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Hypercapnia Prevents Jugular Bulb Desaturation during Rewarming from Hypothermic Cardiopulmonary Bypass

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Background: **The rewarming period of hypothermic cardiopulmonary bypass (CPB) is associated with reduced jugular bulb venous oxygen saturation (SjO_2). This study investigates the effects of normocapnia vs. hypercapnia on changes in SjO_2 during rewarming from hypothermic CPB for coronary artery bypass graft in patients classified as American Society of Anesthesiologists physical status III.**

Methods: **Anesthesia was induced and maintained with fentanyl, midazolam, and continuous infusion of etomidate. Hypothermic CPB (27°C) was managed according to alpha-stat conditions. The SjO_2 percentage was measured using a fiberoptic catheter placed in the right jugular bulb *via* the right internal jugular vein. Data were recorded before and during the rewarming period. Patients were assigned to a normocapnic (Pa_{CO_2}: 36–40 mmHg, n = 10) or hypercapnic (Pa_{CO_2}: 45–50 mmHg, n = 10) Pa_{CO_2} regimen during rewarming.**

Results: **The maximum reduction of SjO_2 occurred during rewarming with the jugular bulb temperature at 35–36°C. In contrast, SjO_2 did not change during rewarming from hypothermia in hypercapnic patients.**

Conclusions: **These results show that mild hypercapnia prevents the desaturation of SjO_2 seen with the normocapnic group during the rewarming period from hypothermic CPB. These data suggest that mild hypercapnia during rewarming from CPB is associated with a better balance between cerebral oxygen supply and demand. (Key words: Brain blood flow; cardiopulmonary bypass; cardiovascular; hypothermia; jugular bulb oxygen saturation; surgery.)**

NEUROLOGIC and neuropsychological dysfunction after coronary artery bypass graft using hypothermic cardiopulmonary bypass (CPB) affects 6-80% of patients.[1-4] Although some patients recover from the initial neuropsychological deficits, persisting deficits may occur in 10-30% of the patients and last for months or even longer.[4-10] Neuropsychological complications appear to be related to the occurrence of gas[11] or particulate matter embolization[12] and to global impaired cerebral oxygenation.

Studies in laboratory animals have shown cerebral venous hemoglobin desaturation with rapid rewarming. This is related to an increase in cerebral metabolic rate for oxygen that is temporarily not accompanied by an adequate increase in CBF.[13] This mismatch may indicate an abnormality in flow-metabolism coupling, leaving the cerebral vasculature unable to vasodilate adequately in response to increases in the cerebral metabolic rate for oxygen. It is unclear whether elevated arterial carbon dioxide tension (Pa_{CO_2}) can antagonize this constrictive effect.

This study investigated the effects of elevated Pa_{CO_2} on jugular bulb venous hemoglobin desaturation during rewarming of patients made hypothermic for CPB for coronary artery bypass graft.

Materials and Methods

After institutional review board approval and informed patient consent were received, we enrolled 20

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patients (American Society of Anesthesiologists physical status III) who were undergoing coronary artery bypass graft in the study. Patients with preexisting neurological dysfunction were not included. All patients were premedicated with flurazepam (1 mg/kg given orally) on the evening before surgery. Sixty minutes before induction of anesthesia, a premedication using dehydrobenzperidol (0.07 mg/kg) and fentanyl (1.5 μg/kg) were given by subcutaneous injection. Anesthesia was induced with fentanyl (10 - 25 μg/kg given intravenously), etomidate (50 μg/kg given intravenously), and pancuronium (100 μg/kg given intravenously) for neuromuscular blockade. After endotracheal intubation, all patients were normoventilated using oxygen in air (F_{IO_2}: 0.3 - 0.5). Anesthesia was maintained with fentanyl (<30 μg/kg intravenously) and midazolam (150 μg/kg intravenously) discontinuously as clinically required and with continuous infusion of etomidate (7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ intravenously). During CPB the etomidate infusion was continued. Catheters were placed into one radial artery and one internal jugular vein for simultaneous measurements of mean arterial blood pressure, drug infusion, and blood sampling.

The jugular bulb venous oxygen saturation (SjO_2) percentage and jugular bulb temperature (JBT) were measured using a fiberoptic thermodilution catheter (Opticath® F 5.5; Abbott Critical Care Systems, Mountain View, CA) placed into the right jugular bulb *via* the right internal jugular vein. Appropriate catheter position was confirmed by x-ray control before the measurements. The catheter was calibrated *in vitro* before insertion. Immediately after insertion and during the observation period, accurate fiberoptic saturation values were verified by drawing blood samples from the catheter and by measuring the oxygen saturation using a cooximeter (OSM 3, Radiometer, Copenhagen, Denmark) every 5 min.

Cardiopulmonary bypass was performed using a membrane oxygenator (Monolyth® Sorin, Biomedica, Saluggia, Italy) and a roller pump (Stöckert Instrumente, Munich, Germany) with an arterial line filter (40 μm). Nonpulsatile perfusion (Q′) through an ascending aortic cannula of 2 - 3 $l \cdot min^{-1} \cdot m^{-2}$ was maintained during the study period. The pump was primed with crystalloid solution, and a hematocrit of 0.22 ± 0.02 was maintained during extracorporal circulation. Cardiopulmonary bypass was managed according to alpha-stat acid-base conditions under moderate hypothermia (27 ± 1°C). During CPB arterial perfusate temperature (APT) was measured continuously at the oxygenator outlet.

After baseline measurements at the end of hypothermia (27°C) were made, hemoglobin concentration, the partial tension of oxygen (Pa_{O_2}), mean arterial blood pressure, pump flow rate (Q′), JBT, ABT, and SjO_2 were monitored continuously and recorded every 5 min during rewarming of CPB. In the normocapnic group (n = 10), Pa_{CO_2} was maintained within a range of 36 - 40 mmHg during rewarming. In the hypercapnic group (n = 10), Pa_{CO_2} was increased with start of rewarming and was maintained within a range of 45 - 50 mmHg. The Pa_{CO_2} in both groups was maintained by adjusting gas flow to the membrane oxygenator and measured at 37°C uncorrected to the patient's temperature (alpha-stat management). At the beginning of rewarming, the regulator of the heater was increased to 40 - 42°C and the APT was measured continuously at any time point.

Normally Pa_{CO_2} was increased in the hypercapnic group by reducing the gas flow of the CPB to near 600 ml/min (*i.e.*, about 60% of the gas flow before the start of rewarming) for 5 - 10 min until the Pa_{CO_2} was increased to >45 mmHg, then for 5 min to 900 ml/min, and after 10 min to 1,200 ml/min to keep the Pa_{CO_2} between 45 - 50 mmHg. To prevent hypoxemia, the F_{IO_2} was increased to 70% during hypercapnic rewarming. Patients were rewarmed until their nasopharyngeal temperature was >36°C and bladder temperature was >35°C. Norepinephrine was used to keep mean arterial blood pressure >40 mmHg during hypothermia and >55 mmHg during normothermia.

Physiologic variables are given as means ± SD. Physiological variables at given time intervals were tested for Gaussian distribution using the Kolmogorow-Smirnow test. Analysis of variance for repeated measurements was used to test for significant differences between and within groups. *Post hoc* data were analyzed using paired or unpaired *t* tests when appropriate, with Bonferroni corrections for multiple comparisons. A probability value <0.05 was considered to indicate a significant difference.

Results

Table 1 shows the demographic variables and CPB times. No significant differences occurred in any parameter between the groups. Table 2 shows the physiologic variables in patients with normocapnia (group 1) or hypercapnia (group 2) during hypothermia and rewarming. The hemoglobin value and mean arterial blood pressure did not change during rewarming com-

Table 1. Demographic Data

	Group 1	Group 2
Patients	10	10
Sex (m/w)	7/3	8/2
Diabetes mellitus (n)	3	1
Arterial hypertension (n)	5	7
Age (yr)	58 ± 10	60 ± 8
Weight (kg)	76 ± 7	78 ± 7
Length (cm)	169 ± 7	172 ± 7
Body surface (m^2)	1.86 ± 0.09	1.91 ± 0.11
CPB time (min)	125 ± 26	113 ± 17

CPB = cardiopulmonary bypass.

Applicable data are presented as mean ± SD.

pared with baseline (*i.e.*, at the end of hypothermic CPB) and were not different between the groups. The amount of vasoactive drugs used was not different between the groups. The JBT and APT were not significantly different between the groups. The Pa_{CO_2} was kept constant in group 1 but was increased in group 2 according to the study protocol. The Pa_{O_2} was not significantly different between groups. Q′ (pump flow rate) was increased in both groups to a similar extent.

Figure 1 shows SjO_2 at baseline, nadir, and at the end of rewarming. In group 2, SjO_2 did not change during rewarming from hypothermia, and no patient showed a SjO_2 <50%. However, in group 1 SjO_2 was reduced to a nadir of 45 ± 4%. Fifteen minutes after the start of rewarming, a maximum reduction of SjO_2 was seen in group 1, when JBT and APT were 36.5 ± 1.1°C and 37.5 ± 0.5°C (table 2).

Discussion

Our data show that the degree of jugular bulb venous hemoglobin saturation during rewarming from CPB is related to the level of Pa_{CO_2}. During normocapnia jugular bulb venous hemoglobin desaturation (SjO_2 <50%) occurred, with the lowest values seen at 36°C JBT. This suggests a mismatch between global cerebral oxygen demand and CBF during the rewarming period. In contrast, desaturation did not occur with hypercapnic acid base management. This suggests that hypercapnic cerebrovascular dilation is effective in reversing the imbalance of oxygen demand and supply during the rewarming period. However, an increased carbon dioxide level could increase the embolic load to the brain.

Table 2. Physiologic Data during Rewarming from Hypothermic CPB

	Time (min)	Sjo_2 (%)	Hb (g/dl)	MAP (mmHg)	Pa_{CO_2} (mmHg)	Pa_{O_2} (mmHg)	Q′ ($L \cdot min^{-1} \cdot m^{-2}$)	JBT (°C)	APT (°C)
Group 1	Hypothermia	61 ± 5	7.7 ± 0.5	60 ± 6	36.4 ± 2.2	194 ± 66	2.1 ± 0.1	27.2 ± 0.8	27.1 ± 0.7
(n = 10):	5	51 ± 3*	7.8 ± 0.6	69 ± 11	34.8 ± 2.2	200 ± 47	2.4 ± 0.3*	32.3 ± 1.7*	35.5 ± 1.1*
normocapnia	10	49 ± 3*	7.8 ± 0.6	69 ± 6	34.8 ± 2.5	206 ± 40	2.5 ± 0.3*	34.9 ± 1.4*	36.5 ± 1.1*
	15	49 ± 5*	7.7 ± 0.4	63 ± 8	37.2 ± 2.9	193 ± 36	2.6 ± 0.2*	36.5 ± 1.1*	37.3 ± 0.7*
	20	51 ± 6*	7.8 ± 0.5	62 ± 10	37.4 ± 2.3	210 ± 52	2.7 ± 0.2*	37.0 ± 1.1*	37.6 ± 0.6*
	25	51 ± 7*	7.8 ± 0.7	66 ± 8	38.9 ± 3.2	197 ± 30	2.7 ± 0.1*	37.5 ± 0.8*	37.1 ± 0.8*
	30	53 ± 6*	8.2 ± 0.7	65 ± 7	38.5 ± 3.2	189 ± 47	2.7 ± 0.2*	37.5 ± 0.9*	36.9 ± 0.7*
	35	53 ± 8	8.2 ± 0.7	62 ± 11	38.0 ± 2.2	193 ± 15	2.8 ± 0.1*	37.5 ± 0.7*	37.0 ± 0.7*
	40	55 ± 6	8.2 ± 0.8	64 ± 9	38.6 ± 2.0	198 ± 23	2.8 ± 0.1*	37.6 ± 0.5*	36.8 ± 0.7*
Group 2	Hypothermia	63 ± 3	7.7 ± 0.6	57 ± 14	37.0 ± 2.6	192 ± 42	2.1 ± 0.1	27.1 ± 0.2	27.0 ± 0.2
(n = 10):	5	66 ± 5†	7.8 ± 0.5	59 ± 13	43.6 ± 3.0*†	191 ± 36	2.3 ± 0.1*	31.4 ± 1.8*	35.1 ± 0.9*
hypercapnia	10	66 ± 4†	7.8 ± 0.5	63 ± 12	46.0 ± 3.5*†	214 ± 51	2.4 ± 0.1*	34.2 ± 1.4*	36.8 ± 0.5*
	15	63 ± 5†	7.9 ± 0.6	70 ± 10	47.7 ± 5.3*†	211 ± 73	2.4 ± 0.1*	36.5 ± 0.9*	37.5 ± 0.5*
	20	64 ± 3†	8.0 ± 0.5	67 ± 7	48.6 ± 5.6*†	210 ± 49	2.6 ± 0.1*	37.2 ± 0.5*	37.5 ± 0.3*
	25	63 ± 3†	8.1 ± 0.5	66 ± 5	47.2 ± 3.8*†	233 ± 47	2.7 ± 0.1*	37.5 ± 0.3*	37.5 ± 0.3*
	30	63 ± 4†	8.2 ± 0.5	63 ± 5	44.6 ± 3.9*†	233 ± 35	2.7 ± 0.1*	37.7 ± 0.4*	37.3 ± 0.4*
	35	64 ± 4†	8.2 ± 0.5	64 ± 6	42.9 ± 3.7*†	222 ± 33	2.7 ± 0.2*	37.7 ± 0.5*	37.1 ± 0.2*
	40	61 ± 3	8.3 ± 0.5	64 ± 8	40.2 ± 3.3	214 ± 47	2.8 ± 0.1*	37.6 ± 0.4*	37.0 ± 0.2*

Sjo_2 = jugular bulb oxygen saturation; Hb = hemoglobin; MAP = mean arterial blood pressure; Pa_{CO_2} = arterial tension of carbon dioxide; Pa_{O_2} = arterial tension of oxygen; Q′ = pump flow rate of CPB; JBT = temperature in jugular bulb; APT = arterial perfusate temperature; CPB = cardiopulmonary bypass.

Data are mean ± SD.

* $P < 0.05$ *versus* hypothermia.

† $P < 0.05$ *versus* group 1 at each respective level.

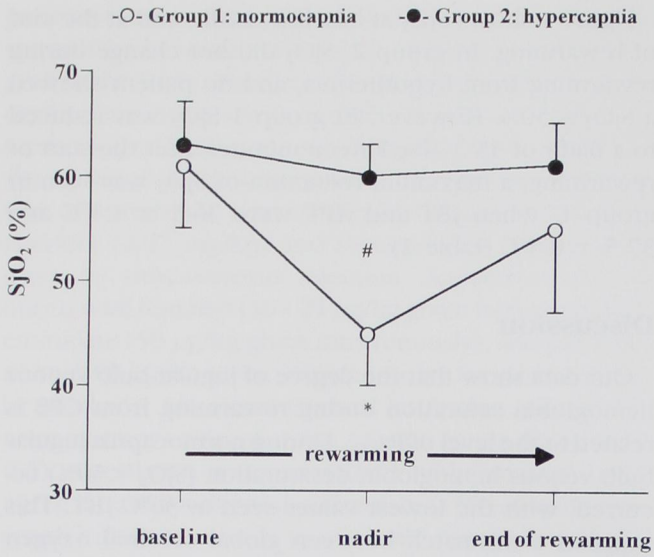

Fig. 1. Jugular bulb oxygen saturation (SjO_2) before and during rewarming with cardiopulmonary bypass (mean ± SD, *P < 0.05 *vs.* hypothermia within the group; #P < 0.05 *vs.* group 1).

Previous studies have shown that rewarming from hypothermic CPB is frequently associated with decreases in SjO_2 (SjO_2 <50%).[6,14-17] These may be related to postoperative cognitive dysfunction.[6] The imbalance may be due to differences in the speed of rewarming within the various tissues and compartments. Studies in rabbits[13] have shown that rewarming from hypothermic CPB decreases cerebral venous hemoglobin saturation as a result of increases in the cerebral metabolic rate for oxygen that are temporarily greater than the increase in CBF. Therefore oxygen extraction was increased and SjO_2 was decreased. This suggests that the rewarming process activates cerebral function despite the fact that the brain temperature is still within the hypothermic range and that cerebral venous hemoglobin desaturation is related to inadequate cerebrovascular dilation as neuronal functional activity increases.

Cerebral venous oxygenation is a function of the position of the oxygen-hemoglobin dissociation curve and the venous oxygen pressure, and decreases in SjO_2 are not necessarily related to pathological conditions. According to a theoretical model of oxygen transfer from the blood to the brain, oxygen transfer depends closely on hemoglobin oxygen affinity.[17] Warm blood with decreased oxygen affinity (increased P_{50} = the oxygen partial pressure at which hemoglobin oxygen saturation equals 0.5) facilitates oxygen transfer from "warm" hemoglobin to the cold brain. This results in desaturation and is expected to occur at the beginning of rewarming, when the temperature gradient between the blood and the brain is most pronounced. In contrast, desaturation in normocapnic patients occurred during minimal temperature differences (JBT: 36.5 ± 1.1°C *vs.* APT: 37.3 ± 0.7°C) between the blood and the brain (*i.e.*, 15 min after the start of rewarming, just before or when normothermia is reached; table 2). However, the JBT probably represents only the area of the brain near the vessels with high perfusion, and the temperature of areas that are less perfused are lower, indicating a temperature gradient in these areas. Twenty-five minutes after the start of rewarming, the JBT is higher than the APT (table 2). This difference may be related to the fact that the two different temperature measurement devices were not independently calibrated.

The P_{50} theory cannot explain the association between cerebral venous hemoglobin desaturation and the neuropsychological impairment found in human studies in which the arterial-jugular-venous oxygen difference and jugular venous hemoglobin desaturation at the end of rewarming was associated with postoperative neuropsychological impairment.[6] Similarly, this model cannot explain the reversal of jugular venous hemoglobin desaturation with hypercapnia during rewarming (group 2).

The fact that mild hypercapnia (45-50 mmHg) during alpha-stat management reversed jugular bulb venous hemoglobin oxygen desaturation seen with the classical alpha-stat approach (36-40 mmHg) tends to support the vascular response issue largely because the *p*H shift produced with mild hypercapnia is not great enough to facilitate unloading. Thus the difference in SjO_2 between the two groups is unlikely related to differences in the cerebral metabolic rate for oxygen, which was not measured in the present study.

In conclusion, these data show that under normocapnia the cerebral vascular reserve to vasodilate may not be exhausted during the rewarming period from hypothermic CPB. Further, these data show that mild hypercapnia during rewarming from hypothermic CPB reverses jugular bulb venous hemoglobin desaturation, possibly suggesting a better balance between oxygen supply and demand.

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