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Influence of Epinephrine on Systemic, Myocardial, and Cerebral Acid–Base Status during Cardiopulmonary Resuscitation

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During cardiopulmonary resuscitation (CPR), arterial *p*H and carbon dioxide tension (P_{CO_2}) do not reflect the marked acidosis and hypercapnia seen in venous blood samples during CPR. Epinephrine causes an increase in myocardial and cerebral blood flow during CPR, but the influence on regional venous P_{CO_2} and *p*H is as yet unknown. Fourteen pigs were allocated to receive either 0.9% saline (n = 7), or 45 μg/kg epinephrine (n = 7) after 5 min of ventricular fibrillation and 3 min of open-chest CPR. Blood samples were obtained during CPR from the aorta, pulmonary artery, great cardiac vein, and sagittal sinus before and 90 s and 5 min after drug administration. Regional blood flow was measured with tracer microspheres. Plasma catecholamines were quantified by high-performance liquid chromatography in arterial blood. P_{CO_2} 90 s after drug administration in arterial, mixed venous, myocardial venous, and cerebral venous blood were (means ± SD) 36 ± 8, 67 ± 9, 74 ± 14, and 79 ± 19 mmHg in the control group and 35 ± 11, 62 ± 12, 73 ± 10, and 71 ± 14 mmHg in the epinephrine group. *p*H values 90 s after drug administration in the same blood samples were 7.29 ± 0.11, 7.11 ± 0.09, 7.04 ± 0.09, and 7.07 ± 0.10 in the control group and 7.31 ± 0.13, 7.17 ± 0.07, 7.08 ± 0.08, and 7.07 ± 0.12 in the epinephrine group. Despite a significant increase in myocardial and cerebral blood flow after epinephrine, P_{CO_2} and *p*H in all blood samples were not different from those of the control group. During CPR and prior to epinephrine, plasma epinephrine concentrations in arterial blood increased from a prearrest value of 1.23 ± 1.90 to 72.1 ± 56.4 ng/ml, and plasma norepinephrine concentrations increased from 0.32 ± 0.38 to 106.8 ± 53.0 ng/ml. After exogenous epinephrine, there was an additional increase to 265.7 ± 82.2 at 90 s in arterial plasma epinephrine but no significant alteration in arterial plasma norepinephrine. No significant correlation between arterial catecholamine concentrations and myocardial or cerebral blood flow was found. We conclude that the effectiveness of vasopressor treatment in improving myocardial and cerebral blood flow during CPR cannot be evaluated by determining the P_{CO_2} and *p*H in regional venous blood. We hypothesize that after epinephrine, more anaerobically produced hydrogen ions are neutralized by the endogenous bicarbonate system, which in turn generates more carbon dioxide. (Key words: Acid–base balance. Brain: blood flow. Heart: cardiopulmonary resuscitation. Measurement techniques: microspheres. Sympathetic nervous system, catecholamines: epinephrine.)

DURING CARDIOPULMONARY RESUSCITATION (CPR), a marked difference in carbon dioxide tension (P_{CO_2}) exists between arterial and mixed venous blood; venous hypercapnia is indicative of poor organ perfusion.[1–9] The American Heart Association currently recommends use of epinephrine to improve myocardial and cerebral blood flow during CPR.[10] Alpha-adrenergic-mediated vasoconstriction of the peripheral circulation is believed to redistribute blood flow to the heart and brain.[11–13] As yet, however, the influence of epinephrine on systemic, myocardial, and cerebral acid–base status is unknown. The purpose of this study was to determine the effect of epinephrine administration during CPR on these parameters. In particular we wanted to assess whether the effectiveness of epinephrine in improving myocardial and cerebral perfusion can be evaluated by measuring P_{CO_2} and *p*H values in regional venous blood.

Materials and Methods

Animal Preparation

This investigation was reviewed and approved by our institutional Animal Care Committee.

Fourteen pigs (21 ± 1 kg; mean ± SD) had anesthesia induced with 10 mg/kg metomidate *via* an ear vein. The pigs then were placed in the dorsal recumbent position and their tracheas intubated. The animals' lungs then were ventilated with a Servo ventilator 900 (Servo, Siemens, FRG) with 65% nitrous oxide in oxygen at 22 breaths per min and with tidal volume adjusted to maintain arterial P_{CO_2} at 35 mmHg. Anesthesia was maintained by a continuous intravenous infusion of metomidate (0.5 $mg \cdot kg^{-1} \cdot h^{-1}$) and a single dose of buprenorphine (0.03 mg/kg). The stability of hemodynamic variables during this phase indicated that the depth of anesthesia was sufficient. Muscular relaxation was achieved with 0.25 mg/kg alcuronium chloride. For further relaxation, hexcarbacholine bromide was injected after 5 min at a dose of 0.25 mg/kg. Relaxation was performed in order to avoid high doses of hypnotic and analgesic agents, which could depress cardiovascular function. Metomidate infusion was stopped at the end of the preparation phase, 10 min before induction of cardiac arrest.

A standard lead II ECG was used for monitoring cardiac rhythm. A double-lumen 7-Fr catheter was advanced by femoral cutdown into the descending aorta to monitor blood pressure. Reference blood samples for the measurement of myocardial and cerebral blood flow were withdrawn from this catheter. Two 5-Fr catheters were inserted *via* femoral cutdowns into the intrathoracic vena cava and into the aorta for withdrawal of blood samples.

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A 5-Fr pulmonary artery catheter (Swan-Ganz, Baxter Edwards Laboratories, Irvine, CA) was placed *via* the external jugular vein into the pulmonary artery.

After the thorax had been opened by median sternotomy, a 5-Fr catheter was introduced under digital control from a branch of the external jugular vein into the coronary sinus. The azygous vein was ligated to ensure that the coronary sinus contained only cardiac venous blood. A 5-Fr catheter was introduced *via* the left auricle into the left atrium. This catheter was used for the bolus injections (5 ml iced saline solution) necessary to measure cardiac output and to inject radionuclide microspheres for the measurements of myocardial and cerebral blood flow. Cardiac output was measured in duplicate by thermodilution with a thermistor (Hoyer, FRG), which was placed *via* femoral artery cutdown in the thoracic aorta. A catheter (Leader Catheters 22-G, Vygon, France) was placed through a hole into the sagittal sinus, with the tip lying 1–2 cm anterior to the confluence of the sinus. This catheter was used to sample cerebral venous blood.

Pressure transducers (model P 23 Db, Gould) were aligned at the level of the right atrium and then zero-established to atmospheric pressure and calibrated with a mercury sphygmomanometer.

Experimental Design

Ventricular fibrillation was induced by a 50-Hz 140-mA alternating current applied directly to the myocardium. After a 5-min period of cardiac arrest, open-chest massage was performed at a rate of 60 compressions per min with the thumb of the right hand placed on the left ventricle while the fingers encircled the right ventricle.

When cardiac massage was begun, ventilation was resumed with 100% oxygen at a respiratory rate of 22 breaths per min and at the tidal volume that had been determined as resulting in normocapnia before arrest.

After 3 min of CPR, animals randomly received either 10 ml normal saline (n = 7) or epinephrine (45 μg/kg in 10 ml normal saline, n = 7) given *via* the central venous catheter over 30 s. Hemodynamic variables, organ blood flow measurements, and blood samples from the aorta, pulmonary artery, great cardiac vein, and sagittal sinus were taken before the arrest, before drug administration (*i.e.*, after a total of 8 min of arrest, including 3 min of CPR), and 90 s and 5 min after drug administration. The investigators were blinded with regard to the use of epinephrine or saline. Cardiac massage always was performed by the same person.

Myocardial and Cerebral Blood Flow

Myocardial and cerebral blood flow were measured with radiolabeled microspheres according to the technique of Heymann *et al.*[14] Microspheres (New England Nuclear) with a mean diameter of 15 ± 1.5 μm were used. They were labeled with niobium[95] and ruthenium[103]. Because of requirements of our radiation control committee, prearrest values were measured only in the control group, and myocardial and cerebral blood flow at 90 s after drug injection was measured only in the epinephrine group. Myocardial and cerebral blood flow 5 min after drug administration was measured in both the control and epinephrine groups. To ensure blinding, normal saline was used instead of tracer microspheres in the epinephrine group prearrest and in the control group at 90 s after drug administration.

Before injection, the microsphere vial was placed in an ultrasonically vibrated water bath for 1 min. For each regional blood flow determination, approximately 5.0×10^5 microspheres diluted in 10 ml saline were injected in the left atrium. With the use of a withdrawal pump (Braun, FRG), blood was withdrawn continuously from the catheter lying in the descending aorta at a rate of 9.91 ml/min, from 10 s before microsphere injection to 80 s after injection. Blood from the two lumina of the aortic catheter was combined, and a single reference sample was used.

The entire myocardium and brain were removed at the end of the experiment. The radioactivity of the blood collected, which served as reference organ, was measured with a gamma scintillation spectrometer (Gammacounter, Berthold, FRG), as was the radioactivity in the homogenized heart and brain.

Validation of Microsphere Technique

We evaluated the microsphere technique during CPR in a pilot study (n = 5 animals). Eighty seconds after microsphere injection, a residual count of 2.2% of the total activity injected was measured in the blood of the left atrium and ventricle; this was considered to be good evidence for microsphere ejection from the heart. The adequate mixing of microspheres and blood was indicated by comparison of right and left cerebral cortices and of right and left renal blood flow, in neither of which was there significant difference (Student's *t* test: $P > 0.05$).

Blood Analysis and Calculations

Blood gases were measured with a blood gas analyzer (IL 1302, Instrumentation Laboratories, Lexington, MA). Plasma lactate concentrations were measured with a lactate analyzer (Roche, FRG).

Myocardial and cerebral blood flow indices express the ratio between the perfusion of the myocardium and cerebrum and the remaining body tissue, and were calculated as follows.

$$\text{Myocardial blood flow index (\%)} = \frac{\text{Myocardial blood flow (ml} \cdot \text{min}^{-1} \cdot 100\ \text{g}^{-1})}{\text{Cardiac index (ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}}$$

$$\text{Cerebral blood flow index (\%)} = \frac{\text{Cerebral blood flow (ml} \cdot \text{min}^{-1} \cdot 100\ \text{g}^{-1})}{\text{Cardiac index (ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1})}$$

Plasma Catecholamine Analysis

Immediately after centrifugation and addition of an antioxidizing stabilizer, the serum was frozen at −76° C until the time of analysis. The analysis of plasma catecholamine concentrations was based on their selective isolation by absorption onto surface-activated aluminum oxide at a *p*H of 8.7 (2 M Tris buffer) and subsequent elution with 0.2 M acetic acid, and was quantitated by high-performance liquid chromatography (HPLC) with electrochemical detection (Waters Associates, Milford, MA).[15] The method is sensitive to less than 0.01 ng/ml of epinephrine or norepinephrine. Interassay coefficients of variation were below 10% for epinephrine and norepinephrine.

Statistical Analysis

All data are reported as means ± SD. The Mann-Whitney–Wilcoxon test was used to determine differences in hemodynamic parameters between the control and epinephrine group. For comparison of hemodynamic parameters within the same group prior to and after drug administration, the Wilcoxon signed-rank test was used. Differences between arterial, mixed venous, myocardial venous and cerebral venous P_{CO_2}; *p*H; lactate; and plasma catecholamine determinations prearrest and during CPR within the same group and between groups were tested by analysis of variance with multiple-comparison testing (with the Newman-Keuls test) when more than two measurements were compared. After logarithmic transformation, correlations between epinephrine and norepinephrine plasma concentrations were tested by linear regression analysis. The significance of the correlation between regional blood flow and plasma catecholamine concentration was evaluated by calculation of the Spearman correlation coefficient. Statistical significance was considered to be the $P < 0.05$ level.

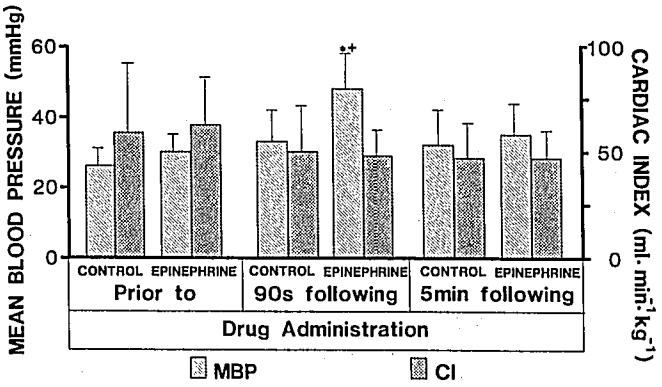

FIG. 1. Mean arterial blood pressure (MBP) and cardiac index (CI) (mean ± SD) during open-chest CPR prior to, 90 s after, and 5 min after administration of saline (control group) or of 45 μg/kg epinephrine. *$P < 0.05$ *versus* epinephrine group prior to drug administration; †$P < 0.05$ *versus* control group 90 s after drug administration.

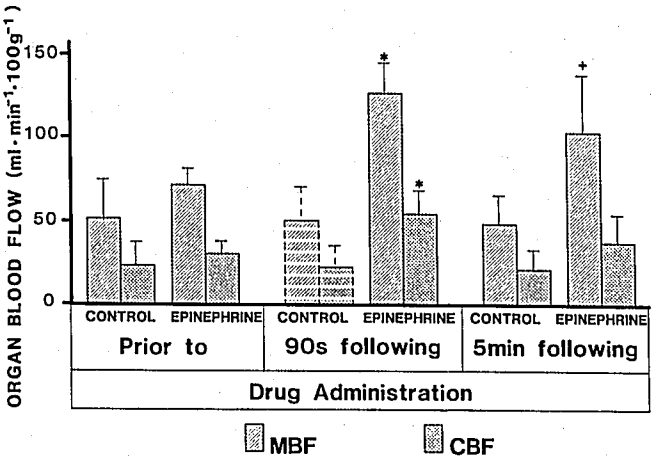

FIG. 2. Myocardial blood flow (MBF) and cerebral blood flow (CBF) (mean ± SD) during open-chest CPR prior to, 90 s after, and 5 min after administration of saline (control group) or of 45 μg/kg epinephrine. Blood flow values at the 90-s point of observation in the control group were calculated as mean values of blood flows prior to and 5 min after saline administration. *$P < 0.05$ *versus* epinephrine group prior to drug administration; †$P < 0.05$ *versus* control group 5 min after drug administration.

Results

Hemodynamic Parameters

Mean arterial blood pressure was significantly higher in the epinephrine group than in the control group at 90 s after drug administration, whereas cardiac index was not different at any point of observation between the two groups (fig. 1).

Myocardial and cerebral blood flow increased significantly 90 s after epinephrine administration in comparison to blood flow prior to drug administration. Myocardial blood flow was significantly higher in the epinephrine group than in the control group 5 min after drug administration (fig. 2). Prior to drug administration, the myocardial blood flow index was not significantly different between groups. Myocardial blood flow index increased significantly, to 3,034 ± 1450% 90 s after epinephrine administration (table 1). Five minutes after drug admin-

TABLE 1. Myocardial and Cerebral Blood Flow Index

Index	Group	Prearrest	CPR (Time Relative to Drug Administration)		
			Prior to	90 s after	5 min after
Myocardial blood flow	Control	1149 ± 221	1165 ± 1081	—	1020 ± 383
	Epinephrine	—	1120 ± 385	3034 ± 1450*	2412 ± 877†
Cerebral blood flow	Control	287 ± 73	371 ± 122	—	397 ± 167
	Epinephrine	—	583 ± 182	1201 ± 439*	799 ± 315†

Mean ± SD.
* $P < 0.05$ *versus* epinephrine group prior to drug administration.
† $P < 0.05$ *versus* control group 5 min after drug administration.

istration, the myocardial blood flow index was significantly greater in the epinephrine group than in the control group. Cerebral blood flow index also was augmented by epinephrine, although the increase was not as marked as in the myocardium.

Acid-Base Effects

There were no significant differences in the blood gas, *p*H, and lactate determinations in arterial, mixed venous, myocardial venous and cerebral venous blood during normal sinus rhythm.

Mixed venous, myocardial venous and cerebral venous P_{CO_2} were significantly higher during CPR in comparison to arterial P_{CO_2} at all points of observation (fig. 3). Prior to drug administration, cerebral venous P_{CO_2} was significantly higher than myocardial and mixed venous P_{CO_2} in both groups. Despite an increase in myocardial and cerebral blood flow in animals given epinephrine, no difference in arterial, mixed venous, myocardial venous, or cerebral venous P_{CO_2} between experimental groups was found at 90 s or at 5 min after drug administration.

Mixed venous, myocardial, and cerebral venous *p*H values were significantly lower during CPR in comparison to arterial *p*H values (fig. 4). The *p*H value at the various venous sites, when compared to that of the control groups, was not influenced by epinephrine administration.

Lactate concentrations were measured in arterial, myocardial venous, and cerebral venous blood. During CPR, lactate concentrations tended to be higher in myocardial venous than in arterial and cerebral venous blood (fig. 5). A significantly higher lactate concentration in myocardial venous blood than in arterial and cerebral venous blood was found only in the epinephrine group prior to drug administration. Again, there was no difference between control and epinephrine groups after drug administration at any of the sampling site.

Plasma Catecholamines

During cardiac arrest and CPR the endogenously released epinephrine and norepinephrine concentrations rose significantly, with norepinephrine showing the larger degree of change (table 2). In the control group, arterial plasma epinephrine increased from 1.00 ± 1.40 prearrest to 78.1 ± 71.3 ng/ml prior to drug administration, and then decreased to 30.5 ± 34.0 and 21.6 ± 10.7 ng/ml at 90 s and 5 min after drug administration. After administration of exogenous epinephrine, there was a significant

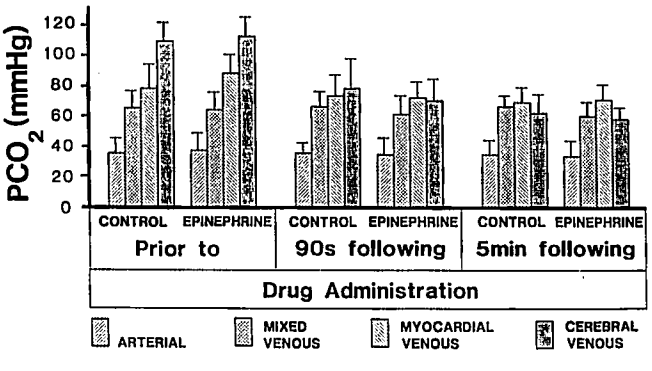

FIG. 3. Arterial, mixed venous, myocardial venous, and cerebral venous P_{CO_2} during open-chest CPR prior to, 90 s after, and 5 min after administration of saline (control group) or of 45 μg/kg epinephrine. No difference in P_{CO_2} at the various sampling sites was found between the control and epinephrine groups.

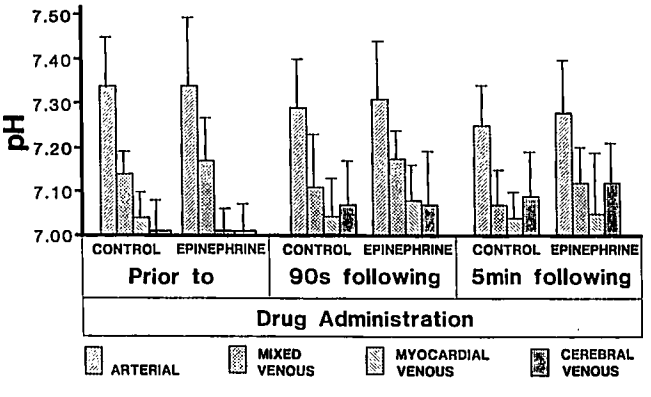

FIG. 4. Arterial, mixed venous, myocardial venous, and cerebral venous *p*H during open-chest CPR prior to, 90 s after, and 5 min after administration of saline (control group) or of 45 μg/kg epinephrine. No difference in *p*H at the various sampling sites was found between the control and epinephrine groups.

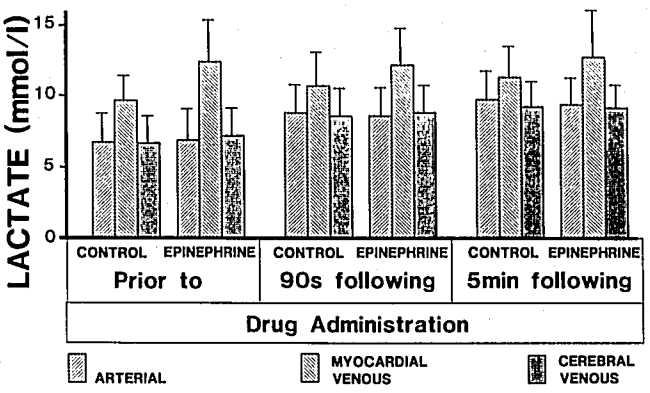

FIG. 5. Arterial, myocardial venous, and cerebral venous lactate concentrations during open-chest CPR prior to, 90 s after, and 5 min after administration of saline (control group) and of 45 μg/kg epinephrine. No difference in lactate concentrations at the various sampling sites was found between the control and epinephrine groups.

difference compared to control group values at 90 s and 5 min after drug administration.

In the control group, arterial plasma norepinephrine increased from 0.18 ± 0.17 prearrest to 137.7 ± 94.1 ng/ml during CPR prior to drug administration, and then decreased to 60.8 ± 55.5 and 37.6 ± 16.1 ng/ml during the remaining course of CPR. In the epinephrine group, arterial plasma norepinephrine increased from 0.32 ± 0.38 prearrest to 106.8 ± 53.0 ng/ml during CPR prior to drug administration and then decreased to 29.2 ± 13.9 and 20.7 ± 14.7 ng/ml at 90 s and 5 min after drug administration. There was a trend toward higher norepinephrine concentrations in the control group in comparison to the epinephrine group after drug administration (but with no significant difference).

After logarithmic transformation, a high correlation (r = 0.944) between endogenous plasma epinephrine and norepinephrine concentrations was found in the control group and in the epinephrine group prior to exogenous epinephrine administration. No such relationship was found 90 s and 5 min after the administration of exogenous epinephrine (r = 0.412 and 0.138, respectively).

Neither myocardial nor cerebral blood flow correlated with plasma catecholamine concentrations in either the control group or in the epinephrine group, either before or after exogenous epinephrine was given.

Discussion

Our study has some methodologic limitations. Because the use of radiolabeled microspheres was restricted, myocardial and cerebral blood flow values 90 s after saline administration were created by averaging the preceding and succeeding values. The epinephrine dose of 45 μg/kg (approximately 1 mg in our animals) was selected according to previous results in pigs with a 4-min period of arrest, in which we found that this dose produced the highest coronary perfusion pressure and myocardial blood flow, and that no further improvement in hemodynamic variables was possible with an increase to 90 μg/kg.[16] After a 10-min period of arrest in pigs, a dose of 200 μg/kg was needed to achieve a myocardial blood flow above 20–25 ml · min^{-1} · 100 g^{-1}, which seems necessary to meet the metabolic needs of the fibrillating myocardium.[11,17]

Furthermore, during ventricular fibrillation, myocardial oxygen consumption is not a static parameter but increases with time.[17] The administration of a single bolus dose causes only a transient increase in perfusion pressures and organ blood flow. Acid–base status was determined at only two points in time after drug administration, and it may well be that we would have obtained different results had we made these measurements at other points in time. In addition, we do not know what effect a continuous infusion of epinephrine, as used in other studies,[12,13,18] would have had on arteriovenous P_{CO_2} and *p*H gradients. Our results are based on a global venous measurement; a possible regional organ redistribution of blood flow (*i.e.*, arteriovenous shunting after epinephrine) and a concomitant influence on regional acid–base status in the myocardium and cerebrum cannot be excluded.

Our study confirms the work of previous investigations that show that a large P_{CO_2} gradient exists between arterial and venous blood during CPR, not only for the body as a whole but also for individual organs.[1–9,19,20] A reduction in organ blood flow in the presence of a constant production and elimination of carbon dioxide results in a

TABLE 2. Arterial Plasma Catecholamine Concentration (ng/ml)

	Group	Prearrest	CPR (Time Relative to Drug Administration)		
			Prior to	90 s after	5 min after
Epinephrine concentration	Control	1.00 ± 1.40	78.1 ± 71.3	30.5 ± 34.0	21.6 ± 10.7
	Epinephrine	1.23 ± 1.90	72.1 ± 56.4	265.7 ± 82.2*†	49.3 ± 20.2†
Norepinephrine concentration	Control	0.18 ± 0.17	137.7 ± 94.1	60.8 ± 55.5	37.6 ± 16.1
	Epinephrine	0.32 ± 0.38	106.8 ± 53.0	29.2 ± 13.9	20.7 ± 14.7

Mean ± SD.
* $P < 0.05$ *versus* epinephrine group prior to drug administration.
† $P < 0.05$ *versus* control group 90 s and 5 min after drug administration.

widening of the arteriovenous P_{CO_2} gradient.[6] The inadequate tissue perfusion during CPR leads to anaerobic metabolism. Despite the decrease in aerobic metabolism and the subsequent decrease in carbon dioxide production from this source, the rise in venous P_{CO_2} during CPR is most likely generated through neutralization of anaerobically produced hydrogen ions by the endogenous bicarbonate system. Because the low tissue perfusion during CPR is inadequate to meet tissue oxygen requirements, lactic acidemia develops. Since epinephrine administration did not lead to a significant change in cardiac index, it is not surprising that we found no significant change in mixed venous P_{CO_2} concentrations after epinephrine administration.

In accordance with other studies, we were able to show that epinephrine increases myocardial and cerebral blood flow during CPR.[11-13] Despite an increase in regional organ blood flow, myocardial and cerebral P_{CO_2} of the epinephrine group did not differ significantly from those of the control group. Even comparison of individual animals—*i.e.*, animals with the greatest myocardial or cerebral blood flow *versus* the animals with the least blood flow—demonstrated no difference in organ venous acid–base status related to organ blood flow.

Still open to discussion is what effect epinephrine has on myocardial and cerebral oxygenation during resuscitation from ventricular fibrillation. After measuring myocardial adenosine triphosphate (ATP) and lactate concentrations in a dog model, Ditchey and Lindenfeld suggested that epinephrine may not improve the balance between myocardial oxygen delivery and consumption during CPR, despite an increase in myocardial blood flow.[18] In that study, closed-chest CPR was started immediately after induction of ventricular fibrillation. In a pig model, Brown *et al.* demonstrated that after a 10-min period of ventricular fibrillation, epinephrine (200 μg/kg) improved myocardial oxygen delivery over myocardial oxygen consumption, as characterized by a decrease in the oxygen extraction ratio after drug administration.[21]

The duration of cardiac arrest seems to determine the effect of epinephrine on myocardial blood flow and on the balance of myocardial oxygen delivery and consumption. The duration of arrest also may influence the effect of epinephrine on myocardial arteriovenous P_{CO_2} gradients. It may be that the effect of epinephrine on organ oxygen consumption outweighs the increase in blood flow, and therefore that more anaerobically produced hydrogen ions are neutralized by the endogenous bicarbonate system, which in turn generates more carbon dioxide. Based on current knowledge, we hypothesize that after epinephrine, changes in hemodynamic rather than in metabolic variables are a better indication of the potential for success in cardiac resuscitation.

Studying the cerebrum, Schleien *et al.* demonstrated in piglets and in dogs that the benefit of increasing oxygen delivery with epinephrine outweighs any potential metabolic stimulation in terms of tissue oxygenation.[12,13] Despite an increase in cerebral blood flow after epinephrine administration, cerebral venous P_{CO_2} concentrations were not significantly different between the two groups in our investigation. Therefore, the improvement in cerebral oxygenation after vasopressor therapy cannot be evaluated by measuring cerebral venous P_{CO_2} concentrations. An additional noteworthy finding was that during the course of CPR, cerebral venous P_{CO_2} concentrations decreased by the same degree in both groups; this perhaps indicates a decrease in carbon dioxide production by an exhaustion of the endogenous bicarbonate buffer system.

It has been demonstrated in humans and in animals that plasma levels of epinephrine and norepinephrine increase dramatically during cardiac arrest and resuscitation.[22-25] In contrast to the investigation performed by Kern *et al.* on dogs,[26] norepinephrine plasma concentration showed a greater degree of change during CPR in our pigs. The initial increase in catecholamine concentration was followed by gradual decrease in the control group. There was a trend toward higher norepinephrine concentrations in the control group as compared to the epinephrine group after drug administration (but without significant difference); this trend may partially mask epinephrine related hemodynamic or metabolic effects.

At none of the points of observation during CPR did myocardial or cerebral blood flow correlate with plasma catecholamine concentrations in either the control group or the epinephrine group. It can be presumed that the absolute level of catecholamine does not guarantee a certain level of blood flow. The response to catecholamines may relate not only to plasma concentration but also to the amount and activation of adrenergic receptors. Foley *et al.* found no significant correlation between plasma catecholamines and the end-diastolic arteriovenous pressure difference (the difference between arterial and right atrial pressure during the relaxation phase),[24] which represents coronary perfusion pressure and determines myocardial blood flow during closed-chest CPR.[11] Foley *et al.* hypothesized that this variability in catecholamine response may be related to differences between individual dogs in catecholamine secretion from the adrenal medulla, which seems to be the predominant source of endogenously released catecholamines.

In accordance with other studies we observed a highly significant correlation between plasma epinephrine and norepinephrine concentrations during CPR without exogenously administered epinephrine.[23,26] This correlation indicates that cardiac arrest and CPR stimulated adrenomedullary release of norepinephrine in addition to epinephrine.

In summary, the high P_{CO_2} in myocardial and cerebral venous blood were not decreased after 45 μg/kg of epinephrine in comparison to a control group, despite an

increase in regional blood flow. Plasma epinephrine and norepinephrine concentrations did not correlate with myocardial and cerebral blood flow either before or after epinephrine administration. The effectiveness of epinephrine to improve heart and brain perfusion cannot be evaluated by measuring P_{CO_2} and *p*H values in myocardial and cerebral venous blood. In further studies, the influence of other treatment modalities, such as the use of alternative sympathomimetic amines and buffer substances on arteriovenous P_{CO_2} gradients, should be pursued.

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