Preservation of Ventricular Function by Adrenergic Influences during Metabolic Acidosis in the Cat

By Jose M. Rocamora and S. Evans Downing

ABSTRACT

Although metabolic acidemia reduces the contractility of cardiac muscle in isolated preparations, it does not do so to the same extent in intact animals or those with a functioning sympathoadrenal system. The present study was designed to determine if the resistance of the heart to acidemia is the consequence of concurrent adrenergic influences on the myocardium. The function of the cat's left ventricle was examined in a preparation that allowed control of aortic pressure, cardiac output, heart rate and temperature. The arterial blood pH, $P_{O_2}$, $P_{CO_2}$, and temperature were continuously measured. Acidemia was produced either endogenously by temporarily diminishing perfusion of peripheral tissues, or by infusion of 0.5N lactic acid. Studies were made before and after beta-receptor blockade with propranolol, 0.25 to 0.5 mg/kg iv or im. In eight control animals, reduction of pH from 7.34 to 7.08 failed to diminish contractility. In 14 animals with beta-receptor blockade, reduction of pH to 7.02 reduced contractility by about 25% ($P < .001$). Correction of the acidemia by infusion of tris(hydroxymethyl)aminomethane returned contractility to approximately 95% of control. Rapid reduction of pH transiently diminished contractility in control animals and severely depressed those with beta-receptor blockade. These data support the position that sympathoadrenal activity is necessary to preserve ventricular function in the presence of severe metabolic acidemia.

ADDITIONAL KEY WORDS

ventricular contractility
myocardial contractility in acidemia

There is much uncertainty concerning the influence of metabolic acidemia on cardiac performance in the human patient and in experimental animals. Recent studies from this laboratory on the effect of a decrease of arterial blood pH on myocardial contractility in both the adult cat (1, 2) and the newborn lamb (3, 4) have not provided consistent evidence of significant depression of left ventricular performance. This appears to be in agreement with the findings of some investigators (5-8), but quite inconsistent with others (9-11).

The main purpose of this communication is to present more data showing that metabolic acidemia has little or no detrimental effect on cardiac function in the intact mammal. An additional objective is to further characterize the physiological abnormalities or experimental procedures which must necessarily accompany an increased arterial hydrogen ion concentration to produce a negative inotropic effect.

Methods

Cats were anesthetized with pentobarbital, 30 mg/kg ip, and prepared for measurement of left ventricular performance (Fig. 1). After tracheal intubation, the chest was opened and the cat was ventilated with a Harvard positive-pressure pump. The respiratory gas mixture was room air supplemented when necessary with...
Auto-supported heart preparation for measuring left ventricular performance. Cardiac output augmented by controlled aorta-to-superior vena cava shunt for performance of ventricular function curves. Mean aortic pressure controlled by constant pressure reservoir. Continuous measurement of arterial pH, Po$_2$, Pco$_2$, and temperature with a Jewett electrode assembly. Left ventricular output measured with electromagnetic flow transducer. Pressures (TR) measured in aortic arch, femoral artery, and left ventricular chamber.

oxygen. Left ventricular output (minus coronary flow) was measured with a Medicon electromagnetic flow transducer placed at the root of the aorta. The descending thoracic aorta was cannulated and the blood flow was diverted through a Sams heat exchanger and returned to the aorta. Cardiac output could be altered over the desired range by pumping blood from the aortic loop to a cannulated innominate vein with a Sams roller pump. Mean arterial pressure was controlled with an adjustable constant-pressure blood reservoir. The use of a Sams heat exchanger in conjunction with a Haake water bath permitted close control of arterial blood temperature (37 ± 1°C) throughout the course of the experiments. The pH, Po$_2$, Pco$_2$, and temperature of arterial blood were continuously measured with a Jewett electrode assembly (1) and the measurements recorded on a Sanborn 4-channel direct-writing recorder. The blood gas and pH values were frequently checked with an Instrumentation Laboratories apparatus. Arterial blood Pco$_2$ in all preparations was 15 mm Hg or less. Heart rate, cardiac output, aortic pressure, left ventricular end-diastolic pressure, left ventricular dP/dt, and femoral arterial pressure were recorded on a Sanborn 8-channel direct-writing recorder. Other details of the preparation have been described elsewhere (2).

Metabolic acidosis was produced in most preparations by intravenous infusion of 0.5N lactic acid at the rate of 1.23 ml/min until the desired pH was obtained. This usually required a 10-min infusion period. Acidosis was produced in four animals by lowering the arterial pressure in the descending thoracic aorta to 30 to 40 mm Hg by partially occluding the tubing to this vessel (Fig. 1). This level of hypotension was maintained until the desired level of endogenous metabolic acidemia was produced. The effects of rapid reduction of pH on cardiac function were studied by injecting 0.5N lactic acid at the rate of 4 ml/minute. Arterial blood pH was corrected to control values by infusing 0.36M buffered tris(hydroxymethyl)aminomethane (THAM) intravenously.

Left ventricular performance was assessed by examining the relation of stroke volume, mean ejection rate, and left ventricular dP/dt max to left ventricular end-diastolic pressure (LVEDP) at a constant aortic pressure and heart rate. Ventricular function curves were obtained under these conditions, and the same variables were measured at an LVEDP of 10 cm H$_2$O for quantitative comparison. Beta-receptor blockade was produced by propranolol, 0.25 to 0.5 mg/kg iv or im. This was usually sufficient to completely block the chronotropic and inotropic responses to a test dose of 0.5 µg of isoproterenol, iv. Occasionally an animal was given additional propranolol until the response to isoproterenol was eliminated. The effects of metabolic acidosis on left ventricular performance were studied in eight animals before, and in five of these after, beta-receptor blockade. In another nine animals, beta-receptor blockade was produced at the beginning of the experiment and maintained throughout its course. Occasionally small additional amounts of propranolol were given these animals if some responsiveness to isoproterenol returned.

**Results**

**EFFECTS OF METABOLIC ACIDOSIS ON MYOCARDIAL CONTRACTILITY BEFORE BETA-RECEPTOR BLOCKADE**

Data from 68 ventricular function curves obtained from eight animals were analyzed (Table 1). The original traces from a representative experiment in which acidosis was produced by lactic acid infusion are reproduced in Figure 2. Arterial blood pH values
Hydrogen Ion Concentration and Left Ventricular Performance

<table>
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<th>Cat no.</th>
<th>n</th>
<th>pH</th>
<th>Stroke volume (ml)</th>
<th>Mean ejection rate (ml/systolic sec)</th>
<th>dp/dt (mm Hg/sec)</th>
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TABLE 1

*Mean values for all determinations.

n = number of ventricular function curves; dp/dt values are the maximal rates of rise of left ventricular pressure. All values obtained at a left ventricular end-diastolic pressure of 10 cm H2O. A = initial control values; B = values during acidemia; C = values following correction of pH with THAM.

were 7.39 and 7.02 under virtually identical conditions of aortic pressure, heart rate, and cardiac output. Severe metabolic acidemia induced no change in LVEDP, dp/dt max, or the duration of left ventricular ejection. Hence there was no detectable alteration of left ventricular contractility as a consequence of the increased arterial hydrogen ion concentration.

Neither the ventricular function curves obtained during acidemia produced by lactic acid infusion nor those obtained during endogenous metabolic acidosis showed any consistent shift from control. The relation between stroke volume or mean ejection rate and left ventricular end-diastolic pressure was unaltered over a broad range of cardiac output. Furthermore, correction of the arterial blood pH by addition of buffered THAM had no discernible influence on the position of the curves obtained at that time.

The effects of repeated sequential changes in arterial blood pH on ventricular dynamics were also studied. When the pH was alternately varied from a mean of 7.38 (range, 7.34 to 7.42) to a mean of 7.01 (range,
6.97 to 7.05) in a typical control animal, at an LVEDP of 10 cm H\textsubscript{2}O there was little or no change of stroke volume or mean ejection rate; the left ventricular dP/dt was more variable, but not related in direction or magnitude to the change of arterial pH.

The data from all of the control animals are tabulated in summary form in Table 1. Reduction of the arterial pH from a mean of 7.34 to 7.08 caused no significant change in the mean values for stroke volume, mean ejection rate or dP/dt when the LVEDP was 10 cm H\textsubscript{2}O. Furthermore, correction of the acidemia by intravenous administration of THAM and return of the mean pH to 7.36 also resulted in no significant alteration of the mean values of these hemodynamic variables.

**EFFECTS OF METABOLIC ACIDEMIA ON LEFT VENTRICULAR PERFORMANCE AFTER BETA-RECEPTOR BLOCKADE**

The influence of metabolic acidemia on myocardial contractility after blockade of sympathoadrenal influences was assessed from 103 ventricular function curves obtained from 14 animals (Table 1). Original traces which illustrate the effects of various levels of hydrogen ion concentration in a cat given propranolol are shown in Figure 3. The mean aortic pressure was 75 mm Hg and the heart rate 200 beats/min. After infusion of lactic acid and reduction of the pH from 7.40 (left panel) to 7.15, the cardiac output and stroke volume were smaller when the LVEDP was greater. Furthermore, the dP/dt max fell from 2275 to 1988 mm Hg/sec. When the pH was further reduced to 7.00 (third panel) the LVEDP increased from 10 to 14 cm H\textsubscript{2}O with the same cardiac output and stroke volume, and the left ventricular dP/dt max fell to 1332 mm Hg/sec. Thus, a progressive reduction of arterial pH was associated with a progressive diminution of left ventricular contractility. Correction of the arterial pH to 7.37 (right panel) by buf-
METABOLIC ACIDOSIS AND VENTRICULAR FUNCTION

Effects of metabolic acidemia in an animal subjected to beta-receptor blockade with propranolol; symbols same as in Figure 2. Aortic pressure constant (75 mm Hg), heart rate, 300 beats/min. Left panel: pH, 7.40; CO, 340 ml; LVEDP, 8.5 cm H₂O and dP/dt, 2275 mm Hg/sec.

fered THAM given intravenously returned the level of performance to control values (right panel).

These findings are presented more completely by the ventricular function curves from the experiment shown in Figure 4. It is clear that during acidemia (pH 6.82) both stroke volume and mean ejection rate at any given LVEDP were very much less than when the pH was normal (7.38). With correction of the acidemia by THAM infusion (pH 7.40) ventricular performance improved to near initial control values.

The effects of sequential changes of pH on ventricular performance in a cat given propranolol are shown in Figure 5. In contrast with results in control animals, each reduction in the arterial pH was associated with a directionally similar change of stroke volume, mean ejection rate, and dP/dt when the LVEDP was 10 cm H₂O. The data from all of the animals with beta-receptor blockade, summarized in Table 1, show the same parallel between changes in pH and in the three variables; these changes were highly significant \(P < .001\). After correction of acidemia by THAM, the values did not differ significantly from the mean values before acidemia \(P < .001\).

EFFECTS OF REPEATED EXPOSURE TO ACIDEMIA

After beta-receptor blockade, some animals exposed to repeated episodes of acidemia became more sensitive to a given level of pH. In the experiment illustrated in Figure 6, for example, when the pH was reduced from 7.45 (run I) to 7.18 (run II) the LVEDP increased from 4.5 to 8.5 cm H₂O, and the dP/dt max fell from 1900 to

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Effects of sequential pH changes following beta-receptor blockade. SV\textsubscript{10} and MER\textsubscript{10} are stroke volume and mean ejection rate at an LVEDP of 10 cm H₂O; % = % of control values.

EFFECTS OF RAPID CHANGES OF ARTERIAL BLOOD pH

It was repeatedly observed during these studies that when lactic acid was infused too rapidly, with an attendant steep fall in pH, a transitory reduction of myocardial contractility occurred in the control animals, and a much more severe depression for a given level of pH developed in animals with beta-receptor blockade. In the experiment shown in Figure 7, 0.5N lactic acid was infused at the rate of 4 ml/min, in contrast with the standard rate of 1.23 ml/min. The arterial pH was reduced from 7.43 to 7.12 in less than 1 minute. This caused marked cardiac failure, indicated by the large reduction of cardiac output, rise of end-diastolic
Effects of rapid change of arterial pH on left ventricular function. Arterial pH reduced from 7.43 to 7.12 in less than 1 minute. Marked depression of cardiac function is indicated by an elevation of end-diastolic pressure in the presence of a sharply reduced cardiac output (CO) and fall of dP/dt max. Rapid chart speed, 100 mm/sec. Slow chart speed, 0.25 mm/sec. Approximately 10 seconds between panels.

Pressure and reduction of dP/dt max. At the end of the infusion, the pH rapidly rose to 7.34, presumably as a consequence of buffering and redistribution of hydrogen ions. This was accompanied by an equally rapid improvement in cardiac performance (Fig. 7, right panel). These findings may be compared with Figure 3 from a similar experiment, but one in which the acid was administered at the standard rate of 1.23 ml/min. It is evident that at a comparable pH the magnitude of cardiac depression was substantially less.

**Discussion**

The present investigations were initiated to provide further information concerning the many factors that may contribute to the maintenance of cardiac function during metabolic acidosis. It has been repeatedly demonstrated that increasing the hydrogen ion concentration of the circulating fluid reduces cardiac contractile strength in submammalian species (13-17), and in isolated mammalian heart-lung preparations (9, 18-22). More nearly intact mammalian preparations, on the other hand, have generally failed to show significant depression of cardiac function in the presence of severe metabolic acidemia (1-5, 7, 8, 23).

Earlier studies from this laboratory showed no consistent reduction of left ventricular contractility during metabolic acidemia in either the cat or the lamb (1-4). There is a major difference between these preparations and isolated hearts in that the sympathoadrenal system is present in the auto-supported heart preparations (2). Thus, although some of the principal cardiovascular autonomic reflex systems, including the peripheral chemoreceptor and baroreceptor systems, were functionally eliminated by interruption of most of the arterial blood supply to the higher portions of the central nervous system, there is no reason to assume that substantial adrenergic activity did not remain. The findings in the present study entirely support this presumption. With sympathoadrenal function intact, metabolic acidemia failed to diminish contractility. In the preparations deprived of sympathoadrenal activity by beta-
receptor blockade, the same level of acidemia produced severe cardiac depression.

Although animals with an intact sympathoadrenal system are highly resistant to acidemia, there does appear to be a threshold, in the dog at least, below which cardiac performance will be depressed. The available evidence suggests that for the dog this may be about 7.1 (7, 11), but for the cat, less than 6.8 (2). The lamb deprived of higher autonomic reflex activity by vascular ligation, but with sympathoadrenal function otherwise intact, manifests little alteration of cardiac function at pH values as low as 6.9 (3).

These apparently differing levels of sensitivity to acidemia are not readily explained. Adler et al. (24) found little change in intracellular pH of diaphragm muscle of rats when the extracellular pH was varied between 7.4 and 6.9. The possibility that the relation between extracellular and intracellular pH is different for cardiac tissue of various species has not been explored. Perhaps of greater importance, however, is the recent observation that myocardial norepinephrine concentration is substantially greater in the cat than in the dog (25). This may account in part for the apparently greater sensitivity of the dog to acidemia. On the other hand, the cardiac norepinephrine concentration in the newborn lamb is low (26), while its tolerance to hydrogen ion appears to be high (3). It is likely, then, that additional factors are operative.

When the arterial pH was reduced with sufficient rapidity a transitory reduction of cardiac contractility occurred in the control animals. Furthermore, in the animals subjected to beta-receptor blockade, contractility was severely depressed with moderate acidemia produced rapidly (Fig. 7). These observations may have a bearing on studies in which acid was introduced directly into the coronary arterial tree in a manner which may have produced a precipitous fall in pH of the blood perfusing the coronary vascular bed. For example, in the experiments reported by Wang and Katz (27) infusion of 5, 5-dimethyl-2, 4-oxazolidinedion which produced a fall of coronary sinus pH of only 0.08 (average) but was accomplished within only 40 to 50 seconds caused a substantial reduction of myocardial contractile force. These findings are also consistent with the report of Lorkovic, who showed that a very rapid reduction of pH will abolish the electrical and mechanical activity of frog ventricle (15).

It has been shown that circulating catecholamine levels are elevated during metabolic acidosis (28, 29). It is our impression from this and other studies in progress that small amounts of tissue or circulating catecholamine are sufficient to prevent significant depression of myocardial contractility during exposure to severe metabolic acidemia. This interpretation is consistent with the work of Smith and Corbascio (5) who have recently suggested the possibility that in situ production of cardiac catecholamine is adequate to maintain the contractility of myocardial tissue when exposed to an elevated hydrogen ion concentration. Thus, only minimal intramyocardial or circulating catecholamine levels may be sufficient to provide adequate adrenergic support to fully compensate for the intrinsic negative inotropic influence of metabolic acidosis (2).

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References

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