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Tissue Hydrogen Ion Concentration in Ischemic Muscle: Effects of Gradual and Acute Arterial Occlusion, with and without Acute Venous Hypertension[1]

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Accurate assessment of extremity ischemia is often a prerequisite to the successful completion of complex arterial reconstructions. Muscle surface pH, reflecting the status of local tissue metabolism, offers a means for continuously monitoring limb perfusion. The present investigation was designed to evaluate muscle surface pH measurements in ischemic canine hindlimbs. These measurements, subjected to careful statistical analysis, were related to extremity blood flow, perfusion pressure, effluent blood pH, and arteriovenous oxygen differences.

MATERIALS AND METHODS

Twenty-five adult mongrel dogs weighing 23.5 to 31.0 kg were anesthetized with intravenous pentobarbital (30 mg/kg) and mechanically ventilated. The infrarenal aorta and vena cava were exposed through a midline abdominal incision and encircled with adjustable vascular clamps. All animals were anticoagulated with intravenous sodium heparin (100 units/kg). Hydration was maintained by administration of lactated Ringer's solution (100 ml/hr). Polyethylene catheters for pressure measurements and blood samples were placed in the thoracic aorta as well as the iliac artery and vein. Catheters were connected to Statham pressure transducers and a Sanborn recorder. Carolina Instruments square wave electromagnetic flow probes, placed about the iliac artery, were connected to a flowmeter and recorder. An Orion glass pH probe was carefully inserted in the hindlimb, on the sartorius muscle surface, and attached to an expanded-scale pH meter. Probes were calibrated before and after use with appropriate adjustments made for body temperature. Baseline measurements were obtained following 30-min stabilization periods. All muscle surface pH values, pH_m, were converted to hydrogen ion concentration, $[H+]_m$. Conversion of muscle surface pH and blood pH, representing exponential expressions of [H+], to hydrogen ions in nanomoles per liter was mandatory before valid statistical comparisons could be made. Results were analyzed by Student's *t* test (*between* Groups I and II), paired *t* test (*within* Groups I and II), or regression analysis (Group III).

Group I

Ten dogs underwent 60-min complete infrarenal aortic occlusion. Ischemic limb venous blood and systemic arterial blood pO_2, pCO_2, and pH were measured under control conditions and at 30-min intervals postocclusion. Blood flow, blood pressure, and pH_m were documented at 10-min intervals. Following aortic declamping, all variables were recorded for an additional 30 min. Blood gases were analyzed 2 min after unclamping.

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Group II

Five animals were subjected to distal inferior vena cava occlusion. Peripheral venous pressures subsequently increased to 20–23 mm Hg. Iliac artery flow, venous and arterial pressures, and pH_m were recorded for 30 min, at which time aortic occlusion for 60 min was effected. Upon aortic clamping, with maintenance of cava occlusion, the protocol outlined in Group I was followed.

Group III

Ten dogs were studied under control conditions with a mean arterial blood pressure of 112 ± 16 mm Hg. Mean perfusion pressures were then lowered sequentially to (a) 100, (b) 70, and (c) 20 to 60 mm Hg upon complete aortic occlusion. Arterial and venous blood pO_2, pCO_2, and pH were measured after 20-min stabilization periods at each pressure. Iliac artery blood flows and pH_m were compared to venous blood gas and pH changes at differing perfusion pressures.

RESULTS

Group I: Aortic Occlusion (Table 1)

The mean control $[H^+]_m$ was 58.9 ± 24.9 nmol/liter, corresponding to a pH_m of 7.23. Sixty-minute aortic occlusion increased $[H^+]_m$ to 91.5 ± 45.6 nmol/liter, representing a pH_m of 7.04. These values were significantly different, $p < 0.01$. Iliac artery flow decreased from 194 ± 79 to 28 ± 19 ml/min with occlusion of the aorta. Ten minutes following declamping, $[H^+]_m$ decreased (65.2 ± 30.0 nmol/liter, pH_m 7.19) toward preexistant levels. All data is presented as mean ± 1 SD.

Control limb venous pO_2 was 43.0 ± 8.3 mm Hg. The venous pO_2 fell significantly to 26.2 ± 4.9 and 28.9 ± 4.5 mm Hg during early and late aortic occlusion, $p < 0.001$ and $p < 0.01$, respectively. After declamping, venous pO_2 increased to 42.1 ± 4.7 mm Hg. The limb venous pCO_2 of 31.8 ± 10.0 mm Hg in controls rose to 34.8 ± 10.4 and 33.2 ± 10.5 during occlusion. These changes, although minimal, proved statistically different, $p < 0.01$. Upon unclamping the aorta venous pCO_2 showed little alteration, 33.0 ± 9.2 mm Hg. The ischemic limb venous blood pH, converted to $[H^+]$, reflected increasing acidosis with arterial occlusion. The control values of 32.1 ± 8.2 nmol/liter rose slightly but significantly to 34.3 ± 7.4 and 33.9 ± 7.5 nmol/liter during the early and late occlusion period, $p < 0.05$ and $p < 0.02$, respectively. Following aortic declamping, the venous $[H^+]$ increased to 35.3 ± 7.8 nmol/liter, a higher level than control values, $p < 0.01$.

Group II: Cava and Aortic Occlusion (Table 2)

The mean control $[H^+]_m$ was 56.6 ± 10.0 nmol/liter, corresponding to a pH_m 7.25. Vena cava occlusion for 30 min did not significantly alter $[H^+]_m$ (61.0 ± 10.0 nmol/liter, pH_m7.21). Vena cava clamping did decrease iliac artery blood flow markedly from 232 ± 110 to 60 ± 23 ml/min, $p < 0.02$. Sixty-minute aortic occlusion, with concomitant cava occlusion, increased $[H^+]_m$ (81.4 ± 13.3 nmol/liter, pH_m7.09). This proved significantly different than the control $[H^+]_m$, $p < 0.001$. Aortic occlusion decreased flow further to 30 ± 11 ml/min. Upon aortic declamping, $[H^+]_m$ returned toward normal (58.0 ± 12.3 nmol/liter, pH_m 7.24).

Ischemic limb venous pO_2 decreased to 26.0 ± 7.0 mm Hg 30 min following cava occlusion. During early and late aortic occlusion, venous pO_2 fell further to 19.6 ± 6.7 and 20.6 ± 6.3 mm Hg. These values were significantly different from those preceding aortic occlusion, $p < 0.01$ and $p < 0.05$, respectively. Release of the aortic clamp resulted in venous pO_2rising to 30.2 ± 8.1 mm Hg. Ischemic limb venous pCO_2, after cava occlusion and before aortic clamping of 33.0 ± 5.1 mm Hg, rose to 40.0 ± 6.8 and 40.4 ± 5.3 mm Hg during early and late aortic occlusion. These changes were significantly

TABLE 1

GROUP I—AORTIC OCCLUSION: MUSCLE SURFACE HYDROGEN ION CONCENTRATIONS (IN NANOMOLES PER LITER)

Animal	Control	During aortic occlusion	After aortic declamping
1	39.8	57.7	38.0
2	93.3	182.0	95.5
3	44.7	61.7	35.5
4	41.7	56.2	44.7
5	24.6	50.1	36.3
6	67.6	114.8	100.0
7	39.8	57.5	43.7
8	58.9	81.3	61.7
9	83.2	102.3	87.1
10	95.5	151.4	109.6
Mean ± 1 SD	58.9 ± 24.9	91.5 ± 45.6*	65.2 ± 30.0**

* Statistically significant $[H^+]_m$ increase in comparison to control ($p < 0.01$).
** No difference in comparison to control.

different, $p < 0.02$, $p < 0.01$, respectively. After aortic declamping, pCO_2 remained elevated in comparison to controls, 41.8 ± 7.0 mm Hg, $p < 0.02$. The ischemic limb venous blood $[H^+]$ of 31.8 ± 2.0 nmol/liter increased significantly to 35.4 ± 3.1 and 36.2 ± 2.6 nmol/liter during early and late aortic occlusion, $p < 0.05$ and $p < 0.02$, respectively. Upon aortic declamping, venous blood $[H^+]$ increased to levels significantly greater than preocclusion values (39.8 ± 3.6 nmol/liter, $p < 0.02$).

Comparison of Group I and II Data

$[H^+]_m$ before, during, and after aortic occlusion were similar in both groups. Rates of the $[H^+]_m$ return toward normal following aortic declamping were also comparable. Vena cava occlusion decreased femoral artery flow markedly but did not affect $[H^+]_m$. Nevertheless, ischemic limb venous blood pO_2 in Group II was significantly lower than Group I at every interval studied (Table 3). Although Group II venous effluent pCO_2 rose slightly

TABLE 2

GROUP II—CAVA AND AORTIC OCCLUSION: MUSCLE SURFACE HYDROGEN ION CONCENTRATIONS (IN NANOMOLES PER LITER)

Animal	Control	Cava occlusion	Aortic + cava occlusion	After aortic declamping
1	43.7	45.7	61.6	38.0
2	52.5	69.9	83.2	64.6
3	70.8	70.8	97.7	69.2
4	60.3	60.3	87.1	55.0
5	55.0	58.9	77.6	63.1
Mean ± 1 SD	56.5 ± 10.0	61.0 ± 10.0*	81.4 ± 13.3**	58.0 ± 12.3*

* No difference in comparison to control.
** Statistically significant $[H^+]_m$ increase in comparison to control ($p < 0.001$).

TABLE 3

ISCHEMIC LIMB VENOUS pO_2 (IN MILLIMETERS OF MERCURY) WITH AORTIC OCCLUSION

	Group I	Group II (following cava occlusion)
Before aortic occlusion	43.0 ± 8.3[a]	26.0 ± 7.0*
30 Minutes after aortic occlusion	26.2 ± 4.9	19.6 ± 6.7**
60 Minutes after aortic occlusion	28.9 ± 4.5	20.6 ± 6.3**
After aortic declamping	42.1 ± 4.7	30.2 ± 8.1*

[a] Group II statistically lower than Group I at each interval; all data expressed as mean ± 1 SD.
* $p < 0.01$.
** $p < 0.05$.

after aortic declamping, a comparison of ischemic limb venous pCO_2 and $[H^+]$ between Groups I and II revealed no significant differences. Systemic arterial blood gases did not change during the study in either Group I or II.

Group III: Gradual Aortic Occlusion

Results of progressive limb ischemia were tested by regression analysis. Iliac artery blood flow decreased linearly with diminutions in limb perfusion pressure (1.41 ± .52 ml/min/mm Hg, slope significantly greater than 0, $p < 0.05$). $[H^+]_m$ rose progressively with decreasing perfusion pressure (Fig. 1) at a rate of −0.12 ± 0.09 nmol/liter/mm Hg (slope significantly less than 0, $p < 0.05$). Arteriovenous oxygen differences increased with diminutions in pressure (Fig. 2) at a rate of −.07 ± .02 ml of O_2/100 cm³/mm Hg (slope significantly less than 0, $p < 0.05$). Limb oxygen consumption (ml of O_2/min) was measured in six dogs. Significant decreases in oxygen consumption, coincident with lowered perfusion pressures, were observed in only two animals.

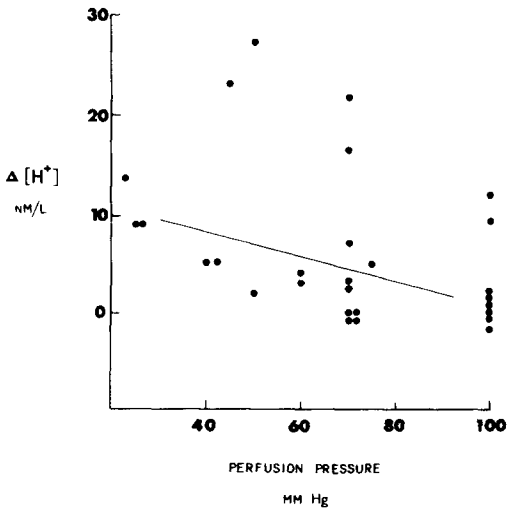

FIG. 1. Progressive $[H^+]_m$ increases with decreased perfusion pressure. Average slope of all studies was −0.12 ± 0.09 nmol/liter/mm Hg (slope significantly less than 0, $p < 0.05$).

DISCUSSION

Successful surgical management of peripheral arterial occlusive disease requires careful evaluation of clinical symptomatology, detailed arteriographic studies, and physiologic measurements documenting functional impairment. Quantitation of tissue ischemia remains an elusive task at the bedside as well as in the laboratory. As arterial reconstructive techniques advance and complex operations become more common, measurements of tissue perfusion assume greater importance. Muscle surface pH measurements utilizing percutaneously placed microelectrodes offer a relatively simple and safe means of quantitating the effectiveness of tissue perfusion.

Acute $[H^+]$ increases are known to occur on various organ surfaces with onset of anaerobic metabolism [3]. Anerobic shifts may be a consequence of direct tissue trauma, hemorrhage, inadequate oxygenation, or arterial occlusion [1, 7, 14].

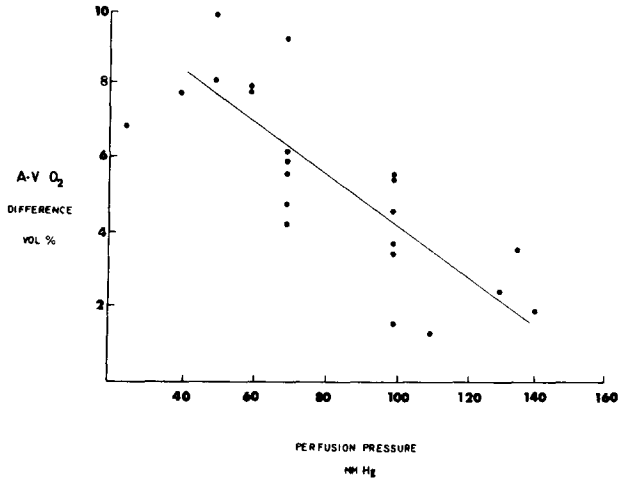

FIG. 2. Arteriovenous oxygen difference increases with diminutions in perfusion pressure. Average slope of all studies was -0.07 ± 0.02 ml of $O_2/100$ cm^3/mm Hg (slope significantly less than 0, $p < 0.05$).

Skeletal muscle metabolism is particularly liable to rapid change with ischemia from oxidative phosphorylation to anaerobic glycolysis. Intricate measurements of muscle gas tensions utilizing mass spectrometry have substantiated the anticipated biochemical changes reflected by $[H^+]_m$ fluctuations [5].

Earlier laboratory experiences support practical applications of pH_m monitoring. Limited clinical use in pediatric and adult patients has provided rather accurate monitoring of systemic acid–base disturbances [4]. One group investigating eight patients undergoing reconstructive arterial surgery reported a low pH_m in ischemic limbs that returned towards normal following successful revascularizations [2]. A recent report has documented lower pH_m measurements in patients experiencing ischemic rest pain compared to those having claudication [12].

In the present investigation all animals exhibited increased hindlimb $[H^+]_m$ with isolated aortic occlusion (Group I). *Systemic* acid–base balance was not appreciably altered. Acidosis and lower oxygen tensions of ischemic limb venous effluent during aortic occlusion are in agreement with previous clinical and laboratory findings [6]. Tissue acidosis abated within 5 to 10 min following normalization of blood flow in the present study. Although aerobic metabolism resumes with normal circulation, it is unlikely that this is responsible for the quick return of $[H^+]_m$ to normal. Rapid equilibrations suggest that the restored circulation effectively "washed out" local increases in hydrogen ion [10, 11]. Actual clearance of acidic metabolites has been documented histochemically in serial biopsies of ischemic and postischemic skeletal muscle [8].

Isolated vena cava occlusion (Group II) produced sustained peripheral venous hypertension. Concomitant diminutions in arterial blood flow with this maneuver were anticipated [15]. Importantly, pH_m in the present study was not altered by the marked decrease in iliac artery flow accompanying cava occlusion. Analysis of ischemic limb venous pO_2, being significantly lower after cava occlusion, provided a possible explanation for this phenomenon. Increased oxygen extraction, facilitated by the venous hypertension of cava occlusion, perhaps favors normal metabolic pathways. This effect may persist in the face of moderate decreases in arterial flow. On the other hand, *complete* aortic occlusion, even with venous hypertension, caused rapid hindlimb $[H^+]_m$ increases. Although venous pO_2 continued to fall in such a setting, compensatory extraction of sufficient oxygen to sustain normal metabolism may have been impossible.

Iliac artery flow declined predictably with gradual reductions in perfusion pressure (Group III). Statistical tests of discrimination revealed consistent increases in $[H^+]_m$ with decreases in iliac artery flow and pressure. Progressive increases in arteriovenous oxygen differences implicated increased local ischemic tissue oxygen extraction, inasmuch as *systemic* arterial $p O_2$ remained stable. Increased arteriovenous oxygen differences in ischemic limbs of human subjects has been correlated with similar decreases in pH_m [9]. In the current study significant increases in mean $[H^+]_m$ followed decreases in perfusion pressure. Occasional animals showed minute or no $[H^+]_m$ differences following small flow reductions at 100-mm Hg perfusion pressures. Slight changes in flow may therefore be undetectable.

Alterations in $[H^+]_m$ must be interpreted in relation to the total body acid–base balance. Changes in systemic blood pH on a respiratory or metabolic basis predictably alters tissue $[H^+]$[13]. Similarly, acute hemorrhage or other sympathetic nervous system stimuli affect tissue pH. $[H^+]_m$ correlates well with limb perfusion when ventilation and blood volume are controlled variables.

This investigation lends credence to the tenet that pH_m monitoring provides a precise indicator of ischemic tissue metabolism. Incremental decreases in flow were easily detectable, especially if associated with hypotension. Discrimination was less sensitive at higher perfusion rates. An unanticipated finding of this study was that the metabolic sequelae of hypoperfusion associated with venous occlusion were seemingly compensated for by an apparent increase in tissue oxygen extraction. This experiment supports clinical usage of muscle surface pH monitoring as an objective means of assessing arterial insufficiency and quantitating the results of arterial reconstructive efforts.

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