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Local Vascular Effects of Alkalosis in the Dog Gracilis Muscle (38041)

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Cardiovascular effects of plasma pH abnormalities have been of interest to both the basic scientist and clinician for decades (1). For example, it is well established that plasma and interstitial pH changes during many conditions such as exercise and ischemia, but the involvement of the H^+ in local blood flow regulation is still uncertain (1). Additionally, many pathological states are associated with some degree of acidosis or alkalosis. While the degree of involvement of the H^+ in local blood flow regulation is debatable (1), the literature is replete with studies which clearly establish the H^+ as a vasodilator in most vascular beds (1, 2). However, the effect of locally decreasing the $[H^+]$ is less well defined, and results are conflicting (1). The discrepancies might be related to the method of alkali administration (mainly IA injection), and the choice of alkali used to induce the change. For example, during $NaHCO_3$ administration, extracellular pH will increase but intracellular pH may not change or may fall, at least initially (3). On the other hand, infusion of NaOH increases both intra- and extra-cellular pH from the onset of infusion (1). There is particularly a paucity of data concerning the effects of alkalosis on skeletal muscle vasculature.

A recent report from our laboratory described the effect of locally increasing the plasma $[H^+]$ on gracilis muscle vascular resistance (2). The current study was undertaken to delineate the vascular effects of locally increasing plasma pH in the gracilis muscle vascular bed, utilizing several different alkali for comparison.

Materials and Methods. Experiments were completed in 47 mongrel dogs of either sex anesthetized with sodium pentobarbital (30 mg/Kg) and anticoagulated with heparin sodium (3 mg/kg). The innervated right gracilis muscle was isolated from the body by appropriately placed ligatures and by cauterization. A Sigma-motor pump was interposed between the right femoral and gracilis arteries for constant flow perfusion of the muscle. Venous blood was returned to the animal through the uninterrupted gracilis vein. All branches of the gracilis artery and vein were ligated except for one side branch of the vein which was cannulated for withdrawing blood samples. Completeness of vascular isolation was confirmed by stopping the perfusion pump and observing the perfusion pressure tracing. Blood pH was determined with a Beckman expanded scale or Astrup pH meter. Femoral artery and gracilis artery (perfusion) pressures were recorded by means of Statham pressure transducers and a Sanborn direct-writing recorder. Since muscle flow was held constant, changes in perfusion pressure were directly proportional to changes in muscle vascular resistance. All dogs were ventilated with a Harvard positive pressure respirator.

Group I. Isotonic solutions (osmolarity confirmed with an Advanced Osmometer) of sodium hydroxide, sodium carbonate, or sodium bicarbonate, were infused separately and randomly upstream to the blood pump with an infusion pump at sequentially faster rates (0.1–2.0 ml/min) in 26 muscles. In some muscles, all of the alkalis were infused, whereas in others, only 1 or 2 were tested (see *N* values on figure below). Infusion at each rate as maintained until perfusion pressure became steady, usually 5–10 min. An isotonic solution of saline was

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infused at the same rate to evaluate the dilutional effect of the test solution.

Group II. In order to raise pH with sodium bicarbonate to levels comparable to the high pH values achieved with the other bases, a second series of 10 dogs was completed in which sodium bicarbonate solution was infused from 0.2–8.0 ml/min. At these infusion rates, systemic pH of the dog was not appreciably altered.

Group III. Sodium bicarbonate was infused at a rapid rate (8 ml/min) which increased pH to approximately 8 units in 11 gracilis muscles. The infusion period was extended to 30 min because the slow diffusion of the bicarbonate ion across the cell membrane may result in temporally related, differential changes in extracellular and intracelluar pH (3, 4).

Statistical comparisons were made using the Student's *t* test for comparison of the means and Student's *t* test modified for within group comparisons. *P* values below 0.05 were considered significant.

Results. Figure 1 shows averaged data from group I. Locally increasing blood pH over the range of 7.46–7.62, 7.46–7.60, and 7.48–7.67 with NaOH, Na_2CO_3, and $NaHCO_3$, respectively, had no effect on average perfusion pressure with respect to equivolume infusions of saline. The fall in perfusion pressure at the higher rates with $NaHCO_3$ was significant when compared to its own control but was of only borderline significance with respect to saline. However, in the case of NaOH or Na_2CO_3, increasing the pH further to a high value caused a striking increase in perfusion pressure, which returned to near control level when the infusion was stopped. These muscles did not appear edematous, and in subsequent experiments, a comparison of the weight of

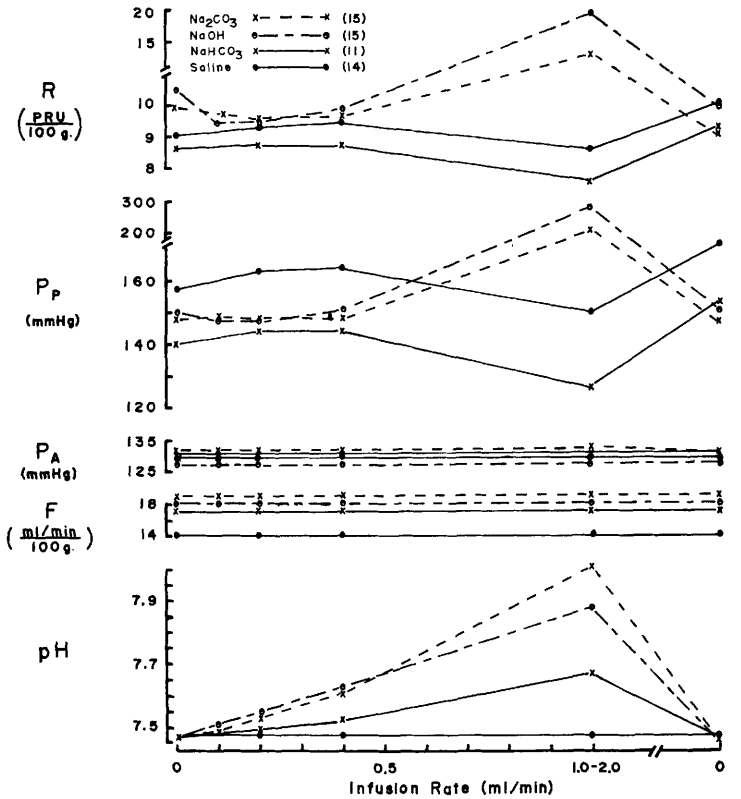

FIG. 1. Average effects of various bases on gracilis muscle vascular resistance (R), perfusion pressure (P_P), dog arterial blood pressure (P_A), muscle flow (F = constant), and gracilis venous pH. Number of experiments are indicated within the parenthesis.

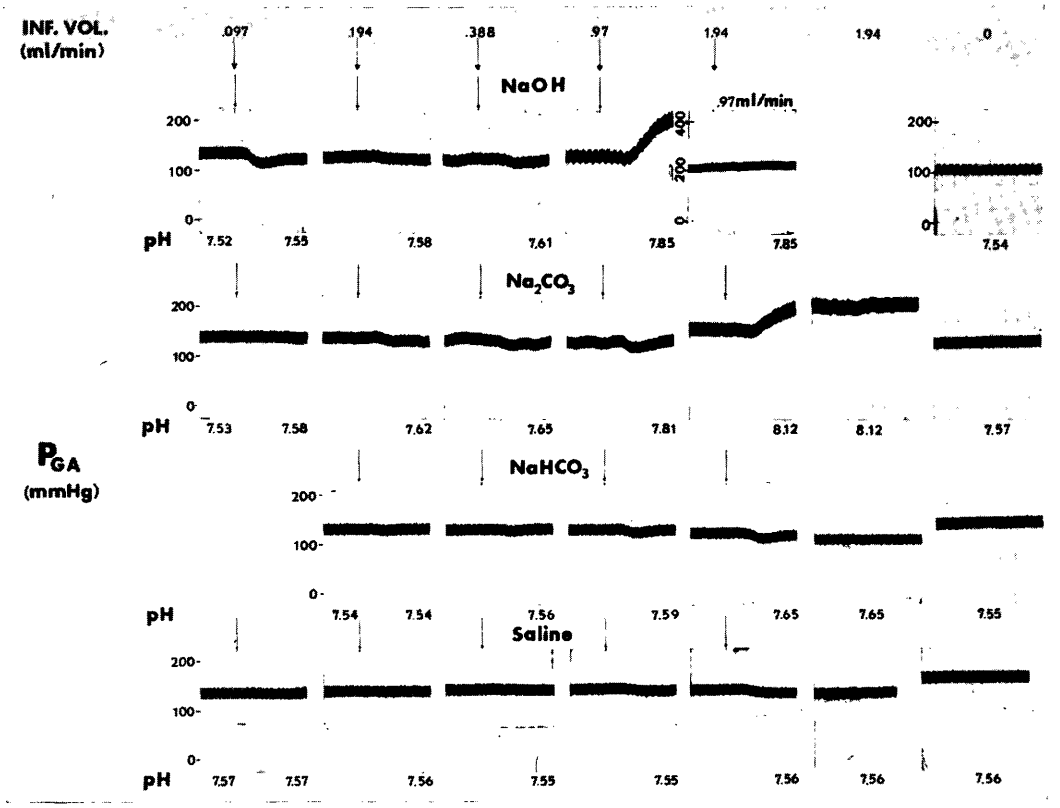

FIG. 2. Representative tracings showing the effects of intra-arterial infusion of various bases on gracilis artery perfusion pressure (P_{GA}) and gracilis venous pH in one constant flow perfused gracilis muscle. *INF. VOL.* = infusion volume of solution.

experimental and contralateral control muscles provided no evidence of significant edema in the perfused muscle. This graph also shows that aortic blood pressures and gracilis muscle flows were unchanged throughout the procedure.

Typical tracings from one experiment of gracilis artery perfusion pressure during infusion of alkali solutions and normal saline are shown in Fig. 2. Note in the upper two tracings that initiating alkali infusion or increasing the rate as frequently accompanied by a transient decrease in perfusion pressure which returned to near control within a minute or two. Note also that raising blood pH to near 8 units was associated with a rapid increase in perfusion pressure. The third tracing from the top illustrates that increasing pH to 7.65 with $NaHCO_3$ infusion caused no change in perfusion pressure except what can be attributed to blood dilution by the carrier solution, as seen in the bottom tracing during isotonic saline infusion.

Figure 3 shows that the resistance increase at a high pH still occurs in the absence of red cells during rapid rates of NaOH infusion. Changes in perfusion pressure were similar in the blood and dextran perfused muscle when pH was raised to a high level.

Figure 4 shows that raising venous blood pH to an average of 8.01 units with a high rate of $NaHCO_3$ infusion did not alter perfusion pressure compared to an equivolume infusion of saline.

Figure 5 is a tracing representative of 11 experiments in which pH as maintained at a high level for 30 min by intra-arterial infusion of $NaHCO_3$ at 8 ml/min (average pH increase was to 7.75 units). Note that perfusion pressure dropped abruptly soon

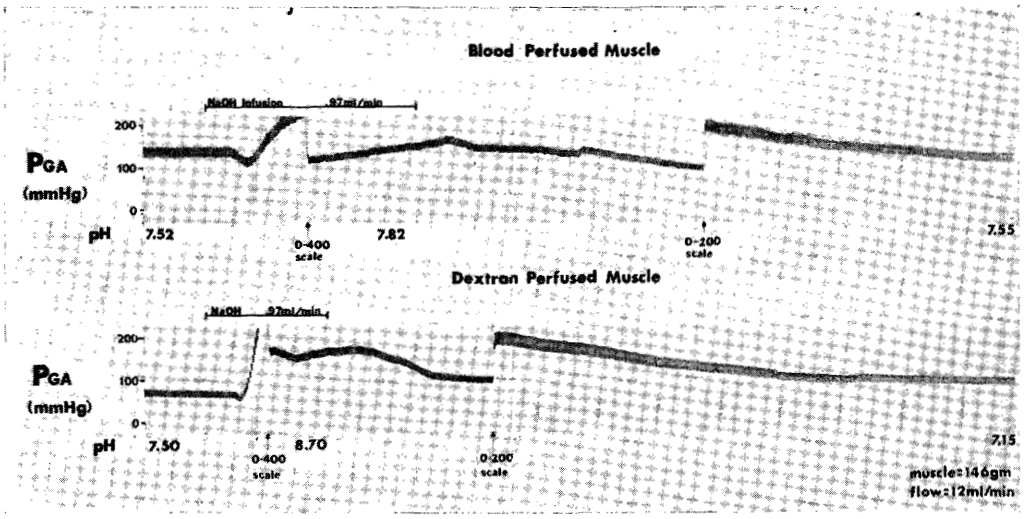

FIG. 3. Representative tracings showing the effects of intra-arterial infusion of NaOH on gracilis artery perfusion pressure (P_{GA}) and gracilis venous pH in one blood and dextran perfused muscle.

after starting $NaHCO_3$ infusion, rose to near control level transiently, and again decreased and remained low until the infusion was stopped. Perfusion pressure fell to approximately the same level during the steady-state as with an equivolume infusion of isotonic saline, which did not change pH.

Discussion. Our data clearly emphasize two points (1) increasing pH stepwise from a normal value to near 7.60 by alkali infusion causes no change in skeletal muscle vascular resistance and (2) the resistance response to raising pH above approximately 7.60 depends upon the alkali employed. Thus, a striking increase in resistance always occurs when pH is elevated to a high level by NaOH or Na_2CO_3 infusion but not when pH is raised to comparable levels in the same muscles by $NaHCO_3$ infusion. It was thought that the slow diffusion of HCO_3^- and the rapid diffusion of CO_2 across the cell membrane during $NaHCO_3$ infusion (3, 4), which would tend to increase extracellular pH and decrease intracellular pH,

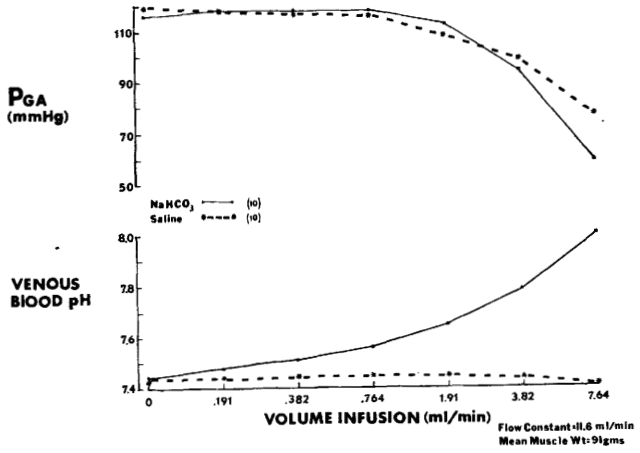

FIG. 4. Average effects of intra-arterial $NaHCO_3$ infusion on gracilis artery perfusion pressure (P_{GA}) and gracilis venous pH in constant flow perfused gracilis muscles. Number of experiments are indicated within the parenthesis.

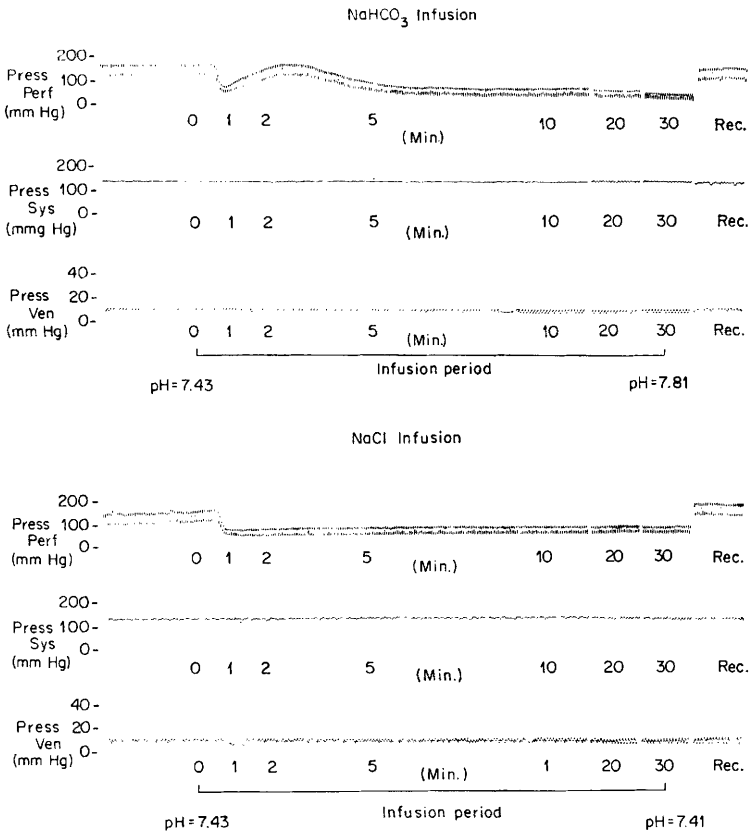

FIG. 5. Representative tracing showing the effects of a 30 min intra-arterial $NaHCO_3$ infusion on gracilis artery perfusion pressure (Press. Perf.), dog arterial blood pressure (Press. sys.), and gracilis venous pressure (Press. Ven.) in constant flow perfused muscle.

might account for the failure of $NaHCO_3$ to affect resistance. However, this is apparently not a critical factor since the response was unaltered when plasma pH was maintained near 8 units for 30 min by $NaHCO_3$ infusion. Perhaps a change in intracellular viscoplastic resistance is involved in this situation (5).

Our data which showed no increase in resistance until pH reached or exceeded 7.6 units agrees with findings of the only other study in which a steady-state infusion of a strong base was achieved. Scott and Haddy (6) found that locally increasing blood pH in the dog forelimb by intra-arterial infusion of isotonic NaOH did not alter limb vascular resistance until pH reached an average value of 7.66, at which point resistance rose markedly.

Local alkalosis in other beds produced by alkali administration reportedly has variable effects (1, 7–11). This apparent variability may be due to different methods of administration (mainly bolus injection), unknown or uncontrolled levels of alkalosis, osmolarity difference of the injectate, etc. Also, as shown in our study, the type of alkali used for making the pH change appears to be a factor which must be considered.

In one study involving pure skeletal muscle, arterial blood pH in the dog hindlimb muscle bed was increased over a wide range by intra-arterial, bolus injections of buffered NaOH solutions of varying pH's (7). Any increase in pH above normal resulted in an increase in flow and fall in resistance. However, in this study the alkali was always injected as a bolus, resulting in transients in concentration and a steady-state

was never achieved. Although it is very difficult to meaningfully compare the two studies and it is recognized that other explanations may be proper, the transient fall in resistance seen in the Deal and Green study (7) following bolus injection of NaOH solution may be analogous to the transient decrease in vascular resistance frequently observed in the present study upon starting alkali infusion or upon increasing the infusion rate.

Summary. Experiments were completed in isolated, constant flow perfused, dog gracilis muscles to determine effects of local intra-arterial (IA) infusion of several alkalis on muscle vascular resistance. Stepwise increases in pH from approximately 7.44–7.60 with NaOH, Na_2CO_3, or $NaHCO_3$ did not alter resistance. Extreme increases in pH were associated with marked increases in vascular resistance, excepting $NaHCO_3$ which caused no change in resistance.

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