Mechanisms of Myocardial Depression After Bolus Injection of Sodium Bicarbonate

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Purpose: **The classic model for the effects of $NaHCO_3$ on myocardial function predicts transient myocardial depression after an intravenous bolus of sodium bicarbonate in association with myocardial acidosis.**

Methods: **Five anesthetized, paralyzed, and ventilated dogs underwent midline sternotomy. Myocardial global function was assessed by cardiac output, left ventricular (LV) dp/dt, LV end-systolic, and LV end-diastolic pressures. Regional myocardial function assessed by measuring the LV regional end-systolic, LV end-diastolic lengths, and LAD coronary blood flow. Coronary sinus, intramyocardial and arterial pH were measured as was free serum Ca^{++}. Animals were made acidemic by infusion of 0.3 N HCl and then given a bolus of sodium bicarbonate. This produced transient depression followed by recovery of myocardial function.**

Results: **During the depression phase there was no significant decrease in interstitial pH or an increase in A-Vco_2 difference as predicted by the current model. However, there was a significant decrease in the serum free Ca^{++} that coincided with myocardial depression.**

Conclusion: **We could not confirm the predictions of the classic model and hypothesize that myocardial depression may be caused by decreased availability of free Ca^{++} of decreased Ca^{++} flux rather than intracellular acidosis.**

METABOLIC ACIDOSIS is one of the most common clinical conditions encountered in critically ill patients. Sodium bicarbonate as an intravenous (IV) bolus or IV infusion is often used to correct severe metabolic acidosis. However, the sodium bicarbonate bolus leads to transient myocardial depression.[3,4,9,10,17,19,26,35,37,38] Several other adverse effects of sodium bicarbonate therapy have been reported,[19,26] including hyperosmolality,[17,37] hypernatremia,[17] hypercapnia with intracellular acidosis,[3,4,10,17,19,26,35,37,38] and a decrease in the availability of serum ionized calcium.[5,6,9,29]

McElroy et al[19] suggested that sodium bicarbonate administration causes a paradoxical drop in intracellular pH. Later, Clancy[4] enlarged on this hypothesis, suggesting that immediately after sodium bicarbonate administration molecular CO_2 readily diffuses from the plasma across the interstitium into cells, thus increasing intracellular $[H]^+$ concentration and reducing intracellular pH, thereby decreasing myocardial function. This hypothesis predicts a negative myocardial veno-arterial CO_2 and HCO_3^- difference, and a decrease in interstitial pH during the myocardial depression phase. In fact, in Clancy's studies on isolated hearts[4] negative veno-arterial CO_2 and HCO_3^- difference were measured after sodium bicarbonate infusion. However, transient intramyocardial tissue pH changes have so far not been measured after sodium bicarbonate administration.

Alternatively, an increase in extracellular pH causes a decrease in the availability of ionized calcium[5,6,9,29] by increasing Ca^{++} binding to proteins and other anions.[24] Decreased free Ca^{++} could also lead to decreased myocardial contractility by hindering excitation-contraction coupling.

We used an in vivo preparation to evaluate two hypotheses as possible mechanisms for transient myocardial depression after sodium bicarbonate bolus: (1) Transient myocardial depression coincides with decreased intramyocardial tissue pH and negative veno-arterial CO_2 and HCO_3^- difference; (2) Transient myocardial depression coincides with decreased free ionized serum calcium.

MATERIALS AND METHODS

All conditions for preoperative care, surgery, and euthanasia were consistent with National Institutes of Health guidelines and were approved by the institutional review Board for Animal Studies. Five mixed-breed dogs of either sex weighing 15 to 20 kg were fasted for 12 hours before the experimental studies. After premedication with aceproma-

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zine 0.1 mg/kg intramuscular (IM). and atropine 0.5 mg IM, anesthesia was induced using sodium pentobarbital 25 mg/kg administered IV. Additional doses of sodium pentobarbital 30 mg were administered every hour to maintain constant levels of anesthesia. To prevent respiratory motion animals were paralyzed with 0.6 mg/kg succinlycholine IV, and repeated 30 to 45 minutes to maintain paralysis throughout the experiment. At no time did we observe spontaneous respiratory motion using this protocol. After anesthesia, animals were intubated and mechanically ventilated (tidal volume 10 mL/kg; respiratory rate adjusted to maintain arterial P_{CO_2} at 35 to 45 mm Hg, 100% O_2).

A large-bore catheter was placed into a femoral vein for administration of fluids and medications, and a second catheter was placed into the femoral artery for monitoring arterial pressure (Part), counting heart rate (HR) and withdrawing blood samples for measurement of arterial pH, P_{CO_2}, P_{O_2}, HCO_3^-, and free Ca^{++}. A micromanometer-tipped catheter (Millar, Houston, TX) was placed retrograde into the left ventricle through a carotid artery for high fidelity recording of LV end-diastolic pressures (LVEDP); LV end-systolic pressures (LVESP), and the first derivative of left ventricular pressure (dp/dt) by electronic differentiation. End-diastole (ED) was defined from the dp/dt trace as the point where the rapid systolic upstroke began. End-systole (ES) was taken as the point 20 ms before the maximal negative deflection of dp/dt.[2]

A midline sternotomy was performed. The pericardium was widely incised and the heart suspended in a pericardial sling. Regional myocardial shortening was measured in the myocardium perfused by the left anterior descending (LAD) coronary artery using a pair of sono-micrometer crystals (Crystal Biotech, Hopkinton, MA). The crystals were placed into the midmyocardium along the orientation of the superficial fibers at a distance of 1 to 2 cm. We measured end-diastolic (ED) and end-systolic (ES) lengths (LVEDL and LVESL respectively) of the myocardial segment. For measurement of coronary blood flow (CBF), the LAD was dissected free distal to the first diagonal branch. A 1.5- or 2-mm "hard" doppler flow velocity probe (Crystal Biotech) was placed around the LAD. Probe size was chosen to snugly fit around the vessel. Because flow is proportional to velocity only if cross-sectional area is constant, this was necessary to minimize the chances of substantial changes in coronary cross-sectional area with changes in pressure. Previous studies by ourselves as well as others[11,30] have confirmed linearity of flow and doppler signal over the physiologic range in this preparation. The probe was left uncalibrated. Thus, measurements involving flow are normalized to baseline values. To measure regional interstitial myocardial pH (IPH) we used a commercially available system (Khuri tissue pH monitor; Vascular Technologies, North Chelmsford, MA).[15,16] This system uses Ag-AgCl probes, 1.5 mm in diameter, 8 mm in length and is referenced to a remote subcutaneous agar bridge electrode to minimize drift. In our laboratory, drift was found to be no more than 0.1 pH units over 6 hours and the 95% response time to step change was found to be 15 seconds. Probes were inserted into the myocardium perfused by LAD and into the left atrial lumen to simultaneously measure myocardial interstitial and arterial pH.

An electromagnetic flow probe, calibrated against simultaneous measurements by the Fick principle, was placed around the ascending aorta for measurement of Cardiac output (CO). Stroke volume (SV) was calculated as CO/HR. A large-bore catheter was placed in the coronary sinus and held in position by placing a purse-string suture around the right atrial wall. Blood samples were collected to measure coronary venous pH, P_{CO_2}, P_{O_2}, HCO_3^- and free Ca^{++}. The position of the catheter tip was assessed visually, and also by following coronary sinus blood P_{O_2}. Position was considered acceptable if coronary sinus P_{O_2} was 10 to 20 torr less than right atrial blood P_{O_2}. Myocardial oxygen consumption (V_{O_2}) was calculated from the product of arterio-venous content difference and CBF. Contents were obtained by using the oxyhemoglobin desaturation curve for dogs and the measured hemoglobin. CO_2 flux was obtained from the product of arterio-venous CO_2 content difference and CBF. CO_2 contents were obtained using the O_2-CO_2 diagram of Rahn and Fenn, correcting for oxyhemoglobin content.[39] The conditions Baseline, Acidosis, and Recovery represent steady state values, hence CO_2 flux is the same as CO_2 production. However, the depression phase is nonsteady state and the term "flux" is more appropriate. The same considerations apply to O_2 consumption. Free Ca^{++} was measured using Model 634 Ca^{++}/pH Stat Analyzer (Ciba-Corning, Norwood, MA). The ventricle was paced at a constant rate of 120 beats/min.

Experimental Protocol

After surgery animals were allowed to stabilize while breathing 100% O_2 for 15 to 20 minutes. Metabolic acidosis was then induced by infusion of 0.3 N HCl through the femoral vein. Arterial pH and myocardial IPH were constantly monitored. On attaining an arterial pH of lower than 7.0, the HCl infusion was slowed so as to maintain a steady state for 10 to 15 min. At this point the acid infusion was stopped. An IV bolus of $NaHCO_3$ (44.6 mEq) was rapidly administered through the femoral vein catheter. All data were collected at the baseline, during metabolic acidosis, during transient myocardial depression, and recovery phases. The myocardial depression phase was defined from the dp/dt tracing as the total period extending from the point of onset in decrease of the dp/dt tracing to the beginning of its recovery.

Data Collection

Data were digitized in 20 second epochs at a frequency of 200 Hz and downloaded onto a hard disk using a microcomputer and commercially available data acquisition software (DASA; Gould Instruments, Cleveland, OH). Variables were also continuously written onto an eight-channel polygraph recorder. Data could be displayed on the computer screen at a rate appropriate to the variable being measured.

Data Analysis

Data were compiled and expressed as mean ± SD. Baseline and metabolic acidosis measurements were analyzed by paired *t*-test analysis. One-way analysis of variance was used to test the significance of the data derived at metabolic acidosis, depression phase, and the recovery

phase. If significance was found, a posthoc test (Newman-Keuls test) was used to determine where significance was coming from. In one case a Wilcoxon matched pairs test was used to assess statistical significance. This is justified and described in Results.

RESULTS

Figure 1 shows an actual data tracing in an animal with metabolic acidosis. Immediately after sodium bicarbonate IV bolus there was a noticeable decrease in LV pressure, dp/dt, and shortening of the left ventricular fiber length as well as an increase in end-diastolic and systolic lengths. In this animal, this phase (depression) lasted approximately 60 seconds, from which it recovered fully to the baseline.

Table 1 shows the mean values for Part, CO, SV, dp/dt, LVESP, LVEDP, LV regional end-systolic length (LVESL), LV end-diastolic lengths (LVEDL), and coronary blood flow velocity (normalized to baseline) during metabolic acidosis, depression, and the recovery phases of the myocardium after an IV bolus of bicarbonate. There was a significant decrease in the function of the myocardium from the baseline to metabolic acidosis as noted by decrease in Part, LVESP, and LV dp/dt. However, there was further depression of myocardial function

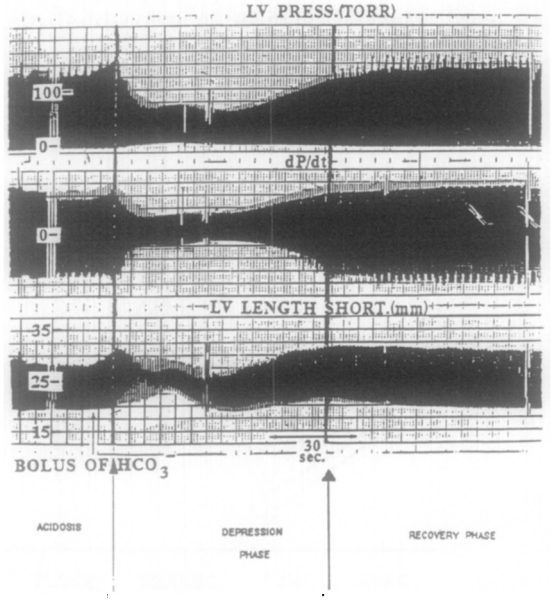

Fig 1. Illustration of simultaneous recording of left ventricular pressure (LV PRESS), dp/dt and left ventricular fiber length shortening (LV LENGTH SHORT) during metabolic acidosis, immediately after the infusion of $NaHCO_3$ (depression phase) and recovery.

after IV bolus of sodium bicarbonate as noted by further decreases in LV dp/dt and increased LVESL and LVEDL. In the case of LVESL and LVEDL, all animals showed an increase from acidosis to depression phases. However, the scatter was large (see SD's) and the change was not significant on paired *t*-test. This is because the assumption of normal distribution did not hold in this case. Therefore, the data were reanalyzed using a nonparametric test (Wilcoxon matched pairs test) to show that there was a significant increasing trend in LVESL and LVEDL from metabolic acidosis to the depression phase.

Simultaneous measurements of arterial, coronary sinus, and the interstitial pH showed a significant increase in arterial and coronary sinus pH, but no change in interstitial pH (Fig 2) after IV bolus of bicarbonate. In particularly, there was no trend towards a decrease in interstitial pH after bicarbonate administration. Arterial and coronary sinus HCO_3^- and PCO_2 are shown in the Figs 3 and 4. In the figures the vertical distance between arterial and venous values represents the veno-arterial difference. At no time did we observe reversal of this gradient. As shown in Table 1, compared with baseline CO_2 flux increased, whereas VO_2 decreased (ns) with acidosis. Postbicarbonate depression was associated with a further decrease in VO_2 and a nonsignificant decrease in CO_2 flux. The increase in CO_2 flux (production) with metabolic acidosis corresponds to a rise in coronary sinus PCO_2 (Fig 4).

There was a significant drop in the free serum Ca^{++} immediately after the sodium bicarbonate administration that coincided with the myocardial depression and a return to normal levels during the recovery (Fig 5).

DISCUSSION

In this report we investigated the mechanisms of transient myocardial depressant effect of sodium bicarbonate when administered as an IV bolus to correct the metabolic acidosis in five anesthetized dogs. The main findings of this study are: (1) It confirms the transient depressant effect of bicarbonate on myocardial function.[3-7,9,10,17,19,26,29,34,35,37,38] (2) We failed to observe several important predictions of the classic model[4] namely, negative veno-arterial differ-

Table 1. Cardiohemodynamic Variables

Variables	Baseline	Met Acid	Depress	Recov
Part: Torr	103.2 ± 30.98	76.4 ± 23.66*	49.0 ± 21.46‡	77.4 ± 30.05
CO.: L/min	1.48 ± 1.07	0.99 ± 0.36	0.47 ± 0.44	0.86 ± 0.82
SV.: mL/min	12.35 ± 8.89	8.23 ± 3.01	3.92 ± 3.66	7.17 ± 6.79
LVESP Torr	83.20 ± 24.22	57.38 ± 17.24†	42.30 ± 15.59	68.76 ± 33.50
LVEDP Torr	11.56 ± 4.28	11.26 ± 2.44	14.32 ± 4.47	11.56 ± 5.3
LV dp/dt	1.00	0.67 ± 0.14†	0.34 ± 0.17§	0.90 ± 0.32¶
LVESL, mm	11.62 ± 1.6	11.85 ± 1.57	13.10 ± 2.24‖	11.55 ± 1.55
LVEDL, mm	12.52 ± 2.03	12.83 ± 2.18	13.63 ± 2.46‖	12.74 ± 1.87
CBF	1.00	0.94 ± 0.30	1.12 ± 0.67	1.05 ± 0.40
Vo_2	1.00	0.57 ± 0.28	0.24 ± 0.18¶	0.81 ± 0.58
Co_2 FLUX	1.00	3.55 ± 2.03*	1.17 ± 1.02	3.14 ± 3.12
Hco_3 FLUX	1.00	0.88 ± 0.21	2.64 ± 1.92	1.23 ± 0.65

Abbreviations: Part, mean arterial pressure; CO, cardiac output; SV, stroke volume; LVESP, left ventricular end-systolic pressure; LVEDP, left ventricular end-diastolic pressure; LV dp/dt, first derivative of left ventricular pressure (normalized to baseline value); LVESL, left ventricular end-systolic length; LVEDL, left ventricular end-diastolic length; CBF, coronary blood flow (normalized to baseline value); Vo_2, oxygen consumption (normalized to baseline value); Co_2, flux (normalized to baseline value); Hco_3, flux (normalized to baseline value); MET ACID, metabolic acidosis; DEPRESS, depression phase; RECOV, recovery phase.

*$P < .05$ *v* baseline (*t*-test).

†$P < .01$ *v* baseline (*t*-test).

‡$P < .02$ *v* MET ACID (ANOVA).

§$P < .002$ *v* MET ACID (ANOVA).

‖$P < .05$ *v* MET ACID (WilcoXon matched pair test).

¶$P < .01$ *v* baseline (ANOVA).

ence and reduced flux of serum bicarbonate (Fig 3) and P_{CO_2} (Fig 4). Thus, we failed to find evidence that CO_2 moves across the interstitium from the plasma into the cell. (3) We failed to find any decrease in the interstitial pH during the myocardial depression phase. (4) The transient depression in myocardial function after an IV bolus of sodium bicarbonate coincided with the transient decrease in the availability of the serum free calcium.[6,7]

Experimental Technique

In this study we used the Khuri pH probe to measure transient changes in myocardial pH.

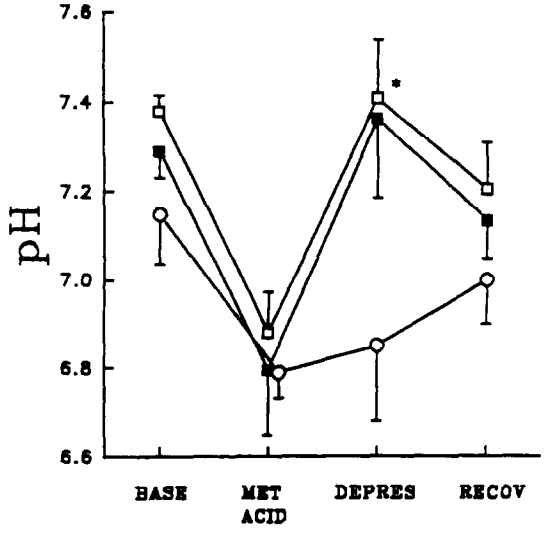

Fig 2. Changes in pH at metabolic acidosis (MET ACID), depression phase (DEPRES), and on recovery phase (RECOV) in arterial (—□—), coronary sinus (—■—) blood, and myocardial interstitium (—○—). All values are mean ± SD. Statistical significance assessed using ANOVA.

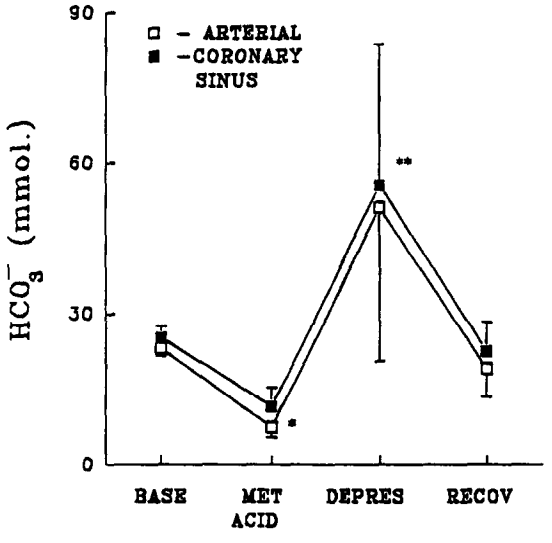

Fig 3. Changes in bicarbonate in arterial and coronary sinus blood at metabolic acidosis (MET ACID), depression phase (DEPRES), and recovery phase (RECOV). All values are mean ± SD. Statistical significance assessed using ANOVA.

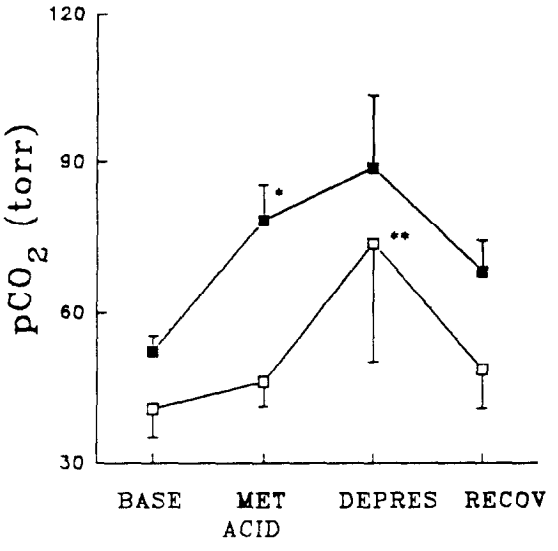

Fig 4. Changes in P_{CO_2} in arterial (—□—) and coronary sinus (—■—) blood at metabolic acidosis (MET ACID), depression phase (DEPRES), and recovery phase (RECOV). All values are mean ± SD. Statistical significance assessed using ANOVA.

Because the pH probe readings are influenced by both interstitial and intracellular pH, transients may not completely reflect the changes in one or the other compartment. However, the probe was fast enough to record the pH changes in arterial blood (Fig 2). Thus, the lack of a decrease in myocardial pH cannot be said to be because of changes being too rapid for the probe to record.

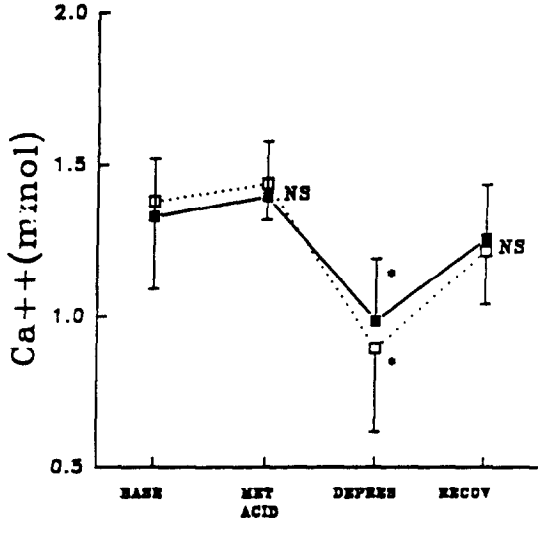

Fig 5. Changes in free ionized calcium (Ca^{++}) level in mmols. in arterial (—□—) and coronary sinus (—■—) plasma at metabolic acidosis (MET ACID), depression phase (DEPRES) and recovery phase (RECOV). All values are mean ± SD. Statistical significance assessed using ANOVA.

Effect of Metabolic Acidosis

Decreasing arterial pH by infusion of HCl led to a significant depression in myocardial function as shown by decreased dp/dt and decreased LVESP with no change in LVESL (Table 1). Mechanisms for this include, decreased ATPase activity,[14,21,22] altered calcium flux across the sarcoplasmic reticulum,[20] and sarcolemmal,[25] decrease in calcium release from sarcoplasmic reticulum,[8] decrease in calcium sensitivity of myofibrils,[32] decrease in calcium binding to troponin,[13,22] and possible competitive inhibition of Ca^{++} on its binding sites by H^+.[33] There was no significant increase in serum free Ca^{++} noted with acidosis. Because acidosis was slowly induced there was most likely time for shift of calcium into other compartments, either an influx of calcium into cells[23] or a shift into nonmeasured stores.

Figure 3 shows an increase in steady-state coronary venous P_{CO_2} from baseline to acidosis. Because coronary flow did not change (Table 1), this suggests an increase in myocardial CO_2 production with acidosis that was confirmed (Table 1). The table also shows that oxygen consumption decreased; however, the change did not reach statistical significance. There was, on the other hand, an increase in oxygen consumption (V_{O_2}) on recovery compared with steady-state acidosis. The trend toward decreasing oxygen consumption could be related to decrease in LV work because of the decrease in arterial pressure, contractility, and/or a basic metabolic effect of acidosis either in substrate use or O_2 availability. The increase in CO_2 production suggests a change in substrate use and/or switch to anaerobic metabolism. We did not measure lactate levels to address this issue here. Suleymanlar et al[36] showed that with metabolic acidosis there was no decrease in glycolysis in the face of decreased myocardial function, suggesting that the metabolic defect of acidosis was on other parts of the respiratory chain beyond glycolysis. Hata et al[12] showed increased oxygen cost of contractility during acidosis and suggested a role for Na^+-H^+ exchange in this phenomenon.

Transient Myocardial Depression

Present concepts of the mechanisms for myocardial depression after bicarbonate administration suggest a paradoxical decrease in intracellular pH[3,4,9,10,17,19,26,35,37,38]; this is supposedly caused by rapid diffusion of CO_2 into cells from plasma. It is true that in this study we did not measure intracellular pH; however, according to the Clancy model[4] changes in intracellular pH are first seen in interstitial pH. Accordingly, one would have expected a decrease in interstitial pH before any change in intracellular pH is noted. Also, acidosis should be more pronounced in the interstitium than in the cell because extracellular fluid has less buffering capacity than the intracellular medium.[5] We did not observe any decrease in interstitial pH as predicted (Fig 2). This suggests that either CO_2 does not diffuse rapidly from intravascular to interstitial compartments or that HCO_3^- diffuses as rapidly as CO_2.

Our observations are consistent with previous studies showing that transiently increasing serum pH or extracellular alkalosis causes intracellular alkalization regardless of compensatory changes in P_{CO_2} or external HCO_3^-.[1] Sessler et al[31] have shown that a prolonged rise in arterial P_{CO_2} after sodium bicarbonate administration failed to produce a paradoxical intracellular acidosis. Similarly, Rhee et al[28] noted no paradoxical intracellular acidosis with sodium bicarbonate infusion.

We found that the transient decrease in myocardial function coincided with the transient decrease in the availability of serum free Ca^{++}. Myocardial contractility depends on the level of plasma ionized calcium.[18] As suggested by Cooper et al[6,7] this is a possible cause for myocardial depression. Sodium bicarbonate is known to decrease the availability of ionized calcium by increasing its binding to serum proteins and other anions in vivo[24] as well as decreasing the membrane calcium and calcium flux.[27] After the depression phase, with the decreasing extracellular pH, the return of membrane calcium and the calcium flux to its normal levels is essential for the recovery of the cell's functions.[27]

Clinical Implications

This study has a number of clinical implications. First, steady state severe acidosis should be corrected. Second, if bolus injection of bicarbonate is to be used as in cardiopulmonary resuscitation, temporary myocardial stunning could result. This could lead to harmful effects on peripheral circulatory function and cardiac output in the immediate postinjection period. Thus, consideration should be given to slow correction. Third, this study emphasizes the association between acid-base balance and free serum calcium. It might be expected that with hypocalcemia the acute effects of administration of sodium bicarbonate would be more deleterious than with normal or increased calcium levels. The presence of calcium channel blockers could also exacerbate this effect.

To summarize, our study failed to confirm prediction of transient decrease in myocardial pH after bicarbonate bolus. This suggests that another factor is responsible for transient myocardial depression. Given the timing of changes in free ionized calcium, this would seem to be a good candidate. The importance of calcium homeostasis after correction of acidosis should be explored in the future.

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