Cerebral Microembolization during Primary Total Hip Arthroplasty and Neuropsychologic Outcome

A Pilot Study

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Abstract

Background Intraoperative cerebral microembolization occurs in a substantial proportion of patients undergoing THA. Historically, postoperative cognitive dysfunction has been attributed to different factors, including anesthesia, but the influence of the surgery has not been thoroughly examined.

Questions/purposes We conducted a prospective, controlled clinical trial to assess intraoperative cerebral microembolization during THA and neuropsychologic outcome.

Methods The presence of a patent foramen ovale (PFO) also was investigated, using transcranial Doppler, to determine whether this affected cerebral microembolic incidence and load and whether microemboli occurred as a

result of specific surgical activity. Forty-five patients were recruited who underwent THA and neuropsychologic assessment; a battery of tests was administered preoperatively and at 6 weeks and 6 months postoperatively.

Results Overall, patients showed improvement in total neuropsychologic change scores at both postoperative intervals. The incidence of cerebral microembolization for THA was 23%. The prevalence of PFO was 37%. PFO did not appear to influence microemboli load or incidence. More microemboli were seen during femoral component insertion and impaction.

Conclusions Intraoperative cerebral microembolization occurs in a substantial proportion of patients during THA recorded by transcranial Doppler. The microemboli load is low and is not influenced by the presence of PFO. Certain surgical activities seem responsible for greater cerebral microemboli generation. However, neuropsychologic outcome was not affected postoperatively by microemboli or other operative or patient variables.

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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Introduction

There is much published work on patients undergoing cardiothoracic surgery, the incidence of cerebral microembolization, and the consequent neuropsychologic (NP) decline after coronary artery bypass grafting surgery (CABG) [13, 46, 50, 55, 69, 72]. This decline is defined as an impairment of concentration, memory, learning, or the speed of mental and visuomotor responses (although not necessarily all of these). The problem of brain damage after CABG is multifactorial, involving microembolism, disturbed perfusion, metabolic derangement, and inflammatory responses. Risk factors for cerebral changes that

have been identified include older age, gender, neurologic disease, diabetes mellitus, and carotid and aortic atherosclerosis. Thus, changes in surgical technique such as the introduction of arterial line filters and membrane oxygenators have led to a reduction of microemboli and neuropsychologic disturbance [42].

The incidence of fat embolism during endoprosthetic surgery has long been recognized, in which, as a result of insertion of an arthroplasty component into the intramedullary canal, the pressure within that canal increases [15, 42, 63]. This seems to be the decisive pathogenic factor for development of fat and bone marrow embolism [16, 36, 41]. Furthermore, with the use of conventional cementing techniques, the intramedullary pressures are raised further and the major component of cement, polymethylmethacrylate, has been implicated in producing a hypercoagulable state local to the site of the operation and systemically through marrow embolization of tissue thromboplastin into the veins [16, 67, 70].

A couple studies [29, 68] reported the incidence of intraoperative cerebral microembolization (of fat and other particulate matter) during total joint arthroplasty as between 40% and 60%, but neither of these studies investigated the effect of microemboli on cerebral function postoperatively. The ultimate fate of these microemboli and their effect is unknown. Presence of embolic material in the right heart is well known during hip and knee surgery, but animal studies suggest microemboli deposition in several end organs, including the brain [3]. The route by which microemboli reach the end organs has been investigated [19, 22, 26, 53, 59] and as a result, several hypotheses have been proposed but none proven in humans. One proposed route of passage is transpulmonary, but much of this work thus far has been in an animal model [18–20]. The other proposed route of passage for microemboli is across a PFO (a congenital/neonatal conduit between the right and left chambers of the heart, which may persist asymptotically in adult life) [21, 39].

Anesthesiologists and surgeons have suspected for many years that some patients may experience a decline in NP outcome after an operation, so-called postoperative cognitive dysfunction. During the past 40 years, many studies have assessed the incidence of these features and attempted to analyze the relationship to the type of anesthesia [6, 11, 12, 37, 38, 40, 51, 57, 60, 64, 74]. The incidence is reportedly between 0% and 26%. Hole et al. [37] reported patients receiving general anesthesia showed poorer NP outcome when compared with those receiving epidural anesthesia for THA, but the NP testing in this study was not robust. Only the study by Williams-Russo et al. [74] used thorough NP testing and no major differences were seen when comparing the two methods of anesthesia for patients undergoing TKA. Overall, 5% of patients showed long-

term clinically important deterioration in cognitive function, and although methods of anesthesia were different, this may be the closest comparative result available. Despite radical changes in anesthetic practice with the development of new drugs and monitoring techniques that should have improved safety, the proportion of patients affected remains similar to earliest reports [12].

Therefore, the null hypotheses tested were (1) there will be no decline in NP outcome after THA, and (2) PFO does not influence cerebral microembolization incidence or load during THA. In addition, we asked (3) does a particular surgical activity during THA generate a greater number of cerebral microemboli, and (4) do any patient characteristics or surgical factors influence the incidence of microemboli or affect NP outcome?

Patients and Methods

We prospectively invited patients meeting specific criteria and scheduled for primary THA for osteoarthritis between December 2001 and December 2003 to participate in this study. The patients came from the waiting list of two consultant orthopaedic surgeons (FSH, AF). One hundred thirty-two patients were invited to participate. Fifty-two patients declined to participate. We recorded age and gender. We excluded patients who were unable to speak and read English (three) (this was essential for conducting NP testing and outcome measurement); patients with a history of transient ischemic attack or stroke or a history of cerebral injury or other ongoing cerebral disease, eg, tumor (one); patients with auditory or visual impairment (this again was essential for NP testing and outcome measurement) (two); patients with a history of or ongoing alcoholism; and patients with carotid artery stenosis. Thus, 74 patients initially were identified during a 24-month period and agreed to participate. Seven of the 74 patients had hip resurfacing; whereas preoperatively we anticipated performing a conventional THA, an intraoperative decision was made that resurfacing would be more suitable and in the best interests of the patients. These 74 patients then were excluded from the study. Of the remaining 67 patients, five were withdrawn from the study at the time of the first NP assessment owing to inability to complete the tests such that a meaningful score could not be obtained and 16 did not attend either of the followup NP assessments. One patient died postoperatively of unrelated causes. Thus, 45 patients were studied. Transcranial Doppler data were collected intraoperatively successfully for all 45 patients. The mean age for the study group was 69.9 years (SD, 9.6 years). Fourteen patients were male and 31 patients were female. There were 26 right and 19 left THAs. No patients were lost to followup. In

accordance with ethics guidance, we obtained fully informed consent from all patients. The trial was explained verbally to patients who then were given a written information sheet to read. Patients were requested to sign a consent form if they agreed to participate.

For patients undergoing THA, the type of prosthesis initially was predetermined using clinical and radiographic evidence. Three main choices of fixation for each component existed: fully cemented, fully uncemented, and hybrid (acetabular component uncemented, femoral component cemented). Once the fixation method was chosen, the prosthesis type was as follows: (1) fully cemented, Stanmore (Biomet, Swindon, UK) polyethylene acetabular component and Spectron (Smith & Nephew Orthopaedics, Warwick, UK) femoral component; (2) fully uncemented, Reflection (Smith & Nephew Orthopaedics) acetabular component and Synergy (Smith & Nephew Orthopaedics) femoral component; or (3) hybrid, Trilogy (Zimmer Ltd, Swindon, UK) acetabular component and Spectron (Smith & Nephew Orthopaedics) femoral component. Unless there was clear evidence intraoperatively that the fixation and prosthesis choices were unsuitable, as deemed by the consultant surgeon, the combinations of components were adhered to as stated previously. If a change was decided on to a prosthesis not listed or a different procedure, we excluded that patient from the study. Thirty-five patients received hybrid THAs, four received fully cemented THAs, and six received uncemented THAs.

All patients were graded preoperatively by the American Society of Anesthesiologists (ASA) grade [62]. Seven patients were ASA Grade 1, 30 were Grade 2, and eight were Grade 3.

Anesthesia induction was done using propofol (3–5 mg/kg). The trachea was intubated with a cuffed oral endotracheal tube. We used intermittent positive pressure mechanical ventilation titrated to maintain an end tidal CO₂ of 4.2 to 4.5 kPa. Maintenance was with a mixture of O₂, air, and desflurane. Although propofol (and etomidate and thiopentane) has potential neuroprotective effects, they are unproven, particularly in humans [30, 31, 43].

A lateral incision was used for all patients. One surgeon used a posterior approach and an anterolateral (Hardinge) approach was used by the other surgeon. There is no evidence to suggest the difference in approach has any effect on microemboli genesis and distribution. The acetabulum was prepared first followed by the femur in all cases. In the cases in which cement was used, third-generation cement mixing techniques were used because the literature supports improved outcomes with these techniques [5, 48].

We used intraoperative transcranial Doppler (TCD) to measure cerebral microemboli load [4, 52]. Monitoring was continuous, beginning before the operation started, ie, before the skin incision, and continuing until no

microembolus had been detected for 2 minutes and when the patient was returned to the supine position after THA. The Doppler machine used was a Nicolet EME Pioneer 2020 transcranial Doppler system (Cardinal Health, Warwick, UK). The middle cerebral artery was insonated using a 2-MHz pulsed-wave transducer and the probe was secured to the skull using an elastic head set, which allowed for prolonged monitoring. The side of the skull insonated was dependent on which hip was being replaced; thus, 26 right and 19 left sides were used for obtaining a TCD trace during THA.

The procedure was subdivided into six phases: femoral osteotomy, acetabular reaming, acetabular component impaction, femoral canal reaming, femoral component insertion, and joint relocation. This enabled relationships between specific surgical activity and microemboli load to the brain to be assessed. The duration of each phase also was noted. The period termed “other time” constitutes the time between surgical stages and the time from joint relocation to skin closure.

Microembolic events were recorded on videotape for subsequent playback and analysis. One of us (RP) counted the microemboli manually “offline” (ie, after the operation) using their unique auditory and visual characteristics. International consensus criteria were used for defining microemboli [61].

The testing for PFO was as follows: microcavitation saline contrast was generated by mixing 9 mL of normal saline and 1 mL of air between two 20-mL syringes connected to a three-way stopcock. The contents of the syringes were exchanged rapidly between each other at least 10 times. After preparation, the contrast was injected as a bolus immediately with a 2-minute interval between each test. A Valsalva maneuver was created by increasing and holding end inspiratory pressure. This was facilitated in the intubated patient by positive pressure ventilation for 5 seconds after the start of the injection and released after 5 seconds had elapsed. The diagnostic window for a microemboli signal to appear was 25 seconds after injection. One or more microembolic signals in the diagnostic window were deemed a positive result. If a positive test occurred, no additional tests were done. We performed three such tests [28]. All testing was performed before surgery started.

Two trained psychologists (JS, JH) did all NP tests and, as much as was practically possible, the same psychologist saw the same patients at the followups. All patients were brought from the ward to the same room where the tests were performed under relaxed conditions preoperatively and from the outpatients’ setting after their consultation with the surgeon (RP).

A battery of nine NP tests was administered on each occasion. The tests selected are widely used for CABG, are

sensitive to change after cardiac surgery [50], and can be performed in the limited time available. The battery consisted of (1) the New Adult Reading Test [49], which was administered preoperatively to obtain an estimation of premorbid IQ; (2) the Rey Auditory Verbal Learning Test [58] which is widely used and involves free recall after repeated verbal presentation of a 15-word list. The total number correctly recalled during the first five trials (verbal learning) and the change between Trials 5 and 7 (delayed recall) are recorded; (3) the Non-Verbal Recognition Memory Test [55] is a computerized timed recognition memory test; (4) Trailmaking A and the following test originally formed part of the Army Individual Test Battery [1] and aim to assess motor speed, attention, and mental flexibility; (5) the Letter Cancellation Test [45] is a paper and pencil task consisting of cancelling a random target letter from rows of letters; (6) the Symbol Digit Replacement Test is a computer-driven task adapted from the paper and pencil version devised by Smith et al. [65], which requires the participant to pair 45 precoded digits with symbols; (7) the Choice Reaction Time Test [49] is a computerized task in which participants are required to discriminate and respond as quickly as possible to two letters (A and B), which are displayed randomly on a computer screen; and (8) Grooved Pegboard—Dominant and Non-dominant [45] is a timed test of manual dexterity and complex fine-motor coordination discriminating differences in right and left hemispheric performance.

All tests were performed preoperatively (usually the day before surgery), 6 to 8 weeks postoperatively, and 6 months postoperatively. The postoperative tests were performed on the day the patient returned for routine followup.

Quality of Life (QoL) was assessed using the EuroQol (EQ-5D) score. EQ-5D (as the descriptive measure is known) [56] is a standardized instrument for use as a measure of health outcome. Scores range from −0.594 (poor) to 1.000 (best outcome) using the UK value set. It has been used extensively and validated in orthopaedic use against other existing QoL measures [14, 17, 33, 56].

Orthopaedic outcome was measured using the WOMAC [7–10], the Harris hip score [35] (HHS), and the Oxford Hip Score [23] (OHS). In contrast to the HHS, the patient completes the OHS. Its validity and reliability have been assessed in comparison to the SF-36 and Charnley hip scores with excellent results [23–25, 47]. In addition, operation time, any complications, and days to discharge were recorded for each patient.

At the 6-week followup, NP tests, WOMAC, and EuroQol were reassessed. At the 6-month interval, NP tests, WOMAC, EuroQol, HHS, and OHS were administered. The author (RP) performed all orthopaedic outcome measures, except the OHS, which is self-administered.

Data were assessed for parametric or nonparametric conformity. The appropriate statistical test in each case then was used. One patient (H2) had a considerably larger number of total microemboli than other patients in the group. She underwent a hybrid THA. Because of this apparent anomalous result, we analyzed the total microemboli count including and excluding this patient.

The primary outcome measure of the study was the standardized change (Z) score [2]. Z scores were calculated for individual tests and to give a total Z score for each group using the SD of the preoperative group performance. The Z score was calculated as $z = (X2 - X1)/\mu SD1$, where X1 is the preoperative score and $\mu SD1$ is the SD of the preoperative group scores. A higher postoperative score gives a positive Z score and a lower postoperative score gives a negative Z score. However, some of the tests are timed tests and a better performance is reflected in a lower time score. Therefore, X2 and X1 are swapped for timed tests to ensure positive Z scores consistently indicate improved performance. The Z change scores represent the performance of the group collectively. In the THA group, some patients will have shown a deficit on their NP tests at either of the followups or both. A deficit is defined as a decline by one or more SD in two or more tests. The performance of these individuals may be masked by the overall trend of the group. From previous published data, we assumed that 40% would have microemboli (30). Assuming those with microemboli would have a 25% incidence of NP deficit, and those with no microemboli would have a 5% incidence of deficit, a total of 75 patients would be required to show this difference in incidence with 80% power at the 5% significance level. The effect size is implicit in the difference between the two incidences, equivalent to a relative risk of five.

The presence of PFO and higher microemboli counts was assessed using the independent t test. The Friedman test also was used to compare the effect of different surgical activity on microemboli generation. Pearson's correlation coefficient was determined on each occasion to assess whether greater total microemboli counts related to age, operative time, or discharge day. The Kruskal-Wallis test was used to determine whether increasing ASA grade or the use of cement related to the presence of microemboli.

Results

The incidence of cerebral microembolization was 23% (n = 10). We observed no decline in the mean NP outcome after primary THA (Table 1). Rather, there was an overall trend toward improvement in the study population on most NP tests (Fig. 1).

Table 1. Mean (SD) neuropsychologic test scores (raw) and mean z change scores for all patients at each interval

Test	Preoperative	6 weeks postoperative	6 week postoperative z score	6 months postoperative	6 month postoperative z score
Choice Reaction Time Test (seconds)*	0.63 (0.22)	0.57 (0.15)	0.14	0.61 (0.22)	-0.004
Grooved Peg Board Test D (seconds) [†]	86.39 (25.48)	84.26 (18.75)	0.02	77.65 (14.48)	0.26
Grooved Peg Board Test ND (seconds) [†]	92.84 (24.51)	97.94 (28.70)	-0.22	88.33 (21.83)	0.16
Letter Cancellation Test (seconds) [†]	85.18 (21.61)	86.40 (22.54)	-0.11	92.30 (23.23)	-0.29
Non-verbal Memory Test (seconds) [†]	80.22 (19.19)	82.35 (23.13)	-0.11	81.24 (21.87)	-0.05
Rey Auditory Verbal Learning Test 1-5 [§]	40.56 (10.59)	43.31 (10.52)	-0.28	44.69 (10.64)	-0.43
Rey Auditory Verbal Learning Test 7-5	-1.44 (2.35)	-2.14 (1.77)	0.17	-2.00 (2.22)	0.25
Symbol Digit Replacement Test (seconds) [†]	208.35 (97.51)	172.31 (44.70)	0.19	169.83 (43.22)	0.20
Trail Making Test A (seconds) [†]	42.47 (13.66)	36.36 (11.18)	0.37	35.48 (12.32)	0.45
Trail Making Test B (seconds) [†]	97.07 (42.60)	77.13 (27.04)	0.12	78.08 (26.04)	0.11
New Adult Reading Test [¶]	33.40 (11.43)				
Speilberger Anxiety Trait	35.75 (8.60)				
Speilberger Anxiety State [¶]	10.47 (4.42)	8.86 (2.90)		8.74 (2.74)	
CSED Depression score [¶]	13.38 (9.10)	11.80 (9.95)		9.52 (7.07)	
Total Z score			0.27		0.12

* Mean response time; [†]time to completion; [‡]total answer time; [§]total number of words recalled in five trials (maximum, 75); ^{||}change in total number of words recalled between Trials 5 and 7; [¶]score on measure; D = dominant; ND = nondominant.

Fig. 1 The mean Z change scores for all neuropsychologic tests at 6 weeks and 6 months postsurgery are shown.

We observed no relationship ($p = 0.23$) between the presence of a PFO and a higher total microemboli count using an independent t test on each occasion. Exclusion of the outlier did not alter the significance of the relationship ($p = 0.21$). The prevalence of PFO was 37% in this study group. The median microemboli count was zero. We

Table 2. Mean (SD) time for each surgical stage and mean emboli load generated during each stage

Stage	Time (minutes/seconds)	Microemboli	Microemboli excluding outlier
Femoral osteotomy	0.48 (0.59)	0 (0)	0 (0)
Acetabular reaming	6.49 (3.46)	0.1 (0.7)	0.03 (0.2)
Acetabular component impaction	4.01 (5.53)	0.5 (2.5)	0.13 (0.8)
Femoral canal reaming	10.22 (9.00)	0.9 (5.3)	0.03 (0.2)
Femoral component impaction	6.09 (1.14)	6.6 (39.5)	0.31 (1.2)
Joint relocation	0.52 (1.57)	0.2 (0.9)	0.11 (0.5)
Other time	72.24 (14.41)	5.8 (24.1)	2.5 (11.9)

Mean time for each surgical stage is similar when excluding the outlier, therefore, not shown.

regrouped the population into those who showed no microemboli and those who did; the presence of a PFO did not confer any increased likelihood ($p = 0.12$) of having microemboli.

Femoral component insertion (and the cement setting time, if used) generated the most ($p = 0.76$) emboli on average (Table 2). It is evident that a substantial proportion of microemboli was detected during the collective period “other time,” ie, the time between stages (Fig. 2). However, no obvious pattern was elicited when analyzing the

Fig. 2 The total microemboli load for each surgical stage during THA is shown. FNO = femoral neck osteotomy; AR = acetabular reaming; AI = acetabular component impaction; FR = femoral reaming; FCI = femoral component insertion; JR = joint relocation.

Table 3. Mean (SD) preoperative and postoperative quality-of-life and orthopaedic outcome measure scores

Score (minimum-maximum)	Preoperative	6 weeks	6 months
EuroQol (0–1.000)	0.450 (0.290)	0.710 (0.236)	0.900 (0.171)
WOMAC (0–96)	48.4 (13.4)	29.0 (14.5)	14.9 (12.8)
Harris hip score (0–100)	52.2 (12.6)		81.8 (12.6)
Oxford hip score (12–60)	39.2 (6.7)		23.4 (8.9)

For the WOMAC score, 0 is the best score, reflecting low disability and pain; for the EuroQol score, 1.000 is the best result; for the Oxford hip score, 12 is the best score, ie, the disability caused by the hip is low; the Harris hip score results can be stratified as excellent (90–100), good (80–89), fair (70–79), and poor (less than 70); 6.7% of patients were Trendelenburg-positive, 46.7% level and 37.8% negative at 6 months.

TCD recordings for these microembolic signals; ie, clusters of microemboli were not noticed between the same surgical steps.

We observed no correlation among total microemboli and age ($R = 0.09$; $p = 0.60$), operative time ($R = 0.03$; $p = 0.80$), or discharge day ($R = 0.22$; $p = 0.20$). Furthermore, rank ordering the microemboli counts for patients undergoing THA suggested a particular ASA grade did not influence ($p = 0.60$) the number of microemboli. Finally, excluding the outlier, the use of cement was not related ($p = 0.30$) to the presence cerebral microemboli.

Good QoL and orthopaedic outcome were apparent at the 6-month followup (Table 3).

Discussion

Cerebral microembolization does occur in a substantial proportion of patients undergoing THA [29, 59]. Studies

have attempted to analyze NP outcome, but often the tests used have been unvalidated and perhaps insensitive to the subtle changes in cognitive function that occur. Furthermore, neither the influence of the surgery on cerebral microemboli generation nor the influence a PFO may have on the incidence of cerebral microembolization has been studied. Thus, we wanted to examine NP outcome after THA using validated methods, assess the influence of PFO, specific surgical activities, and patient characteristics on the incidence and load of cerebral microembolization and NP outcome.

There are several limitations of this pilot study worth noting. First, our power calculations show our sample size to be smaller than required. Thus, it is possible the null hypotheses are accepted simply because of low patient numbers; however, there was no borderline significance in any statistical analysis we performed and we suspect larger, adequately powered studies would confirm our findings. Second, the numbers of fully cemented and fully uncemented THAs were low and thus any analysis of these subgroups must be interpreted with caution. We also recognize that fully uncemented arthroplasty is the most common type performed in patients in the United States, and although its popularity with surgeons is increasing in the United Kingdom, at the time of this study, the surgeons at our institution performed hybrid THA in the majority of patients.

The most important finding of our study is NP performance does not worsen as a consequence of arthroplasty. Z change score analysis showed a trend toward improvement in most tests for patients undergoing THA. The learning effect seems well proven because most patients improved between repeat assessments. NP outcome, in short, may be influenced by several factors: methods of testing (ie, appropriate tests, test conditions, effect of the postoperative period including pain and physical limitations), test variables (ie, postoperative testing intervals, test length and difficulty, learning effect), and patient variables (ie, age, gender); we accept that refinement of the existing battery of tests may be necessary to make them more sensitive.

We found no correlation between the presence of PFO and increased incidence and higher load of cerebral microemboli using the independent t test. Patients who were PFO-positive and -negative had cerebral microembolization. The overall prevalence of PFO in the study population was 37%, similar to that of the general population [34]. Few studies implicate PFO as a possible conduit for embolic material to reach the systemic circulation [22, 26, 27, 53, 71, 73], but no study attempted to identify the presence of PFO in vivo using validated techniques. After the findings in the study by Byrck et al. in mongrel dogs, hypothesizing that transpulmonary passage of fat emboli was possible, PFO may not be the only route available for

passage of microemboli into the systemic circulation [18]. We presume that even in the presence of a PFO, emboli are unlikely to traverse this conduit, because pressure gradients across the chambers of the heart are unfavorable. However, in some patients (low systemic arterial pressure), threshold pressures may be reached and intracardiac blood flow altered to facilitate passage of emboli from the right to the left side of the heart, but this likely is infrequent, particularly in the setting of elective surgery and controlled anesthesia. This may explain low cerebral microembolic load even in patients in this study who were PFO-positive. Therefore, it appears that the respiratory system may be responsible for effectively filtering the microembolic load generated by arthroplasty, adding weight to the hypothesis proposed by Byrick et al. [18], especially if threshold loads are reached to allow transpulmonary passage of emboli or diseased lung states confer poorer filtering capacity. It also may be plausible that pulmonary filtering of emboli eventually causes an increase in right-sided intracardiac pressure, which may facilitate right to left shunting of blood flow through a PFO.

In relation to specific surgical steps for THA and microemboli load recorded, impaction of the femoral component (with or without cement) was associated with the greatest mean microembolic load. The total number of microemboli was high for this stage (259), but this was contributed to in large part by the outlier; removing the contribution from the outlier, the total dropped to 12, still greater than any other surgical step. This result correlates well with reported mechanisms [15, 42, 54, 63, 66, 67, 70]; the decisive pathogenic factor is the increase in intramedullary pressure. With the surgical activity findings in mind, it may be pertinent to suggest surgical techniques to reduce the increase of intramedullary pressure in the case of THA (such as the bone vacuum venting technique described by Pitto et al. [54]) may minimize microemboli generation and subsequent passage into the circulation, thereby minimizing complications and sequelae of microemboli in the end organs and optimizing outcome. Analysis of the videotapes was performed to ensure that clusters of emboli were not seen between certain surgical stages, ie, microemboli in the period "other time." No pattern was uncovered and we assume there to be a steady generation of emboli during THA, which is enhanced by specific surgical activity.

The outlier in the study group showed considerably greater microemboli than any other patient (438), but this did not alter the analyses of any group relationship with other variables. In this patient, we identified no patient characteristics, intraoperative events, or other predisposing factors that may have influenced this result. The outlier's NP performance showed improvement between the intervals and this suggests the relationship between microemboli and NP outcome is complex as established by

numerous studies in cardiac surgery, most pertinently, a study by Whitaker et al. investigating the effect of a leukocyte-depleting filter on cerebral microemboli and NP outcome in CABG [72]. They reported a reduction in microemboli but no major improvement in NP outcome. They postulated such filters may be neuroprotective but other mechanisms may play a role in cerebral injury during CABG.

The use of cement during arthroplasty and the consequent effect on cerebral microembolization were analyzed. Unfortunately, the numbers in the fully cemented and fully uncemented groups were low, but nevertheless, analysis revealed no relationship between fixation method and microemboli generation. The use of cement has been implicated in the etiology of postoperative deep venous thrombosis and fat embolism syndrome in numerous studies [32, 44, 73, 75]. The pathophysiology of systemic polymethylmethacrylate and its thrombogenic properties is complex and not fully understood; some authors believe cement is not responsible for activation of clotting pathways, whereas others do. This study suggests the use of cement does not considerably influence cerebral microembolization. It is the increase in intramedullary pressure that is responsible for embolization to occur, which may be irrespective of cement use. However, cement may trigger clotting and other physiologic cascades, which in turn may heighten this response.

Using standardized Z change scores, we found no conclusive evidence THA negatively affects NP outcome. No relationship was found between the presence of PFO and cerebral microemboli incidence or load. A substantial proportion of microemboli was recorded after femoral component insertion during THA, and the use of cement did not influence microemboli incidence or load. Additional study is needed to explore the relationship of surgical activity and cerebral microembolization, perhaps with the inclusion of modifications to surgical technique.

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