Hemodynamic Studies on Cholera

Effects of Hypovolemia and Acidosis

By RÉJANE M. HARVEY, M.D., YALE ENSON, M.D., MILENA L. LEWIS, M.D., WILLIAM B. GREENOUGH, M.D., KHAIROON M. ALLY, M.B.B.S., AND ROSALIND A. PANNO, B.A.

SUMMARY

The hemodynamic effects of hypovolemia and acidosis were studied in 23 patients with cholera. Studies were made before and during fluid replacement and administration of alkali.

The major hemodynamic abnormalities encountered before rehydration can be ascribed to a reduction in circulating blood volume. Hypovolemia was associated with a reduction in cardiac output, blood pressures, and central blood volume. Restoration of blood volume returned these variables toward normal.

The chief effect of acidosis appeared to be a redistribution of blood from the peripheral to the central circulation; consequently, central blood volume, lesser circulation pressures, and cardiac output were relatively well maintained despite hypovolemia. Fluid administration without correction of acidosis favored a disproportionate increase in central blood volume, while reduction in hydrogen ion concentration attending fluid replacement resulted in a more even distribution of the circulating blood volume and reduced the possibility of engorgement of the pulmonary bed.

It is postulated that this redistribution of blood stems from peripheral venoconstriction and a reduction in the capacity of venous reservoirs induced by acidosis.

Additional Indexing Words:

Shock Distribution of total blood volume Central blood volume Venoconstriction

THE COPIOUS STOOLS and vomitus which characterize cholera are capable of producing severe dehydration and circulatory collapse with terrifying rapidity. Loss of bicarbonate in the dejecta is responsible for the metabolic acidosis which accompanies the reduction in circulating blood volume.[1] Intravenous administration of fluids has been shown to restore the blood volume and to relieve shock, while intravenous administration of alkali relieves the acidosis.[2]

Certain features of the disease and of the response to fluid repletion are unusual: First, Snow's classic description of necropsy material

From the Department of Medicine, Columbia University, College of Physicians and Surgeons and the Cardiopulmonary Laboratories of the Columbia Medical Division of Bellevue Hospital, the Manhattan Veterans Administration Hospital, New York, New York, and the Pakistan-SEATO Cholera Research Laboratory, Dacca, East Pakistan.

Investigation was supported in part by HE-02001-20 and HE-05741 from the National Heart Institute, U. S. Public Health Service, and by U. S. Public Health Service Research Career Program Award 5-K6-HE 16, 603-05 from the National Heart Institute. The Pakistan-SEATO Cholera Research Laboratory is a part of the SEATO-Cholera Research Program and is supported by the U.S. Department of State, Agency for International Development, the National Institutes of Health, the National Communicable Disease Center of the Department of Health, Education and Welfare, U.S. Public Health Service, and by the Governments of Pakistan, the United Kingdom, and other SEATO nations. The NIH Cholera Advisory Committee coordinates the research program.

Dr. Enson is a recipient of investigatorship of the Health Research Council of the City of New York under Contract I-176.

called attention to the engorgement of the pulmonary circulation and right heart cavities.[3] The presence of pulmonary congestion in patients dying of the disease has been confirmed by Dammin and co-workers.[4] Some observers have postulated redistribution of the circulating blood volume to explain this phenomenon.[5] Second, evidences of pulmonary and peripheral congestion during the course of fluid repletion have been reported on occasion, especially in the older literature, at a time when hydration was still incomplete.[4] Third, the frequency with which pulmonary congestion is encountered has been reduced by correction of the acidosis,[6] as has the mortality,[7] but the mechanism by which this effect of alkali is mediated remains unclear.

Our interest in the effects of an increased hydrogen ion concentration on the pulmonary circulation prompted us to undertake this study of the hemodynamic alterations which accompany metabolic acidosis in patients with cholera, in the expectation that the manner in which pulmonary congestion develops might be clarified.

Methods

Twenty-three patients presenting with an acute syndrome compatible with the diagnosis of cholera were studied in the Pakistan-SEATO Cholera Research Laboratory, Dacca, East Pakistan, during the epidemic of January to March, 1965. Bacteriological identification of *Vibrio cholerae Inaba* was subsequently made in the excreta of 18 of these patients and of *V. cholerae Ogawa*, in two. The remaining three patients resembled the others in all respects, but the organism could not be demonstrated by darkfield examination or culture of stool specimens.[8, 9] In only two individuals were other diseases suspected; one was found to have an abnormal glucose tolerance curve, and the other a neurological picture suggestive of multiple sclerosis. The rectal temperature at the time of study varied from 96 F to 100.4 F; in only two did it exceed 100 F. Seventeen patients were male and six female. The average age was 33 years with a range of 16 to 63 years.

The patients chosen for study demonstrated marked dehydration, profound acidosis, or both. Shock was reversible, and all recovered uneventfully from their disease. They were studied without sedation. Nine had received no food for at least 12 hr, while the remainder gave a history suggesting abstinence for 2 to 12 hr prior to study. The majority of these patients could not be considered to be in a basal state; they were apprehensive, frequently restless, and several experienced muscle cramps.

Studies were performed on a fluoroscopic table, the top of which had been replaced by a canvas stretcher. The stretcher had a central hole and was covered by a plastic sheet made with a funnel which led through the hole into a graduated bucket. In this way the "rice water" stool could be collected and its quantity measured without contaminating the catheterization field or disruption of the various procedures. A 12-lead electrocardiogram was then taken. Cardiac catheterization was carried out in the usual fashion through an antecubital vein. A systemic artery was cannulated with a Cournand needle.

Pulmonary arterial, pulmonary "wedge," right ventricular, right atrial, and systemic arterial blood pressures were recorded by means of Statham pressure transducers and a photographic technique.*

Cardiac output was measured by the direct Fick principle or by a dye-dilution method using T-1824, or by both. At the time that blood flow was determined, the catheter lay in the pulmonary artery. The dye curves were inscribed with a Gilford densitometer.† Plasma concentration of T-1824 was measured with a Unicam-500 Spectrophotometer.‡ The curves were calibrated by use of the pooled sample method of McNeeley and Gravallese.[10] Expired air was collected in neoprene balloons from which 30-ml aliquots were immediately drawn for analysis utilizing the micro-Scholander analyzer. The remaining volume was then measured in a gastrometer§ which had been calibrated previously against a Tissot spirometer. When expired air was not collected, oxygen consumption was calculated from the cardiac output as determined by the indicator-dilution technique, and the arteriovenous oxygen difference. Blood samples were analyzed for oxygen content and capacity and for carbon dioxide content by the method of Van Slyke and Neill. The carbon dioxide tension was calculated from the whole blood carbon dioxide content with the line charts of Van Slyke and Sendroy. The pH of

*Model IR-4 monitor with accompanying 4-channel camera, Electronics for Medicine, Inc., White Plains, New York.

†Model 103-IR, Gilson Instrument Laboratories, Inc., Oberlin, Ohio.

‡Unicam Instruments, Ltd., Cambridge, England.

§CD-1 meter, Parkinson Cowan Industrial Products, London, England.

arterial and mixed venous blood was determined with a Model 33B Vibron Electrometer pH meter.*

Plasma proteins were measured by means of a Bausch and Lomb serum protein meter. The initial estimates of plasma and total blood volume were made from the plasma concentration of T-1824 10 min after injection of the dye, a time interval previously demonstrated to introduce a negligible error in calculation of plasma volume in patients in shock,[11] and from the hematocrit reading. The latter was corrected for trapped plasma[12] and adjusted to body hematocrit.[13] Because significant volumes of parenteral fluids were administered between the time of injection of dye and the time of drawing the 10-min specimen, a correction was introduced in the observed dye concentration, D_t, according to the suggestions of Noble and Gregersen[11]:

$$D_o = D_t \times \frac{H'crit_o}{H'crit_t}$$

where D_o is the theoretic dye concentration which would have been observed had the plasma volume not changed during the sampling interval, $H'crit_o$ is the hematocrit value observed at the time of injection of dye, and $H'crit_t$ is that observed at the time the 10-min specimen was drawn. To avoid the problems inherent in following sequential changes in blood volume by re-injecting T-1824, especially since the dye was already being used to follow alterations in blood flow, plasma and blood volume were subsequently calculated from the initial volume and from the observed changes in plasma protein or hematocrit, according to the considerations of Noble and Gregersen[11] and Phillips[2]:

$$P.V._t = P.V._o \times \frac{P.P._o}{P.P._t}$$

where $P.V._o$ is the control plasma volume evaluated with T-1824, $P.P._o$ is the plasma protein concentration observed at that time, and $P.P._t$ is the plasma protein concentration observed at the time of the new determination of plasma volume, $P.V._t$; in three subjects, in whom plasma protein estimations were not available, hematocrit was substituted for plasma proteins. A modified central blood volume was calculated as the product of stroke volume and the mean circulation time between pulmonary and brachial arteries, according to the Hamilton formula.[14]

Values for blood flow, blood volumes, and oxygen consumption are reported in terms of body surface area calculated on the basis of weight at the time of the patients' discharge from the hospital to avoid errors in estimation of body weight due to dehydration. It must be borne in mind that the surface area of these patients is significantly less (average, 1.40 m^2; range, 1.09 to 1.62) than that upon which accepted normal values are based. This discrepancy may result in an erroneous characterization of the data with respect to normalcy.

Since cholera produces dehydration and acidosis concomitantly, it was necessary to vary the protocol so that the influence of each could be identified.

Four patients were studied immediately after admission in the dehydrated, acidotic state. After the initial measurements were made, two were hydrated with solutions of isotonic saline and two with solutions of isotonic alkali, administered intravenously. In order to avoid chills consequent to the intravenous administration of large volumes of cold fluids, all solutions were warmed to approximately body temperature.

Three additional patients were first treated for 2 to 3 days with intravenous administration of solutions containing alkali until an optimal state of hydration and acid-base balance was felt to have been achieved. Eight to 9 hr prior to study they were allowed to purge without replacement of fluid loss; during this interval only small amounts of alkalinizing solution sufficient to maintain blood pH were administered. Initial measurements were then made and were repeated after further dehydration and, in two, subsequent rehydration. Blood pH was maintained at essentially the same level throughout the study by small infusions of alkali.

In the remaining 16 patients, initial measurements were obtained within 1 to 46 hr of admission during which time administration of isotonic saline had corrected in whole or in part their dehydrated state. Subsequently, one patient received further infusions of saline before measurements were repeated; three received further infusions of saline, followed by infusions of alkali with measurements being made during each infusion period; in seven, observations were repeated during administration of alkali alone. The sequential measurements obtained in the remaining five are not included in this report.

The electrocardiogram was constantly monitored. Blood pressures in the systemic and pulmonary circulations were recorded every 10 to 15 min. Plasma protein concentration and the pH of arterial blood were measured frequently to provide a guide as to the state of the patient. Measurements of cardiac output and total and central blood volumes were repeated at the end of each period before a new state was initiated.

*Electronic Instruments Ltd., Richmond Surrey, England.

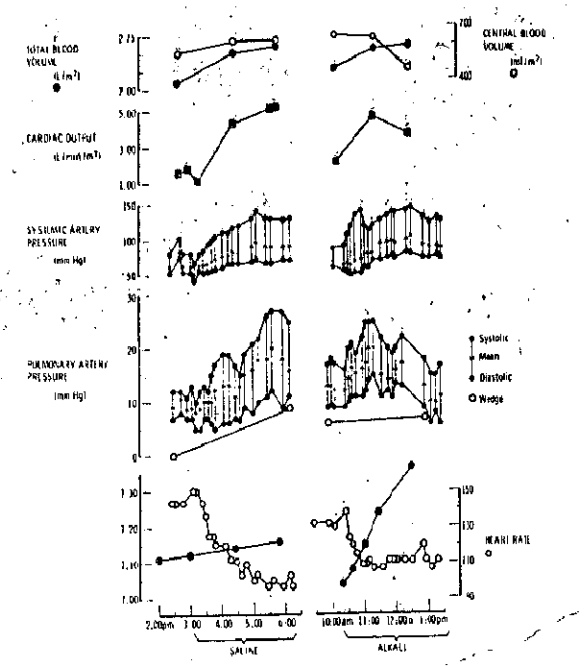

Figure 1

Graphic representation of hemodynamic events during fluid replacement in two patients with vascular collapse due to cholera. The initial increase in circulating blood volume in both patients is accompanied by a rise in blood flow and all intravascular pressures. The further administration of saline to the patient on the left caused a continued rise in these variables, while correction of acidosis in the patient on the right resulted in a fall in central blood volume, cardiac output, and pulmonary arterial pressure. The second and last measurements of cardiac output in the patient on the left were obtained by use of the Fick principle, the remainder by the dye-dilution technique. All measurements of blood flow in the other patient were made by the dye-dilution technique.

Tables containing the data of the individual patients have been deposited with the American Documentation Center.

Results

Studies in Untreated Patients (Fig. 1)

Three of the four patients who were studied prior to fluid replacement displayed a fairly uniform hemodynamic pattern. They were severely acidotic and had considerable increase in plasma proteins and hematocrit. There was a striking reduction in total blood volume, cardiac output, and stroke volume. The central blood volume and the ratio of central to total blood volume, however, were within normal limits in two of the patients and very low in the third. Systemic arterial pressures were low, as were pulmonary arterial, pulmonary "wedge," and right heart filling pressures. Rapid sinus tachycardia was present. The fourth patient was also severely acidotic, but his hematocrit and plasma protein concentration, although elevated, were not as high as the others. His total and central blood volumes, cardiac output, and systemic blood pressures were within normal limits. His pulmonary arterial, pulmonary "wedge," and right heart filling pressures were low.

Two of the four patients were hydrated with isotonic saline and two with alkalinizing solutions. Administration of saline was associated with a slight rise in pH (0.02 to 0.04 units). One of the patients receiving alkali had a progressive rise in pH from 7.04 to 7.37; hydrogen ion concentration was not measured in the other, but consideration of the small amount of alkali given to this patient, and of the response to alkali of other patients in this series, suggests that the increase in pH could not have been more than 0.08 units. The three patients who had the smallest change in hydrogen ion concentration had similar responses to fluid replacement. The total blood volume promptly rose to normal or above normal limits. The central blood volume also increased and in two patients the proportion of central blood volume to total blood volume became larger, while it remained essentially unchanged in the third. The cardiac output rose above 3.5 L/min/m^2 in all. The systemic arterial, pulmonary arterial, and right and left ventricular filling pressures rose. Although systemic arterial blood pressures remained within normal limits, the pulmonary arterial diastolic and mean pressures exceeded 10 and 15 mm Hg, respectively, in two patients. Only one patient displayed a "wedge" pressure above 10 mm Hg. Heart rate fell progressively as did the hematocrit and plasma protein concentration.

The early response of the fourth patient, who was treated with a large amount of alkali, differed in no way from the others. However, in the latter part of the study when the blood pH approached normal values, the

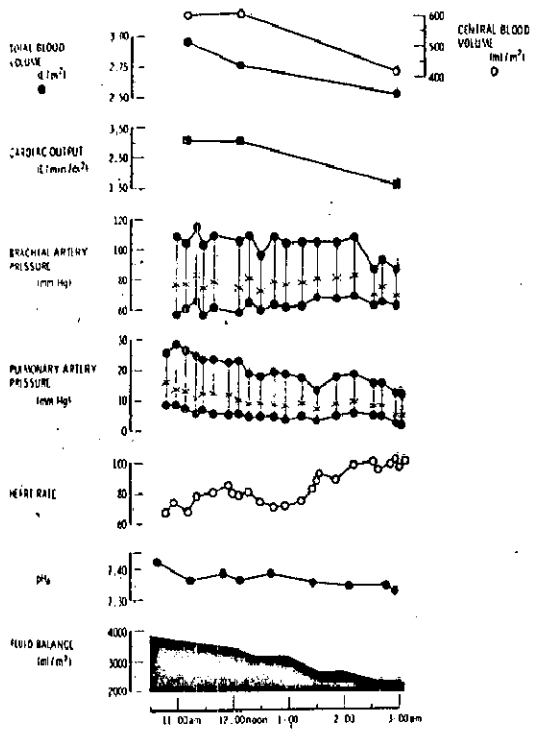

Figure 2

Graphic representation of hemodynamic events during fluid loss consequent to purging in a patient with cholera. The pH of the blood was maintained by small amounts of intravenously administered alkali. Fluid balance was calculated as the difference between total fluid intake (oral and parenteral) and total fluid output (stool, vomitus, urine). For discussion, see text.

central blood volume, cardiac output, and pulmonary arterial pressures fell despite a continued increase in total blood volume and maintenance of brachial arterial pressures. The heart rate, which had fallen progressively, stabilized.

Studies in Patients Undergoing Dehydration (Fig. 2)

Two of the three patients, whose fluid balance (that is, fluid intake − fluid output) was allowed to fall through purging while their hydrogen ion concentration was maintained at nearly normal levels by small infusions of alkalinizing agents, had initial hemodynamic findings similar in some respects to those who had not been treated. The total blood volume was at the lower limits of normal or was markedly decreased, and the plasma protein concentration was elevated. However, the ratio of central blood volume to total blood volume was low, and the central blood volume was also low. Cardiac output and stroke volume were also reduced. Sinus tachycardia was present. Brachial arterial blood pressures were well maintained, although pulmonary arterial and "wedge" pressures were low. The total blood volume of the third patient was slightly above normal at the time the initial measurements were made, but all other values were within normal limits.

Further purging resulted in a slight fall in pH (0.02 to 0.04 units) in all three patients although alkalinizing agents were continuously administered. All experienced a fall in total blood volume, cardiac output, and stroke volume. Central blood volume also fell, and in two the ratio of central to total blood volume became smaller. Brachial arterial pressures

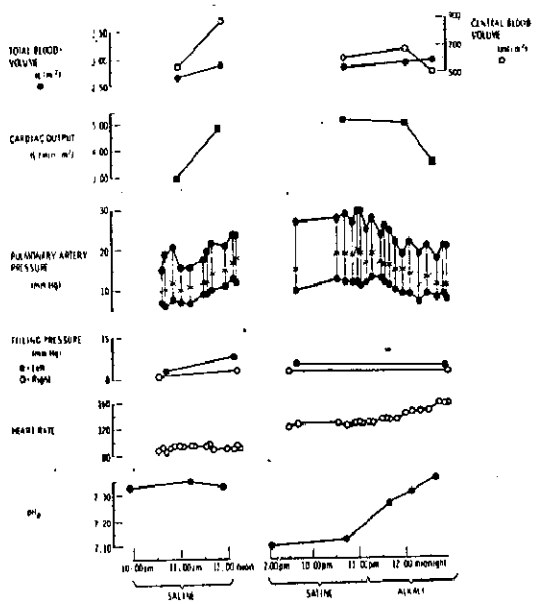

Figure 3

Graphic representation of hemodynamic events during fluid administration in two patients with cholera who had received some saline intravenously before the first measurements were made. The patient on the left subsequently received only saline and remained acidotic. The patient on the right subsequently received isotonic alkalinizing solution. Correction of acidosis resulted, as in figure 1, in a fall in central blood volume, cardiac output, pulmonary arterial and ventricular filling pressures despite a continued increase in total blood volume.

fell in two patients and the previously normal pulmonary arterial pressures of one fell to the low range seen originally in the others. Sinus tachycardia developed in the patient who previously had a normal rate, while in the other two heart rate remained unchanged.

Rehydration was carried out in two of these patients with a combination of saline and a small volume of alkalinizing solutions; blood pH was therefore maintained. Hemodynamic changes accompanying hydration were similar to those previously described in the untreated patients.

Studies in Patients Partially or Wholly Hydrated (Fig. 3)

Sixteen patients had received varying amounts of isotonic saline intravenously prior to study. All were acidotic, the pH varying from 6.98 to 7.35. Although five patients had total blood volumes within normal limits as usually defined,[15] the plasma protein concentration was elevated in the three in whom it was measured. The total blood volume was above normal limits (+18.8 to +39.9%) in the remaining 11 patients. One of these also had an increased plasma protein concentration; in the remaining 10 it varied from 6.0 to 7.1 g/100 ml. Central blood volume was within normal limits in all 12 patients in whom it was measured. The percentage of total blood volume which constituted the central blood volume varied from 20.7 to 36.9%. The cardiac output was within normal limits in three patients and above 3.5 L/min/m^2 in the remaining 13. Systemic blood pressures were normal. Mild but definite pulmonary hypertension was present in eight patients, and in four of these the "wedge" pressure was also elevated. All but four patients had a sinus rate above 90 beats/min.

After these initial measurements had been secured, fluid therapy was continued with isotonic saline or alkali as described previously. During the administration of isotonic saline, the pH varied from −0.03 to +0.04 units while the administration of bicarbonate caused a rise in pH of 0.12 to 0.43 units. Two different hemodynamic responses appeared which could at least in part be related to changes in hydrogen ion concentration.

In the four subjects who received saline, total blood volume rose above normal levels. The central blood volume became larger in the three in whom it was measured, and in two the proportion of central to total blood volume also increased. Cardiac output and stroke volume rose. There was a variable response in heart rate and systemic blood pressure. Pulmonary arterial and "wedge" pressures rose slightly in three patients and strikingly in the fourth, in whom it reached abnormal levels.

The administration of alkalinizing solutions was associated with a rise in total blood volume in eight patients and with little change in the remaining two. In five of the seven patients in whom central blood volume was measured it remained unchanged; it fell in one and rose in another. The ratio of central to total blood volume fell in four patients, showed no change in one, and rose in one. Cardiac output fell in six patients, showed no change in two, and rose in two. Stroke volume fell or remained unchanged. Heart rate showed a variable response. Systemic arterial pressures rose in all but three patients, in whom it showed little change. Pulmonary arterial pressures rose in only one individual. In all the others, regardless of the level at which they were initially found, they remained unchanged or fell. Pulmonary "wedge" pressures also fell in all but one patient. This patient's complete study is depicted in figure 4 because he presented a hemodynamic pattern which was different from that of the others who received alkali. An infusion of saline rapidly brought his total and central blood volumes, cardiac output, pulmonary arterial, and right and left heart filling pressures to well above normal levels. This was effected with little change in blood pH. Substitution of alkali for saline caused a marked rise in pH, a continued rise in total and central blood volumes, a slight further rise in filling pressures, and a marked drop in cardiac output. This is the only patient whose cardiac output did not follow his filling pressures and

Table 1

Estimating Equations Describing Relationships Between Multiple Hemodynamic Variables

Equation	Relationship between observed and predicted values				Relationship between observed and predicted change		
	N	r	P	SE	N	r	P
(1) CBV = −424.24 + 4.92 $[H]^+$ + 288.70 TBV	24	0.882	< 0.001	94.2	23	0.580	< 0.005
(2) PA_W = −10.40 + 0.02 CBV + 0.53 R	11	0.945	< 0.001	3.81	11	0.929	< 0.001
(3) CO = 0.99 − 0.05 $[H]^+$ + 0.50 TBV + 0.027 $[H]^+$ • TBV	31	0.772	< 0.001	1.37	31	0.760	< 0.001
(4) PA_d = 5.87 + 0.70 PA_W	14	0.972	< 0.001	1.03	14	0.960	< 0.001
(5) PA_s = 1.08 + 1.54 PA_d + 0.02 SV	32	0.888	< 0.001	3.76	32	0.957	< 0.001
(6) PA_m = −0.55 + 1.25 PA_d + 0.05 SV	32	0.967	< 0.001	1.59	32	0.958	< 0.001
(7) HR = 211.82 − 0.91 age − 27.93 TBV	32	0.629	< 0.001	16.7	32	0.442	< 0.02

Abbreviations: CBV = central blood volume, ml/m² BSA; CO = cardiac output, L/min/m² BSA; $[H]^+$ = hydrogen ion concentration (mμEq/L); HR = heart rate, beats/min; N = number of observations; P = probability; PA_d = pulmonary arterial diastolic pressure, mm Hg; PA_m = pulmonary arterial mean pressure, mm Hg; PA_s = pulmonary arterial systolic pressure, mm Hg; PA_W = pulmonary "wedge" pressure, mm Hg; R = rate of infusion, ml/min/m² BSA; r = correlation coefficient; SE = standard error of estimate; SV = stroke volume, ml; and TBV = total blood volume, L/m² BSA.

whose central blood volume rose when cardiac output fell.

Statistical Analysis

The data presented above were obtained while a number of factors were changing simultaneously. Although broad patterns of response to alterations of blood volume and of blood hydrogen ion concentration emerge from a consideration of the data grouped according to the protocols employed, an evaluation of the response to these variables in the group as a whole by statistical analysis clarifies these patterns to a considerable extent with respect to both the wide range of initial values observed and the changes which occurred during the study.

Figure 4

Hemodynamic events in a patient who received a large volume of isotonic saline at a rapid rate, followed by the rapid administration of alkalinizing solution. The fall in cardiac output despite an increase in central blood volume and filling pressures indicates that ventricular failure had developed.

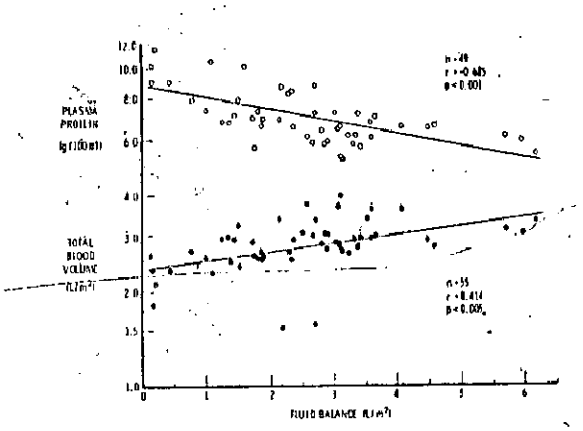

Figure 5

Graphic representation of the relationship of fluid balance, as defined in figure 2, plasma protein concentration, and total blood volume.

The relationship between variables was determined by the Gauss method of least mean squares. When only two variables were considered, the initial measurements as well as those obtained subsequent to further manipulations were utilized, except in the equation relating pulmonary arterial diastolic pressure to "wedge" pressure. In this instance only the initial values obtained were used so that prediction of subsequent values could be tested. When three or more variables were simultaneously considered, only data secured at the time of the initial measurements were made were utilized in solving the various equations, unless otherwise specified. Using constants thus obtained, the level of a particular variable during the changing state as well as its direction and magnitude of change were predicted and compared with observed values. In table 1 are given the estimating equations, as well as the coefficients of correlation between values predicted on the basis of the equations and the observed values, and the level of significance of these predictions.

Hydrogen Ion Concentration

The range of concentration of hydrogen ion of the arterial blood encountered and engendered in this study was wide, ranging from 104.80 (pH 6.98) to 32.36 mμEq/L (pH 7.49). The pH of the mixed venous blood was on the average 0.02 units less than that of the arterial blood with a range of 0 to 0.05 units. The arterial-mixed venous pH difference did not vary with the level of pH. Severe acidosis persisted when hydration was carried out with isotonic saline. The fall in hydrogen ion concentration produced by the administration of alkali was proportional to the amount of alkali infused.

Total Blood Volume and Plasma Proteins

The total blood volume and the concentration of plasma proteins varied as would be expected with the fluid balance (fluid intake – fluid output). The more positive the fluid balance, the larger was the total blood volume and the lower the concentration of plasma proteins (fig. 5).

Central Blood Volume

The central blood volume and the ratio of central blood volume to total blood volume were related to the total blood volume ($r = 0.821$, $P < 0.001$, and $r = 0.422$, $P < 0.005$, respectively), to the hydrogen ion concentration of the blood ($r = 0.496$, $P < 0.001$, and $r = 0.600$, $P < 0.001$, respectively), and to minute ventilation ($r = 0.519$, $P < 0.005$, and $r = 0.630$, $P < 0.005$, respectively). The larger the total blood volume, or the higher the hydrogen ion concentration or ventilation, the larger was the central blood volume. The level of central blood volume (CBV) as well as its magnitude and direction of change could be predicted best (table 1) by an equation of the following type where total blood volume (TBV) and hydrogen ion concentration are considered simultaneously:

$$CBV = K_1 + a_1 [H]^+ + b_1 TBV \quad (1)$$

Thus, as shown in figure 6, at any given level of total blood volume the more acidotic was the patient, the larger was his central blood volume. It is also apparent that changes in central blood volume depended not only on changes in total blood volume but also on changes in hydrogen ion concentration. If a patient sustained a marked rise in total blood volume and little change in hydrogen ion concentration, his central blood volume would rise; however, if a similar increment in total blood volume was accompanied by a striking

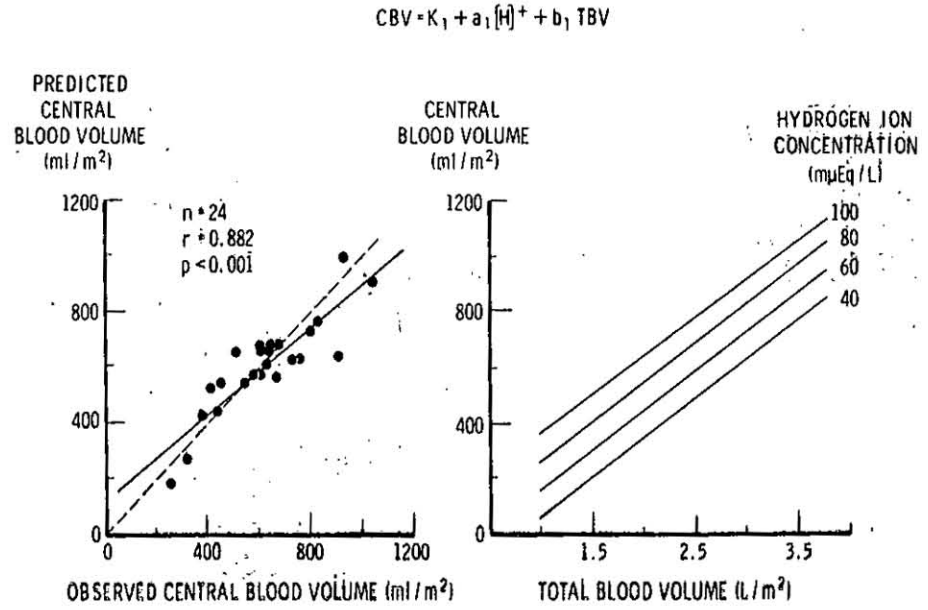

Figure 6

Relationship between central blood volume (CBV), hydrogen ion concentration, and total blood volume (TBV). On the left are plotted the predicted values for CBV against those observed. The solid line is the regression and the broken one the line of identity. On the right is a schematic representation of the equation which relates the three variables.

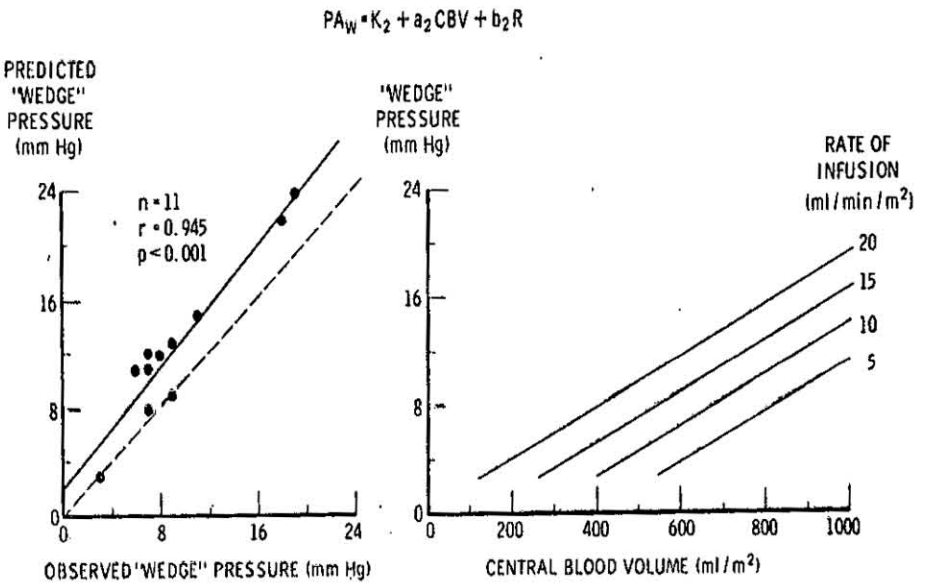

Figure 7

Graphic representation of the mean pulmonary "wedge" pressure (PA_w), central blood volume (CBV), and rate of infusion (R). On the left are plotted the predicted values of PA_w against those observed. The solid line is the regression and the broken one the line of identity. On the right is a schematic representation of the equation which relates the three variables.

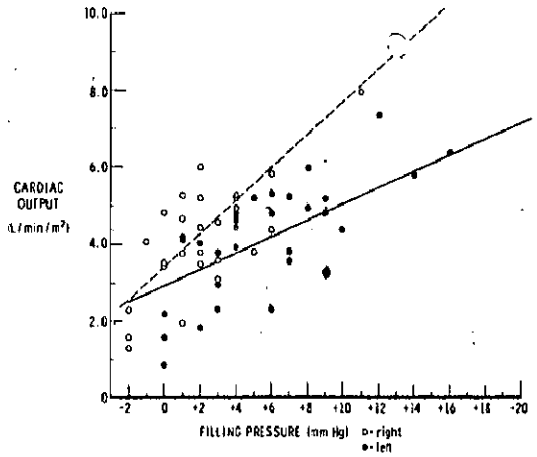

Figure 8

Graphic representation of the relationship between cardiac output (CO) and ventricular filling pressures. The black circles indicate the points relating CO and the mean pulmonary "wedge" pressure; the solid line is the regression line indicating this relationship. The open circles indicate the points relating CO and right atrial mean pressure; the interrupted line is the regression line representing this relationship.

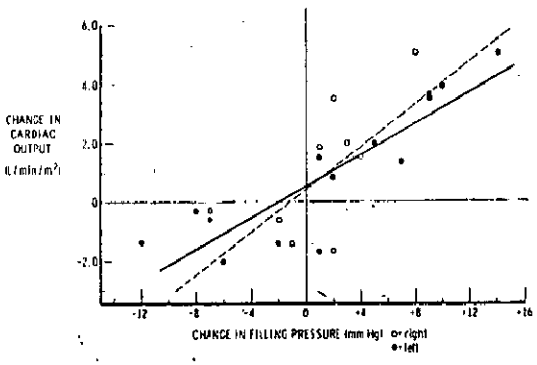

Figure 9

Graphic representation of the relationship between changes in cardiac output and changes in mean pulmonary "wedge" (PA_w) and right atrial pressures (RA), respectively. The black circles and the regression line (solid line) indicate the relationship between CO and PA_w. The open circles and regression line (interrupted line) indicate the relationship between CO and RA.

reduction in hydrogen ion concentration, central blood volume would not rise and, indeed, might fall.

Equation 1 can also be written by substituting minute ventilation for hydrogen ion concentration.

The rate at which the infusion was given bore no relationship to the central blood volume ($r = 0.240$, $P < 0.20$) or to the ratio of the central blood to the total blood volume ($r = 0.141$, $P < 0.40$). Furthermore, inclusion of the rate of infusion in equation 1 did not improve the prediction of central blood volume.

Ventricular Filling Pressures

The pulmonary "wedge" pressure was found to be related to the central blood volume ($r = 0.687$, $P < 0.001$) and to the rate of infusion ($r = 0.686$, $P < 0.001$). However, changes in this filling pressure could not be related to changes in either of these variables considered alone. The direction and magnitude of change of wedge pressure, as well as the actual level, were most closely predicted by a simultaneous consideration of the central blood volume and the rate of infusion (R):

$$PA_w = K_2 + a_2 CBV + b_2 R \qquad (2)$$

As seen in figure 7, the pulmonary "wedge" pressure rose as did the central blood volume, but at any given level of central blood volume, the faster the rate of infusion the higher was the "wedge" pressure. No relationship could be demonstrated between the hydrogen ion concentration and the "wedge" pressure.

The right atrial mean pressure also appeared to be related to the rate of the infusion ($r = 0.456$, $P < 0.05$), and to the total blood volume ($r = 0.448$, $P < 0.05$). Although no significant relationship was found between the level of the right heart filling pressure and hydrogen ion concentration, the right atrial mean pressure was expressed best by a simultaneous consideration of the rate of infusion, the total blood volume, and the hydrogen ion concentration, $r = 0.601$, $P < 0.01$. Since the number of observations of right atrial mean pressure were so few, all data were utilized to derive this relationship; hence predictions as to the magnitude and direction of change in right atrial mean pressure could not be attempted.

Both right and left heart filling pressures

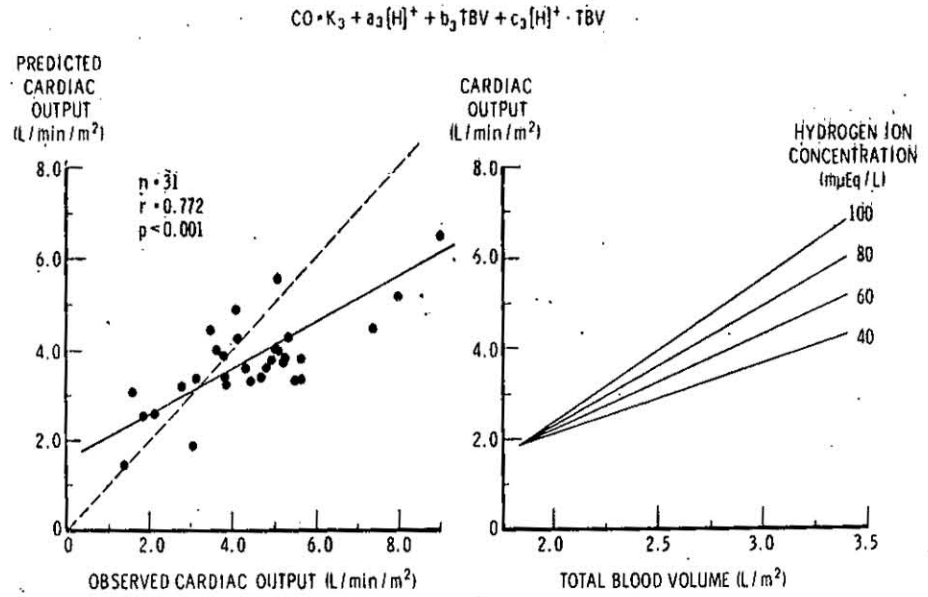

Figure 10

Graphic representation of the relationship of cardiac output (CO), hydrogen ion concentration, and total blood volume (TBV). On the left are plotted the predicted values of CO against those observed. The solid line is the regression and the broken one the line of identity. On the right is a schematic representation of the equation which relates the three variables.

moved in the same direction: as one rose or fell so did the other.

Cardiac Output

Cardiac output was closely related to the level of pulmonary "wedge" pressure, $r = 0.939$, $P < 0.001$, and to the right atrial mean (or right ventricular diastolic) pressure, $r = 0.793$, $P < 0.001$. The slopes of these regressions, however, differed significantly from each other, $P < 0.001$ (fig. 8). In similar fashion, the degree of change in cardiac output was related to changes in "wedge" pressure, $r = 0.883$, $P < 0.001$, and to changes in right atrial mean (or right ventricular diastolic) pressure, $r = 0.670$, $P < 0.05$. There was a greater change in left than in right ventricular filling pressure, $P < 0.05$, for a given change in cardiac output (fig. 9).

A significant correlation was also found between cardiac output and total blood volume, $r = 0.699$, $P < 0.001$, and hydrogen ion concentration, $r = 0.345$, $P < 0.02$, but not with ventilation, $r = 0.163$, $P < 0.40$. However, changes in cardiac output were encountered which could not be ascribed to changes in either independent variable alone. When cardiac output (CO) was considered as a joint function of blood volume and hydrogen ion concentration, then not only its level, but the magnitude and direction of change could be predicted with reasonable accuracy (table 1):

$$CO = K_3 + a_3 [H]^+ + b_3 TBV + c_3 [H]^+ \cdot TBV \qquad (3)$$

As the total blood volume increased (and, in turn, central blood volume and filling pressures rose) so did the cardiac output provided there was little change in hydrogen ion concentration. A marked fall in the latter would be accompanied by a fall in cardiac output and, as previously described, central blood volume and filling pressures (fig. 10).

Pulmonary Arterial Pressures

The level of pulmonary arterial diastolic pressure (PA_d) and its direction and magnitude of change were closely related (fig. 11) to the level of the "wedge" pressure (PA_w) and could be predicted from the equation:

$$PA_d = K_4 + a_4 PA_w \qquad (4)$$

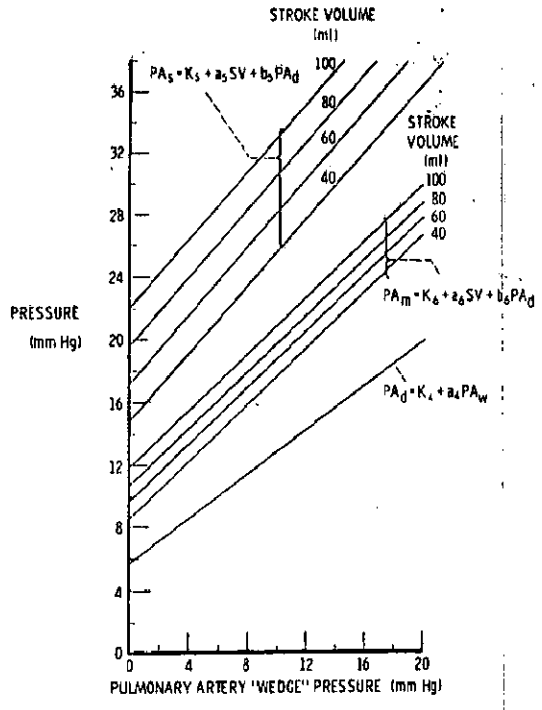

Figure 11

Schematic representation of the equations used to predict pulmonary arterial systolic (PA_s), mean (PA_m), and diastolic (PA_d) pressures.

A small gradient existed between the diastolic and "wedge" pressures which became progressively less as the latter rose or increased as the latter fell.

The pulmonary arterial systolic pressure (PA_s) varied with both the pulmonary arterial diastolic pressure and the stroke volume (SV):

$$PA_s = K_5 + a_5\,SV + b_5\,PA_d \qquad (5)$$

Pulmonary arterial mean pressure (PA_m) could also be predicted from the stroke volume and the pulmonary arterial diastolic pressure (fig. 11):

$$PA_m = K_6 + a_6\,SV + b_6\,PA_d \qquad (6)$$

Pulmonary arterial mean pressure was higher the larger the central blood volume, $r = 0.753$, $P < 0.001$, and the higher the hydrogen ion concentration, $r = 0.453$, $P < 0.001$. It was also found to increase with the rate of infusion, $r = 0.532$, $P < 0.001$.

Systemic Arterial Blood Pressure

Although brachial arterial mean pressure was related to the total blood volume, $r = 0.413$, $P < 0.005$, changes in total blood volume were not always followed by changes in blood pressure. Brachial arterial mean pressure also showed some relationship to cardiac output, $r = 0.317$, $P < 0.02$, but again variations in mean pressure could not be predicted from changes in blood flow. No relationship was found between the level of systemic arterial mean pressure and hydrogen ion concentration, but changes in pressure did show some relationship to changes in hydrogen ion concentration, $r = 0.380$, $P < 0.05$.

Heart Rate

The level of the heart rate was found to vary inversely with the total blood volume, $r = -0.544$, $P < 0.001$, and with the age of the patient, $r = -0.628$, $P < 0.001$. Changes in heart rate were inversely related to changes in brachial arterial mean pressure, $r = -0.541$,

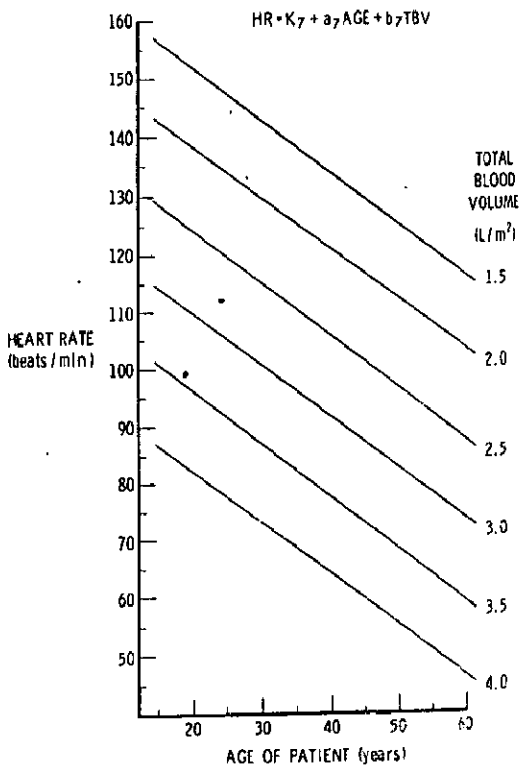

Figure 12

Schematic representation of the equation which relates heart rate, total blood volume, and the age of the patient.

shock induced by hemorrhage lead to an increase in the concentration of circulating catecholamines, and with their correction, the concentration falls.[18-25] In the presence of acidosis, however, the effects of catecholamines are apparently lessened, at least under certain circumstances.[18, 26-34] The ultimate response, however, may be determined by the relative concentration of hydrogen ion and catecholamines and may vary from one part of the circulation to another.[18, 30, 32, 35] In the ensuing discussion we will attempt to assess the relative contributions of the levels of circulating blood volume, hydrogen ion concentration, and sympatho-adrenal activity to the hemodynamic patterns observed in this study.

The total circulating blood volume was strikingly reduced in untreated patients, or in those in whom purging was associated with insufficient fluid replacement. The finding of a normal blood volume, as judged by western standards, at a time when the plasma protein concentration was elevated is undoubtedly related to the small size of these patients. When an adequate amount of fluid was administered intravenously, the blood volume was restored. A reduction in central blood volume, cardiac output, and intravascular pressures accompanied hypovolemia as did tachycardia. These variables returned toward normal as the total blood volume was expanded unless alkali administration produced a large reduction in hydrogen ion concentration. Under this circumstance the central blood volume, right atrial and pulmonary "wedge" pressures, and cardiac output did not continue to rise with the total blood volume, and, indeed, might fall.

While the normal range of the central blood volume in resting supine man is wide, it represents a relatively constant fraction of the total blood volume.[36-41] Moreover, rapid expansion of the total blood volume in man by dextran or saline is usually accompanied by a proportionate increase in central blood volume.[37, 38, 42-44] In the present investigation the ratio of the central blood volume to total blood volume was highest in the acidotic patients and fell when the infusion of alkali caused a marked drop in hydrogen ion concentration which suggests that the distribution of the total blood volume was being influenced by the blood hydrogen ion concentration.

It was not unexpected to find that the pulmonary "wedge" pressure followed the central blood volume since the left veno-atrial system contains a considerable portion of this volume. However, the importance of the rate of infusion in determining the level of filling pressures was not foreseen. In the many studies during which rapid infusions have been given to normal man, the rate of infusion has been kept constant throughout the individual series. As a consequence, the effect of rate upon filling pressures has not been apparent. The mechanism whereby the rate of infusion can affect these pressures remains obscure. It is possible that the faster the rate of infusion, the larger will be the total blood volume and hence the larger the volume in the heart and pulmonary circulation with correspondingly higher pressures. In this study, the rate of infusion did not appear to influence the central blood volume or the ratio of central blood volume to total blood volume. However, since the distribution of blood in the various vascular segments which contain the central blood volume in these patients is unknown, it remains a possibility that the rate of infusion to some extent determined the distribution of blood within this vascular compartment. On the other hand, it is conceivable that some portions of the vascular bed are relatively resistant to deformation; so the rate at which their volumes increase becomes a factor in the determination of pressure.

Changes in cardiac output followed changes in filling pressures with one exception and were independent of changes in total blood volume if alkali administration induced a considerable reduction in hydrogen ion concentration. Since central blood volume also varied as did cardiac output and filling pressures, the most likely explanation for this uniform behavior is that venous return was being influenced by the concentration of hydrogen ion.

Sharpey-Schafer and his associates[45] have shown that a large increase in hydrogen ion concentration can cause venoconstriction and a reduction in the capacity of the peripheral venous bed. They postulated that venous blood volume would thereby be reduced and venous return to the heart would be increased. It seems likely that in the presence of widespread venoconstriction, the central blood volume would not fall as much as the total blood volume during the development of dehydration and acidosis in patients with cholera. Enlargement of the total blood volume without correction of the acidosis would favor a disproportionate rise in central blood volume, lesser circulation pressures, and cardiac output. Relief of venoconstriction and expansion of the venous bed by alkali administration would result in a more uniform distribution of the circulating blood volume and a dimunition of the volume of blood returning to the heart and pulmonary circulation. The reduced incidence of pulmonary congestion in treated patients with cholera can be reasonably ascribed to the use of alkali.

There is no direct evidence for venoconstriction in cholera. Venoconstriction has been postulated in patients with other forms of hypovolemic shock and acidosis since an abnormally high pressure gradient has been found between peripheral veins and the right atrium.[46, 47]

The mechanism whereby an increased hydrogen ion concentration effects venoconstriction is not known. It may be directly related to a change in hydrogen ion concentration of the muscle cell, to the migration of other ions, to alterations of the cell membrane,[48] or to the level of minute ventilation.[49] Since variations in oxygen tension have been shown to alter the effect of acidosis on the pulmonary arterial tree,[50-53] it is conceivable that the effect of the hydrogen ion might vary with the blood oxygen tension from one venous bed to another. It is also possible that the catecholamines, known to cause venoconstriction,[54] are ultimately responsible for the distribution of blood volume in these acidotic patients. Frye and Braunwald[42] have shown that the distribution of blood in induced hypervolemia may be modified by ganglionic blockade, presumably by inactivation of systemic venous baroreceptors. It may be that acidosis alters the activity of the autonomic nervous system in a fashion resembling ganglionic blockade.

The occasional appearance of pulmonary congestion, with or without fluid replacement, in patients with other forms of acidosis as may be encountered in diabetes mellitus, renal insufficiency, burns, or other trauma also may be related to a redistribution of blood volume. Attention should be called to the fact that in some other forms of hypovolemic shock, for example, hemorrhage, acidosis appears after the hypovolemic state is established. Systemic venoconstriction under these circumstances may have little discernible effect or even quite different consequences.

It would be difficult to explain the patterns of response of central blood volume, filling pressure, and blood flow by invoking an effect of the hydrogen ion on the myocardium. Most investigators have demonstrated that an increase in hydrogen ion concentration causes deterioration of myocardial function[29-32, 55-62]; others, that it has little discernible effect.[35, 63] To explain the high levels of filling pressures and cardiac output (once the blood volume has been expanded) in the presence of acidosis and the fall in these variables during administration of alkali, it would be necessary to postulate that a high hydrogen ion concentration enhanced myocardial contractibility or decreased ventricular compliance. These suggestions are at variance with most, if not all, experimental data. Moreover, this explanation would not account for the fall in central blood volume induced by alkali. It is possible that catecholamine activity was, in part, responsible for the high levels of flow during acidosis, since Downing and his associates[35] and Bendixen and co-workers[32] have found that myocardial contractibility can still be enhanced by the administration of norepinephrine or epinephrine in the face of an increased concentration of hydrogen ion.

In only one patient was hemodynamic evidence of heart failure produced (fig. 4): a rise

to abnormal levels in filling pressures without a corresponding rise in cardiac output, but rather a fall. This precipitation into heart failure appeared to be related to hypervolemia rather than to acidosis.

The main determinant of the level of the pulmonary arterial pressures was the pulmonary "wedge" pressure. This implies that as the left atrial pressure rose, pulmonary blood volume increased. The contribution of the stroke volume to the level of the pulmonary arterial systolic and mean pressures was small but could be detected nonetheless at low levels of flow and pressure. The passive and mechanical response of the pulmonary vasculature to changes in left and right ventricular performances is once again emphasized by these observations.

A high concentration of hydrogen ion has been shown to produce pulmonary arterial vasoconstriction in man and animals.[35, 50-53, 64-66] Although a close relationship existed between the concentration of hydrogen ion and the mean pulmonary arterial pressure in this study, no direct effect of the hydrogen ion on the pulmonary vasculature could be demonstrated. The marked changes in the pulmonary "wedge" pressure and stroke volume occurring in this investigation preclude any attempt to define the role of the hydrogen ion in the regulation of pulmonary arterial pressures.

While relatively large fluctuations in lesser circuit pressures were encountered in this study, brachial arterial blood pressures showed little change when the total blood volume was restored to normal. Although no relationship could be established between the level of mean arterial blood pressure (or peripheral resistance) and the concentration of hydrogen ion, it is noteworthy that a large reduction in hydrogen ion concentration was associated with a rise in brachial arterial mean pressure. Vasodilation of the systemic arterial system is generally found in the presence of an increased hydrogen ion concentration.[67-71] Hence, correction of acidosis might well lead to vasoconstriction and a rise in brachial arterial pressure. However, reflex vasoconstriction secondary to the fall in cardiac output which attended the reduction in hydrogen ion concentration cannot be excluded.

The influence of age on heart rate is rarely detected in the adult, unless individuals are subjected to severe stress, such as maximal exercise.[72-76] Under this latter circumstance, heart rate is appreciably lower in older age groups. In exploring the cause of this phenomenon, Frol'kis and associates[75] demonstrated that the tonic influence of the vagus and sympathetic nerves on the heart is reduced in older persons. The stress of cholera, particularly hypovolemia and acidosis, could well have resulted in an increase in circulating catecholamines to which the younger patients were more responsive. One, however, cannot overlook the possibility that the demonstrated relationship between total blood volume and heart rate results from baroreceptor activity.

The high rate of oxygen consumption found in this study may be more apparent than real inasmuch as the standard used to evaluate the normalcy of the level is the body surface area. Patients with cholera are not febrile nor do they display histological evidence of a marked cellular response to their disease; thus these mechanisms cannot be invoked to explain the high rate. Apprehension, restlessness, and hyperventilation were present and any one could be held to be responsible. However, many patients in this study were not restless and indeed one slept throughout most of the procedure. Those who were restless became quiet as hydration and alkalinization were carried out, but a reduction in oxygen consumption did not occur. Indeed, the higher the total blood volume, the higher was the oxygen consumption. If an increase in circulating catecholamines was responsible for the high rate, it would appear that a high concentration of hydrogen ion in the presence of hypocapnia does not greatly interfere with the action of catecholamines on effector organs nor does it appreciably depress oxidative metabolism.[18]

The hyperventilation displayed by these patients can be in part ascribed to acidosis and possibly to an increase in catecholamines.

Correction of acidosis and hypovolemia however did not invariably lead to a decrease in minute ventilation. These findings are in accord with those of Richards and Cournand in their studies of shock.[46, 47, 77]

The slight but definite reduction in arterial oxygen saturation in some of these patients has been noted previously in shock by other investigators, as has its persistence with fluid replacement.[47, 78–81] Previous authors have suggested that this reduction in arterial oxygen tension results from admixture with blood of low oxygen content.[78, 79, 81] The considerations of Briscoe[82] on distribution of ventilation-perfusion ratios indicate that, even in the presence of such inhomogeneities as exist in the normal lung, the alveolar-arterial oxygen gradient increases as the mixed venous oxygen tension falls. The increase in the physiological dead space found in this study suggests that this inhomogeneity may have been accentuated. Others have described an increased physiological dead space in animals when hemorrhage has produced shock. This augmentation of the dead space returns toward, but not to, normal as blood is reinfused.[78, 79, 81] Gerst and co-workers[79] attributed this finding to closure of pulmonary capillaries consequent to a marked reduction in pulmonary blood flow. The demonstration that the central blood volume is maintained in the acidotic patient at the expense of the peripheral circulation, suggests that the level of physiological shunt flow (for example, Thebesian and bronchial veins) also may be relatively well maintained in the face of a reduced cardiac output. In the presence of a low systemic blood flow, the contribution of this component of venous admixture to arterial blood unsaturation would be enhanced.

Acknowledgment

The authors wish to thank Dr. M. Irené Ferrer, Dr. Harry W. Fritts, Jr., and Miss Madelaine Bohman of the Cardiopulmonary Laboratory of the Columbia Medical Division of Bellevue Hospital, Dr. Robert S. Gordon, Jr., and Mrs. Doris Parkinson of the National Institutes of Health, and Dr. Abram S. Benenson and Dr. John S. Lindenbaum formerly of the Pakistan-SEATO Cholera Research Laboratory for support of this study.

References

1. Watten, R. H., Morgan, F. M., Songkhla, Y. A., Vanikiati, B., and Phillips, R. A.: Water and electrolyte studies in cholera. J Clin Invest 38: 1879, 1959.
2. Phillips, R. A.: Water and electrolyte losses in cholera. Fed Proc 23: 705, 1964.
3. Richardson, B. W.: Snow on Cholera. New York, The Commonwealth Fund, 1936, p. 12.
4. Dammin, G. J., et al.: Clinical and histopathologic correlations in acute diarrheal disease. *In* Proceedings of Cholera Research Symposium. Washington, D.C., U.S. Department of Health, Education, and Welfare, 1965, p. 205.
5. Pollitzer, R.: Cholera. Geneva, World Health Organization, 1959.
6. Carpenter, C. C. J., et al.: Clinical studies in Asiatic cholera: II. Development of 2:1 saline: lactate regimen; comparison of this regimen with traditional methods of treatment, April and May 1963. Bull Hopkins Hosp 118: 174, 1966.
7. Sellards, A. W., and Shaklee, A. W.: Indications of acid intoxication in Asiatic cholera. Philipp J Sci 6B: 53, 1911.
8. Lindenbaum, J., Greenough, W. B., Benenson, A. S., Oseasohn, R., Rizvi, S., and Saad, A.: Non-vibrio cholera. Lancet 1: 1081, 1965.
9. Carpenter, C. C. J., et al.: Clinical studies in Asiatic cholera. Bull Hopkins Hosp 118: 243, 1966.
10. McNeeley, W. F., and Gravallese, M. A., Jr.: Measurements of cardiac output by dye dilution technique: Use of an "integrated" sample collection in calibration of the photometric instrument. J Appl Physiol 7: 55, 1954.
11. Noble, R. P., and Gregersen, M. I.: Blood volume in clinical shock; I. Mixing time and disappearance rate of T-1824 in normal subjects and in patients in shock; determination of plasma volume in man from 10-minute sample. J Clin Invest 25: 158, 1946.
12. Chaplin, H., and Mollison, P. L.: Correction for plasma trapped in the red cell column of the hematocrit. Blood 7: 1227, 1952.
13. Chaplin, H., Mollison, P. L., and Vetter, H.: Body/venous hematocrit ratio: Its constancy over a wide hematocrit range. J Clin Invest 32: 1309, 1953.
14. Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. C.: Studies on the circulation: IV. Further analysis of the injection method, and of changes in hemodynamics under physiological and pathological conditions. Amer J Physiol 99: 534, 1932.
15. Samet, P., Fritts, H. W., Jr., Fishman, A. P.,

AND COURNAND, A.: Blood volume in heart disease. Medicine 36: 211, 1957.

16. SEVERINGHAUS, J. W.: Blood gas concentrations. In Handbook of Physiology, Section 3: Respiration, vol. 2, edited by Wallace O. Fenn and Hermann Rahn. Washington, D. C., American Physiology Society, 1965, p. 1475.
17. RADFORD, E. P.: Ventilation standards for use in artificial respiration. J Appl Physiol 7: 451, 1955.
18. NAHAS, G. G., LIGOU, J. C., AND MEHLMAN, B.: Effects of pH changes on O_2 uptake and plasma catecholamine levels in the dog. Amer J Physiol 198: 60, 1960.
19. NAHAS, G. G., MANGER, W. M., MITTELMAN, A., AND ULTMANN, J. E.: Use of 2-amino-2-hydroxymethyl-1, 3-propanediol in the correction of addition acidosis and its effect on sympathoadrenal activity. Ann NY Acad Sci 92: 596, 1961.
20. MANGER, W. M., BOLLMAN, J. L., MAHER, F. T., AND BERKSON, J.: Plasma concentration of epinephrine and norepinephrine in hemorrhagic and anaphylactic shock. Amer J Physiol 190: 310, 1957.
21. MILLAR, R. A., AND BENFEY, B. G.: Fluorimetric estimation of adrenaline and noradrenaline during hemorrhagic hypotension. Brit J Anaesth 30: 158, 1958.
22. GREEVER, C. J., AND WATTS, D. T.: Epinephrine levels in the peripheral blood during irreversible hemorrhagic shock in dogs. Circulation Research 7: 192, 1959.
23. WALTON, R. P., RICHARDSON, J. A., WALTON, R. P., JR., AND THOMPSON, W. L.: Sympathetic influences during hemorrhagic hypotension. Amer J Physiol 197: 223, 1959.
24. WALKER, W. F., ZILELI, M. S., REUTTER, F. W., SHOEMAKER, W. C., FRIEND, D., AND MOORE, F. D.: Adrenal medullary secretion in hemorrhagic shock. Amer J Physiol 197: 773, 1959.
25. WEIDNER, M. G., JR., ALBRECHT, M., AND CLOWES, G. H., JR.: Relationship of myocardial function to survival after oligemic hypotension. Surgery 55: 73, 1964.
26. BURGET, G. E., AND VISSCHER, M. B.: Variations of the pH of the blood and the response of the vascular system to adrenalin. Amer J Physiol 81: 113, 1927.
27. CAMPBELL, G. S., HOULE, D. B., CRISP, N. W., JR., WEIL, M. H., AND BROWN, E. B., JR.: Depressed response to intravenous sympathicomimetic agents in humans during acidosis. Dis Chest 33: 18, 1958.
28. TOBIAN, L., MARTIN, S., AND EILERS, W.: Effect of pH on norepinephrine induced contractions of isolated arterial smooth muscle. Amer J Physiol 196: 998, 1959.
29. DARBY, T. D., ALDINGER, E. E., GADSDEN, R. H., AND THROWER, W. B.: Effects of metabolic acidosis on ventricular isometric systolic tension and the response to epinephrine and levarterenol. Circulation Research 8: 1242, 1960.
30. DARBY, T. D.: Effects of 2-amino-2-hydroxymethyl-1, 3-propanediol during shock and catecholamine administration. Ann NY Acad Sci 92: 674, 1961.
31. THROWER, W. B., DARBY, T. D., AND ALDINGER, E. D.: Acid-base derangements and myocardial contractility: Effects as a complication of shock. Arch Surg (Chicago) 82: 56, 1961.
32. BENDIXEN, H. H., LAVER, M. B., AND FLACKE, W. E.: Influence of respiratory acidosis on circulatory effect of epinephrine in dogs. Circulation Research 13: 64, 1963.
33. LIGOU, J. D., AND NAHAS, G. G.: Effects of pH and catecholamine blood levels on oxygen uptake. Trans Amer Soc Artif Intern Organs 5: 279, 1958.
34. MANGER, W. M., NAHAS, G. G., HASSAM, D., HABIF, D. V., AND PAPPER, E. M.: Effect of pH control and increased O_2 delivery on the course of hemorrhagic shock. Ann Surg 156: 503, 1962.
35. DOWNING, S. E., TALNER, N. S., AND GARDNER, T. H.: Cardiovascular responses to metabolic acidosis. Amer J Physiol 208: 237, 1965.
36. EBERT, R. V., BORDEN, C. W., WELLS, H. S., AND WILSON, R. H.: Studies of the pulmonary circulation: I. Circulation time from the pulmonary artery to the femoral artery and the quantity of blood in the lungs in normal individuals. J Clin Invest 28: 1134, 1949.
37. DOYLE, J. T., WILSON, J. S., ESTES, E. H., AND WARREN, J. V.: Effect of intravenous infusions of physiologic saline solution on the pulmonary arterial and pulmonary capillary pressure in man. J Clin Invest 30: 345, 1951.
38. WITHAM, A. C., FLEMING, J. W., AND BLOOM, W. L.: Effect of the intravenous administration of dextran on cardiac output and other circulatory dynamics. J Clin Invest 30: 897, 1951.
39. DOYLE, J. T., WILSON, J. S., AND WARREN, J. V.: Pulmonary vascular responses to short-term hypoxia in human subjects. Circulation 5: 263, 1952.
40. KOPELMAN, H., AND LEE, DE J.: Intrathoracic blood volume in mitral stenosis and left ventricular failure. Clin Sci 10: 383, 1951.
41. DOCK, D. S., KRAUS, W. L., MCGUIRE, L. B., HYLAND, J. W., HAYNES, F. W., AND DEXTER, L.: Pulmonary blood volume in man. J Clin Invest 40: 317, 1961.
42. FRYE, R. L., AND BRAUNWALD, E.: Studies on

Starling's law of the heart: I. Circulatory response to acute hypervolemia and its modification by ganglionic blockade. J Clin Invest 39: 1043, 1960.

43. DE FREITAS, F. M., FARACO, E. Z., DE AZEVEDO, D. F., ZADUCHLIVER, J., AND LEWIN, I.: Behavior of normal pulmonary circulation during changes of total blood volume in man. J Clin Invest 44: 366, 1965.
44. GIUNTINI, C., MASERI, A., AND BIANCHI, R.: Pulmonary vascular distensibility and lung compliance as modified by dextran infusion in normal subjects. J Clin Invest 45: 1770, 1966.
45. SHARPEY-SCHAFER, E. P., SEMPLE, S. J. G., HALLS, R. W., AND HOWARTH, S.: Venous constriction after exercise: Its relation to acid-base changes in venous blood. Clin Sci 29: 397, 1965.
46. COURNAND, A., et al.: Studies of the circulation in clinical shock. Surgery 13: 964, 1943.
47. RICHARDS, D. W.: Circulation in traumatic shock in man. Harvey Lect 39: 217, 1944.
48. ALEXANDER, R. S.: Site of action of H-ion on veins. Fed Proc 26: 554, 1967.
49. ECKSTEIN, J. W., HAMILTON, W. K., AND MCCAMMOND, J. M.: Pressure-volume changes in the forearm veins of man during hyperventilation. J Appl Physiol 37: 956, 1958.
50. ENSON, Y., GIUNTINI, C., LEWIS, M. L., MORRIS, T. Q., FERRER, M. I., AND HARVEY, R. M.: Influence of hydrogen ion concentration and hypoxia on the pulmonary circulation. J Clin Invest 43: 1146, 1964.
51. RUDOLPH, A. M., AND YUAN, S.: Response of the pulmonary vasculature to hypoxia and H^+ ion concentration changes. J Clin Invest 45: 399, 1966.
52. LLOYD, T. C.: Influence of blood pH on hypoxic pulmonary vasoconstriction. J Appl Physiol 21: 358, 1966.
53. HARVEY, R. M., ENSON, Y., BETTI, R., LEWIS, M. L., ROCHESTER, D. F., AND FERRER, M. I.: Further observations on the effect of hydrogen ion on the pulmonary circulation. Circulation 35: 1019, 1967.
54. ECKSTEIN, J. W., AND HAMILTON, W. K.: Pressure-volume responses of human forearm veins during epinephrine and norepinephrine infusions. J Clin Invest 36: 1663, 1957.
55. GREMMELS, H., AND STARLING, E. H.: On the influence of hydrogen ion concentration and of anoxaemia upon the heart volume. J Physiol 61: 297, 1926.
56. PRICE, H. L., AND HELRICH, M.: Effect of cyclopropane, diethyl ether, nitrous oxide, thiopental, and hydrogen ion concentration on the myocardial function of the dog heart-lung preparation. J Pharmacol Exp Ther 115: 206, 1955.
57. NAHAS, G. G., AND CAVERT, H. M.: Cardiac depressant effect of CO_2 and its reversal. Amer J Physiol 190: 483, 1957.
58. MCELROY, W. T., JR., GERDES, A. J., AND BROWN, E. B., JR.: Effects of CO_2, bicarbonate and pH on the performance of isolated perfused guinea pig hearts. Amer J Physiol 195: 412, 1958.
59. OPIE, L. H., KADAR, T., AND GEVERS, W.: Effect of pH on the function and glucose metabolism of the heart. Lancet 2: 551, 1963.
60. WANG, H., AND KATZ, R. L.: Effects of changes in coronary blood pH on the heart. Circulation Research 17: 114, 1965.
61. OPIE, L. H., AND PHIL, D.: Cardiac metabolism: Effect of some physiologic, pharmacologic, and pathologic influences. Amer Heart J 69: 401, 1965.
62. LORKOVIC, H.: Influence of changes in pH on the mechanical activity of cardiac muscle. Circulation Research 19: 711, 1966.
63. GOODYER, A. V. N., ECKHARDT, W. F., OSTBERG, R. H., AND GOODKIND, M. J.: Effects of metabolic acidosis and alkalosis on coronary blood flow and myocardial metabolism in the intact dog. Amer J Physiol 200: 628, 1961.
64. BERGOFSKY, E. H., LEHR, D. E., AND FISHMAN, A. P.: Effect of changes in hydrogen ion concentration on the pulmonary circulation. J Clin Invest 41: 1492, 1962.
65. LILJESTRAND, G.: Chmeical control of the distribution of the pulmonary blood flow. Acta Physiol Scand 44: 216, 1958.
66. CHU, J., et al.: Pulmonary hypoperfusion syndrome. Pediatrics 36: 733, 1965.
67. KESTER, N. C., RICHARDSON, A. W., AND GREEN, H. D.: Effect of controlled hydrogen ion concentration on peripheral vascular tone and blood flow in innervated hind leg of the dog. Amer J Physiol 169: 678, 1952.
68. DEAL, C. P., JR., AND GREEN, H. D.: Effects of pH on blood flow and peripheral resistance in muscular and cutaneous vascular beds in the hind limb of the pentobarbitized dog. Circulation Research 2: 148, 1954.
69. FLEISHMAN, M., SCOTT, J., AND HADDY, F. J.: Effect of pH change upon systemic large and small vessel resistance. Circulation Research 5: 602, 1957.
70. HADDY, F. J.: Role of chemicals in local regulation of vascular resistance. Circulation Research 18, 19 (suppl. I): 1-14, 1966.
71. FURCHGOTT, R. F.: Metabolic factors that influence contractility of vascular smooth muscle. Bull NY Acad Med 42: 996, 1966.
72. ROBINSON, S.: Experimental studies of physical fitness in relation to age. Arbeitsphysiologie 10: 18, 1938.

73. Morris, A. H., Nathan, N. W., and Yiengst, M. J.: Age changes in heart rate and blood pressure responses to tilting and standardized exercise. Circulation 8: 521, 1953.
74. Astrand, P. O.: Human physical fitness with special reference to sex and age. Physiol Rev 36: 307, 1956.
75. Frol'kis, V. V., Golovchenko, S. F., Dukhovichnyi, S. M., and Tanin, S. A.: Functional changes of circulation and respiration with age. Klin Med (Moskva) 40: 87, 1962.
76. Becklake, M. R., Frank, H., Dagenais, G. R., Ostiquy, G. L., and Guzman, C. A.: Influence of age and sex on exercise cardiac output. J Appl Physiol 20: 938, 1965.
77. Cournand, A., et al.: Chemical, clinical, and immunological studies on the products of human plasma fractionation: VIII. Clinical use of concentrated human serum albumin in shock, and comparison with whole blood and with rapid saline infusion. J Clin Invest 23: 491, 1944.
78. Merriman, J. E.: Pulmonary circulation in hemorrhagic shock. *In* Shock and Circulatory Homeostasis, edited by H. D. Green. New York, Josiah Macy, Jr. Foundation, 1955, p. 208.
79. Geist, P. H., Rattenborg, C., and Holaday, D. A.: Effects of hemorrhage on pulmonary circulation and respiratory gas exchange. J Clin Invest 38: 524, 1959.
80. Weidner, M. G., Jr., and Simeone, F. A.: Physiology of prolonged oligemic hypotension: Investigation of pulmonary function. Ann Surg 156: 493, 1962.
81. Freeman, J., and Nunn, J. F.: Ventilation-perfusion relationships after hemorrhage. Clin Sci 24: 135, 1963.
82. Briscoe, W. A.: Method for dealing with data concerning uneven ventilation of the lung and its effects on oxygen transfer. J Appl Physiol 14: 291, 1959.

NEW ADDRESS OF EDITORIAL OFFICES OF CIRCULATION

Manuscripts being submitted to CIRCULATION for publication should be addressed after June 1, 1968, as follows:

Dr. Howard B. Burchell
Editor-in-Chief—CIRCULATION
Box 505
University of Minnesota Medical School
412 Union Street S.E.
Minneapolis, Minnesota 55455