Carbon Dioxide Insufflation During Cardiac Surgery: A Meta-analysis of Randomized Controlled Trials

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Despite the widespread use of carbon dioxide insufflation (CDI) in cardiac surgery, there is still paucity of evidence to prove its benefit in terms of neurologic protection. Therefore, we conducted a meta-analysis of available randomized controlled trials comparing CDI vs standard de-airing maneuvers. Electronic searches were performed to identify relevant randomized controlled trials. Primary outcomes investigated were postoperative stroke, neurocognitive deterioration, and in-hospital mortality. Risk difference (RD) was used as summary statistic. Pooled estimates were obtained by means of random-effects model to account for possible clinical diversity and methodological variation between studies. Eight studies were identified with 668 patients randomized to CDI (n = 332) vs standard de-airing maneuvers (n = 336). In-hospital mortality was 2.1% vs 3.0% in the CDI and control group, respectively (RD 0%; 95% confidence interval [CI] –2% to 2%; $P = 0.87$; $I^2 = 0\%$). Incidence of stroke was similar between the 2 groups (1.0% vs 1.2% in the CDI and control group, respectively; RD 0%; 95% CI –1% to 2%; $P = 0.62$; $I^2 = 0\%$). Neurocognitive deterioration rate was 12% vs 21% in the CDI and control group, respectively, but this difference was not statistically significant (RD: –7%; 95% CI –0.22% to 8%; $P = 0.35$; $I^2 = 0\%$). The present meta-analysis did not find any significant protective effect from the use of CDI when compared with manual de-airing maneuvers in terms of clinical outcomes, including postoperative neurocognitive decline.

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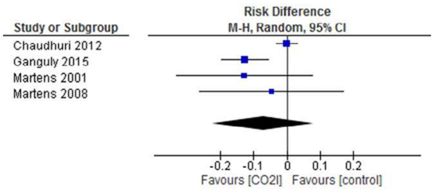
Keywords: carbon dioxide insufflation, cardiac surgery, meta-analysis, neurocognitive decline



Forest plot for carbon dioxide insufflation (CDI) vs control on the incidence of postoperative neurocognitive decline.

Central Message

The present systematic review and meta-analysis showed that despite its widespread use, to date, there is little evidence on any protective effect of carbon dioxide insufflation in open heart surgery.

Perspective Statement

Despite its widespread use, to date, there is little evidence on any protective effect of carbon dioxide insufflation in open heart surgery. In view of the increased costs and increased risk of systemic hypercapnic acidosis, it seems there is an urgent need for further evidence to conclusively justify the routine use of carbon dioxide insufflation during cardiac surgery.

Neurologic impairment following cardiac surgery may take the form of stroke or postoperative neurocognitive deterioration (NCD). The former is devastating but fortunately rare. However, a decline in attention, memory, or fine motor skills can be documented in up to 30% of patients postoperatively.[1] Neurocognitive decline particularly affects elderly patients and those with other comorbidities. The scale of the problem has increased in the last 2 decades due to the increasing number of older and sicker patients referred for surgery. Several mechanisms are implicated in cerebral injury after cardiac surgery, including air microembolism[2]; a recent study reports that their number correlates with the degree of postoperative neuropsychological disorder.[3] Various de-airing techniques have been proposed to minimize air microembolization during open heart surgery.[4,5] Classical manual de-airing techniques have proved unsatisfactory and even when meticulously adhered to, large numbers of microemboli still occur.[4,5] Carbon dioxide insufflation (CDI) into the pericardial cavity, first proposed in 1958,[6] has become widespread (Video 1), the rationale being its increased density and solubility relative to air, potentially leading to fewer gaseous microemboli entering the bloodstream.[7,8] However, there is still a paucity of conclusive evidence to justify the routine use of CDI.[9-11] We sought to get insights into the role of CDI in open heart surgery by conducting a meta-analysis of available randomized controlled trials (RCTs).

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METHODS

Literature Search Strategy

This work was designed as a systematic review and network meta-analysis, with reporting following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[12]

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Data Sources and Searches

Two investigators (UB and MC) independently searched relevant studies on PubMed, EMBASE, BioMed Central, and the Cochrane Central Register. Our aim was to find all RCTs comparing CDI vs de-airing maneuvers alone in cardiac surgery. Only RCTs were included in the present meta-analysis. To achieve the maximum sensitivity of the search strategy and identify all studies, we combined the terms "'carbon dioxide'" with "'randomized controlled trial'" as both keywords and MeSH headings. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies. All relevant articles identified were assessed with application of the inclusion and exclusion criteria.

Selection Criteria

Eligible studies for the present meta-analysis included those which met the following criteria: (1) the studies had to include patients undergoing cardiac surgery including valve surgery with or without coronary artery bypass grafting (CABG), aortic vascular surgery, or their combinations; (2) studies had to be RCTs, and assigned patients into CDI group or control group randomly. When centers have published duplicate trials with accumulating numbers of patients or increased lengths of follow-up, only the most updated reports were included for qualitative appraisal at each time interval. All publications were limited to human subjects. Non-English articles were not excluded. Abstracts, case reports, conference presentations, editorials, and expert opinions were excluded.

Study End Points

Primary outcomes of interest were NCD, postoperative stroke, and in-hospital mortality. Individual study definition was adopted for NCD. Secondary outcome was the quantity of gaseous microemboli in heart chambers at the end of the procedure (aortic cross clamp removal) detected by transesophageal echocardiogram. We also investigated creatinine kinase, MB isoenzyme (CK-MB) release at 24 hours as a marker of myocardial injury potentially related to coronary air microembolization and hospital stay length.

Data Extraction and Quality Assessment

Baseline, procedural, outcome, and follow-up data were independently abstracted by 2 investigators. Data were analyzed according to the intention-to-treat principle whenever possible. The internal validity and risk of bias of included trials were appraised by 2 independent investigators (UB and GG) according to the "risk of bias assessment tool" developed by the Cochrane collaboration.[12] Briefly, for each trial, 7 domains were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data reporting, selective reporting, and presence of other bias. Presence of possible source of bias in each domain was assessed, and a final judgment of low, moderate, or high risk of bias was assigned.

Statistical Analysis

Standard meta-analysis using Mantel-Haenszel method originally derived for odds-ratio estimates does not use the information from double-zero studies. As double-zero studies point to no differences in treatment effects, at least in balanced trials, deleting them might bias the treatment effect away from the null. To account for double-zero studies in the present meta-analysis, we used a method proposed by Greenland and Robins based on the analysis of risk differences (RDs) for primary outcomes. For the secondary outcomes, we used standardized mean difference (SMD) to account for variation in outcome measurement methods used in individual trials. Tests were used to study heterogeneity between trials. I^2 statistic was used to estimate the percentage of total variation across studies, owing to heterogeneity rather than chance. An I^2 value of greater than 50% was considered substantial heterogeneity. In the present meta-analysis, the results using the random-effects model were presented to take into account the possible clinical diversity and methodological variation between studies. All *P* values were 2-sided. Post hoc analysis power calculation was obtained for all outcomes investigated. All statistical analysis was conducted with Review Manager Version 5.1.2 (Cochrane Collaboration, Software Update, Oxford, UK) and G*Power Version 3.1.9.2 (Franz Faul, Germany).

RESULTS

Quantity and Quality of Trials

A total of 290 references were identified through the 5 electronic database searches. After exclusion of duplicate or irrelevant references, 19 potentially relevant articles were retrieved. After detailed evaluation of these articles, 12 studies remained for assessment. After applying the selection criteria, 8 RCTs[13-20] were selected for analysis (Fig. 1). The study characteristics of these trials are summarized in Tables 1-3. In these 8 studies, 668 patients were randomized to CDI (n = 332) vs standard de-airing maneuvers (n = 336). Sample size determination was reported only in 2 out of 8 studies. Tests and timing used for neurocognitive assessment varied among studies. Different methods were used for carbon dioxide delivery. The 8 RCTs were assessed qualitatively using tools designed to measure the risk of bias, as recommended by the Cochrane collaboration. A summary of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias identified in each individual RCT is presented in Figure 2.

Meta-analysis

Data regarding in-hospital mortality and stroke was available for all studies included (for 2 studies, authors provided data when contacted by email). A total of 4 RCTs (n = 567) reported on the incidence of postoperative neurocognitive dysfunction. Five studies (n = 226) reported on the quantity of gaseous microemboli in heart chambers at aortic cross clamp removal detected by transesophageal echocardiogram. CK-MB levels and length of stay were reported by 3 RCTs, including 162 and 143 patients, respectively.

Meta-analytic estimates for primary and secondary outcomes are summarized in Figures 3 and 4, respectively. In-hospital mortality was 2.1% vs 3.0% in the CDI and control group, respectively (RD 0%; 95% confidence interval [CI] −2% to 2%; $P = 0.87$; $I^2 = 0\%$). Incidence of stroke was similar between the 2 groups (1.0% vs 1.2% in the CDI and control group, respectively) (RD 0%; 95% CI −1% to 2%; $P = 0.62$; $I^2 = 0\%$). Neurocognitive decline rate postoperatively

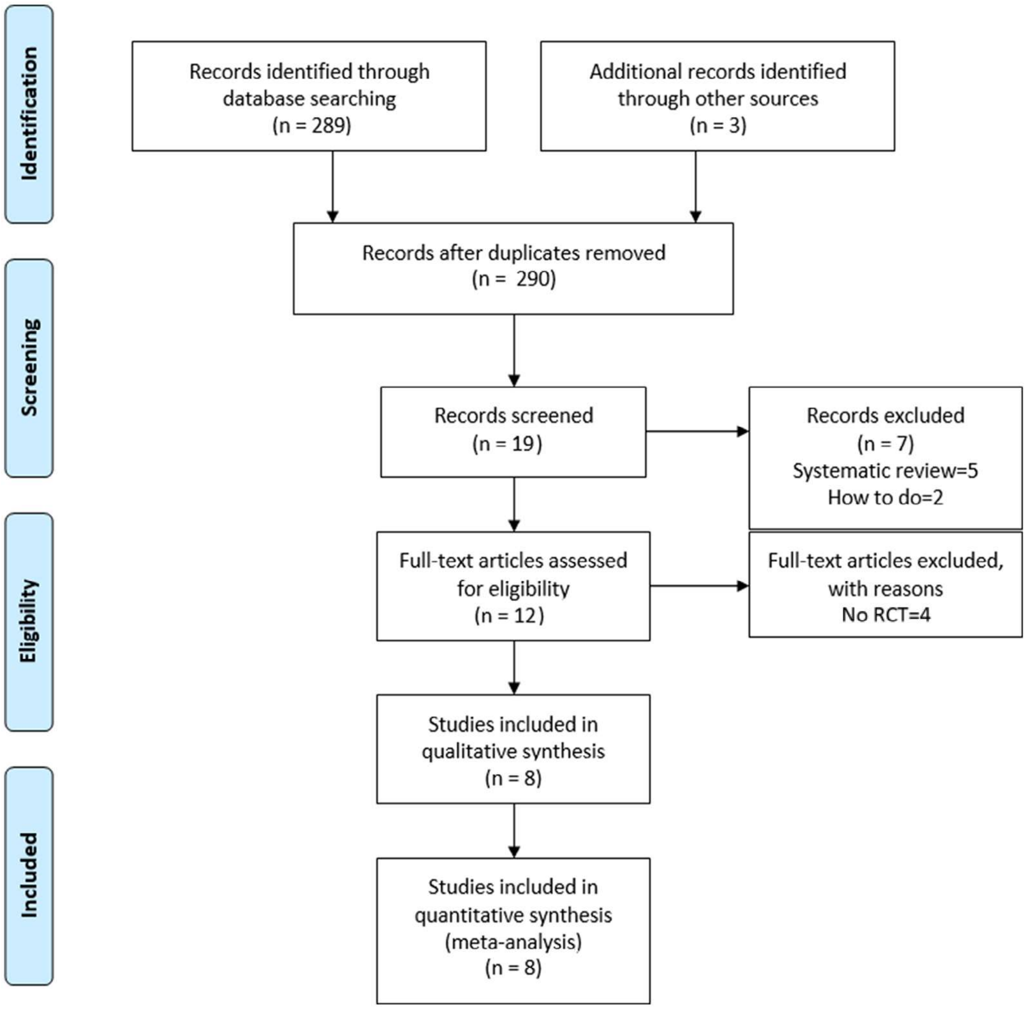


Figure 1. Study flow diagram.

Table 1. Studies Overview

Study	CDI (n)	Control (n)	Sample Size Calculation	CDI Age (SD)	Control Age (SD)	CDI M/F	Control M/F	Type of Procedure
Al-Rashidi et al (2011)	10	10	No	71 (13)	70 (13)	5/5	5/5	Isolated valve 85%; CABG + valve 15%
Chaudhuri et al (2012)	63	62	No	68 (11)	68 (12)	31/32	41/21	Isolated valve 65%; CABG + valve 35%
Ganguly et al (2015)	150	150	Yes	43 (14)	43 (15)	87/63	82/68	Isolated valve: 65%; isolated CABG 35%
Kalpokas et al (2003)	10	8	No	62 (10)	61 (10)	6/4	7/1	Isolated valve 50%; CABG + valve 50%
Martens et al (2001)	31	31	No	62 (3)	63 (2)	15/16	18/13	Isolated valve 40%; CABG + valve 60%
Martens et al (2008)	39	41	No	66 (12)	67 (11)	20/19	24/17	Isolated valve 65%; CABG + valve 35%
Skidmore et al (2006)	21	22	Yes	61 (NR)	60 (NR)	13/9	12/10	Isolated valve 70%; CABG + valve 30%
Svenarud et al (2014)	10	10	No	75 (13)	75 (15)	7/3	6/4	Isolated valve 60%; CABG + valve 40%

CABG, coronary artery bypass grafting; CO_2, carbon dioxide; SD, standard deviation.

Table 2. Study Characteristics

Study	Device	Flow	Expected Carbon Dioxide Concentration	Primary Outcome	Method Used to Quantify Cerebral Microembolization	Discrimination of Nature of Cerebral Microemboli	Outcomes of Interest Reported
Al-Rashidi et al (2011)	Gas diffuser	10L/min	100%	Air emboli in heart chambers using TEE Microembolic signal using TCD	TCD	No	Death, stroke, heart chambers microemboli, hospital stay
Chaudhuri et al (2012)	Gas diffuser	5L/min	98.5%	Neurocognitive testing Air emboli in heart chambers using TEE	None	–	Death, stroke, NCD, heart chambers microemboli
Ganguly et al (2015)	Vent catheter with multiple side holes	5 L/min	NR	Neurocognitive testing	None	–	Death, stroke, NCD
Kalpokas et al (2003)	Oxygen cannula	6 L/min	NR	Air emboli in heart chambers using TEE	None	–	Death, stroke, heart chambers microemboli
Martens et al (2001)	Perfusion line	3 L/min	NR	Neurocognitive testing S100B, neuron specific enolase [NSE]	None	–	Death, stroke, NCD, CK-MB
Martens et al (2008)	Perforated drain	2 L/min	90%	Neurocognitive testing P300 auditory-evoked potentials	None	–	Death, stroke, NCD, CK-MB, hospital stay
Skidmore et al (2006)	Perforated drain	6 L/min	96%	Air emboli in heart chambers using TEE Segmental wall motion abnormalities	None	–	Heart chambers microemboli, hospital stay
Svenarud et al (2014)	Gas diffuser	10 L/min	100%	Air emboli in heart chambers using TEE	None	–	Heart chambers microemboli, CK-MB

TCD, transcranial Doppler; TEE, transesophageal echocardiogram; NCD, neurocognitive deficit.

Table 3. Neurocognitive Tests Performed and Neurocognitive Deficit Definition in Individual Studies

	Neurocognitive Tests	Cognitive Domain Investigated	Timing of Neurocognitive Tests	Definition of Neurocognitive Deficit	Study Finding
Chaudhuri et al (2012)	6 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.	4 Domains: psychomotor, episodic memory, attention and working memory, executive function	Between 1 and 4 wk preoperatively and at 6 wk postoperatively	A change in z score between preoperative and postoperative test performance of 1 SD	CDI not protective
Ganguly et al (2015)	Mini-Mental State Examination, Trail-Making Test B, Digits Forward and Digits Backward tests, and the Wechsler Adult Intelligence Scale digit symbol substitution test	8 Domains: attention, language, verbal and visual memory, visual construction, executive function, psychomotor, and motor speed	At 5 d preoperatively and at 1 wk and 4 wk postoperatively	When at least 3 tests showed a reduction of 1 SD or when 1 test showed a reduction of 2 SD and another showed a reduction of 1 SD or more	CDI protective
Martens et al (2001)	Block design test (problem-solving strategies, recognition and analysis of forms), Benton test (describing constructive abilities), Trail making (cognitive achievement at speed), Digit span (short-term memory, memory of figures), and d2 test (concentration performance)	Not specified	Preoperatively and 5 d after surgery	A decline in performance from the initial test interval that exceeded 20% in 2 or more tests was considered to represent a deficit	CDI not protective
Martens et al (2008)	Block design test (problem-solving strategies, recognition and analysis of forms), Benton test (describing constructive abilities), Trail making (cognitive achievement at speed), Digit span (short-term memory, memory of figures) and d2 test (concentration performance)	Not specified	Preoperatively and 5 d after surgery	A decline in performance from the initial test interval that exceeded 20% in 2 or more tests was considered to represent a deficit	CDI not protective

CDI, carbon dioxide insufflation.

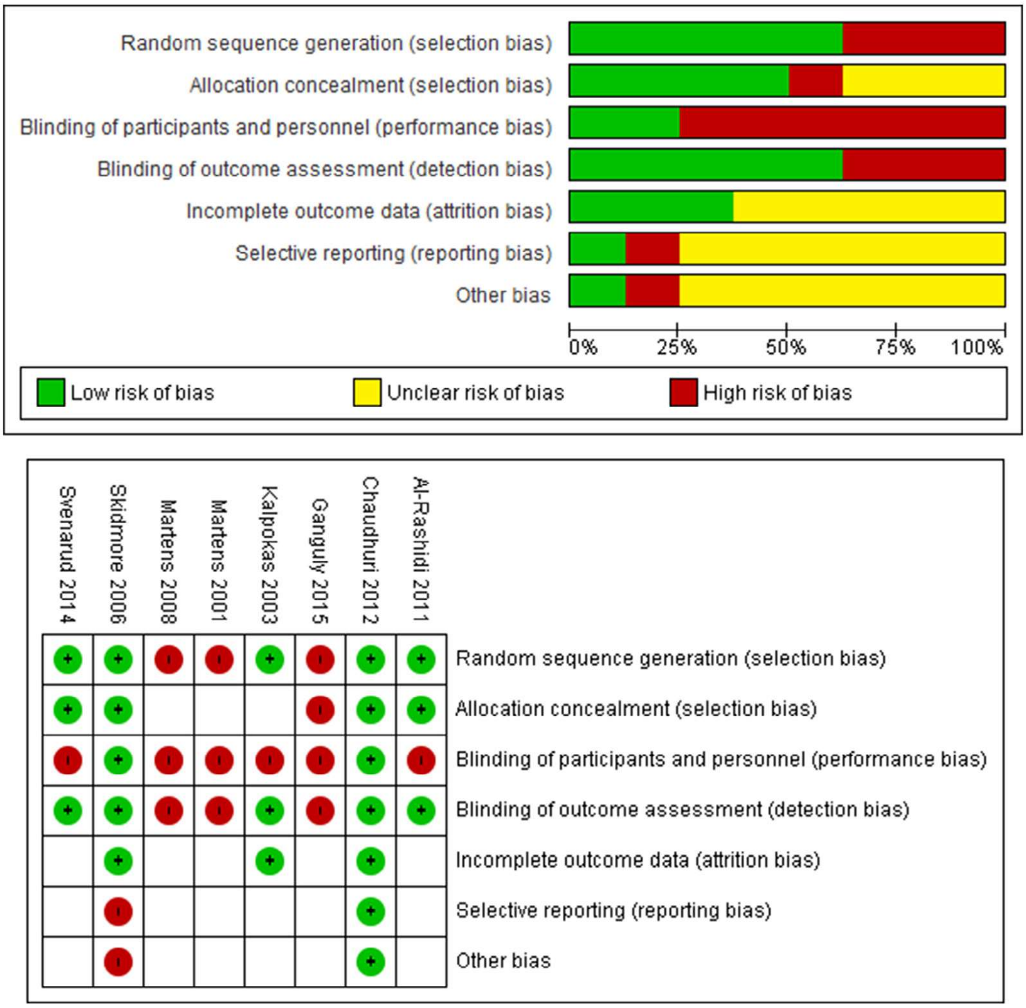


Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study (top) risk of bias item presented as percentages across all included studies (bottom).

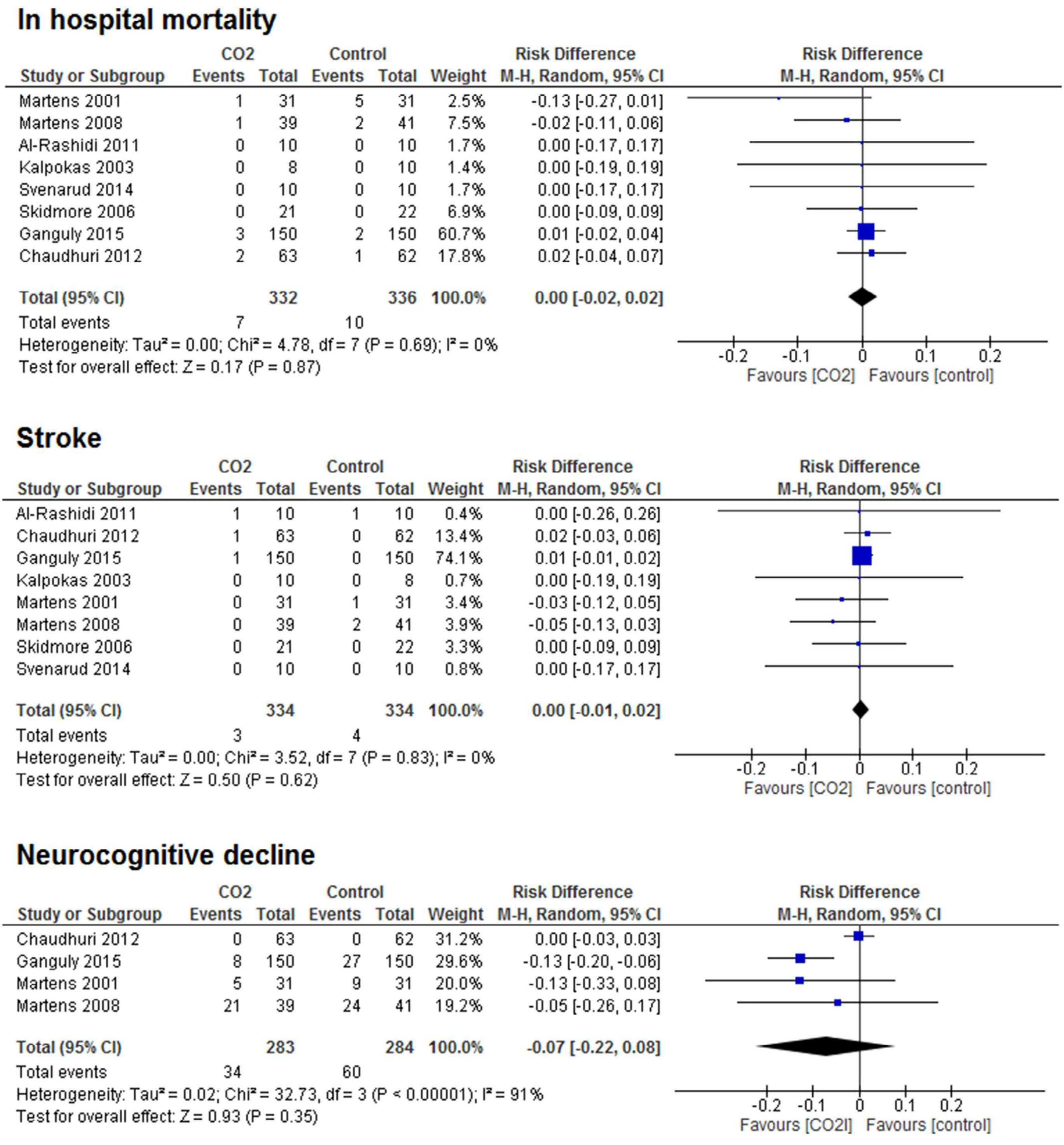
was 12% vs 21% in the CDI and control group, respectively, but this difference was not statistically significant (RD: −7%; 95% CI −0.22% to 8%; $P = 0.35$; $I^2 = 0\%$). Post hoc power calculation was 8% for hospital mortality, 2.5% for stroke, 80% for NCD.

The amount of gaseous microemboli detected by transesophageal echocardiogram was significantly lower in the CDI group vs the control group (RD −0.94; 95% CI −1.63 to −0.25; $P = 0.008$; $I^2 = 77\%$). Finally, CK-MB levels (SMD 0.16; 95% CI −0.41 to 0.73; $P = 0.58$; $I^2 = 66\%$) and length of hospital stay were not different between the 2 groups (SMD 0.08; 95% CI −0.25, 0.41; $P = 0.62$; $I^2 = 0\%$). Post hoc power calculation was 100% for quantity of gaseous microemboli, 13% for CK-MB levels, and 24% for hospital stay length.

DISCUSSION

By pooling data from 8 RCTs, including 668 patients, we found that CDI was associated with a smaller quantity of gaseous microemboli in the heart chambers after cross clamp removal, but it did not significantly influence the incidence of postoperative neurocognitive decline when compared with standard de-airing maneuvers.

The etiology of neurologic impairment following cardiac surgery is multifactorial and includes systemic inflammation, hypotension, and microembolization during cardiopulmonary bypass.[21] Microemboli include atherosclerotic emboli that are often released during aortic manipulation and gaseous microemboli that occur particularly during open chamber surgery.[22] Although most research on cerebral embolization has focused on the issue of atherosclerotic microemboli, a recent study demonstrated that most emboli (~80%) are gaseous.[22] Gaseous microemboli are theorized to lead to cerebral injury by occluding small vessels. Manual de-airing techniques are commonly used, but unfortunately they are unable to fully eliminate microemboli. CDI into the pericardial cavity has been proposed to improve de-airing.[5,6] However, there is little good quality evidence to support its efficacy in preventing neurocognitive decline. By pooling data from available RCTs, we did not find any significant protective effect from CO_2 in terms of clinical outcomes, including postoperative neurocognitive decline. Although the present analysis was sufficiently powered (80%) to detect a difference between the 2 groups in terms of neurocognitive decline, it was largely underpowered to detect difference in terms of mortality and stroke. For



In hospital mortality

Study or Subgroup	CO2 Events	CO2 Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Martens 2001	1	31	5	31	2.5%	-0.13 [-0.27, 0.01]
Martens 2008	1	39	2	41	7.5%	-0.02 [-0.11, 0.06]
Al-Rashidi 2011	0	10	0	10	1.7%	0.00 [-0.17, 0.17]
Kalpokas 2003	0	8	0	10	1.4%	0.00 [-0.19, 0.19]
Svenarud 2014	0	10	0	10	1.7%	0.00 [-0.17, 0.17]
Skidmore 2006	0	21	0	22	6.9%	0.00 [-0.09, 0.09]
Ganguly 2015	3	150	2	150	60.7%	0.01 [-0.02, 0.04]
Chaudhuri 2012	2	63	1	62	17.8%	0.02 [-0.04, 0.07]
Total (95% CI)		**332**		**336**	**100.0%**	**0.00 [-0.02, 0.02]**
Total events	7		10			

Heterogeneity: Tau² = 0.00; Chi² = 4.78, df = 7 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.87)

Stroke

Study or Subgroup	CO2 Events	CO2 Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Al-Rashidi 2011	1	10	1	10	0.4%	0.00 [-0.26, 0.26]
Chaudhuri 2012	1	63	0	62	13.4%	0.02 [-0.03, 0.06]
Ganguly 2015	1	150	0	150	74.1%	0.01 [-0.01, 0.02]
Kalpokas 2003	0	10	0	8	0.7%	0.00 [-0.19, 0.19]
Martens 2001	0	31	1	31	3.4%	-0.03 [-0.12, 0.05]
Martens 2008	0	39	2	41	3.9%	-0.05 [-0.13, 0.03]
Skidmore 2006	0	21	0	22	3.3%	0.00 [-0.09, 0.09]
Svenarud 2014	0	10	0	10	0.8%	0.00 [-0.17, 0.17]
Total (95% CI)		**334**		**334**	**100.0%**	**0.00 [-0.01, 0.02]**
Total events	3		4			

Heterogeneity: Tau² = 0.00; Chi² = 3.52, df = 7 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)

Neurocognitive decline

Study or Subgroup	CO2 Events	CO2 Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Chaudhuri 2012	0	63	0	62	31.2%	0.00 [-0.03, 0.03]
Ganguly 2015	8	150	27	150	29.6%	-0.13 [-0.20, -0.06]
Martens 2001	5	31	9	31	20.0%	-0.13 [-0.33, 0.08]
Martens 2008	21	39	24	41	19.2%	-0.05 [-0.26, 0.17]
Total (95% CI)		**283**		**284**	**100.0%**	**-0.07 [-0.22, 0.08]**
Total events	34		60			

Heterogeneity: Tau² = 0.02; Chi² = 32.73, df = 3 (P < 0.00001); I² = 91%
Test for overall effect: Z = 0.93 (P = 0.35)

Figure 3. Forest plot of comparison: carbon dioxide insufflation (CO_2) vs control, outcome: in-hospital mortality, stroke, and neurocognitive decline.

secondary outcomes such as CK-MB levels, some trials have reported results with means from very highly skewed distributions, which increase the uncertainty of calculated estimates.

A variety of CO_2 delivery devices were used in the available trials investigating the efficacy of CDI. It has been shown that tubes with open-end or multiperforated catheter blowing CO_2 have undesirable result of air turbulence and do not provide a satisfied de-airing procedure (19.5%-51.7% remaining air).[23] The most efficient de-airing (≤1% remaining air) in a cardiothoracic wound model was provided by a gas diffuser at a carbon dioxide flow of 10 L/min. In the present meta-analysis, 5 of the 8 studies did not use a gas diffuser. Therefore, de-airing by CDI was likely to be ineffective in these

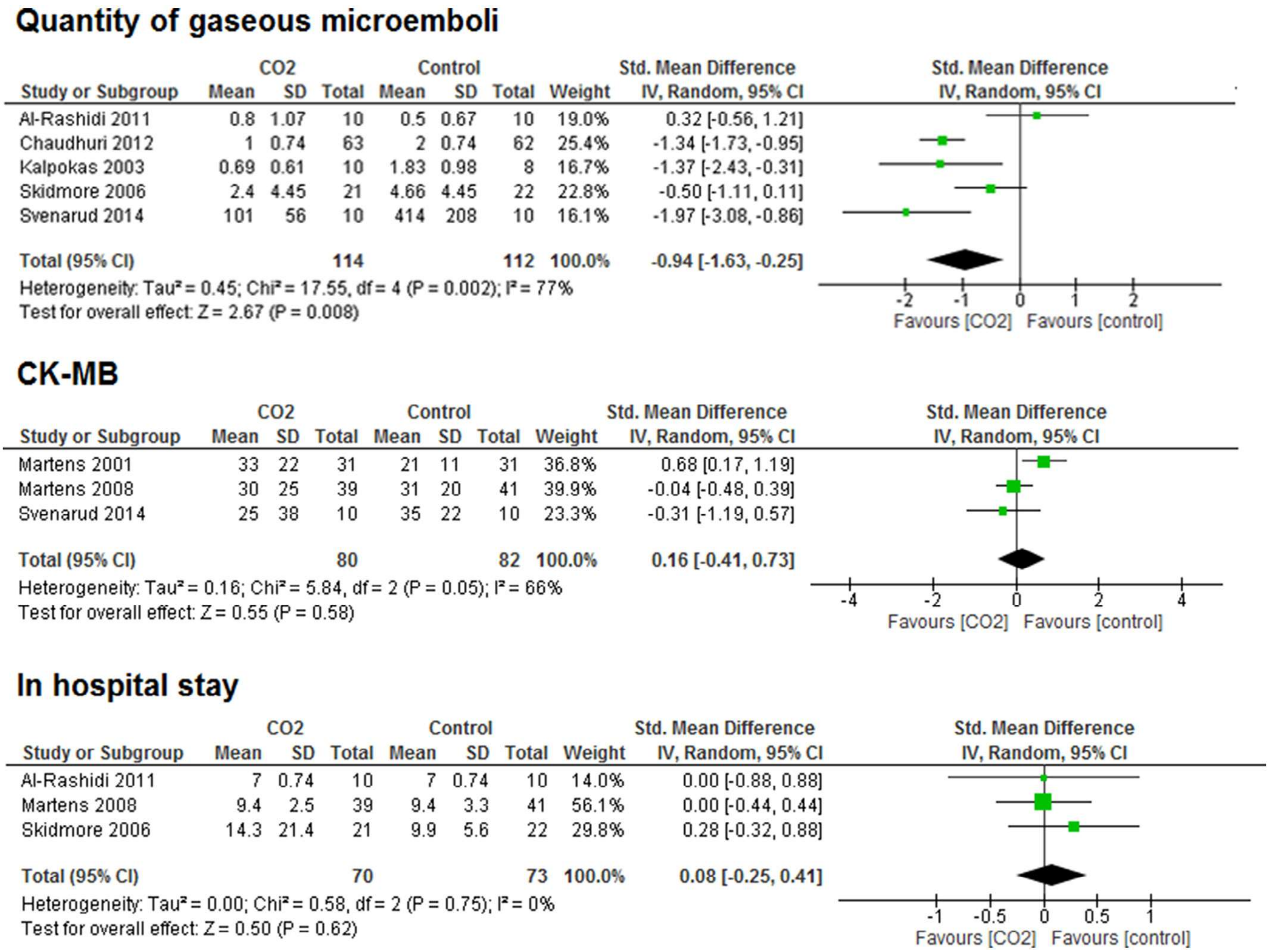


Figure 4. Forest plot of comparison: carbon dioxide insufflation (CO_2) vs control, outcome: quantity of gaseous microemboli in heart chambers, CK-MB, and hospital stay length.

trials, and this might translate into an underestimation of carbon dioxide protective effect. Moreover, different battery of psychometric tests were used and performed at different times to assess neurologic dysfunction. It is well known that psychometric tests are affected by anesthesia and analgesia drugs; hence, they may fail to distinguish the impairment that stemmed from embolism.[24,25] Selnes et al[26] reported that psychometric tests should not be performed earlier than 3 months postoperatively to avoid the influence of anesthesia and analgesia. In the present meta-analysis, 3 out of 4 studies reporting on neurocognitive decline performed psychometric tests during the first week after surgery. They found CDI protective in terms of neurocognitive decline. Only Chaudhuri et al[14] performed psychometric tests at 6 weeks postoperatively and concluded that CDI was not protective. Although in these trials neurocognitive decline has been used as a surrogate outcome for cerebral air microembolization, they cannot exclude the solid material embolization known to take place during open heart surgery (ie, calcium fragments, platelets aggregate). Al-Rashidi et al[13] investigated the effect of CDI on cerebral microembolization by means of transcranial Doppler, but they were unable to discriminate between gas and solid emboli. Several RCTs investigating CDI used quantity of gaseous microemboli in heart chambers at cross clamp time removal as primary outcome and CDI has been consistently associated with smaller amount of air bubbles. However, this does not necessarily translate into reduced cerebral gas microembolization, as in principle prolonged standard de-airing maneuvers can minimize this risk. Of note, in the present meta-analysis, blinding of operators to treatment allocation was present only in 2 out of 8 trials and this might have led surgeons to prolong standard venting maneuvers in the control group, thus neutralizing the effect of CDI.

The importance placed on surrogate markers of air microembolism has resulted in different conclusions. Despite its widespread use, to date, there is little evidence on the protective effect of CDI in open heart surgery. In addition to the increased costs (~$30 total cost each case, including $5 for CO_2 cylinder and $25 for gas diffusers available on the market), CDI induces significant systemic hypercapnic acidosis also when standardized protocol are employed for continuous delivery.[11] Insufflation of CO_2 into the cardiothoracic wound cavity during left-sided cardiac surgery can induce hypercapnic acidosis and increased cerebral blood flow. The finding of altered cerebral hemodynamics with CO_2 insufflation raises the concern that the protective effects of CO_2 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 models[27] could support this theory. 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. Finally, it has been recently observed that CO_2 insufflation is associated with a large number of damaged red blood cells in the circuit tubing, and its potential clinical effects need to be further investigated.[11]

In conclusion, despite its widespread use, to date, there is little evidence on any protective effect of CO_2 insufflation in open heart surgery. Therefore there is an urgent need for further evidence to conclusively justify its routine use during cardiac surgery.

Acknowledgments

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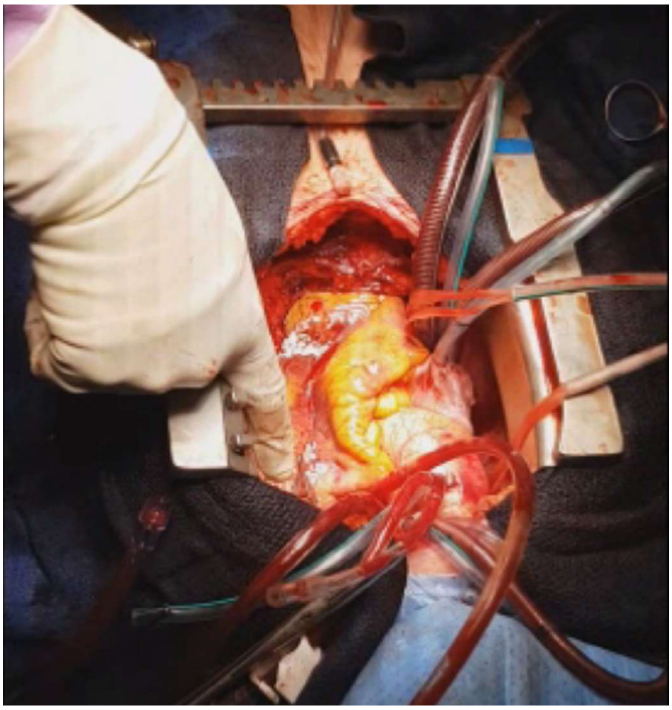
SUPPLEMENTAL MATERIAL

The following is the supplementary data to this article:



Video 1. Carbon dioxide insufflation use at Bristol Heart Institute.

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