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Myocardial Hypercarbic Acidosis Reduces Cardiac Resuscitability

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Background: The severity of spontaneous myocardial hypercarbic acidosis during cardiac arrest previously has been predictive of the likelihood of restoring spontaneous circulation. The present study investigated whether hypercarbia itself impairs cardiac resuscitation. Since coronary perfusion pressure is the overriding determinant of cardiac resuscitability, we used a porcine model of cardiac arrest in which coronary perfusion pressure was controlled.

Methods: In 31 domestic pigs anesthetized with pentobarbital, the lungs were mechanically ventilated. Myocardial carbon dioxide tension and hydrogen ion concentration were measured by sensors advanced into the myocardium. After 15 min of untreated ventricular fibrillation, venoarterial extracorporeal circulation was initiated. Animals were randomized to receive a carbon dioxide gas fraction in the extracorporeal perfusate of 0.00, 0.10, 0.30, or 0.50 with oxygen concentration maintained constant at 0.50. Extracorporeal flow

was adjusted to maintain a coronary perfusion pressure in the range of 60–80 mmHg, a level of predictive resuscitability.

Results: The proportion of animals successfully resuscitated and the proportion of animals maintaining spontaneous circulation for 60 min or longer decreased with increasing perfusate P_{CO_2} and concurrent increases in myocardial CO_2 tension in the absence of altered oxygen utilization ($P < .01$).

Conclusions: Hypercarbia, in this experimental setting, was therefore a quantitative determinant of both myocardial resuscitability and the restoration of spontaneous circulation. (Key words: Carbon dioxide; hypercarbia. Extracorporeal circulation. Heart, resuscitation: myocardial acidosis.)

PREVIOUSLY we demonstrated increases in myocardial CO_2 tension (PM_{CO_2}) with corresponding increases in myocardial $[H^+]$ during ventricular fibrillation in pigs.^{1,2} PM_{CO_2} was inversely correlated with the coronary perfusion pressure (CPP) generated during precordial compression, and both predicted the likelihood of re-establishing spontaneous circulation after external countershock.[¶] However, the earlier studies did not distinguish the effect of hypercarbia independently from that of CPP. Hypercarbia reduces myocardial contractility in the isolated heart muscle preparations^{3,4} and also may be detrimental in the intact animal.⁵ In the isolated perfused heart, CO_2 produced a decrease in contractility to approximately 20% of control values.⁶ In the intact animal, Walley⁵ demonstrated a substantial reduction in contractility in dogs when respiratory acidosis was induced in animals during spontaneous circulation.

It was our hypothesis that the progressive myocardial hypercarbia that occurs spontaneously during cardiac arrest was an independent determinant of the success of resuscitation efforts. This hypothesis was supported by earlier studies in rats. When the lungs of rats were ventilated with gas mixture containing 0.50 CO_2 and 0.50 O_2 during cardiac arrest, this precluded successful resuscitation.⁷

The present study was therefore designed to specifically investigate the effects of hypercarbia under con-

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ditions in which the CPP and arterial oxygenation were controlled. Accordingly, we used extracorporeal circulation (ECC), which had been used previously by our group⁸ and by others,⁹ as an alternative to cardiac compression for restoring coronary perfusion, thereby making it possible to resuscitate the heart after unusually protracted intervals of untreated cardiac arrest. In the present studies, ECC was used to restore CPP before attempted defibrillation after a 15-min interval of untreated ventricular fibrillation.

Methods

The studies were approved by our Institutional Animal Care Committee. Animal care and procedures were in accord with the *Guide for the Care and Use of Laboratory Animals*, edited by the Institute of Laboratory Animals Resources of the National Research Council.

Animal Preparation

Thirty-six domestic pigs weighing 25–35 kg were investigated. The animals were fasted for 12 h but were provided free access to water. Anesthesia was initiated by intramuscular ketamine (20 mg/kg), followed by ear vein injection of pentobarbital (30 mg/kg). After tracheal intubation, the animals' lungs were ventilated with a volume-controlled ventilator (Puritan Bennett, model MA-1, Los Angeles, CA), with a tidal volume of 15 ml/kg, $F_{I_{O_2}}$ of 0.50, peak flow of 15 L/min, and respiratory rate adjusted to maintain end-tidal CO_2 (ET_{CO_2}) between 30 and 35 mmHg. ET_{CO_2} was measured using an infrared CO_2 analyzer (Instrumentation Laboratories, model 200, Lexington, MA). ET_{CO_2} was measured on the expiratory plateau of the capnogram with corrections for ambient pressure, temperature, and water vapor. Neuromuscular blockade was induced by intravenous injection of pancuronium bromide (0.09 mg/kg) and maintained with doses of 0.05 mg/kg at intervals of 60 min. Anesthesia was supplemented with intravenous doses of pentobarbital (8 mg/kg) at intervals of 30 min.

For hemodynamic measurements, a 7-French thermolubric catheter was advanced into the pulmonary artery from a surgically exposed right femoral vein. Through the surgically exposed left cephalic vein, a 7-French angiographic catheter was advanced into the great cardiac vein under fluoroscopic guidance. After surgically exposing the left external carotid artery, an 8-French angiographic catheter was advanced into the thoracic aorta. All catheter positions were confirmed

by fluoroscopy, by characteristic pressure pulse morphology, and at autopsy.

The technique of ECC has been described previously.⁸ In brief, two 14-French cannulas were advanced through both surgically exposed femoral arteries with the tips positioned at the level of external iliac arteries. A 17-French thin-walled cannula with multiple orifices at its tip was advanced under fluoroscopic guidance from the left external jugular vein to the inferior vena cava. A membrane oxygenator was connected in series with a centrifugal pump. The flow was nonpulsatile and adjustable over the range of 0–5 L/min. The components were connected in series using bypass tubing (American Bentley, Irvine, CA, model TM70). Bovine heparin (100 IU/kg) was infused into the venous side of the ECC circuit. The system was primed with approximately 600 ml 6% hydroxyethyl starch supplied through the courtesy of DuPont Critical Care (DuPont-Merck, Wilmington, DE). Extracorporeal flow was continuously measured at the efferent side of the oxygenator with an ultrasonic flow meter. Blood temperature was measured in the pulmonary artery and maintained between 37° C and 38° C before ECC with external infrared lamps. During resuscitation, temperature declined to a minimum of 35.5° C, which was restored to the range of 37–38° C within 3 min by use of infrared heating lamps.

For measurement of PM_{CO_2} , an ion-sensitive field effect transistor sensor was used. For myocardial pH measurements, a miniature glass electrode was used with a thermistor for myocardial temperature measurements. Myocardial pH was measured using a Khuri pH monitor by techniques previously described by us.¹ The 95% *in vitro* response time to step changes in hydrogen ion concentration was faster than 3 s with a linear response over the range of interest.^{10,11} The probe was calibrated *in vitro* before and after the experiments with buffer solution with a pH of 4.0 and 7.0 pH units. The validity of these measurements under these experimental conditions of extreme hypercarbic acidosis have been reported previously.¹ For placement of P_{CO_2} , pH, and temperature myocardial sensors, a midline laparotomy was performed and subdiaphragmatic structures were mobilized and reflected inferiorly. A window of approximately 5 × 8 cm was created through the tendinous portion of the diaphragm. Through a small pericardial window, the P_{CO_2} , pH, and temperature sensors were inserted into the inferior wall of the left ventricle to a depth of approximately 5 mm. The pericardial window was closed with a purse-string suture, and the

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sensors anchored to the closed pericardium. A potassium chloride reference electrode was inserted in a subcutaneous pocket in proximal left posterior leg.

Measurements

Dynamic data, including lead II electrocardiogram, intravascular and intracardiac pressures, end-tidal CO_2 , myocardial and blood temperature, myocardial pH, and P_{CO_2} were recorded continuously. Systemic vascular resistance was calculated as follows: $\text{SVR} (\text{dynes} \cdot \text{s} \cdot \text{cm}^{-5}) = [(\text{MAP} - \text{RAP})/\text{CO}] \times 79.9$, where MAP (mmHg) = mean aortic pressure; RAP (mmHg) = mean right atrial pressure; and CO (L/min) = cardiac output. When ECC was used, CO represented measured pump flow (L/min).

Arterial, central venous, and great cardiac vein blood gases, including pH, P_{CO_2} , P_{O_2} , O_2 content, and lactic acid were measured by techniques described previously.^{12,13}

Coronary arteriovenous oxygen difference was calculated as the arithmetic difference between time-coincident aortic oxygen content and great cardiac vein oxygen content (ml/100 ml blood).

Myocardial oxygen extraction was calculated as the coronary arteriovenous oxygen content difference divided by arterial oxygen content and expressed as percent.

Myocardial lactate extraction was calculated as the coronary arteriovenous lactate content difference divided by arterial lactate content and expressed as percent (%).

Experimental Protocol

Ventricular fibrillation was induced by delivering 10 mA AC current to the right ventricular epicardium. The $\text{F}_{\text{I}\text{O}_2}$ then was increased to 1.00 and maintained at this level for the duration of the experiment. Prior to start of ECC, the animal was randomized to one of four subsets in which CO_2 fractional gas concentration supplied to the oxygenator (F_{O_2}) was established at 0.00, 0.10, 0.30, or 0.50 during resuscitation. This yielded extreme levels of myocardial hypercarbia comparable to those previously observed during experimental cardiac arrest.¹ The O_2 fractional gas concentration (F_{O_2}) supplied to the oxygenator was kept constant at 0.50 for each subset. Extracorporeal circulation was initiated after 15 min of untreated ventricular fibrillation, an interval identical to that of earlier studies in which ECC yielded more than 90% resuscitability.¹⁴ Coronary perfusion pressure was defined as the difference between end-diastolic aortic pressure and time-coincident

right atrial pressure. The flow of the extracorporeal system initially produced a CPP in the range of 60–100 mmHg. It was then adjusted to achieve levels ranging from 60–80 mmHg based on measurements of mean aortic and right atrial pressure. After 3 min of ECC, a 300-J transthoracic countershock was delivered and, if unsuccessful, repeated once after an interval of 10 s using a DC defibrillator (Physio-Control, model 911, Redmond, WA). Early experiences demonstrated an increase in myocardial P_{CO_2} with 90% equilibration within 3 min following increases in $\text{F}_{\text{I}\text{CO}_2}$ over the range of 0–0.50. If ventricular fibrillation persisted or recurred, additional pairs of 300-J countershocks were administered at 3-min intervals. Once a regular supra-ventricular electrically organized rhythm was restored, ECC was interrupted for a 30-s interval to assess whether spontaneous circulation had returned. These attempts were repeated at 3-min intervals until an unsupported mean aortic pressure ≥ 60 mmHg was sustained. Resuscitation was defined as restoration of a native mean aortic pressure ≥ 60 mmHg for a minimum interval of 3 min. Animals that maintained spontaneous circulation with a mean aortic pressure of 60 mmHg or greater for a minimum interval of 240 min after discontinuation of ECC were designated survivors. Extracorporeal circulation was discontinued if defibrillation failed to resuscitate after an interval of 60 min. Survivors were killed after 4 h by the intravenous injection of pentobarbital (150 mg/kg). Autopsy was performed to verify catheter and sensors placement and inspect intrathoracic and intra-abdominal structures to identify potential injuries to vital organs.

Statistical Analysis

Data are reported as mean \pm SD. For continuous data, differences among the four subsets were analyzed by analysis of variance using the Scheffe method for multiple comparison. Outcome differences in initial resuscitability and survival among the four F_{O_2} subsets were analyzed for overall differences and for dose effect using chi-square test for trend analysis.¹⁵

The cumulative power (J) required for successful resuscitation was significantly skewed. Accordingly, the nonparametric Kruskal-Wallis analysis of variance test by ranks was used.

Results

Resuscitation and Survival

Five animals were excluded from analysis. Exclusion was based on autopsy findings that demonstrated pre-

existing pulmonary consolidation due to pneumonia (2), left ventricular perforation during myocardial sensor insertion (2), and air embolization during pressure calibration (1). A residual of 31 animals constituted the group herein reported.

With increasing oxygenator CO₂ (F_OCO₂), there was a corresponding decrease in the success of resuscitation and survival (table 1). When the F_OCO₂ was 0.00, all animals survived. There was a progressive decrease in the success of resuscitation with 0.10, 0.30, and 0.50 CO₂ such that the success of resuscitation declined to 88%, 75%, and 43%, respectively. With F_OCO₂ at 0.30 and 0.50, there was a decrease in survival of resuscitated animals such that only one of seven animals with F_OCO₂ of 0.5 survived.

The duration of ECC before return of spontaneous circulation progressively increased with increasing oxygenator CO₂ concentration from an average of 3 to 22 min (table 1). The cumulative power (J) required for restoration of an electrically organized rhythm is presented in table 1. It demonstrated significant differences ($P < .02$) between F_OCO₂ 0.00 and each of the subsets in which F_OCO₂ was augmented.

Coronary Perfusion Pressure

The arterial and right atrial pressures prior to cardiac arrest and during ECC were maintained at levels that yielded CPP ≥ 60 mmHg. These would predict resuscitability.^{16,17} There were no significant differences between the four subsets. With oxygenator P_{CO}₂ (F_OCO₂) of 0.00 or 0.10, the average extracorporeal flow required to maintain CPP ≥ 60 mmHg was 3.44 ± 0.75 and 3.50 ± 0.63 L/min. This contrasted with animals for which F_OCO₂ was 0.30 or 0.50 for which only flows of 2.44 ± 0.87 and 2.53 ± 0.83 L/min were required to maintain the same levels of CPP ($P < .01$) (table 2). Corresponding differences in systemic vascular resistance did not achieve statistical significance.

Myocardial P_{CO}₂ and H⁺

Myocardial P_{CO}₂ (P_MCO₂) and hydrogen ion concentration ([H⁺]) in the control animals (F_OCO₂ = 0.00) spontaneously increased to an average of 280 mmHg and 582 nmol, respectively, levels comparable to those previously reported by our group for survivors. With progressive increases in F_OCO₂, there were moderate increases in P_MCO₂ to an average maximum of 437 mmHg with F_OCO₂ of 0.50 (table 3). However, there were no significant differences in [H⁺] among the four subsets immediately prior to attempted defibrillation

Table 1. Outcome, ECC duration, and Cumulative Power before Resuscitation

F _O CO ₂	Resuscitation*/ Total No. of Animals	Survival*/ Total	ECC Duration (min)	Joules†
0	7/7	7/7	3 ± 0	342 ± 113
0.1	8/9	8/9	7 ± 4‡	1000 ± 580§
0.3	6/8	4/8	11 ± 7‡	1050 ± 734§
0.5	3/7	1/7	22 ± 16‡¶	1329 ± 1313§

Values for ECC duration and Joules are mean ± SD.

F_OCO₂ = fractional concentration of CO₂ delivered to the extracorporeal oxygenator; ECC = extracorporeal circulation.

* $P < .01$ for trend.

† Total power of countershocks prior to successful resuscitation.

‡ $P < .05$ versus F_OCO₂ 0.

§ $P < .02$ versus F_OCO₂ 0.

¶ $P < .05$ versus F_OCO₂ 0.1.

(table 3). Accordingly, the differences in resuscitability and survival were related to selective increases in P_MCO₂ rather than increases in myocardial [H⁺]. P_MCO₂ and [H⁺] at time of successful defibrillation are presented in table 4. Under these circumstances, animals were successfully defibrillated, but only after a larger number of defibrillation attempts and an additional 12 min or more of equilibration time. This would be likely to explain disproportionately greater myocardial [H⁺].

Arterial and Venous Blood Gases

During ventricular fibrillation with mechanical ventilation, the pH of aortic blood progressively increased and the P_{CO}₂ decreased. At 13 min, it was $7.88 \pm .11$ and 10 ± 4 mmHg, respectively (table 5). No statistically significant differences were observed between groups. During ECC when F_OCO₂ was increased to 0.50, P_aCO₂ increased from 36 ± 6 mmHg to 225 ± 29 mmHg ($P < .001$). There was a corresponding decrease in the pH of aortic blood from $7.26 \pm .04$ to $6.60 \pm .05$ ($P < .001$).

Right atrial blood gas measurements demonstrated progressive decreases in pH and increases in P_{CO}₂ during ventricular fibrillation. However, there were no statistically significant differences among groups. During ECC, maximal increases in F_OCO₂ to 0.50 increased P_{CO}₂ of right atrial blood from 69 ± 12 mmHg to 174 ± 26 mmHg ($P < .001$). The pH of right atrial blood simultaneously decreased from $7.08 \pm .05$ to $6.69 \pm .10$ ($P < .001$). Nevertheless, we observed no significant differences in the lactate content of right atrial blood between groups (table 5).

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Table 2. Hemodynamic Measurements

	F _O CO ₂	All Animals (n)	Prearrest (-5 min)	Ventricular Fibrillation (13 min)	Extracorporeal Circulation (+2 min)	Resuscitated Animals (n)	Spontaneous Circulation (+60 min)
MAP (mmHg)	0	7	116 ± 10	8 ± 5	91 ± 20	7	91 ± 14
	0.1	9	113 ± 10	8 ± 2	76 ± 9	8	94 ± 13
	0.3	8	105 ± 17	9 ± 1	78 ± 10	6	68 ± 30
	0.5	7	117 ± 16	9 ± 2	82 ± 12	3	71 ± 26
RAP (mmHg)	0	7	7 ± 2	8 ± 4	5 ± 3	7	6 ± 3
	0.1	9	7 ± 2	8 ± 2	5 ± 4	8	8 ± 2
	0.3	8	6 ± 2	9 ± 1	5 ± 5	6	7 ± 2
	0.5	7	5 ± 3	8 ± 2	5 ± 4	3	7 ± 1
CPP (mmHg)	0	7	97 ± 9	0 ± 1	86 ± 21	7	67 ± 13
	0.1	9	95 ± 7	0 ± 2	71 ± 23	8	72 ± 13
	0.3	8	88 ± 20	0 ± 3	72 ± 14	6	57 ± 33
	0.5	7	102 ± 21	1 ± 2	78 ± 14	3	64 ± 27
Flow (L/min)	0	7	—	—	3.44 ± 0.75	—	—
	0.1	8	—	—	3.50 ± 0.63	—	—
	0.3	7	—	—	2.44 ± 0.87*†	—	—
	0.5	6	—	—	2.53 ± 0.83*†	—	—
SVR (dyne · s ⁻¹ · cm ⁻⁵)	0	7	1649 ± 369	—	2061 ± 499	7	1760 ± 969
	0.1	9	1599 ± 393	—	1462 ± 763	8	1360 ± 295
	0.3	8	2022 ± 947	—	2485 ± 535	6	1635 ± 1193
	0.5	7	2238 ± 1406	—	2664 ± 927	3	1017 ± 443
Cardiac output (L/min)	0	7	5.5 ± 1.3	—	—	—	—
	0.1	9	5.5 ± 1.0	—	—	—	—
	0.3	8	4.4 ± 1.3	—	—	—	—
	0.5	7	4.9 ± 1.7	—	—	—	—

Values are mean ± SD.

MAP = mean aortic pressure; RAP = mean right atrial pressure; CPP = coronary perfusion pressure; SVR = systemic vascular resistance.

* $P < .05$ versus F_OCO₂ 0.

† $P < .05$ versus F_OCO₂ 0.1.

Table 3. Myocardial P_{CO}₂ (P_MCO₂) and [H⁺]

F _O CO ₂		All Animals (n)	Prearrest (5-min)	Ventricular Fibrillation (4 min)	Ventricular Fibrillation (13 min)	Extracorporeal Circulation (+2 min)	Resuscitated Animals (n)	Spontaneous Circulation (+60 min)
0	P _M CO ₂	5	58 ± 6	167 ± 76	397 ± 100	280 ± 60	5	83 ± 32
	[H ⁺]		79 ± 12	189 ± 79	691 ± 283	582 ± 332		126 ± 39
0.1	P _M CO ₂	5	65 ± 4	167 ± 54	365 ± 70	310 ± 41	4	75 ± 9
	[H ⁺]		67 ± 13	152 ± 49	590 ± 257	484 ± 134		108 ± 26
0.3	P _M CO ₂	5	58 ± 8	106 ± 51	366 ± 102	377 ± 94	4	86 ± 22
	[H ⁺]		60 ± 3	103 ± 37	412 ± 229	480 ± 213		98 ± 17
0.5	P _M CO ₂	5	67 ± 15	147 ± 37	391 ± 89	437 ± 69*	3	93 ± 17
	[H ⁺]		66 ± 14	109 ± 20	496 ± 322	583 ± 450		119 ± 35

Values are mean ± SD.

F_OCO₂ = fractional concentration of CO₂ delivered to the extracorporeal oxygenator.

* $P < .02$ versus F_OCO₂ 0.

Table 4. Myocardial P_{CO_2} (PM_{CO_2}) and $[H^+]$ at Time of Successful Defibrillation

$F_{O_{CO_2}}$	N	PM_{CO_2}	H^+
0	5	184 ± 57	434 ± 90
0.1	5	114 ± 31	254 ± 68
0.3	5	216 ± 73	394 ± 78
0.5	3	282 ± 178	648 ± 320*

Values are mean ± SD.

$F_{O_{CO_2}}$ = fractional concentration of CO_2 delivered to the extracorporeal oxygenator.

* $P < .05$ versus $F_{O_{CO_2}}$ 0.1.

During ventricular fibrillation, adequate blood samples were obtained by aspiration of blood from the great cardiac vein in a majority of the trials. The results are shown in table 6. Blood sampled from the great cardiac vein demonstrated the same increases in P_{CO_2} and decreases in pH during ventricular fibrillation that were reported previously by us.¹ During ECC, great cardiac vein P_{CO_2} averaged 68 mmHg. It progressively increased with increasing $F_{O_{CO_2}}$ to a maximum of 240 ± 38 mmHg ($P < .001$). The great cardiac vein pH was $7.04 \pm .13$ with $F_{O_{CO_2}}$ of 0.00 but progressively decreased when the $F_{O_{CO_2}}$ was increased to 0.5 such that it reached a minimum of $6.54 \pm .06$ ($P < .001$). Once again, we observed no significant differences in the coronary venous lactate content with increasing $F_{O_{CO_2}}$ nor in the coronary arteriovenous oxygen content differences during ECC-induced hypercarbia (table 6). Calculated oxygen extraction and lactate extraction ratios also failed to demonstrate significant differences between the four groups (table 7).

Discussion

Venous hypercarbic acidosis during low-flow states of cardiopulmonary resuscitation and circulatory shock has been well documented in several animal species and in human patients.¹⁸⁻²² During cardiac resuscitation, these are accompanied by increases in coronary vein P_{CO_2} to levels exceeding 150 mmHg.^{1,17} Myocardial P_{CO_2} is concurrently increased to an average of 346 mmHg, and myocardial $[H^+]$ to 441 mmol/L.¶ With progressive increases in PM_{CO_2} , there were corresponding decreases in resuscitability.

MacGregor *et al.*²³ used mass spectroscopy to investigate myocardial P_{CO_2} during cardiac arrest in dogs induced by aortic cross-clamping. None of six dogs with PM_{CO_2} exceeding 400 mmHg were resuscitated. This

contrasted with six dogs in which PM_{CO_2} was 310 mmHg or less, all of which were resuscitated. Magovern *et al.*²⁴ also demonstrated a decrease in resuscitability and an increase in need for inotropic support after cardiopulmonary bypass in human patients with disproportionately greater PM_{CO_2} . Accordingly, the levels of PM_{CO_2} produced by increases in $F_{O_{CO_2}}$ in the current experiment, were of a magnitude comparable to those that are spontaneously generated during extreme low flow states.

These studies confirmed that this hypercarbia is associated with decreased cardiac resuscitability, independently of acidosis. Hypercarbic acidosis reduced resuscitability and survival and prolonged the duration of ECC required prior to restoration of spontaneous circulation. These effects, however, were independent of CPP and myocardial oxygen utilization.

Myocardial P_{CO_2} and $[H^+]$ failed to return to baseline levels at 60 min after restoration of spontaneous circulation (table 3). Comparable increases in myocardial $[H^+]$ at 60 min after resuscitation were reported by von Planta M *et al.*¹ This delay in reversal is the subject of ongoing research with special focus on post-resuscitation myocardial dysfunction.

Coronary perfusion pressure and, more specifically, myocardial blood flow are predictive of resuscitability during cardiac resuscitation, whether produced by precordial compression, open-chest cardiac compression, or ECC.^{8,25,26} A CPP of 20 mmHg or greater in dogs and rats and of 10 mmHg or greater in pigs predicted successful immediate resuscitation after electrical defibrillation in more than 80% of trials.^{16,21,27} In human patients, Paradis *et al.*²⁸ demonstrated that a CPP of 15 mmHg or greater in victims of cardiac arrest was required for successful restoration of spontaneous circulation after external defibrillation. In the present studies, ECC was used to secure a CPP that substantially exceeded the threshold levels for successful cardiac resuscitation in the porcine model.

The P_{O_2} of aortic blood was noticeably greater with higher levels of $F_{O_{CO_2}}$ (0.30, 0.50). We have not identified the mechanism that would account for this, but suspect it may be related to the lesser ECC flows required to achieve the target ranges of CPP with increasing $F_{O_{CO_2}}$ and therefore more efficient O_2 transfer across the oxygenator membrane as shown in table 2.

The likelihood that hypercarbia may compromise coronary blood flow by effects on coronary vascular resistance is remote. Increases rather than decreases in coronary blood flow accompany hypercarbia in animal

Table 5. Aortic (AO) and Right Atrial (RA) Blood Gas Measurements

	F _{O₂}	Prearrest (-5 min)						Ventricular Fibrillation (13 min)						Extracorporeal Circulation (+2 min)						Spontaneous Circulation					
		AO		RA		n		AO		RA		n		AO		RA		n		AO		RA			
		Value	n	Value	n	Value	n	Value	n	Value	n	Value	n	Value	n	Value	n	Value	n	Value	n	Value	n		
P _{O₂} (mmHg)	0	34 ± 2	7	44 ± 2	7	10 ± 4	7	58 ± 5	7	69 ± 12	7	36 ± 6	7	69 ± 12	7	47 ± 4	7	58 ± 8	7	47 ± 8	7	63 ± 11	7		
	0.1	40 ± 5	9	49 ± 7	9	18 ± 15	9	60 ± 12	9	97 ± 12*	9	76 ± 13*	9	97 ± 12*	9	54 ± 12	9	66 ± 13	9	54 ± 10	9	69 ± 15	9		
	0.3	41 ± 5	8	48 ± 6	8	16 ± 10	8	60 ± 5	8	138 ± 17†	8	150 ± 28†	8	138 ± 17†	8	43 ± 12	8	64 ± 11	8	46 ± 3	8	59 ± 5	8		
P _{O₂} (mmHg)	0.5	38 ± 4	7	45 ± 5	7	11 ± 5	7	54 ± 12	7	174 ± 26†	7	225 ± 29†	7	174 ± 26†	7	50 ± 5	7	66 ± 12	7	40	7	52	7		
	0	210 ± 37	7	45 ± 10	7	264 ± 62	7	31 ± 5	7	31 ± 8	7	55 ± 15	7	31 ± 8	7	240 ± 58	7	52 ± 13	7	187 ± 58	7	46 ± 9	7		
	0.1	187 ± 92	9	42 ± 10	9	202 ± 108	9	33 ± 6	9	37 ± 4	9	67 ± 10	9	37 ± 4	9	156 ± 58	9	48 ± 4	9	190 ± 66	9	42 ± 6	9		
pH (units)	0.3	148 ± 59	8	46 ± 6	8	197 ± 93	8	34 ± 6	8	47 ± 9	8	101 ± 27	8	47 ± 9	8	217 ± 64	8	46 ± 20	8	219 ± 52	8	46 ± 5	8		
	0.5	216 ± 111	7	45 ± 14	7	276 ± 99	7	34 ± 10	7	48 ± 10	7	108 ± 30	7	48 ± 10	7	220 ± 58	7	57 ± 7	7	302	7	42	7		
	0	7.45 ± 0.02	7	7.42 ± 0.02	7	7.88 ± 0.11	7	7.29 ± 0.03	7	7.08 ± 0.05	7	7.26 ± 0.04	7	7.08 ± 0.05	7	7.22 ± 0.06	7	7.18 ± 0.07	7	7.21 ± 0.08	7	7.15 ± 0.08	7		
Lactate (mm)	0.1	7.37 ± 0.08	9	7.32 ± 0.08	9	7.70 ± 0.24	9	7.24 ± 0.08	9	6.98 ± 0.06*	9	6.98 ± 0.06*	9	6.91 ± 0.07*	9	7.12 ± 0.06	9	7.09 ± 0.05	9	7.11 ± 0.07	9	7.07 ± 10	9		
	0.3	7.36 ± 0.08	8	7.32 ± 0.08	8	7.71 ± 0.22	8	7.23 ± 0.07	8	6.78 ± 0.06†	8	6.75 ± 0.09†	8	6.78 ± 0.06†	8	7.20 ± 0.09	8	7.08 ± 0.13	8	7.19 ± 0.02	8	7.17 ± 0.02	8		
	0.5	7.41 ± 0.07	7	7.37 ± 0.09	7	7.84 ± 0.16	7	7.25 ± 0.10	7	6.69 ± 0.05†	7	6.60 ± 0.05†	7	6.69 ± 0.10†	7	7.17 ± 0.04	7	7.10 ± 0.08	7	7.30	7	7.21	7		
Lactate (mm)	0	0.6 ± 0.2	7	0.6 ± 0.2	7	2.0 ± 0.3	7	1.9 ± 0.9	7	5.9 ± 0.7	7	5.8 ± 0.6	7	5.9 ± 0.7	7	4.7 ± 0.6	7	4.6 ± 0.3	7	5.6 ± 0.5	7	5.3 ± 0.5	7		
	0.1	0.9 ± 0.5	9	1.0 ± 0.4	9	2.4 ± 0.7	9	2.2 ± 0.8	9	6.1 ± 1.2	9	5.9 ± 1.2	9	6.1 ± 1.2	9	5.7 ± 1.1	9	5.5 ± 1.2	9	6.7 ± 1.3	9	6.5 ± 1.2	9		
	0.3	1.0 ± 0.6	8	0.9 ± 0.6	8	2.4 ± 0.5	8	2.0 ± 0.5	8	6.2 ± 0.5	8	5.8 ± 1.1	8	6.2 ± 0.5	8	6.5 ± 1.6	8	6.4 ± 1.5	8	6.3 ± 0.4	8	6.1 ± 0.5	8		
Lactate (mm)	0.5	1.2 ± 0.7	7	1.0 ± 0.7	7	2.2 ± 0.4	7	2.0 ± 0.4	7	5.9 ± 0.7	7	5.9 ± 0.7	7	5.9 ± 0.5	7	5.7 ± 0.5	7	5.7 ± 0.3	7	6.3	7	6.2	7		

* P < .001 versus F_{O₂} 0.† P < .001 versus F_{O₂} 0 or 0.1.‡ P < .001 versus F_{O₂} 0, 0.1, or 0.3.

Table 6. Great Cardiac Vein Blood Gas Measurements

	F _O CO ₂	Prearrest		Ventricular Fibrillation		Extracorporeal Circulation		Spontaneous Circulation			
		n	(-5 min)	n	(13 min)	n	(+2 min)	n	(+60 min)	n	(+180 min)
P _{CO} ₂ (mmHg)	0	7	47 ± 3	3	150 ± 38	7	68 ± 29	6	57 ± 5	7	57 ± 9
	0.1	9	52 ± 3	5	119 ± 64	8	90 ± 10	8	61 ± 11	7	63 ± 13
	0.3	8	48 ± 5	6	70 ± 18	7	158 ± 36*†	5	61 ± 8	3	55 ± 4
	0.5	6	47 ± 4	2	165 ± 140	6	240 ± 38*†‡	2	58 ± 7		—
A-V _O ₂ difference (mmHg)	0	7	7.9 ± 1.0	3	9.7 ± 2.3	7	2.4 ± 1.3	6	5.2 ± 2.0	7	7.6 ± 1.4
	0.1	9	8.3 ± 1.6	5	8.2 ± 2.9	8	2.6 ± 2.3	8	4.8 ± 1.4	7	5.8 ± 2.5
	0.3	8	6.9 ± 2.0	6	8.0 ± 2.3	7	3.7 ± 3.5	6	7.0 ± 3.3	3	7.7 ± 3.0
	0.5	6	9.2 ± 2.0	2	7.4 ± 2.8	6	2.9 ± 3.3	2	2.9 ± 2.6		—
pH (units)	0	7	7.39 ± 0.02	3	6.62 ± 0.29	7	7.04 ± 0.13	6	7.19 ± 0.03	7	7.16 ± 0.08
	0.1	9	7.29 ± 0.07	5	6.72 ± 0.39	8	6.87 ± 0.11	8	7.10 ± 0.06	7	7.04 ± 0.16
	0.3	8	7.31 ± 0.06	6	7.10 ± 0.15	7	6.71 ± 0.14*	5	7.08 ± 0.10	3	7.18 ± 0.02
	0.5	6	7.35 ± 0.07	2	6.74 ± 0.23	6	6.54 ± 0.06*†	2	7.10 ± 0.01		—
Lactate (mm)	0	7	0.3 ± 0.2	3	4.7 ± 0.4	7	7.5 ± 0.8	6	4.3 ± 0.5	7	5.1 ± 0.5
	0.1	9	0.65 ± 0.3	5	4.5 ± 2.0	8	7.5 ± 1.3	8	5.4 ± 1.2	7	6.5 ± 1.1
	0.3	8	0.7 ± 0.9	6	2.8 ± 0.9	7	6.7 ± 0.9	5	5.9 ± 1.6	3	6.2 ± 0.2
	0.5	6	0.8 ± 0.7	2	5.2 ± 0.3	6	7.1 ± 0.3	2	5.2 ± 0.1		—

Values are mean ± SD.

A-V_O₂ difference = arteriovenous oxygen difference.

* *P* < .001 versus F_OCO₂ 0.

† *P* < .001 versus F_OCO₂ 0.1.

‡ *P* < .001 versus F_OCO₂ 0.3.

models.²⁹ In recently published studies³⁰ with the same porcine model but in the absence of ECC, we also observed increases in peripheral vascular resistance. However, coronary blood flow measured in the left anterior descending coronary artery increased 2.5-fold and, simultaneously, coronary vascular resistance decreased by 40%. Accordingly, hypercarbia induces coronary vasodilation in the pig.

It is also unlikely that these differences are explained by altered oxygen availability and consumption because arteriovenous oxygen differences, O₂ extraction ratios,

and lactate extraction (production) by the heart were not altered specifically by myocardial hypercarbia. Therefore, increases in myocardial CO₂ are likely to be determinants of resuscitability that are independent of these indexes of myocardial ischemia.

The detrimental effects of hypercarbia on myocardial function have been more directly documented in perfused isolated heart preparations and intact animals. Recent observations in the isolated perfused rat heart⁶ supported the observation of Jerusalem and Starling³ on isolated frog myocardium and those of Cobbe and

Table 7. Myocardial Oxygen Extraction Ratio (MOE) and Myocardial Lactate Extraction (L_E)

	F _O CO ₂	All Animals (n)	Prearrest (-5 min)	Extracorporeal Circulation (+2 min)	Resuscitated Animals (n)	Spontaneous Circulation	
						(+60 min)	(+180 min)
MOE (%)	0	7	77 ± 5	30 ± 17	6	43 ± 14	60 ± 11
	0.1	9	79 ± 5	30 ± 18	8	39 ± 14	43 ± 13
	0.3	8	62 ± 20	31 ± 21	5	55 ± 27	52 ± 20 (3)
	0.5	6	79 ± 8	23 ± 5	2	32 ± 6	—
L _E (%)	0	7	53 ± 26	-32 ± 21	6	6 ± 7	9 ± 5
	0.1	9	30 ± 35	-22 ± 12	8	5 ± 7	4 ± 5
	0.3	8	37 ± 29	-23 ± 31	5	10 ± 8	4 ± 5 (3)
	0.5	6	36 ± 26	-21 ± 14	2	6 ± 7	—

Values are mean ± SD; no statistical differences observed.

MYOCARDIAL HYPERCARBIA

Poole-Wilson³¹ on perfused interventricular septum preparations of rabbits that CO₂ selectively impairs myocardial function. Recently, Walley *et al.*,⁵ using ultrasonic crystals to estimate left ventricular volume, documented that hypercarbia decreases myocardial contractility in dogs during spontaneous circulation and in the absence of cardiac arrest.

Hypercarbia induces prolongation of the myocyte action potential. For instance, Poole-Wilson and Langer,⁴ using rabbit papillary muscle, observed prolongation in the action potential when the P_{CO₂} of the muscle bath was increased. This contrasted with its absence under conditions of normocarbic (metabolic) acidosis.

Since the present study used a model of electrically induced ventricular fibrillation as the cause of cardiac arrest, it does not directly address myocardial, hypoxic, metabolic, or hypovolemic mechanisms of cardiac arrest. Moreover, the study was designed to test effects of CO₂ after a protracted interval of cardiac arrest, and its applicability to cardiac arrest of shorter duration is accordingly constrained. We also recognize the cytoprotective actions of acidosis in other settings of extreme low blood flow^{32,33} and therefore do not exclude potential benefits thereof. Finally, this study does not fully distinguish between primary cardiac and systemic effects of hypercarbia and the role of endogenous catecholamine release accompanying hypercarbia.³⁴

On the other hand, our investigations call attention to the potential usefulness of myocardial P_{CO₂} as a parameter of interest and especially for monitoring during cardiac surgery before and after weaning from ECC support.

Whether the detrimental effects induced by hypercarbic acidosis are selectively due to the CO₂ molecule or whether they result from CO₂ diffusion into myocytes with accompanying intracellular acidosis is not yet resolved. The observation that resuscitation outcome was closely related to P_{MCO₂} and largely unrelated to myocardial [H⁺] lends support to the concept that CO₂ may act by mechanisms other than the intracellular generation of protons. The blunted response of myocardial H⁺ to increases in F_{O₂} levels partly may reflect a time delay in the hydration of CO₂ to carbonic acid due to the absence of carbonic anhydrase in heart muscle.³⁵⁻³⁷ We also confirm that alterations in arterial pH do not translate directly into changes in myocardial pH. Regardless of the mechanisms involved, however, the current studies implicate excesses of CO₂ as detrimental for restoration of spontaneous circulation after cardiac arrest in settings of cardiac resuscitation.

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