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Influence of arterial carbon dioxide tension on systemic vascular resistance in patients undergoing cardiopulmonary bypass

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Background: The effects of induced hypothermia in cardiac surgical patients are not yet fully understood. Despite numerous studies on the effects of acid-base management on organ blood flow, only little information is available on the effects of α-stat versus pH-stat management on systemic haemodynamics. We therefore compared the effect of α-stat and pH-stat acid-base management on systemic haemodynamics in a prospective, controlled, cross-over study.
Methods: Twenty patients undergoing coronary artery bypass surgery were included in the study. Cardiac output was measured by thermodilution. Cardiac index and systemic vascular resistance were calculated according to standard formulae. Measurements were performed under hypo- and hypercapnia after induction of anaesthesia. Measurements were repeated at the end of two 30-min periods of pH-stat and α-stat acid-base management, respectively.
Results: Systemic vascular resistance at the lower $PaCO_2$-levels (hypocapnia and α-stat, respectively) was significantly higher than those at the higher level (hypercania and pH-stat, respectively). The periods of different $PaCO_2$-levels were comparable with respect to haematocrit, blood viscosity and temperature. Systemic vascular resistance was not significantly different from the control period.
Conclusions: This study demonstrates that during hypothermic cardiopulmonary bypass, systemic vascular resistance under α-stat acid-base management is higher than under pH-stat management. As obvious from measurements during the control period, this finding can be completely explained by the difference in $PaCO_2$.

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Key words: Carbon dioxide tension; vascular resistance; cardiopulmonary bypass; hypothermia.

THE EFFECTS of induced hypothermia in cardiac surgical patients are not yet fully understood. Despite numerous studies on the effects of acid-base management on organ blood flow, little information is available on the effects of α-stat versus pH-stat management on systemic haemodynamics (1–3). In particular, the effects of acid-base management during hypothermic cardiopulmonary bypass (CPB) have not yet been compared with respective changes of arterial carbon dioxide partial pressure ($PaCO_2$) at normothermia. We therefore asked if the type of acid-base management during hypothermic cardiopulmonary bypass has specific effects on systemic haemodynamics and if such effects are comparable to haemodynamic reactions occurring with changes in $PaCO_2$ during spontaneous circulation at normothermia. To answer this question we investigated the effects of different $PaCO_2$-levels both before and during cardiopulmonary bypass in patients undergoing coronary artery surgery.

Methods

After institutional approval by the local ethics committee on human research, written intormed consent was obtained from all patients. Twenty male patients were studied before and during elective coronary artery bypass graft surgery. The mean age of patients was 55 yr (range 46–66 years), their mean body height and weight were 173±5 cm and 85±10.3 kg, respectively (mean±SD).

Preanaesthetic medication consisted of 2 mg flunitrazepam in the evening and the morning before surgery. Individual preoperative medication, especially cardiac medication, was continued until the day of surgery.

Prior to induction of anaesthesia, routine haemodynamic monitoring was established including electrocardiography (leads II and V5) and arterial, central venous and pulmonary arterial catheterization. Induction of anaesthesia was performed by i.v. administration of 10 $\mu g\ kg^{-1}$ fentanyl and 0.2 $mg\ kg^{-1}$ midazolam, and tracheal intubation was facilitated by 0.1 $mg\ kg^{-1}$ pancuronium bromide. Anaesthesia was maintained by intravenous infusions of 7 $\mu g\ kg^{-1}\ h^{-1}$ fentanyl and 105 $\mu g\ kg^{-1}\ h^{-1}$ midazolam.

After intubation, all patients were mechanically ventilated with an inspiratory oxygen concentration (FiO_2) of 0.3. After a 30-min period of haemodynamic steady state, the tidal volume of the ventilator was sequentially adjusted to reach two different $PaCO_2$ levels with a difference of about 1.8 kPa. The sequence of ventilatory changes was randomized in order to minimize any time-related effects on systemic haemodynamics (control period). Each level of $PaCO_2$ was kept constant for 30 min, and haemodynamic measurements were performed only during steady-state conditions. As patients underwent hypothermic cardiopulmonary bypass, all measurements were repeated using α-stat and pH-stat acid base management, respectively (CPB-period).

Cardiopulmonary bypass technique consisted of a centrifugal pump (Sarns Delphin, 3M Health Care, Ann Arbor, MI, USA) and a membrane oxygenator (Bard HF 5000, W. Harvey, Tewksbury, MA, USA). During cardiopulmonary bypass, a mixture of oxygen in air with an inspiratory concentration of 0.35 was used. Non-pulsatile flow of 2.2 $l\ min^{-1}\ m^{-2}$ was established during the CPB-period. The priming volume of extracorporeal circuit consisted of 1000 ml of lactated Ringer's solution, 500 ml of glucose 5%, 400 ml of human albumin 20%, and sodium bicarbonate 100 ml. Cardiac arrest and myocardial protection were obtained by administration of Bretschneider's cardioplegic solution (Custodiol™, Köhler Chemie, Ansbach, Germany) at 4°C immediately after cross-clamping. No additional infusion of cardioplegic solution was performed. Patients' blood was cooled to a venous blood temperature of 30°C and α-stat and pH-stat acid-base management were sequentially initiated. Under α-stat conditions carbon dioxide tension was maintained at 40 mmHg measured at 37°C; no carbon dioxide was added to the oxygenator. pH-stat was initated by adding carbon-dioxide to the fresh gas flow of the oxygenator (FiO_2: 0.35) to maintain a temperature-corrected $PaCO_2$ of about 40 mmHg.

At each measurement arterial, central venous, pulmonary arterial and pulmonary wedge pressure were recorded on an 8-channel chart recorder; thermodilution measurements of cardiac output were taken at 3 random times during the respiratory cycle (Polymed CO computer, System 1281, Siemens, Munich, Germany). During cardiopulmonary bypass, measurements of systemic blood flow were obtained from an electromagnetic flow meter (Sarns Delphin, 3 M Health Care, Ann Arbor, MA, USA). Systemic vascular resistance was calculated according to standard formula. Blood samples for measurements of viscosity (Cone/Plate Viscosimeter LVT, Wells Brookfield, Stoughton, MA, USA) oxygen saturation and haemoglobin concentration (CO-Oximeter IL 282, Rotron Manufacturing, Woodstock, NY, USA) and oxygen as well as carbon dioxide partial pressure (ABL 3, Radiometer, Copenhagen, Denmark) were drawn twice, at the beginning and at the end of each registration period. Measurements of blood viscosity were performed at actual blood temperature.

Results are expressed as mean±standard deviation (SD). The effects of cardiopulmonary bypass and different $PaCO_2$-levels were tested by two-way analysis of variance using a repeated-measures design (MANOVA). If significant interactions between the two within-subject factors occurred, subsequent paired *t*-tests were used for post hoc comparison. A level of $P<0.05$ was considered statistically significant. All statistical procedures were performed on a microcomputer with the SPSS/PC^{+TM} statistical software package.

Results

The periods of different $PaCO_2$-levels before (control period) and during cardiopulmonary bypass (CPB-period) were comparable with respect to haematocrit (hct), blood viscosity (visc) and nasopharyngeal temperature (T_{np}) (Table 1). The absolute levels of mean arterial carbon dioxide tension differed slightly between the control and the CPB-period as the standardized change in acid-base management could not completely reproduce the $PaCO_2$ values of the control period. However, the difference between the lower and the higher levels of arterial carbon dioxide tension were nearly identical during both periods (Table 1).

Systemic vascular resistance during cardiopulmonary bypass was not significantly different from the control period. However, SVR values at the lower $PaCO_2$-level (hypocapnia and α-stat, respectively) were significantly higher compared to those at the higher level (hypercapnia and pH-stat, respectively) (Fig. 1). No interaction of factors ($PaCO_2$ and type of circulation) could be observed. Similarly, mean ar-

Table 1

Haemodynamic and metabolic data in patients during the control and the study period. Values for $PaCO_2$, PaO_2 and pH are given at 37°C.

	Control period		CPB-period	
	hypocapnia	hypercapnia	α-stat	pH-stat
HR [min^{-1}]	58±10	57±9	–	–
MAP [mmHg]	80±12	75±10	84±15	80±16
CVP [mmHg]	6.8±2.4	68±2.4	7.7±3.7	6.5±4 1
CI [1 min^{-1} m^{-2}]	2.24±0.65	2.35±0.71	2.20±0.24	2.26±0.24
SVI [ml m^{-2}]	39±10	41 6±10 3	–	–
SVR [dyn s cm^{-5}][a]	1437±438	1278±361	1482±390	1337±376
$PaCO_2$ [kPa][a,b]	4 4±0 4	6.3±0.7	5.0±0.3	6.7±0.4
PaO_2 [kPa][b]	15.3±2.3	14.4±3.6	24.4±4.26	25.9±3.9
pH[a]	7.44±0.04	7.34±0.06	7 39±0 03	7.27±0.03
hct [%][b]	38.1±3.0	38.1±3.0	24.6±2.5	24.9±2.5
visc [mPas s][b]	4.54±0.43	4.42±0.47	3.52±0.63	3.63±0.57
T_b [°C][b]	35 3±0.3	35.3±0.3	30.2±0.6	30.1±0.6

Values are mean±SD. HR=heart rate, MAP=mean arterial pressure, CVP=central venous pressure, CI=cardiac index, SVI=stroke volume index, SVRI=systemic vascular resistance index, $PaCO_2$=arterial carbon dioxide partial pressure, PaO_2=arterial oxygen partial pressure, hct=haematocrit, visc=blood viscosity, T_b=venous blood temperature. [a]significant difference between the two $PaCO_2$-levels ($P \leq 0.05$), [b]significant difference between control and CPB-period.

terial pressure during cardiopulmonary bypass was not different under α-stat and pH-stat acid-base management. During the control period, cardiac index at hypercapnia significantly exceeded values at hypocapnia (Table 1).

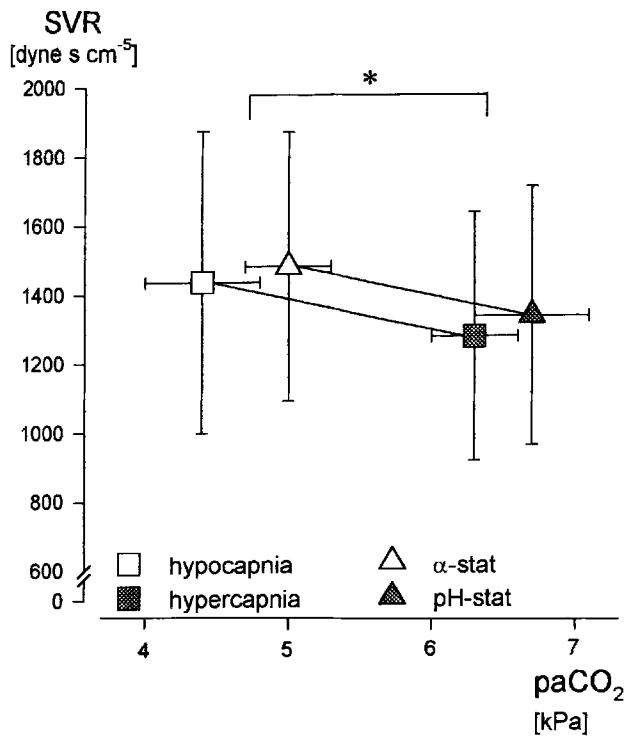

*Fig. 1. Relationship between carbon dioxide tension ($PaCO_2$) and systemic vascular resistance (SVR) during control (hypo-, hypercapnia) and CPB-period (α-stat and pH-stat, respectively). *$P \leq 0.05$ between control and CPB-period.*

Discussion

This study demonstrates that 1) in patients undergoing hypothermic cardiopulmonary bypass systemic vascular resistance is higher under α-stat than under pH-stat conditions, and that 2) this difference in systemic vascular resistance is equivalent to haemodynamic effects associated with changes in $PaCO_2$ during normothermia and spontaneous circulation.

Changes in systemic haemodynamics during cardiopulmonary bypass may be related to several factors such as changes in flow rate, flow characteristics, hypothermia and viscosity (4, 5). The effects of arterial carbon dioxide tension on systemic haemodynamics and organ blood flow are, however, still a matter of discussion (6–8).

Under conditions of spontaneous circulation, the effects of arterial carbon dioxide tension on systemic haemodynamics have been investigated in 1974 by Cullen and Eger (9). They found that an increase in arterial $PaCO_2$ is associated with a decrease in systemic vascular resistance and a concomitant increase in cardiac output (9). Similar results have been described by Gregory and co-workers and Kazmaier et al., which are in accordance with the changes that occurred during the control period in our patients (10, 11). The effects of arterial carbon dioxide tension have also been investigated in patients undergoing cardiopulmonary bypass (3, 4, 12, 13). In a study by Alston et al., no significant changes in systemic vascular resistance could be observed when two groups of patients undergoing either α-stat or pH-stat management were compared; however, in both groups of pa-

tients systemic vascular resistance increased with duration of cardiopulmonary bypass (4). The authors suggested, that the progressive increase in SVR was related to changes in vasomotor tone due to impairment of tissue perfusion and active constriction of metarterioles and precapillary sphincters (4). However, in this study target values for α-stat and pH-stat management were not reached; nevertheless, a significant difference in arterial $PaCO_2$ could be obtained. The findings of Alston et al. are in accordance with the results of Mündemann et al. who found no difference in systemic vascular resistance between patients undergoing cardiopulmonary bypass with α-stat and pH-stat management, respectively (12). Paterson, in contrast, found that hypocapnia during cardiopulmonary bypass caused an increase in mean arterial pressure (13). As the mean flow rate did not differ between groups this suggested an increase in systemic vascular resistance with decreasing $PaCO_2$.

Our investigation differed from previous studies in two major points. First, the present study was performed in a randomized cross-over design and each patient served as his own control. Second, we additionally investigated the effects of $PaCO_2$ on systemic haemodynamics during spontaneous circulation in the same patients and compared the effects with respective changes during hypothermic CPB. Our results demonstrate that SVR during hypothermic CPB is higher under α-stat than under pH-stat conditions. The comparison between the control period and the study period furthermore shows that identical changes in $PaCO_2$ are associated with the same changes in systemic vascular resistance during normothermia and hypothermic cardiopulmonary bypass, respectively. Because of the combined changes in $PaCO_2$ and pH the present data do not, however, allow to discriminate whether these changes in systemic vascular resistance are a direct effect of either carbon dioxide partial pressure, hydrogen ion concentration or both.

The effects of flow rate and flow characteristics (i.e. non-pulsatile or pulsatile flow) on the systemic circulation have also been the subject of clinical studies (4, 12, 14). Alston and coworkers studied the effects of flow rate on systemic haemodynamics in 24 patients undergoing coronary artery bypass surgery. In their study, systemic vascular resistance was inversely related to the flow rate, because SVR was significantly lower at a pump flow of 1.5 l min^{-1} m^{-2} than at a flow of 2 l min^{-1} m^{-2} (4). In the present study, an additional effect of flow rate on systemic vascular resistance can be excluded, because flow rate during the CPB-period was kept constant and did not differ between the two types of acid-base management. As other factors such as temperature, haematocrit and viscosity were also stable within the control and the CPB-period, this suggests that differences in SVR were primarily related to changes in $PaCO_2$.

Although many investigations have failed to verify an influence of flow character on haemodynamics (15–17), pulsatile perfusion in other studies has been stated to result in lower systemic vascular resistance when compared to non-pulsatile perfusion during CPB (l4). Such an effect of non-pulsatile flow in our study, however, may only be of relevance for the comparison between spontaneous and extracorporeal circulation, as the type of pump flow was not changed during the CPB-period. Since the relative changes in SVR between the two levels of $PaCO_2$ during cardiopulmonary bypass did not differ from respective changes during the control period, our findings also suggest that the CO_2-reactivity of SVR is neither impaired by moderate hypothermia nor by non-pulsatile flow.

Comparing the data of the control and the CPB-period, the effects of haemodilution have to be considered as well. A major reduction in haematocrit is known to decrease vascular resistance *in vivo*, although it is not yet clear if the reason for this effect is basically given by the decrease in viscosity of blood (8), the concomitant decrease in O_2-content (19), or both (20). Because haemodilution during cardipulmonary bypass in our patients was associated with a decrease in viscosity and in haematocrit by 20 and 35%, respectively, a global decrease in SVR could be expected. Controlled hypothermia, on the other hand, is known to cause peripheral vasoconstriction and may increase total SVR (21). The finding that SVR values during the CPB-period did not differ from respective values during the control period suggests that the effects of haemodilution on SVR were nearly completely counterbalanced by the effects of hypothermia.

In summary, we conclude that in patients undergoing hypothermic cardiopulmonary bypass for coronary artery bypass grafting, systemic vascular resistance under α-stat conditions is slightly higher than under pH-stat conditions. This difference, however, is equivalent to respective changes associated with variation of arterial carbon dioxide tension during normothermia and spontaneous circulation. The difference in systemic vascular resistance associated with a change in acid-base mangement at constant CPB-flow further suggests that $PaCO_2$-induced changes in systemic haemodynamics during spontaneous circulation are rather caused by effects on SVR than by $PaCO_2$-induced changes in cardiac function.

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