

Acid-Base Interactions with Noradrenaline-induced Contractile Response of the Rabbit Isolated Aorta

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The effect of acidosis and alkalosis on vascular smooth muscle contractions evoked by noradrenaline was studied. Helical strips of rabbit aorta were mounted for isometric tension recording. Acidosis (pH 7.24-6.51) was obtained by either increasing the P_{CO_2} (hypercapnic) and/or lowering the HCO_3^- concentration (hypobicarbonatic). Acidosis shifted the noradrenaline concentration-response curve to the right in a competitive manner. The maximal developed tension was unchanged at pH 7.24-6.90 and decreased by 30% at pH 6.51. Alkalosis (pH 7.61-8.04) did not alter noradrenaline-evoked contractions. The results suggest that hydrogen ions during acidosis (pH < 7.40) but not during alkalosis (pH > 7.40) exert α -adrenoceptor blocking properties. (Key words: Acid-base equilibrium; bicarbonate; carbon dioxide. Muscle, smooth; vascular. Sympathetic nervous system: catecholamines, norepinephrine.)

DEVIATION from normal in acid-base equilibrium may induce profound metabolic alterations and lead to unfavorable circulatory conditions.¹⁻⁴

The effects of varying pH and carbon dioxide tension (P_{CO_2}) on myocardial function has been investigated extensively,⁵⁻⁹ whereas information is scanty regarding acid-base effects on vascular smooth muscle (VSM).¹⁰⁻¹³

The purpose of this *in vitro* study was to investigate the influence of different acid-base conditions on VSM contraction evoked by the α -adrenoceptor agonist noradrenaline (NA).

Materials and Methods

The composition of the control salt solution (SS) was (mm): Na^+ 144.2, K^+ 4.9, Ca^{2+} 1.3, Mg^{2+} 1.2, Cl^- 126.7, HCO_3^- 25, $H_2PO_4^-$ 0.4, SO_4^{2-} 1.2, and glucose 11.1. Employing mutual equimolar replacement of $NaHCO_3$ against NaCl, two additional SS with bicarbonate concentrations of 10 and 40 mM, respectively, were used. To prevent autooxidation of NA, $CaNa_2EDTA$ (3×10^{-5}

M) and ascorbic acid (1.1×10^{-4} M) were added.¹⁴ The gas mixtures used for aeration of the salt solutions contained 18.40, 7.98, 4.97, 2.98 and 1.66% (v/v) carbon dioxide (CO_2) in oxygen (O_2), respectively (Lloyd-Haldane analysis).¹⁵ For control measurements the SS containing 25 mM $NaHCO_3$ was aerated with the CO_2 - O_2 gas mixture containing 4.97% CO_2 . CO_2 -dependent (capnic) pH deviations were obtained by bubbling the 25 mM $NaHCO_3$ SS with four different gas mixtures of 18.40, 7.98, 2.98, and 1.66% CO_2 in O_2 , respectively. $NaHCO_3$ -dependent (bicarbonatic) pH deviations were obtained using SS containing either 10 or 40 mM $NaHCO_3$ aerated with 4.97% CO_2 in O_2 . "Mixed" pH deviations were obtained using 18.40% CO_2 for aerating the 10 mM $NaHCO_3$ solution and 1.66% CO_2 in O_2 for aerating the 40 mM $NaHCO_3$ solution.

The oxygen tension (P_{O_2}), P_{CO_2} , and pH were measured at 37.0° C with the aid of a blood-gas analyzer (ABL 1®).† The calibration of the pH electrode was controlled in the range pH 5.00-8.00 employing P. L. Soerensen's buffer solutions.¹⁶ The expected P_{CO_2} values (x) of the gas mixtures used for aeration of the SS were calculated for the fractional carbon dioxide concentrations corrected for barometric pressure and saturated water pressure and correlated to the values measured with the ABL 1 CO_2 electrode (y). Specifications for this electrode are guaranteed minimum range 5.0-150.0 mmHg, repeatability $\pm 1\%$ of reading, and absolute accuracy $\pm 2\%$ of reading. The equation for the regression line calculated by the method of least squares is: $y = 0.79x + 6.4$ (N = 57, r = 0.999). The stated values of pH and P_{CO_2} of this study are the means of three separate measurements of immediately (<2 s) analyzed samples of freshly prepared tissue bath fluid anaerobically obtained at 37.0° C after an equilibration period of at least 15 min.

PROCEDURE

The method developed by Furchgott and Bhadrakom¹⁷ was followed. Inbred male albino rabbits weighing 2-3 kg were killed by stunning and exsanguination. Four helically cut strips, each approximately 30 mm long and 3 mm wide, were made from the thoracic aorta and then

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TABLE 1. Overview of the Experimental Acid-Base Conditions—with Regard to Random Allocation of Strip Groups

CO ₂ Content (v/v)	NaHCO ₃ Concentration (mM)								
	10			25			40		
	Segmental Group	pH	P _{CO₂} (mmHg)	Segmental Group	pH	P _{CO₂} (mmHg)	Segmental Group	pH	P _{CO₂} (mmHg)
1.66				2	7.82	15	2	8.04	14
2.98				3	7.61	24			
4.97	3	7.02	33	1,2,3,4 (controls)	7.40	38	4	7.63	36
7.98				4	7.24	52			
18.40	1	6.51	108	1	6.90	115			

CO₂ content (v/v) denotes volume per cent carbon dioxide in aerating gas mixture (CO₂ in O₂).

P_{CO₂} denotes measured carbon dioxide tension (mmHg). pH and P_{CO₂} values are means of three measurements.

mounted for isometric tension recording in organ baths filled with 20 ml salt solution. Resting tension was adjusted to 2.0 g during an initial equilibration period of 30 min, during which the SS was replaced every 15 min. Then, to avoid increasing sensitization to the agonist during the experiment and optimize results¹⁷ each tissue was subjected twice to (-)-noradrenaline hydrochloride** (10⁻⁷ M) with subsequent washings. After a subsequent resting period of 30 min with the SS replaced twice and readjustment of the resting tension, cumulative concentration-response curves for NA were determined by increasing the calculated final bath concentration of NA in steps of 0.5 log units (10⁻¹⁰ to 10⁻⁴ M). Developed contractile tension was recorded by means of SWEMA[®] isometric transducers (type No. SG4-90),†† which were connected to Omnigraphic[®] 3000 recorders (type No. 54)‡‡ via especially constructed amplifiers.§§ Experiments were carried out with two preparations simultaneously. The temperature of the tissue bath was kept at 37.0 ± 0.2° C by means of a HETO[®] warm water circulation device.¶¶

STRIP ALLOCATION

The four segmental strips of each aorta were designated by the numbers 1-4, advancing from the aortic arch (1) to the diaphragmatic end (4), and the segmental strips from each of eight aortas, *i.e.*, altogether 32 strips, were tested for the contractile response to NA while subjected to the control conditions (pH 7.40; P_{CO₂} 38 mmHg).

The effect of various changes in pH from the control situation on the contractile response to NA was studied by subjecting a specific segmental strip (1, 2, 3, or 4) from eight aortas to one of eight differing acid-base conditions. The segmental-pH relationship was determined by random allocation with the limitation that each seg-

mental strip from eight aortas was represented by two different series, each subjected to a specific acid or base condition (table 1).

DATA MANAGEMENT AND STATISTICAL ANALYSIS

The contractile response to cumulative doses of NA measured in grams was converted into percentage of the maximal developed tension in grams of each group. For the control situation a single cumulative concentration-response curve was constructed for each segmental strip, with the negative logarithm of the NA concentration as abscissa and the contractile response in percentage of the maximal developed tension as ordinate. The latter were the mean values derived from eight independent experiments employed with corresponding segmental strips from different aortas. Analogic curves were constructed for each acid or base condition deviating from the control situation.

Based on the contractile response values in the range from 15 to 85% of the maximal developed tension in grams of each group, simple linear least-squares regression was applied to the data of each curve, and the derived values for the slope and EC₅₀ (the NA concentration necessary to produce half the maximal developed contractile response) were used to characterize the location of the regression lines.

The Statistical Package for the Social Sciences (SPSS)¹⁸ was used for the statistical analysis (release 9.0-UW1.0, July 1982) of the data on a digital computer (UNIVAC 1100, Sperry Univac). The subprograms used were: NEW REGRESSION (multiple regression) to compare the regression lines for identity, and MANOVA (regular multiple two way analysis of variance) to compare the maximal developed tensions. As to the latter, differences relating to both pH and the contractile characteristics of the different segmental strips were determined. Consequently, a one-way analysis with a least significant difference (LSD) test was applied to itemize such differences.

A level of significance of *P* < 0.05 was required to reject the null hypothesis.

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Results

CONTRACTILE EFFECT OF NA AT CONTROL CONDITIONS

NA (10^{-9} – 10^{-4} M) contracted the aorta (fig. 1). Location and slope values (table 2) indicate that the sensitivity of the postsynaptic α -adrenoceptors did not differ between the four segments (1–4) of the aorta (table 1). The maximal developed tension evoked by NA (10^{-4} M) decreased gradually from the proximal (1) to the most distal segment (4) relative to the aortic arch,¹⁹ with a statistical significant difference between strip segments 1 and 4 (table 2). Consequently, comparisons of maximal developed tensions were made for corresponding segmental strips only, in contrast to the multiple comparisons made for the regression lines.

EFFECT OF ACIDOSIS ON NA-EVOKED CONTRACTIONS

The values of EC_{50} decreased with decreasing pH of the bath fluid, signifying an increasing right shift of the concentration–response curve with increasing acidity. At pH 6.90 and 6.51, these changes were statistically significant (table 3). The derived slope coefficients of regression lines (based on contractile response data ranging from 15 to 85% of maximal developed tension in grams of each group) obtained during acidosis (table 3) did not change significantly from control groups and other groups (table 2). Therefore, the right shift of the concentration–response curves during acidosis was horizontal (parallel). This parallel right shift with increasing hydrogen ion activity indicates that acidosis caused a competitive inhibition of the contractions elicited by exogenous NA (10^{-9} – 10^{-4} M).²⁰ Compared with the corresponding segmental control groups, the mean maximal developed tension was decreased significantly (approx. 30%) at the lowest pH (6.51) and unaltered at other acidotic pH values (6.90–7.24) (tables 2 and 3; fig. 1).

EFFECT OF ALKALOSIS ON NA-EVOKED CONTRACTIONS

Alkalosis (pH 7.61–8.04) (table 3) essentially did not alter the contractile response elicited by NA (10^{-9} – 10^{-4} M) compared with control conditions (table 2).

Discussion

Extra-intracellular ratios of ions like sodium, potassium, chloride, bicarbonate, and calcium may have been affected by the different acid–base situations to an extent that may influence vasomotor activity.²¹ As the volume of perfusate relative to the aortic tissue used was approximately 200:1, the extracellular ion concentrations can be considered as virtually constant. However, secondary intracellular changes of ion concentrations, of which almost

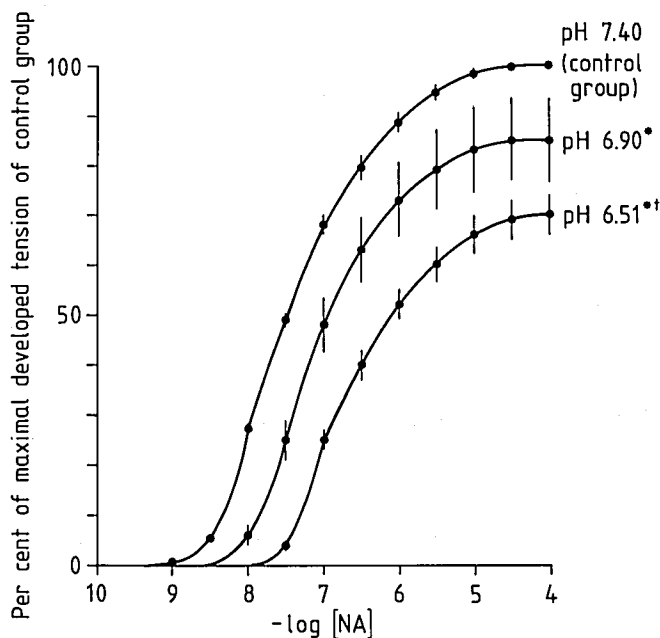


FIG. 1. Effect of pH on the relationship between concentration of exogenous noradrenaline (NA) and contractile response of isolated rabbit aortic strips. Abscissa—negative logarithm of molarity of NA. Ordinate—mean contractile tension in per cent of maximum response in grams of control group. Each curve was constructed as the mean of eight discrete series of measurements using strips from the identical aortic segment (1) of eight different animals. The bars denote \pm SEM. * A statistically significant right shift from the control situation has taken place. † Maximal developed tension is significantly lower (30%) than in control situation.

nothing is known, may alter the slope of concentration–response curves, absolute contractile response, and force–velocity relations.^{9,12,22–26} Nevertheless, parallel right shifts of concentration–response curves afford presumptive evidence of a competitive mechanism by an antagonist at an agonist–receptor complex.²¹ As the contractile response of VSM to NA is mediated by postjunctional α -adrenoceptors,^{17,19,27–29} the parallel right shift of the con-

TABLE 2. Description of Cumulative Concentration Response to Noradrenaline (NA) in Different Segments of Rabbit Aorta. Control Conditions (pH 7.40, P_{CO_2} 38 mmHg)

Segmental Group	n	r	$-\log EC_{50}$	Slope	Maximal Developed Tension (g)
1	33	0.94	7.41	31.5	5.79* \pm 0.44
2	33	0.97	7.44	30.7	4.82 \pm 0.49
3	31	0.97	7.46	34.6	4.72 \pm 0.29
4	30	0.97	7.46	35.9	3.91* \pm 0.46

For each segmental group, N = 8. n: number of observations included for regression analysis, based on contractile response values ranging from 15–85% of maximal developed tension. r: correlation coefficient for the interdependence between the NA concentration and the contractile response. $-\log EC_{50}$: derived negative logarithm of NA concentration producing half maximal developed tension. Slope: derived slope coefficient of regression lines. Maximal developed tension: mean maximal developed tension to NA (10^{-4} M) in grams \pm SEM.

* Segment 1 and 4 differed significantly ($P < 0.05$) from each other.

TABLE 3. Description of Cumulative Concentration Response to Noradrenaline (NA) in Rabbit Aortic Strips Subjected to Different Acid or Base Environments

pH	Segmental Group	P _{CO₂} (mmHg)	NaHCO ₃ (mM)	n	r	-log EC ₅₀	Slope	Maximal Developed Tension (g)
6.51	1	108	10	27	0.96	6.66*	34.1	4.04† ± 0.23
6.90	1	115	25	29	0.90	7.03*	34.1	4.95 ± 0.49
7.02	3	33	10	30	0.94	7.29	33.4	4.14 ± 0.20
7.24	4	52	25	30	0.94	7.25	34.3	4.17 ± 0.48
7.61	3	24	25	29	0.97	7.41	37.2	3.89 ± 0.35
7.63	4	36	40	29	0.92	7.55	34.6	3.82 ± 0.20
7.82	2	15	25	32	0.97	7.41	39.0	4.82 ± 0.27
8.04	2	14	40	30	0.93	7.46	31.5	4.54 ± 0.23

For each segmental group, N = 8. n: number of observations included for regression analysis, based on contractile response data ranging from 15 to 85% of maximal developed tension. r: correlation coefficient for the interdependence between the NA concentration and the contractile response. P_{CO₂}: measured carbon dioxide tension. NaHCO₃: sodium bicarbonate concentration. -log EC₅₀: derived negative logarithm of NA concentration producing half maximal developed

tension. Slope: derived slope coefficient of regression lines. Maximal developed tension: mean maximal developed tension to NA (10⁻⁴ M) in grams ± SEM.

* Intercept of regression lines is significantly different from both the control groups and other groups (P < 0.05).

† Significant difference from corresponding segmental control group (P < 0.05).

centration-response curves during acidosis, therefore, indicates that hydrogen ions (H⁺) exert postjunctional α-adrenergic blockade²⁰ during acidosis (pH < 7.40). However, the identical slope values in all segmental groups investigated suggest unchanged sensitivity to NA of the α-adrenoceptor during all acid-base states used for the study.

In strips subjected to control conditions (pH 7.40), there was a decrease in maximal developed tension from proximal (segmental group 1) to distal (segmental group 4). This is in accordance with earlier findings¹⁹ and probably reflects local differences in anatomical microstructure.

The physical properties of H⁺ and CO₂ may affect different aspects of the local modulation of NA and influence other than adrenergic vasomotor tone-regulating mechanisms as well. Thus, some evidence exists that a shift from α₁ to α₂ agonism may occur with increasing H⁺ concentration.²⁷ Furthermore, several studies have shown that acidosis relaxes myogenically active VSM and that the contractile response of different isolated blood vessels to other agonists and sympathetic nerve stimulation is depressed during acidosis.^{10,11,20,28,30-32} At the nerve terminals, an increase in H⁺ activity apparently depresses calcium entry resulting in inhibition of transmitter release, which, however, is partly masked by depression of tissue reuptake of the agonist.^{13,20,22} Moreover, an intracellular contest for VSM between calcium and hydrogen ions is assumed, apparently involving a reduced sensitivity of the actomyosin ATP-ase to calcium when intracellular pH is low.^{12,20,22,24,33} The inhibition of α-adrenergic transmission as shown in this study, therefore probably is non-specific. The marked (approximately 30%) acidotic inhibition of the maximal contractile response to NA with a pH of 6.51 may have involved all intracellular as well as extracellular mechanisms responsible for maintenance of VSM tone.

Because of the great membrane permeability of CO₂, it might be expected that CO₂ would have a greater depressant action than H⁺ at identical pH. However, even if a pure hypercapnic acidosis at pH 6.90 seems to increase the demand for NA to obtain EC₅₀ relatively much more than a hypobicarbonatic acidosis with a pH of 7.02 (table 3), this study was not designed to detect such differences. The available literature on these aspects of acidotic inhibition of the circulation^{7,9,10,23,27,29,32} is confusing—presumably because of differing experimental models and poorly defined acid-base states. The problem is open for future research.

In the alkalotic range of our study, essentially no deviation from the control situation could be demonstrated. However, activation of calcium influx and enhancement of contractile response of VSM to some agonists and sympathetic nerve stimulation by alkalosis has been postulated.^{10-12,20,24,28,29,33} One reason for this apparent controversy may originate from different methods and the inappropriate use of statistics.

The findings of our study seem to be in accordance with the increasing evidence suggesting that an acidosis *per se* by inhibition of glycolysis depresses cardiovascular performance, thus conserving carbohydrate reserves and energy stores, which, in turn, may facilitate recovery after ischemia and hypoxia. In contrast, alkalosis almost invariably is reported to increase metabolism.^{5,6,9,25,34-37}

Secondary compensatory mechanisms to such clinical conditions as depressed cardiovascular function and the ion extracellular to intracellular ratio changes that occur *in vivo* may be eliminated fully in the *in vitro* situation, where autonomous reflexes cannot supervene and a large perfusate pool has stable ion concentrations. Extrapolation of our findings to clinical care therefore cannot be made.

In conclusion, the results apparently reflect competitive α-adrenergic blocking properties by hydrogen ions during acidosis (pH < 7.40) but not during alkalosis (pH > 7.40).

This acidotic inhibition is probably nonspecific. Simultaneous involvement of other mechanisms responsible for the maintenance of vascular smooth muscle tone remains to be established but probably took place at a very low pH (6.51).

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