Randomized Trial of Hypotensive Epidural Anesthesia in Older Adults

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Background: Data are sparse on the incidence of postoperative cognitive, cardiac, and renal complications after deliberate hypotensive anesthesia in elderly patients.

Methods: This randomized, controlled clinical trial included 235 older adults with comorbid medical illnesses undergoing elective primary total hip replacement with epidural anesthesia. The patients were randomly assigned to one of two levels of intraoperative mean arterial blood pressure management: either to a markedly hypotensive mean arterial blood pressure range of 45–55 mmHg or to a less hypotensive range of 55–70 mmHg. Cognitive outcome was assessed by within-patient change on 10 neuropsychologic tests assessing memory, psychomotor, and language skills from before surgery to 1 week and 4 months after surgery. Prospective standardized surveillance was performed for cardiovascular and renal outcomes, delirium, thromboembolism, and blood loss and replacement.

Results: The two groups were similar at baseline in terms of age (mean, 72 yr), sex (50% women), comorbid conditions, and cognitive function. After operation, no significant differences in the incidence of early or long-term cognitive dysfunction were observed between the two blood pressure management groups. There were no significant differences in the rates of other adverse consequences, including cardiac, renal, and thromboembolic complications. In addition, no differences occurred in the duration of surgery, intraoperative estimated blood loss, or transfusion rates.

Conclusions: Elderly patients can safely receive controlled hypotensive epidural anesthesia with this protocol. There was no evidence of greater risks, or early benefits, with the use of the more markedly hypotensive range. (Key words: Computerized anesthesia record; geriatrics; memory; neuropsychologic; postoperative.)

◆ This article is accompanied by an Editorial View. Please see: Raja SN, Haythornthwaite JA: Anesthetic management of the elderly: Measuring function beyond the immediate perioperative horizon. ANESTHESIOLOGY 1999; 91:909–11

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DELIBERATE hypotensive anesthesia offers significant advantages for surgical procedures that require dry surgical fields or are associated with substantial blood loss. These advantages must be balanced against the risks of ischemic injury in nonsurgical regions, such as the brain and heart. The use of hypotensive anesthesia generally has been limited to healthy young patients and to surgical procedures that cannot be performed under normotensive conditions.

Total hip replacement (THR) surgery is a clearly beneficial procedure performed most often in older adults.[1] Hypotensive anesthesia for THR offers several benefits: a drier surgical field, better visualization of anatomy, and reduced intraoperative blood loss.[2,3] However, the use of deliberate hypotension in elderly patients raises concerns of hypoperfusion and ischemic injury to the brain, heart, or other vital organs.[4-7] Cerebral injury could take the form of obvious stroke or more subtle long-term loss of cognitive function.[8-11] Previous controlled prospective studies of hypotensive anesthesia lacked rigorous

surveillance for postoperative cognitive outcomes, had limited generalizability, or had low power because of small patient populations.[2,12-15]

A recently developed technique for induced hypotension with epidural anesthesia offers a way to preserve or augment cardiac output and systemic flow despite significant systemic hypotension.[16,17] The purpose of this randomized controlled trial was to assess the risks and benefits of hypotensive epidural anesthesia with this technique for elderly patients with comorbid cardiovascular disease undergoing THR. Patients were randomized to have their intraoperative mean arterial blood pressure (MAP) maintained within one of two levels during surgery: in the range of 45-55 mmHg or 55-70 mmHg. The surveillance protocol for detecting perioperative changes in neuropsychologic performance was previously developed and tested for a trial comparing the effects of epidural and general anesthesia on cognitive outcomes after total knee replacement.[18]

Methods

Assembly of Patients

All patients older than 50 yr who were undergoing elective unilateral primary THR with participating surgeons at the Hospital for Special Surgery between March 1993 and August 1995 were screened. All patients gave signed informed consent according to the Institutional Human Rights Committee's approved protocol.

Inclusion Criteria. To be eligible, patients had to be 70 yr or older or 50–69 yr and have at least one of the following.

Cardiac Disease. Cardiac disease was defined as S/P myocardial infarction (patients hospitalized for chest pain who had either new Q waves in at least two leads, new ST segment depression, or new T-wave inversion, with elevation of creatine kinase [CK] or CK-MB isoenzyme levels[19]); history of angina as defined by the Rose criteria[20]; S/P coronary artery bypass grafting; or a history of congestive heart failure including pulmonary edema, paroxysmal nocturnal dyspnea, or dyspnea on exertion (by Rose criteria) that required continued pharmacologic therapy.

Hypertension. Hypertension was defined as systolic pressure of >160 mmHg, diastolic pressure >95 mmHg, or treatment with a medication used explicitly to treat the patient's blood pressure.[21]

Diabetes Mellitus. Diabetes mellitus was marked by treatment with insulin or oral hypoglycemic agents or an elevated fasting glucose level on more than one occasion (plasma >140 mg/dl; whole blood >120 mg/dl).

Exclusion Criteria. Exclusion criteria consisted of the following.

Contraindications to Epidural Anesthesia. Contraindications to epidural anesthesia were ankylosing spondylitis, bleeding diathesis, and use of systemic anticoagulants.

Contraindications to Hypotensive Anesthesia. Hemodynamically significant aortic valve or mitral valve stenosis (documented by Doppler echocardiography or cardiac catheterization) and severe carotid artery stenosis (>70% occlusion) were contraindications to hypotensive anesthesia.

Conditions Seriously Affecting Cognitive Testing Performance. Deafness, blindness, severe hand deformity or dysfunction, psychosis, and nonfluency in English were conditions that would affect cognitive testing performance and were therefore included as exclusion criteria.

Allocation of Interventions

A blocked randomization schedule was prepared before the start of the trial and was known only by the study statistician. Opaque allocation assignment envelopes were opened by the treating anesthesiologist in the operating room just before surgery.

Preoperative Evaluation

The preoperative evaluation performed 1–7 days before surgery assessed demographic status, including education and occupational history; medical, psychiatric, and surgical history, including past perioperative complications; medication use and substance abuse; physical examination; and preoperative laboratory values. The Charlson comorbidity score, a weighted index accounting for the number and seriousness of comorbid medical conditions, was computed for all patients.[22]

Cognitive Assessment

The perioperative cognitive assessment protocol has been described in detail, including the definition of a minimally important clinical difference in score for each test (appendix 1). The battery includes 10 tests: the Boston Naming, Controlled Word Association, Digit Symbol, Trail Making A and B, Digit Span, Benton Visual Retention, Benton Visual Recognition, Mattis–Kovner Verbal Recall, and Mattis–Kovner Verbal Recognition. Neuropsychologic testing was repeated 1 week and 4

months after operation. The Ammons Quick Test[23] for verbal IQ was performed before operation.

Anesthesia Protocol

No premedication was given. All patients received oxygen supplementation *via* nasal cannula. Oxygen saturation was monitored using disposable fingertip sensor pulse oximeters. Cardiac rate, rhythm, and waveform were monitored continuously using a displayed anterior chest lead. Continuous arterial systolic, diastolic, and MAPs were monitored *via* radial arterial lines. All patients had central venous catheters placed, and central venous pressures were transduced and displayed. Patients with a history of congestive heart failure or severe renal insufficiency also had pulmonary artery catheter monitoring.

Bupivacaine (20–25 ml), 0.75%, was administered *via* epidural catheter using standardized techniques.[24,25] Adjunctive medications for sedation included midazolam, fentanyl, and thiopental sodium. All patients received a low-dose intravenous epinephrine infusion at an infusion range of 1–5 μg/min to maintain circulatory stability, as previously described.[16,17]

Mean arterial blood pressure was maintained within the range of 45–55 mmHg or 55–70 mmHg during the operative procedure. These levels of hypotension resulted from the epidural anesthetic alone in all patients; no additional agents were used to decrease blood pressure. The MAP was stabilized in the target range by adjusting the epinephrine infusion rate and by intravenous infusion of Ringer's lactate solution to replace lost blood and to maintain a stable central venous pressure, limited to a maximum of approximately 1.5 l crystalloid. If the MAP decreased to less than the target range despite a maximal infusion rate of 5 μg/min epinephrine, an infusion of phenylephrine, boluses of intravenous ephedrine, or both were used to increase the MAP.

At the end of the surgical procedure, the MAP was increased to 70–75 mmHg in both groups using intravenous boluses of ephedrine. In the postanesthesia care unit, both groups had MAP maintained at more than 70–75 mmHg with fluid replacement and intravenous boluses of ephedrine.

Intraoperative Assessment and Data Collection

One of the investigators (J.H.) created a customized software data collection system to record and analyze intraoperative surgical, anesthetic, and hemodynamic THR data for this study. A research assistant in the operating room entered events on a laptop computer using the program and pop-up menus. The events included incision, cementing, relocation, and so forth, and also all medications and fluids administered during the procedure. Simultaneously, the digital form of the physiologic data collected and analyzed by the anesthesia monitor was downloaded every 20 s from the monitor to the study computer *via* an RS 232 connection to allow exact temporal correlation of events and hemodynamic parameters. Downloading of intraoperative hemodynamic data was successful in 233 of 235 patients; in the other two cases, copies of operating room monitor trends data yielded adequate intraoperative MAP data.

Intraoperative blood loss was measured using a standardized nursing protocol for THR. Blood loss was calculated as the sum of sponges weighed as they were passed off the surgical field plus the difference between irrigation and suction volumes.

Postoperative Surveillance

The standardized surveillance for cognitive and cardiovascular complications included at least once-daily examinations by study personnel from the postoperative anesthesia care unit through the seventh postoperative day or discharge. The postoperative examination focused on cardiopulmonary and neurologic status. Electrocardiograms were performed within 6 h after surgery (in the postanesthesia care unit) and on postoperative days 1, 2, and 3.[26] If significant electrocardiographic changes (as described in Cardiovascular Outcomes) were observed, cardiac isoenzymes were measured.

Definition of Outcomes

Change in Cognitive Function. The primary outcome of change in cognitive function was within-subject change in score for each neuropsychologic test (score at 4 months after surgery minus the score before surgery). The mean within-subject change in the two blood pressure groups was compared for each test. Change from baseline to 1 week after operation was also assessed to provide a basis for attributing changes observed at 4 months to the acute perioperative period.

Other Outcomes. Cardiac complications included the perioperative occurrence of definite or probable myocardial infarction, pulmonary edema, cardiopulmonary arrest, or death. Definite postoperative myocardial infarction required a CK-MB level of > 5% and one of the following significant electrocardiographic changes: (1) new Q waves lasting more than 0.03 s and more than 1 mm in depth in more than two leads in the absence of a new conduction abnormality or a marked change in the

QRS axis; and (2) T-wave and ST segment changes lasting more than 48 h in more than two leads (in the absence of new electrolyte abnormalities or the new use of digitalis): new inversions of previously upright T waves; new ST depression of more than 1 mm; an additional 1 mm or more of ST depression if ST depression existed previously; previously depressed ST segments that returned to normal; or unequivocal ST elevation of more than 2 mm (excluding J point elevation). Changes in T waves from biphasic to inverted or vice versa were not counted as significant T-wave changes.

Probable myocardial infarction required a CK-MB level of >3% and one of the significant electrocardiographic changes. Pulmonary edema required a pulmonary capillary wedge pressure >25 cm water or rales heard over two thirds of the lung fields with a typical chest radiograph for pulmonary edema.

Renal dysfunction was defined as an increase in the serum creatinine of >20% that persisted for >48 h beginning in the first 3 days after surgery. In a previous study, this change had a true-positive rate of 67% in identifying patients whose decrease in postoperative creatinine clearance was >50%.[21]

The outcome definition of postoperative delirium was based on an algorithm developed and used in two previous studies of older adults undergoing elective joint replacement.[18,27] The diagnosis required the presence of cognitive impairment of acute onset and fluctuating course and evidence of a significantly impaired attention disorder, plus at least two of the following signs: disorientation, disorganized thought, altered level of consciousness, hyperactive or hypoactive psychomotor activity, perceptual disturbances, or memory impairment.

Blinding

The anesthesiologists, surgeons, and study personnel recording data in the operating room could not be blinded to the type of blood pressure management. Because the purpose of blinding is to prevent bias in the evaluation of outcomes, the physicians assessing delirium and cardiac and renal outcomes were blinded to the intraoperative blood pressure range.

Statistical Analyses

Comparison between the two blood pressure groups of within-subject change in score on each of the 10 neuropsychologic tests was performed using the Student t test for two samples, using PROC TTEST, which is available in the Statistical Analysis System (SAS Institute, Cary, NC). The customary alpha level of significance of 0.05 was adjusted for the 10 different comparisons to $P < 0.005$ (using Bonferroni correction for multiple outcomes). All P values were two tailed. The one-sample paired comparisons t test was used to test for a significant change from before surgery to 1 week and 4 months after surgery. Examination of simultaneous effects of blood pressure level and other covariates thought to be of potential significance was performed with a multiple linear regression model using PROC GLM in SAS. The dependent variable in this model was the change from baseline to 4 months after operation on the 10 neuropsychologic tests. The Fisher exact test was used to compare the incidence of cardiovascular and other categorical outcomes.

Results

Summary of Patient Screening and Enrollment

During the enrollment period, from March 1993 to August 1995, 461 patients were eligible. The most common reasons for ineligibility were nonparticipating surgeon, revision procedure, and not meeting entry criteria. In all, 235 patients agreed to participate. With regard to the effects of the entry criteria (age > 70 yr or age 50–69 yr plus hypertension, cardiac disease, or diabetes), there was no difference between the younger and older groups in the prevalence of cardiac disease (30% and 27%, respectively) or diabetes (10% and 8%), although more of the younger patients were hypertensive (75% vs. 42%; $P < 0.001$).

Baseline Preoperative Characteristics and Comparability

One hundred seventeen patients were randomized to the 45–55 MAP range and 118 patients to the 55–70 MAP range. There were no statistically significant differences in baseline demographic and medical characteristics between the two groups (table 1). The age range of patients was 50 to 88 yr, with a mean of 72 yr; one half were women; one third of patients were working, either full or part time; and none of the patients resided in a long-term care institution. Table 2 shows the baseline test scores before surgery on the neuropsychology tests. There were no statistically significant differences between the baseline scores of the two intervention groups on any of the 10 tests.

Intraoperative Management

All patients received epidural anesthesia except two patients who had inadvertent injections of 0.75% bupiv-

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Table 1. Baseline Preoperative Demographic and Clinical Characteristics

	45–55 MAP (n = 117)	55–70 MAP (n = 118)
Mean age (SD)	71.5 (6.8)	71.9 (8.1)
% Women	44	55
Education (%)		
< High school	12	3
High school	18	29
College	38	34
Post-college	32	34
Work status (%)		
Full time	18	23
Part time	12	9
Not working	70	68
Charlson comorbidity score (%)		
0	55	61
1	24	22
2	14	13
>3	8	3
% Hypertensive	44	50

No significant differences between groups.

MAP = mean arterial pressure.

acaine into the subarachnoid space resulting in a "total spinal," which was diagnosed by shallow ventilation and a decrease in oxygen saturation to the low 90s. One patient had tracheal intubation and the other received assisted ventilation for 30 min. Neither patient was eliminated from the study.

The overall mean intraoperative MAP in the lower MAP range group was 50 ± 3.6 (SD) mmHg, compared with 65 ± 4.8 (SD) mmHg in the higher MAP group ($P < 0.0001$). Variability around the mean MAP was minimal, with a mean standard deviation around the mean MAP of 3.2 mmHg in the lower and 4.4 mmHg in the higher MAP group. In the 45–55 MAP group, less than 14% of all MAP measurements exceeded the upper limit of 55 mmHg. In the 55–70 MAP group, only 2.5% of all MAP measurements were less than the lower limit of 55 mmHg. The mean duration of surgery in both groups was 75 min.

As expected, the percentage of patients who received a phenylephrine infusion was significantly greater in the higher pressure range group at 50%, compared with 7% in the lower pressure range group. Patients in the higher pressure range group received significantly more intraoperative fluid: 1,750 ml Ringer's lactate solution compared with 1,600 ml in the lower pressure range group ($P = 0.022$).

Compliance with Follow-up

In-hospital outcome surveillance was completed for all 235 patients. Long-term follow-up interviews were completed by 216 patients (92%). Nineteen patients were not available for follow-up, with equal attrition rates in the two MAP groups. The reasons for attrition included two deaths from cancer; one patient with severe intercurrent illness caused by cancer diagnosed at the time of THR; two patients had moved out of the area; and 14 patients refused.

Cognitive Outcomes

Comparison by Intraoperative Pressure Range. Table 3 shows the results for within-subject change in score at both postoperative time points for each of the 10 neuropsychological tests. There were no significant differences between the two intraoperative blood pressure groups from baseline to 4 months after operation, with a power of more than 99% (at a two-sided alpha level of 0.005) to detect a difference between the two arms of the trial greater than or equal to the minimally clinically important difference for each test. Similarly, analysis of within-patient change from baseline to 1 week after operation revealed no significant differences between the two groups.

Multivariate Analysis. Increased age was not a significant predictor of decline in neuropsychologic performance 4 months after surgery on any of the 10 tests but

Table 2. Neuropsychologic Test Results at Preoperative Baseline

	45–55 MAP	55–70 MAP
Linguistic		
Boston naming	25.7 (3.5)	25.6 (3.8)
Controlled word	40.9 (13.1)	40.1 (13.1)
Psychomotor and attention		
Digit Symbol	42.5 (11.8)	43.3 (12.3)
Trails A	45.3 (20.9)	48.9 (38.7)
Trails B	112.6 (64.0)	109.5 (64.8)
Digit span	14.8 (3.7)	15.1 (4.1)
Memory		
Visual recall	5.3 (2.2)	5.5 (2.0)
Visual recognition	7.4 (2.1)	7.8 (1.5)
Verbal recall	11.0 (3.7)	11.6 (3.4)
Verbal recognition	2.8 (0.8)	2.9 (0.6)
Ammons IQ	110.9 (14.4)	111.3 (13.6)

Values are given as mean score (SD). No significant differences between groups. A higher score signifies better performance on all tests except trail making A and B, in which a longer completion time signifies worse performance.

MAP = mean arterial pressure.

Table 3. Cognitive Outcome: Within-subject Change from Preoperative Baseline Score

	1 Week after Surgery		4 Months after Surgery	
	45–55 MAP	55–70 MAP	45–55 MAP	55–70 MAP
Linguistic				
Boston naming	0.2 (2.4)	0.2 (2.6)	0.8 (2.7)	0.8 (4.6)
Controlled word	−0.6 (8.5)	1.5 (8.2)	1.8 (7.7)	1.3 (8.5)
Psychomotor and attention				
Digit symbol	−4.2 (6.2)	−2.7 (6.3)	2.3 (8.9)	2.3 (5.7)
Trails A	0.2 (15.7)	−3.2 (35.0)	−4.7 (14.5)	−6.4 (35.6)
Trails B	11.8 (51.2)	4.9 (44.2)	−9.8 (48.9)	−5.3 (45.1)
Digit span	−0.3 (2.6)	0.1 (2.5)	−0.2 (2.7)	0.5 (2.8)
Memory				
Visual recall	0.2 (2.2)	−0.1 (1.9)	0.3 (1.6)	0.4 (1.6)
Visual recognition	0.0 (1.9)	−0.1 (1.9)	0.5 (2.1)	0.5 (1.7)
Verbal recall	−0.1 (3.4)	−0.4 (3.0)	0.6 (3.2)	0.0 (3.8)
Verbal recognition	−0.2 (0.7)	−0.2 (0.7)	0.0 (0.8)	0.0 (0.7)

Values are given as mean change score (SD). No significant differences in change scores between groups at either time point. A positive change represents improvement on all tests except the trail making A and B tests, for which a positive value of change represents poorer performance.

MAP = mean arterial pressure.

was predictive of poorer performance on one test 1 week after surgery (Controlled Word Association, $P < 0.005$). However, age explained only 4% of the observed variance ($r^2 = 0.04$). Multivariate analysis of age, blood pressure group, and an age–MAP group interaction term showed no significant interactive effect on any of the 10 neuropsychologic tests. Intraoperative variables such as duration of surgery, mean MAP during surgery, and the product of the duration of surgery and mean MAP were not predictive of long-term cognitive declines. Noncognitive postoperative complications were also not predictive of long-term cognitive declines.

Cognitive Outcome: Temporal Patterns. There was a generalized pattern of decline at 1 week after surgery, followed by a return to baseline levels or an improvement on most tests by 4 months after surgery. A significant transient deterioration in performance was observed at 1 week compared with baseline on two of the 10 tests: Digit Symbol, and Mattis–Kovner verbal recognition (by paired t test, $P < 0.001$).

Other Outcomes. No in-hospital deaths occurred. Table 4 shows the incidence of noncognitive outcomes by intervention group. The incidence of myocardial infarction or ischemia was similar in the two groups, at 6% in the 45–55 MAP and 4% in the 55–70 MAP groups. Only one of these events was a new Q-wave myocardial infarct; this occurred in the higher MAP group. There were no cerebrovascular accidents. The power of this study to detect a 5% difference in cardiovascular complications was 85%.

The incidence of postoperative renal dysfunction was not significantly different, at 1% in the 45-55 MAP and 4% in the 55-70 MAP groups. No patient experienced persistent renal failure; one patient in the higher MAP group had renal dysfunction associated with transient acute renal failure. The onset of transient renal failure occurred late in the first week after surgery and was deemed to have been secondary to postoperative complications and management. The power of this study to detect a 5% difference in renal complications was 82%.

Overall, the incidence of delirium was 7%: 9% in the lower pressure arm compared with 4% in the higher

Table 4. Noncognitive Outcomes

	45–55 MAP (n = 117)	55–70 MAP (n = 118)
Cardiovascular complications (%)	6	4
Renal dysfunction (%)	1	4
Delirium (%)	9	4
Transfusions (%)		
≥1 U autologous	75	71
≥1 U allogeneic	5	6
None	22	23
Estimated blood loss (ml)		
Mean	199	212
SD	106	101
Mean LOS (days)	8.4	8.5
Positive doppler and/or venogram (%)*	11	6

No significant differences between groups.

LOS = length of stay.

*n = 111 for the 45–55 MAP group and n = 108 for the 55–70 MAP group.

pressure arm ($P = 0.3$). The significant positive predictors of delirium were male sex (11% of men compared with 3% of women) and poorer preoperative performance on 7 of the 10 neuropsychology tests. Age was not a significant predictor of delirium. No patient with delirium progressed to stupor, coma, or death, nor did they have an increased rate of other postoperative complications or long-term cognitive deterioration. The length of stay was greater in patients with delirium, at 10.9 days compared with 8.2 days ($P < 0.03$). The power of this study to detect a 6% difference in the incidence of delirium was 62%, compared with a 93% power to detect a 10% difference.

As shown in table 4, no significant difference occurred in intraoperative blood loss, with mean blood losses of 199 ml and 212 ml in the lower and higher MAP groups, respectively. There were also no significant differences between the two groups in the mean total number of units transfused or the percentage of patients who received any autologous units, any allogeneic units, or no blood transfusion. There were also no significant differences between the groups in length of hospital stay.

A postoperative lower extremity Doppler study or a venogram was performed in 219 of the 235 patients. The overall rate of distal lower extremity clot was 8%: 11% in the lower and 6% in the higher MAP groups ($P = 0.12$). No proximal clots or pulmonary emboli were found.

Discussion

In this study, we found no difference in long-term postoperative cognitive deterioration between patients randomized to a markedly hypotensive intraoperative MAP range of 45–55 mmHg or a mildly to moderately hypotensive range of 55–70 mmHg during epidural anesthesia for THR. The power of the study to have detected an important deterioration on any one of the neuropsychologic tests in the study battery was more than 99%. There were also no differences in the rates of early cognitive dysfunction, delirium, adverse cardiovascular outcomes, renal dysfunction, or thromboembolism. The overall incidence of major cardiovascular complications was low, despite the high prevalence of comorbid cardiovascular risk factors in our study population.

The concern was that systemic hypotension could lead to brain hypoperfusion and subtle permanent cognitive dysfunction. The physiologic effect of the decrease in systemic pressure depends on the lower limit for cerebral autoregulation, which is higher in patients with hypertension.[6,11,28] The evidence provided by this study suggests that elderly patients, including those with documented cardiovascular disease, can safely tolerate a period of significant systemic hypotension under the controlled conditions of this anesthesia management protocol. This does not include patients with occlusive carotid disease (>70% occlusion) or hemodynamically significant aortic valve or mitral valve stenosis, who were specifically excluded from participating in the study. Complication rates after elective THR observed in this study of high-risk patients are similar to or lower than those of previous studies of elective hip and knee replacement in unselected patients receiving normotensive anesthesia.[18,29-31]

Several previous studies specifically addressed the safety of deliberate hypotension for THR, but they had limited generalizability or inadequate outcome surveillance. For example, one randomized study found no difference in complications between patients given hypotensive or normotensive anesthesia, but it excluded patients with a history of stroke, transient ischemic attack, myocardial infarct, renal disease, or poorly controlled hypertension.[2] Another study of hypotensive anesthesia for THR did not find any evidence of increased complications, but it considered only death or major stroke.[8] A large case series at our own institution found no evidence of an increase in adverse events, even in elderly hypertensive patients, but it was not a controlled trial with a strict complication surveillance protocol.[31]

Reported intraoperative blood loss during THR with normotension varies from 500 to 1,800 ml.[2,17,32-34] Reduced blood loss has been reported in patients receiving spinal and epidural anesthesia compared with general anesthesia and in patients with controlled hypotension.[2,35,36] Orthopedic surgeons strongly believe that the relatively bloodless field provided by hypotensive anesthesia facilitates their performance of the procedure because anatomic structures can be better seen.[2] This trial, however, did not find evidence of clinically or statistically significant differences between the mildly and markedly hypotensive groups in intraoperative blood loss, duration of surgery, or transfusions of either autologous or nonautologous blood. The lack of a difference in estimated blood loss may be due to imprecision in the measurement technique, particularly because blood loss in the higher MAP group was already reduced to an average of 212 ml.[37] It is important to note that both levels of intraoperative MAP were relatively hypotensive compared to patients' preoperative MAP. More

than 95% of patients had a mean intraoperative MAP that was at least 20 mmHg less than their preoperative MAP. The benefits of controlled reduction of intraoperative MAP on these outcomes may reach a plateau beyond which further benefit does not occur.

One potential benefit not tested in this study is that a drier surgical field may reduce the amount of blood at the cement–bone interface, thus improving the quality of fixation of the prosthesis to the bone.[38-41] Aseptic loosening of the prosthesis from the bone is the most common cause of failure of a cemented THR.[42] The surgeons in the study could discern differences in the wetness of the field as a function of the level of intraoperative blood pressure ($P < 0.001$), but prosthesis loosening cannot be assessed until follow-up 5–10 yr after surgery.

Different techniques for inducing intraoperative hypotension may be associated with different risks of hypoperfusion injury and complication rates,[4,43] as described for patients receiving high levels of inspired isoflurane,[44] intravenous nitroprusside,[45-48] autonomic blocking agents,[12-14] or combinations of these agents. This study, in contrast, achieved hypotension *via* epidural anesthesia, which produces a chemical sympathectomy with profound peripheral venodilatation. The epinephrine infusion does not directly affect MAP,[16] but maintains normal stroke volumes, is associated with improved cardiac indices without increases in preload, and may prevent significant bradycardia.[16] Therefore, although diastolic perfusion pressure decreases, the work and metabolic demands of the heart are reduced. This method of deliberate hypotensive epidural anesthesia appears to have maintained blood flow and oxygen delivery at adequate levels despite low systemic MAPs. An important caveat of this study is that the demonstrated safety of hypotensive epidural anesthesia in older adults with comorbid diseases is limited to the protocol described in this study, including the use of continuous hemodynamic monitoring, supplemental oxygen, and avoidance of hypovolemia. The results are not necessarily generalizable to other techniques of hypotensive anesthesia.

In conclusion, this randomized trial found no differences between two different levels of intraoperative blood pressure management during epidural anesthesia for THR, specifically MAP ranges of 45–55 and 55–70 mmHg, in early and long-term cognitive, cardiac, and renal complications in elderly patients.

Appendix 1. The Neuropsychologic Battery

Linguistic Domain
Boston Naming Test.[49] Patients are asked to name a sequence of pictured objects. The 60-picture version was split into odd and even items. Possible scores would range from 0 to 30. The minimal clinically important difference (CID) in score on repeated administrations is 4 or more.

Controlled Word Association.[50] This is a test of oral word fluency consisting of three 1-min trials of production of spoken words beginning with a specific letter. Possible scores range from 0 to 70 (CID $\geq$ 13).

Psychomotor–Attention Domain
Digit Symbol.[51] A subtest of the Wechsler Adult Intelligence Scale, Revised (WAIS-R), Digit Symbol tests psychomotor performance and speed and requires symbol substitution and copying. Possible scores range from 0 to 93 (CID $\geq$ 12).

Trail Making Tests A and B.[52] These tests measure visuomotor speed, conceptual tracking, and attention. Part A requires patients to connect circles containing numbers in ascending numeric order. Part B requires patients to alternate between numbered circles and lettered circles. Possible scores range from 0 to 300 s (Part A, CID $\geq$ 22 s; Part B, CID $\geq$ 85 s).

Digit Span.[51] This subtest of the WAIS-R combines Digits Forward and Digits Backward. The tester reads aloud progressively longer series of digits, and the patient repeats each series from memory. After reaching their maximum series forward, the task is changed to repeat the digit series back in reverse sequence. Possible scores range from 0 to 28 (CID $\geq$ 4).

Memory Domain
Benton Visual Retention.[53] This measures immediate visual recall memory and visuospatial ability. Patients are presented with a series of 10 progressively more complex geometric designs and asked to draw each design from memory. Possible scores range from 0 to 10 (CID $\geq$ 2).

Benton Visual Recognition. This is a test of visual recognition memory performed in tandem with the visual retention test. After each recall drawing, patients are shown four designs and asked to select the correct original. Possible scores range from 0 to 10 (CID $\geq$ 2).

Mattis–Kovner Verbal Recall and Verbal Recognition.[54] This measures verbal recall and verbal recognition memory. The recall test consists of repeated trials to learn a 20-word list of words in a common category. The recall score is the best percentage of words correctly remembered. A probe list of 40 words containing the 20 words on the recall learning list plus an additional 20 words is then given for recognition. The recognition score is derived from the percentage of true positives and the percentage of false positives, which are used to compute the signal detection theory measure of accuracy, d'.[55] Possible recall scores range from 0 to 100 (CID $\geq$ 15). Possible recognition scores range from 0 to 3.93 (CID $\geq$ 0.7).

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