Reprinted from
ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Volume 150, Article 3, Pages 577-583
August 14, 1968

HEMODYNAMIC EFFECTS OF METABOLIC ACIDOSIS IN CHOLERA: IMPLICATIONS FOR FLUID REPLETION IN SEVERE BURNS*

Y. Enson,† R. M. Harvey,‡ M. L. Lewis,§ W. B. Greenough,¶
K. M. Ally,** R. A. Panno††

INTRODUCTION

Patients with severe burns manifest a number of physiologic alterations commonly observed in cholera. The plasma volume is usually markedly diminished, and severe metabolic acidosis may be present. Further, an occasional patient with either diagnosis may develop evidence of pulmonary congestion during the course of fluid repletion despite a clinical status that suggests a need for the administration of additional fluid.

Clinical experience in the treatment of cholera has suggested that correction of the acidosis during fluid replacement may lessen the risk of pulmonary congestion. For this reason we recently conducted a study of hemodynamic events in cholera patients at the Pakistan–SEATO Cholera Research Laboratory with particular emphasis on the effects of hypovolemia, acidosis, and fluid therapy. Consequently, we have drawn some conclusions concerning the hemodynamic effects of acidosis in cholera which may be relevant to patients with severe burns. Support for this analogy is furnished by a comparison of the levels of arterial blood pH observed in a group of cholera patients, on the left in FIGURE 1, with those encountered in a group of patients with severe burns,[1] on the right. Degrees of metabolic acidosis as marked as those which develop in moderately severe cases of cholera may occur as a result of burns.

MATERIALS AND METHODS

Twenty-three patients were studied utilizing the technique of right heart catheterization. Serial measurements were made of arterial blood pH, total and central blood volumes, cardiac output and systemic arterial, pulmonary arterial, pulmonary "wedge" and right atrial or right ventricular pressures.

In FIGURE 2 are depicted the responses of two patients in shock to the i.v.

* This research was supported in part by HE-02001-10 and HE-05741 from the National Heart Institute, U.S. Public Health Service, and by a Public Health Service research career program award (5-K6-HE 16,603-03) from the National Heart Institute, and by Research Agreement 196802 between the National Institutes of Health, Bethesda, Maryland and the Pakistan–SEATO Cholera Research Laboratory, Dacca, East Pakistan.

† Y. Enson is a recipient of investigatorship of the Health Research Council of the City of New York under contract I-176. He is with the Department of Medicine, Columbia University, College of Physicians and Surgeons, and the Cardiopulmonary Laboratory of the Columbia Medical Division of Bellevue Hospital, New York, N. Y.

‡ R. M. Harvey is with the Department of Medicine, Columbia University, College of Physicians and Surgeons, and the Cardiopulmonary Laboratory of the Columbia Medical Division of Bellevue Hospital, New York, N. Y.

§ M. L. Lewis is with the Manhattan Veterans Administration Hospital, New York, N. Y. and with the Department of Medicine, Columbia University, College of Physicians and Surgeons.

¶ W. B. Greenough is with the Pakistan–SEATO Cholera Research Laboratory, Dacca, East Pakistan.

** K. M. Ally is with Pakistan–SEATO Cholera Research Laboratory, Dacca, East Pakistan.

†† R. A. Panno is with the Cardiopulmonary Laboratory of the Columbia Medical Division of Bellevue Hospital, New York, N. Y.

administration of either isotonic saline or of isotonic alkalinizing solution. At the time of the first measurements both patients displayed a marked reduction in total blood volume and cardiac output. The systemic arterial, pulmonary arterial and filling pressures of the right and left hearts were also strikingly reduced. Severe acidosis was present: the pH was 7.12 and 7.04 respectively. During the next two hr each patient received approximately one and a half liters of fluid and showed a prompt return towards normal levels in total blood volume, cardiac output, and all pressures.

Further fluid replacement with isotonic saline, on the left, caused little alteration in pH and was accompanied by a continued rise in total blood volume, cardiac output, and all pressures. In contrast, the infusion of additional isotonic alkalinizing solution, on the right, which produced a rise in pH, was attended by a decrease in central blood volume, cardiac output, and lesser circulation pressures despite a further rise in total blood volume.

The initial response to fluid replacement indicates that hypovolemia was responsible for the low level of cardiac output and blood pressures. Once the initial shock was overcome, however, pH could then be shown to influence the ensuing train of events.

Thirteen patients were rehydrated to varying degrees with isotonic saline prior

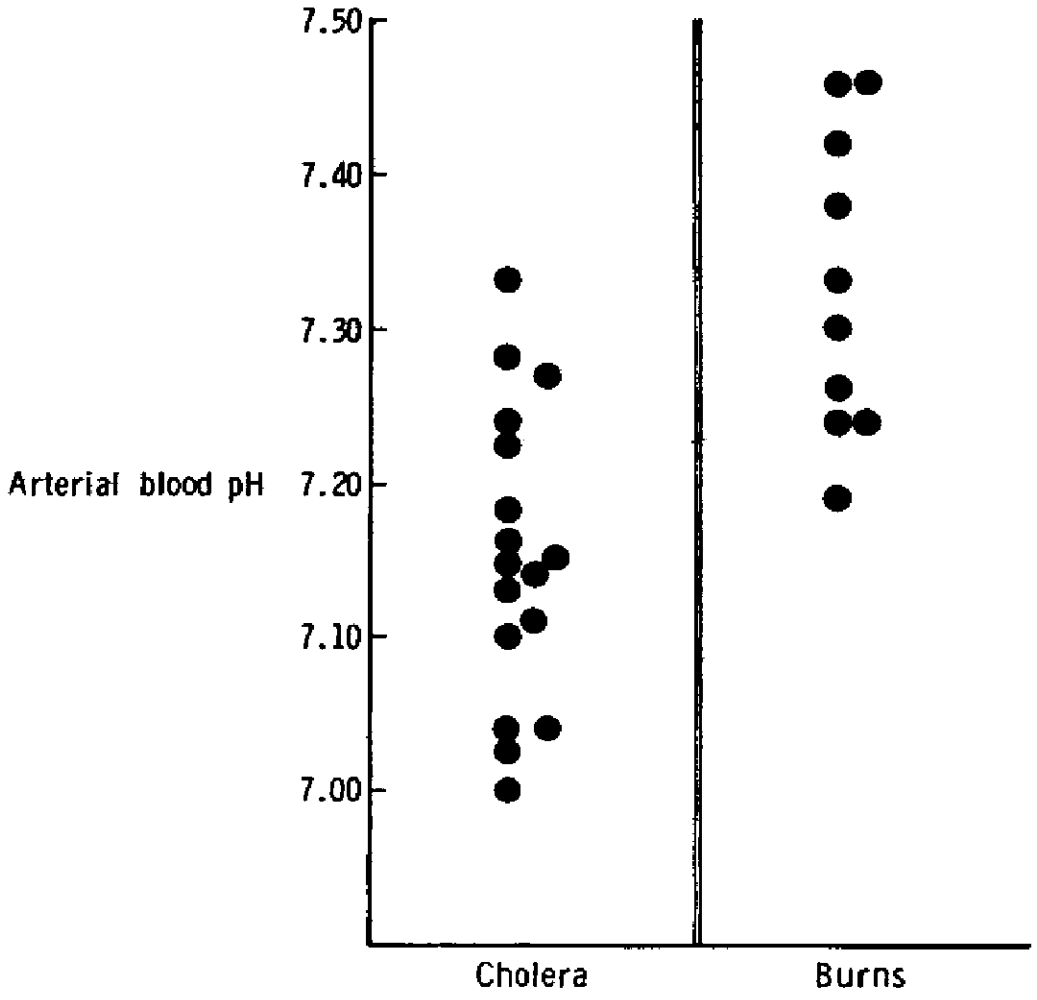

FIGURE 1. Comparison of levels of arterial blood pH in patients with cholera and severe burns at the time of admission to hospital in shock. For discussion see text.

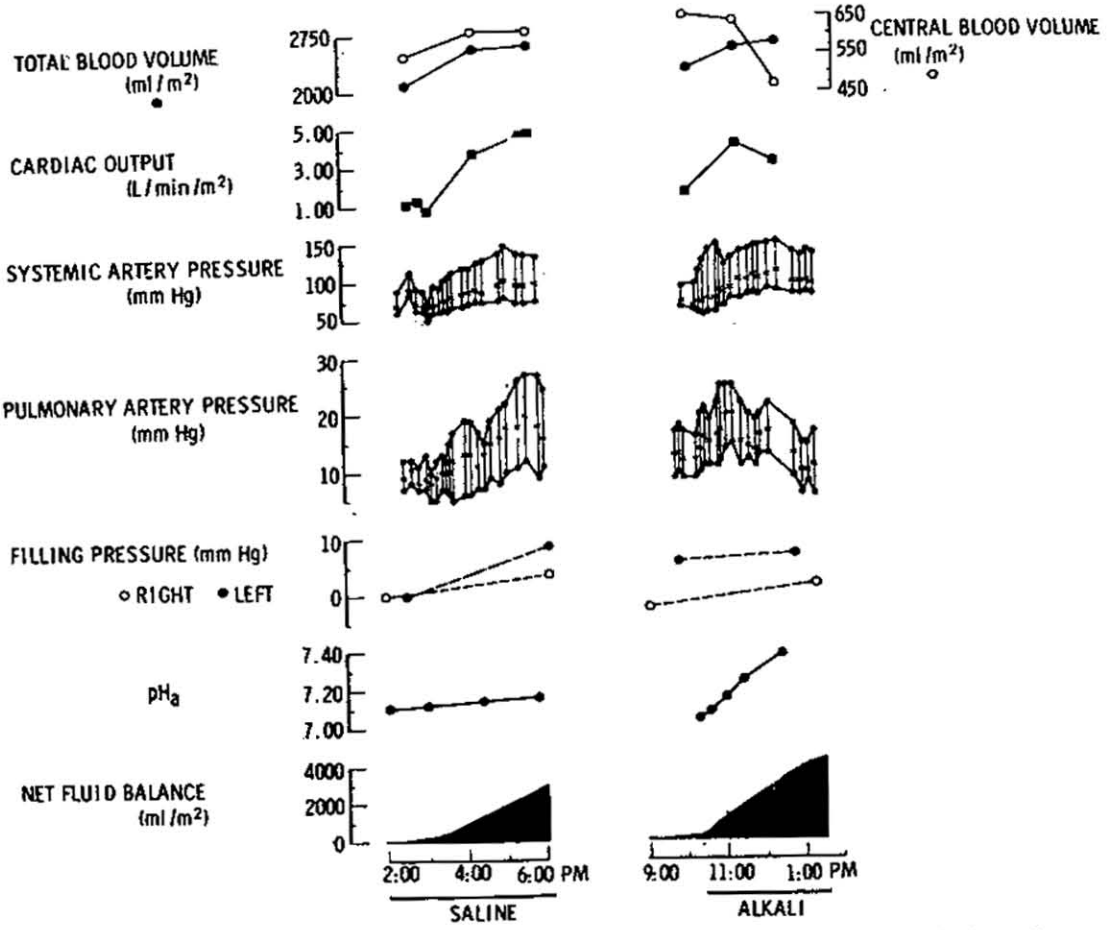

FIGURE 2. Schematic representation of hemodynamic events during fluid repletion of two patients with vascular collapse due to cholera.[11] The patient whose data are indicated in the column on the left received only saline, and blood pH was unaltered. The patient on the right received alkalinizing solution. For discussion see text. (Reproduced by permission of the Transactions of the Association of American Physicians.)

to study. Severe acidosis, however, persisted. Hemodynamic measurements were then obtained, more fluid administered either in the form of isotonic saline or isotonic alkalinizing solutions, and observations continued. The results of two representative studies, seen in FIGURE 3, indicate that the pattern of response is the same: when the pH is unchanged, cardiac output and lesser circuit pressures increase with the rising blood volume; when acidosis is corrected, however, there is a fall in pulmonary arterial and ventricular filling pressures, plus a slight reduction in cardiac output. Of special interest is the observation that the levels of pressure attained here, during uncorrected acidosis, exceed normal limits.

Let us turn now to an examination of the probable site and mechanism of action of alterations in pH. It is possible that acidosis increases contractility or decreases compliance of the ventricular myocardium, or both. If such a mechanism were responsible for the relatively high flow and filling pressures observed during acidosis, correction of the acidosis would then result in a return to normal pressure-flow relationships, with a possible decrease in flow and filling pressure. This premise, however, is at variance with most experimental data.[2-9] Moreover, it fails to explain the decrease in central blood volume which accompanies the drop in filling pressure and cardiac output.

A more tenable explanation for the observed fall in central blood volume, filling pressures and cardiac output produced by the infusion of alkalinizing solutions is that venous return to the heart is diminished as the pH rises, despite a continued increase in total blood volume. We postulate that acidosis constricts the peripheral venous bed, and that alkalinization relaxes this constriction, with a consequent diminution in the volume of blood returning to the heart. This assumption is in agreement with the data of Sharpey-Schafer and his associates, who have demonstrated peripheral veno-constriction and a reduction in the capacity of the peripheral venous bed in the presence of acidosis.[10]

Statistical analysis of our data suggests that this mechanism may indeed be operative. Proof that a redistribution of the circulating blood volume was responsible for alterations in cardiac output and filling pressures requires a demonstration that ventricular volumes rise or fall with changes in hydrogen ion concen-

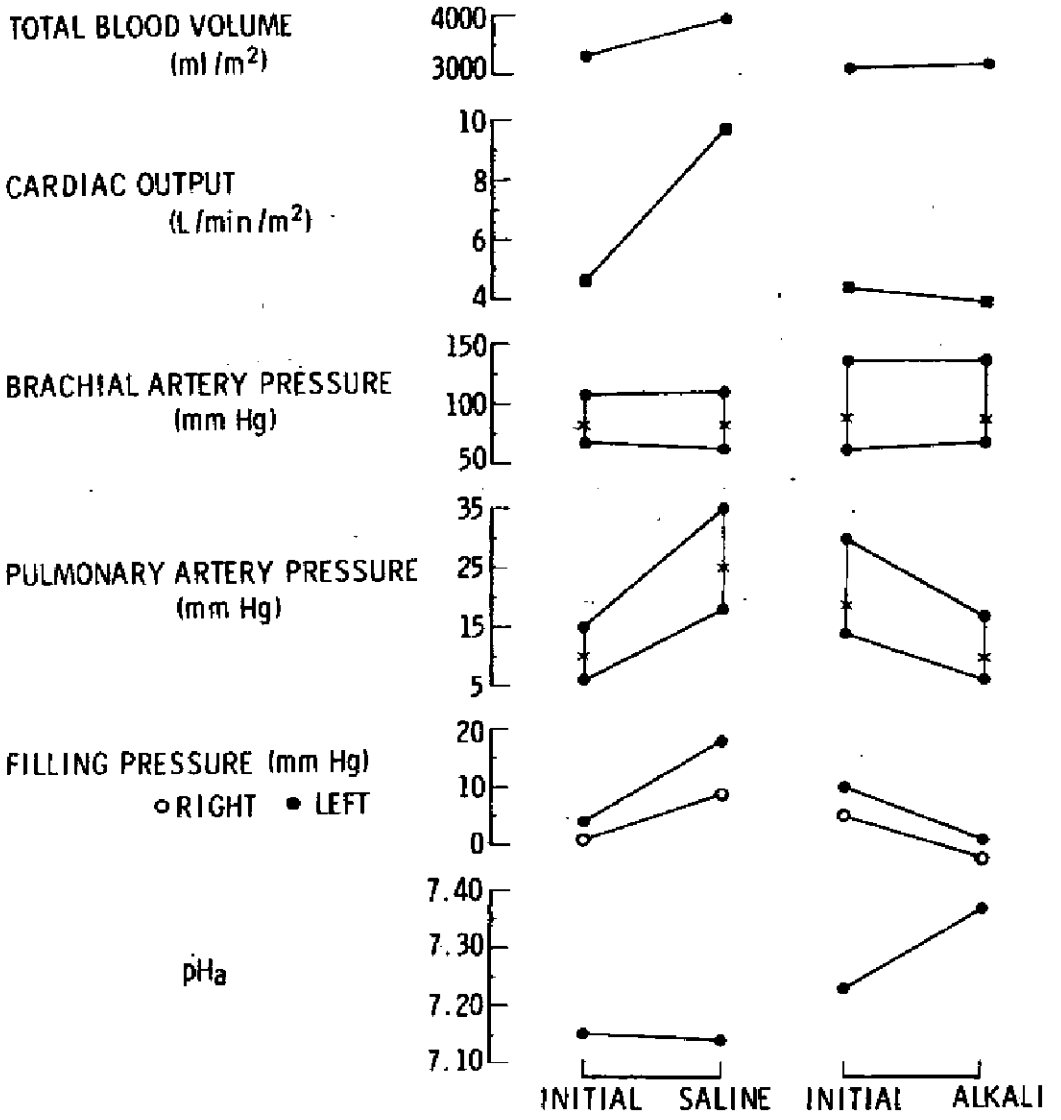

FIGURE 3. Schematic representation of the hemodynamic effects of fluid administration in two partially treated patients with cholera.[11] While the patient on the left received only saline and remained acidotic, the patient on the right received isotonic alkalinizing solution. For discusson see text. (Reproduced by permission of the Transactions of the Association of American Physicians.)

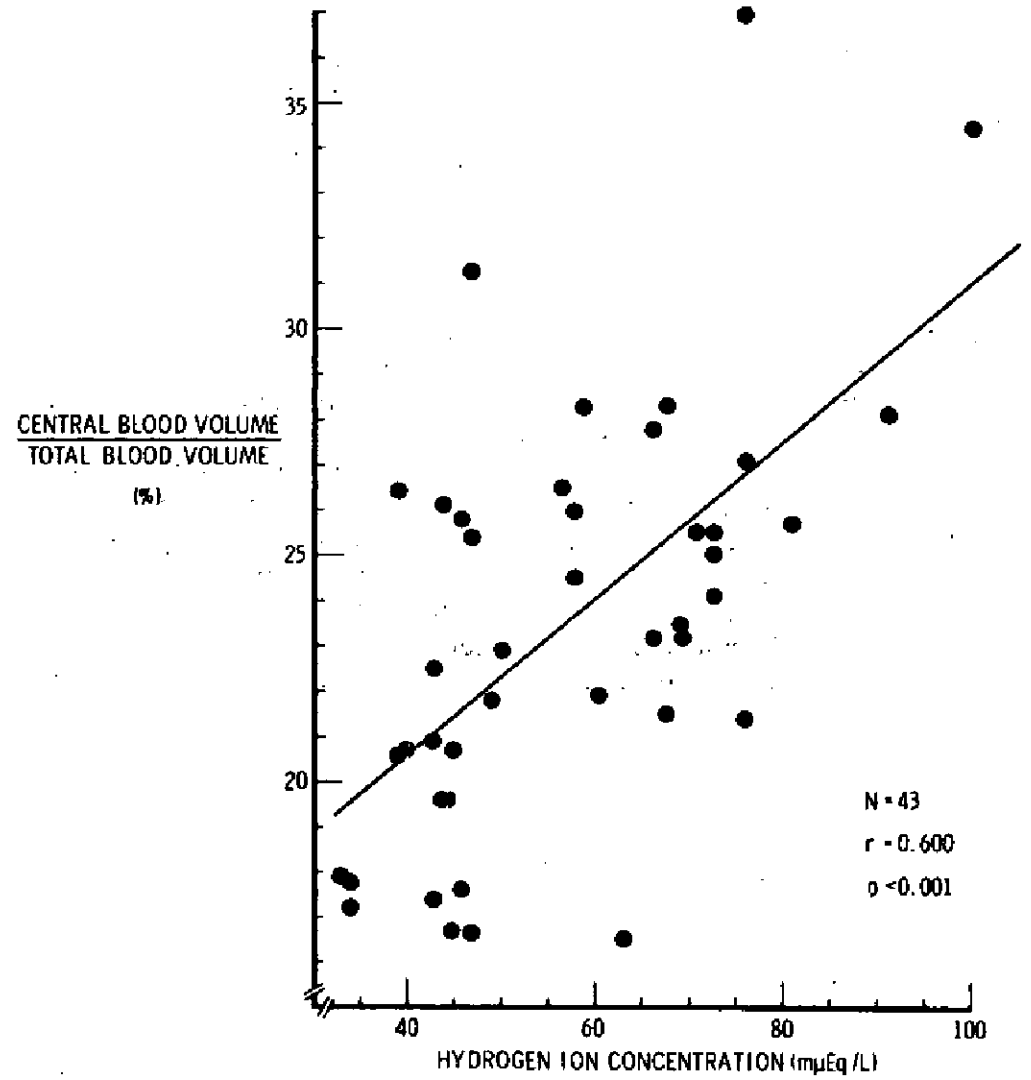

FIGURE 4. Graphic representation of the relationship between hydrogen ion concentration and the ratio of central blood volume to total blood volume in patients with cholera.[11] Forty-three observations were made in 23 subjects. (Reproduced by permission of the Transactions of the Association of American Physicians.)

tration, as well as with changes in total blood volume. Lacking such data, we have used the central blood volume, the volume of blood contained between the pulmonary and brachial arteries, as an index of ventricular volume. As seen in FIGURE 4, a close relationship was found between pH, expressed here as hydrogen ion concentration, and the ratio of central blood volume to total blood volume. The higher the hydrogen ion concentration (i.e., the lower the pH), the greater was the portion of the total blood volume that constituted the central blood volume. It was possible to express the central blood volume as a function of the total blood volume and hydrogen ion concentration, and to predict its level from the values of total blood volume and pH observed during our initial determinations. The direction and magnitude of change in central blood volume observed during alterations in the two independent variables produced by fluid repletion could also be predicted.

It is not surprising then, that if cardiac output is considered as a simultaneous function of both total blood volume and pH, as indicated in FIGURE 5, we can

predict not only its level, but also the magnitude and direction of its change during fluid therapy. If blood volume rises strikingly and changes in pH are small, cardiac output will rise. When the increment in blood volume is modest but the pH rises sharply the cardiac output will fall. The filling pressure of the left heart demonstrated a similar relationship to blood volume and pH.

Summary

To summarize the train of events in cholera as we visualize them: Severe dehydration results in hypovolemia, and cardiac output and all pressures fall. Acidosis causes peripheral venous constriction, thereby reducing the capacity of the venous reservoirs and maintaining, to some extent, venous return to the heart. Fluid administration without correction of acidosis favors a disproportionate venous return to the heart and pulmonary circulation. Alleviation of acidosis during fluid replacement results in a more even distribution of the circulating blood volume and reduces the possibility of engorgement of the pulmonary bed.

This mechanism may also explain the occasional appearance of pulmonary congestion in patients with severe burns and metabolic acidosis. Fluid therapy without correction of acidosis in such patients may also favor a disproportionate venous return to the heart and pulmonary circulation. Treatment of the acidosis

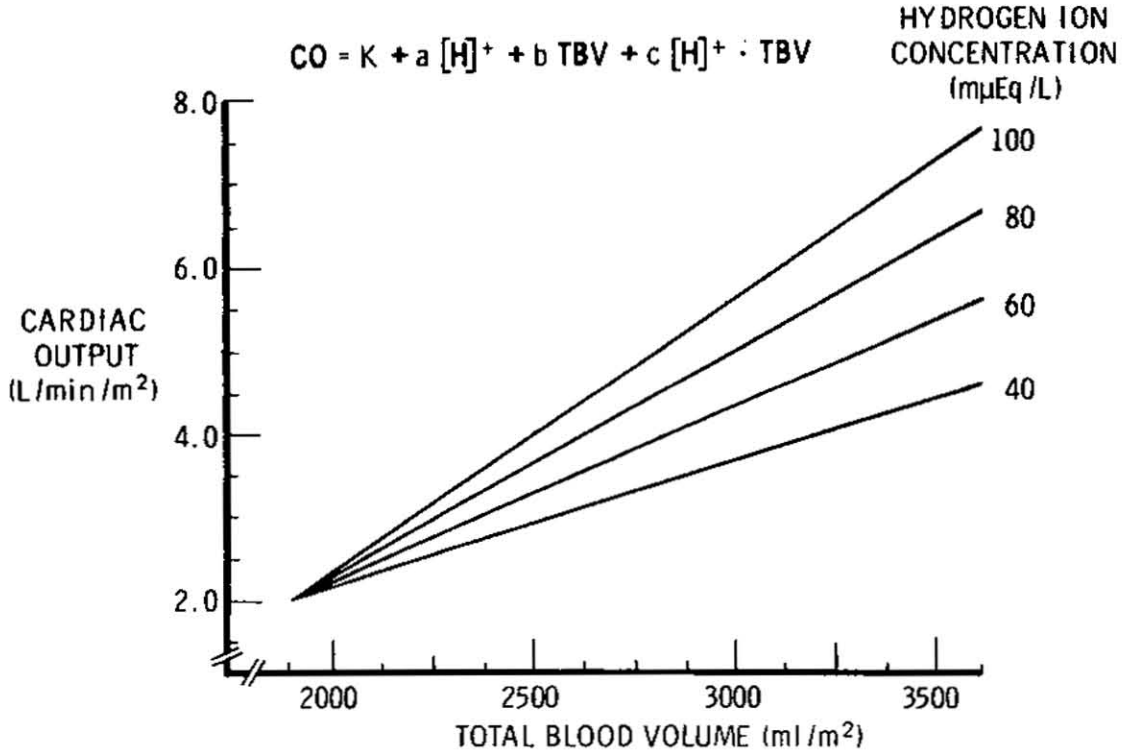

FIGURE 5. Graphic representation of the relationship between cardiac output, total blood volume, and hydrogen ion concentration in patients with cholera.[11] In the estimating equation, K, a, b, and c are constants whose values were obtained by the Gauss method of least mean squares, from data secured at the time initial measurements were made of cardiac output (CO), arterial blood hydrogen ion concentration ($[H]^+$), and total blood volume (TBV). The validity of the equation was tested by its prediction of the level of cardiac output in subsequent states, as well as the direction and magnitude of change in cardiac output. (Reproduced by permission of the Transactions of the Association of American Physicians.)

may be expected to reduce, in these patients as well, the possibility of pulmonary engorgement.

In conclusion, these data indicate that the blood pH affects the distribution of the circulating blood volume and thereby influences the volume of blood returning to the heart, and through it, the central blood volume, ventricular filling pressures and cardiac output. We suggest that the site of action is in the peripheral venous bed.

References

1. Cournand, A. Unpublished observations.
2. Salant, W. & R. L. Johnston. 1924. The response of the isolated frog heart to changes in hydrogen ion concentration and adrenalin. J. Pharmacol. Exptl. Therap. **23**: 373.
3. Gremels, H. & E. H. Starling. 1926. On the influence of hydrogen ion concentration and of anoxemia upon the heart volume. J. Physiol. **61**: 20.
4. Price, H. L. & M. Helrich. 1955. The effect of cyclopropane, diethyl ether, nitrous oxide thiopental, and hydrogen ion concentration on the myocardial function of the dog heart lung preparation. J. Pharmacol. Exptl. Therap. **115**: 206.
5. Nahas, G. G. & H. M. Cavert. 1957. Cardiac depressant effect of CO_2 and its reversal. Am. J. Physiol. **190**: 483.
6. McElroy, W. T., Jr., A. J. Gerdes & E. B. Brown, Jr. 1958. Effects of CO_2, bicarbonate, and pH on the performance of isolated perfused guinea pig hearts. Am. J. Physiol. **195**: 412.
7. Darbey, T. D., E. E. Aldinger, R. H. Gadsen & W. B. Thrower. 1960. Effects of metabolic acidosis on ventricular isometric systolic tension and the response to epinephrine and levarterenol. Circulation Res. **8**: 1242.
8. Opie, L. H., T. Kadas & W. Gevers. 1963. Effect of pH on the function and glucose metabolism of the heart. Lancet **2**: 551.
9. Downing, S. E., N. S. Talner & T. H. Gardner. 1965. Cardiovascular responses to metabolic acidosis. Am. J. Physiol. **208**: 237.
10. Sharpey-Schafer, E. P., S. J. G. Semple, R. W. Halls & S. Howarth. 1965. Venous constriction after exercise; its relation to acid-base changes in venous blood. Clin. Sci. **29**: 397.
11. Harvey, R. M., Y. Enson, M. L. Lewis, W. B. Greenough, K. M. Ally & R. A. Panno. 1966. Hemodynamic effects of dehydration and metabolic acidosis in Asiatic cholera. Tr. Ass. Am. Physicians **79**: 177.