Deliberate Hypotension for Hip Arthroplasty: Still More Questions Than Answers

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For >4 decades, investigators have debated the potential advantages and disadvantages of deliberate hypotension during anesthesia for total hip arthroplasty.[1] Available data from randomized clinical trials suggest that deliberate hypotension may reduce intraoperative blood loss,[2] although past studies conflict regarding the impact of such techniques on the need for postoperative transfusion.[2,3] Moreover, because most available trials predate modern transfusion approaches,[4] little definitive evidence exists regarding the potential benefits of deliberate intraoperative hypotension for patients undergoing hip arthroplasty in current practice.

One key gap in knowledge related to the safety of hypotensive anesthesia for hip arthroplasty concerns the potential for such techniques to produce adverse neurologic consequences such as stroke. To date, available trials[2,3] have not observed large differences in the rate of such outcomes among patients undergoing hypotensive anesthesia versus other regimens for hip arthroplasty, yet these studies have varied markedly in their approaches to assess such outcomes and have been underpowered to detect differences in the rate of rare events such as postoperative stroke, which may occur in approximately 2 of every 1000 patient undergoing hip arthroplasty.[5] In this context, Bombardieri et al.[6] present new work in this issue of *Anesthesia & Analgesia* related to the potential effects of hypotensive anesthetic techniques on cerebral perfusion; and although the data that they present do not offer definitive evidence regarding the risks or benefits of hypotensive techniques for hip arthroplasty, they offer insights that may help to guide practitioners' decisions regarding the use or avoidance of such techniques and to inform future investigations in this area.

Bombardieri et al. studied 52 patients without known prior cerebrovascular disease undergoing hypotensive epidural anesthesia, a technique initially described by Sharrock and Salvati[7] that uses extensive epidural blockade and continuous epinephrine infusion guided by invasive hemodynamic monitoring. Bombardieri et al. used transcranial Doppler ultrasound to measure changes in cerebral blood flow velocity that accompanied the intraoperative reductions of blood pressure to an average mean arterial blood pressure value of approximately 50 mm Hg compared with an average baseline value (measured after the initiation of sedation but before epidural blockade) of 84 mm Hg. Although the authors found only small changes in the average change in cerebral blood flow velocity of the patients in their sample, the extent of change varied markedly from patient to patient. For example, at the first measurement taken under hypotensive anesthesia, the change in mean cerebral blood flow velocity ranged from a relative decrease of 44% from baseline to a relative increase of 87% with no clear correlation observed between mean arterial blood pressure and mean cerebral blood flow velocity. Over the course of the hypotensive episode, nearly one-fourth of their sample experienced relative decreases in cerebral blood flow velocity of 20% or more.

On a basic level, the article highlights the caution that needs to be exercised in drawing inferences for individual patients from population averages. An old joke is relevant here. Three statisticians go duck hunting. The first one shoots and misses a foot too high. The second one misses a foot too low. The third declares: "We got it!" In an analogous sense, the observation of Bombardieri et al. that cerebral blood flow velocity hardly changed at all on average is true in a statistical sense, yet it also obscures the article's more ambiguous, and more useful, finding that changes in cerebral blood flow varied widely across their sample with a substantial minority of patients experiencing potentially worrisome decreases.

Placing emphasis on the heterogeneity of the authors' findings can help move us away from binary questions about whether hypotensive epidural anesthesia is "safe" or "unsafe" in some general sense and instead encourage us to think quantitatively about the specific risks and benefits that this type of anesthesia might hold for an individual patient. Importantly, the observational, nonrandomized design of the present study precludes causal inferences regarding the effect of hypotensive epidural anesthesia on cerebral blood flow. These data highlight the need for further investigations to quantify the risk of meaningful reductions in cerebral blood flow with hypotensive anesthesia compared with other techniques and the relative importance of such reductions to neurologic outcomes that may be influenced

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Accepted for publication August 21, 2015.

Funding: Support was provided from institutional/departmental sources and the National Institute on Aging, Bethesda, MD (K08AG043548).

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0000000000001000

by cerebral blood flow and other factors such as baseline comorbidities and cerebral metabolic rate.

Although it is encouraging that the authors note that no patients in the present cohort experienced an adverse neurologic event, postoperative cognitive or neurologic outcomes were not formally assessed; moreover, given the low incidence of postoperative stroke, the relatively small samples of this and prior studies[8] preclude quantification of the risks of this technique for neurologic end outcomes. Moreover, the present work does not speak to how the risks of this approach might vary when applied outside the single center in which this study occurred. All the patients in the present cohort experienced short operative times and received care from anesthesia providers who had substantial experience with this technique. Neither the present work nor the past literature that the authors cite[3,7,8] speak to what risks and benefits this technique might carry if applied in a different context with longer surgical times or less experienced providers.

In the end, providers and researchers should think carefully about what potential benefits might be gained in terms of concrete patient outcomes in deciding where to go next with techniques such as hypotensive epidural anesthesia. Although the present study raises concern for potential adverse effects that need to be taken seriously, adequately powered randomized trials are still needed to better define the extent and magnitude of these risks. Absent these, the present work may serve as a note of caution to practitioners and patients who are considering such techniques and as a call to advocates of hypotensive anesthesia to work to more clearly quantify the potential risks and benefits of these techniques for patient outcomes.

DISCLOSURES

Name: Ignacio J. Badiola, MD.
Contribution: This author wrote the first draft of the manuscript and made critical revisions to the paper.
Attestation: Ignacio J. Badiola approved the final version of the manuscript.
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Contribution: This author made critical revisions to the paper.
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Contribution: This author made critical revisions to the paper.
Attestation: Mark D. Neuman approved the final version of the manuscript.
This manuscript was handled by: Gregory Crosby, MD.

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Section Editor: **Gregory J. Crosby**

An Observational Study of Cerebral Blood Flow Velocity During Hypotensive Epidural Anesthesia

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BACKGROUND: Hypotensive epidural anesthesia (HEA), as practiced at our institution, uses sympathetic blockade to achieve mean arterial blood pressure (MAP) of ≤50 mm Hg while administering epinephrine by infusion to support the circulation. HEA has not been associated with gross adverse effects on neurologic outcome or cognitive function in the postoperative period, suggesting adequate cerebral blood flow (CBF). However, the use of MAPs well below the commonly accepted lower limit of CBF autoregulation suggests that CBF should be significantly reduced below normal levels. To examine these conflicting hypotheses, we performed a prospective investigation of the effects of HEA on CBF velocity (CBFV), an accepted index of cerebral perfusion.

METHODS: Fifty-two hip replacement patients were studied. HEA was induced by lumbar epidural injection of local anesthetic and infusion of epinephrine to achieve an MAP of ≤50 mm Hg. Propofol/midazolam sedation was administered. Baseline CBFV was recorded pre-HEA (after sedation and before local anesthetic injection) and continuously thereafter.

RESULTS: During HEA, MAP decreased by 40% and was stable throughout. The CBFVmean at baseline and at 3 HEA intervals during surgery was 46 ± 12 (SD), 45 ± 12, 47 ± 14, and 47 ± 14 $cm \cdot s^{-1}$, respectively. Although mean CBFVmean did not vary, there was considerable heterogeneity among patients. Twelve patients (23%) experienced reductions of CBFVmean of >20% during HEA intervals (99% lower confidence limit: 9%) and 6 (12%) reductions of >30% (99% lower confidence limit: 1%). There was no correlation between CBFVmean and MAP for MAPs between 100 and 40 mm Hg ($R^2 = 0.0015$, $P = 0.44$). There were no instances of gross postoperative neurologic injury.

CONCLUSIONS: Both hypotheses proved partially correct. CBFV was sometimes well maintained during HEA, despite MAPs well below the commonly accepted lower limit of autoregulation. However, there was considerable interindividual heterogeneity with 23% of subjects having CBFV reductions >20% (99% lower confidence limit: 9%), with some reductions approaching the threshold for ischemic injury. The present data do not allow us to determine whether hypotension would be similarly tolerated in other circumstances. (Anesth Analg 2016;122:226–33)

Hypotensive epidural anesthesia (HEA), as practiced in our institution, uses deliberate reduction of mean arterial blood pressure (MAP) to 40 to 50 mm Hg by epidural anesthetic-induced sympatholysis, with the simultaneous infusion of epinephrine to provide circulatory support.[1] One of the authors of this report has been administering HEA to patients undergoing hip replacement surgery since 1987. The technique has been applied with consistently good clinical outcomes and without adverse postoperative events or adverse effects on postoperative cognitive and renal function.[1–4] However, the contemporary view of the lower limit of autoregulation (LLA) of cerebral blood flow (CBF) in adult humans inevitably leads to the concern that CBF might be precariously reduced by this technique in some patients.[5] Furthermore, an early investigation of arterial blood pressure (BP) reduction to similar levels using ganglionic blockade (without infusion of epinephrine) reported the frequent occurrence of symptoms suggestive of cerebral ischemia in nonanesthetized volunteers as MAPs approached or decreased <55 mm Hg.[6] Accordingly, the investigators entertained 2 conflicting hypotheses, that is, first, on the basis of apparently favorable outcomes over many years, that CBF is well maintained during HEA; and second, that MAP during HEA is less than the generally accepted LLA and that CBF velocity (CBFV) would be below normal levels. To attempt to resolve the inherent uncertainty empirically, we performed the present prospective investigation to examine the effects of initiation and maintenance of HEA on CBFV, an accepted index of cerebral perfusion.

METHODS

After obtaining approval from the IRB of the Hospital for Special Surgery (IRB 29075) and written informed consent

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Accepted for publication August 6, 2015.

Funding: This study was supported by funds from the Department of Anesthesiology at the Hospital for Special Surgery, New York City, NY.

Conflict of Interest: See Disclosures at the end of the article.

The study was presented, in part, at the annual meeting of the American Society of Anesthesiologists on October 20, 2010, in San Diego, CA, and at the 65th Annual Post Graduate Assembly in Anesthesiology, at the Resident Research Contest, on December 10, 2011, in New York City, NY.

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DOI: 10.1213/ANE.0000000000000985

from the study subjects, 61 patients undergoing total hip replacement with HEA were enrolled in this prospective, observational study from March to November 2010. Exclusion criteria were the presence of an indication for general anesthesia and age <18 years. Nine of the consenting subjects were eventually excluded because of an inadequate temporal window.

Patients received no premedication before arriving in the operating room. The anesthetic technique, which has been previously described,[4] was standardized and anesthesia was provided to all patients by the same anesthesiologist. After application of standard American Society of Anesthesiologists (ASA) monitoring equipment and administration of oxygen via a nasal cannula, the patients were sedated with IV midazolam (5 mg). An infusion of propofol was initiated and titrated such that subjects remained responsive at all times to loud voice or forehead tap and such that end-tidal CO_2 ($ETCO_2$) was not >45 mm Hg. The latter was monitored continuously from a sampling port in the orifice of a nasal airway. This depth of sedation was maintained for the entire study period. A radial arterial catheter was placed at the wrist, and a central venous catheter was inserted via the right internal jugular vein. Both pressures were recorded with transducers positioned at the level of the right atrium at all times. The epidural was performed with a 17-gauge Tuohy needle inserted via a paramedian approach at the L1-L2 interspace. Twenty-five to 30 mL of a mixture of 2% lidocaine and 0.75% bupivacaine was injected to achieve an anesthetic level at T4 or above. An epidural catheter was inserted, and the patient was prepared for surgery. Supplemental doses of epidural local anesthetic, which were very infrequent, were administered if hypotension or analgesia was inadequate.

The BP decreased progressively in all patients after the epidural injection. Infusion of epinephrine through the central venous catheter was initiated immediately after the epidural injection, and the infusion rate was adjusted (1–8 $\mu g \cdot min^{-1}$) to maintain a heart rate (HR) between 55 and 80 bpm and MAP between 40 and 50 mm Hg. From the outset, patients received an infusion of lactated Ringer's solution at a rate of approximately 250 $mL \cdot h^{-1}$. A "fluid load" was not administered. The rate of infusion of lactated Ringer's solution was adjusted intraoperatively as needed to replace blood loss and to maintain central venous pressure (CVP) at 0 to 5 mm Hg. The protocol provided for blood administration as needed. However, none of the patients received blood products during surgery. The continuous infusion of epinephrine was discontinued during the surgical closure. At that time, titrated boluses of ephedrine were administered to achieve a systolic BP of 90 to 100 mm Hg.

Invasive BP, HR, electrocardiogram, Spo_2, CVP, and $ETCO_2$ were monitored continuously. Data were stored electronically on a computer that downloaded hemodynamic information in real time from the monitors in the operating room.

CBFV in the middle cerebral artery (MCA) was measured by transcranial Doppler (TCD) ultrasonography with a 2-MHz probe (Sonara TCD, CareFusion, WI) using a transtemporal window, according to the method described by Aaslid et al.[7–9] All velocities were measured as close as possible to a depth of 50 mm. The MCA on the side of the operated limb was insonated to facilitate continuous monitoring in the lateral decubitus position. The Doppler signal was optimized by adjusting the position of the probe, the scale and the gain of the measurement, and the angle of insonation to obtain the best signal-to-noise ratio. All measurements were taken by a single operator. CBFV was first recorded with the patient unsedated and in the supine position. The site at which the optimal Doppler signal was identified was noted with a marking pen. After sedation, a continuous propofol infusion was initiated and, before placing the patient in the lateral position, the TCD signal was reacquired at the marked site, the probe was secured with a custom-built head band that held the TCD probe in a constant position throughout the remainder of the study period. Patients were then placed in the lateral decubitus position and remained in that position throughout surgery. All subsequent CBFV measurements were recorded in that position. "Baseline" data were obtained after establishing stable, constant propofol sedation but before epidural anesthesia was initiated. CBFV was recorded continuously to the hard drive of the TCD device throughout surgery. Data were stored for subsequent analysis. The TCD device automatically and continuously measures the following (in $cm \cdot s^{-1}$): (1) the maximal CBFV during the systolic phase of a cardiac cycle (CBFVsyst), (2) the minimum CBFV just before the acceleration phase (systole) of the next waveform (CBFVdiast), and (3) the time-averaged value of the moment-by-moment maximal velocity envelope over one cardiac cycle (CBFVmean). In addition, it calculates the Gosling pulsatility index (PI). The PI, which is dimensionless, is calculated as: (CBFVsyst – CBFVdiast)/CBFVmean.[10]

To ensure the fidelity of the data, a single operator reviewed all data using software-operated cursors to verify the accuracy of the CBFV, CBFVsyst, CBFVdiast, and CBFVmean, and the PI data that are automatically generated by the TCD device. We observed that the automated CBFV parameter identification process occasionally identified inaccurate Doppler envelopes or miscalculated HR. Accordingly, the indices for all CBFV data were calculated using manually placed cursors. CBFVmean was then calculated using the formula: (CBFVsyst – CBFVdiast)/3 + CBFVdiast, and PI was calculated as (CBFVsyst – CBFVdiast)/CBFVmean.

We observed 2 apparent deficiencies inherent to the automatically derived TCD readings that led us to consider that those data were occasionally unreliable. The TCD device in some circumstances appeared unable to distinguish between the dicrotic notch and end-diastole on the Doppler waveform, thereby yielding erroneous readings for the CBFVdiast. Second, because of artifacts in the electrocardiogram, the TCD apparatus was occasionally unable to derive HR accurately. The CBFVmean determination is dependent on an HR detection algorithm intended to identify the beginning and end of each cardiac cycle. We observed that in some instances the system misidentified the beginning and the end of cardiac cycles, erroneously detecting very rapid HRs and giving incorrect measures of CBFVsyst, CBFVdiast, and CBFVmean. Therefore, to ensure the fidelity of the data, a single operator, who was not blinded to the time point to which each of the derived CBFV measures corresponded, reviewed all data using software-operated

cursors to verify the accuracy of the CBFV parameters automatically generated by the TCD apparatus. When horizontal cursors are displayed, the CBFV parameters can be recalculated using values calculated from the placement of the cursors. At specific time points, the screen was frozen and horizontal cursors were placed on the spectrum window for manipulation: one horizontal cursor was located at the level of the highest velocity of a waveform corresponding to the CBFVsyst and the other horizontal cursor at the level of the area of the waveform before the acceleration phase (systole) of the next waveform, thus measuring the CBFVdiast. CBFVmean was then calculated using the formula: (CBFVsyst – CBFVdiast)/3 + CBFVdiast, and PI was calculated as (CBFVsyst – CBFVdiast)/CBFVmean.

The specific measurement intervals at which data were tabulated were as follows: baseline (after sedation, in the lateral decubitus position before epidural injection); 3 specific time points (HEA1, HEA2, HEA3) during the period of hypotension; after ephedrine (after MAP had recovered to at least MAP >70 mm Hg); and end of surgery (at completion of wound closure). HEA1 was designated as the time point after initiation of the epidural anesthetic at which MAP had been stable within the target range (40–50 mm Hg) for at least 5 consecutive minutes; HEA2 was immediately after the insertion of the acetabular component; HEA3 was immediately after the insertion of the femoral component of the prosthesis. Demographic information (age, sex, height, weight, ASA physical status classification) and cardiovascular risk-related information were collected.

Statistical Analysis

Continuous variables are presented as mean ± SD among subjects. To examine the changes in TCD parameters (CBFVsyst, CBFVdiast, CBFVmean, PI) with respect to baseline values, we modeled the TCD parameters as functions of time using linear regression with inference based on the generalized estimating equation (GEE) method,[11,12] with an autoregressive (1) correlation structure. The GEE method accounts for the correlation between repeated measurements on the same patient, where the autoregressive (1) correlation structure assumes a greater degree of correlation among measurements recorded closer in time, which was the observed pattern in our sample data. The GEE method is able to consider correlations between repeated measures. Unlike the conventional repeated-measures analysis of variance method, which requires variables to be normally distributed, the GEE does not require a particular distribution, thus providing a robust parameter estimation. In addition, GEE is more efficient than repeated-measures analysis of variance in estimation when there are missing data, for which the latter cannot make allowance.[11] Bonferroni corrections were performed to adjust for the multiple comparisons of principal interest, that is, baseline versus HEA1, 2, and 3, after ephedrine and end of surgery. To examine the relationship between MAP and CBFV, a Pearson correlation coefficient was calculated, using all the individual data pairs (MAP and corresponding CBFV) obtained at baseline and during the 3 HEA intervals in the 52 patients. Because Pearson correlation does not consider repeated measures within subjects, it yields inflated degrees of freedom when used in a longitudinal data setting. This results in a conservative estimation of the true correlation. A 99% asymptotic lower confidence limit[13] was calculated for the percentage of patients that experienced reductions of CBFVmean >10%, 20%, and 30%, respectively. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC). The significance level was set at 0.05. Bonferroni corrections were performed to adjust for the 5 comparisons between baseline values and each of the 5 assessments (HEA1, 2, and 3, after ephedrine and end of surgery). We had no a priori knowledge of the variability of CBFV in our anticipated population of hip replacement candidates. Accordingly, our sample size was arbitrary and was determined entirely by the number of eligible and accessible patients who presented during the time available to execute this investigation.

RESULTS

Sixty-one patients gave consent to participate in the investigation. Nine were excluded because of our inability to identify a cranial window that would permit an adequate TCD signal. The demographics and clinical characteristics of the remaining 52 patients are presented in Table 1. HEA was performed uneventfully in all patients.

There were a limited number of missing data elements as follows: CBFVmean, 2; CBFVsyst, 2; CBFVdiast 2; MAP, 4; $ETCO_2$, 12; CVP, 10; HR, 8; SpO_2, 18. The mean rate of propofol infusion was 130 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Table 2 presents the $ETCO_2$ values at all measurement intervals. Mean $ETCO_2$ was statistically unchanged at all time points. However, the ranges of $ETCO_2$ values were relatively wide. Specifically at baseline, 38 ± 5 mm Hg (range 28–46), at HEA1, 39 ± 6 mm Hg (range 25–50), at HEA2, 39 ± 6 mm Hg (range 26–53), and at HEA3, 39 ± 5 mm Hg (30–53). As a matter of established institutional practices, arterial blood gases were not obtained routinely. However, arterial blood gases were obtained during the period of hypotension in 4 patients. At the time of those 16 determinations, mean $ETCO_2$ was 37 ± 5 and mean $PaCO_2$ was 47 ± 3 mm Hg. The total volume of lactated Ringer's

Table 1. Patient Demographics and Clinical Characteristics (*n* = 52)

Sex, F/M	18/34
Age, y	59 ± 11 (range 39–85)
Height, cm	174 ± 11
Weight, kg	87 ± 22
Body mass index	30 ± 10
ASA physical status I/II/III	10/29/13
Arterial blood pressure as measured in holding area or at arrival in operating room, mm Hg[a]	
Systolic	140 ± 22
Diastolic	77 ± 11
Mean	101 ± 15
Cardiovascular risk factors (*n*)	
Hypertension	17
S/P myocardial infarction and stent	4
Atrial fibrillation	4
Others (AV block, branch block)	3
Diabetes	2

Categorical variables are presented as frequencies and continuous variables as mean ± SD.

F = female; M = male; S/P = status post; AV = atrioventricular.

[a]Noninvasive arterial blood pressure measurement before sedation.

Table 2. Physiologic Values Over Time

	Baseline[a]	HEA 1	HEA 2	HEA 3	Post-ephedrine	End of surgery
MAP, mm Hg	84 ± 11	50 ± 6[b]	49 ± 7[b]	49 ± 6[b]	70 ± 10[b]	75 ± 8[b]
HR, bpm	76 ± 12	72 ± 11	73 ± 12	73 ± 12	80 ± 13[c]	82 ± 15[d]
CVP, mm Hg	3 ± 3	3 ± 2	2 ± 3	3 ± 2	2 ± 2	2 ± 2
Spo_2, %	97 ± 3	99 ± 1[c]	99 ± 1	99 ± 1	99 ± 1	99 ± 1[c]
$ETCO_2$, mm Hg	38 ± 5	39 ± 6	39 ± 6	39 ± 5	38 ± 5	37 ± 5

Listed are the results of the univariate generalized estimating equations regression model in which time was the only covariate. Values are presented as mean ± SD.

HEA = hypotensive epidural anesthesia; MAP = mean arterial blood pressure; HR = heart rate; CVP = central venous pressure; Spo_2 = oxygen saturation; $ETCO_2$ = end-tidal carbon dioxide; HEA = hypotensive epidural anesthesia.

[a]Baseline data were acquired after sedation and before activation of the epidural.

[b]$P = 0.0005$ compared with baseline.

[c]$P = 0.05$ compared with baseline.

[d]$P = 0.01$ compared with baseline.

solution was between 1000 and 1500 mL in all patients. In the recovery room, all patients were awake and interactive. No neurologic deficits or cardiac events were apparent in the postanesthesia care unit.

Table 2 presents the physiologic data (systolic and diastolic BP, MAP, HR, CVP, Spo_2, $ETCO_2$) at the various recording intervals. Subsequent to establishing sedation by administration of midazolam and propofol by infusion (the time point that we designate as baseline), MAP decreased from the preoperative mean value of 101 ± 15 (the first noninvasive BP recorded upon arrival in the operating room) to 84 ± 11 mm Hg. After the administration of epidural local anesthetic, MAP decreased further. At HEA1, MAP decreased by 39% ± 10% (range 25%–64%), at HEA2 by 40% ± 12% (range 16%–60%), and at HEA3 by 41% ± 11% (range 17%–63%) from the baseline values. With the administration of ephedrine at the conclusion of joint replacement ("Post-Ephedrine" in Fig. 1) and with completion of the surgery ("End of Surgery"; Fig. 1), MAP recovered toward baseline levels. The time course of the study, expressed as time elapsed between measurement intervals, was as follows: baseline to HEA1, 27 ± 9 minutes; HEA1 to HEA2, 26 ± 11 minutes; HEA2 to HEA3, 21 ± 9 minutes; HEA3 to post-ephedrine, 12 ± 9 minutes; post-ephedrine to end of surgery, 8 ± 4 minutes. The total of target level hypotension (HEA1 to HEA2 + HEA2 to HEA3) was 47 ± 14 minutes.

The changes in CBFV-related parameters (CBFVmean, CBFVsyst, CBFVdiast, PI) are presented in Table 3 and Figure 1. In the description that follows, CBFV parameters are reported as mean ± SD of the estimated differences over time from baseline values. Range data are provided for only CBFVmean, which we view as the parameter that best reflects total blood flow, and because the patterns of variability for CBFVmean, CBFVsyst, and CBFVdiast were parallel and similar.

With sedation, CBFVmean decreased from 55 ± 11 (range 35–80) $cm \cdot s^{-1}$ to 48 ± 18 (range 25–90) $cm \cdot s^{-1}$. Patients were then turned to the lateral decubitus position (in which position our baseline data were obtained). Baseline CBFVmean was 46 ± 12 (range 23–70) $cm \cdot s^{-1}$. At HEA1, the mean difference ± SD in CBFVmean was −0.64 ± 8.54 $cm \cdot s^{-1}$. The mean percentage change from baseline CBFVmean at HEA1 was 1% ± 21% (range −44% to +87%). At HEA2, the mean difference in CBFVmean was 0.52 ± 9.66 $cm \cdot s^{-1}$, with a mean percentage change of 2% ± 22% (range −34% to +63%) from baseline. At HEA3, the mean difference in CBFVmean was 0.51 ± 8.28 $cm \cdot s^{-1}$, with a mean percentage change of 2% ± 19% (range −34% to +60%) from baseline values.

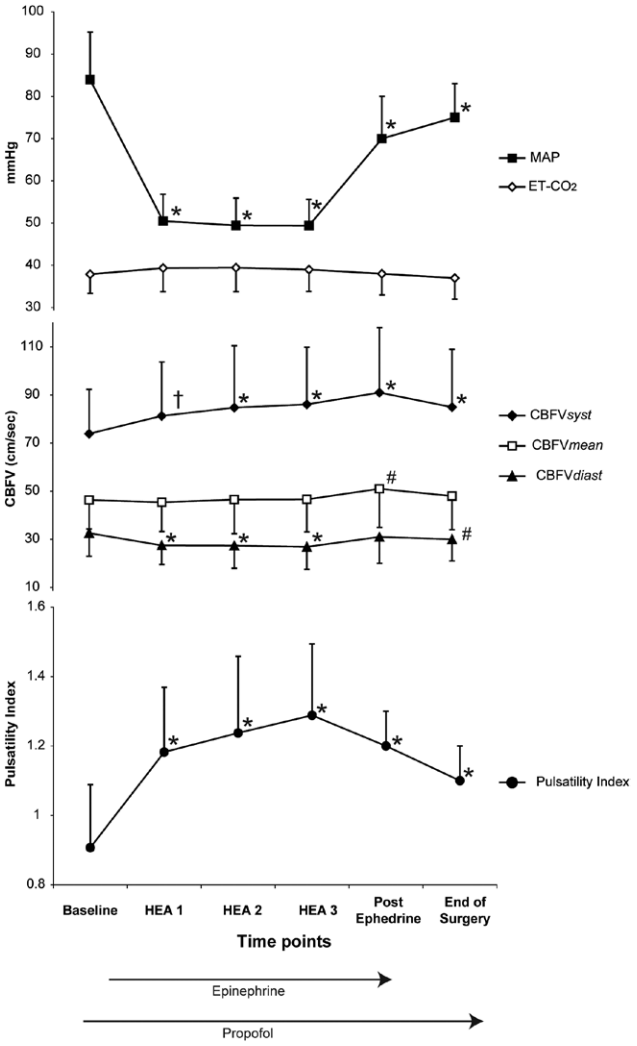

Figure 1. Changes in mean arterial blood pressure (MAP), end-tidal CO_2, cerebral blood flow velocity (CBFVsyst), CBFVdiast, CBFVmean, and pulsatility index in 52 patients during hypotensive epidural anesthesia (HEA). Values are mean ± SD. Baseline indicates values obtained after sedation and before placing the epidural. The *P* values reported are obtained from the univariate analysis. #$P = 0.03$ compared with baseline; †$P = 0.002$ compared with baseline; *$P = 0.0005$ compared with baseline.

Table 3. Cerebral Blood Flow Velocities Values Over Time Shown as Estimated Differences from Baseline Values

	Baseline value	D1 [HEA1-base] (95% CI)	D2 [HEA2-base] (95% CI)	D3 [HEA3-base] (95% CI)	D4 [post-ephedrine-base] (95% CI)	D5 [end surgery-base] (95% CI)
Mean CBFV (cm/s)	46 ± 12	−0.64 ± 8.54	0.52 ± 9.66	0.51 ± 8.28	4.51 ± 11.42[a]	2.23 ± 9.29
Peak CBFV (cm/s)	74 ± 19	8.06 ± 14.76[a]	11.62 ± 16.24[b]	12.91 ± 14.44[b]	17.51 ± 18.83[b]	11.78 ± 16.93[b]
Diastolic CBFV (cm/s	33 ± 10	−4.98 ±6.78[b]	−5.02 ± 8.01[b]	−5.69 ± 6.66[b]	−1.99 ± 9.04	−2.53 ± 6.79[a]
PI	0.9 ± 0.1	0.28 ± 0.18[b]	0.34 ± 0.23[b]	0.39 ± 0.2[b]	0.30 ± 0.19[b]	0.24 ± 0.18[b]

Listed are the results of the unadjusted generalized estimating equations analysis where time was the only covariate. Values are presented as mean ± SD of the estimated difference from baseline values.

Baseline = before placing the epidural; base = baseline; D = estimated difference from baseline; HEA = hypotensive epidural anesthesia; CBFV = cerebral blood flow velocity; PI = pulsatility index.

[a]$P = 0.01$ compared with baseline.

[b]$P < 0.0001$ compared with baseline.

- CBFVsyst at baseline was 74 ± 19 cm·s^{-1}. Thereafter, the pattern was one of the modest sustained and significant increases in mean CBFVsyst: at HEA1, the mean difference was 8.06 ± 14.76 cm·s^{-1} ($P = 0.002$ versus baseline); at HEA2, 11.62 ± 16.24 ($P = 0.0005$); at HEA3, 12.91 ± 14.44 ($P = 0.0005$).
- CBFVdiast at baseline was 33 ± 10 cm·s^{-1}. Thereafter, the pattern was one of the modest sustained and significant decreases in CBFVdist: at HEA1, the mean difference was −4.98 ± 6.78 cm·s^{-1} ($P = 0.0005$ versus baseline); at HEA2, −5.02 ± 8.01 ($P = 0.0005$) cm·s^{-1}; and at HEA3, −5.69 ± 6.66 ($P = 0.0005$) cm·s^{-1}.
- In keeping with the changes just mentioned, that is, CBFVsyst increases, CBFVdiast decreases, and an unchanged CBFVmean, PI increased significantly from baseline: baseline 0.90 ± 0.18, with a mean difference at HEA1, 0.28 ± 0.18 ($P = 0.0005$ versus baseline); at HEA2 0.34 ± 0.23 ($P = 0.0005$); and at HEA3 0.39 ± 0.2 ($P = 0.0005$).
- While mean CBFVmean did not change during HEA, as is demonstrated by the CBFV range data presented earlier, there was considerable heterogeneity among patients. Twenty-three of the 52 patients (44%) experienced reductions in CBFVmean of >10% (99% lower confidence limit: 28%), 12 of whom (23%) had reductions >20% (99% lower confidence limit: 9%), and 6 of whom (12%) had reductions >30% (99% lower confidence limit: 1%). The greatest reduction in CBFVmean observed in an individual patient at any HEA interval was 44%. There was, however, no correlation between mean CBFV and MAP for values of MAP ranging from 100 to 40 mm Hg ($R^2 = 0.0015$, $P = 0.44$; Fig. 2).

DISCUSSION

Our observations revealed that CBFV was on average well preserved during HEA, as performed by us using an infusion of epinephrine for circulatory support. During a 40% reduction of MAP, from a mean 84 ± 11 mm Hg to a mean 50 ± 6 mm Hg, mean CBFVmean remained at baseline values. However, while mean values remained at baseline, there was substantial interindividual variability such that 12% of the population experienced reduction of CBFV of >30% (99% lower confidence limit: 1%). The results thus indicate that the hypothesis that at an MAP of 50 mm Hg would result in substantial reduction of CBF is only occasionally correct. The results therefore imply that an MAP of 50 mm Hg is below the LLA for some, although not for all, middle-aged adults. This latter conclusion is consistent with numerous investigations that indicate that there is considerable variability in the adult human LLA.[6,14,15] In those investigations, all performed in normotensive subjects; the LLA of individual subjects varied from 41 to 113 mm Hg.[5] Despite the CBF reductions that occurred in some individuals, the present observations are also nonetheless consistent with the minimal central nervous system morbidity that has been associated with our HEA technique over a long period of time.[1,3,4] Central nervous system ischemia, as revealed by clinical signs or electroencephalogram-evoked response changes, does not typically occur until CBF has been reduced by 40% to 60% of baseline values[6,16–19] and even at these threshold levels is not rapidly injurious.[17,20,21] The results do, however, indicate that at MAPs of 50 mm Hg, some individuals are likely to be close to the limits of cerebral tolerance for BP reduction. That concern is consistent with previous investigations of BP reduction using ganglionic blockade (without infusion of epinephrine) in which symptoms suggestive of cerebral ischemia were observed frequently in nonanesthetized volunteers with MAPs in the range of 50 to 55 mm Hg.[6,16] We are uncertain as to whether or to what extent the sedation (midazolam and propofol) used in our patients contributed to the apparent tolerance of the substantial CBFV reduction that occurred in some patients. However, on the basis of investigations of patients undergoing carotid endarterectomy, we doubt that the effect was clinically significant. Those investigations indicate that CBFV reduction in the MCA up to 70% is frequently tolerated and that the tolerance is similar in patients receiving either general anesthesia with electroencephalogram monitoring or local-regional anesthesia with neurologic examination with no or minimal sedation.[22–26] It should be noted that none of the patients enrolled in the present study had a known history of cerebral vascular disease and that while there were no gross neurologic deficits in the immediate postoperative period, neither detailed postoperative neurologic examination nor cognitive function testing was part of our protocol.

There are at least 3 factors inherent to our HEA anesthetic technique that may have contributed to the maintenance of mean CBFV at prehypotensive baseline levels. The first is hypercapnia. On the basis of our limited comparisons of E_{TCO_2} and arterial CO_2 (see Results section), we suspect that $Paco_2$ was between 47 and 49 mm Hg in the majority of our

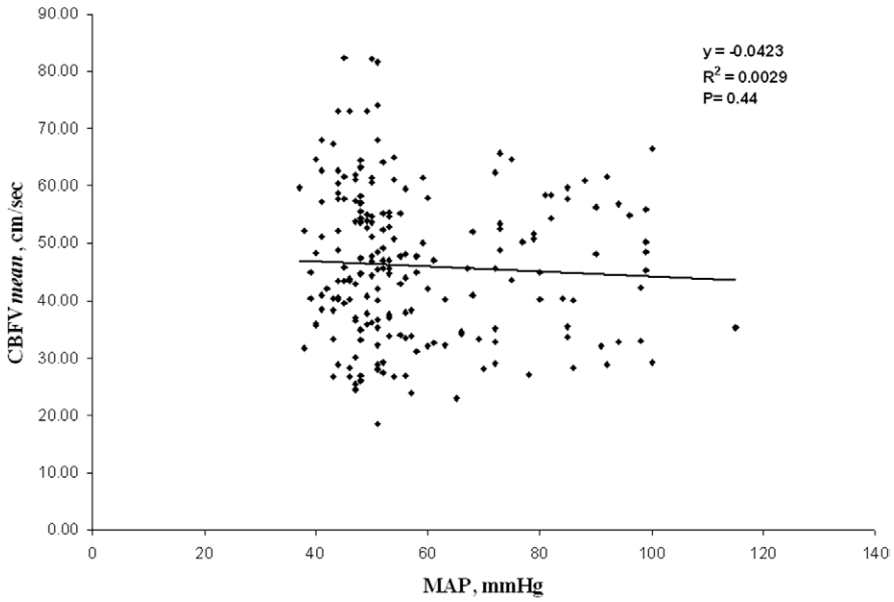

Figure 2. Scatter plot of the lowest mean cerebral blood flow velocity (CBFVmean) observed in the 52 patients at any of the 3 hypotensive epidural anesthesia intervals plotted against the simultaneous mean arterial blood pressure (MAP).

study subjects during HEA. Hypercapnia has been shown to increase CBFV during propofol sedation.[27] Accordingly, the cerebral vasodilatory effect of hypercapnia, which can augment CBF even when CBF has decreased as a result of reduction of MAP to levels below the LLA,[28] may have contributed to the preservation of CBFV. Because $ETCO_2$ was constant over time (Fig. 1), it seems unlikely that the results were influenced between measurement intervals by intrastudy $Paco_2$ variation. Nonetheless, it is possible that more than appreciated hypercapnia contributed to the maintenance of CBFV in some of our subjects.

Second, sedation may have blunted the autonomic response to hypotension. The sympathetic response to the decreasing of BP has been shown to contribute to the reduction of CBF that occurs during hypotension.[29] This is thought to be mediated, at least in part, via adrenergic innervation of extracranial and proximal intracranial arteries,[30,31] because CBF reduction is attenuated by blocking or extirpating the cervical sympathetic chain.[29] It is possible that this sympathetic response was reduced by the sedation (a combination of midazolam and propofol) that our patients received and that, in the absence of sedation, greater reductions in CBF might have been observed.

The third is the use of an epinephrine infusion to maintain MAP during HEA. There are 3 possible mechanisms by which epinephrine may have influenced our results: (1) direct effects of epinephrine on CBF; (2) an effect of epinephrine on the diameter of the MCA; and (3) indirect effects of epinephrine on CBF via effects on cardiac output (CO). (1) Epinephrine in large doses has been shown to cause an increase in CBF, probably secondary to an increase in cerebral metabolic rate.[32] This effect may have caused some augmentation of CBFV in our patients. (2) The use of CBFV as a surrogate for CBF requires that the diameter of the insonated vessel (the MCA) remains constant. Numerous investigations suggest that this is the case in most physiologic circumstances (with vasospasm being the conspicuous exception; see Moppet and Mahajan[9] for discussion). Although intraluminal epinephrine in clinically used doses is not recognized to be a vasoconstrictor of vessels in the vicinity of the circle of Willis, we cannot exclude the possibility of some increase in CBFV as a result of vasoconstriction of the MCA. (3) Of the 3 mechanisms, we consider CO to be the most likely to be significant. Epinephrine is used in our HEA protocol to support MAP. However, as previously demonstrated by Sharrock et al.,[33] epinephrine in the dose range used in the present investigation augments CO during HEA. Furthermore, in that investigation, not only was CO better preserved with epinephrine for MAP support than with phenylephrine[33,34] but at comparable MAPs symptoms suggestive of cerebral hypoperfusion were sometimes evident when epinephrine was not administered.[33] In that investigation, permitting MAP to decrease without epinephrine support led to significant reduction in filling pressure, systemic vascular resistance, HR, and CO. When cardiac index was <1.8 $l \cdot min^{-1} \cdot m^{-2}$ symptoms of drowsiness, nausea, and yawning occurred, suggesting reduced cerebral perfusion.

Although the widely reproduced diagrams of CBF autoregulation, depicting CBF as a function of MAP (or cerebral perfusion pressure), do not acknowledge CO as a relevant variable, there is, in fact, considerable additional evidence that, in at least some circumstances, it is.[35–42] Ogoh et al.[35] reported a linear relationship between CO and MCA mean blood velocity at rest and during exercise that was independent of $Paco_2$. Ide et al.[36] observed that the increase in CBFV that normally occurs during intense exercise was attenuated by β-blockade. Because β-blockade had no effect on CBFV during minimal exercise, they surmised that the effect was the result of limitation of CO. The same authors reported that patients with atrial fibrillation also had a reduced ability to increase cerebral perfusion during exercise, which they attributed to their impaired ability to increase the CO.[37,39] A study by Kim et al.[42] revealed that increases in CO without changes in MAP increased CBF in the setting of cerebral vasospasm after subarachnoid hemorrhage. In this context, we note that our observations of frequent preservation of CBFV during hypotension stand in apparent contrast

to those of Minville et al.[43] Those authors studied the effect of spinal anesthesia on CBFV in elderly patients and found a decrease in CBFV in patients who developed hypotension (MAP 74 mm Hg).[43] However, pressors and inotropes were not administered to those patients (and CO was not measured). In composite, the literature just cited suggests that preservation of total systemic blood flow by epinephrine infusion may also have contributed to the maintenance of CBFV observed in the present investigation.

In developing the present study protocol, we initially considered comparing phenylephrine and epinephrine as agents to achieve MAP support during HEA. However, considering the long history of successful application of the current HEA protocol and the results just cited, we concluded that the approach would be unethical. But because of the absence of the phenylephrine comparator group and measurements of CO, we cannot draw any conclusion about the precise role of epinephrine on our observations of CBFV. However, we believe that epinephrine infusion maintained CO during HEA and contributed to the preservation of CBFV in the patient cohort reported herein. Accordingly, we feel that our observations of the effect of hypotension on CBF should not be assumed to apply to any other hypotensive regimens.

In addition to CBFVmean, which we have accepted as the TCD parameter that best reflects total CBF, we have reported CBFVsyst, CBFVdiast, and the Gosling PI. We observed that, while mean CBFVmean was unchanged during HEA, there was, in general, a small but significant increase in CBFVsyst and a small but significant decrease in CBFVdiast. The increase in CBFVsyst is probably the result of the autoregulation-mediated decrease in cerebral vascular resistance that occurs during hypotension; and the decrease in CBFVdiast is probably related to the decrease in diastolic pressure observed during HEA. Reflecting the increase in CBFVsyst and the decrease in CBFVdiast, PI was increased. Although increased PI has been reported by others during hypotension,[40] the physiologic significance of this increase is uncertain.[9,44]

Previous studies have demonstrated that HEA is associated with early recovery of cognitive function.[1,45] Although no gross postoperative delirium or cognitive dysfunction was observed in our patients in the immediate postoperative period, neither detailed postoperative neurologic examination nor cognitive function testing was part of our protocol. In this context, it should also be noted that the period of hypotension in the present investigation was also relatively brief, that is, 47 ± 14 minutes.

In summary, our observations revealed that, during an HEA regimen that includes circulatory support using epinephrine by infusion, CBFV is on average well maintained, despite an MAP reduction to 40 to 50 mm Hg. However, there was considerable interindividual variability in the CBFV response to HEA such that 12% of our patients experienced CBFV reduction of >30% (99% lower confidence limit: 1%) of the prehypotension levels and were therefore probably encroaching on the thresholds for cerebral ischemia. In our CBFV observations, our data did not allow determination of the role of epinephrine, which has previously been shown to provide CO support in this setting. However, we doubt that our observations should be assumed to apply to other hypotensive regimens. The determination as to whether CBF is similarly well preserved with other induced hypotensive techniques will require focused investigation of those specific regimens. ■

DISCLOSURES

Name: Anna Maria Bombardieri, MD, PhD.
Contribution: This author developed the protocol, collected all the data, wrote first draft of the manuscript, did extensive editing of the manuscript, and is the archival author.
Attribution: Anna Maria Bombardieri approved the final manuscript.
Conflict of Interests: None.
Name: Nigel E. Sharrock, BMedSci, MB, ChB.
Contribution: This author developed the study concept and design and performed anesthesia for all subjects.
Attribution: Nigel E. Sharrock approved the final manuscript.
Conflict of Interests: None.
Name: Yan Ma, PhD, FCCP.
Contribution: This author performed statistical analysis.
Attribution: Yan Ma approved the final manuscript.
Conflict of Interests: None.
Name: George Go, BS.
Contribution: This author helped in technical assistance with data collection and preparation of the figures.
Attribution: George Go approved the final manuscript.
Conflict of Interests: None.
Name: John C. Drummond, MD, FRCPC.
Contribution: This author developed the study concept and design and did extensive editing of the manuscript.
Attribution: John C. Drummond approved the final manuscript.
Conflict of Interests: John C. Drummond has received lecture honoraria from Hospira in connection with dexmedetomidine.
This manuscript was handled by: Gregory Crosby, MD.

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