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# **Carbon Dioxide Insufflation during cardiac surgery. Meta-Analysis of Randomized Controlled Trials.**

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## **Abbreviations**

CDI: carbon dioxide insufflation

CK-MB: Creatinine kinase, MB isoenzyme

NCD: Neurocognitive deterioration

RCT: randomized controlled trials

RD: risk difference

SMD: standardized mean difference

**Abstract (word count: 221)**

**Objective(s):** 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 neurological protection. Therefore, we conducted a meta-analysis of available randomized controlled trials (RCT) comparing CDI versus standard de-airing manoeuvres.

**Methods:** Electronic searches were performed to identify relevant RCTs. Primary outcomes investigated were postoperative stroke, neurocognitive deterioration (NCD), and in-hospital mortality. Risk difference (RD) was used as summary statistic. Pooled estimates were obtained by means of random-effects model to account the possible clinical diversity and methodologic variation between studies.

**Results:** A total of 8 studies were identified with 668 patients randomized to CDI (n=332) versus standard de-airing manoeuvres (n=336). In hospital mortality was 2.1% versus 3.0% in the CDI and control group respectively (RD 0%; 95%CI -2% to 2%; P=0.87; I<sup>2</sup>=0%). Incidence of stroke was similar between the two groups (1.0% versus 1.2% in the CDI and control group respectively (RD 0%; 95%CI -1% to 2%; P=0.62; I<sup>2</sup>=0%). NCD rate was 12% versus 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<sup>2</sup>=0%).

**Conclusions:** The present meta-analysis did not find any significant protective effect from the use CDI when compared with manual de-airing manoeuvres in terms of clinical outcomes including postoperative neurocognitive decline.

**Keywords:** Carbon dioxide insufflation; cardiac surgery; meta-analysis

**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 its use during cardiac surgery.

Neurological 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 two 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 reporting that their number correlates with the degree of postoperative neuropsychological disorder [3]. Various de-airing techniques have been proposed to minimise air microembolisation 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 been 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 its routine use [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 (RCT).

## **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].

### ***Data sources and searches***

Two investigators (U.B, M.C.), independently searched relevant studies on PubMed, Embase, BioMed Central, and the Cochrane Central register. Our aim was to find all RCTs comparing CDI versus de-airing manoeuvres 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+/- coronary artery bypass grafting (CABG), aortic vascular surgery or their combinations; 2) studies had to be RCTs, and to assign patients into CDI group or control group randomly. When centres 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 transoesophageal 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 analysed 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 (U.B., G.G.) 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 (RD) 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 methodologic 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, United Kingdom) 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 [14-21] were selected for analysis (Figure 1). The study characteristics of these trials are summarized in Table 1,2 and 3. In these 8 studies, 668 patients were randomized to CDI (n=332) versus standard de-airing manoeuvres (n=336). Sample size determination was reported only in two 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 Figures 2.

### ***Meta-analysis***

Data regarding in-hospital mortality and stroke was available for all studies included (for two studies, authors provided data when contacted by email). A total of four 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 transoesophageal 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 Figure 3 and 4 respectively. In hospital mortality was 2.1% versus 3.0% in the CDI and control group respectively (RD 0%; 95%CI -2% to 2%; P=0.87; I<sup>2</sup>=0%). Incidence of stroke was similar between the two groups (1.0% versus 1.2% in the CDI and control group respectively (RD 0%; 95%CI -1% to 2%; P=0.62; I<sup>2</sup>=0%). Neurocognitive decline rate postoperatively was 12% versus 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<sup>2</sup>=0%). Post-hoc power calculation was 8% for hospital mortality, 2.5% for stroke, 80% for NCD.

The amount of gaseous microemboli detected by transoesophageal echocardiogram was significantly lower in the CDI group versus the control group (RD -0.94; 95%CI -1.63 to -0.25; P=0.008; I<sup>2</sup>=77%). Finally, CK-MB levels (SMD 0.16; 95%CI -0.41 to 0.73; P=0.58; I<sup>2</sup>=66%) and length of hospital stay were not different between the two groups (SMD 0.08; 95%-0.25, 0.41; P=0.62; I<sup>2</sup>=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 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 to standard de-airing manoeuvres.

The aetiology of neurological impairment following cardiac surgery is multifactorial and includes systemic inflammation, hypotension and microembolization during cardiopulmonary bypass [22]. Microemboli include atherosclerotic emboli that are often released during aortic

manipulation and gaseous microemboli that occur particularly during open chamber surgery [23]. Although most research on cerebral embolization has focused on the issue of atherosclerotic microemboli, a recent study demonstrated that most emboli (~80%) are gaseous [23]. 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. Carbon dioxide insufflation 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<sub>2</sub> in terms of clinical outcomes including postoperative neurocognitive decline. Although the present analysis was sufficiently powered (80%) to detect a difference between the two groups in terms of neurocognitive decline, it was largely underpowered to detect difference in terms of mortality and stroke. For 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<sub>2</sub> 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 carbon dioxide have undesirable result of air turbulence and do not provide a satisfied de-airing procedure (19.5%-51.7% remaining air) [24]. The most efficient de-airing ( $\leq 1\%$  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, five of the 8 studies did not use gas diffuser. Therefore, de-airing by CDI was likely to be ineffective in these 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 time to assess neurological dysfunction. It is well known that psychometric tests are affected by anaesthesia and analgesia drugs, hence they may fail to distinguish the impairment that stemmed from embolism [25,26].

Selnes et al. [27] reported that psychometric tests should not be performed earlier than 3 months postoperatively to avoid the influence of anaesthesia and analgesia. In the present meta-analysis, three 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. [15] 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 (i.e. calcium fragments, platelets aggregate). Al-Rashidi et al. [14] 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 manoeuvres can minimize this risk. Of note, in the present meta-analysis blinding of operators to treatment allocation was present only in two out of 8 trials and this might have led surgeons to prolong standard venting manoeuvres 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 protective effect of CDI in open heart surgery. In addition to the increased costs (~30\$ total cost each case including 5\$ for CO<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> insufflation raises the concern that the protective effects of CO<sub>2</sub> 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 [29] 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<sub>2</sub> 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<sub>2</sub> insufflation in open heart surgery. Therefore there is an urgent need for further evidence to conclusively justify the routine its use during cardiac surgery.

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Table 1. Studies overview

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

CO<sub>2</sub>: Carbon Dioxide; SD: standard deviation; CABG: coronary artery bypass grafting

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 2011	Gas diffuser (Cardia Innovation AB)	10L/min	100%	air emboli in heart chambers using TEE	TCD	No	death,stroke, heart chambers microemboli, hospital stay
Chaudhuri 2012	Gas diffuser (Cardia Innovation AB)	5L/min	98.5%	Microembolic signal using TCD Neurocognitive testing	None	-	death, stroke, NCD, heart chambers microemboli
Ganguly 2015	vent catheter with multiple side holes	5L/min	NR	air emboli in heart chambers using TEE Neurocognitive testing	None	-	death, stroke, NCD
Kalpokas 2003	oxygen cannula (Maersk Medical, Sydney, Australia)	6L/min	NR	air emboli in heart chambers using TEE	None	-	death, stroke, heart chambers microemboli
Martens 2001	perfusion line (2-mm inner diameter)	3L/min	NR	Neurocognitive testing  S100B, neuron specific enolase [NSE]	None	-	death, stroke, NCD, CK-MB

Martens 2008	perforated drain (Jackson-Pratt)	2L/min	90%	Neurocognitive testing	None	-	death, stroke, NCD, CK-MB, hospital stay
Skidmore 2006	perforated drain (Jackson-Pratt)	6L/min	96%	P300 auditory- evoked potentials air emboli in heart chambers using TEE	None	-	heart chambers microemboli, hospital stay
Svenarud 2014	Gas diffuser (Cardia Innovation AB)	10L/min	100%	Segmenal wall motion abnormalities air emboli in heart chambers using TEE	None	-	heart chambers microemboli, CK- MB

TCD: transcranial Doppler; TEE: trans-oesophageal 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 2012	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.	4 domains: psychomotor, episodic memory, attention and working memory, executive function.	Between 1 and 4 weeks preoperatively and at 6 postoperative weeks.	A change in z score between preoperative and postoperative test performance of 1 SD	CDI not protective
Ganguly 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	5 days preoperatively and at 1 week and 4 weeks postoperatively	when at least 3 tests showed a reduction of 1 SD or when one test showed a reduction of 2 SD and another showed a reduction of 1 SD or more	CDI protective

Martens 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 days after surgery	A decline in performance from the initial test interval that exceeded 20% in two or more tests was considered to represent a deficit.	CDI not protective
Martens 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 days after surgery	A decline in performance from the initial test interval that exceeded 20% in two or more tests was considered to represent a deficit.	CDI not protective

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CDI: carbon dioxide insufflation

## **Figure legend**

**Figure 1.** Study flow diagram.

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

**Figure 3.** Forest plot of comparison: carbon dioxide insufflation (CO<sub>2</sub>) vs control, outcome: in-hospital mortality, stroke, neurocognitive decline.

**Figure 4.** Forest plot of comparison: carbon dioxide insufflation (CO<sub>2</sub>) vs control, outcome: quantity of gaseous microemboli in heart chambers; CK-MB and hospital stay length.

**Central Picture.** Forest plot for Carbon dioxide insufflation (CO<sub>2</sub>) vs control on the incidence of postoperative neurocognitive decline

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

