

Effects of Respiratory Alkalosis and Acidosis on Myocardial Blood Flow and Metabolism in Patients with Coronary Artery Disease

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Background: Variation of the arterial carbon dioxide partial pressure (P_{aCO_2}) is not uncommon in anesthetic practice. However, little is known about the myocardial consequences of respiratory alkalosis and acidosis, particularly in patients with coronary artery disease. The aim of the current study was to investigate the effects of variation in P_{aCO_2} on myocardial blood flow (MBF), metabolism, and systemic hemodynamics in patients before elective coronary artery bypass graft surgery.

Methods: In 10 male anesthetized patients, measurements of MBF, myocardial contractility, metabolism, and systemic hemodynamics were made in a randomized sequence at P_{aCO_2} levels of 30, 40, and 50 mmHg, respectively. The MBF was measured using the Kety-Schmidt technique with argon as a tracer. End-diastolic left ventricular pressure and the maximal increase of left ventricular pressure were assessed using a manometer-tipped catheter.

Results: The cardiac index significantly changed with varying P_{aCO_2} levels (hypocapnia, -9%; hypercapnia, 13%). This reaction was associated with inverse changes in systemic vascular resistance index levels. The MBF significantly increased by 15% during hypercapnia, whereas no change was found during hypocapnia. Myocardial oxygen and glucose uptake and the maximal increase of left ventricular pressure were not affected by varying P_{aCO_2} levels.

Conclusions: In anesthetized patients with coronary artery disease, short-term variations in P_{aCO_2} have significant effects on MBF but do not influence global myocardial oxygen and glucose uptake. Changes in systemic hemodynamics associated with respiratory alkalosis and acidosis are caused by changes in systemic vascular resistance rather than by alterations in myo-

cardial contractility. (Key words: Argon wash-in technique; carbon dioxide; hemodynamics; myocardium.)

ALTHOUGH unintended or deliberate variation of the arterial carbon dioxide partial pressure (P_{aCO_2}) is common in anesthetic practice, little is known about the myocardial consequences of respiratory alkalosis and acidosis in humans. Previous experimental studies have shown inconsistent results with respect to the effects of P_{aCO_2} on myocardial blood flow (MBF), myocardial metabolism, and global hemodynamics. This may have been caused in part by differences in the experimental design of the investigations.¹⁻⁶ Although most studies have shown that hypercapnia augments MBF above metabolic demands,^{3,7-9} the results with respect to the effects of hypocapnia vary.^{3,4} Furthermore, it seems questionable to transfer conclusions from experimental studies of coronary perfusion to respective reactions of MBF in humans. The clinical effects of varying P_{aCO_2} levels on myocardial and systemic hemodynamics, however, are of particular interest in patients with coronary artery disease because a reduction in coronary perfusion pressure associated with P_{aCO_2} -induced changes in systemic vascular resistance may increase the risk of myocardial ischemia. Furthermore, stenotic coronary arteries may not react normally to changes in P_{aCO_2} . Conversely, a P_{aCO_2} -induced increase in coronary vascular resistance (CVR)⁴ may produce a reduction in global coronary blood flow that may not meet metabolic demands.

The aim of this investigation was to study the effects of short-term changes in P_{aCO_2} on MBF, myocardial metabolism and function, and systemic hemodynamics in patients before coronary artery bypass graft surgery.

Materials and Methods

The study was approved by the local institutional review board, and written informed consent was obtained from each patient.

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Table 1. Demographic Data and Medication of Investigated Patients

Patient Number	Age (yr)	Weight (kg)	Height (cm)	BSA (m ²)	Hypertension	History of MI	Cardiovascular Medication	Location of CAD
1	56	81	179	1.99	—	—	mol, met	LAD, Cx, RCA
2	59	74	169	1.85	+	—	nif, pen, ate	LAD, Cx, RCA
3	67	100	180	2.19	+	—	iso, mol, pir, lis	LAD, Cx, RCA
4	62	77	168	1.87	—	+	iso, tal	LAD, Cx, RCA
5	58	75	176	1.91	+	—	iso, bis	LAD, Cx, RCA
6	69	80	168	1.90	—	—	mol, fur	LAD, Cx
7	69	82	175	2.00	—	—	iso	LAD, Cx, RCA
8	62	72	168	1.82	+	—	mol, ate	LAD, Cx, RCA
9	59	89	176	2.01	+	—	iso, nit, mol bis,	LAD, Cx
10	67	63	165	1.69	+	+	iso, mol, ram	LAD, Cx

ate = atenolol; bis = bisoprolol; BSA = body surface area; Cx = circumflex coronary artery; fur = furosemide; iso = isosorbiddinitrate; LAD = left anterior descending coronary artery; lis = lisinopril; met = metoprolol; mol = molsidomine; nif = nifedipine; nit = nitrendipine; pen = pentaerithryltetranitrate; pir = piretanid; ram = ramipril; tal = talinolol; RCA = right coronary artery; MI = myocardial infarction.

Patients

Ten men (age, 62.8 ± 4.9 yr; weight, 78.8 ± 9.6 kg; height, 172 ± 5 cm [mean \pm SD]) with angiographically verified coronary artery disease were examined before elective coronary artery bypass graft surgery. Table 1 lists individual demographic data, locations of the coronary artery disease, and long-term medications used by these patients. Patients with stenosis of the left main coronary artery; valvular heart disease; impaired left ventricular function (ejection fraction $< 50\%$); or cerebral, hepatic, or renal disease were excluded from the study. Antiarrhythmic and antihypertensive medications were continued until the day of surgery. Preanesthetic medication consisted of 2 mg flunitrazepam administered orally on the evening before surgery and on the following morning before the study period began.

Anesthesia and Catheterization

Before induction of anesthesia, electrocardiographic leads were attached and continuous ST segment analysis of lead II and V₅ (60 ms after the j-point; Sirecust 1281; Siemens, Erlangen, Germany) was initiated. A 20-gauge catheter was placed in the radial artery to measure mean arterial pressure and to collect blood samples. Anesthesia was induced with 2 μ g/kg sufentanil and 0.1 mg/kg pancuronium bromide. After tracheal intubation, patients were ventilated by a volume-controlled respirator (AV 1, Dräger, Lübeck, Germany) with an inspiratory fraction of oxygen of 0.3. During the measurement period, anesthesia was maintained by a continuous infusion of sufentanil ($3.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$). Body temperature was kept constant using warm covers. Subsequently, the following catheters were inserted: a flow-directed pulmonary artery catheter (Hands-off thermodilution catheter

AH-0500; ARROW, Erding, Germany) *via* the left subclavian vein to measure mean pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output; a 5-French manometer-tipped catheter (Millar Instruments, Houston, TX) *via* the left femoral artery to measure end-diastolic left ventricular pressure and the maximal rate of left ventricular pressure (dp/dt_{max}) increase; a catheter *via* the right internal jugular vein into the superior caval vein to measure central venous pressure and administer drugs and fluids; and a gas-tight 7-French Goodale-Lubin catheter (Bard GmbH, Unterschleißheim, Germany) *via* the right internal jugular vein into the coronary sinus to measure coronary sinus pressure and to collect coronary sinus blood. A second Goodale-Lubin catheter was connected to the arterial cannula. The catheters had an identical dead space and were known to exhibit only minimal loss of gas by diffusion. The positioning of the coronary sinus catheter, the left ventricular manometer-tipped catheter, and the pulmonary artery catheter was controlled by fluoroscopy.

Clinical Protocol and Measurements

Measurements were performed after induction of anesthesia at hypo-, normo-, and hypercapnia in a randomized sequence. Hyper-, normo-, and hypocapnia were defined as PaCO₂ levels of 50, 40, and 30 mmHg, respectively. Respiratory rate and tidal volume were adjusted to reach the respective PaCO₂ levels without increasing peak inspiratory airway pressure more than 25 cm H₂O. Arterial blood gas analyses (ABL 500; Radiometer, Brønshøj, Denmark) and continuous end-expiratory carbon dioxide measurements (Capnomac Ultima; Datex, Helsinki, Finland) were taken to control the effects of

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changes in ventilation. After achieving the respective P_{aCO_2} level, a period of at least 20 min was included to ensure steady state conditions.

At the beginning of each measurement, heart rate, mean arterial pressure, central venous pressure, coronary sinus pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, end-diastolic left ventricular pressure, and dp/dt_{max} were recorded on an eight-channel chart recorder (Sirecust 1281, Siredoc 220, Siemens, Erlangen, Germany). Cardiac output was assessed by the thermodilution method as the mean of three injections of 10-ml ice-cooled isotonic saline randomly spread during the respiratory cycle. Arterial and coronary sinus blood samples were drawn in duplicate immediately before and after each period of MBF measurement to determine the pH (pH_{art} , pH_{cs}); the acid base status; the blood gas tensions (P_{aO_2} , P_{csO_2} , P_{aCO_2} , P_{csCO_2} ; ABL 500, Radiometer); the oxygen saturation (Sa_{O_2} , Scs_{O_2}); and the hemoglobin (CO-Oximeter IL 282; Rotron Manufacturing, Woodstock, NY), glucose, lactate (standard test kits; Boehringer, Mannheim, Germany), and electrolyte concentrations (NOVA CRT 1; Waltham, MA), respectively. The mean of both samples was calculated and used for further analysis. The MBF was measured using the Kety-Schmidt technique using argon as a tracer^{10,11} (coefficient of variation, 5.1%). A previously prepared gas mixture containing 70% argon and 30% oxygen was administered to the anesthetized patient *via* the endotracheal tube. Blood samples from the arterial and the coronary sinus catheters were withdrawn into a glass syringe at a constant rate during the saturation period in duplicate using a high-precision aspiration pump (modified Unita I; Braun, Melsungen, Germany). Wash-in periods of 5 min were used for all measurements. Triple determinations of argon concentrations in each arterial and coronary-venous blood sample were made after vacuum extraction by gas chromatography and ionization detection. An argon myocardium-blood partition coefficient of 1.1 was used to calculate MBF.

Calculations

The cardiac index (CI), stroke volume index, systemic and pulmonary vascular resistance indices, and arterial and coronary sinus oxygen content (Ca_{O_2} , Ccs_{O_2}) were calculated according to standard formulas. Myocardial uptake of oxygen (MV_{O_2}) and of glucose (MGU) were calculated as the product of the respective arterial-coronary sinus content differences and MBF. Myocardial lactate extraction (MLE) was calculated as the ratio between the arterial-coronary sinus content difference

Table 2. Blood Gas Analytic Parameters

	Hypocapnia	Normocapnia	Hypercapnia
Sa_{O_2} (%)	97.2 ± 0.7	96.9 ± 0.9	96.8 ± 0.5
Pa_{O_2} (mmHg)	117.1 ± 26.5	118.9 ± 27.1	119.0 ± 22.7
Pa_{CO_2} (mmHg)	31.2 ± 4.1*	40.0 ± 4.1	50.4 ± 4.3*
pH_{art}	7.48 ± 0.05*	7.40 ± 0.05	7.32 ± 0.04*
Scs_{O_2} (%)	36.4 ± 5.8*	38.7 ± 5.7	41.3 ± 6.9*
Pcs_{O_2} (mmHg)	21.8 ± 2.6*	24.2 ± 2.8	27.3 ± 3.8*
Pcs_{CO_2} (mmHg)	39.0 ± 4.8*	49.2 ± 4.5	59.8 ± 4.8*
pH_{cs}	7.45 ± 0.05*	7.37 ± 0.04	7.29 ± 0.04*
Hb (g · dl) ⁻¹	11.9 ± 1.8*	12.2 ± 1.9	12.1 ± 1.8

Values are mean ± SD of the following: arterial and coronary sinus oxygen saturation (Sa_{O_2} , Scs_{O_2}), oxygen partial pressure (Pa_{O_2} , Pcs_{O_2}), carbon dioxide partial pressure (Pa_{CO_2} , Pcs_{CO_2}), pH (pH_{art} , pH_{cs}), and hemoglobin concentration (Hb).

* $P < 0.05$ versus normocapnia, adjusted for multiple test procedures.

and the arterial lactate content. Coronary perfusion pressure was calculated as the mean diastolic pressure minus the end-diastolic left ventricular pressure, and CVR was calculated as the ratio between coronary perfusion pressure and MBF.

Statistics

Results are expressed as mean ± SD. Parametric statistical analysis was performed by one-way analysis of variance using a repeated-measures design. Paired Student's *t* tests were used for *post hoc* comparison of normocapnia with hypo- and hypercapnia, respectively. Because duplicate tests were necessary to assess the effects between the different P_{aCO_2} levels for each variable, the levels of significance were adjusted by a sequentially rejecting multiple test procedure according to Holm to reduce the probability of type 1 errors. All statistical procedures were performed using a microcomputer with the SPSS/PC+ statistical software package (SPSS, Chicago, IL).

Results

Table 2 shows mean values and standard deviations of blood gas analytic variables. Mean P_{aCO_2} levels for normocapnia and hyper- and hypocapnia were 40.0, 50.4, and 31.2 mmHg, respectively. Changes in P_{aCO_2} caused proportional changes in arterial hydrogen ion concentrations with a mean decrease during hypocapnia of 17% and a mean increase during hypercapnia of 20%. Oxygen pressure and saturation in arterial blood remained unchanged during the entire study. Arterial and venous concentrations of sodium and potassium also remained unchanged.

Table 3. Global and Myocardial Hemodynamic and Myocardial Metabolic Parameters

	Hypocapnia	Normocapnia	Hypercapnia
CI ($L \cdot \min^{-1} \cdot m^{-2}$)	$1.8 \pm 0.3^*$	1.9 ± 0.3	$2.2 \pm 0.3^*$
SVI ($ml \cdot m^{-2}$)	33 ± 7	35 ± 7	$40 \pm 8^*$
HR (\min^{-1})	55 ± 9	57 ± 10	56 ± 10
MAP (mmHg)	69 ± 9	68 ± 7	70 ± 11
CVP (mmHg)	8.2 ± 3.3	6.5 ± 2.0	7.2 ± 3.5
PAP (mmHg)	13.7 ± 3.4	14.5 ± 4.0	15.9 ± 3.2
PCWP (mmHg)	11.2 ± 3.4	10.4 ± 4.3	10.1 ± 3.3
LVEDP (mmHg)	10.9 ± 2.7	10.4 ± 2.5	11.5 ± 2.4
SVRI ($\text{dyn} \cdot s \cdot \text{cm}^{-5} \cdot m^2$)	$2830 \pm 631^*$	2587 ± 613	$2348 \pm 576^*$
PVRI ($\text{dyn} \cdot s \cdot \text{cm}^{-5} \cdot m^2$)	114 ± 126	156 ± 106	$205 \pm 86^*$
CPP (mmHg)	50.2 ± 9.6	49.0 ± 8.5	51.0 ± 10.3
MBF ($ml \cdot 100 g^{-1} \cdot \min^{-1}$)	68.2 ± 17.1	66.2 ± 14.9	$76.2 \pm 14.7^*$
CVR ($\text{mmHg} \cdot ml^{-1} \cdot \min \cdot 100 g$)	0.77 ± 0.2	0.77 ± 0.2	$0.69 \pm 0.16^*$
MV _{O₂} ($ml \cdot 100 g^{-1} \cdot \min^{-1}$)	6.6 ± 1.0	6.3 ± 0.8	7.0 ± 1.3
MGU ($mg \cdot 100 g^{-1} \cdot \min^{-1}$)	0.8 ± 0.3	1.0 ± 0.7	1.0 ± 0.5
MLE (%)	-1.1 ± 6.0	3.9 ± 9.4	6.3 ± 9.7
dp/dt _{max} ($\text{mmHg} \cdot s^{-1}$)	817 ± 161	825 ± 146	877 ± 223

CI = cardiac index; SVI = stroke volume index; HR = heart rate; MAP = mean arterial pressure; CVP = central venous pressure; PAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; LVEDP = left ventricular end-diastolic pressure; SVRI = systemic vascular resistance index; PVRI = pulmonary vascular resistance index; CPP = coronary perfusion pressure; MBF = myocardial blood flow; CVR = coronary vascular resistance; MV_{O₂} = myocardial oxygen uptake; MGU = myocardial glucose uptake; MLE = myocardial lactate extraction; dp/dt_{max} = maximal rise in left ventricular pressure.

Values are mean \pm SD.

* $P < 0.05$ versus normocapnia, adjusted for multiple test procedures.

Table 3 shows mean values and standard deviations of MBF, coronary perfusion pressure, CVR, and myocardial metabolic variables. Figure 1 shows individual data for MBF. Coronary perfusion pressure was not affected by changes in Pa_{CO₂}. During hypercapnic conditions, mean MBF significantly increased by 15%. This increase was associated with a significant decrease in CVR by 12%. During hypocapnic conditions, in contrast, MBF and CVR did not significantly change when compared with normocapnia. However, mean MVO₂ and MGU remained virtually unchanged during the entire study.

The values for Pcs_{O₂} and Scs_{O₂} changed significantly with varying Pa_{CO₂} levels. Mean Pcs_{O₂} and Scs_{O₂} decreased during hypocapnia by 10% and 6%, respectively; in contrast, both parameters increased during hypercapnia by 13% and 7%. These changes in myocardial oxygen extraction were not associated with significant changes in mean MLE. Individual analysis of MLE data reveals that in two patients who showed positive MLE values more than 5% during normo- and hypercapnia, MLE reached negative values greater than -5% during hypocapnia, possibly indicating myocardial production of lactate. However, continuous ST segment analysis did not show any abnormalities during the entire study.

Variations of Pa_{CO₂} resulted in comparable changes of

mean CI. Mean CI during hypocapnia decreased by 9%. During hypercapnia, the mean CI (fig. 1) and stroke volume index increased by 13% and 15%, respectively. Heart rate and mean dp/dt_{max} were not significantly altered by variations of Pa_{CO₂}.

The mean systemic vascular resistance index (fig. 1) increased during hypocapnia by 9% and decreased during hypercapnia by the same amount. Because of the concomitant changes in CI, mean arterial pressure remained constant during the entire study. Similarly, pulmonary capillary wedge pressure, end-diastolic left ventricular pressure, and central venous pressure remained unchanged. Compared with Pa_{CO₂}-induced reactions in the systemic vascular resistance index, mean pulmonary vascular resistance index was affected inversely by the different Pa_{CO₂} levels.

Discussion

The aim of this clinical study was to investigate the effects of short-term variations in Pa_{CO₂} on MBF, metabolism, and global hemodynamics in patients undergoing coronary artery bypass graft surgery. The results indicate that respiratory acidosis causes moderate myocardial overperfusion, resulting in reduced myocardial oxygen extraction. Hypocapnia, in contrast, did not change

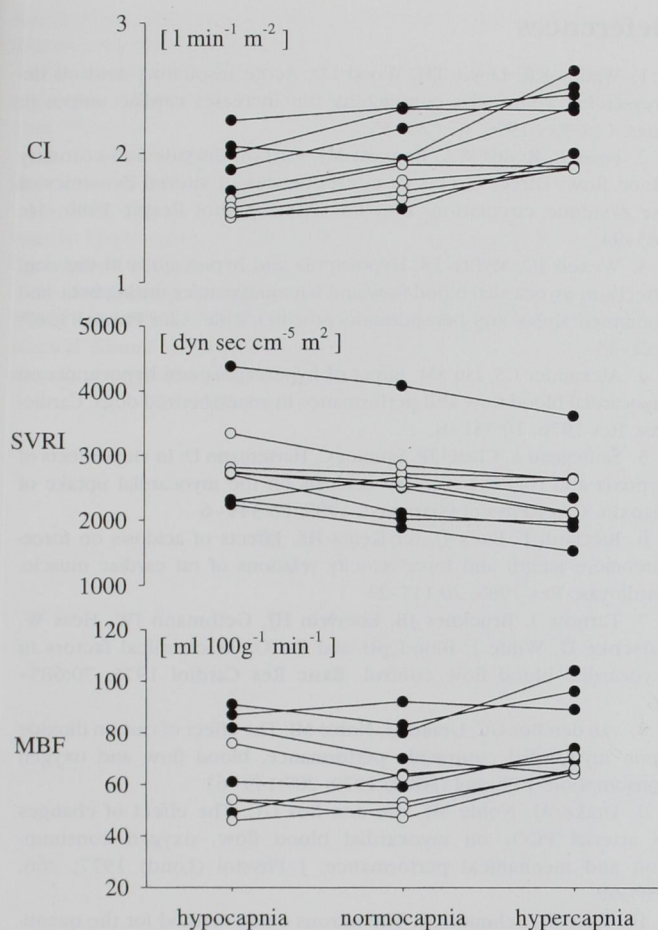
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Fig. 1. Individual data of cardiac index (CI), systemic vascular resistance index (SVRI), and myocardial blood flow (MBF). Solid circles = patients pretreated with β -blockers; open circles = patients without β -blockers.

global MBF, MVO_2 , or MGU. Negative myocardial lactate extraction occurred in two patients. The CI increases during hypercapnia and decreases during hypocapnia. These changes in CI are not associated with respective changes in dp/dt_{max} .

Several factors may influence MBF. Diastolic filling time and coronary perfusion pressure, endothelial hormones,¹² autonomous nervous system activity, and myocardial metabolism are important determinants of MBF. Our results show that moderate respiratory acidosis causes an increase in MBF. Similarly, Wexels *et al.*¹³ found an increase in MBF during hypercapnic conditions in dogs. When pH was normalized by administration of sodium carbonate, however, MBF returned to normocapnic levels. They concluded that the increase is caused entirely by the concomitant

decrease in pH and not by elevated P_{aCO_2} *per se*. Other experimental studies,⁷⁻⁹ however, showed that pH and P_{aCO_2} both may influence MBF. Whether our findings are caused by respiratory variations of pH or P_{aCO_2} remains unclear.

In our patients, MVO_2 and MGU were not affected by respiratory acidosis, and coronary perfusion pressure remained constant. The increase in MBF, therefore, cannot be explained by increased metabolic demands or by changes in perfusion pressure. Similar to that seen with dogs, this suggests that a direct vasodilatation of coronary vasculature in response to respiratory acidosis occurs also in patients with coronary artery disease. A decreased sensitivity of the contractile proteins of the coronary vessel musculature^{14,15} and reduced calcium liberation by the sarcoplasmic reticulum^{6,16} are possible explanations for this vasodilatation induced by respiratory acidosis.

In previous investigations, a decrease of MBF and an increase in myocardial oxygen extraction were found during hypocapnia.^{13,17} Similarly, Neill and Hattenhauer¹⁸ found a reduction of MBF in awake hyperventilating humans. Because of this effect, Engelmann *et al.*¹⁹ suggested deliberate hypocapnia to treat patients with myocardial infarction. The rationale was to induce an inverse steal phenomenon by increasing CVR in unobstructed areas of the coronary vasculature. The results of our study show that MBF and CVR are not reduced significantly by moderate hypocapnia in patients undergoing coronary artery bypass graft surgery. Myocardial oxygen extraction, however, slightly increased. Nevertheless, in two cases, MLE decreased to negative values, indicating either respiratory alkalosis-induced lactate production of the myocardium or lactate washout. The leftward shift of the oxyhemoglobin dissociation curve associated with alkalosis should be considered, in part, as a possible reason for these metabolic effects. Because ST segment analysis did not reveal pathologic changes in those patients, the clinical significance of this metabolic effect remains unclear.

Another factor influencing MBF is sympathetic activity. Research has shown in dogs that the activation of β_1 - and β_2 -receptors induces coronary artery vasodilatation that is independent of metabolic demands.²⁰ Conversely, Wexels *et al.*³ found that in the presence of β -blockade the extent of coronary vasodilatation, induced by hypercapnia, remained unchanged when compared with changes occurring without β -block-

ade. Although six of our patients were pretreated with β -receptor antagonists, we have no reason to assume that the observed changes in MBF during hypercapnia may have been severely influenced by preexisting β -blockade.

Several studies have shown an increase in sympathetic activity associated with hypercapnia. In particular, myocardial contractility during hypo- or hypercapnia may be influenced by concomitant changes in autonomous nervous system activity. Studies in awake persons of the effects of variations in Pa_{CO_2} ²¹ therefore may differ substantially from studies of anesthetized patients. In our patients, MVO_2 , MGU, and $\text{dp/dt}_{\text{max}}$ as an estimate of myocardial contractility remained virtually unchanged. Because hypercapnia is known to have negative inotropic effects,²² our findings suggest that direct myocardial consequences of increased Pa_{CO_2} may have been at least partially counterbalanced by increased sympathetic activity.²³

Our results regarding global hemodynamic changes associated with varying Pa_{CO_2} levels agree with findings from other clinical studies.²⁴⁻²⁶ In awake hypercapnic patients, Cullen and Eger²¹ found an increase in CI, stroke volume index, heart frequency, mean arterial pressure, and indices of myocardial contractility. They concluded that these changes were related to the increased sympathetic activity associated with hypercapnia. In our patients, the observed changes in CI were not paralleled by respective changes in $\text{dp/dt}_{\text{max}}$, whereas the systemic vascular resistance index changed inversely. As found recently in patients undergoing cardiopulmonary bypass,²⁷ this indicates that in anesthetized patients Pa_{CO_2} -induced changes in CI and stroke volume index are caused by the direct effects of P_{CO_2} on vascular resistance rather than by changes in myocardial contractility.

In conclusion, in anesthetized patients with coronary artery disease, moderate variations in Pa_{CO_2} have significant effects on global hemodynamics and MBF but do not alter global MVO_2 and MGU. Hypercapnia causes an increase in MBF and a concomitant reduction of myocardial oxygen extraction, indicating moderate myocardial overperfusion. Moderate hypocapnia does not affect MBF but seems to increase myocardial oxygen extraction. Changes in CI associated with hypo- and hypercapnia are caused by Pa_{CO_2} -induced changes in the systemic vascular resistance index rather than by alterations of myocardial contractility.

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