Effect of severe acidosis on vasoactive effects of epinephrine and norepinephrine in human distal mammary artery

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Objective: Acidosis is a very common pathologic process in perioperative management. However, how to correct severe acidosis to improve the efficacy of vasoconstrictors in hemodynamically unstable patients is still debated. The present study investigated whether severe extracellular acidosis influences the vasoactive properties of vasoconstrictors on human isolated arteries.

Methods: Segments of intact distal internal mammary arteries were removed from 41 patients undergoing artery bypass grafting. The arterial rings were washed in Krebs-Henseleit solution and suspended in an organ bath. The rings were set at a pretension equivalent of 100 mm Hg, and the relaxation response to 10 μ M acetylcholine was verified. Concentration–response curves for epinephrine, norepinephrine, methoxamine ($\alpha_{1A/D}$ -adrenoceptor agonist), phenylephrine (equipotent agonist of $\alpha_{1A/B}$ -adrenoceptors), and clonidine (α_2 -adrenoceptor agonist) were achieved under control conditions (pH 7.40) and under acidic conditions by substitution of the Krebs-Henseleit solution with a modified solution.

Results: Decreasing the pH from 7.40 to 7.20, 7.0, or 6.80 did not significantly alter the potency and efficacy of epinephrine and norepinephrine, although the standardized effect size was sometimes large. Severe acidosis (pH 6.80) did not significantly change the potency and efficacy of phenylephrine and clonidine, although it increased the efficacy and potency of methoxamine ($P < .001$ and $P = .04$ vs paired control conditions, respectively).

Conclusions: Extracellular acidosis did not impair the vasoactive properties of epinephrine and norepinephrine in human medium-size arteries until pH 6.80. The results of the present study also suggest that acidosis might potentiate arterial responsiveness to vasoconstrictors, mostly by way of the α_{1D} -adrenoceptor. (J Thorac Cardiovasc Surg 2014;147:1698-705)

Epinephrine or norepinephrine should be initiated to restore arterial pressure and organ perfusion in hemodynamically unstable patients, especially during perioperative management.¹ Epinephrine and norepinephrine act mainly through the α_1/α_2 -adrenoceptors, increasing the intracellular calcium concentration in the vascular smooth muscle cells.² Unlike

norepinephrine, epinephrine can restore blood pressure by way of the cardiac β_1 -adrenoceptors. The β -adrenergic effects of epinephrine are marked at low doses and α_1 -adrenergic effects at higher doses. Epinephrine enhances coronary blood flow by an increased duration of diastole, which counterbalances the α_1 -mediated coronary vasoconstriction.³ Epinephrine has been used for cardiac arrest and as a second-line treatment of isovolemic shock resistant to dobutamine or in the case of refractory septic shock. Norepinephrine is mainly an α_1 -adrenergic receptor agonist with slight β -agonist activity. Norepinephrine increases the systolic and diastolic blood pressure and has a minimal effect on cardiac output.³ Norepinephrine has commonly been used as a first-line treatment for isovolemic septic shock.

The effects of acidosis on the cardiovascular system have been investigated, especially in left ventricular depressant dysfunction and systemic vasodilatation.^{2,4} Acidosis can also promote the development of severe ventricular arrhythmia after reperfusion for myocardial infarction.⁵ However, the influence of acidosis on the efficacy of vasopressor agents is still debated, although severe acidosis (pH < 7.10) can be viewed as an indication for hemofiltration in patients with shock.⁶ Moreover, the use of bicarbonate to treat severe metabolic acidosis has been challenged in

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The present study was supported by Research Unit UPRES EA220 and the Medical Intensive Care Unit, Hôpital Européen Georges Pompidou and not by any financial grant.

Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication June 7, 2013; revisions received Oct 17, 2013; accepted for publication Nov 8, 2013; available ahead of print Dec 11, 2013.

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0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2013.11.013>

Abbreviations and Acronyms

CI = confidence interval

d = standardized effect size

humans; however, no study has demonstrated a benefit in terms of hemodynamic improvement.⁷⁻⁹ Chronic diseases of the circulatory system could also affect the efficacy of vasoconstrictors in critically ill patients. Few studies have investigated the effects of severe acidosis on the vasoactive properties of vasoconstrictors from fresh complete human tissues. Intact fresh resistance microvessels (internal diameter < 200 μm) are more difficult to obtain from humans than intact conductance vessels (internal diameter > 500 μm). However, the internal mammary artery, the graft of choice for myocardial revascularization, is more easily obtainable, and the distal internal mammary artery is pharmacologically responsive to vasoconstrictors. The present study investigated whether severe extracellular acidosis influences the vasoconstriction induced by epinephrine and norepinephrine on distal segments of human isolated internal mammary arteries.

METHODS

Tissue Preparations

Our local ethics committee (Comité de Protection des Personnes se Prêtant à la Recherche Biomédicale Ile de France VIII, France) approved the present study, and patients gave informed consent before their scheduled surgery. Internal mammary arteries were obtained from 41 patients (34 men and 7 women; mean age, 65 ± 11 years) undergoing artery bypass grafting in 2 cardiovascular surgery departments in Paris. All vasoactive medications were suspended the evening before the surgical procedure. Excised segments of the distal arteries were immediately immersed and washed thoroughly in oxygenated Krebs-Henseleit solution (NaCl 119 mM, KCl 4.7 mM, CaCl_2 2.5 mM, KH_2PO_4 1.2 mM, NaHCO_3 29 mM, and glucose 11.7 mM) to remove any intraoperative drug residue. The tissues were maintained at 4°C and transported to the laboratory as soon as possible. After removal of the adhering connective tissues, the rings of tissue were prepared and suspended on hooks in a 5-mL organ bath containing Krebs-Henseleit solution, gassed with 95% oxygen and 5% carbon dioxide (pH 7.40), and maintained at 37°C . Each preparation was connected to a force displacement transducer, and the isometric tension changes were recorded and postprocessed with iox2 and datanalyzer software (EMKA Technologies, Paris, France). The arterial rings were set at a pretension equivalent of 100 mm Hg, calculated from the internal circumference and the wall tension derived from the Laplace law.^{10,11}

Experimental Protocol

The arterial rings were washed again and equilibrated for ≥ 60 minutes with changes of fresh Krebs-Henseleit solution (pH 7.40, 37°C) every 10 minutes during the first 30 minutes of the initial equilibration period. The rings were then challenged by the addition of 90 mM KCl, which stimulates the voltage-dependent Ca^{2+} channels, to stabilize the preparations and ensure reproducible contractile responsiveness, as previously reported.¹² The functional integrity of the endothelium was then verified by the relaxation response ($\geq 20\%$) to $10 \mu\text{M}$ acetylcholine. The baseline tension was restored by washing the rings 4 times with Krebs-Henseleit solution. The addition of epinephrine or norepinephrine, 2 α_1 - and α_2 -subtype, nonselective

adrenoceptor agonists, in the organ bath was randomly determined for each arterial ring, limiting the selection bias. Concentration–response curves were constructed for epinephrine (10^{-9} to 3.10^{-5} M) and norepinephrine (10^{-9} to 10^{-4} M) by applying increasing concentrations, at 5-minute intervals, under standard conditions (pH 7.40, 37°C). After washing and restabilization, the pH was decreased in the organ bath from 7.40 to 7.20, 7.0, or 6.80 by substitution of Krebs-Henseleit solution with a modified solution (NaHCO_3 , 23, 17, or 11 mM, respectively). After equilibration in the pH-modified solution for 20 minutes, the concentration–response curves were obtained again under acidic conditions, with each ring serving as its own control. In the preliminary experiments, reversing the standard and acidic conditions in the organ bath did not influence the contraction elicited by epinephrine or norepinephrine (data not shown).

Pharmacologic Interventions

To investigate the effect of acidosis on the α -adrenoceptor subtypes, a second set of experiments was performed according to the same experimental protocol using an $\alpha_{1A/D}$ -adrenoceptor agonist (10^{-9} to 10^{-4} M methoxamine), an equipotent agonist of $\alpha_{1A/B}$ -adrenoceptor (10^{-9} to 3.10^{-5} M phenylephrine) and a peripheral α_2 -adrenoceptor agonist (10^{-9} to 10^{-4} M clonidine).

Drugs

Epinephrine came from Aguettant (Lyon, France). Norepinephrine was purchased from Renaudin (Itxassou, France). Methoxamine, phenylephrine, clonidine, and acetylcholine were purchased from Sigma-Aldrich (St Louis, Mo). KCl was purchased from B-Braun (Melsungen, France). All drugs were dissolved in distilled water and then diluted in Krebs-Henseleit solution. The final amount of distilled water in the organ bath was negligible.

Statistical Analysis

The data are presented as the mean $\pm$ standard deviation. The results were analyzed using the Wilcoxon signed rank test, and differences within the standard curves were analyzed using 1-way repeated measures analysis of variance, with Bonferroni adjustments for multiple comparisons, when required (StatView, version 5.0; SAS Institute, Cary, NC). Because inadequate statistical power could not be ruled out, the standardized effect size, *d*, for the difference between the mean values was calculated to determine whether the observed effect of acidosis was small ($|d| \geq 0.20$), medium ($|d| \geq 0.50$), or large ($|d| \geq 0.80$), according to the Cohen conventions.¹³ The 95% confidence interval (CI) for *d* was calculated to determine the uncertainty around the real effect of acidosis. The basal tone was expressed in tension (g), measured just before the addition of drugs in the organ bath. Changes in the arterial ring tone are expressed in tension (g) and the percentage of the maximal contraction induced by 90 mM KCl under standard conditions, because acidosis had significantly decreased the maximal contraction induced by 90 mM KCl in the preliminary experiments (1.69 ± 0.42 g at pH 6.80 vs 2.96 ± 0.5 g at pH 7.40; $n = 11$; $P < .001$). The efficacy of the agonist corresponded to the change in the arterial ring tone obtained with the highest agonist concentration tested. The potency of the agonists was defined as the negative logarithm of the molar concentration of the agonist producing 50% of the maximal effect and was calculated from the concentration–response curves. Arterial rings with contraction induced by 90 mM KCl < 1 g or with an absence of relaxation to acetylcholine were excluded from the analysis, because the response was considered a reliable dysfunction marker.

RESULTS

Sample

A total of 57 arterial rings were tested, and 47 rings were functional and eligible for analysis.

TABLE 1. Effects of extracellular acidosis on human arterial basal tone and responsiveness to epinephrine and norepinephrine

TABLE 1. Effects of extracellular acidosis on human arterial basal tone and responsiveness to epinephrine and norepinephrine					
pH conditions	n	Epinephrine		Norepinephrine	
		Measurement	<i>d</i> (95% CI)	Measurement	<i>d</i> (95% CI)
Basal tone (g)					
7.20	11	1.61 ± 0.20	−0.33 (−0.51 to 1.18)	1.33 ± 0.19	−0.69 (−1.55 to 0.17)
7.40		1.67 ± 0.14		1.47 ± 0.20	
7.0	10	1.70 ± 0.22	−0.30 (−1.18 to 0.58)	1.75 ± 0.10	−0.82 (−1.73 to 0.10)
7.40		1.77 ± 0.23		1.89 ± 0.21	
6.80	11	1.90 ± 0.27	−0.73 (−1.59 to 0.14)	1.56 ± 0.13	−0.95 (−1.83 to 0.07)
7.40		2.10 ± 0.26		1.67 ± 0.09	
<i>E</i> _{max} (g)					
7.20	11	4.59 ± 0.40	0.23 (−0.61 to 1.07)	3.89 ± 0.37	−0.05 (−0.89 to 0.78)
7.40		4.48 ± 0.52		3.91 ± 0.36	
7.0	10	5.56 ± 0.76	−0.02 (−0.90 to 0.85)	5.49 ± 0.82	0.29 (−0.59 to 1.17)
7.40		5.58 ± 0.81		5.24 ± 0.83	
6.80	11	4.79 ± 0.47	−0.08 (−0.92 to 0.75)	3.57 ± 0.26	0.61 (−0.25 to 1.46)
7.40		4.83 ± 0.46		3.40 ± 0.28	
pD ₂ (log unit)					
7.20	11	7.34 ± 0.31	0.37 (−0.47 to 1.21)	6.52 ± 0.28	0.62 (−0.24 to 1.47)
7.40		7.23 ± 0.26		6.35 ± 0.25	
7.0	10	6.73 ± 0.17	0.48 (−0.41 to 1.37)	6.31 ± 0.20	0.09 (−0.78 to 0.97)
7.40		6.66 ± 0.10		6.29 ± 0.21	
6.80	11	7.48 ± 0.15	0.80 (−0.08 to 1.65)	6.56 ± 0.10	−0.91 (−1.79 to 0.03)
7.40		7.34 ± 0.19		6.71 ± 0.20	

Data presented as mean ± standard deviation, *d*, and 95% CI for the difference between the mean values. The observed effect of acidosis was small ($|d| \geq 0.20$), medium ($|d| \geq 0.50$), or large ($|d| \geq 0.80$) according to the Cohen convention.¹³ The 95% CI for *d* consisted of the uncertainty around the real effect of acidosis. The basal tone was measured just before the addition of the vasoconstrictor in the organ bath. Efficacy of agonist corresponded to the change in arterial tone (g) obtained with the highest agonist concentration tested. *pD*₂ of the agonists defined as the negative logarithm of the molar concentration of the agonist producing 50% of the maximal effect and was calculated from the concentration–response curves (Figure 1, A, C, and E). Each experiment served as its own control. No difference between acidosis and the standard condition (pH 7.40) was statistically significant ($P > .05$). *d*, Standardized effect size; CI, confidence interval; *pD*₂, potency; *E*_{max}, efficacy.

Effect of Extracellular Acidosis on Arterial Basal Tone

Acidosis did not significantly change the basal tone of the arterial rings in the organ bath except at a low pH level (6.80), at which acidosis increased the arterial basal tone (Tables 1 and 2). As indicated by the standardized effect sizes, the observed effect of acidosis on basal tone was often medium or large, but the 95% CI revealed great uncertainty, limiting the conclusions that could be drawn about the real effect of acidosis on the basal tone.

Effect of Extracellular Acidosis on Contraction Induced by Epinephrine and Norepinephrine

Acidification of the organ bath to a pH of 6.80 did not significantly alter the efficacy and potency of epinephrine and norepinephrine in the human distal internal mammary artery (Table 1, Figures 1 and 2). The standardized effect sizes showed that the observed effect of acidosis on the efficacy of epinephrine and norepinephrine was small, but the 95% CI indicated continued uncertainty (Table 1). In contrast, the effect of severe acidosis (pH 6.80) on the potency of epinephrine and norepinephrine was large, as shown by the standardized effect sizes. The uncertainty around the real effect was moderate, suggesting severe acidosis might increase the potency of epinephrine and decrease the potency of norepinephrine (Table 1).

Effect of Extracellular Acidosis on Contractions Induced by Methoxamine, Phenylephrine, and Clonidine

We set the lower pH at 6.80 to test methoxamine, phenylephrine, and clonidine, because of the limited availability of tissues and because no significant changes in the basal tone and responsiveness were observed until a pH of 7.0. Acidification of the organ bath from 7.40 to 6.80 sensitized the arterial rings to methoxamine but did not significantly change their responsiveness to phenylephrine and clonidine (Table 2 and Figure 3). As shown by the standardized effect size and its 95% CI, the effect of severe acidosis on the efficacy and potency of methoxamine was powerful (Table 2).

DISCUSSION

The results of the present study have demonstrated that severe extracellular acidosis does not alter the contraction of human distal internal mammary artery induced by epinephrine and norepinephrine, which act by way of the α_{1B} - and α_{1A} -adrenoceptors. In contrast, acidosis increased the potency and efficacy of methoxamine, an $\alpha_{1A/D}$ -adrenoceptor agonist.^{14,15} Moreover, acidosis did not significantly influence the contractile response mediated by clonidine, a peripheral α_2 -adrenoceptor agonist, or by phenylephrine, an α_1 subtype, nonselective agonist.¹⁶ Overall, these results have also suggested that severe acidosis might modulate

TABLE 2. Effect of severe extracellular acidosis (pH 6.80) on human arterial basal tone and responsiveness to methoxamine, phenylephrine, and clonidine

Measurement	n	pH 7.40	pH 6.80	d (95% CI)
Basal tone (g)				
Methoxamine	10	1.64 ± 0.14	2.18 ± 0.28*	2.34 (1.20 to 3.47)
Phenylephrine	10	1.85 ± 0.23	1.88 ± 0.32	0.10 (−0.77 to 0.88)
Clonidine	5	2.10 ± 0.32	2.84 ± 0.49*	1.61 (0.19 to 3.04)
E _{max} (g)				
Methoxamine	10	3.73 ± 0.40	4.80 ± 0.41†	2.53 (1.35 to 3.71)
Phenylephrine	10	5.11 ± 0.60	5.43 ± 0.59	0.52 (−0.38 to 1.41)
Clonidine	5	3.89 ± 0.41	4.26 ± 0.34	0.89 (−0.41 to 2.19)
pD ₂ (log unit)				
Methoxamine	10	5.28 ± 0.11	5.54 ± 0.10*	2.37 (1.23 to 3.51)
Phenylephrine	10	6.93 ± 0.17	6.66 ± 0.24	−1.24 (−2.20 to −0.29)
Clonidine	5	6.32 ± 0.31	6.17 ± 0.20	−0.52 (−1.78 to 0.74)

Data presented as mean ± standard deviation, d, and 95% CI for the difference between the mean values. The observed effect of acidosis was small ($|d| \geq 0.20$), medium ($|d| \geq 0.50$), or large ($|d| \geq 0.80$) according to the Cohen convention.¹³ The 95% CI for d consisted of the uncertainty around the real effect of acidosis. E_{max} corresponded to change in arterial tone (g) obtained with the highest agonist concentration tested; pD₂ of the agonists was defined as the negative logarithm of the molar concentration of the agonist producing 50% of the maximal effect and was calculated from the concentration–response curves (Figure 3, A, C, and E). Each experiment served as its own control. E_{max}, Efficacy; d, standardized effect size; CI, confidence interval; pD₂, potency. *P < .05, acidosis vs standard condition. †P < .01, acidosis vs standard condition.

the arterial responsiveness to vasoconstrictors by way of the intracellular signaling pathways, mainly triggered by the α_{1D} -adrenoceptor. However, we could not rule out that the size effects of acidosis made some of our results inconclusive. Thus, caution is needed before generalizing the present findings. Given that our experimental model was conducted with large conductance vessels, the results of our study must be seen at the functional level only, and extrapolating our data to clinical outcomes was beyond the scope of our study.

At least partially consistent with our results using whole human tissue, Huang and colleagues¹⁷ showed in a canine model that metabolic acidosis increased the peripheral vasoconstriction induced by epinephrine or norepinephrine.¹⁷ Furthermore, hypercapnic acidosis did not alter the vasoactive response to phenylephrine in large arterioles from rats.¹⁸ Acidosis seems to have an overall relaxant effect; however, this overall outcome does not reflect the influence of H⁺ on each intracellular signaling pathway involved in the modulation of the vascular smooth muscle contraction.⁴ H⁺ might interact with the voltage-dependent Ca²⁺ channels by inhibiting the influx of calcium ions across the cell membrane, with the adenosine triphosphate-sensitive K⁺ channels leading to membrane hyperpolarization and relaxation.^{19–21} In addition, both α_{1A} - and α_{2} -adrenoceptors interact with the voltage-dependent Ca²⁺ channels by changes in membrane polarization.²² We observed that acidosis enhances the responsiveness to methoxamine but not to phenylephrine. Unlike methoxamine, epinephrine and norepinephrine not only stimulate the α_1 - and α_2 -adrenoceptors, but also the β -adrenoceptors, and phenylephrine is an equipotent agonist of $\alpha_{1A/B}$ -adrenoceptors.¹⁶ Because methoxamine stimulates the $\alpha_{1A/D}$ -adrenoceptors, our results strongly suggest that acidosis could increase the vasoactive response to vasoconstrictors mainly by sensitizing the

α_{1D} -adrenoceptor. Thus, the standardized effect sizes also indicate that severe acidosis could increase the potency of epinephrine and decrease the potency of norepinephrine, suggesting more norepinephrine and less epinephrine would be required in cases of severe acidosis.

The reactivity of the human internal mammary artery graft to sympathomimetic drugs is mostly dependent on the $\alpha_{1A/B/D}$ - and α_2 -adrenoceptors, because the internal mammary artery has a small number of β -adrenoceptors.^{14,23} The stimulation of α_1 -adrenoceptors activates phospholipase C, which increases the inositol triphosphate intracellular concentration, stimulating Ca²⁺ release from the sarcoplasmic reticulum.²⁴ In addition, the α_{1A} -adrenoceptor subtype indirectly activates the chloride channels, resulting in membrane depolarization that opens the voltage-dependent Ca²⁺ channels.²² At a greater concentration, the α_1 -adrenoceptors might also activate intracellular cyclic adenosine monophosphate.²⁵ In contrast, the stimulation of α_{2A} -adrenoceptors closes the voltage-dependent Ca²⁺ channels and inhibits adenylate cyclase, leading to a decrease in intracellular cyclic adenosine monophosphate and an enhancement of K⁺ efflux.²⁶ We have established that acidosis does not significantly alter the arterial contraction dependent from the postjunctional α_2 -adrenoceptor stimulated by clonidine. However, the effect of acidosis on intracellular Ca²⁺ concentrations remains unclear, because the inositol triphosphate-induced increase in cytosolic free Ca²⁺ could be compensated for by a decreasing influx of Ca²⁺ across the cell membrane owing to inhibition of the voltage-dependent Ca²⁺ channels. Moreover, it has been shown that acidosis can increase or decrease the intracellular inositol triphosphate and cytosolic free Ca²⁺ concentrations, according to the cell type and species.^{24,27}

FIGURE 1. Concentration–response curves for epinephrine in human distal internal mammary arteries in absence (pH 7.40) and presence of extracellular acidosis: A and B, pH of 7.20 ($n = 11$); C and D, pH of 7.0 ($n = 10$); and E and F, pH of 6.8 ($n = 11$). Contraction expressed in g (A, C, and E) and percentage of the maximal contraction induced by 90 mM KCl under standard conditions (pH 7.40; B, D, and F). Data presented as mean $\pm$ standard deviation. Each experiment served as its own control. No differences between acidosis and the standard condition (pH 7.40) were statistically significant ($P > .05$ for all).

FIGURE 2. Concentration–response curves for norepinephrine in human distal internal mammary arteries in absence (pH 7.40) and presence of extracellular acidosis: A and B, pH of 7.20 ($n = 11$); C and D, pH of 7.0 ($n = 10$); and E and F, pH of 6.8 ($n = 11$). Contraction expressed in g (A, C, and E) and percentage of the maximal contraction induced by 90 mM KCl under standard conditions (pH 7.40; B, D, and F). Data presented as mean $\pm$ standard deviation. Each experiment served as its own control. No differences between acidosis and the standard condition (pH 7.40) were statistically significant ($P > .05$ for all).

In the present study, we observed that the real effect of acidosis on the arterial basal tone remained unpredictable. Arterial relaxation is mediated by endothelial nitric oxide, and nitric oxide production is reduced in the presence of human atherosclerosis.²⁸ β -Adrenergic dilation of the

large arteries is also dependant on the vascular endothelium.²⁹ Atherosclerosis can affect the internal mammary artery; however, surgical and experimental procedures can also damage the vascular endothelium.³⁰ It has also been shown that extracellular acidosis causes endothelial

FIGURE 3. Concentration–response curves for (A and B) methoxamine, an $\alpha_{1A/D}$ -adrenoceptor agonist ($n = 10$); C and D, phenylephrine, an equipotent agonist of $\alpha_{1A/B}$ -adrenoceptors ($n = 10$); and (E and F) clonidine, a peripheral α_2 -adrenoceptor agonist ($n = 5$), in human distal internal mammary arteries in the absence (pH 7.40) and presence (pH 6.80) of severe extracellular acidosis. Contraction expressed in g (A, C, and E) and percentage of the maximal contraction induced by 90 mM KCl under standard conditions (pH 7.40; B, D, and F). Acidosis sensitized human arterial rings to methoxamine but did not significantly alter the arterial responsiveness to phenylephrine and clonidine. Data presented as mean $\pm$ standard deviation. Each experiment served as its own control. * $P < .05$, ** $P < .001$, acidosis vs standard condition (pH 7.40).

dysfunction by inhibiting store-operated Ca^{2+} entry and nitric oxide production in cultured porcine aortic endothelial cells.³¹ Taken together, these findings and our results

suggest that acidosis could directly alter endothelium function in a pH-dependent manner in human large vessels.

The major limitation of the present study was the use of medium-size arteries, given that most systemic vascular resistance and control of tissue blood flow comes from the arteriolar resistance vessels. The ligand–receptor interactions could be different, depending on the tissue type. However, agonists such as epinephrine and norepinephrine will have the same dissociation constant, which is related to the affinity and potency of each agonist, for the same receptor, regardless of the tissue or cell. Another limitation of the present study was that the internal mammary artery is an α_1 -adrenoceptor–dominant artery with little α_2 - or β -function.³² Finally, our findings should not be overinterpreted, because the present study focused mainly on the effect of severe acidosis on epinephrine and norepinephrine potency for the α_1 -adrenoceptor. Because potency is a measure of drug activity expressed in terms of the dose required to produce an effect of given intensity, our experimental model could have clinical relevance in perioperative management.

CONCLUSIONS

Severe extracellular acidosis did not influence the vasoactive properties of epinephrine and norepinephrine in human isolated mammary artery until a pH of 6.80. From a pharmacologic viewpoint, the results of the present study could be an argument for not consistently increasing the doses of vasoconstrictors in the case of severe acidosis. From a clinical viewpoint, acidosis could affect the overall dynamic (eg, cardiac function, peripheral vasculature, coronary vasculature, and brain vasculature) in perioperative management. Thus, the question of whether to tolerate a lower pH in patients receiving vasoconstrictors requires future investigations based on the results of the present study to determine the best tolerance threshold of acidosis.

The authors thank the surgical nurses of the departments of cardiovascular surgery for their assistance during the collection of tissues.

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