

## Original Articles

# Incidence of Cerebral Microemboli in Single-Dose vs. Multidose Cardioplegia in Adult Cardiac Surgery

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**Abstract:** Cerebral microemboli have been associated with neurocognitive deficits after cardiac operations using cardiopulmonary bypass (CPB). Interventions by the perfusionist and alterations in blood flow account for a large proportion of previously unexplained microemboli. This study compared the incidence of microemboli during cardiac operations using conventional (multidose) and del Nido (single-dose) cardioplegia delivery. Transcranial Doppler ultrasonography was used to detect microemboli in bilateral middle cerebral arteries of 30 adult patients undergoing cardiac operations using CPB and aortic clamping. Multidose conventional blood cardioplegia (CBC) was used in 15 patients and single-dose del Nido cardioplegia (DNC) in 15. Manual count of microemboli during cross-clamp and during administration of cardioplegia was performed. Baseline preoperative characteristics were

similar between groups. There were no differences in the ascending aortic atheroma grade ( $1.4 \pm .4$  CBC vs.  $1.6 \pm .7$  DNC,  $p = .44$ ), bypass times ( $141 \pm 36$  minutes CBC vs.  $151 \pm 33$  minutes DNC,  $p = .64$ ), and cross-clamp times ( $118 \pm 32$  minutes CBC vs.  $119 \pm 45$  minutes DNC,  $p = .95$ ). The use of multidose CBC was associated with a seven-fold increase in the number of microemboli per minute of bypass ( $1.65 \pm 1$  vs.  $.24 \pm .18$  emboli/min DNC,  $p = .0004$ ). In this prospective pilot study, we found that the use of single-dose cardioplegia strategy led to fewer cerebral microemboli when compared with the traditional multidose approach. Our findings warrant further investigation of various cardioplegia strategies and neurologic outcomes in larger cohorts. **Keywords:** cardioplegia, cerebral microemboli, transcranial Doppler ultrasonography, cardiac surgery. *J Extra Corpor Technol. 2018;50:143–8*

## INTRODUCTION

Although advances in cardiopulmonary perfusion and surgical techniques have yielded persistent reductions in morbidity and mortality, the incidence of neurologic complications after cardiac surgery remains relatively high. Several studies have reported that 50–70% of patients exhibit cognitive deficits 1 week after coronary bypass operations (1,2), whereas 30–40% suffer from long-term cognitive impairment (3,4). Cerebral microemboli, gaseous and particulate both, have been widely implicated in the

etiology of these deficits with several studies demonstrating worse cognitive outcomes for patients with greater numbers of emboli (5–16). Nonetheless, there remains an element of controversy in the subject of post-cardiopulmonary bypass (CPB) cognitive decline as Selnes et al. showed that a similar incidence of cognitive decline occurs in non-surgical patients with comparable cardiovascular and cerebrovascular disease (6).

Emboli can be detected during cardiac surgery using transcranial Doppler (TCD) ultrasonography (1–16). Although many are associated with specific maneuvers, such as aortic cannulation and initiation of CPB (11–13), up to 50% of emboli on CPB are not coincident with surgical manipulation (13–15). Several reports have established a relationship between perfusionist interventions (including cardioplegia and drug administration) and increased number of emboli (17,18). Nonetheless, most of

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these interventions are necessary to provide myocardial protection and CPB. During the past three decades, multidose Buckberg “conventional” blood cardioplegia (CBC) has been the most commonly used method for myocardial protection for arrested hearts (19,20). More recently, however, the del Nido solution has gained popularity in adult cardiac surgery due to its less frequent administration and ease of delivery (20). Del Nido cardioplegia (DNC) also provides the benefit of quicker resumption of spontaneous regular cardiac rhythm (21,22). In addition to the potassium-mediated diastolic arrest achieved with CBC, DNC uses lidocaine and magnesium which have been shown to provide myocardial quiescence for 90–180 minutes in patients with acquired and congenital cardiac disease (21,22). Thus far, clinical outcomes using DNC have been acceptable and comparable with those obtained with CBC (19,20).

Although these distinct cardioplegia strategies have been compared with regards to myocardial injury and other clinical outcomes, potential differences in the number of cerebral emboli have not yet been evaluated. The present study was performed to prospectively compare the incidence of cerebral microemboli as detected by TCD during adult coronary artery bypass grafting (CABG) and valve surgeries using multidose CBC and single-dose DNC cardioplegia strategies.

## METHODS

From July to August 2016, 40 consecutive adult patients (age 18 years or greater) undergoing elective cardiac operations were consented and considered for the study. Patients were excluded if they had cranial anomalies, decubitus ulcers on the head, and unusable or inadequate TCD signals from the middle cerebral artery (MCA). After these exclusions, 30 subjects remained and were included for analysis. The study was approved by the Institutional Review Board at the University of California, Los Angeles, and written informed consent was obtained for each patient. Clinical characteristics were extracted from the electronic medical records for all patients. Statistical analysis was performed using STATA (StataCorp, College Station, TX) with the application of the independent sample *t*-test for unequal sample size and Fisher’s exact test, as appropriate. An alpha of less than .05 was considered significant.

### Anesthetic Management and CPB

Anesthetic management consisted of induction with a combination of opiates, benzodiazepines, and propofol followed by maintenance with isoflurane/sevoflurane and propofol. All patients received a Swan–Ganz catheter placed through the right internal jugular vein, a peripheral

IV placed through the left/right antecubital fossa, and an arterial line placed through the left/right radial/femoral arteries.

The CPB circuit consisted of an Affinity Fusion Hard-shell Venous reservoir (Medtronic Inc., Minneapolis, MN), an Affinity NT Hollow Fiber Membrane Oxygenator (Medtronic Inc.), a 32- $\mu$ m Affinity Arterial Filter (Medtronic Inc.) and a nonpulsatile arterial roller head pump on a Terumo Advanced Perfusion System 1 Heart Lung Machine (Terumo Corp., Tokyo, Japan). CPB was established with arterial inflow via cannulation of the ascending aorta with a 20 F Optisite Cannula (Edwards Lifesciences, Irvine, CA) and venous drainage through a single dual-stage/triple-stage, or bicaval right angle metal cannulae. The priming volume for the circuit ranged between 600 and 700 mL, and mean arterial pressure (mmHg) was maintained at 50–60 mmHg with CPB flow rates between 1.8 and 2.3 L/min/m<sup>2</sup>. The level in the reservoir ranged between 300 and 3000 mL, when cardioplegia was given. Heater Cooler Sorin T3 (LivaNova, London, England) was used. Systemic cooling was performed at the discretion of individual surgeons, with a minimum systemic temperature of 33°C (range 33–34°C) (bladder). Patients were rewarmed to 36–37°C with an average maximum CPB arterial perfusate during rewarming of 36°C (34.0–37.0°C). Blood gases were controlled in the course of cooling with the  $\alpha$ -stat strategy and hematocrit was maintained >20%. In all recorded cases, no (red blood cells, fresh frozen plasma, platelets, cryoglobulin) were used. Albumin 25% was used in all recorded cases (range 100–200 mL). On CPB, isoflurane inhaled anesthetic (1–5%) was used. Perfusionists administered drugs into the bypass circuit using a manifold directly connected to the top of the venous reservoir.

### Cardioplegia

The cardioplegia circuit uses two tubes of varying diameters and a single roller pump to create the admixture. The blood component is drawn from the arterial line before the 30-micron filter. Patients received either DNC or CBC administrations at the discretion of the operating surgeon. Both CBC and DNC solutions were composed of oxygenated blood and crystalloid, albeit in differing concentrations. The blood:crystalloid ratio was 4:1 for CBC and 1:4 for DNC. The temperature of cardioplegia at administration ranged between 2 and 6°C in both CBC and DNC groups.

Two different cardioplegia techniques were used: antegrade through the aortic root and retrograde via the coronary sinus. Patients in both groups received antegrade and retrograde doses. In the DNC group, cardioplegia was administered every 80–90 minutes vs. every 15–20 minutes in the CBC group. No other perfusion interventions took place while cardioplegia was given.

### Transcranial Doppler Detection and Analysis of Microemboli

TCD was performed using a Terumo 150 PMD multirange, multifrequency transcranial Doppler device (Spencer Technologies, Seattle, WA). The probes of the device were fixed trans-temporally by a head brace. Doppler recordings of bilateral middle cerebral arteries were obtained through the temporal window (Figure 1).

Recordings began during sternotomy and concluded following arterial decannulation. We calculated the total emboli for three phases: during surgical interventions, during perfusionist interventions, and at baseline. Surgical interventions were defined as the 60-second period following aortic cannulation or decannulation, cross-clamp application/removal, and starting or stopping CPB. Perfusionist interventions were defined as the 60-second periods following cardioplegia or drug administration. Baseline was defined as all other time periods during CPB.

Each event type described previously was time-stamped on the TCD machine in real-time while in the operating room. We used a detection threshold over baseline of 12 dB, as previously validated (23–25). TCD time stamping was performed by a single medical student, who was trained by an attending cardiac surgeon familiar with the TCD machine use, before study initiation.

### RESULTS

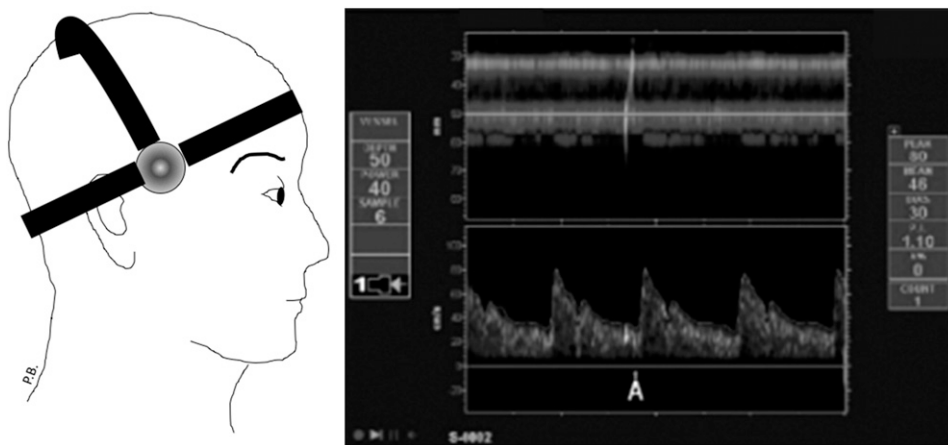
Of the 30 patients included for analysis, 15 received single-dose DNC and 15 multidose CBC. No pre-procedural differences were noted between the groups, including grade of ascending aortic atheroma, ejection fraction, age, gender, body mass index, hypertension, dyslipidemia, diabetes mellitus, and chronic lung disease. Intraoperative variables—type of procedure, CPB, and

cross-clamp times—were not statistically different as shown in Table 1.

In operations (CABG, aortic valve replacement (AVR), mitral valve replacement (MVR), AVR + MVR, and AVR + MVR + CABG) in which DNC was used, two doses were administered (antegrade and retrograde routes with first dose, antegrade route only with second dose) throughout the operation for a total volume ranging between 1,450 and 1,700 mL. In operations in which multidose CBC was used, an average of seven doses were administered (retrograde and antegrade routes used with every dose) throughout the operation for a total volume ranging between 3,300 mL and 4,300 mL. Therefore, on average, multidose CBC was dosed 3.5× more frequently than single-dose DNC.

Cerebral microemboli were detected in all patients. Total cumulative number of emboli ranged between 140–710 in the single-dose DNC group and 320–1,335 in the multidose CBC group. The relative proportion of microemboli detected during various phases of the operation is shown in Figure 2 for both groups. Aside from periods of cardioplegia administration, the comparison of total microemboli associated with other events revealed no statistically significant differences between groups.

Use of multidose CBC was associated with a seven-fold increase in the number of microemboli per minute of bypass ( $1.65 \pm 1$  vs.  $.24 \pm .18$  emboli/min DNC,  $p < .0001$ ). Microemboli were recorded on the TCD with each cardioplegia administration. Moreover, in both groups, fewer microemboli per minute were detected during antegrade cardioplegia than retrograde cardioplegia (Figure 3). Postoperative clinical outcomes, including lengths of hospitalization ( $11 \pm 1$  days CBC vs.  $11 \pm 2$  days DNC,  $p = 1.0$ ) and intensive care unit stay ( $6 \pm 1$  days CBC vs.  $6 \pm 1$  days DNC,  $p = 1.0$ ) were similar between groups. There was no incidence of inpatient mortality, myocardial infarction, or stroke.



**Figure 1.** Left: TCD probes positioned and secured bilaterally over temporal regions. Right: TCD imaging showing flow through the MCA. The arrow labelled “A” shows the point where a microembolus has caused disruption of the signal.

**Table 1.** Operative characteristics.

	CBC (n = 15)	DNC (n = 15)	p-Value
Type of procedure:	–	–	.98
CABG only, n (%)	4 (26.7)	4 (26.7)	–
AVR only, n (%)	5 (33.3)	5 (33.3)	–
MVR only, n (%)	4 (26.7)	3 (20)	–
AVR + MVR, n (%)	1 (6.7)	1 (6.7)	–
AVR + MVR + CABG, n (%)	1 (6.7)	2 (13.3)	–
CPB time, (mean ± SD), min	141 ± 36	151 ± 33	.43
Cross-clamp time, (mean ± SD), min	118 ± 32	119 ± 45	.94
Intraoperative PRBC transfusion, (mean ± SD), units	0	0	N/A
Microemboli per minute (of CPB) (mean ± SD)	1.65 ± 1	.24 ± .18	<.0001

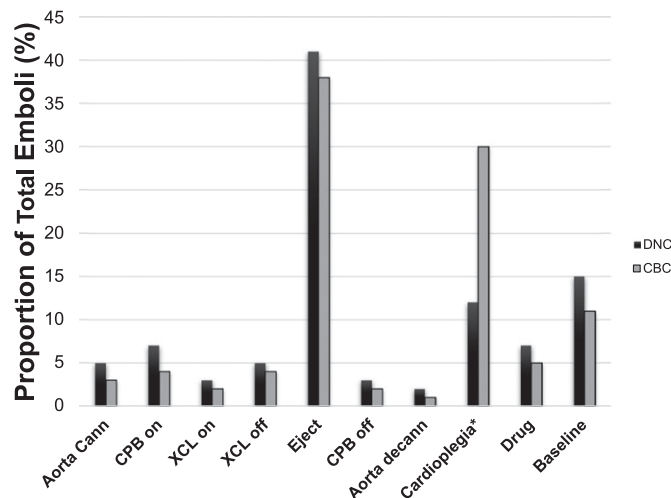
PRBC, packaged red blood cells.

**DISCUSSION**

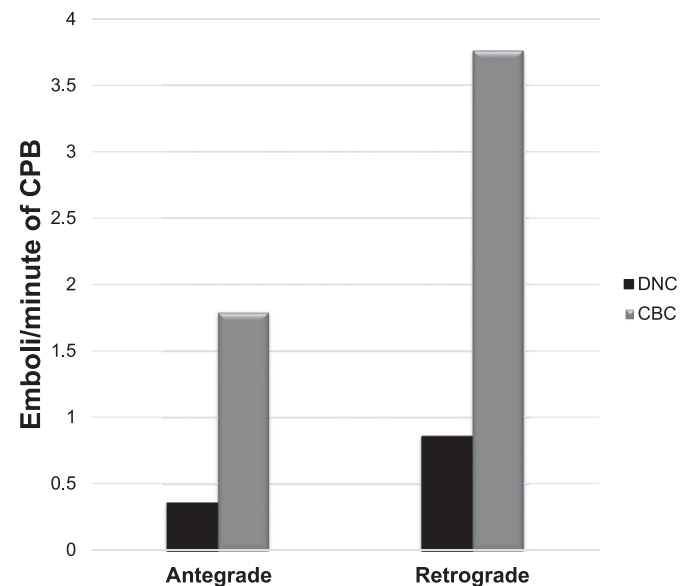
Cerebral microembolization has increasingly been imputed as an important cause for neurologic impairment after cardiac surgery. Fewer cerebral microemboli during CPB are associated with a lower incidence of neurologic impairment. Several studies have shown that a significant amount of previously unexplained microemboli are not directly associated with surgical manipulation (11–15). In the present study of adult cardiac surgical patients, administration of multidose CBC was associated with a 3.5-fold increased dosage frequency and a seven-fold increase in the number of TCD-detected cerebral emboli when compared with DNC. In agreement with Taylor et al., our investigation demonstrated substantial incidence of microemboli production associated with perfusionist interventions, including cardioplegia and drug administration (17). Interestingly, with regards to use of differing cardioplegia

strategies, we noted fewer emboli with single-dose DNC. Prior studies have shown that DNC is as safe as CBC and provides the benefit of quicker resumption of spontaneous regular cardiac rhythm (21,22). This study shows that DNC likely leads to vastly reduced number of emboli to its inherent nature of being re-dosed much less frequently, adding to the notion that “more is not always better.”

Some of the practical differences among these solutions are worth noting. Firstly, although both are mixed with blood, DNC uses a small proportion of blood that is drawn from the bypass arterial circuit before the arterial line filter. Secondly, inherent to its nature, DNC was re-dosed much less frequently, likely leading to the vastly different number of emboli between groups. Although CBC and DNC have been compared with regards to myocardial injury and other clinical outcomes, this study is the first to compare differences in cerebral embolization with various cardioplegia strategies.



**Figure 2.** Proportion of total microemboli detected during each event. Aorta cann, Aortic cannulation; XCL on, cross-clamp on; XCL off, cross-clamp off; Eject, start of cardiac ejection after cross-clamp removal; Aorta decann, aortic decannulation; Cardioplegia\*, cardioplegia administrations; Drug, drug administrations.



**Figure 3.** Average number of emboli per minute of CPB during antegrade and retrograde cardioplegia administrations.

Using TCD for the duration of the operation, our results indicate the highest number of emboli to occur after cross-clamp removal and at the onset of cardiac ejection, a finding corroborated by Linden and Casimir-Ahn (26). This likely represents ejection of gaseous rather than solid emboli from the aortic root and the heart itself (27). Interestingly, perfusionist interventions, including administration of cardioplegia, likely lead to production of gaseous emboli as noted by Borger and coworkers (18). Although gaseous emboli may be less detrimental than atherosclerotic debris, reduction in the number of cerebral emboli has been associated with improved neurologic outcomes (5–16).

The finding of more embolic events with retrograde cardioplegia is interesting and has also previously been reported by Baker (28). Although the true mechanism is unknown, this phenomenon may be explained by at least two hypotheses. Firstly, as suggested by Baker, retrograde cardioplegia may wash arterial atheromatous debris into the aortic root which then enters the circulation. By contrast, the debris transported by antegrade cardioplegia would likely get trapped in the capillary beds and not necessarily reach the systemic circulation. However, our finding of a higher number of emboli with retrograde cardioplegia in all patients including those free of significant coronary artery disease does not support this reasonable hypothesis. In addition, retrograde cardioplegia is scavenged via the aortic root vent, a small cannula with active suction on a partially collapsed root. This may lead to cavitation and entrainment of atmospheric air, leading to increased number of emboli in the reservoir. A study of various levels of suction on the aortic root may provide further insight into the observed difference in antegrade and retrograde delivery methods.

This study has several limitations. First, non-randomization which may lead to selection bias. However, patients were blinded, therefore, were unaware whether they were in the CBC or DNC group. Second, our study has relatively small sample size. However, its prospective nature and high fidelity recording of individual events might mitigate this constraint. Therefore, subclinical deficits might exist in this population. Nevertheless, based on previous work, reduction of cerebral emboli may lead to improved neurologic outcomes (5,6,8–11).

## CONCLUSION

In this prospective pilot study of adult CABG and valve patients, we found that the use of CBC was associated with a seven-fold increase in the number of TCD-detected cerebral microemboli as compared with the DNC cardioplegia strategy. This finding indicates that use of DNC or other solutions with less frequent administration may be an important factor in reducing incidence cerebral emboli.

Furthermore, retrograde administration of cardioplegia led to significantly more cerebral emboli than antegrade. Our findings warrant further investigation of various cardioplegia strategies and neurologic outcomes in larger cohorts.

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