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Microemboli are not associated with delirium after coronary artery bypass graft surgery

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Abstract

Delirium is an acute change in cognition which occurs frequently after coronary artery bypass graft (CABG) surgery. Cerebral microemboli, from plaque, air, or thrombus, have been hypothesized to contribute to delirium and cognitive decline after CABG. The purpose of this study was to determine if there was an association between cerebral microemboli and delirium after cardiac surgery. Non-delirious patients (n=68) were prospectively enrolled and underwent intraoperative monitoring of the middle cerebral arteries with transcranial Doppler (TCD). TCD signals were saved and analyzed postoperatively for microemboli manually, according to established criteria. Postoperatively, patients were assessed for delirium with a standardized battery. Thirty-three patients (48.5%) developed delirium after surgery. Microemboli counts (mean $\pm$ SD) were not significantly different in those with and without delirium (303 $\pm$ 449 vs. 299 $\pm$ 350; p=0.97). While intraoperative microemboli were not associated with delirium after CABG, further investigation into the source and composition of microemboli can further elucidate the long-term clinical impact of microemboli.

Introduction

Delirium, an acute deficit in attention and cognition, is a major cause of morbidity among hospitalized and post surgical patients. Published studies have identified that between 32-50% of elderly CABG patients develop significant delirium postoperatively^{1, 2}. Studies on general surgical patients have shown a significant relationship between delirium and surgical events, such as hypotension³, blood loss⁴, and hypothermia^{3, 5}, which are common during CABG.

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Delirium in surgical patients has demonstrated increased short-term and long-term mortality^{3, 6}, hospital length of stay⁷, and likelihood of being discharged to a nursing home.⁸

Direct cerebral tissue hypoxia from microemboli has been hypothesized to contribute to neurological changes following CABG⁹. Microemboli are gas bubbles, biological aggregates (i.e. coagulated thrombus) or inorganic debris (i.e. disrupted calcified plaque)¹⁰, which may cause subclinical damage that does not result in a clinical stroke. Microemboli have different echogenic properties than blood and can be detected non-invasively with transcranial Doppler ultrasound (TCD) during cardiac surgery, without harm or discomfort to the anesthetized patient^{11, 12}. The middle cerebral artery (MCA) is more readily insonated because the MCA is closer to the cranium than the anterior cerebral artery (ACA)¹³ and microemboli preferentially travel through the MCA as opposed to the ACA¹⁴. The region of brain fed by the MCA is responsible for many higher brain functions including language, executive function, and attention¹⁵; microinfarction of this region may cause delirium.

While prior work has assessed microemboli and postoperative cognitive dysfunction, the relationship between microemboli and delirium has not been studied. Delirium is generally considered an acute disorder of attention and level of consciousness, with reversible cognitive changes. However, delirium has been linked to longer term cognitive dysfunction.¹⁶

Additionally, delirium is a clinical diagnosis made at the bedside after briefly assessing a patient's attention, consciousness, and thought. Conversely, postoperative cognitive dysfunction is considered more subtle requiring sensitive neuropsychological assessments to be administered preoperatively and at least 3 months postoperatively.¹⁷ While the neuropsychological assessments can be administered at the bedside, analysis of these results frequently requires normative data and advanced statistical analysis beyond what is possible at the bedside. Attention is a key cognitive domain for both delirium and postoperative cognitive dysfunction, as well as, following instructions in the perioperative recovery, discharge, and rehabilitation periods after cardiac surgery. Thus, delirium and postoperative cognitive dysfunction may impact functional recovery after surgery.

The purpose of this study was to determine the relationship between microemboli during CABG surgery and postoperative delirium. We hypothesized that patients who developed delirium would be exposed to higher cerebral microembolic counts. Secondary aims were to look at the impact of carotid stenosis, ascending aortic plaque, as well as, cross clamping procedures on cerebral microemboli counts. We undertook a prospective cohort study to assess the relationship of microemboli and delirium.

Methods

Patient Recruitment

We recruited 80 participants undergoing CABG at the Veterans Administration Boston Healthcare System which serves as a tertiary referral center. The study cohort recruitment and flow data have been reported previously.¹⁸ Participants with delirium at baseline, those with inadequate TCD windows, and those who underwent valve replacement/repair or combined CABG-valve were excluded. All patients provided their written informed consent and the study was approved by the human subjects committee.

Microemboli Measurement and Counting

The number of bilateral MCA microemboli that occurred during cardiac surgery was measured using a Nicolette 8080 four-channel TCD system with 2MHz probes. We obtained bilateral intraoperative TCD signals of the middle cerebral artery M1 segment from the opening of the pericardium until the closure of the chest cavity. The TCD technologist kept a written log of

the course of events (application / removal of cross clamp) during the operation, as well as marking events on the TCD output. The TCD waveform data was saved for off-line counting of microemboli. Microemboli were counted manually using the criteria established by the Consensus Committee of the Ninth International Cerebral Hemodynamics Symposium¹⁹.

Delirium

A board certified physician administered a brief delirium assessment (<15 min) preoperatively and on postoperative days 2 and 5. Participants were not assessed on postoperative days 0 or 1 because of the intensive medical care required after the CABG procedure. Prior work has demonstrated that the peak prevalence of postoperative delirium is on postoperative day 2 and most delirium cleared by postoperative day 5^{3, 6}. A standardized mental status interview was conducted, which included the Mini Mental State Exam (MMSE)²⁰, digit span, the Delirium Symptom Interview²¹, and the Memorial Delirium Assessment Scale (MDAS)²². The MMSE is a 30-point standardized assessment of global cognitive function where higher scores indicate better cognitive function. Digit span is a assessment of attention in which patients are asked to repeat a series of random numbers forward and backwards. The Delirium Symptom Interview is a standardized questionnaire to elicit 8 features of delirium. The MDAS is a severity scale for delirium that requires additional attention testing (digit span). After the standardized assessment, delirium was assessed by the physician using the validated diagnostic algorithm of the Confusion Assessment Method²³, which requires an acute onset, inattention and either disorganized thinking or altered level of consciousness. The CAM has been shown to have a sensitivity of 94% and a specificity of 89% for the diagnosis of delirium²⁴.

Covariates

Demographic variables including age, sex, were collected from the patient. Information necessary to calculate the Charlson Comorbidity Index, a weighted scale of comorbidity which is associated with hospital mortality, was collected from the medical record²⁵. As a part of preoperative care, most patients underwent preoperative Duplex carotid ultrasound and the degree of carotid stenosis was reported by an independent radiologist²⁶. Additionally, most patients underwent intraoperative trans-esophageal echocardiogram as part of the routine operative procedure and the ejection fraction and degree of ascending aortic plaque were scored by an independent cardiologist²⁷. Additional operative data was collected from the operative report, anesthesiology flow sheet, and the perfusion record.

Operative procedure

Patients underwent general anesthesia with a standard protocol of induction, paralysis, and intubation. Anesthesia was induced with etomidate (0.3mg/kg) and midazolam (0.3 mg/kg). Paralysis was obtained with vecuronium. General anesthesia was maintained with inhaled isoflurane titrated as needed (0.3-1.5%) to maintain effect. The attending surgeon performed the operation with use of a single or serial cross clamp at his discretion. The perfusion strategy featured the following components: 1) closed cardiopulmonary bypass system to minimize the blood-gas interface; 2) low-normal systemic core temperature (>35°C); 3) low-dose heparin protocol using heparin-bonded circuits (Medtronic Inc., Minneapolis, MN); and 4) minimization of hemodilution elements. Initial cardiopulmonary bypass flow was 3.5 L/min. Cerebral oximetry (Somanetics Inc, Troy, MI) was performed on all patients. Flow velocity and partial pressure of carbon dioxide (pCO₂) were altered as needed to maintain cerebral oxygen saturation at ≥65%. To minimize air to blood interface and avoid stagnation of stored blood, a double-stage venous cannula; directional arterial cannula; and a collapsible, soft-shell, venous reservoir (Medtronic Inc., Minneapolis, MN) were used. To monitor anticoagulation, activated clotting time was monitored every 15 minutes and maintained near a goal of 250 seconds. To minimize hemodilution, the perfusion lines were kept short and the crystalloid

prime was replaced by retrograde filling of the circuit with the patient's blood resulting in a prime volume of ≤ 800 ml whenever clinically possible.

At the end of bypass, the HEPCON Heparin Management System (HMS) (Medtronic, Inc.) heparin-protamine titration assay was used to assess the circulating heparin level and to determine the precise dose of protamine necessary for heparin reversal. Aminocaproic acid (Amicar®, Xanodyne Pharmaceuticals, Inc., Florence, KY) at a dose of 10g was given at the same time of the initial heparin dose with another 10g dose given immediately after protamine administration. Additionally, field suction and blood remaining in the CPB circuit was directed to a cell saving device (Haemonetics Corp, Braintree, MA), processed into washed red cells suspended in saline (hematocrit 50-55%), and transfused to the patient upon cessation of CPB.

Power Analysis

The sample size ($n=68$) had sufficient power ($1-\beta=0.9$; $\alpha=0.05$) to detect a mean difference of 100 microemboli between the groups with and without delirium assuming that the standard deviation was half of the mean.

Analysis Plan

For the bivariable analysis, we compared those with and without delirium using a Student's t-test for continuous variables and a Chi-square for dichotomous variables. Microemboli counts are traditionally distributed nonparametrically (non-normal) with most participants having modest microemboli and a few participants with a large number of microemboli. To address the skew of the total microemboli counts, a Wilcoxon rank-sum test was used for dichotomous outcomes and a Kruskal-Wallis signed ranked test for categorical outcomes. Further, the counts were divided into tertiles and we examined the delirium rate with increasing microemboli tertile using a Chi-square test for trend. Multivariable analysis used logistic regression to adjust for variable which were associated with delirium. All statistical analyses were performed with SPSS v11.5 (SPSS Inc, Chicago, IL)

For secondary aims, we compared the microemboli counts in participants with carotid stenosis, ascending aortic plaque, and cross clamp and those without use using a Wilcoxon rank sum because of the nonparametric distribution.

Results

The overall population and specifically, those with and without delirium, is described in Table 1. Of the 80 patients enrolled, six patients were excluded because of inadequate TCD windows and 6 patients underwent valve procedures, yielding a final population of 68 participants. Thirty-three patients (48%) developed delirium on postoperative day 2. On postoperative day 5, twelve patients (18%) continued to have delirium. No patient without delirium on postoperative day 2 developed delirium on postoperative day 5. Patients with delirium tended to be older and have lower MMSE scores. Patients with carotid stenosis and moderate-severe ascending aortic plaque were more likely to develop delirium. Intraoperative factors such as duration of cardiopulmonary bypass, temperature, and hematocrit were not associated with delirium.

In the continuous analysis, microemboli were not associated with delirium (303 ± 449 vs. 299 ± 350 ; $p=0.97$). Figure 1 displays the microemboli counts in those with and without delirium. The analysis of microemboli tertiles found no significant association with microemboli and delirium (Table 2). Additionally, patients with persistent delirium (delirium on both postoperative days 2 and 5) had microemboli counts (339 ± 358) that were not significantly different ($p=.93$) than those with a transient delirium (only on postoperative day 2) (283 ± 501)

and those without delirium (299 ± 350). After adjustment for age, comorbidity, MMSE, carotid stenosis, and moderate-severe ascending aortic plaque, delirium was not associated with microemboli (adjusted Odds Ratio 0.5 per tertile increase, 95% confidence interval 0.2, 1.4).

The observed difference (4 microemboli) would have required over 160,000 participants to detect a significant change. Figure 2 describes the distribution of microemboli during the case. Most microemboli (82%) occurred while the patient was on cardiopulmonary bypass, particularly during the period in which the cross clamp(s) were applied (63%).

Microemboli significantly decreased with increasing ipsilateral carotid stenosis (<50% stenosis: 168 ± 245 microemboli; 50-69% stenosis: 123 ± 119 microemboli; >70% stenosis: 47 ± 41 microemboli; $p=0.02$). Also, ascending aortic plaque was not significantly associated with microemboli (moderate-severe plaque 412 ± 513 vs. less plaque 291 ± 387 ; $p=0.22$). The use of multiple cross clamps did not significantly increase the number of emboli (single clamp 383 ± 537 vs. multiple 244 ± 243 ; $p=0.92$).

Discussion

While delirium is common after cardiac surgery, this prospective study found that the number of cerebral microemboli was not associated with delirium after cardiac surgery. This is an important finding because the results are counter to a common belief that microembolization is a major contributor to postoperative delirium^{28, 29} and longer-term postoperative cognitive dysfunction¹⁰. While further study is necessary to confirm and validate these findings, future work should recognize the limits of establishing the causal link of microemboli and cognitive outcomes.

Intraoperative microemboli occur during nearly all cardiac surgical procedures^{30, 31}. The underlying pathophysiology where microemboli occlude a small arteriole suggests that there should be a detectable cognitive decline with increased microembolic load. In a recent systematic review, Martin and colleagues identified 14 studies which assessed perioperative cognitive function and microemboli and four of the fourteen studies found a relationship of cognitive function with intraoperative microemboli³². Of the 6 studies that assessed cognitive function in the early postoperative period (≤ 10 days), one found memory deficits were associated with microemboli³³ and another found general cognitive function was impaired³⁴. Thus, there is not clear and convincing evidence that microemboli are associated with delirium in the early postoperative period.

Delirium is a clinical syndrome that occurs when a predisposed patient is exposed to one or more noxious insults. Patients with more predisposing factors (preoperative cognitive impairment, poor function, prior stroke, or depression) are at higher risk² and will require fewer insults to precipitate delirium. Patients at low-risk are less likely to develop delirium despite the insults associated with cardiac surgery.³⁵ The balance between predisposing factors and precipitating stressors is highlighted in our study by carotid stenosis. Patients with increased atherosclerosis, measured by carotid stenosis or ascending aortic plaque, are at increased risk for delirium, because atherosclerosis is associated with preexisting cognitive impairments.³⁶ Prior work found that carotid stenosis >70% is associated with reduced flow¹⁸ and thus, reduced ipsilateral microemboli. While intraoperative microemboli, especially particulate emboli, may contribute to the operative stressors, they are unlikely to be the sole cause of delirium or cognitive impairment.

There are numerous other stressors delivered during perioperative period after cardiac surgery including: inflammation, anesthesia, psychoactive medications⁴, cardiopulmonary bypass, fluid shifts, transfusion, sleep deprivation, and pain. Patients at high risk are likely to develop delirium because of a combination of these insults, not the microembolic load alone. To

definitively establish a causal link between microemboli and postoperative cognitive impairment, future work will need to systematically address these factors.

There are several key points that our findings can contribute to future work examining the relationship between microemboli and cognition after surgery. First, delirium may be an important intermediary in the development of long-term functional and cognitive deficits. As such, studies of postoperative cognitive dysfunction should include a postoperative assessment for delirium. Second, because of the large number of perioperative factors that can cause delirium, studies will need to have sufficient power to simultaneously adjust for and assess the independent impact of multiple variables. Third, measuring microemboli in the MCA captures a proportion (>70%) of the microemboli traveling to the brain¹⁴, but the anterior and posterior cerebral arteries are additional pathways for microemboli to travel to the brain. Future studies could better elucidate the contribution of the anterior and posterior cerebral arteries. Fourth, the correlation of microemboli with markers of inflammation and cerebral injury would improve our understanding of the clinical impact of microemboli. Finally, the composition of the microemboli needs to be better elucidated, because particulate microemboli are less likely to be absorbed and more likely to cause brain injury than air microemboli. Dual phase TCD monitoring has been reported to distinguish the air from particulate microemboli.³⁷

There are strengths and limitations of this study which warrant mention. First, the study population consisted largely of men, which limits its generalizability. However, >70% of all cardiac surgery performed in the U.S. is performed in men.³⁸ Second, the cardiopulmonary bypass system used a low heparin protocol with biocompatible surfaces, which may have reduced microemboli from thrombus and potentially reduced our power to determine an effect of microemboli on delirium. Third, our detection and standardized counting of microemboli are considered the standard of practice and follow consensus recommendations. We counted microemboli from the opening to closing of the pericardium; however, other studies found cerebral microemboli during sternotomy.³⁹ Thus, our estimate of microemboli may be an underestimate, but this should not challenge internal validity because the counting was consistent across the population. Fourth, our assessment of delirium occurred with a sensitive, state-of-the-art battery, by a physician. This may account for the high delirium rate compared to other studies after cardiac surgery. Finally, our study is limited by the monitoring of delirium on postoperative day 2 and day 5 and would have benefited from daily postoperative monitoring. However, there is evidence in the literature that the peak incidence of postoperative delirium is postoperative day 2 and that the incidence of delirium on subsequent days is low.^{3, 6}

In conclusion, while microemboli are often hypothesized to cause cognitive changes after cardiac surgery, this prospective study found no relationship between intraoperative cerebral microembolic load and delirium after CABG surgery. Further investigation of the source, composition, and clinical impact of microemboli is needed to definitively determine the role of microemboli in postoperative cognitive changes after cardiac surgery.

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Figure 1. Microemboli counts and Delirium. The points indicate a wide distribution of microemboli counts in patients with and without delirium.

Figure 2. Distribution of Microemboli During CABG. Most microemboli occur the period when the cross clamp is applied.

Table 1

Characteristics of the Patients enrolled

Characteristic	Total Population (n=68) Mean (SD) n (%)	Delirium (n=33) Mean (SD) n (%)	No Delirium (n=35) Mean (SD) n (%)	p-value
Patient Characteristics				
Age (years)	70.7 (8.2)	75.1 (6.7)	66.5 (7.4)	<.001
Male	67 (98%)	33 (100%)	34 (97%)	.33
Charlson Comorbidity Index	3.0 (1.6)	3.4 (1.8)	2.7 (1.2)	.09
Body Mass Index (kg/m ²)	29.4 (6.2)	29.6 (6.6)	29.3 (5.8)	.87
Preoperative Mini Mental State Examination	26.5 (2.6)	25.8 (2.5)	27.2 (2.4)	.02
Carotid Stenosis*	31 (50%)	16 (76%)	5 (16%)	<.01
Ejection Fraction (%)	50 (10)	49 (10)	50 (10)	.71
Moderate-Severe Ascending Aorta Plaque [†]	14 (23%)	11 (38%)	3 (10%)	.03
Preoperative Hematocrit	39.3 (5.3)	38.8 (5.3)	39.7 (5.4)	.45
Operative Characteristics				
Operative Time (min)	260 (58)	259 (50)	261 (66)	.88
Cardiopulmonary Bypass Time (min)	93 (28)	94 (28)	92 (28)	.72
Cell Saver Volume (mL)	820 (170)	804 (175)	835 (166)	.47
Lowest Hematocrit (%)	25.7 (3.2)	25.7 (2.6)	25.6 (3.6)	.89
Lowest Core Temperature (°C)	34.7 (1.5)	35.0 (1.0)	34.4 (1.8)	.12
End Core Temperature (°C)	36.5 (1.0)	36.7 (0.8)	36.3 (1.2)	.10
Multiple Cross Clamp	38 (56%)	20 (61%)	18 (53%)	.53
Vessels Bypassed (#)	2.9 (0.6)	3.0 (0.5)	2.8 (0.8)	.14
Postoperative Day 1 Hematocrit (%)	31.8 (3.3)	31.6 (3.5)	32.1 (3.1)	.57

* 6 patients did not have Duplex carotid ultrasound

[†] 8 patients did not have intraoperative transesophageal echocardiography for ascending aortic plaque

Table 2

Microemboli and Delirium

	Delirium (n=33)	No Delirium (n=35)	p-value
	Mean (SD)	Mean (SD)	
Microemboli	303 (449)	299 (350)	.97
Microemboli Tertiles *			
<100 microemboli (n=22)	12 (36%)	10 (29%)	.60
100-299 microemboli (n=28)	14 (42%)	14 (40%)	
≥300 microemboli (n=18)	7 (21%)	11 (31%)	

* analyzed with a Chi-square trend test