Carbon dioxide insufflation in open-chamber cardiac surgery: A double-blind, randomized clinical trial of neurocognitive effects

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Objective: The aims of this study were first to analyze neurocognitive outcomes of patients after open-chamber cardiac surgery to determine whether carbon dioxide pericardial insufflation reduces incidence of neurocognitive decline (primary end point) as measured 6 weeks postoperatively and second to assess the utility of carbon dioxide insufflation in cardiac chamber deairing as assessed by transesophageal echocardiography.

Methods: A multicenter, prospective, double-blind, randomized, controlled trial compared neurocognitive outcomes in patients undergoing open-chamber (left-sided) cardiac surgery who were assigned carbon dioxide insufflation or placebo (control group) in addition to standardized mechanical deairing maneuvers.

Results: One hundred twenty-five patients underwent surgery and were randomly allocated. Neurocognitive testing showed no clinically significant differences in *z* scores between preoperative and postoperative testing. Linear regression was used to identify factors associated with neurocognitive decline. Factors most strongly associated with neurocognitive decline were hypercholesterolemia, aortic atheroma grade, and coronary artery disease. There was significantly more intracardiac gas noted on intraoperative transesophageal echocardiography in all cardiac chambers (left atrium, left ventricle, and aorta) at all measured times (after crossclamp removal, during weaning from cardiopulmonary bypass, and at declaration of adequate deairing by the anesthetist) in the control group than in the carbon dioxide group ($P < .04$). Deairing time was also significantly longer in the control group (12 minutes [interquartile range, 9–18] versus 9 minutes [interquartile range, 7–14 minutes]; $P = .002$).

Conclusions: Carbon dioxide pericardial insufflation in open-chamber cardiac surgery does not affect postoperative neurocognitive decline. The most important factor is atheromatous vascular disease. (J Thorac Cardiovasc Surg 2012;144:646-53)

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The use of carbon dioxide insufflation into the pericardial well is standard practice in cardiac surgery in many centers around the world. The rationale behind this practice is the

increased density and solubility of carbon dioxide relative to air, potentially leading to fewer gaseous microemboli entering the bloodstream. Previous studies have argued that gaseous microemboli are a cause of type II neurocognitive decline after cardiac surgery.^{1,2} Despite the widespread use of carbon dioxide in cardiac surgery, however, it has recently been acknowledged that no study has conclusively proved its benefit in decreasing postoperative neurocognitive impairment.³⁻⁵

The main aim of this study was to analyze critically the neurocognitive outcomes of patients after open-chamber cardiac surgery to determine whether carbon dioxide pericardial insufflation reduces the incidence of neurocognitive decline (primary end point) as measured at 6 postoperative weeks. The secondary end point was to assess the utility of carbon dioxide insufflation in deairing of cardiac chambers as assessed by transesophageal echocardiography (TEE).

MATERIALS AND METHODS

A multicenter, prospective, double-blind, randomized, controlled trial was conducted to compare neurocognitive outcomes in patients undergoing open-chamber (left-sided) cardiac surgery who were assigned carbon

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Abbreviations and Acronyms

DASS = Depression Anxiety Stress Scale

TEE = transesophageal echocardiography

dioxide insufflation (carbon dioxide group) or medical air placebo (control group) in addition to undergoing standardized mechanical deairing maneuvers.

Inclusion criteria were as follows: listing for mitral or aortic valve operation, age older than 18 years and younger than 90 years, and adequate English language. Exclusion criteria were as follows: emergency operation, previous cerebrovascular event, active psychiatric conditions, preexisting cognitive impairment (Montreal Cognitive Assessment score less than 26 at preoperative screening). After written, informed consent was obtained, the recruited patients were randomly allocated on the morning of surgery. The randomization code was computer generated (Edgar II) with a 4-block randomization technique with unequal replication of treatments.

Carbon Dioxide Delivery Method

The CarbonAid device (Cardia Innovation AB, Stockholm, Sweden) is a gas diffuser reported to achieve the highest concentrations of carbon dioxide in the pericardial field.⁶ A pilot study of 7 patients was undertaken to analyze the levels of carbon dioxide achieved in the pericardial field. The CarbonAid gas diffuser achieved carbon dioxide concentrations greater than 98.56% at 5-L/min flow, and this was used for the carbon dioxide group. The control group had 0.5-L/min flow of medical air insufflated into the pericardial well, again with a CarbonAid device. All staff except the perfusionists were blinded to the gas being delivered to the patient. The diffuser was placed in the pericardial cavity 5 cm deep to the wound at the caudal end of the sternotomy, over the diaphragm, and carbon dioxide or medical air was delivered from just before opening of a left-sided chamber until closure of all left-sided chambers. The venous line was deaired before commencement of cardiopulmonary bypass. During the operation, all suction was kept out of the pericardial field when not in use to avoid transient reductions in carbon dioxide concentrations in the field, as previously recommended.⁵ When applied, the cardiomyotomy suction was limited to a maximum rate of 10 L/min to avoid affecting the carbon dioxide concentrations in the field.

Standardized deairing maneuvers were used by all surgeons and included an aortic root vent and right superior pulmonary vein vent into the left ventricle. Mechanical deairing maneuvers used included steep Trendelenburg positioning during deairing and manipulation of the heart by hand to dislodge pockets of air. The aortic root was left in situ until the patient was weaned from cardiopulmonary bypass and was removed just before commencement of protamine. This was done before crossclamp removal until adequate deairing had been achieved, as determined by TEE examination of the cardiac chambers. This technique was standard across all surgeons in the study.

Operative Procedure

Cardiopulmonary bypass was conducted with a roller pump and hollow-fiber membrane oxygenator maintaining nonpulsatile perfusion at 2 to 2.4 L/(min · m²), an arterial line filter was used, mean arterial pressure maintenance at 70 and 90 mm Hg, and cooling to 32°C to 34°C. All cardiomyotomy and vent return was filtered through an integrated depth filter. The venous return was filtered by an integrated 47-μm screen filter. Vacuum assisted venous drainage was not used. Gas sweep flows were adjusted to maintain PaCO₂ at 35 to 40 mm Hg with the alpha stat method. Perfusionist interventions into the venous circuit were monitored.

All patients were anesthetized with a balanced total intravenous technique consisting of propofol by continuous infusion, midazolam (0.05–0.1 mg/kg), and fentanyl (15–2 μg/kg), and muscle relaxation was maintained with long-acting nondepolarizing neuromuscular blockade. Bispectral index depth of anesthesia monitoring (Covidien plc, Dublin, Ireland) was routinely used, and anesthesia was adjusted to maintain a bispectral index of 40 to 60. Intraoperative hemodynamic monitoring consisted of invasive arterial pressure monitoring, pulmonary artery catheter, and real-time TEE in every case.

TEE was used for continuous recording of intracardiac gas in the chambers at the time of removal of the aortic crossclamp until declaration of adequate deairing and on weaning from cardiopulmonary bypass. The time taken to achieve adequate deairing, as declared by the anesthetist, was also recorded. Midesophageal aortic valve long-axis views displaying the left ventricle, left ventricular outflow tract, and proximal ascending aorta were used to assess intracardiac air at the time of removal of the aortic crossclamp and on weaning from cardiopulmonary bypass. Further echocardiographic loops were captured once the anesthetist declared adequate deairing to have occurred. The recorded loops were graded by blinded assessors for each of the left atrium, left ventricle, and aorta according to the scale adapted from Kalpokas and colleagues⁷ (grade 0, no bubbles; grade 1, few bubbles; grade 2, moderate bubbles; grade 3, large bubbles).

Aortic atheromatous disease was also graded according to the following scale: grade 1, normal; grade 2, intimal thickening greater than 2 mm with or without calcification; grade 3, atheroma less than 4 mm with or without calcification; grade 4, atheroma at least 4 mm with or without calcification; and grade 5, any mobile or ulcerated lesion with or without calcification.⁸ Grading was performed with TEE by the anesthetist assessing the first part of the ascending, transverse, and descending thoracic aorta, a method previously outlined as reliable.⁹

Neurocognitive Testing

The primary outcome measure of neurocognitive decline was assessed by a battery of tests performed preoperatively (between 1 and 4 weeks before surgery) and at 6 postoperative weeks. A combination of computerized testing and conventional tests was used, administered by trained assessors under the supervision of neuropsychologists and a neurologist. Sex, education level, and handedness were noted for each subject. Mood was also tested on the Depression Anxiety Stress Scale (DASS).

Six conventional neuropsychometric tests (Grooved Pegboard, Stroop test–Victoria version, Digit Span Forward and Digit Span Backward, 3 Letter Verbal Fluency Test [COWAT-F, A, S test], Five Point Design Fluency) and 5 tests (International Shopping List Delayed Recall, Detection Task, Identification Task, 1 Back-Working Memory Task, 1 Card Learning Task) on a computerized battery (CogState Ltd, Melbourne, Australia) were used. The 4 domains examined were psychomotor, episodic memory, attention and working memory, and executive function. All testing was performed in a quiet room. Neurocognitive test results were converted to *z* scores according to published normative data with adjustments for age, sex, and education as appropriate. A change in *z* score between preoperative and postoperative test performance of 1 SD was considered to be clinically significant.

The trial was registered with the Australian and New Zealand Clinical Trials Registry on September 30, 2009, under the registration number ACTRN12609000844246. The study was conducted after approval had been gained from both the Alfred Hospital human rights and ethics committee (HREC) (approval number, 361/09) and the Epworth Hospital human rights and ethics committee (approval number, 48710).

Statistical Analysis

Data were analyzed with the SAS statistical software package (version 9.2; SAS Institute Inc, Cary, NC). Group comparisons were conducted with χ^2 tests for equal proportions, paired Student *t* tests for normally distributed data, and Wilcoxon rank sum tests otherwise. Results were reported as the

FIGURE 1. Study flow diagram, compliant with Consolidated Standards of Reporting Trials 2010.

number of patients with percentage, mean $\pm$ SD, or median with interquartile range as indicated. Neurocognitive test data were converted to z scores and adjusted for age, sex, and education. Unweighted averages of the z scores were determined for each domain (chosen a priori). Changes in neurocognitive function during the first 6 weeks were found to be well approximated by a normal distribution, so linear regression was used to determine the relationship with other variables. With 62 subjects per group, this study has an 80% power to detect a difference in continuously normally distributed outcomes equivalent to half of 1 SD with a 2-sided P value of .05. This difference of 0.5 SD was to detect differences in the group data and not differences within the individual subjects, for which 1 SD was considered significant.

RESULTS

Recruitment

One hundred forty-six patients were interviewed for enrollment between February 2010 and January 2011. Eleven patients were found to have a degree of preexisting cognitive impairment, as indicated by a Montreal Cognitive Assessment score lower than 26, and were therefore excluded. Of the 135 patients recruited, 1 withdrew consent, 3 subsequently refused surgery, 3 died while waiting for surgery, and 3 underwent surgery at another hospital. A total of 125 patients were therefore randomly allocated and underwent surgery (Figure 1).

There were no significant differences between groups in baseline demographic data except for baseline DASS depression score. Although the difference between groups was significant, it was not considered to be a clinically relevant difference because it represented an effect size less than 0.15 (Table 1).

There were no significant differences between groups in any of the operative variables (Table 2). There was

significantly more intracardiac gas noted on intraoperative TEE in all cardiac chambers (left atrium, left ventricle, and aorta) and at all measured time points (after cross-clamp removal, during weaning from cardiopulmonary bypass, and at declaration of adequate deairing by the anesthetist) in the control group than in the carbon dioxide group ($P < .04$). Deairing time was also significantly longer in the control group (12 minutes [interquartile range, 9–18 minutes] versus 9 minutes [interquartile range, 7–14 minutes]; $P = .002$; Table E1). There were no significant differences in rates of cardiac complications or postoperative DASS scores (Table E2). In addition, no statistical differences were observed in DASS scores from baseline to postoperative testing in either group (not shown).

Neurocognitive testing showed no clinically significant differences in z scores between preoperative and postoperative testing (defined as a change of >1 SD; Table 3). Unweighted averages of the z score results for the various tests were used to determine neurocognitive domain scores (Table 3). Unfortunately, normalized z scores were not available for the International Shopping List tests, and a pooled result for episodic memory thus could not be calculated. The remaining 3 domains showed no differences between groups in their pooled results.

Linear regression was used to identify factors associated with decline in neurocognitive function. Table 4 shows negative parameter estimates, indicating that as the particular factor increases, it has a negative effect on neurocognitive outcome. The R^2 statistic provides estimates of the percentages of variation in outcome that can be explained by each

TABLE 1. Baseline demographic data

Characteristic	Control (n = 62)	Carbon dioxide (n = 63)	P value
Male/female ratio (no.)	41/21 (66%:34%)	31/32 (49%/51%)	.06
Age (y, mean $\pm$ SD)	68.8 $\pm$ 11.1	67.5 $\pm$ 12.3	.55
Education (no.)			.21
Left before finishing high school	46 (74%)	42 (67%)	
Completed high school	9 (15%)	12 (19%)	
Tertiary diploma/degree	7 (11%)	9 (14%)	
Montreal Cognitive Assessment (mean $\pm$ SD)	27.9 $\pm$ 1.29	28.13 $\pm$ 1.43	.36
DASS baseline (z scores, median and interquartile range)			
DASS Depression	−0.14 (−0.58 to 0.81)	−0.28 (−0.86 to 0.14)	.022
DASS Anxiety	0.07 (−0.52 to 0.89)	0.07 (−0.35 to 0.65)	.69
DASS Stress	−0.52 (−0.76 to 0.35)	−0.39 (−1 to 0.04)	.5
Preoperative sedatives or analgesia (no.)	9 (15%)	9 (15%)	.72
Hypertension (no.)	46 (74%)	48 (76%)	.84
Hypercholesterolemia (no.)	41 (66%)	36 (57%)	.36
Diabetes mellitus (no.)	13 (21%)	8 (13%)	.22
Respiratory disease (no.)	11 (18%)	8 (13%)	.45
Congestive heart failure (current, no.)	8 (13%)	3 (5%)	.11
Atrial fibrillation (no.)	17 (27%)	12 (19%)	.27
Thyroid disorder (no.)	3 (5%)	1 (2%)	.36
Peripheral vascular disease (no.)	2 (3%)	3 (5%)	.70
Preoperative creatinine (μ mol/L, mean $\pm$ SD)	112.23 $\pm$ 38.06	94.49 $\pm$ 18.96	.36
Infective endocarditis (no.)	3 (5%)	0	.24
Breathless symptoms (New York Heart Association functional class, no.)			.37
Class I	8 (13%)	11 (17%)	
Class II	33 (53%)	35 (56%)	
Class III	20 (32%)	15 (24%)	
Class IV	1 (2%)	2 (3%)	
Angina symptoms (Canadian Cardiovascular Society class, no.)			.97
Class 0	49 (79%)	50 (80%)	
Class I	2 (3%)	2 (3%)	
Class II	9 (15%)	8 (13%)	
Class III	2 (3%)	3 (5%)	
Cardiac pathology (no.)			
Previous sternotomy	8 (13%)	5 (8%)	.36
Aortic valve disease	48 (77%)	51 (81%)	.24
Aortic stenosis	35 (59%)	39 (63%)	.69
Aortic regurgitation	13 (22%)	16 (25%)	.63
Mitral valve disease	19 (31%)	15 (24%)	.29
Mitral stenosis	1 (2%)	0	.50
Mitral regurgitation	18 (30%)	15 (24%)	.47
Coronary artery disease	22 (35%)	22 (35%)	.95

DASS, Depression Anxiety Stress Scale; SD, Standard deviation.

predictor variable. All data collected on the patients was entered into this analysis to ensure that every potential factor was assessed. Graded assessment of gas in the left-sided chambers showed no correlation with neurocognitive outcomes. The factors most strongly associated with neurocognitive decline were hypercholesterolemia, aortic atheroma grade, and coronary artery disease.

DISCUSSION

We found no difference in neurocognitive outcomes at 6 weeks with the use of carbon dioxide versus standard mechanical deairing maneuvers alone during open-chamber

cardiac surgery. Carbon dioxide use did lead to fewer gaseous emboli in the cardiac chambers during weaning from cardiopulmonary bypass, and it shortened deairing times by at least 3 minutes. This did not translate into improved neurocognitive outcomes at 6 weeks, however, suggesting that sufficient deairing can be achieved through mechanical deairing maneuvers alone.

This study was performed in patients undergoing surgery through a midline sternotomy only. In minimally invasive open-chamber cardiac surgery, the ability to perform mechanical deairing maneuvers is more limited, and in these circumstances carbon dioxide may have a more important

TABLE 2. Operative variables

Characteristic	Control (n = 62)	Carbon dioxide (n = 63)	P value
Operations (no.)			.676
Aortic valve replacement	43	47	
Mitral valve replacement	7	3	
Mitral valve repair	8	10	
Aortic root	2	2	
Ascending aorta	2	1	
Valve type (no.)			.370
Bioprosthetic valve	39	40	
Mechanical valve	12	10	
Concomitant coronary artery bypass grafting (no.)	22 (35%)	22 (35%)	.95
No. of coronary grafts (mean $\pm$ SD)	1.76 $\pm$ 0.83	1.73 $\pm$ 0.93	.90
Aortic atheroma grade			.28
Grade 1	33	29	
Grade 2	18	16	
Grade 3	7	13	
Grade 4	1	4	
Missing data	3	1	
CPB time (min, mean $\pm$ SD)	118.3 $\pm$ 48.5	113.4 $\pm$ 47.2	.56
Crossclamp time (min, mean $\pm$ SD)	91.8 $\pm$ 42.4	88.9 $\pm$ 38.1	.68
Reperfusion time* (min, mean $\pm$ SD)	16.35 $\pm$ 9.15	18.4 $\pm$ 15.6	.38
Lowest temperature (°C, mean $\pm$ SD)	33.3 $\pm$ 2.23	33.5 $\pm$ 1.0	.54
Lowest potassium (mEq/L, mean $\pm$ SD)	4.72 $\pm$ 0.66	4.67 $\pm$ 0.59	.68
Cannulation (no.)			.214
Unicaval	44 (71%)	51 (81%)	
Bicaval	18 (30%)	12 (19%)	
Chambers opened (no.)			
Aorta opened	49 (79%)	53 (84%)	.42
Left atrium opened	15 (24%)	16 (25%)	.85
Both pleura opened	3 (5%)	3 (5%)	>.999
Venting (no.)			
Right superior pulmonary vein vent	58 (94%)	58 (92%)	.41
Aortic root vent	60 (97%)	59 (94%)	.24
Vent problems	0	3 (5%)	.73
Gas after deairing	4 (6%)	5 (8%)	>.999
Gas in venous line	4 (6%)	4 (6%)	>.999
No. of blood samples during CBP (mean $\pm$ SD)	4.4 $\pm$ 2.6	4.2 $\pm$ 2.4	.73
No. of medication injections (median and IQR)	5 (3–10)	7 (4–10)	.16
Total perfusion interventions (median and IQR)	9 (7–15)	11 (8–17)	.29

(Continued)

role to play. Previous studies looking at pericardial carbon dioxide insufflation have mostly concentrated on detection of intracardiac air.³ Two studies have included

TABLE 2. Continued

Characteristic	Control (n = 62)	Carbon dioxide (n = 63)	P value
Perioperative complications (no.)			
Ventricular fibrillation	4 (7%)	11 (17%)	.06
ST segment changes on electrocardiograph during weaning from CPB (no.)	6 (10%)	1 (2%)	.06

CPB, Cardiopulmonary bypass; IQR, interquartile range; SD, Standard deviation.
*Reperfusion time represents the duration between crossclamp release and the end of cardiopulmonary bypass.

neurocognitive testing, and neither showed a difference in neurocognitive outcome^{4,10}; however, the test battery in those 2 studies was very small, and the testing was conducted very early postoperatively (5 days), when the results could have been confounded by the effects of analgesia and anesthesia.

In 1995, a Statement of Consensus recommended a battery of tests for neurocognitive testing in cardiac patients.¹¹ This statement is now outdated, however, and we chose to use a larger battery of tests combining both conventional and computerized testing to ensure that 4 neurocognitive domains (chosen a priori) were adequately tested. On the basis of efficiency of administration, reduction of practice effects, and high correlation with conventional testing, Cog-State, a computerized test battery that has been well validated in the literature, was chosen.^{12,13}

Once gaseous microemboli reach the brain, the proposed mechanisms of cerebral injury are occlusion of small vessels causing distal ischemia and activation of the inflammatory cascade to exacerbate such injury and reactive hyperemia.¹ There is difficulty in proving that gaseous microemboli cause organic brain lesions, however, because of the inability to distinguish reliably between solid and gaseous emboli with various detection modalities. A recent systematic review concluded that there is insufficient evidence at this time to prove a causal link between intraoperative cerebral microemboli and postoperative cognitive function.¹⁴ That study focused on high-intensity transient signals in patients undergoing cardiac, carotid, and orthopedic surgery and did not discriminate between gaseous and particulate microemboli. In light of the failure to find a causal link when including all types of microemboli, it may be even more difficult to prove a link when investigating gaseous emboli alone.

There are other benefits of carbon dioxide use reported in the literature, such as prevention of coronary artery gas embolism. We recorded surrogate markers of coronary artery gas embolism, such as ventricular fibrillation after crossclamp removal and ST segment elevation during or after coming off bypass, but found no statistically significant differences between groups, although there was a trend

TABLE 3. Neurocognitive z scores

Neurocognitive tests	Control (n = 62)	Carbon dioxide (n = 63)	P value
Psychomotor Domain			
Grooved Pegboard			
Preoperative	-0.61 (-3.06 to -0.29)	-0.48 (-2.12 to -0.4)	.68
Postoperative	-1.5 (-3.31 to -0.13)	-1.08 (-3.48 to -0.23)	.49
Difference	-0.63 (-1.26 to -0.17)	-0.6 (-1.52 to -0.03)	.69
Detection Task			
Preoperative	-0.33 (-0.73 to -0.07)	-0.13 (-0.47 to -0.07)	.07
Postoperative	-0.16 (-0.53 to -0.13)	-0.13 (-0.8 to -0.2)	.63
Difference	0.17 (-0.06 to 0.20)	0 (-0.33 to 0.17)	.028
Episodic Memory Domain			
One Card Learning Task			
Preoperative	-0.27 (-0.47 to -0.16)	-0.07 (-0.33 to -0.2)	.12
Postoperative	-0.13 (-0.47 to -0.13)	-0.07 (-0.33 to -0.13)	.59
Difference	0.14 (0.00-0.03)	0.00 (0.00 to -0.07)	.671
Delayed Recall Shopping List			
Preoperative	7.7 ± 2.08	7.82 ± 2.55	.79
Postoperative	7.84 ± 2.56	8.09 ± 2.24	.57
Difference	0.13 ± 1.62	0.26 ± 2.45	.74
Attention/Working Memory Domain			
Digit Span Forward			
Preoperative	-2 (-2 to 0)	-1 (-2 to 0)	.52
Postoperative	-2 (-3 to -1)	-2 (-3 to 0)	.87
Difference	0 (0-0)	0 (0-0)	.47
Digit Span Backward			
Preoperative	-2 (-3 to -1)	-2 (-3 to -1)	.84
Postoperative	-2 (-3 to -1)	-2 (-3 to -1)	.97
Difference	0 (0-0)	0 (-0.5 to 1)	.39
One Back Task			
Preoperative	-0.1 (-0.63 to -0.23)	-0.2 (-0.6 to -0.27)	.84
Postoperative	0.13 (-0.23 to -0.4)	0.2 (-0.33 to -0.53)	.8
Difference	0.23 (0.0 to -0.53)	0.20 (0.07 to -0.60)	.92
Identification Task			
Preoperative	-0.13 (-0.4 to -0.1)	-0.07 (-0.4 to -0.07)	.88
Postoperative	-0.07 (-0.27 to 0.27)	-0.07 (-0.33 to 0.20)	.78
Difference	0.20 (-0.07 to 0.47)	0.07 (0.0 to 0.47)	.57
Executive Function Domain			
Stroop Test			
Preoperative	-0.108 ± 0.63	0.036 ± 0.71	.23
Postoperative	0.103 ± 0.66	0.034 ± 0.69	.58
Difference	0.2 ± 0.46	-0.03 ± 0.47	.01
3 Letter Verbal Fluency			
Preoperative	0.0034 ± 1.29	0.33 ± 1.24	.15
Postoperative	0.227 ± 1.24	0.46 ± 1.32	.32
Difference	0.28 (0 to -0.61)	0.24 (-0.08 to -0.56)	.55
Five Point Test			
Preoperative	-0.42 (-1.31 to -0.71)	-0.12 (-0.95 to -0.71)	.39
Postoperative	-0.36 (-1.31 to -0.71)	0 (-0.71 to -1.07)	.17
Difference	0 (-0.23 to -0.48)	0.18 (-0.12 to -0.47)	.36
Neurocognitive domain scores			
Psychomotor			
Preoperative	-0.59 (-1.67 to 0.04)	-0.46 (-1.97 to 0.18)	.57
Postoperative	-0.78 (-2.31 to -0.11)	-0.51 (-1.94 to 0.02)	.41
Difference	-0.2 (-0.6 to 0.18)	-0.17 (-0.76 to 0.24)	.86

(Continued)

TABLE 3. Continued

Neurocognitive tests	Control (n = 62)	Carbon dioxide (n = 63)	P value
Attention/Working Memory			
Preoperative	−0.63 (−1.15 to −0.35)	−0.72 (−1.41 to −0.15)	.9
Postoperative	−0.71 ± 0.74	−0.57 ± 0.76	.31
Difference	0.05 ± 0.37	0.08 ± 0.51	.72
Executive function			
Preoperative	−0.1 ± 0.86	0.14 ± 0.88	.13
Postoperative	0.05 ± 0.78	0.26 ± 0.96	.2
Difference	0.14 (−0.01 to 0.42)	0.18 (−0.08 to 0.39)	.69

Results reported as median with interquartile range or mean ± SD.

toward less ST segment elevation in the carbon dioxide group. In this trial, we did not observe any of the previously reported complications of carbon dioxide use such as hemodynamic compromise, hypercarbia,¹⁵ or hyperkalemia caused by increased carbon dioxide leading to leaching of potassium ions.¹⁶

We used linear regression analysis to identify factors associated with neurocognitive decline in our patient cohort. Unlike previous studies, we found no association between the total number of perfusionist interventions and neurocognitive decline^{1,2}; however, we did find age, hypercholesterolemia, aortic atheroma grade, and coronary artery disease to be strong predictors of neurocognitive impairment in this study. It could be argued that all these factors are essentially markers for a single

risk factor, atheromatous vascular disease. Increasing age has also been demonstrated to predict independently neurocognitive decline after cardiac surgery.¹⁷

Numerous studies have implicated atheromatous disease in type II neurocognitive dysfunction after cardiac surgery and have recommended techniques such as avoidance of crossclamping of the aorta.¹⁸ Furthermore, atherosclerosis of the heart is closely correlated with microvascular disease of the brain and thus with the potential for greater susceptibility to neurocognitive insult after cardiac surgery.¹⁹ All these findings point to the higher relative importance of solid microemboli compared with gaseous microemboli when considering neurocognitive impairment. Cardiopulmonary bypass itself has also been implicated in postoperative neurocognitive dysfunction, but a recent meta-analysis of on-pump versus off-pump coronary artery bypass grafting failed to find significant differences between groups.²⁰

Selnes and colleagues²¹ compared medically treated patients with coronary artery disease with cardiac surgical patients for five years and found no significant differences in neurocognitive decline between groups²¹; however, neurocognitive decline was seen in both groups during the 5-year period. This finding supports preexisting cerebrovascular disease as more influential than intraoperative factors in long-term neurocognitive decline in cardiac surgical patients.^{19,22}

Subjective cognitive complaints from patients and relatives after cardiac surgery have identified memory as the most commonly affected neurocognitive domain.²³ Perhaps that is because it is the cognitive area that is most identifiable to patients and their families. More objective assessments of patients after cardiac surgery have identified attention and information processing speed as the cognitive areas most likely to be affected.^{24,25}

One possible limitation of this study is that we did not collect data on which patients underwent carotid artery screening. We screen patients for carotid disease if they have a history of cerebrovascular accident or transient ischemic attack. Such patients would have been excluded from enrolment in this trial. We also screen for patients who have left main stenosis.

TABLE 4. Factors associated with decline in neurocognitive function

Variable	Estimate	SE	P value	R ²
Variables associated with decline in executive function domain				
Hypercholesterolemia	−0.33	0.09	.001	9.69
Coronary artery disease	−0.27	0.10	.006	6.14
Age	−0.01	0.00	.020	4.47
Hypertension	−0.24	0.11	.03	3.93
Grade gas in left atrium	0.10	0.05	.057	3.09
Grade gas in left ventricle	0.10	0.06	.078	2.65
Grade gas in aorta	0.10	0.06	.088	2.49
Variables associated with decline in attention domain				
Hypercholesterolemia	−0.229	0.081	.0052	6.42
Number coronary artery grafts	−0.100	0.040	.0141	5.00
Coronary artery disease	−0.097	0.042	.0218	4.38
Aortic atheroma grade	−0.104	0.046	.0236	4.38
Hypertension	−0.203	0.093	.0316	3.86
Age	−0.007	0.003	.0513	3.18
Postoperative atrial fibrillation	−0.155	0.087	.0777	2.61
Gas after deairing	0.198	0.154	.2020	1.39
Variables associated with decline in psychomotor domain				
Aortic atheroma grade	−0.37	0.11	.0016	8.37
Hypercholesterolemia	−0.60	0.21	.0041	6.78
Ventricular fibrillation after removal of crossclamp	−0.72	0.31	.0218	4.42
Grade gas in left ventricle	0.21	0.12	.0709	2.79
Grade gas in aorta	0.43	0.30	.1596	1.73
Grade gas in left atrium	0.26	0.21	.2347	1.24

In conclusion, this study shows that carbon dioxide pericardial insufflation in open chamber cardiac surgery does not affect postoperative neurocognitive decline and that the most important factor is atheromatous vascular disease. The usefulness of carbon dioxide insufflation in minimally invasive and robotic surgery was not assessed in this trial, but given the inherent restrictions on deairing maneuvers in those types of operations, it is likely that carbon dioxide use will remain beneficial, although this has not been formally studied to our knowledge.

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TABLE E1. Transesophageal assessment of intracardiac air

Characteristic	Control (n = 62)	Carbon dioxide (n = 63)	P value
Maximal gas bubble grade*			
After crossclamp removal			
Left atrium	1 (1–2)	1 (1–1)	.009
Left ventricle	2 (1–2)	1 (1–1)	.001
Aorta	1 (0–2)	1 (0–1)	.038
During weaning from cardiopulmonary bypass			
Left atrium	1 (1–2)	1 (1–2)	.019
Left ventricle	2 (1–2)	1 (0–1)	<.0001
Aorta	1 (1–2)	1 (0–1)	.0003
After adequate deairing			
Left atrium	1 (1–2)	1 (0–1)	.002
Left ventricle	1 (0–1)	1 (0–0)	<.0001
Aorta	1 (0–1)	1 (0–0)	.0035
Duration of gas bubbles			
Total deairing time (mean)	12 (9–18)	9 (7–14)	.002

*Data are median with interquartile range except as marked.

TABLE E2. Postoperative data

Characteristic	Control (n = 62)	Carbon dioxide (n = 63)	P value
Death	1 (1.61%)	2 (3.17%)	.319
Cerebrovascular accident (type I neurologic injury)	0	1	.568
Prolonged mechanical ventilation*	12	5	.112
Prolonged inotrope use (>4 h)	22	15	.160
Low cardiac output syndrome	14	5	.024
Low systemic vascular resistance syndrome	9	3	.073
Perioperative acute myocardial infarction	0	0	1.0
Perioperative cardiogenic shock	1	1	1.0
Atrial fibrillation	23 (37%)	18 (29%)	.75
Deep sternal wound infection	0	0	1.0
Postoperative sedatives or analgesia at 6 wk	9 (15%)	7 (11%)	.69
DASS postoperative (z scores)			
DASS Depression	−0.14 (−0.72 to 0.75)	−0.42 (−0.86 to 0)	.09
DASS Anxiety	−0.15 (−0.74 to 0.5)	−0.15 (−0.96 to 0.26)	.24
DASS Stress	−0.52 (−0.91 to 0.09)	−0.65 (−1 to 0.15)	.25

Data are number of patients or median with interquartile range. DASS, Depression Anxiety Stress Scale. *Mechanical ventilation longer than 24 hours in duration.