Reducing delirium and cognitive dysfunction after off-pump coronary bypass: A randomized trial

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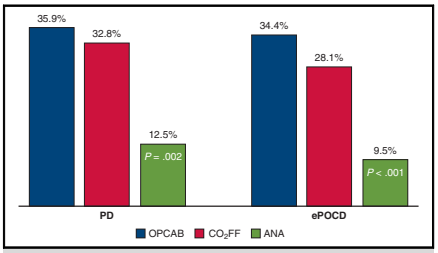
ABSTRACT

Background: Neuropsychiatric complications of surgical coronary revascularization are inconspicuous but frequent and clinically relevant. So far, attempts to reduce their occurrence, such as the introduction of off-pump coronary artery bypass (OPCAB) grafting method, have not brought the desired results. The aim of this trial was to determine whether using any of the 2 selected modifications of OPCAB could decrease the incidence of these undesired sequelae.

Methods: In this single-center, assessor- and patient-blinded, superiority, randomized controlled trial, 192 patients scheduled for elective isolated OPCAB were randomized to 3 parallel arms. The control arm underwent ''conventional'' OPCAB with vein grafts. The first study arm underwent anaortic OPCAB (ANA) with total arterial revascularization. The second study arm underwent OPCAB with vein grafts using carbon dioxide surgical field flooding (CO_2FF). Outcomes included the incidence of postoperative delirium (PD) and early postoperative cognitive dysfunction (ePOCD).

Results: The incidence of PD was 35.9% in the control (OPCAB) arm, 32.8% in the CO_2FF arm, and 12.5% in the ANA arm (χ^2 [2, N = 191] = 10.17; $P = .006$). Post hoc tests revealed that the incidence of PD in the ANA arm differed from that in the OPCAB arm (odds ratio [OR], 0.26; 95% confidence interval [CI], 0.09-0.68; $P = .002$). The incidence of ePOCD was 34.4% in the OPCAB arm, 28.1% in the CO_2FF arm, and 9.5% in the ANA arm (χ^2 [2, N = 191] = 11.58; $P = .003$). Post hoc tests revealed that the incidence of ePOCD differed between the ANA and OPCAB arms (OR, 0.20; 95% CI, 0.06-0.58; $P < .001$).

Conclusions: Performing ANA significantly decreases the incidence of PD and ePOCD compared with ''conventional'' OPCAB with vein grafts, whereas CO_2FF is inconsequential in this regard. These results, which probably reflect decreased delivery of embolic load to the brain in ANA, may have practical applicability in daily practice to improve clinical outcomes. (J Thorac Cardiovasc Surg 2021;161:1275-82)



Incidence of neuropsychiatric complications after 3 types of off-pump coronary bypass.

Central Message

Performing off-pump coronary artery bypass grafting using the anaortic technique results in a 3-fold reduction in the incidence of postoperative neuropsychiatric complications.

Perspective

This trial identifies an operating technique that meaningfully reduces the incidence of neuropsychiatric complications after off-pump coronary artery bypass grafting. It has practical applicability in daily clinical practice because using this technique can accelerate patient recovery time and decrease the risk of nosocomial complications, as well as healthcare costs.

See Commentaries on pages 1283 and 1285.

Coronary artery bypass grafting is one of the most widely performed major surgeries worldwide. Unfortunately, however, its neuropsychiatric complications remain common even after the introduction of preventative strategies, such as the off-pump coronary artery bypass

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Abbreviations and Acronyms

ANA = anaortic off-pump coronary artery bypass
CI = confidence interval
CO_2FF = off-pump coronary artery bypass with vein grafts using carbon dioxide surgical field flooding
ePOCD = early postoperative cognitive dysfunction
LAD = left anterior descending artery
LIMA-LAD = left internal mammary artery to left anterior descending artery bypass
OPCAB = off-pump coronary artery bypass with vein grafts
OR = odds ratio
PD = postoperative delirium
RASS = Richmond Agitation-Sedation Scale

(OPCAB) grafting method. Considering that up to 30.5% of post-OPCAB patients develop postoperative delirium (PD) and up to 51.3% experience early postoperative cognitive dysfunction (ePOCD), identifying an operating technique to reduce these undesired sequelae is a worthwhile goal,[1,2] especially because treating these complications after onset is difficult, and even their diagnosis is troublesome. It is estimated that without proper screening, up to 84% of PD cases may go unnoticed because the patient exhibits lethargy rather than agitation.[3,4] Thus, the PD seen in everyday postoperative clinical practice may only be the tip of the iceberg. Moreover, in contrast to PD, long-term neuropsychological changes are no longer attributed to surgery alone. As a result, study of cognitive decline becomes gradually limited to a dedicated research setting on perioperative brain injury. Consequently, despite their frequency, both PD and ePOCD are often undervalued by clinicians. This is an unfavorable tendency, in view of their association with significantly prolonged recovery time and substantially higher healthcare costs, as well as a 10-fold increased risk of hospital death and a 5-fold increased risk of nosocomial complications.[5,6]

The objective of this trial was to investigate whether reducing OPCAB's embolic load by using the anaortic (ANA) technique or the practice of carbon dioxide surgical field flooding (CO_2FF) could decrease the incidence of postoperative neuropsychiatric complications. The hypothesis was that avoiding a major source of solid microemboli (ie, manipulation of the ascending aorta during proximal vein graft anastomosis) in ANA and reducing the risk of gaseous microemboli formation in CO_2FF would be of significant benefit compared with "conventional" OPCAB.

MATERIALS AND METHODS

Trial Design and Approval

The CANON trial (CO_2 Surgical Field Flooding and Aortic No-Touch Off-Pump Coronary Artery Bypass Grafting to Reduce Neurologic Injuries After Surgical Coronary Revascularization) was a single-center, assessor- and patient-blinded, superiority, randomized controlled trial with 3 parallel arms (ClinicalTrials.gov identifier NCT03074604). The study protocol was approved by the local Bioethics Committee (project identifier KB 70/2017) and published in an open-access journal.[7] The research was completed according to the standards established in the Declaration of Helsinki, and written informed consent was obtained from all subjects.

Participants

Participants were recruited among patients scheduled for elective isolated OPCAB. Exclusion criteria included a history of neurologic or psychiatric illness, alcohol or drug abuse, use of tranquilizers or antipsychotics, previous cardiac surgery, left ventricular ejection fraction <31%, and carotid artery stenosis >70% in an obligatory preoperative ultrasound. In addition, patients with isolated left anterior descending (LAD) artery stenosis, who could not be randomized due to the current standard of care requiring left internal mammary artery to LAD (LIMA-LAD) bypass in this condition, were also excluded from the trial.

Each candidate meeting the aforementioned criteria was screened with the Mini-Mental State Examination and Hospital Anxiety and Depression Scale to identify preexisting cognitive impairment and mood disorders that could confound the outcomes of this research. Scoring below age- and education-adjusted cutoff scores on the Mini-Mental State Examination resulted in exclusion from the study, whereas scoring >7 points on the subscales of the Hospital Anxiety and Depression Scale prompted a psychiatric consultation to objectively evaluate the patient's eligibility.

Study Setting

Participants were recruited at the Department of Cardiac Surgery, Dr Antoni Jurasz Memorial University Hospital, Bydgoszcz, Poland. This tertiary care center performs more than 400 coronary artery bypass surgeries annually. The OPCAB technique is the standard in all these procedures. During 2017 and 2018, the OPCAB technique was used in 98.65% of surgical coronary interventions, and there were 0.36% conversions to on-pump surgery. The postoperative stroke rate after all operations of this type performed in this center during 2017 and 2018 was 1.7%.

Interventions

Patients were randomized at a 1:1:1 ratio to 1 of 2 study arms (ANA or CO_2FF) or the control arm (OPCAB). To reduce the bias of operator training, only the most experienced surgeons, who had performed at least 500 ANA procedures, participated in this trial. The grafting techniques used in each study arm are described in Appendix E1. All interventions in this trial were performed under the same anesthetic protocol (induction with fentanyl and etomidate; maintenance with propofol, sevoflurane, and fentanyl). When required, postoperative sedation was achieved with dexmedetomidine, and analgesia was provided according to recent guidelines.[8] All patients were treated before and after surgery in accordance with contemporary European Society of Cardiology Guidelines.

Outcomes

Early postoperative cognitive dysfunction evaluated on day 7 after surgery, defined as a decline from preoperative performance of >20% in more than 2 cognitive domains, was chosen as the primary outcome measure. To assess ePOCD, a battery of well-established neuropsychological

tests was chosen according to the Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery.[9] Details on the selection of ePOCD definition, the design of cognitive test battery, and its administration have been published previously.[7]

The secondary outcome was PD diagnosed with the Confusion Assessment Method for the Intensive Care Unit[10] within 7 days after surgery. To avoid confounding results with postanesthetic emergence delirium, which is usually of short duration and minimal clinical consequence,[11] screening for delirium was started 24 hours postoperatively and then performed twice daily at 0800 and 2000 hours for 6 days. Three motoric subtypes of delirium were determined based on the Richmond Agitation-Sedation Scale (RASS) score,[12] which was measured before each screening. Hyperactive delirium was diagnosed when the RASS score was consistently positive (+1 to +4), hypoactive delirium was diagnosed when the RASS score was consistently negative or neutral (−3 to 0), and mixed delirium was diagnosed when the RASS score was alternately positive (+1 to +4) and negative or neutral (−3 to 0).[13] Unresponsive patients (RASS score -5 or -4) were excluded from further assessment and defined as comatose.

Sample Size

The sample size was calculated for the primary outcome based on a previous pilot study that demonstrated a 50% incidence of ePOCD after OPCAB and a 50% reduction in ePOCD after ANA.[2] Consequently, the expected failure rate was 0.5 in the OPCAB arm and 0.25 in the ANA arm. With significance set at 0.05 and power set at 80%, the sample size required to detect differences was 58 for each of these arms. There was insufficient evidence for predicting the rate of ePOCD in the CO_2FF arm, and this arm's sample size was arbitrarily set at 58, in line with the other study arms. To compensate for any causes of missing data, the sample size was increased by 10% in each arm, for a total of 192 patients.

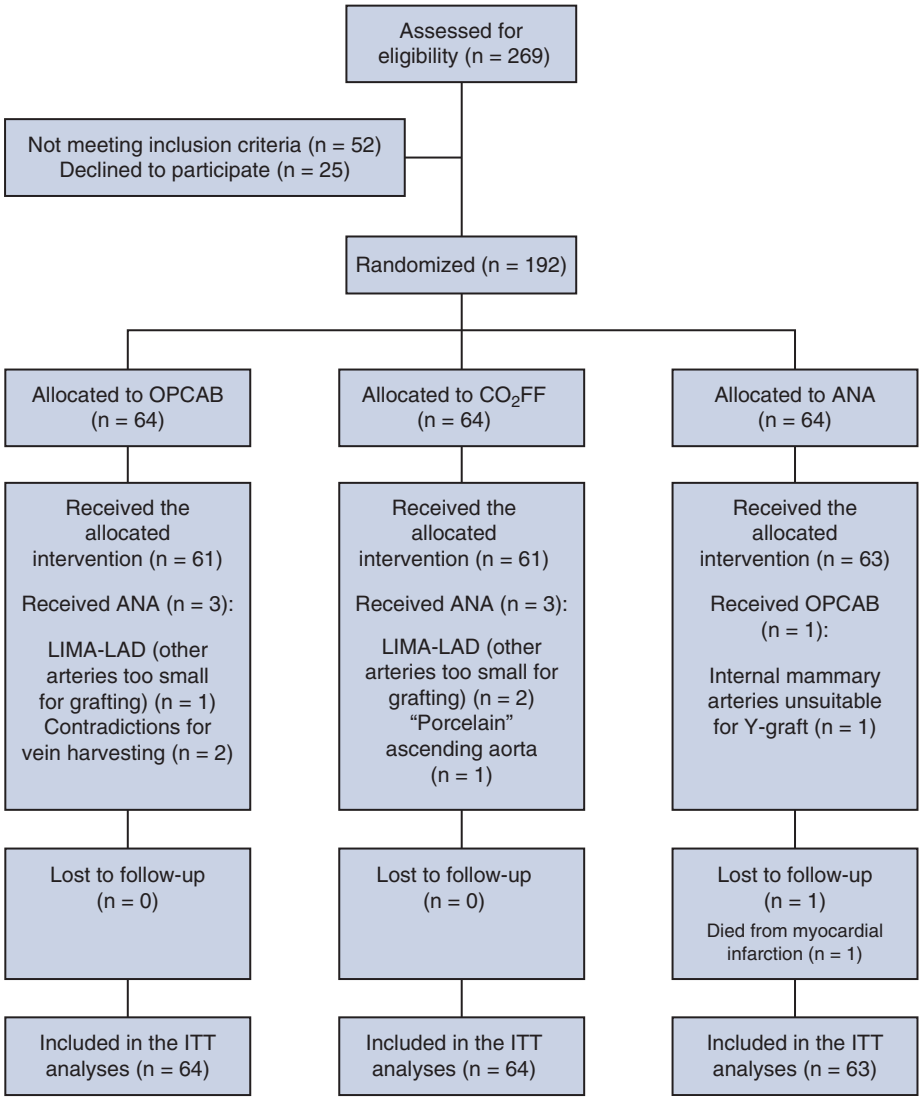


FIGURE 1. Participants' flow through the trial. *OPCAB*, Off-pump coronary artery bypass surgery; *CO_2FF*, off-pump coronary artery bypass surgery using carbon dioxide surgical field flooding; *ANA*, anaortic off-pump coronary artery bypass surgery; *LIMA-LAD*, left internal mammary artery to left anterior descending artery bypass; *Y-graft*, right internal mammary artery anastomosed onto left internal mammary artery allowing for complete arterial revascularization; *ITT*, intention to treat.

TABLE 1. Preoperative characteristics

Characteristic	OPCAB	CO_2FF	ANA
Preoperative data for risk evaluation by the EuroSCORE II*			
Age, y, mean ± SD or median (IQR)	66.3 ± 9.0	64.0 (61.0-69.0)	65.2 ± 7.7
Female sex, n (%)	14 (21.9)	22 (34.4)	15 (23.4)
Renal impairment, n (%)			
Normal (creatinine clearance >85 mL/min)	43 (67.2)	35 (54.7)	37 (57.8)
Moderate (creatinine clearance 50-85 mL/min)	18 (28.1)	26 (40.6)	25 (39.1)
Severe (creatinine clearance <50 mL/min)	3 (4.7)	2 (3.1)	2 (3.1)
Dialysis	0 (0.0)	1 (1.6)	0 (0.0)
Extracardiac arteriopathy, n (%)	6 (9.4)	5 (7.8)	4 (6.3)
Chronic lung disease, n (%)	5 (7.8)	3 (4.7)	2 (3.1)
Diabetes mellitus (type 1 or 2) insulin-dependent, n (%)	17 (26.6)	17 (26.6)	14 (21.9)
New York Heart Association class, n (%)			
I	6 (9.4)	3 (4.7)	5 (7.8)
II	10 (15.6)	13 (20.3)	12 (18.8)
III	3 (4.7)	4 (6.3)	1 (1.6)
IV	0 (0.0)	0 (0.0)	0 (0.0)
Canadian Cardiovascular Society class 4 angina, n (%)	8 (12.5)	4 (6.3)	10 (15.6)
Left ventricular function, n (%)			
Good (>50%)	49 (76.6)	54 (84.4)	55 (85.9)
Moderate (31%-50%)	15 (23.4)	10 (15.6)	9 (14.1)
Poor or very poor (≤30%)	0 (0.0)	0 (0.0)	0 (0.0)
Recent myocardial infarction (≤90 d), n (%)	22 (34.4)	22 (34.4)	22 (34.4)
Logistic EuroSCORE II for operative risk, %, median (IQR)	0.9 (0.7-1.2)	0.9 (0.7-1.1)	0.8 (0.6-1.2)
Other selected preoperative data			
Atrial fibrillation, n (%)	1 (1.6)	4 (6.3)	5 (7.8)
Body mass index, kg/m^2 mean ± SD or median (IQR)	28.2 ± 4.2	28.7 (26.9-31.7)	27.8 ± 4.5
Diabetes mellitus (type 2) non-insulin-dependent, n (%)	6 (9.4)	10 (15.6)	7 (10.9)
Education, y, median (IQR)	12.0 (12.0-12.0)	12.0 (12.0-12.0)	12.0 (11.5-12.0)
Hyperlipidemia, n (%)	43 (67.2)	30 (46.9)	35 (54.7)
Hypertension, n (%)	52 (81.3)	55 (85.9)	53 (82.8)
Previous myocardial infarction (>90 d), n (%)	12 (18.8)	12 (18.8)	14 (21.9)
Smoker within past year, n (%)	28 (43.8)	27 (42.2)	28 (43.8)

There were no statistically significant differences among the study arms. *OPCAB*, off-pump coronary artery bypass surgery; *CO_2FF*, off-pump coronary artery bypass surgery using carbon dioxide surgical field flooding; *ANA*, anaortic off-pump coronary artery bypass surgery; *EuroSCORE II*, European System for Cardiac Operative Risk Evaluation model II; *SD*, standard deviation; *IQR*, interquartile range. *Data not included were covered by the study's exclusion criteria.

Randomization

Participants were randomized at a 1:1:1 ratio to the 3 study arms according to a computer-generated list of random numbers. This sequence was prepared by an independent statistician, sealed in sequentially numbered envelopes, and stored in the operating block. Immediately before the first incision, the surgical team chief opened the next consecutively numbered envelope to identify which intervention to perform. The final decision on the type of intervention was based on patient safety and was made by the surgical team chief after intraoperative assessment.

Blinding

Investigators and patients were blinded to study arm allocation. However, in trials involving total arterial revascularization, there is an inherent potential for unblinding because of the absence of vein harvest wounds after ANA. Considering this risk, patients were asked not to disclose any information about the surgery to the research staff. In addition, clinical staff were instructed to cover the patients' legs during each neuropsychiatric assessment.

Statistical Methods

Categorical variables were reported as numbers and percentages and compared among the 3 study arms with the χ^2 test for multiple groups. Continuous variables were reported as mean ± standard deviation or median and interquartile range if skewed and compared among the 3 study arms with 1-way analysis of variance or the Kruskall-Wallis test as appropriate. Multiple comparison tests were conducted when a P value of <.025 was obtained. $P < .025$ was considered to indicate statistical significance. Odds ratios (ORs) and 95% confidence intervals (CIs) between the control arm and each of the study arms were calculated for outcome data that showed statistically significant differences. All analyses were performed with the R version 3.4.3 (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Participant Flow

Between March 2017 and June 2018, a total of 269 patients scheduled for elective OPCAB were screened for study participation; of these, 192 were recruited and assigned at random to the OPCAB arm (n = 64), CO_2FF arm (n = 64), or ANA arm (n = 64). Three patients in the OPCAB arm, 3 patients in the CO_2FF arm, and 1 patient in the ANA arm did not receive the allocated intervention. Figure 1 shows the participants' flow through the trial.

TABLE 2. Selected intraoperative and postoperative data

Parameter	OPCAB	CO_2FF	ANA
Intraoperative data			
Time of surgery, min, mean ± SD or median (IQR)	214.5 ± 46.0	220.3 ± 50.7	235.0 (205.0-285.0)*
Distal anastomoses, n, median (IQR)	3 (2-3)	3 (2-3)	3.0 (2-3)
Nadir mean arterial pressure at surgery, mm Hg, mean ± SD or median (IQR)	54.9 ± 6.6	52.5 (46.7-56.7)†	55.33 (50.0-60.3)
Nadir hematocrit during surgery, %, mean ± SD	33.5 ± 4.3	32.7 ± 4.9	33.3 ± 4.5
Nadir hemoglobin during surgery, g/dL, mean ± SD or median (IQR)	11.4 ± 1.4	10.8 (9.9-11.6)	11.4 ± 1.5
Red cell concentrate transfusion during surgery, n (%)	11 (17.2)	17 (26.5)	12 (18.8)
Postoperative data			
Time of intubation, min, median (IQR)	595.0 (507.5-740.0)	630.0 (515.0-747.5)	705.0 (562.5-807.5)
Nadir mean arterial pressure in ICU, mm Hg, mean ± SD or median (IQR)	66.7 (60.0-73.3)	65.5 ± 11.4	70.0 (60.0-76.7)
Inotropes in ICU, n (%)	22 (34.4)	31 (38.4)	27 (42.2)
Nadir hematocrit in ICU, %, mean ± SD or median (IQR)	30.8 (27.9-34.4)	29.4 ± 4.4†	31.2 ± 4.2
Nadir hemoglobin in ICU, g/dL, mean ± SD or median (IQR)	10.3 ± 1.3	9.6 (8.7-10.7)	11.1 ± 5.0
Red cell concentrate transfusion in ICU, n (%)	11 (17.2)	18 (28.1)	12 (18.8)
Nadir blood glucose in ICU, mg/dL, mean ± SD	102.5 ± 22.4	99.5 ± 22.7	100.0 ± 19.4
Antipsychotics in ICU, n (%)	10 (15.6)	15 (23.4)	3 (4.7)*
Prolonged ICU stay (>48 h), n (%)	8 (12.5)	14 (21.9)	10 (15.9)
Prolonged hospitalization (>7 d), n (%)	19 (29.7)	19 (29.7)	14 (21.9)

OPCAB, Off-pump coronary artery bypass surgery; *CO_2FF*, off-pump coronary artery bypass surgery using carbon dioxide surgical field flooding; *ANA* anaortic off-pump coronary artery bypass surgery; *SD*, standard deviation; *IQR*, interquartile range; *ICU*, intensive care unit. *Differences in surgery time and the use of antipsychotics between ANA and OPCAB were statistically significant. †Differences in nadir mean arterial pressure during surgery and nadir hematocrit in ICU between CO_2FF and OPCAB as well as between CO_2FF and ANA were statistically significant.

There were no cases of unblinding. One patient in ANA arm died from myocardial infarction and was not included in the final intention-to-treat analyses of primary and secondary outcomes. All other participants completed postoperative assessments with no missing data.

Baseline Data

There were no statistically significant differences in perioperative variables between the ANA and OPCAB arms, with the exception of longer duration of ANA surgery and less frequent postoperative use of antipsychotics after ANA (Tables 1 and 2). However, none of these differences can explain the superior outcomes in ANA arm. In addition, there were no statistically significant differences in baseline mood and neurocognitive tests between the study arms. Our multivariable analysis is described in Appendix E2.

Delirium Outcomes

PD occurred in 23 of 64 patients (35.9%) treated with OPCAB, compared with 21 of 64 patients (32.8%) treated with CO_2FF and 8 of 63 patients (12.5%) treated with ANA (Figure 2, Table 3). This was a statistically significant association (χ^2 (2, N = 191) = 10.17; P = .006). Post hoc tests revealed that the incidence of PD in ANA arm differed from that in the OPCAB arm (OR, 0.26; 95% CI, 0.09-0.68; P = .002). Per protocol analysis showed similar results in the incidence of PD: 23 of 61 patients (37.7%) treated with OPCAB, compared with 21 of 61 (34.4%) treated with CO_2FF and 8 of 62 (12.9%) treated with ANA, a statistically significant association (χ^2 (2, N = 185) = 11.04; P = .004). Post hoc tests revealed that the incidence of PD in the ANA arm differed from that in the OPCAB arm (OR, 0.25; 95% CI, 0.09-0.65; P = .002).

Additional (not preplanned) examination of delirium motoric subtype distribution exposed a statistically significant difference in the between-arm incidence of hypoactive PD (χ^2 (2, N = 191) = 9.04; P = .01) (Table 3). Post hoc tests revealed that the incidence of hypoactive PD in the ANA arm differed from that in the OPCAB arm (OR, 0.17; 95% CI, 0.03-0.63; P = .003).

Neurocognitive Outcomes

ePOCD occurred in 22 of 64 patients (34.4%) treated with OPCAB, compared with 18 of 64 (28.1%) treated with CO_2FF and 6 of 63 (9.5%) treated with ANA (Figure 2, Table 3), a statistically significant association (χ^2 (2, N = 191) = 11.58; P = .003). Post hoc tests revealed that the incidence of ePOCD in the ANA arm differed from that in the OPCAB arm (OR, 0.20; 95% CI, 0.06-0.58; P < .001). Per protocol analysis showed similar results regarding the incidence of ePOCD: 22 of 61 patients (36.1%) treated with OPCAB, compared with 17 of 61 (27.9%) treated with CO_2FF and 6 of 62 (9.7%) treated with ANA, a statistically significant association (χ^2 (2, N = 185) = 12.16; P = .002). Post hoc tests revealed that the incidence of ePOCD in the ANA arm differed from that in the OPCAB arm (OR, 0.19; 95% CI, 0.06-0.55; P < .001). Additional analyses of neuropsychological test results are available in Appendix E3.

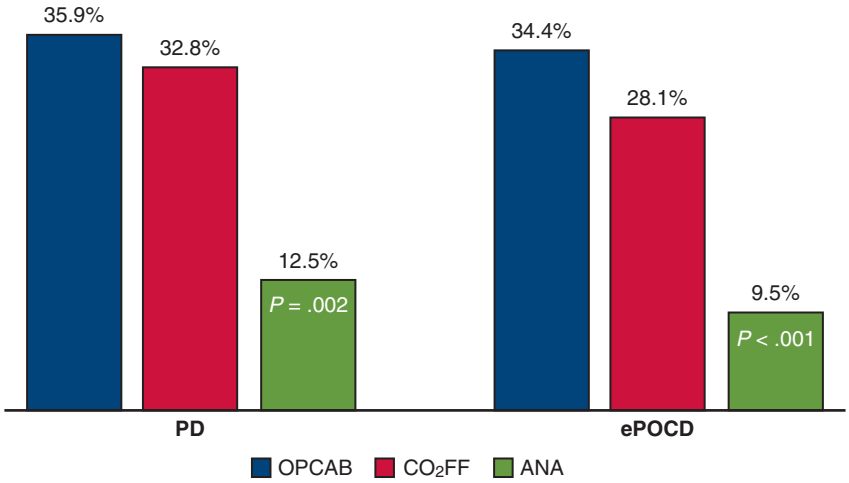


FIGURE 2. Performing anaortic off-pump coronary artery bypass grafting (*ANA*) results in a 3-fold reduction in the incidence of postoperative delirium (*PD*) and early postoperative cognitive dysfunction (*ePOCD*) as compared with off-pump coronary artery bypass grafting with vein grafts (*OPCAB*), whereas performing off-pump coronary artery bypass with vein grafts using CO_2 surgical field flooding (*CO_2FF*) is inconsequential in this regard.

DISCUSSION

The results of this trial suggest that performing ANA significantly decreases the incidence of PD and ePOCD in patients undergoing OPCAB, whereas using CO_2FF is inconsequential in this regard. It should be noted that in the ANA arm, the PD reduction is primarily in the hypoactive motoric subtype, a condition characterized by apathy, slowed mentation and movement. Importantly, PD with these features is the easiest to overlook by medical staff, and thus, like ePOCD, it is recognized primarily during specific clinical research.[4] As a result, a significant advantage of using the ANA technique for PD and ePOCD prevention might not be readily noticeable.

Manipulation of the ascending aorta, such as using a site-biting clamp to perform proximal vein anastomoses during OPCAB, causes embolic showers that can be seen on transcranial Doppler.[14] The total omission of this maneuver in ANA has been shown to reduce cerebrovascular accidents in the scarce research on this topic.[15,16] while its effect on neuropsychiatric complications has been tested

TABLE 3. Outcomes and adverse events

Outcome/event	OPCAB	CO_2FF	ANA	*P* value	OPCAB-CO_2OPCAB, OR (95% CI); *P* value	OPCAB-anOPCAB, OR (95% CI); *P* value
Primary outcome						
ePOCD, n (%)	22 (34.4)	18 (28.1)	6 (9.5)	.003	0.75, (0.33-1.69); .45	0.20 (0.06-0.56); <.001
Secondary outcomes						
Overall incidence of PD, n (%)	23 (35.9)	21 (32.8)	8 (12.5)	.006	0.87 (0.39-1.93); .71	0.26 (0.09-0.68); .002
Motoric subtype of PD, n (%)						
Hyperactive	7 (10.9)	6 (9.4)	3 (4.8)	.43		
Hypoactive	15 (23.4)	12 (18.8)	3 (4.8)	.011	0.76 (0.29-1.93); .52	0.17 (0.03-0.63); .003
Mixed	1 (1.6)	3 (4.7)	2 (3.2)	.60		
Stroke, n (%)	2 (3.1)	1 (1.6)	0 (0.0)	.36		
Transient ischemic attack, n (%)	0 (0.0)	1 (1.6)	0 (0.0)	.37		
Adverse in-hospital events						
All-cause mortality, n (%)	0 (0.0)	1 (1.6)	1 (1.6)	.60		
Major bleeding, n (%)	1 (1.6)	3 (4.7)	0 (0.0)	.17		
Myocardial infarction, n (%)	1 (1.6)	1 (1.6)	1 (1.6)	.44		
Repeat revascularization, n (%)*	3 (4.7)	5 (7.8)	1 (1.6)	.25		
Deep sternal wound infection, n (%)	2 (3.1)	0 (0.0)	1 (1.6)	.36		
Atrial fibrillation, n (%)	8 (12.5)	8 (12.5)	11 (17.2)	.67		
Acute kidney injury, n (%)	9 (14.1)	9 (14.1)	5 (7.8)	.45		

OPCAB, off-pump coronary artery bypass surgery; *CO_2FF*, off-pump coronary artery bypass surgery using CO_2 surgical field flooding; *ANA*, anaortic off-pump coronary artery bypass surgery; *OR*, odds ratio; *CI*, confidence interval; *ePOCD*, early postoperative cognitive dysfunction; *PD*, postoperative delirium. *All repeat revascularizations were by percutaneous coronary intervention.

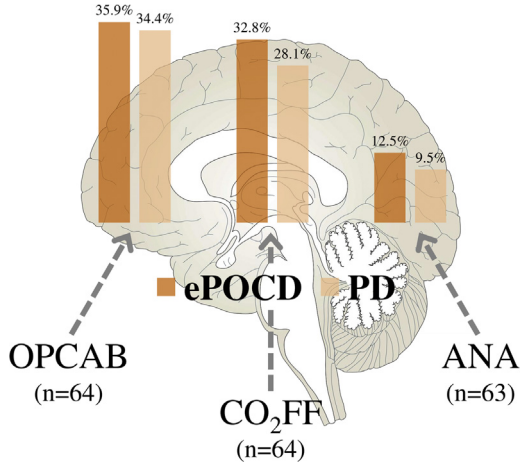
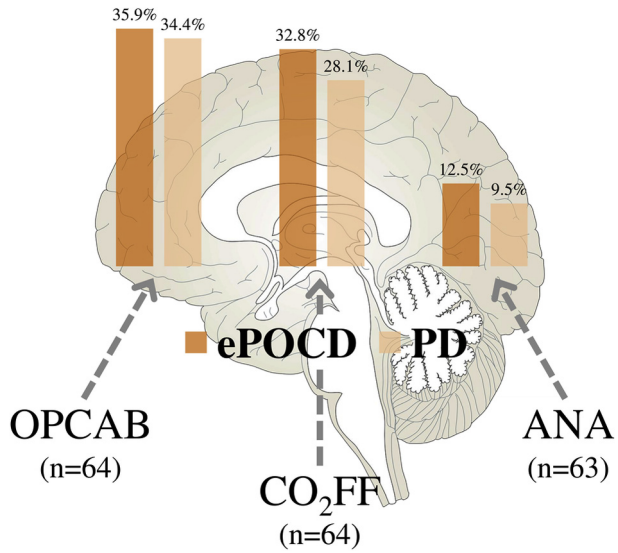


FIGURE 3. Performing anaortic off-pump coronary artery bypass grafting (*ANA*) results in a 3-fold reduction in the incidence of postoperative delirium (*PD*) and early postoperative cognitive dysfunction (*ePOCD*) as compared with off-pump coronary artery bypass grafting with vein grafts (*OPCAB*) while performing off-pump coronary artery bypass with vein grafts using CO_2 surgical field flooding (CO_2FF) is inconsequential in this regard.

only in this trial's pilot study.[2] It is very important that favorable results afforded by ANA not only apply to relatively rarely occurring postoperative stroke, but also cover ubiquitous PD and ePOCD, which meaningfully impact everyday postoperative clinical practice.

Although the ANA technique can reduce the number of solid emboli that are exceptionally dangerous to the central nervous system, formation of gaseous emboli remains a threat. This hazard may possibly be mitigated by the use of CO_2FF to displace air in the surgical field. Carbon dioxide (CO_2) does not form any bubbles, because it is 25 times more soluble in blood than air and is rapidly discharged from the body through breathing. Although it remains relatively underused in OPCAB, CO_2 has been used in cardiac operations since the 1950s. There have been consistent reports of its neuroprotective qualities in heart valve surgery, none of which focused on OPCAB, however.[17] Considering the results of the present trial, it is possible that OPCAB is not sufficiently invasive to benefit from the effect of CO_2FF.



VIDEO 1. A video summary of the trial's impact on patients' postoperative recovery. Video available at: https://www.jtcvs.org/article/S0022-5223(19)32091-4/fulltext.

Generalizability

Similar results can be expected in other treatment centers; however, they may be dependent on individual surgeon competence in ANA technique. Importantly, the CANON operators were highly skilled in this method, as underscored by the fact that only a single crossover occurred in the ANA arm. Thus, the outcomes of this relatively demanding procedure were not affected by surgeons' inexperience.

Limitations

This trial's limitations include its single-center design and the inability to blind the surgical team. In addition, although planned in the protocol, magnetic resonance imaging was not used in this study. This entailed a change in sample size, because it was originally calculated for the radiologic outcome. Finally, future research of this type should consider performing longitudinal follow-ups because the negative effects of PD and ePOCD may extend beyond the immediate postoperative period. Some data associate PD with lower health-related quality of life even at 18 months after surgery, while ePOCD has been correlated with loss of social function and independence, resulting in increased reliance on social welfare payments and earlier withdraw from the labor market.[18,19]

CONCLUSIONS

Performing ANA significantly decreases the incidence of PD and ePOCD compared with OPCAB with vein grafts, whereas CO_2FF is inconsequential in this regard (Figure 3 and Video 1). These results may reflect decreased delivery of an embolic load to the brain in ANA and have practical applicability in daily practice to possibly significantly improve clinical outcomes.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: cardiac surgery, coronary artery disease surgery, neurologic events, neuropsychiatric complications, delirium, postoperative cognitive dysfunction

APPENDIX E1. GRAFTING PROCEDURE COMPLETED IN THE CONTROL ARM: OFF-PUMP CORONARY ARTERY BYPASS WITH VEIN GRAFTS (OPCAB)

All procedures were done via a median sternotomy without the use of or conversion to cardiopulmonary bypass. The heart was exposed using Starfish heart positioning device (Medtronic, Minneapolis, Minn) or deep pericardial traction sutures (Lima stitch). Proximal anastomoses were performed using a site-biting clamp. Distal anastomoses were performed using an Octopus coronary stabilizer (Medtronic) and a ''soft'' bulldog clamp. All left anterior descending (LAD) artery lesions were bypassed with a skeletonized left internal mammary artery to LAD (LIMA-LAD) graft. Other lesions were bypassed using saphenous vein grafts. The quality of anastomoses was assessed by intraoperative transit time flow measurements.

GRAFTING PROCEDURE COMPLETED IN THE FIRST STUDY ARM: OFF-PUMP CORONARY ARTERY BYPASS WITH TOTAL ARTERIAL REVASCULARIZATION (ANA)

All procedures were done via a median sternotomy without the use of or conversion to cardiopulmonary bypass. The heart was exposed using a Starfish heart positioning device (Medtronic) or deep pericardial traction sutures (Lima stitch). Distal anastomoses were performed using an Octopus coronary stabilizer (Medtronic) and a ''soft'' bulldog clamp. Complete arterial revascularization was achieved with bilateral skeletonized internal mammary arteries, using the Y-grafting technique when necessary. No other vascular conduits were used. The quality of the anastomoses was assessed by intraoperative transit time flow measurements.

GRAFTING PROCEDURE COMPLETED IN THE SECOND STUDY ARM: OFF-PUMP CORONARY ARTERY BYPASS WITH VEIN GRAFTS USING CARBON DIOXIDE SURGICAL FIELD FLOODING (CO_2FF)

All procedures were done via a median sternotomy without the use of or conversion to cardiopulmonary bypass. In this study arm, the chest cavity was insufflated with CO_2 at a flow of >5 L/min during the entire procedure. The heart was exposed using a Starfish heart positioning device (Medtronic) or deep pericardial traction sutures (Lima stitch). Proximal anastomoses were performed using a side-biting clamp. Distal anastomoses were performed using an Octopus coronary stabilizer (Medtronic) and a ''soft'' bulldog clamp. All LAD lesions were bypassed with skeletonized LIMA-LAD grafts. Other lesions were bypassed using saphenous vein grafts. The quality of the anastomoses was assessed by intraoperative transit time flow measurements.

APPENDIX E2.

Potential confounders were selected in 2 steps. In the first step, they were identified based on the information obtained from research literature. Thus, patient age, years of education, smoking status, logistic EuroSCORE, diagnosis of diabetes and/or atrial fibrillation, and red cell concentrate (RCC) transfusions during surgery were chosen as possible risk factors for postoperative neuropsychiatric complications. In the second step, univariable analyses were used to identify other potential covariates for the prediction of PD and ePOCD. Variables with a P value of $<.20$ were chosen.

MULTIVARIABLE ANALYSIS OF PD

The following categorical variables were entered into the model: ANA arm, Canadian Cardiovascular Society class 4, diabetes, atrial fibrillation, hyperlipidemia, New York Heart Association (NYHA) class I, NYHA class III, RCC transfusion during surgery, RCC transfusion in intensive care unit (ICU), and smoker within the past year. The following continuous variables were added: age, body mass index (BMI), logistic EuroSCORE, Mini Mental State Exam score, and years of education.

Multivariable analysis was performed with multiple logistic regression analysis. The stepwise forward method was applied to build the model. The following factors were significantly and independently related to PD: ANA arm, RCC transfusions in ICU, BMI, and age (Table E1). The bootstrap was used for internal model validation. The discrimination ability of the model was indicated by an area under the receiver operating characteristic curve of 0.75. The Hosmer-Lemeshow goodness-of-fit test indicated that the model fit the data well ($P = .13$).

MULTIVARIABLE ANALYSIS OF ePOCD

The following categorical variables were entered into the model: acute kidney injury, ANA arm, Canadian Cardiovascular Society class 4, diabetes, diabetes on insulin, atrial fibrillation, hyperlipidemia, NYHA classification class III, recent myocardial infarction, RCC transfusion during surgery, RCC transfusion in the ICU, smoker within the past year, and sternal wound infection. The following continuous variables were also added into the model: age, BMI, logistic EuroSCORE, and years of education.

Multivariable analysis was performed with multiple logistic regression analysis. The stepwise forward method was applied to build the model. The following factors were significantly and independently related to ePOCD: ANA arm, smoker within the past year, diabetes on insulin, and RCC transfusion in the ICU (Table E2). The bootstrap was used for internal model validation. The discrimination ability of the model was indicated by an area under the receiver operating characteristic curve of 0.74. The

Hosmer-Lemeshow goodness-of-fit test indicated that the model fit the data well ($P = .44$).

APPENDIX E3

Although performing ANA was associated with decreased impairment in most of the neuropsychological tests, in 3 of these tests this effect did not reach statistical significance (Table E3). While exceptional resilience of the examined cognitive domains cannot be ruled out, a more likely explanation for this result can be provided. Analysis of preoperative data (Table E4) reveals that approximately one-half of the patients were unable to complete the first Trail Making Test, part B, and that most of them had low initial scores in Digit Span Test–Forward and Backward. Thus, their outcomes could have been affected by the so-called "floor effect," meaning that poor preoperative measurements of these instruments possibly concealed some postoperative deterioration, mainly in the OPCAB arm. Moreover, scoring <5 in the initial Digit Span tests meant that even the smallest deterioration in follow-up met the applied criterion of cognitive impairment. Thus, this instrument might have been too sensitive, qualifying too many patients as cognitively impaired, mainly in the ANA arm. These observations emphasize the need for optimal psychometric battery and preinclusion dementia screening to avoid distorting ePOCD research results.

TABLE E1. Significant variables included in the model

Variable	β	OR (95% CI)	*P* value
ANA arm	0.44	0.27 (0.11-0.64)	.003
RCC transfusion in ICU	0.40	2.57 (1.17-5.65)	.019
BMI	0.04	1.01 (1.01-1.19)	.021
Age	0.03	1.06 (1.00-1.12)	.048
Constant	2.32	0.001 (0.00-0.07)	.002

OR, Odds ratio; *CI*, confidence interval; *ANA*, anaortic off-pump coronary artery bypass surgery; *RCC*, red cell concentrate; *ICU*, intensive care unit; *BMI*, body mass index.

TABLE E2. Significant variables included in the model

Variable	β	OR (95% CI)	*P* value
ANA arm	0.49	0.22 (0.08-0.57)	.002
Smoker within past year	0.36	2.14 (1.03-4.45)	.043
Diabetes on insulin	0.51	4.69 (1.72-12.77)	.003
RCC transfusion in ICU	0.42	2.36 (1.04-5.35)	.039
Constant	0.32	0.21 (0.11-0.39)	<.001

OR, Odds ratio; *CI*, confidence interval; *ANA*, anaortic off-pump coronary artery bypass surgery; *RCC*, red cell concentrate; *ICU*, intensive care unit.

TABLE E3. Incidence of cognitive impairment related to specific test

Test	Tested domains	OPCAB	CO_2FF	ANA
Stroop Test, part A, n (%)	Speed of processing	19 (29.7)	18 (28.1)	7 (11.1)*
Stroop Test, part B, n (%)	Attention, automaticity, parallel distributed processing	19 (29.7)	17 (26.6)	6 (9.5)*
Trail Making Test, part A, n (%)	Psychomotor speed	22 (34.4)	26 (40.6)	9 (14.3)*
Trail Making Test, part B, n (%)	Selective attention, shifting ability	19 (29.7)	21 (32.8)	13 (20.6)
Digit Span Test–forward, n (%)	Auditory attention, short-term retention	17 (26.6)	13 (20.3)	14 (22.2)
Digit Span Test– backward, n (%)	Verbal working memory	26 (40.6)	21 (32.8)	19 (30.2)
Rey Auditory Verbal Learning Test, trials I-V combined, n (%)	Immediate memory function, learning	11 (17.2)	6 (9.4)	1 (1.6)*
Rey Auditory Verbal Learning Test, delayed recall, n (%)	Delayed memory function	18 (28.1)	11 (17.2)	4 (6.4)*

Additional (not preplanned) analyses showed that patients treated with ANA exhibited a significantly lower prevalence of cognitive impairment in 5 out of 8 neuropsychological tests. Cognitive impairment was defined as decline from preoperative performance of >20%. *OPCAB*, Off-pump coronary artery bypass surgery; *CO_2FF*, off-pump coronary artery bypass surgery using CO_2 surgical field flooding; *ANA*, anaortic off-pump coronary artery bypass surgery. *The differences between Stroop Test part A, Stroop Test part B, Trail Making Test part A, Rey Auditory Verbal Learning Test trials I-V combined, and Rey Auditory Verbal Learning Test – delayed recall between ANA and OPCAB were statistically significant.

TABLE E4. Preoperative results of mood and neurocognitive tests

Test	OPCAB	CO_2FF	ANA
Hospital Anxiety and Depression Scale– Anxiety, mean ± SD or median (IQR)	6.7 ± 3.3	7.5 ± 3.1	7.0 (5.0-8.0)
Hospital Anxiety and Depression Scale– Depression, median (IQR)	4.0 (2.0-7.0)	4.0 (2.0-6.3)	4.0 (2.0-6.0)
Mini-Mental State Exam, median (IQR)	29.0 (28.0-30.0)	30.0 (28.0-30.0)	29.0 (28.0-30.0)
Stroop Test part A, median (IQR)	28.5 (25.0-33.0)	28.0 (23.0-32.0)	28.5 (25.0-33.0)
Stroop Test part B, median (IQR)	83.0 (66.0-96.5)	71.0 (61.0-82.0)	74.5 (63.0-89.5)
Stroop Test part B ≥20 errors, n (%)	8 (12.5)	4 (6.3)	8 (12.5)
Trail Making Test, part A, median (IQR)	42.5 (32.0-55.3)	37.0 (28.8-45.3)	39.5 (32.0-53.0)
Trail Making Test, part B, median (IQR)	93.5 (72.5-131.8)	84.0 (69.0-100.0)	89.0 (72.0-126.0)
Trail Making Test, part B, >300 s, n (%)	38 (59.4)	27 (42.2)	33 (51.6)
Digit Span Test–forward, median (IQR)	4.0 (4.0-5.0)	4.0 (4.0-6.0)	4.0 (3.8-5.0)
Digit Span Test–backward, median (IQR)	4.0 (3.0-5.0)	4.0 (3.0-4.0)	4.0 (3.0-5.0)
Rey Auditory Verbal Learning Test, trials I-V, combined score, mean ± SD or median (IQR)	33.2 ± 9.0	34.0 ± 7.3	32.0 (25.8-39.0)
Rey Auditory Verbal Learning Test, delayed recall, mean ± SD or median (IQR)	6.4 ± 2.7	6.9 ± 2.6	6.0 (5.0-8.3)

There were no statistically significant differences among the study arms. *OPCAB*, Off-pump coronary artery bypass surgery; *CO_2FF*, off-pump coronary artery bypass surgery using CO_2 surgical field flooding; *ANA*, anaortic off-pump coronary artery bypass surgery; *SD*, standard deviation; *IQR*, interquartile range.