Intraoperative Magnesium Administration Does Not Improve Neurocognitive Function After Cardiac Surgery

Joseph P. Mathew, MD, MHSc; William D. White, MPH; David B. Schinderle, MD; Mihai V. Podgoreanu, MD; Miles Berger, MD, PhD; Carmelo A. Milano, MD; Daniel T. Laskowitz, MD; Mark Stafford-Smith, MD; James A. Blumenthal, PhD; Mark F. Newman, MD; for the Neurologic Outcome Research Group (NORG) of The Duke Heart Center

Background and Purpose—Neurocognitive decline occurs frequently after cardiac surgery and persists in a significant number of patients. Magnesium is thought to provide neuroprotection by preservation of cellular energy metabolism, blockade of the N-methyl-D-aspartate receptor, diminution of the inflammatory response, and inhibition of platelet activation. We therefore hypothesized that intraoperative magnesium administration would decrease postoperative cognitive impairment.

Methods—After approval by the Duke University Health System Institutional Review Board, 389 patients undergoing cardiac surgery were enrolled in this prospective, randomized, double-blind, placebo-controlled clinical trial. Subjects were randomized to receive magnesium as a 50 mg/kg bolus followed by another 50 mg/kg infusion for 3 hours or placebo bolus and infusion. Cognitive function was assessed preoperatively and again at 6 weeks postoperatively using a standardized test battery. Mean CD11b fluorescence and percentage of platelets expressing CD62P, which are markers of leukocyte and platelet activation, respectively, were assessed by flow cytometry as a secondary outcome. The effect of magnesium on postoperative cognition was tested using multivariable regression modeling, adjusting for age, years of education, baseline cognition, sex, race, and weight.

Results—Among the 389 allocated subjects (magnesium: n=198; placebo: n=191), the incidence of cognitive deficit in the magnesium group was 44.4% compared with 44.9% in the placebo group (P=0.93). The cognitive change score and platelet and leukocyte activation were also not different between the groups. Multivariable analysis revealed a marginal interaction between treatment group and weight such that heavier subjects receiving magnesium were less likely to have cognitive deficit (P=0.06).

Conclusions—Magnesium administered intravenously during cardiac surgery does not reduce postoperative cognitive dysfunction.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00041392. (Stroke. 2013;44:3407-3413.)

Key Words: blood platelets ■ cardiopulmonary bypass ■ cognition

Neurocognitive dysfunction remains a common occurrence after cardiac surgery, with approximately one-third of patients demonstrating cognitive deficits at 6 weeks after surgery. Although initial reports suggested that impairment at discharge was associated with decline 5 years after surgery, studies incorporating nonsurgical control groups propose that postoperative dysfunction is more transient, with no relationship between immediate and delayed cognitive injury. Proposed mechanisms for the neurocognitive dysfunction include genetic predisposition, transcerebral platelet activation, cerebral embolism or hypoperfusion, cell salvage, valve surgery, systemic inflammatory responses, hemodilution, hyperglycemia, and hyperthermia. Quality of life is diminished for patients with cognitive decline who would otherwise expect that surgery would improve the quality of their lives. Magnesium is a common intracellular cation that has long been reported to exert neuroprotective properties via multiple mechanisms including preservation of cellular energy metabolism, noncompetitive inhibition of the N-methyl-D-aspartate receptor, attenuation of presynaptic excitatory amino acid release, potentiation of presynaptic adenosine, blockade of voltage-gated calcium channels, and vascular smooth muscle relaxation leading to improved cerebral blood flow. In a study of 171 patients undergoing coronary revascularization with cardiopulmonary bypass (CPB), treatment with the
N-methyl-D-aspartate receptor antagonist remacemide was associated with favorable effects on postoperative neurocognitive performance. Furthermore, magnesium inhibits platelet activation, a biological process that is associated with neurocognitive decline after surgery. We therefore hypothesized that intravenous magnesium administered intraoperatively would reduce postoperative neurocognitive dysfunction. As a secondary outcome, we also assessed whether magnesium would attenuate the platelet activation associated with CPB.9

Methods

Study Population

After approval by the Duke University Health System Institutional Review Board at all enrolling sites and written informed consent, 389 patients who were scheduled to undergo coronary artery bypass grafting, valve, or coronary artery bypass grafting plus valve surgery with CPB were enrolled into this prospective, randomized, double-blind, placebo-controlled clinical trial. Patients were excluded if they were undergoing circulatory arrest, had a history of symptomatic cerebrovascular disease (eg, stroke with a residual deficit), psychiatric illness (any clinical diagnoses requiring therapy), renal failure (serum creatinine >2 mg/dL), liver disease (aspartate aminotransferase, alanine aminotransferase >1.5x the upper limit of normal), or higher alcohol consumption (>2 drinks per day), were unable to read, had less than a seventh-grade education, or scored <24 on a baseline Mini Mental State examination. Subjects were randomized to 2 treatment groups: (1) magnesium group: 50 mg/kg bolus for 20 minutes after induction of anesthesia followed by another 50 mg/kg infusion for 3 hours (total dose 100 mg/kg) or (2) placebo group: normal saline administered as a bolus and an infusion with identical volume and rate changes as that of the treatment group such that blinding was preserved. A group assignment schedule was prepared using a randomization function in SAS (Cary, NC) and stored in consecutively numbered sealed envelopes until allocation. Randomization occurred before surgery on the planned surgical procedure and use of CPB was confirmed. Magnesium dosing was based on unpublished pharmacokinetic data from a pilot study in 38 patients that revealed a good safety profile and a trend toward improved learning at 6 weeks in the treatment group.

Patient Management

Anesthesia was induced and maintained with midazolam, fentanyl, and isoflurane. All patients underwent nonpulsatile hypothermic (30°C–32°C) CPB with a membrane oxygenator and an arterial line filter. The pump was primed with crystalloid, and serial hematocrit levels were kept at 20.21. Before initiation of CPB, all patients received heparin anticoagulation (300–400 U/kg) to achieve a target activated coagulation time of >480 s. Neither the pump prime nor received heparin anticoagulation (300–400 U/kg) to achieve a target activated coagulation time of >480 s. Neither the pump prime nor cognitive index.

Measurement of Neurocognitive Function

Experienced psychometricians blinded to the treatment group examined subjects with a well-validated battery of 5 cognitive tests on the day before surgery and again at 6 weeks after surgery. In accordance with the Consensus Statement on Assessment of Neurobehavioral Outcomes after Cardiac Surgery, we used a cognitive test battery comprising the following 5 instruments that yielded 10 scores: Short Story module of the Randt Memory Test, Digit Span subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Test, Modified Visual Reproduction Test from the Wechsler Memory Scale, Digit Symbol subtest of the WAIS-R, and Trail Making Test (part B).

Laboratory Assessments

Blood was sampled at baseline, admission to intensive care unit, and 24 and 48 hours after the bolus for measurement of magnesium levels. An additional sampling point immediately after the magnesium bolus was added after patient No. 121. In the first 100 subjects, whole blood samples were also drawn at baseline, end of bolus, 10 minutes after the end of CPB, and 24 and 48 hours after the bolus, and were immediately fixed in 1% paraformaldehyde in phosphate-buffered saline. Platelet P-selectin expression was measured using fluorochrome-conjugated monoclonal antibodies, with the platelet-specific monoclonal antibodies (ie, anti-CD41a [glycoprotein Ib/IIa] and anti-CD62P [P-selectin]), both purchased from Pharmingen (San Diego, CA). Whole blood samples were fixed, washed, and labeled with monoclonal antibodies as previously described. The percentage of P-selectin+ platelets was determined by labeling with fluorescein isothiocyanate–anti-CD41a and phycoerythrin–anti-CD62P. Leukocyte–platelet binding, an additional cellular marker of platelet activation, was determined by labeling samples with fluorescein isothiocyanate–anti-CD41a and phycoerythrin–anti-CD45 (Pharmingen), phycoerythrin–anti-CD41a, and phycoerythrin–Cy5–anti-CD14 (Beckman Coulter; Miami, FL). Leukocyte activation was examined using monoclonal antibodies to CD45 (used primarily to exclude red blood cells and platelets during the cytocentrifuge analysis) and CD11b.

Statistical Analysis

To characterize cognitive function over time while minimizing potential redundancy in the cognitive measures, a factor analysis was performed on the 10 cognitive test scores from baseline as previously described. The 10 scores were incorporated into a principal components analysis with orthogonal rotation (a linear transformation of the data) to produce uncorrelated factors. The factor analysis was conducted on the enrolled subjects in this study, and scoring coefficients for all time points were determined using the baseline rotated factor scores of this sample. Thus, cognitive domains remained consistent over time. We chose a 4-factor solution, which accounts for 84% of the variability in the original 10 test scores and represents 4 cognitive domains: (1) verbal memory, (2) abstraction and visuospatial orientation (executive function), (3) visual memory, and (4) attention and concentration. Two summary measures were calculated to represent cognitive function: (1) cognitive deficit (the binary outcome) was defined as a decline of ≥1 SD in ≥1 of the 4 domains; (2) to quantify overall cognitive function and the degree of learning (ie, practice effect from repeated exposure to the testing procedures), a baseline cognitive index was first calculated as the mean of the 4 preoperative domain scores. A continuous change score (the continuous outcome) was then calculated by subtracting the baseline from the follow-up cognitive index.

The primary analyses were conducted according to the intention-to-treat principle. Categorical and continuous demographic characteristics were compared between the treatment groups with Pearson χ², Fisher exact, and t tests. The effect of magnesium treatment on the cognitive change score and cognitive deficit was tested using multivariable linear and logistic regression modeling, respectively, accounting for age, years of education, baseline cognition, sex, race, and weight. The association of platelet and leukocyte activation with magnesium treatment group was tested using repeated-measures ANOVA. Log transformation was conducted on the positively skewed cellular activation data to meet assumptions of normality. All analyses were performed with SAS version 9.3 (SAS Institute Inc; Cary, NC); p<0.05 was considered significant.

On the basis of the preliminary data, we expected that the incidence of cognitive deficits in patients undergoing cardiac surgery would be ≤40%. We hypothesized that magnesium treatment would decrease this incidence to 25%, and a sample size of 170 per group would yield power of 80% at a significance level of 0.05 to detect this difference. To allow for a 15% loss to follow-up, we intended to recruit a total of 400 patients.

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Results
From January 1, 2002, to April 24, 2008, a total of 487 patients were consented to participate in the study (Figure 1). Ninety-eight of these subjects were not subsequently treated (11 refused neurological testing, 45 withdrew consent, 40 exclusion criteria, and 2 had changes in surgical schedule), leaving 198 subjects who were allocated to the magnesium group and 191 to the placebo group (n=389).

Demographic and clinical characteristics of the randomized subjects are listed in Table 1. As expected from randomization, characteristics were similar between the treatment groups. Patients who did not return for follow-up testing at 6 weeks were older (P=0.013) and had a lower level of education (P<0.001) and a lower preoperative cognitive score (P<0.001) but were otherwise similar to those who returned for testing. Among the 326 subjects (83.8%) who returned for follow-up testing (Figure 1), 316 completed all cognitive tests.

Neurocognitive deficits at 6 weeks after surgery were present in 44.4% (71 of 160) of the subjects who were randomized to magnesium and in 44.9% (70 of 156) of the subjects who were randomized to placebo (P=0.93). The continuous cognitive change score was also not significantly different between the treatment groups (magnesium: 0.07±0.28 versus placebo: 0.13±0.28; P=0.31). Multivariable analysis revealed a marginal interaction between the treatment group and weight such that subjects weighing more in the magnesium group were less likely to have cognitive decline (binary outcome: P=0.06; continuous outcome: P=0.16; Figure 2A and 2B; Tables 2 and 3). In a secondary as-treated analysis, 5 placebo patients were reassigned to the magnesium group. One of these patients was incorrectly randomized, whereas the other 4 received magnesium (2 g) intraoperatively for arrhythmia management. Multivariable analysis once again revealed an interaction between treatment group and weight (binary outcome: P=0.02; continuous outcome: P=0.21). As expected, magnesium levels were significantly higher in the magnesium group (Figure 3A). Platelet activation (percentage of P-selectin+ platelets) increased with the onset of CPB and remained above baseline at 48 hours after surgery. Leukocyte activation (mean CD11b fluorescence) also increased significantly with CPB but peaked intraoperatively. However, there was no difference between the treatment groups in platelet–leukocyte binding (P>0.05). The use of statin or platelet inhibitor therapy (preoperatively and postoperatively) was also not different between the treatment groups (Table 1).

Adverse events were not significantly different between the treatment groups; serious adverse events were recorded in 18.7% of magnesium and 16.8% of placebo subjects (P=0.62). Postoperative stroke was diagnosed in 5 patients (2.5%) in the

| Table 1. Characteristics of the Subjects Allocated to Treatment |
|-----------------|-----------------|
| Variable                  | Magnesium (n=198) | Placebo (n=191) |
| Age (SD), y               | 68.6 (8.4)        | 68.4 (8.0)       |
| Sex, % female             | 27.3             | 34.6             |
| Race, % white             | 81.3             | 76.4             |
| Weight (SD), kg           | 83.2 (15.1)       | 81.4 (15.0)      |
| History of hypertension, %| 81.2             | 80.0             |
| Diabetes mellitus, %      | 35.4             | 34.7             |
| Previous MI, %            | 32.6             | 33.5             |
| Ejection fraction (SD)    | 52 (12)          | 53 (13)          |
| Years of education (SD)   | 13.2 (3.6)        | 13.1 (3.4)       |
| Preoperative statins, %   | 58.1             | 52.9             |
| Preoperative platelet inhibitors, % | 72.7             | 62.9             |
| Preoperative cognitive score (SD) | 0.002 (0.50)      | −0.03 (0.48)     |
| Magnesium level at baseline (SD) | 1.93 (0.24) | 1.92 (0.28)     |

Surgical procedure, %
- CABG: 78.3 vs. 78.5
- CABG+valve: 15.2 vs. 15.7
- Valve: 6.6 vs. 5.8
- Redo surgery, %: 1 vs. 0
- No. of grafts (SD): 3.1 (1.3) vs. 3.1 (1.3)
- Cross-clamp time (SD), min: 85 (36) vs. 82 (36)
- CPB time (SD), min: 137 (52) vs. 135 (55)

Platelet inhibitors included aspirin, clopidogrel, dipyridamole, and ticlopidine. CABG indicates coronary artery bypass grafting; CPB, cardiopulmonary bypass; and MI, myocardial infarction.

Figure 1. CONSORT diagram showing the flow of participants.
Magnesium group and 6 patients (3.1%) in the placebo group. The length of hospital stay was 6 days (interquartile range, 5–7) in the magnesium group and 6 days (interquartile range, 5–8) in the placebo group ($P=0.60$). In-hospital and 6-week mortality rates were not different between magnesium and placebo groups (1.51% versus 0.52%; $P=0.33$ and 3.54% versus 2.09%; $P=0.39$, respectively).

**Discussion**

In this prospective, placebo-controlled, randomized study of administration of intravenous magnesium during adult cardiac surgery with CPB, magnesium did not improve postoperative neurocognitive function. In addition, magnesium did not reduce perioperative platelet or leukocyte activation. In secondary post hoc analyses, a marginal interaction between magnesium and weight was detected such that heavier patients receiving magnesium were less likely to exhibit neurocognitive deficits.

Despite encouraging data from preclinical and preliminary human studies supporting the neuroprotective benefits of magnesium, several large trials in different types of brain injury have failed to demonstrate the efficacy of magnesium. Mortality was in fact doubled in patients who were randomized to a targeted magnesium level between 3.04 and 6.08 mg/dL. In another study of 1204 patients admitted to the hospital within 4 days of aneurysmal subarachnoid hemorrhage, magnesium was also not superior to placebo for reduction of poor outcome. Similarly, in 2386 patients, magnesium given within 12 hours of acute stroke did not reduce the risk of death or disability at day 90. Mortality also trended to be slightly higher in the magnesium-treated group (hazard ratio, 1.18 [0.97–1.42]; $P=0.098$). Median time to treatment was 7 hours in this trial, with only 3% treated within 3 hours of onset, which raises concerns that such delayed therapy would not be effective because salvageable brain tissue is limited.

In the perioperative arena, Heyer et al randomized 108 patients undergoing carotid endarterectomy to receive 1 of 3 magnesium-dosing strategies provided as a bolus followed by an infusion for 24 hours. Neurocognitive function measured only on postoperative day 1 was improved with magnesium therapy (odds ratio, 0.27 [0.10–0.74]; $P=0.01$). Subgroup analyses, however, revealed a benefit only with low-dose magnesium, whereas patients receiving high-dose magnesium were not different from the placebo-treated

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>Odds Ratio (95% Confidence Limits)</th>
<th>$P$ Value</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.015</td>
<td>1.015 (0.983–1.048)</td>
<td>0.371</td>
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<tr>
<td>Years of Education</td>
<td>–0.077</td>
<td>0.926 (0.851–1.004)</td>
<td>0.067</td>
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<td>Preoperative cognitive index</td>
<td>0.629</td>
<td>1.876 (0.992–3.601)</td>
<td>0.055</td>
</tr>
<tr>
<td>Women</td>
<td>–0.145</td>
<td>0.865 (0.486–1.525)</td>
<td>0.618</td>
</tr>
<tr>
<td>Whites</td>
<td>0.293</td>
<td>1.796 (0.949–3.436)</td>
<td>0.074</td>
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<tr>
<td>Magnesium treatment</td>
<td>1.355</td>
<td></td>
<td>0.062</td>
</tr>
<tr>
<td>Weight</td>
<td>–0.021</td>
<td>0.963 (0.938–0.989)</td>
<td>0.024</td>
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<tr>
<td>Weight-magnesium</td>
<td>–0.016</td>
<td></td>
<td>0.060</td>
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</table>
group. Furthermore, the lack of long-term (postdischarge) neurocognitive assessment is a limitation. Bhudia et al ran randomized 350 patients undergoing cardiac surgery to receive magnesium both as a bolus and infusion for 24 hours along with dosing during CPB to maintain magnesium levels of $\geq 3.6$ mg/dL. A neurological assessment with the Western Perioperative Neurologic Scale revealed better performance in the magnesium group at 24 and 96 hours postoperatively, but neurocognitive function at 3 months after surgery was not different. The lack of comprehensive long-term neurocognitive assessment is once again a shortcoming.

A wealth of data from randomized clinical trials now suggests that magnesium has no clinically significant effect on neurological outcome after different types of brain injury, especially beyond hospital discharge. In the largest perioperative trial of magnesium, we are also unable to demonstrate any benefit to magnesium. The interaction between weight and magnesium treatment is intriguing, but it is a weak association. Furthermore, in post hoc analyses, we are unable to demonstrate any significant correlations between weight, magnesium levels, intraoperative insulin dose, or pH. Nevertheless, because postbolus magnesium levels were not available in all enrolled subjects, it is still plausible that serum magnesium levels are related to cognitive outcome. Perioperative data on serum levels are conflicting as outlined previously, with 1 study demonstrating benefit only with low-dose therapy, whereas the other showing some benefit to maintaining levels $>3.6$ mg/dL.39,40 The lack of efficacy in our trial may also be explained by the fact that intravenous magnesium does not readily cross the blood–brain barrier.41,42 Although blood–brain barrier disruption is common during cardiac surgery, it is not present in all patients.43 Finally, the link between platelet activation and cerebral ischemia is well established in nonoperative settings,44–46 and magnesium is known to inhibit platelet activation.21 It is possible that any protective effect of magnesium was overwhelmed by the marked platelet activation associated with CPB.

Methodological limitations of studies of postoperative neurocognitive function include the lack of control groups and the inconsistent definition of postoperative cognitive decline. The placebo group in the present study served as a control group. We also examined neurocognitive function as both a dichotomous and continuous measure and found that magnesium was not associated with neurocognitive decline regardless of how decline was assessed. Loss to follow-up was also a study limitation. Patients lost to follow-up were older and had lower baseline cognitive function, but the other demographic characteristics were not different. Importantly, the rate of loss to follow-up was not different between the 2 treatment groups (19.2% magnesium versus 18.3% placebo; $P=0.83$), indicating that differential

### Table 3. Multivariable Linear Regression Model Predicting Cognitive Change (Continuous Outcome) at 6-Week Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>DF</th>
<th>Parameter Estimate (95% Confidence Limits)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1</td>
<td>$-0.005$ ($-0.009$ to $-0.001$)</td>
<td>0.012</td>
</tr>
<tr>
<td>Years of education</td>
<td>1</td>
<td>0.024 ($0.014$ to $0.034$)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Preoperative cognitive index</td>
<td>1</td>
<td>$-0.201$ ($-0.283$ to $-0.120$)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Women</td>
<td>1</td>
<td>$-0.083$ ($-0.156$ to $-0.011$)</td>
<td>0.024</td>
</tr>
<tr>
<td>Whites</td>
<td>1</td>
<td>$-0.117$ ($-0.199$ to $-0.035$)</td>
<td>0.005</td>
</tr>
<tr>
<td>Magnesium treatment</td>
<td>1</td>
<td>$-0.299$ ($-0.653$ to $0.053$)</td>
<td>0.096</td>
</tr>
<tr>
<td>Weight</td>
<td>1</td>
<td>0.001 ($-0.004$ to $0.002$)</td>
<td>0.762</td>
</tr>
<tr>
<td>Weight-magnesium</td>
<td>1</td>
<td>0.003 ($-0.001$ to $0.007$)</td>
<td>0.160</td>
</tr>
</tbody>
</table>
dropout was not responsible for our observed findings. We also noted that the lack of postbolus magnesium levels in all of the enrolled subjects was a study limitation such that we are unable to completely assess the marginal relationship between weight, magnesium levels, and neurocognitive outcome.

In summary, despite significantly higher magnesium levels in the perioperative period, intraoperative magnesium therapy did not improve neurocognitive function after cardiac surgery. Magnesium also did not diminish the platelet activation that was previously associated with neurocognitive decline. The marginal interaction between weight and magnesium therapy suggests that a more comprehensive evaluation of magnesium pharmacokinetics during CPB is warranted.

Appendix

Neurologic Outcome Research Group of the Duke Heart Center

Director: Joseph P. Mathew, MD; Codirector: James A. Blumenthal, PhD.

Anesthesiology: Manuel A. Fontes, MD; Miklos D. Kertai, MD; Frederick W. Lombard, MD; Joseph P. Mathew, MD; David L. McDonagh, MD; Terri G. Monk, MD; Mark F. Newman, MD; Mihai V. Podgoreanu, MD; Mark Stafford-Smith, MD; Madhav Swaminathan, MD; David S. Warner, MD; Bonita L. Funk, RN, CCRP; Narai Balajounda, MD; Roger L. Hall, AAS; Tiffany Bisanar, RN, BSN; Karen L. Clemmons; Yi-Ju Li, PhD; Greg Pecora, BA; Barbara Phillips-Bute, PhD; Yanne Toulgoat-Dubois, BA; Peter Waweru, CCRP; William D. White, MPH.

Behavioral Medicine: Michael A. Babyak, PhD; James A. Blumenthal, PhD; Jeffrey N. Browndyke, PhD; Kathleen A. Welsh-Bohmer, PhD.

Cardiology: Daniel B. Mark, MD, MPH; Michael H. Sketch Jr, MD.

Neurology: Ellen R. Bennett, PhD; Carmelo Graffagnino, MD; Daniel T. Laskowitz, MD; Warren J. Strittmatter, MD.

Perfusion Services: Stanlin Alexander, BS, CCP; Kevin Collins, BS, CCP; Greg Smiglia, BS, CCP; Ian Shearer, BS, CCP.

Surgery: Mark F. Berry, MD; Thomas A. D’Amico, MD; Mani A. Daneshmand, MD; R. Duane Davis, MD; Jeffrey G. Gaca, MD; Donald D. Glower, MD; R. David Harpole, MD; G. Chad Hughes, MD; Robert D.B. Jaquiss, MD; Shu S. Lin, MD; Andrew J. Lodge, MD; Carmelo A. Milano, MD; Mark W. Onaitis, MD; Jacob N. Schroeder, MD; Peter K. Smith, MD; Betty C. Tong, MD.

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Disclosures

None.

References


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for the Neurologic Outcome Research Group (NORG) of The Duke Heart Center

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