Systemic effects of carbon dioxide insufflation technique for de-airing in left-sided cardiac surgery

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Objective: Systemic effects of carbon dioxide (CO₂) insufflation during left-sided cardiac surgery were evaluated in a prospective randomized study, with regard to acid–base status, gas exchange, cerebral hemodynamics, and red blood cell morphology.

Methods: Twenty patients undergoing elective left-sided cardiac surgery were randomized to de-airing procedure either by CO₂ insufflation technique (CO₂ group, n = 10) or by Lund technique without CO₂ insufflation (Lund group, n = 10). Groups underwent assessment of acid–base status by intermittent arterial blood gases and in-line blood gas monitoring. Capnography was used to determine volume of CO₂ produced. Cerebral hemodynamics was measured by transcranial Doppler sonography and near-infrared spectroscopy. Red cell morphology from cardiectomy suction and vent tubing was studied by scanning electron microscopy.

Results: Patients in the CO₂ group consequently developed significantly higher levels of hypercapnia with a concomitant increase in the volume of CO₂ produced despite significantly higher oxygenator gas flows compared with the Lund group. Effects on cerebral hemodynamics were observed in the CO₂ group with significantly higher blood flow velocities in the middle cerebral artery and higher regional cerebral saturation. Red blood cell damage was observed in the CO₂ group by scanning electron microscopy (97% in CO₂ group vs 18% in Lund group).

Conclusions: Insufflation of CO₂ into the cardiectomy wound cavity during left-sided cardiac surgery can induce hypercapnic acidosis and increased cerebral blood flow and local blood cell damage. These systemic effects should be monitored by in-line capnography and acid–base measurements for early and effective correction by increase in gas flows to the oxygenator. (*J Thorac Cardiovasc Surg* 2014;147:295-300)

Insufflation of carbon dioxide (CO₂) into the pericardial cavity during left-sided cardiac surgery can reduce residual intracardiac air and reduce the risk of air embolism.¹⁻³ However, reports have described development of hypercapnic acidosis from CO₂ insufflation.^{2,4,5} Furthermore, hypercapnia by its vasodilator effect is known to increase cerebral blood flow,⁶ which could contribute to increased risk of cerebral embolism. Our group has previously described a technique for de-airing (Lund technique) of the left heart that does not utilize CO₂.⁷⁻⁹ In a prior prospective randomized study,⁹ we compared the Lund technique to the CO₂ insufflation technique, and observed significantly higher rates of air emboli recorded by transesophageal echocardiography and micro-embolic signals by transcranial Doppler sonography (TCD) associated with CO₂ insufflation.⁹ In this study we evaluated

systemic effects of CO₂ insufflation with regard to acid–base balance, gas exchange, cerebral hemodynamics, and red blood cell morphology in the previously described prospective sample.⁹

MATERIALS AND METHODS

Study Population

Patients scheduled for elective open aortic surgery were considered for study inclusion as previously described.⁹ Preoperative exclusion criteria were a history of carotid artery disease, chronic obstructive pulmonary disease and emphysema, previous thoracic surgery, and patients who were being considered for left internal thoracic artery harvesting. Intraoperative exclusion criteria were accidental opening of the pleura during sternotomy in the CO₂ group, failure to wean from the cardiopulmonary bypass (CPB), and failure to obtain adequate Doppler signals from the middle cerebral arteries. Twenty consecutive patients were randomized to either the Lund de-airing technique (Lund group, n = 10) or the CO₂ insufflation technique (CO₂ group, n = 10) during induction of anaesthesia by opening envelopes indicating de-airing technique created from a computer generated randomization list. The study was approved by the ethics committee of Lund University, Sweden, and all included patients provided written informed consent. The study protocol was registered with ClinicalTrials.gov (identifier No. NCT00934596).

Operative Management

Patients were anaesthetized and monitored during surgery using standardized procedures, including intraoperative transesophageal echocardiography. Patients were ventilated using a SERVO-i ventilator (Maquet Inc, Solna, Sweden) equipped with a module for calculation of CO₂ minute production (Capnostat, Respirationics Novamatrix Inc, City, Conn). Surgery was

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Disclosures: Authors have nothing to disclose with regard to commercial support. Received for publication Aug 2, 2012; revisions received Oct 3, 2012; accepted for publication Nov 6, 2012; available ahead of print Dec 14, 2012.

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0022-5223/\$36.00

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<http://dx.doi.org/10.1016/j.jtcvs.2012.11.010>

Abbreviations and Acronyms

CO ₂	= carbon dioxide
CPB	= cardiopulmonary bypass
LV	= left ventricle
rSO ₂	= regional cerebral oxygen saturation
SEM	= scanning electron microscopy
TCD	= transcranial Doppler sonography

performed using standard surgical technique. CPB was established using a membrane oxygenator (Compact Flow EVO Phiso; Sorin Group, Mirandola, Italy), an arterial filter (Cobe Century; Sorin Group, Mirandola, Italy), and polyvinylchloride tubing (silicone tubing in the pump heads). Roller pumps (Stockert S3; Sorin Group GmbH, Munich, Germany) and a heat exchanger (T3; Sorin Group, Mirandola, Italy) were used in all patients. CPB was maintained with a nonpulsatile blood flow rate of approximately 2.5 L/minute/m² at normothermia. During CPB, patients were cooled to 25°C–28°C as measured in the urinary bladder or tympanic membrane depending on whether the aortic arch was replaced or not, respectively. Antegrade cold blood cardioplegia was used for myocardial protection and the left ventricle (LV) was vented through the apex in all patients using a 15F Polystan LV drainage catheter (Maquet Inc, Solna, Sweden).

The Lund De-Airing Technique

The Lund de-airing technique has been described by us previously.^{7–9} It comprises induced collapse of both lungs by opening the pleura bilaterally and disconnection of the ventilator before opening the heart to prevent air from entering the pulmonary veins, and a gradually staged cardiac filling and lung ventilation before CPB weaning, to expel air trapped in the pulmonary veins.

The CO₂ Insufflation De-Airing Technique

In this group the pleural cavities were left intact. During CPB, patients were ventilated with 1 L/minute, 5 breaths/minute, and positive end expiratory pressure 5 cm water. Before cannulation for CPB, CO₂ insufflation was initiated with a gas diffuser placed in the cardi thoracic cavity (Cardia Innovation AB, Stockholm, Sweden) according to the manufacturer's instructions as follows.¹⁰ CO₂ flow was set at 10 L/minute and continued until 10 minutes post-CPB. Following completion of the surgical procedure and closure of the heart, the heart and lungs were passively filled, the heart was massaged, and the left heart de-aired continuously through the LV vent. Full ventilation was then resumed, and the aortic root was de-aired by active suctioning with the LV vent clamped. The aortic crossclamp was released and the LV vent opened again. After good cardiac contractions, the LV preload was gradually increased by reducing the venous return to the CPB circuit, and the de-airing continued through the vent in the LV apex under transesophageal echocardiography monitoring. When no air emboli were observed in the left atrium, LV, and aortic root, the drainage in the LV was reduced and the heart was allowed to eject. De-airing was continued, and when no air emboli were observed in the left side of the heart, the patients were weaned from CPB and the LV vent was clamped in situ.

Monitoring of Arterial Blood Gases and Gas Dynamics

Arterial blood samples were drawn intermittently every 15 minutes for analysis of blood gases (ABL800 FLEX; Radiometer, Copenhagen, Denmark). Temperature-corrected blood gases were used to facilitate alpha-stat pH management. In addition, pH and CO₂ partial pressure were continuously monitored from the arterial line using an in-line blood gas monitor (CDI Blood Parameter Monitoring System 500; Terumo Cardiovascular System,

Ann Arbor, Mich). CO₂ partial pressure was targeted to 5.5 to 6.5 kPa for both groups and the gas flow in the oxygenator readjusted when CO₂ partial pressure diverged from this interval. CO₂ concentration at the gas outlet on the oxygenator was measured using a capnograph (IRMA CO₂; Phasein AB, Danderyd, Sweden). CO₂ minute production (VCO₂ mL/min) from the oxygenator was calculated as gas flow in the oxygenator multiplied by the concentration of CO₂ at the oxygenator gas outlet. Total volume of CO₂ in the CO₂ group was thus the sum of CO₂ from dead space ventilation measured in the ventilator and CO₂ measured at the oxygenator gas outlet. In the Lund group CO₂ minute production was measured at the oxygenator gas outlet only as the ventilator was disconnected during CPB. For clinical comparison an upper cut-off value at 60 minutes of CPB time was chosen for 2 reasons: (1) to retain adequate number of observations in both groups for statistical comparison, and (2) to permit comparison between the groups when all patients are in cooling or early rewarming phase of surgery.

Arterial and mixed venous oxygen content in blood was calculated according to the following formula:

$$\text{Oxygen content mL/L} = \text{Haemoglobin (g/L)} \times 1.36 \times \text{saturation (\%)} / 100 + 0.0031 \times \text{oxygen tension (kPa)}$$

Oxygen consumption (VO₂) was calculated according to the following formula:

$$\text{VO}_2 \text{ mL/min} = \text{arteriovenous oxygen content difference} \times \text{pump flow (L/min)} / 100$$

Respiratory quotient (RQ) was calculated according to the formula:

$$\text{RQ} = \text{volume of CO}_2 \text{ (mL/min)} / \text{VO}_2 \text{ (mL/min)}$$

TCD Monitoring

Middle cerebral arteries of both hemispheres were monitored continuously for mean blood flow velocities using multifrequency TCD sonography (Doppler box; DWL, Singen, Germany) beginning at the start of surgery and continuing up to 10 minutes after weaning of CPB.¹¹ The bilateral probes were fixed transtemporally by head brace. The insonation and reference gate depths were between 50 and 60 mm, sample volume 10 mm, power 180 mW, and gain 10.

Scanning Electron Microscopy (SEM)

At the conclusion of CPB in patients 4 and 5 from the CO₂ group, clot formation was suspected in the cardiectomy suction tubing close to the pump head. However SEM imaging of the PVC tubings from these patients showed no clot formation but varying degrees of damaged red blood cells. Segments of the PVC cardiectomy suction and vent tubings immediately proximal to the respective pump heads were consequently sent for SEM study in the remaining 10 patients from both groups. Two 15-mm long sections from each tubing sample were fixed in 2% glutaraldehyde in Sorensen buffer at pH 7 for 2 hours. Each tubing segment was then cut in half along the long axis and dehydrated in a series of graded ethanol concentrations until a dry ethanol critical point drying was reached. Each section was mounted on stub, sputtercoated with 20 nm gold and examined under a Philips 515 scanning electron microscope by 1 expert who was blinded to intervention groups. All images were recorded at the same magnification. Four representative images from each individual, 20 from each group, were thus available for the comparative study. Five images from each group were randomly selected for detailed calculation of the proportion of damaged red blood cells in each image.

Statistical Analysis

The randomization list was generated using the Plan procedure in SAS version 8.2 (SAS Institute, Cary, NC). Data were analysed using the stat

and Hmisc packages of R software (R Foundation for Statistical Computing, Vienna, Austria), version 2.6.0. Continuous parameters are unless otherwise stated expressed as median and first and third quartiles. The Wilcoxon signed-rank test was used for group comparisons.

RESULTS

Patient groups did not differ significantly in major preoperative characteristics (summarized in Table 1). All patients survived the surgical procedure and were discharged from the hospital in good clinical condition. One patient in the CO₂ group experienced transient aggravation of a paresis of the right arm that was present preoperatively. One patient from the Lund group experienced mild perioperative stroke on day 2; symptoms regressed by discharge. The median duration of CPB was 94 minutes in the CO₂ group and 117 minutes in the Lund group. One patient in the Lund group was excluded from calculation of CO₂ volume and respiratory quotient due to failure to obtain data from the gas outlet on the oxygenator (Table 2).

There was no difference in CO₂ partial pressure between groups before institution of CPB (Figure 1). In the CO₂ group, CO₂ partial pressure increased significantly at 15- and 30-minute intervals compared with the Lund group. CO₂ partial pressure, however, could be kept within the targeted normal levels in the CO₂ group at the expense of significant increase in gas flows through the oxygenator at 30-, 45-, and 60-minute time intervals (Figure 1). At 45 minutes the gas flow in the CO₂ group was more than twice as high as in the Lund group: 2.20 (1.63-3.10) versus 0.65 (0.60-1.25) L/minute. Similarly, at 60 minutes the gas flow in the CO₂ group was 2.65 (1.78-3.38) L/minute compared with the Lund group's 0.80 (0.70-1.45) L/minute. There was no difference in arterial blood pH between groups before initiation of CPB. After initiation of CPB, pH decreased to significantly lower levels at 15-, 30-, and 45-minute time intervals in the CO₂ group (Figure 1). No significant difference in concentration of blood lactate was found between groups. In the CO₂ group the highest level of lactate during CPB was 1.1 mmol/L (0.9-1.6) at 60 minutes and in the Lund group it was 1.0 mmol/L (0.6-1.2) at 45 minutes. CO₂ volume during CPB was at all times higher in the CO₂ group compared with the Lund group (Figure 1). However, differences in CO₂ volume between the groups were statistically significant at 30-, 45-, and 60-minute intervals only. At 60 minutes CO₂ volume peaked in the CO₂ group to 198.0 (152.0-229.0) mL/minute compared with 69.6 (39.2-105.6) mL/minute in the Lund group (Figure 1). In contrast, the amount of CO₂ measured from dead space in the ventilator was 4.5 (4.0-8.0) mL/minute at 15 minutes, 5.0 (3.0-6.0) mL/minute at 30 minutes, 5.0 (4.0-6.0) mL/minute at 45 minutes, and 5.0 (3.8-6.5) mL/minute at 60-minute intervals in the CO₂ group.

No significant difference in oxygen consumption was found during CPB between the groups (Table 2). Fraction of inspired oxygen administered during CPB was similar

TABLE 1. Patient characteristics

	CO ₂ group (n = 10)	Lund group (n = 10)	P value
Age (y)	71 (56-78)	70 (59-77)	.942
Male/female	5/5	5/5	
Body surface area (m ²)	2.0 (1.76-2.16)	1.85 (1.76-2.06)	.743
Original surgical procedures			
Aortic valve replacement	6 (60%)	7 (70%)	
Aortic valve repair	3 (30%)	1 (10%)	
Bentall operation	1 (10%)	2 (20%)	
Aortic arch replacement	1 (10%)	0	
Cardiopulmonary bypass time (min)	94 (84-154)	117 (105-135)	.252
Aortic crossclamp time (min)	59 (52-88)	89 (77-108)	.074
Postoperative ventilator time (h)	6 (4-7)	6 (4-8)	.882
Intensive care unit stay (h)	22 (21-24)	21 (20-22)	.293

Data are presented as mean (range) or n (%). CO₂, Carbon dioxide.

for both groups at all intervals. In the CO₂ group, the respiratory quotient was significantly higher at 30-, 45-, and 60-minute intervals during CPB than in the Lund group (Table 2).

Blood gas values obtained from intermittent sampling of blood from the CPB circuit and the in-line blood gas monitoring showed a common trend. No statistically significant differences in CO₂ partial pressure and pH measurements were observed between the 2 methods at any time interval.

Blood flow velocity measured in the middle cerebral artery during CPB was higher bilaterally in the CO₂ group than in the Lund group (Figure 2). There was a significant increase in velocity in both hemispheres in the CO₂ group from 30 minutes on CPB ($P < .01$) until end of CPB ($P < .001$) (Figure 2). In the right hemisphere, statistically significant differences were seen after 30 minutes on CPB and onward in the CO₂ group. In the left hemisphere these differences were significantly different already at 15 minutes on CPB and onward. Regional cerebral oxygen saturation (rSO₂) is presented in absolute values (Figure 2). In the CO₂ group significantly higher rSO₂ values were

TABLE 2. Calculated oxygen consumption and respiratory quotient

	CO ₂ group (n = 10)	Lund group (n = 9)	P value
Time on CPB (min)			
Oxygen consumption (mL/min)			
15	109.8 (72.9-134.5)	118.3 (77.4-52.6)	.912
30	115.8 (77.0-120.5)	114.9 (76.6-139.6)	.481
45	100.6 (84.5-150.9)	109.7 (91.4-151.2)	.579
60	125.9 (97.2-137.4)	109.2 (101.9-151.5)	.905
Respiratory quotient			
15	0.78 (0.56-1.01)	0.52 (0.39-0.69)	.065
30	1.01 (0.85-1.45)	0.44 (0.27-0.59)	<.001
45	1.47 (1.29-1.66)	0.45 (0.27-0.66)	<.001
60	1.47 (1.16-2.36)	0.61 (0.49-0.67)	<.001

Continuous variables are presented as median (interquartile range). CPB, Cardiopulmonary bypass; CO₂, carbon dioxide.

FIGURE 1. Arterial blood gases and extracorporeal gas dynamics before, during, and at the end of cardiopulmonary bypass (CPB). Circles indicate the carbon dioxide group, triangles indicate the Lund group. PaCO₂, Partial pressure of carbon dioxide; VCO₂, volume of carbon dioxide produced. **P* < .05; ***P* < .01; ****P* < .001 for between-group comparisons.

recorded from both cerebral hemispheres until CPB was terminated when compared with the Lund group. No statistically significant difference in hematocrit was found between the 2 groups at corresponding time intervals.

The SEM images of the cardiotomy suction and LV vent tubings showed a higher degree of red blood cell damage in the CO₂ group (Figure 3). This finding was consistent in the final 5 patients in the CO₂ group despite restricted use of

cardiotomy suction in this group. The fraction of damaged red cells in the CO₂ group was 0.97 (0.64-1.0) compared with 0.18 (0.11-0.30) in the Lund group. In both the groups the activated clotting times and the heparin concentration was within therapeutic limits throughout CPB.

DISCUSSION

In our study, CO₂ insufflation of the operative field employing a standardized and recommended protocol induced significant hypercapnic acidosis (Figure 1). This occurred despite early and continuous correction by increased gas flow to the oxygenator based on in-line monitoring of blood gases (Figure 1). The increase in CO₂ partial pressure corroborates the observed concomitant increase in CO₂ volume in the CO₂ group (Figure 1), which illustrates the effect of CO₂ insufflation on gas dynamics and indicates the necessity to take early and effective compensatory action to avoid acidosis. High arterial partial pressures of CO₂ after insufflation of CO₂ in the operative field and the necessity of compensational increases in oxygenator gas flows have been described in several previous reports.^{2,4,5,12} During CO₂ insufflation, blood from the pericardium returning to the CPB circuit by cardiotomy suction has a high CO₂ content.¹ Therefore, use of cardiotomy suction in this study was restricted to a minimum. We consistently used a gas diffuser that has been validated previously to provide a sufficient concentration of CO₂ in the wound cavity.¹³

The use of a capnograph at the oxygenator gas outlet is a simple adjuvant in controlling appropriate gas flows to avoid adverse effects of CO₂ insufflation.¹² Because the systemic effects of CO₂ insufflation seem to rapidly develop, in-line monitoring constitutes an important complement or alternative to conventional intermittent blood gas analysis. Consistent with other reports,¹² the gas flow through the oxygenator was increased to nearly twice normal to prevent hypercarbic acidosis during CO₂ insufflation. There were no differences in oxygen consumption (Table 2) and concentration of lactate between the groups indicating no metabolic component to the acidosis seen in the CO₂ group. Also, the contribution of CO₂ from the bronchial circulation in the CO₂ group during CPB consisted only of a small fraction of total CO₂ volume, indicating that the increased CO₂ volume derived from gas insufflation. The CPB time was similar between the groups and the aortic crossclamp time was relatively shorter for the CO₂ group (Table 1). The CO₂ insufflation was, however, not terminated until 10 minutes after the end of CPB, so the difference in aortic crossclamp time would not have an influence on the difference in CO₂ volume between groups.

Cerebral hemodynamics were affected by CO₂ insufflation; the mean blood flow velocities in both middle cerebral arteries were significantly higher in the CO₂ group than in the Lund group (Figure 2). This observation suggests that the effect of CO₂ insufflation on cerebral blood velocity

FIGURE 2. Cerebral hemodynamics measured by transcranial Doppler (TCD) and regional cerebral oxygen saturation (rSO₂) measured by near-infrared spectroscopy before, during, and at end of cardiopulmonary bypass (CPB). Circles indicate carbon dioxide group, triangles indicate Lund group. **P* < .05; ***P* < .01; ****P* < .001 for between-group comparisons.

FIGURE 3. A, Scanning electron microscope pictures of the cardiectomy and/or left ventricular vent tubings showing morphology of the red blood cells in the carbon dioxide group. B, Scanning electron microscope pictures of the cardiectomy and/or left ventricular vent tubings showing morphology of the red blood cells in the Lund group. The fraction of damaged red cells in the carbon dioxide group was 0.97 compared with 0.18 in the Lund group.

occurs early and thereafter reaches a plateau because CO₂ partial pressure is held within targeted limits by corresponding increases in gas flow to the oxygenator. Increased velocities in the middle cerebral artery as measured by TCD, could theoretically be caused by increased intracranial vascular resistance, or by increased blood flow to the brain secondary to vasodilatation.¹⁴ In this study rSO₂ increased significantly during the entire period of CPB in the CO₂ group (Figure 2), suggesting that the increased blood flow velocity in the CO₂ group is likely to result from a vasodilator effect of CO₂. This is consistent with the general understanding that CO₂ has a vasodilating effect.^{15,16} The effect of CO₂ insufflation on intracranial pressure was not studied by us because methods to estimate intracranial pressure from blood flow velocity as measured with TCD are based on pulsatile flow and thus not applicable in our study with continuous flow on CPB. In our study, assessment of cerebral blood flow with the TCD technique was not feasible because the diameter of the middle cerebral artery was not known, and probably, variable in size.¹¹ Amongst possible methods for investigation of cerebral blood flow is Xenon-133 clearance, by which a correlation of cerebral blood flow to cerebral blood flow velocities has been reported during CPB,¹⁷ but the relation between velocity and cerebral blood flow is weaker during hypothermic CPB.^{18,19} In a previous report from our group⁹ the amount of microembolic signals was significantly lower with the Lund technique compared with the CO₂ technique. However, compared with conventional de-airing methods, other groups have described CO₂ insufflation technique to be more effective.^{1,2} The rationale for insufflation of CO₂ is its greater solubility in blood than air. Injected air emboli have, in animal models, been more detrimental than CO₂.²⁰ The finding of altered cerebral hemodynamics in our study raised the concern that the

protective effects of CO₂ insufflation potentially could be counterbalanced, because a higher number of cerebral emboli, solid or gaseous, could access the cerebral circulation on account of cerebral vasodilatation. The observation that hypocapnia reduced the risk of cerebral embolization during CPB in animal models²¹ could support this theory.

However, in minimally invasive open cardiac procedures, CO₂ insufflation may prove to be the better option because manual de-airing is generally not possible. A vent is often used in the pulmonary artery, where the contact of CO₂ to blood is minimized. It is unknown if systemic side effects also can be induced by CO₂ insufflation used for minimally invasive procedures, but because the wound in minimally invasive procedures is smaller, the corresponding lower flow rates of CO₂ insufflation could have the same potential hazards as in conventional surgery.

The finding of a large number of damaged red blood cells in the cardiectomy and vent suction tubing in the CO₂ group was not anticipated. This side effect in association with CO₂ insufflation has not been reported so far in the English medical literature to the best of our knowledge. From our study it appears that this phenomenon does not seem to affect oxygen consumption in a significant manner in patients undergoing left-sided cardiac surgery with relatively short periods of CPB and aortic crossclamp times (Table 2). However, one should take this statement with caution because our study was relatively small and not primarily aimed at studying this accidental finding in detail.

The patient population in our study was limited. However, the results presented here are consistent in showing that insufflation of CO₂ into the cardi thoracic wound during left-sided cardiac surgery can impose systemic side effects that need to be compensated for in the oxygenator. In-line monitoring of CO₂ partial pressure is of importance for early and effective compensation actions to prevent the

development of severe hypercapnic acidosis. The observation of damaged red blood cells from inside the CPB circuit tubing, and its potential clinical effects, needs to be further investigated in a systematic manner in a separate study.

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