to subliminal perfusion.

of these patients are presented in Tables 3–7. The data on the arterial blood chemistry include the pH, the calculated whole blood buffer base, and the percentage of oxygen saturation. The pCO_2 values are given when they were abnormal or pertinent to an understanding of the acid-base problem. In each instance the hemodynamic data include, when available: the cardiac index, total peripheral vascular resistance calculated from the cardiac output and the mean arterial blood pressure, and the central venous pressure.

For purposes of comparison with each other and with the data from those patients who were not acidotic, given in Table 2, an attempt has been made to classify them according to the type of acidosis which developed. The decision to place each individual in one or another of these groups is

TABLE 5. *Combined Hypercapnic and Hypoxic Acidosis—Circulatory Dynamics*

Case No.	Name	Age	Sex	Time	Arterial Blood Chemistry pH	Buffer Base mEq/L.	O_2 % Sat.	pCO_2	Circulatory Dynamics Cardiac Index L./M.²/min.	Tot. Per. Resistance Dyne-sec./cm.⁻⁵	Venous Pressure Cm. H_2O	Remarks
11	L. B.	48	M	Preoperative	7.39	47	87		4.78	929	3	Inadequate ventilation. Recovery
	Lobectomy			Late operation	*7.22*	42	59	58	*2.04*	2,258	12	
				Extubation	*7.27*	41	84	48	*6.80*	626	1	
				Postop. 5 hours	7.40	46	88		1.61	2,749	3	
				7 days	7.40	46	91		4.03	885	4	
12	M. S.	53	F	Preoperative	7.36	46	94		2.31	1,934	4	Pneumonia. Inadequate respiratory exchange. Death, 10 days
	Right hemi-colectomy			Operation	7.45	46	92		1.76	2,437	7	
				Postop. 1 day	7.45	48	88		2.24	2,072	5	
				3 days	7.45	47	90		2.36	2,174	3	
				5 days	7.40	49	86		2.76	1,673	3	
				9 days	*7.26*	45	62	56	*2.01*	2,342	4	
				9 days	*7.18*	43	46	70	*1.71*	2,781	5	
13	A. N.	36	M	Preoperative	7.37	43	89		2.19	1,903	10	Pneumonitis. trache-ostomy. Death, 3 days
	Aortic valvulo-plasty open			Postop. 1 day	7.44	46	82		4.13	1,679	9	
				2 days	7.32	42	59		3.42	2,360	20	
				3 days	*7.17*	36	43	51	*2.01*	2,731	22	
14	B. W.	37	F	Preoperative	7.41	48	88		1.11	3,348	5	Pneumonitis. Low out-put. Death, 8 days
	Mitral valvulo-plasty open			Postop. 2 days	7.40	43	98		1.49	2,272	15	
				7 days	*7.19*	39	41	54	*1.31*	2,743	21	
15	V. S.	51	F	Preoperative	7.47	45	91		2.33	2,301	7	Pneumonitis. Trache-ostomy +$NaHCO_3$. Recovery
	Mitral valvulo-plasty open			Extubation	7.33	42			2.16	2,883	18	
				Postop. 20 min.	*7.21*	42	43	61	*2.02*	2,889	20	
				1.5 hrs.	*7.18*	38	54	57	*1.13*	3,204	23	
				3 hours	7.36	42	82		1.75	2,394	12	
				7 days	7.43				2.68	1,725	6	
16	A. A.	32	F	Preoperative	7.36	45	93		3.18	1,203	3	Inadequate ventilation. Recovery
	Pericardiectomy			Late operation	7.39	44	90		2.20	1,817	12	
				Extubate	*7.24*	42	62	57	*3.56*	1,264	17	
				Postop. 4 hours	7.42	46	82		1.64	2,279	4	
				1 day	7.39	47	87		1.61	2,209	5	
				7 days	7.44	46	92		3.25	2,295	3	

TABLE 5.—(*Continued*)

Case No.	Name	Age	Sex	Time	Arterial Blood Chemistry				Circulatory Dynamics			Remarks
					pH	Buffer Base mEq/L.	O_2 % Sat.	pCO_2	Cardiac Index L./M.²/min.	Tot. Per. Resistance Dyne-sec./cm.⁻⁵	Venous Pressure Cm. H_2O	
17	C. D.	35	F	Preoperative	—	—	—		1.64	2,113	40	Pneumonitis. Inadequate respiratory exchange. Recovery
	Drainage pericardium. (Pericarditis and pneumonia)			End operation	*7.25*	44	73	59	*1.83*	1,972	34	
				Postop. 3 hours	7.28	44	70	54	1.40	2,766	24	
				1 day	7.20	40	65	65	1.38	2,868	25	
				3 days	7.29	42	69	51	3.08	1,394	18	
				5 days	7.43	46	89	37	3.10	1,300		
18	P. A.	29	F	Preoperative	7.44	44	85		1.50	2,498	20	Pneumonitis. Inadequate respiratory exchange. Tracheostomy. Recovery
	Mitral valvuloplasty open			Late operation	*7.17*	38	73	58	*0.62*	7,508	26	
				Extubation	7.39	41	81		1.92	2,775	21	
				Postop. 3 hours	7.37	40	87		2.05	2,175	12	

based upon the clinical course and the chemical findings in the arterial blood.

Severe Hypercapnic Acidosis. As shown in Table 3 seven patients developed severe acidosis due to an abnormal increase of the arterial pCO_2. Four had undergone pulmonary operations and three had had cardiac procedures. All recovered from the immediate effects of this type of acidosis, although one subsequently died of pneumonia 11 days later. It is noteworthy that pure hypercapnic acidosis occurred only during the operations or in the first few hours thereafter. In each instance it was related to depressed respiration and inadequate ventilation of the lungs.

A representative example of this situation is given in Figure 6 which portrays the course of Case 1 (H. J.), a 38-year-old man who was admitted to the hospital with extensive tuberculosis of his right lung and underwent a pneumonectomy. The preoperative pulmonary function studies indicated that he had an adequate respiratory reserve to withstand the procedure well, and a review of his other systems disclosed no abnormalities. In the early part of the operation the pH of his arterial blood decreased to 7.19 due to retention of carbon dioxide and an elevation of the pCO_2 to 60 mm. Hg. At this time his cardiac index was reduced, but not much more than might be expected under eucapnic conditions (Fig. 4). However, the CO_2 retention continued and shortly before closing the chest the pCO_2 of the arterial blood had risen to 64 mm. Hg. By this time his cardiac index had decreased to 0.97 L./M.²/min., only 41 per cent of his preoperative output. This is well below that usually encountered and cannot be explained by loss of blood in this case. The arterial blood remained reasonably well oxygenated, but a moderate degree of metabolic acidosis developed with a decrease of the buffer base from 45 to 37 mEq/L. Subsequently his cardiac output returned to the basal value, but more slowly than under normal

TABLE 6. *Low Cardiac Output Metabolic Acidosis—Circulatory Dynamics*

Case No.	Name	Age	Sex	Time	Arterial Blood Chemistry				Circulatory Dynamics			Remarks
					pH	Buffer Base mEq/L.	O_2 % Sat.	pCO_2	Cardiac Index L./M.²/min.	Tot. Per. Resistance Dyne-sec./cm.$^{-5}$	Venous Pressure Cm. H_2O	
19	E. C.	56	M	Preoperative	7.45	46	92	36	2.81	1,379	7	Progressively low output. Metabolic acidosis. Death, 5.5 hours
	Aortic valvuloplasty open			Late operation	7.60	43	90	22	1.65	4,010	10	
				End operation	7.50	36	94	18	1.32	3,842	8	
				Postop. 2 hours	*7.28*	33	93	27	—	—	—	
				5 hours	*7.22*	28	86	25	*0.64*	3,567	11	
20	E. W.	51	F	Preoperative	7.38	49	91		1.00	2,910	26	Low output. Metabolic acidosis. Death, 6 hours
	Mitral valvuloplasty open			Late operation	7.28	38	95		0.82	3,172	26	
				Extubation	7.33	40	93		0.62	3.243	16	
				Postop. 4 hours	*7.25*	36	90		*0.54*	2,531	27	
21	R. S.	15	M	Preoperative	7.39	44	81		1.51	3,160	4	Low output. Metabolic acidosis. Death, 4 hours
	Repair unilocular ventricle and partial transposition			End operation	7.37	36	84		0.94	4,730	19	
				Postop. 3 hours	*7.16*	34	69	51	*0.72*	—	20	
22	J. L.	21	M	Preoperative	7.42	48	92		1.45	2,520	9	Inadequate ventilation. Low output. Metabolic acidosis. Sudden death, 5 days
	Aortic valvuloplasty open			Late operation	*7.10*	36	90	63	*0.51*	4,398	11	
				Extubated	*7.25*	32	90	25	*0.60*	—	—	
				Postop. 3 hours	7.38	40	94	30	0.61	4,732	15	
				2 days	7.40	40	87	25	0.87	3,953	15	
				5 days	7.40	41	85		0.91	3,821	—	
23	C. O.	12	M	Preoperative	7.50	44	89		2.1	1,821	12	Alkalosis. Low output. Metabolic acidosis Recovery
	Repair septal defect and infundibular stenosis			Late operation	7.50	39	92	17	1.2	2,931	9	
				Extubated	*7.23*	36	95	37	*1.1*	3,122	11	
				Postop. 3 hours	*7.33*	41	95	36	*1.5*	2,176	15	
				1 day	7.44	42	90		1.6	2,231	14	

TABLE 7. *Diabetic Acidosis—Circulatory Dynamics*

Case No.	Name	Age	Sex	Time	Arterial Blood Chemistry				Circulatory Dynamics			Remarks
					pH	Buffer Base mEq/L.	O_2 % Sat.	pCO_2	Cardiac Index L./M.²/min.	Tot. Per. Resistance Dyne-sec./cm.$^{-5}$	Venous Pressure Cm. H_2O	
24	V. M.	33	F	Preoperative	—	—	—	—	—	—	—	Marked hypercapnea.
	Drainage inguinal abscess			Operation	—	—	—	—	—	—	—	Temp. 40° C.
				Postop. 4 hours	*7.24*	24	99	13	*2.4*	1,832	3	Temp. 38° C.
				7 hours	*7.30*	33	98	24	*1.0*	2,651	4	Recovered
				11 hours	7.43	40	98	26	1.6	2,178	5	
				15 hours	7.42	41	95	28	1.5	2,625	5	
				22 hours	7.46	48	94	35	1.5	2,824	3	
				46 hours	7.41	46	96	35	2.9	2,017	4	
25	G. S.	48	M	Admission	*7.22*	26	96	18	*2.2*	3,527	4	Semicoma. Marked
	Cellulitis foot and leg			Postadmiss. 6 hours	*7.36*	33	95	26	*2.6*	2,943	5	hypercapnea. Recovered
				4 days	7.38	44	94	38	3.2	2,637	4	

conditions. It is important to note that despite the low cardiac output encountered during the anesthetic and the operation the arterial blood pressure remained essentially unchanged, being maintained by a considerable increase in the total peripheral resistance.

Case 2 exhibited a similar reaction to hypercapnia, the cardiac output being reduced to a marked extent only when the arterial pH had fallen below 7.2. J. H. (Case 4) failed to raise his cardiac output to the extent which would be expected normally when he awoke with a pH at 7.23, but he had normal venous and arterial pressures at the time. The remainder of the patients including two cardiac operations who had arterial pH values of 7.20 and 7.18, respectively, showed cardiac outputs which were not significantly different from those expected (Fig. 5) under normal conditions. All of these patients accumulated fixed acids to some extent at the time of the hypercapnia as shown by moderate reduction of the whole blood buffer base. However, in contrast to those who developed hypoxic acidosis, the lactic acid content of the blood in this group exceeded 200 per cent of the control value in only one case.

Severe Hypoxic Acidosis. Only three patients exhibited severe oxygen desaturation of the arterial blood without hypercapnia. Their data are set forth in Table 4. The patient J. W. (Case 8) early in the course of a gastrectomy and vagotomy with an arterial blood pH of 7.24 actually exhibited a marked increase of the cardiac output to nearly twice his preoperative control value. On the other hand, Cases 9 and 10 both developed pulmonary abnormalities postoperatively which resulted in severe arterial oxygen desaturation and an accumulation of fixed acids with pH values of 7.22 and 7.24 respectively. Both of these showed a significant reduction of cardiac output to approximately one half that usually observed at comparable times. In

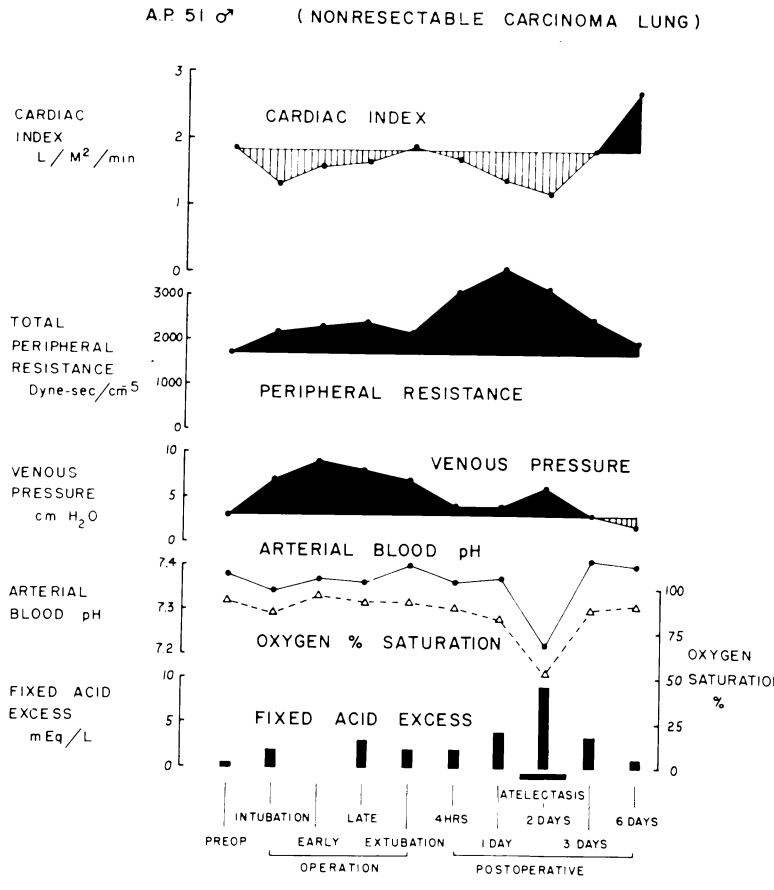

FIG. 7. The circulatory effect of hypoxia, not accompanied by an elevation of the arterial pCO_2, which was caused by atelectasis on the second postoperative day after exploratory thoracotomy.

both this was accompanied by a significant rise of venous pressure. The first improved and increased his cardiac output, as shown in Figure 7, when an atelectasis was corrected. The other, who underwent an open mitral valvuoplasty, progressed to a metabolic acidosis due in part to an increase in pulmonary congestion which caused a reduction of the arterial oxygen saturation to 52 per cent 20 hours postoperatively. Hypoxia combined with her cardiac output (1.39 L./M.²/min.), much below that normally encountered in cardiac patients during this part of the postoperative period, resulted in an increase of fixed acids and progressive heart failure (cardiac index 0.79 L./M.²/min.). She died shortly after the last chemical determination 22 hours postoperatively.

Severe Acidosis Due to Combined Hypercapnia and Hypoxia. Eight patients developed acidosis due to oxygen lack and the retention of carbon dioxide. In four of them this occurred during the operation, was promptly corrected, and was followed by recovery. However, of the four patients who became severely acidotic because of pneumonitis or atelectasis in the postoperative period it was possible to restore respiratory function with recovery in only one. This was V. S., a 51-year-old woman who had undergone an open repair of mitral insufficiency (Case 15). Her course is illustrated in Figure 8. Having completed the operation with only a minor degree of metabolic acidosis and no hypercapnia, insufficient attention was paid to the fact that she had lungs damaged by prolonged pulmonary hypertension and some degree of ventilatory obstruction of an asthmatic type. Her ventilation was inadequate. She failed to recover consciousness and had a thin

pulse with a blood pressure of 92/65 in the immediate postoperative period. The arterial blood pH was 7.21, and the oxygen saturation was 43 per cent. Assisted respiration for one hour produced little improvement in her condition. Another arterial blood sample disclosed that the pH had decreased to 7.18, although the oxygen content had risen slightly to 54 per cent saturation. At this time the whole blood buffer base was 38 mEq./L. The blood pressure had fallen to 75/52 mm. Hg. The cardiac index which was 2.16 L./M.^{2}/min. when she was extubated and 2.02 shortly thereafter, had fallen to 1.13 L./M.^{2}/min. as the metabolic acidosis was superimposed upon the already present hypercapnia. At this point a tracheostomy was performed which permitted vigorous ventilatory activity by a respirator. She was given 55 mEq. of sodium as $NaHCO_3$. Shortly after this she awoke and began to breath spontaneously, with a marked improvement in color and pulse. At three hours postoperatively the arterial pH was 7.36, her pCO_2 was normal, and the buffer base was 42 mEq./L. The cardiac index had risen to 1.75 L./M.^{2}/min., but it remained well below that observed at the time of extubation (2.02 L./M.^{2}/min). It was not until the third postoperative day that her cardiac output was found to have risen above the preoperative basal value.

The other three patients (Cases 12, 13, and 14) died within one day after the development of a combined hypoxic and hypercapnic acidosis associated with pneumonia. Each showed an arterial pH value below 7.20 accompanied by a marked decrease of cardiac output and an increase of venous pressure from that previously observed. In each instance observed there was an elevation of the total peripheral resistance.

The acidosis encountered in four cases

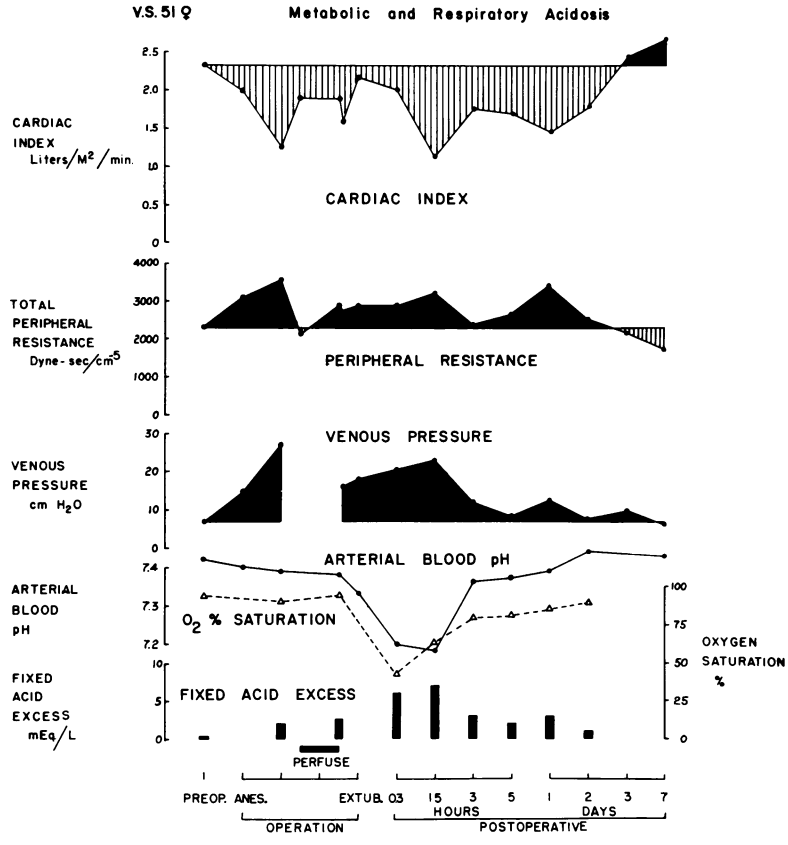

FIG. 8. The profound circulatory failure induced by a combination of hypoxia and hypercapnia due to inadequate ventilation and pulmonary gas diffusion in the immediate postoperative period. Although this was corrected by tracheostomy and the administration of $NaHCO_3$ at two hours postoperatively, the cardiac output remained low for the next two days.

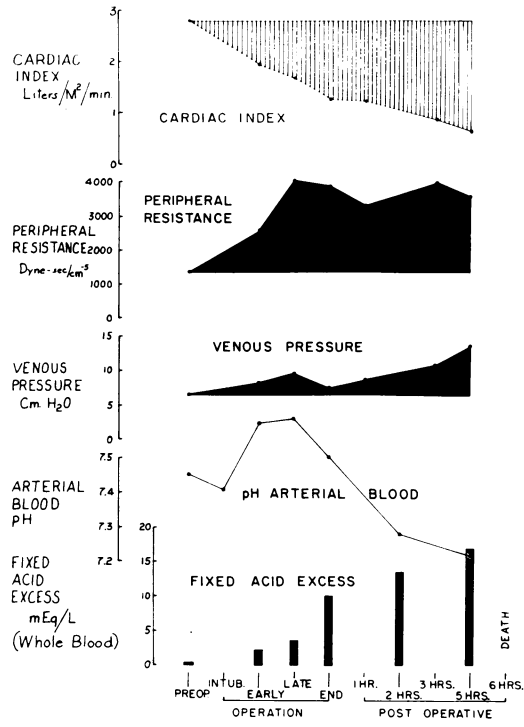

FIG. 9. An example of the type of metabolic acidosis induced in the presence of normal arterial pO_2 and pCO_2 by an inadequate cardiac output. When the acidosis ultimately becomes decompensated, it results in further circulatory failure and a vicious circle is established.

during anesthesia was less prolonged than that which developed during the immediate postoperative period. In only one (Case 18) was the pH below 7.22. She alone exhibited any significant reduction of the cardiac output below the usual values. Her cardiac index fell from a preoperative value of 1.50 to 0.62. At the same time she showed a remarkable increase of peripheral resistance to three times that found preoperatively.

Low Cardiac Output Metabolic Acidosis. Of the five postoperative cardiac patients, presented in Table 6, in whose blood fixed acids inexorably accumulated due to very low cardiac outputs and inadequate perfusion of the tissues, there was only one in whom the vicious circle was broken to result in recovery. This was a 12-year-old boy, Case 23, who had undergone repair of a ventricular septal defect and correction of an infundibular stenosis of the right ventricle. Having completed the intracardiac portion of the operation with a moderate reduction of buffer base and an arterial pH of 7.50, the cardiac index was only 1.2. The pH decreased to 7.23 by the time the endotracheal tube was removed despite the presence of a normal pCO_2 and oxygen content in the arterial blood. At this time and throughout the next day the venous pressure and the peripheral resistance remained elevated. Within the first three hours after the operation the cardiac index rose to 1.5 with a reduction of the concentration of excess fixed acids in the blood by 5 mEq./L.

Illustrated in Figure 9 is the course of a patient in whom the progression of metabolic acidosis and a further reduction of cardiac output could not be arrested. E. C., a 56-year-old steel worker (Case 19), was operated upon to correct an aortic stenosis and regurgitation of rheumatic origin. The operation, performed with the aid of hypothermia and extracorporeal circulation under direct vision, appeared satisfactory. However, soon afterward the cardiac index was 1.32 and proceeded to fall to 0.64 L./M.²/min. Assisted ventilation of the lungs was continued. The arterial oxygen content was normal, and the pCO_2 remained either normal or low. Five hours postoperatively the excess fixed acid amounted to 17 mEq./L. He died shortly thereafter with an elevation of both venous pressure and the total peripheral resistance.

Diabetic Acidosis. The data from observations of two patients in severe diabetic ketosis are presented in Table 7. Both exhibited a marked reduction of the whole blood buffer base to 24 and 26 mEq./L. respectively when first seen. Both were very hyperpneic with very low pCO_2 values in the fully oxygenated arterial blood. It is notable that both had low cardiac outputs which took a long time to return to normal after correction of the acidosis.

Indeed, Case 24, a 33-year-old woman

who had undergone a laparotomy and drainage of a right inguinal abscess, actually had a serious decrease of her cardiac output as the ketosis was being treated with insulin and glucose, potassium, and $NaHCO_3$ intravenously. Her course is illustrated in Figure 10. When her arterial pH rose from 7.24 to 7.30 the cardiac index declined from 2.4 to 1.0 L./M.^{2}/min. and she was in a state of mild hypotension (BP 90/62). She was pale and her pulse was rapid and thin. At this point the peripheral resistance had increased moderately and the venous pressure had risen only very slightly above normal. Her rectal temperature reached 40 ° C. and she was placed in ice packs to keep it below 38° C. Gradually her cardiac output, blood pressure and venous pressure returned to normal.

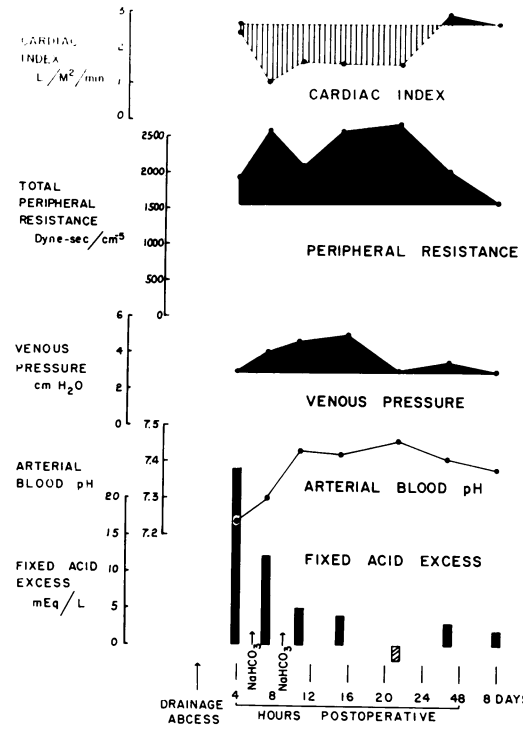

FIG. 10. An example of the mild heart failure and lack of venous return caused by the profound metabolic derangements present in severe diabetic acidosis. Note the slow return of the cardiac output to normal after correction of the acidosis.

Discussion

Data on the endocrine, blood gas, electrolyte, and acid-base alterations caused by illness and trauma are now available.[42] In most instances their functional significance is not clearly understood. Among these, severe acidosis, in particular, has been described during [2, 7, 24, 40, 55] and after [3, 36, 41] surgical operations. Viewed, as it is, with alarm because of the well known neurological depression [7, 13] which takes place in profound acidosis, it has been considered a probable cause of hypotension during surgical operations.[40] A variety of experiments have been conducted on the circulatory effects of an increase in the hydrogen ion concentration of the blood.

To evaluate the behavior of the circulation under these conditions, one must consider not only the absolute value for the hydrogen ion concentration but also the mechanisms which caused the change. An increase of the hydrogen ion in the various compartments of the body suggests overburdening or failure of the regulatory mechanisms which normally guard the pH values of body fluids within the narrow margins considered to be normal. These are, of course, the intracellular and extracellular buffers, the respiratory system, and the kidneys. Acid may be retained as in respiratory acidosis or renal shutdown. Although in both cases there is retention of acid, even here the associated biochemical situation is entirely different. Acid may be added as in the experiments on hyperchloremia, or it may be endogenously produced as observed in the metabolic acidosis of hypoxia, subliminal perfusion, or diabetes. On occasion an acute decompensated acidosis might be produced by loss of cations, but such is rare. In the series of experiments here presented we have examples of the behavior of the circulation in the intact mammalian organism under stress of the first three types of acidosis.

The clinical observations on man in this study, as shown in Table 1, relate only to the retention of carbon dioxide or to the

development of metabolic acidosis, including subliminal perfusion of tissues, or to combinations thereof. Further, in comparing the circulatory or other functional effects of acidosis it must be emphasized that the production of fixed acids in metabolic acidosis is a phenomenon related to an interference with the normal metabolic pathways used for energy production. Hypoxia, ranging from 65 to 75 per cent arterial oxygen saturation, usually produces an increase of blood flow throughout the body and oxygen consumption is not greatly altered.[33] Below 65 per cent the oxygen consumption is decreased progressively.[26] The heart meets this load of extra work also with an increase of coronary flow.[14, 25] An oxygen debt starts to develop with the release of phosphates, lactate, and pyruvate into the blood stream, largely from skeletal muscles and the liver.[16, 37]

The heart muscle itself, containing enzymes which are 95 per cent geared to aerobic metabolism, is incapable of continuing its normal activity for long in the absence of oxygen.[8, 45] Gremels and Starling[28] observed dilation of the heart and failure below a critical oxygen saturation of 35 per cent in the arterial blood. More recently Gorlin and Lewis[26] described sudden failure as was seen in our series of hypoxic animals when the arterial oxygen saturation fell below 20 per cent for a period of more than a few minutes. The coronary flow could not increase adequately to supply the myocardial oxygen requirements. Thus, there are two factors at work on the heart and circulation in the type of hypoxic metabolic acidosis commonly seen in postoperative surgical patients. 1) the change of the hydrogen ion concentration from the accumulation of fixed acids during anaerobic glycolysis; and 2) the interference with aerobic metabolic production of energy, particularly within the heart muscle itself.

The cardiac output determinations in the clinical and experimental observations, checked as they were against other methods, were found to be within an average range of 12 per cent agreement. Therefore, it is apparent that relative changes in these data are of greater significance than exact quantitative values. Thus, the cardiac outputs in the results from the experiments are expressed as the per cent of the control values. The circulatory parameters measured: cardiac output, venous and arterial pressure and the calculated total peripheral resistance, simply give an over all picture of the behavior of the circulation under the varying circumstances. No function of the left heart, other than its output, can be estimated from the data. Broader studies would have required the determination of pulmonary vascular pressures and volumes, not practical in our patients. Failure of the left side of the heart is only reflected in the central venous pressure when the right heart becomes decompensated in its turn. In addition to measuring the ability of the right heart to pump the blood returned to it into the pulmonary circuit at a given end-diastolic pressure, the venous pressure also is an indication of the venomotor tone and the blood volume producing a gradient of flow toward the heart.[5] Although we have measurements of the total peripheral vascular resistance, these data give us no indication of the actual distribution of blood to one or another vascular bed. This we can deduce only from clinical observation or other experimental data under similar circumstances. Thus, we have a picture from these studies only of the circulation in its entirety comprized as it is by three chief elements: the pump, the vascular resistance, and the venous return which includes available blood volume and the capacity of the venous plexus.

Difficulty is experienced in obtaining control hemodynamic values, especially in the clinical observations, for comparison with the hemodynamic findings under a given set of acidotic conditions. This has been attempted by two means: 1) the establish-

ment of a pattern of circulatory response to uncomplicated operations without any abnormal metabolic variaitons; and 2) by comparing an individual acidotic patient's situation with that which obtained before or after the metabolic derangements took place. The normal uncomplicated circulatory response to both cardiac, and non cardiac operations is presented in Table 2. These data are of importance not only for comparison but indicate that a cardiac index near 2.5 L./M.^{2}/min. is adequate for a normal unventful convalescence.

This is in agreement with other observations.[10, 34] Inspection of Figures 4 and 5 suggests that this is true both for the patients who had undergone heart operations as well as for those who had abdominal or other thoracic procedures. Furthermore, as previously shown,[11, 18, 19, 50] the presence of a general anesthetic tends to depress the cardiac output. Therefore, alterations in circulatory dynamics apparently related to metabolic derangements can only be compared with other measurements made under the same anesthetic and at the same depth of anesthesia. Perhaps the reason for the very slight changes in cardiac output from the preoperative basal values during the uncomplicated operations upon the heart may be that a minimum of anesthesia was employed, most of them being accomplished with a 50 per cent nitrous-oxide oxygen mixture, supplemented in many cases by the addition of curareform drugs. It is well known that deep anesthesia is undesirable and often results in hypotension and serious cardiac arrhythmias.[22]

Changes in the circulation caused by an increase of the hydrogen ion concentration in the absence of metabolic acidosis appear in part to be related to the arterial pCO_2 value and the catechol amine blood levels present at the moment. Richardson *et al.*[49] found that a change of the arterial pH to 7.25 and the pCO_2 from 42 to 58 mm. Hg in human volunteers resulted in an increase of cardiac output of 45 per cent. This, they demonstrated, was not due merely to the added work of hyperpnea. Our experimental results in curarized dogs appear to confirm this, and study of Table 3 will indicate that the cardiac output was greater in Case 4 at a pH of 7.23 when extubated, a period of adrenergic activity,[31, 32] than earlier in the operation at a pH of 7.27. Similarly, in Case 5 at a postoperative pH of 7.20 with a pCO_2 of 58 mm. Hg, the cardiac index was 1.64 L./M.^{2}/min. This compares with an index of 1.29 L./M.^{2}/min. observed a day later with normal acid-base balance. A similar observation was made in Case 6. Of the seven patients who exhibited essentially pure hypercapnia significant reduction of cardiac output was exhibited only by two (Case 1, 2) whose arterial pH values dropped to 7.12 and 7.08, respectively, during anesthesia. It is of interest that each of these developed an excess of fixed acids in the blood amounting to about 7 mEq./L. This moderate metabolic acidosis took place despite the presence of adequately oxygenated blood, an observation in agreement with those of Elkington *et al.*[15] and Altschule and Sulzbach.[1] Doubtless this was due to the maintenance of normal arterial blood pressure and concomitant increase of total peripheral resistance (Fig. 6) which probably deprived certain vascular beds, not the coronary vessels, of adequate perfusion.[29] All of the hypercapnic patients showed an increase of peripheral resistance when the cardiac output was reduced. But none exhibited any significant increase of venous pressure. Both of these findings are confirmed by the experiments on the hypercapnic dogs. As shown in Figure 1, only when the arterial pH had fallen to 6.8 was the cardiac output significantly reduced and did the venous pressure and peripheral resistance notably increase.

From these data on the circulatory response to hypercapnia and from the observations of Sechzer *et al.*[51] we can conclude that the presence of an abnormally high carbon dioxide tension in the absence

of hypoxia stimulates sympathetic activity responded to by the peripheral vascular system with an increase in resistance. An increase of pCO_2 appears to constrict the normally innervated vessels of an extremity but to dilate those that are denervated.[39, 49] It is also demonstrated that the vessels of the brain [38] and heart [29] dilate under these circumstances. The part played by the neuroendocrine system in protecting the hypercapnic organism is further substantiated by the earlier work of Clowes, Hopkins and Simeone [8] and Hackel and Clowes [29] who demonstrated that animals which were sympathectomized and adrenalectomized rapidly died of circulatory failure if the pH of the arterial blood was lowered below 7.1 by the administration of carbon dioxide. Campbell [6] produced evidence that the heart of acidotic animals is more sensitive to vagal stimuli, and Nahas and Cavert [43] showed that the isolated failing heart can be restored by administration of adrenaline.

In the range of acidosis induced by carbon dioxide retention down to a pH of 7.0, encountered in this series of patients, it appears both from the clinical observations and the experiments that heart failure was not responsible entirely for the observed reduction of cardiac output. If this had been the case, the venous pressure, in all probability, would have risen to a greater extent than it did. In Cases 1 and 2 it was no higher than normally is expected when the chest is open. Therefore, it is probable that the sympathoadrenal stimulation in hypercapnia is not reflected in marked contraction of the venous bed as observed in the response to acute hypoxia.[21] Possibly blood is accommodated in some portion of the capillary or venous plexus and is not effectively returned to the heart.

When one compares in Figure 2 the experimental circulatory effects of reducing the arterial pH by the infusion of HCl with those of an increase in pCO_2, one is struck by the similarity of the response. In both experiments the cardiac output did not decrease significantly until the pH of the arterial blood fell below 7.1. Although the peripheral arterial resistance increased so that the blood pressure changed but little until the heart suddenly failed, the animals infused with HCl showed a rise of venous pressure significantly less than that encountered in the animals rendered hypercapnic until shortly before death. Perhaps this is evidence to support Richardson's [49] findings in conscious human volunteers that acidemia with arterial pH of 7.25 induced with lactic acid infusions produced no change in circulatory dynamics in contrast to those with hypercapnia. He concludes that the increase of hydrogen ion concentration is far less effective in stimulating sympathoadrenal activity than is the retention of carbon dioxide. Gertler, Hoff and Humm,[23] in experiments similar to these, concluded that acute dilation of the heart and failure of repolarization of the myocardium only took place when a critically low pH value had been attained.

Another possibility must be considered to explain the lack of venous pressure increase until a short time before death. Blood may well be trapped in the peripheral vascular system. Selkurt *et al.*[52] and Quintero *et al.*[48] showed that among other stimuli acidosis of any sort causes the pressure to rise in the portal system of the dog if the arterial pH falls below 7.2. This portal hypertension frequently is accompanied by congestion of both the intestines and the liver, and is thought to be due to contraction of the venous sphincters in the liver.[17] Such a mechanism has not been proven to be active in man. However, increase in the hydrogen ion concentration in man may cause changes in other parts of the venous system and could result in effective or relative oligemia. Indeed, the acidosis may render the whole vascular system somewhat less sensitive to circulating adrenaline as suggested by Page and Olmsted.[46]

Interpretation of the experiments con-

ducted on hypoxic acidosis is extremely difficult because of the dynamic response of the circulation. From an earlier set of experiments we pointed out the extreme fluctuations of pulse and blood pressure prior to cardiac arrest in dogs rendered severely hypoxic.[8] This was also true in the present series as far as cardiac output was concerned. In fact, the variations of cardiac output were so rapid that they could be followed only by the electromagnetic flow meter. The data in Figure 3, therefore, are only at best an approximation of the situation as metabolic acidosis increased in severely hypoxic dogs. As previously mentioned, the initial response to hypoxia is an increase in cardiac output and a decrease in peripheral resistance even though some degree of arterial hypertension is apt to be present.[26] As has been shown the oxygen consumption of the body remains normal until the arterial blood oxygen saturation is less than 65 per cent. Below this the oxygen consumption decreases and results in the accumulation of fixed acids despite a cardiac output greater than normal. Such probably was the situation in Case 8 shown in Table 4.

On the other hand, as Gorlin and Lewis [26] have shown, animals in very severe hypoxia with oxygen saturation below 20 per cent enter what they refer to as Stage IV in which the heart shortly arrests preceeded by a reduction in cardiac output and an increase of both venous pressure and peripheral resistance. At this stage, as is shown by the data in Figure 3 from animals which had begun to develop uncompensated metabolic acidosis, the heart is in failure as judged by the significant elevation of venous pressure. Doubless the patient presented as Case 10 in Table 4 was in this state despite the fact that her arterial oxygen saturation was 52 per cent. The fact that she had a diseased heart with initially low output may well have made her more susceptible to lesser degrees of hypoxia than are people with normal hearts.

The clinical occurrence of severe hypoxic acidosis is relatively rare compared to that combined with an increase of the arterial carbon dioxide tension in the presence of respiratory impairment. In Table 5 are presented eight such examples. As we have pointed out before,[9] this situation if not corrected within a few hours is apt to be fatal when the arterial pH falls to values near 7.2. An example of this problem which occurred in a patient with a normal heart as a result of pneumonia is Case 12. The day prior to her death the arterial blood pH was 7.18 and she had begun to develop a combined respiratory and metabolic acidosis with an oxygen saturation of 46 per cent and a pCO_2 of 70 mm. Hg. At that time her cardiac index had dropped in a four hour period from 2.01 to 1.71 L./M.^{2}/min. A similar situation occurred in Case 13. That this hypoxia-hypercapnic type of acidosis can be reversed by prompt action to improve respiratory function is shown by Cases 15 and 18. The course of the first of these is illustrated in Figure 8. When her cardiac output pattern is compared with that of the uneventful cardiac operations in Figure 5 it will be apparent that she reached the dangerously low level of 1.13 L./M.^{2}/min. This actually occurred more than an hour after she had been shown to have an index of 2.02 L./M.^{2}/min. at nearly as low an arterial pH. Time plays a part in the adverse circulatory effects of metabolic acidosis. This is even more forcibly emphasized by the two diabetic patients presented in Table 7.

Boyd and his associates [4] have clearly shown that "sudden death" following cardiac operations was preceeded by an abnormally low oxygen content of the mixed venous blood and a very low cardiac output. This simply means that the tissues are being inadequately perfused and are extracting more than the usual amount of oxygen on each circulation of the blood provided that the respiratory function and ventilation are adequate. The situation is quite

comparable to the metabolic hypoxic acidosis encountered in low flow perfusions during "cardiopulmonary bypass" with a pump oxygenator.[12, 47] As may be seen in Table 6, this is a serious situation, only one of the five recovered. Eventually as the fixed acids accumulate the acidosis becomes uncompensated and the lungs can no longer remove sufficient carbon dioxide to maintain a normal pCO_2 and pH in the arterial blood. A bad situation becomes worse and the heart ultimately fails. Figure 9 illustrates the course of a patient who died in this condition. To avoid the vicious circle in the presence of good pulmonary function, it appears that a patient must have a minimum cardiac output of 1.25 L./M.^{2}/min. This was shown by three patients who developed only moderate acidosis with low outputs following cardiac operations. A damaged lung which diffuses gas inadequately as was present in the patient whose course is illustrated in Figure 8 requires that a higher output be present to satisfy the tissue needs, in this case at least 1.5 L./M.^{2}/min.

Another type of acidosis which is kown to be lethal if not treated is that found in severe diabetic ketosis. Two such patients who came into the emergency ward untreated are presented in Table 7. The record of one of them is shown in Figure 10. She serves to illustrate the fact that it is not the shift of hydrogen ion concentration in the extracellular fluid which causes cardiovascular failure in severe ketosis. At the time when first seen her arterial pH was 7.24, a level at which little change in the circulation occurs even in hypoxic acidosis. Even as the pH rose to 7.30 under treatment, her cardiac output fell to the very low level of 1.03 L./M.^{2}/min. Despite return of the arterial pH and the buffer base to normal, within 10 hours, the cardiac output remained at one half the normal value for 24 hours or more. This was not due to right heart failure for the venous pressure never rose significantly despite the fact that she was given 3,500 cc. of fluid intravenously in the first day. Again one wonders about the possibility of failure of venous return and dilation of the venous plexus under these conditions. The total peripheral resistance responded in normal fashion so one may not postulate failure of the normal reflex vasoconstrictor mechanisms initiated by the baroreceptors in the aorta and carotid bodies.[35]

On the basis of these observations one may conclude that there is probably a slight adrenergic and sympathetic response to the presence of an elevated hydrogen ion concentration in the blood. Experiments upon the isolated heart [43, 54] and upon the sympathectomized adrenalectomized animal [8, 29] suggest that both catechol amines and corticoids exert a protective effect on the acidotic heart. It is, however, apparent that neither the venous return nor the peripheral arterial resistance respond to the acidosis per se as they do to the powerful adrenergic stimulus of hypoxia.

Despite the greater extent of catechol amine secretion engendered by hypoxia than by hypercapnia, it is apparent that a greater elevation of the hydrogen ion concentration is required seriously to damage the energy producing metabolic processes of the myocardium and other parts of the vascular system in the absence of hypoxia than when it is present. Thus, a patient who can withstand several hours of hypercapnia and an arterial pH of 7.15 may rapidly die with severe hypoxia at a pH of 7.25. It must also be remembered that the enzymatic abnormalities reflected by the accumulation of fixed acids become progressively more severe as time passes. The reserve stores of glycogen and other substrates are used up, and the whole homeostatic situation deteriorates. Not only does the energy production become less effective, but as was demonstrated in certain of the patients with hypercapnia alone, and in those with an inadequate postoperative cardiac output, a subliminal perfusion of the

tissues augments the accumulation of acid in the blood.

The cumulative progressive nature of circulatory injury caused by severe metabolic acidosis, therefore, makes it mandatory to prevent it or to remove its causes as soon as possible. The appearance of peripheral vascular constriction, stasis cyanosis, or pallor may be the only clinical indicators of severe acidosis besides a thin and thready pulse. The arterial blood pressure, as demonstrated, changes only late when the peripheral vascular system can no longer maintain its resistance. A decrease of blood pressure under these condtiions is a very poor prognostic sign. Therefore, one is left with the necessity of protecting the lungs from damage and seeing to it that adequate respiratory exchange is continued at all times. The use of dye dilution curves is very helpful to evaluate a given situation when used in conjunction with blood gas and buffer base analysis of arterial blood.

Summary

To asses the effect of severe acidosis on the circulation and the part it may play in circulatory failure the hemodynamic measurements in 104 surgical patients were correlated with arterial blood gas and electrolyte determinations made at intervals throughout their operative and convalescent periods. The circulatory response of 56 patients, who had operations on the heart, lungs, or abdomen without acidosis or complications, is characterized by a moderate reduction of cardiac output during anesthesia and the operation. This is less marked in the lightly anesthetized cardiac patients. On awakening all of the patients with uncomplicated courses displayed elevations of the cardiac output above the preoperative values. With but brief exceptions the cardiac index remained at or above 2.5 L./M.^{2}/min. throughout the first postoperative week. The circulatory behavior of these patients serves as a control for comparison with the hemodynamic response in those patients who were acidotic. There were 33 patients considered to be in mild acidosis with arterial pH values ranging from 7.34 to 7.29 at one time or another. Except in five of these people, whose cardiac outputs were reduced for other reasons, there were no significant circulatory alterations.

Among the 25 patients who were *severely acidotic* (arterial pH below 7.29) there were seven who were subject to *carbon dioxide retention* without hypoxia. In but two, whose arterial pH had dropped to 7.1 or below, was the cardiac output seriously reduced to less than one half the basal value. *Hypoxia* itself or in combination with hypercapnia was the cause of severe acidosis in 11 patients. Under these conditions, a reduction of the arterial pH to a level between 7.25 and 7.20 was usually associated with a serious reduction in the cardiac output and an increase of the total peripheral arterial resistance. There were two patients in *severe diabetic ketosis* who, like the others with severe hypoxic metabolic acidosis, demonstrated that circulatory depression, a very low cardiac output resulting from a combination of cardiac failure and inadequate venous return, does not return to normal for as much as several days despite correction of the acidosis. Five patients exhibited the progressive *metabolic acidosis of an inadequate cardiac output* after operations upon the heart. In only one could the vicious circle be broken permanently.

From these observations and from three series of experiments on induced acidosis in animals it is concluded that interference with the metabolic processes responsible for cardiac and vascular function requires a considerably greater increase in the hydrogen ion if metabolic acidosis is not present than when it is. The fall of the arterial blood pH when uncompensated metabolic acidosis takes place, from whatever cause, is a reflection of serious derangements with the intracellular energy producing metabolism. It is apparent that as the pH falls

the metabolic acidosis of inadequate tissue perfusion augments the hydrogen ion concentration still more and will result eventually in acute cardiac failure.

Acidosis in the presence of severe hypoxia is not tolerated for more than a few hours, and if not corrected, is fatal.

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Discussion

Dr. Mark A. Hayes: This is a wonderful set of papers on what happens during an operative procedure and in the early postoperative period with relation to acidosis. It is amazing the changes that can be seen with relatively minor degrees of operative trauma if one conducts the studies that these gentlemen have presented today.

If we direct our attention entirely to the problem of acidosis itself, I would like to comment briefly from some studies in dogs that we have awaiting publication in the Annals of Surgery.* We have confirmed these in human beings.

Basically, there are three mechanisms compensating for acidosis: respiratory function, tissue buffers, and renal function.

For a long time, we all have been frightened into accepting the fact that it is dangerous to give electrolyte-containing solutions during an operative procedure, that it would produce edema with all its complications. Metabolic acidosis, however, can be exaggerated by tissue trauma; by delivering enough sodium to the distal tubule, another mechanism of compensating for acidosis is activated in the immediate postoperative period.

Hydrogen ion cannot be excreted, potassium cannot be excreted, unless sodium is delivered from the glomerular filtrate to the distal tubular exchange site, which is impossible if patients are maintained by 5.0 per cent dextrose in water. As a matter of fact, the addition of an osmotic diuretic to assist the delivery of a sodium ion to its exchange site is also helpful.

I wonder if we should not reverse our thinking and go back some 15 to 20 years and intelligently administer a physiologic extracellular fluid to our patients to help their tissues and bodies compensate for the acidosis that we and our anesthetist colleagues produce in patients.

I have learned much from these two presentations.

* July and August, 1961.

Dr. Harold Laufman: I want to mention something that occurred ten years ago when I had an unusual opportunity of making a number of physiologic observations on a patient with profound accidental hypothermia, observations which appear to have implications to this day. I believe this lady still holds the record for recovery from accidental hypothermia of 18° C.

Among the many amazing observations was the finding of a blood pH of 7.17 when her temperature was 18° C.; up to that time, this pH was thought to be inconsistent with life. You can imagine our dismay when, as she was being warmed, the blood pH came back from the laboratory at 6.9.

It was at that time, in line with what you have just heard, I believe, that our patient went into respiratory failure, and tracheostomy had to be done. It was not until oxygen in high concentrations was directed through the tracheostomy tube that the patient began to improve.

It is interesting that Dr. Ballinger and his group have suggested that the acidosis of hypothermia is related to the liver, since our data have shown, as indicated on this slide (Slide) certain other presumptive evidence of the liver's inability to function properly. Note this 438 mg. per cent blood sugar, which was undoubtedly evidence of unmetabolized prodigious amounts of alcohol consumed just prior to freezing. Perhaps this was her life-saver—I do not know—or it may represent the paralysis of the pancreas' ability to put out insulin.

I did not hear any comment about insulin in the previous paper in which the suppression of the external secretions of the pancreas was discussed.

Other figures on this slide probably represent diminution in kidney function, as well as perhaps compensatory mechanisms, such as the serum sodium being higher than it should be, and a number of other things. The wealth of material supplied by this case served to raise many ques-