SPECIAL ARTICLE

Challenging Conventions to Make a Difference in Patient Care

The 2017 Gaston Labat Award Lecture

Nigel E. Sharrock, MB, ChB, BMedSci

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When reviewing the topic for this talk, I realized my overarching mission in research has been to challenge conventions to improve patient outcomes. I shall focus on 4 areas of research that were developed at the Hospital for Special Surgery (HSS).

First, some chronology. I am from New Zealand, and I am the second New Zealander to receive this award. Sir Robert Reynolds Macintosh was born in Oamaru, close to where I went to medical school in Otago. He was the second Labat awardee and recognized worldwide for developing the Macintosh laryngoscope blade. In regional anesthesia, he is recognized for developing the Macintosh balloon, a device to measure loss of resistance to aid in identification of the epidural space.[1] His patron and supporter was Lord Nuffield, who funded a number of Nuffield chairs at Oxford and insisted on one for his friend Robert Macintosh. He became the first Nuffield professor of anesthesia in Oxford and in Great Britain.[2] Like me, he developed his career overseas—in his case at Oxford, and in mine, Boston and New York.

I completed my medical school training in 1971, having done a year of research on exercise physiology and metabolism.[3] After graduating, I came to the United States in December 1972 and completed a residency at Albert Einstein Hospital in the Bronx, then worked at Peter Bent Brigham Hospital in Boston for 2 years, Lenox Hill Hospital in New York City for 9 years, and have been at the HSS in New York City since 1986. Each location was formative in its own way.

I shall present 4 conventions I have challenged. First, that shoulder surgery should be performed under general anesthesia; second, that general anesthesia is the anesthetic of choice for total hip arthroplasty (THA) and total knee arthroplasty (TKA); third, that the best thromboprophylaxis for total joint is potent anticoagulants following surgery, and finally, I shall challenge the concept that hypotension is contraindicated in the elderly high-risk patients if hypotensive epidural anesthesia (HEA) is used.

The first convention: All shoulder surgeries must be performed under general anesthesia. Alon Winnie[4] was the sixth recipient of the Gaston Labat Award in 1982, and he developed the concept of plexus anesthesia and described the interscalene block (ISB) in 1970. His classic article is worth reading. In it, he noted, "The interscalene technique is particularly useful in patients who are unable to cooperate due to inebriation, disorientation, or the extremes of age."

From the Department of Anesthesia, Hospital for Special Surgery, New York, NY.
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Address correspondence to: Nigel E. Sharrock, MB, ChB, BMedSci, Department of Anesthesiology, Hospital for Special Surgery, 535 E 70th St, New York, NY 10021 (e-mail: sharrockn@hss.edu).
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In this context, I performed my first ISB in 1974 in the Bronx on a catatonic schizophrenic patient who had a forearm fracture. He did not budge with the skin puncture but moved as I advanced the needle. I considered this as a paresthesia and injected a healthy dose of local anesthetic, and the block worked fine. At the Peter Bent Brigham, I published my first article on regional anesthesia in 1976 entitled, "An Improved Technique for Locating the Interscalene Groove."[5] By the time I had left Lenox Hill Hospital in 1986, I had performed more than 1000 cases of ISBs, all using the paresthesia technique. I arrived at the HSS proficient at ISB.

In the 16 years since Winnie's original description of ISB, there were only a handful of publications of the technique for shoulder anesthesia—mainly manipulation of the shoulder. The convention was general anesthesia for shoulder surgery. In 1971, Balas[6] described using ISB in combination with a T1–T2 paravertebral block for major shoulder surgery, which I had done, and this was the recommendation in 1986. This approach seemed impractical for general use and carried the risk of pneumothorax or total spinal anesthesia.

I had a chance conversation with a fellow surgeon, Allan Inglis, who also taught anatomy at Cornell Medical School. I asked him whether an ISB alone would be sufficient for open shoulder surgery. We discussed the relevance of the paravertebral block, and his belief was that ISB alone should be fine. So I went ahead and gave an ISB alone for a total shoulder replacement, and it worked fine.

Next thing, the sports medicine surgeons wanted to use ISB for shoulder surgery in the sitting position rather the lateral position because this gave them better exposure with less risk of traction nerve palsy. Within a couple of months, the sports surgeons were describing the technique at meetings. They published a series of 50 cases with a photograph of a patient awake in the sitting position.[7] The technique benefited both the patient and the surgeon. It enabled the surgeons to be more comfortable using the sitting position, thus making surgery easier. The surgeons promoted the technique, and ISB became the standard for shoulder surgery around the world.

I thought this was totally novel, so I asked our librarian to do a thorough literature search. There were 2 reports of ISB for open shoulder surgery: in 1979, 2 case reports from Singapore,[8] and in 1982, a series of 46 cases with 20% failure or complication rate.[9] The evidence suggests that the concept of being able to reliably perform major surgery on the shoulder under ISB was novel. In addition, operating in the sitting or beach-chair position under regional anesthesia was novel and changed the standard for shoulder surgery. We went on to publish several articles on ISB for shoulder surgery[10,11]—most notably, the landmark article by Bill Urmey et al[11] documenting the diaphragm paralysis with an ISB. He went on to publish many articles on this, defining the physiology in detail.

Convention 2: Total hip and knee arthroplasties are best performed under general anesthesia. This was the standard of care in 1986 when I arrived at HSS. At that time, HSS was performing 1% of all THAs and TKAs in the United States. The standard of care was general anesthesia, although some patients received

spinal anesthesia. Although it was known that spinal or epidural reduced blood loss and deep vein thrombosis (DVT), this had had little impact on anesthetic practice.

One of the major questions in anesthesia was: Is regional anesthesia safer than general anesthesia? The Hospital for Special Surgery was a place to potentially study this question. I had the belief that regional anesthesia had to be better for total joint arthroplasty for 3 reasons: it resulted in less blood loss, less DVT, and, as Henrik Kehlet and Philip Bromage[12] (prior Gaston Labat awardees) had pointed out, metabolic injury is modulated with effective regional anesthesia.

In 1986, I made a number of changes to the care of patients having joint replacements. We replaced general anesthesia with epidural or spinal anesthesia, improved postoperative care, utilized hemodynamic monitoring more frequently, and introduced hypotensive anesthesia for THA.

By 1992, we had 5 years of experience (1987–1991) to compare with prior years (1981–1985 inclusive), so we examined all-cause in-hospital mortality for the 2 periods. We excluded 1986 as this was a transition year. Fractured hips and total hip for metastatic cancer were excluded, so we studied only elective THA and TKA. In addition, we collected a randomized sample of 100 THAs and 100 TKAs from each time period to assess patients' profiles, anesthetic practice, and perioperative care in the 2 time periods.[13]

The limitations of the study are that it was not randomized, was performed at a single institution, and it was retrospective. However, this is a natural experiment with a hard outcome (death), assessing a large cohort of patients (approximately 15,000), and there were significant differences between groups.

First, there was an almost complete conversion from general to epidural anesthesia (Fig. 1) within 12 months. This resulted in a significant reduction in all-cause mortality for THA (0.36% to 0.1%, $P = 0.03$) and for TKA (0.44% to 0.1%, $P = 0.01$). The overall mortality in the 2 groups was 23 of 5874 patients in 1981–1985 compared with 10 of 9685 patients in 1987–1991 (0.39% to 0.1%, $P = 0.0003$).

The role for regional anesthesia is most compelling in patients undergoing TKA for several reasons. The surgery remained much the same, the perioperative fluids were similar, and the change from general to epidural (Fig. 1) was almost complete.

The differences between the THA cohorts in the 2 time periods are a little more complex. The intraoperative fluid was 3100 mL in 1981–1985 compared with 1563 in 1987–1991. The blood loss was

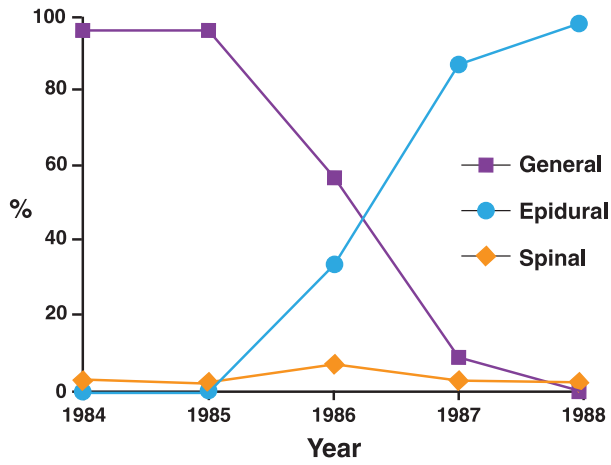

FIGURE 1. The percentage of patients who received general, epidural, or spinal for TKA at the HSS from 1984 to 1988. Reprinted with permission from Sharrock et al.[14]

841 mL compared with 295 mL, respectively. The use of hypotensive anesthesia increased from 15% to 100%.

One other observation was noted in this study; there was a lower rate of fatal pulmonary embolism (PE) in the 1987–1991 time frame. There were 7 deaths of 5874 patients in 1981–1985 compared with 2 of 9685 in 1987–1991 ($P = 0.02$). This was the first study to demonstrate the effect of epidural anesthesia on fatal PE.

Fast forward 20 years to 2013. Memtsoudis et al[15] published data from a national database verifying a 2-fold increased risk of death with general anesthesia compared with neuraxial anesthesia for total joint arthroplasty. It is my view that this difference may be even greater (closer to 4-fold) if optimal regional anesthesia is used. Nowadays, neuraxial block is considered the optimal care in many countries, especially those with national health care systems, and it is widely recognized as the method of choice in the orthopedic community.[16]

Convention 3: Thromboembolism following total joint arthroplasty should be managed with potent anticoagulants. This approach began in 1970 and gained momentum with the introduction of low-molecular-weight heparin (LMWH) in the 1980s. The known adverse effect of these agents was the ever present risk of postoperative bleeding.

In 1986, when I arrived at HSS, the following was recognized. In the 1960s, the rate of fatal PE following THA was 1%, falling to 0.1% to 0.2% by the mid-1980s. The treatment was solely reliant on postoperative potent anticoagulation using either warfarin or LMWH. It was also known that epidural or spinal anesthetic somewhat lowered the rate of DVT. Nevertheless, the rate of proximal DVT in THA was still 20% to 30%. Finally, there was some evidence that DVT began during, rather than following, surgery.[17]

This posed the question: If DVT forms during surgery, could anesthesiologists impact thromboembolism? Furthermore, if anesthesiologist could lower the rate of DVT, it may be sufficient to enable the use of less powerful anticoagulants, thereby reducing the risk of postoperative bleeding.

In 1986, the setting at HSS was conducive to studying this issue. Approximately a thousand THAs were performed annually, and all patients had operative limb venography on postoperative days 5 to 7 as part of their standard care. This provided a setting to study DVT in a large cohort of patients.

The first question to study was: Could intraoperative interventions lower DVT rates? To address this, we elected to study intraoperative intravenous unfractionated heparin on DVT rates. We chose a dose of 1000 U/h based on conversations with Peter Harpel, a research hematologist. We performed a double-blind randomized trial of intravenous unfractionated heparin compared with saline on rates of DVT. The heparin was given intravenously as a dose of 1000 U at incision, with top-up doses of 500 U every 30 minutes until the end of surgery. Epidural catheters were placed 1 hour prior to the first dose of heparin.[18]

One hundred twenty-six patients received venograms and were included in the analysis. Twenty-four percent developed DVT in the saline group compared with 8% in the heparin group ($P = 0.03$). The proximal rates were 9% and 2%, respectively. This proved the concept that an intraoperative intervention such as intraoperative heparin could lower DVT rate. It also showed that the proximal rate of 2% with heparin was one-tenth the expected rate at that time.

The next question was: Can epidural anesthesia also influence DVT rate with TKA performed under tourniquet as well as THA? To study this, we utilized the natural experiment occurring at HSS during the transition from general to epidural anesthesia (Fig. 1). We performed a retrospective review of all cases from September 1984 until December 1988, excluding the few cases performed

under spinal anesthesia. All patients had operative limb ascending venography and had either epidural or general anesthesia.[14]

Five hundred forty-one patients were included: 264 received general, and 277 received epidural anesthesia. The overall DVT rate was 64% with general and 48% with epidural ($P < 0.0001$). This represents only a 25% reduction. However, the proximal DVT rate was more impressive, a 2-fold difference (9% vs 4%, $P < 0.05$). This demonstrated that DVT rate was lower with epidural in TKA, but the impact was less impressive than THA.

The next question was: What modifiable factors contributed to DVT during THA? To study this, we studied a cohort of 441 consecutive patients performed by a single surgeon. Three hundred eighty-one had operative limb venography successfully performed. Two variables were assessed—duration of surgery and whether hemodynamics were stabilized by an epinephrine infusion or crystalloids alone during surgery.[19]

Both the duration of surgery and the use of low-dose epinephrine (LDE) intravenous infusions reduced both DVT rates and proximal DVT rates. The difference is clinically most significant with proximal DVT rates (Fig. 2). The proximal DVT rate with surgery of less than 70 minutes was similar between groups (3.3% vs 1.8%). By contrast, if surgery lasted more than 70 minutes, the rate was 13.3% and 3% in the crystalloid and LDE groups, respectively. The 3% rate with LDE was a fraction of the expected rate at the time, whereas 13.3% was similar to the expected rate.

This raised the question: How was epinephrine acting to reduce DVT rate—especially proximal DVT rate? We wondered whether this was due to an effect on fibrinolysis or blood flow. To study this, we randomized 30 patients undergoing THA to receive LDE infusion or phenylephrine during surgery.[20] Mean arterial blood pressure (MAP) was maintained at 50 mm Hg in both groups.

Fibrinolytic activity was similar in both groups, so this was not the mechanism. By contrast, there were significant differences in cardiac output between groups. Cardiac index was preserved with LDE but was reduced 30% with phenylephrine ($P < 0.001$). Our conclusion was that LDE was reducing DVT rate by increasing blood flow and reducing venous stasis, so we chose to study this: Could LDE infusion increase lower-extremity deep venous blood flow during surgery to account for the low DVT rate?

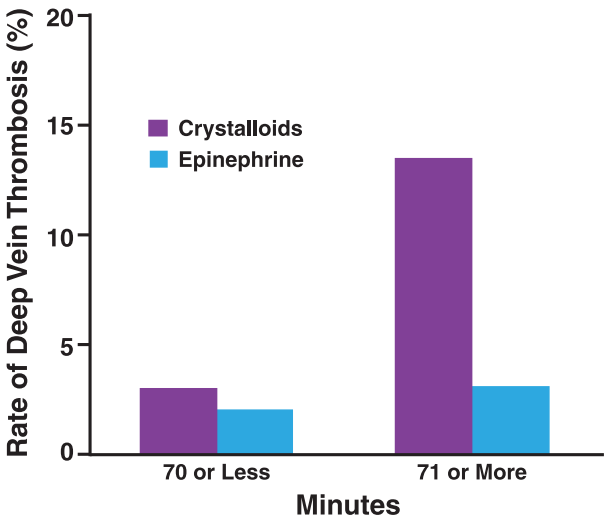

FIGURE 2. The proximal DVT rate in patients receiving crystalloid alone or low-dose epinephrine infusions. Patients are subdivided further according to surgical duration of less than or longer than 70 minutes. Similar rates of proximal DVT are seen in patients receiving low-dose epinephrine irrespective of surgical duration, whereas higher rates are observed in patients receiving crystalloid alone when surgery lasted longer than 70 minutes. Reprinted with permission from Sharrock et al.[19]

To examine this, we performed a complex crossover study design in patients undergoing THA. We measured deep venous blood flow with occlusion plethysmography at baseline, following infusions of both epinephrine and norepinephrine (NE) (2 μg/min each). Epidural anesthesia was then induced and MAP maintained at 50 mm Hg using both LDE and NE. The order of infusing LDE or NE was randomized.[21]

Calf blood flow was reduced with NE. By contrast, calf blood flow increased with LDE both before and after the epidural. Calf blood flow increased from 3.7 mL/100 mL per minute at baseline to 6.3 mL/100 mL per minute with LDE infusion during epidural anesthesia, a 70% increase despite a MAP of 50 mm Hg. This suggested that enhanced blood flow during surgery may be a very important factor in reducing DVT, especially during longer cases.

The next issue to study was: Exactly when during surgery are clots beginning to form—is it throughout surgery or during specific phases? The work of Planès et al[22] demonstrated that during surgery on the femur, the femoral vessels are kinked and that this period of femoral venous occlusion may be the most important factor. To define the timing of clot formation, we studied markers of thrombogenesis during different phases of surgery.

When thrombin is formed, it acts on fibrinogen to form fibrin. In the process, a cleavage product, fibrinopeptide A (FPA), is formed. Fibrinopeptide A has a half-life of 5 minutes, so it can define the timing and magnitude of thrombogenesis. In a series of studies, we measured FPA and other markers of thrombogenesis during different phases of surgery, for which we received the John Charnley Award from the American Hip Society.[23] This study demonstrated that there was minimal activation of thrombosis during the first phase of surgery including insertion of the acetabular component. During surgery on the femur, there was a profound increase in thrombogenesis, which rapidly decreased following surgery.

The effect of a single dose of heparin administered following insertion of the acetabulum prior to surgery on the femur was then studied. Using a blinded randomized trial, we assessed 3 groups: a placebo (saline) and 2 doses of intravenous heparin, that is, 10 and 20 U/kg, groups, following insertion of the acetabular component.[24] As can be seen in Figure 3, there is no increase in FPA following insertion of the acetabulum. Fibrinopeptide A increased markedly in the placebo group during surgery on the femur ($P < 0.0001$) and decreased 30 minutes following surgery. Heparin in both doses of 10 and 20 U/kg suppressed the response, so we considered the effective dose to be 15 U/kg of heparin. Bleeding was not increased by this single dose of intravenous heparin.

The natural question was: How effective would this single injection be in a large cohort of patients on PE, bleeding complications, and other clinical outcomes? We prospectively studied a cohort of 1947 patients having THA performed by 2 surgeons and a single anesthesiologist (N.E.S.) who had 15 U/kg of unfractionated heparin injected intravenously following insertion of the acetabular component.[25] All patients were followed up at 3 months. There were 12 patients with clinical evidence of PE (0.6%). There were no deaths from PE. The transfusion rate was 6%, the periprosthetic infection rate was 0.1%, and there were no strokes. One patient died (0.05%). This verified the safety and clinical effectiveness of this technique. Eighty-eight percent of the patients received aspirin postoperatively; the remainder received warfarin.

Improving blood flow following surgery is also important to prevent DVT. We studied the effect of different types of pneumatic compression devices, which demonstrated they all increase femoral

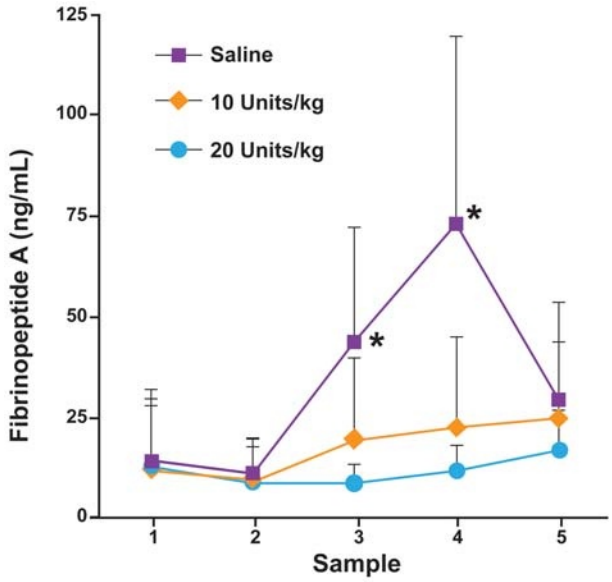

FIGURE 3. Blood levels of FPA during hybrid total hip replacement. Note the increase in FPA in the saline group and the significant suppression in the 10- and 20-U/kg heparin groups during insertion of the femoral component. Values are mean ± SD. *P = 0.0001 compared with 10 and 20 U/kg. Reprinted with permission from Sharrock et al.[24]

venous blood flow.[26] Interestingly, peak femoral venous blood flow was markedly increased by active foot flexion/extension exercises, which are now routinely recommended.

These studies lead to the concept of multimodal thromboprophylaxis.[27,28] It is based on enhanced deep venous blood flow in the legs during and following surgery. Periods of femoral venous occlusion are minimized during femoral implantation, and selective intravenous heparinization is used prior to femoral implantation. These maneuvers decrease the risk of DVT so that aspirin 325 mg twice daily can be the only chemical thromboprophylaxis agent. This approach is less expensive and safer and may be more effective than potent anticoagulants.

To study this issue, we performed a systematic review comparing multimodal thromboprophylaxis against powerful anticoagulants (LMWH, etc).[29] All case series were followed for at least 6 weeks, and all-cause mortality and clinical PE were recorded. All-cause mortality was significantly lower with multimodal prophylaxis (0.41% vs 0.19%, P = 0.01). Likewise, clinical PE was lower using multimodal DVT prophylaxis. (0.6% vs 0.35%, P = 0.02).

The next year, 2009, the American Association of Orthopaedic Surgeons Recommendations on Thromboprophylaxis was published advocating aspirin as an ideal agent in noncomplicated cases.[30,31] One of the authors of this publication recently e-mailed us in November 2016 to say that at a national meeting 83% of orthopedic surgeons are using aspirin rather than powerful anticoagulants, up from 62% the prior year. He jested that it may be 100% next year (personal communication [e-mail] from Javad Parvizi, MD, November 13, 2016).

This has been a cooperative endeavor with input from multiple specialties—epidemiology, hematology, cardiology, orthopedics, statistics, and anesthesiology. We "took on the big pharma" and won.

The final convention to be challenged was: Do not lower blood pressure especially in the elderly vasculopathic patients as they are likely to stroke out or die. The pressure to challenge this convention was due to the setting at HSS in 1986. The average intraoperative blood loss was approximately 1 L, 50% to 80% were transfused, and many developed acute respiratory distress syndrome following surgery from fluid overload.

What was known in 1986 was that hypotensive anesthesia could reduce blood loss, but was advocated only for young healthy patients—not the elderly vasculopathic patients undergoing THA. In addition, it was known that epidural anesthesia reduced blood loss and DVT compared with general anesthesia. The question was: Could it be possible to safely combine the benefits of hypotension and epidural anesthesia for this elderly high-risk cohort of patients? The aim was to develop a technique combining both the benefits of hypotension and epidural anesthesia mainly to lower blood loss and lower DVT/PE rate.

Our first study in 1986 was an observational cohort with patients awake to assess cognitive function. Patients also had a V5 electrocardiogram lead and pulmonary artery catheters to assess cardiac ischemia and performance. The inclusion criteria were 1-stage bilateral THA, complex revision THA, or unilateral THA in medically high-risk patients.[32]

We tried lowering blood pressure alone using fluid to support blood pressure, but this resulted in a reduced cardiac output. We infused different vasopressors: isoproterenol, dopamine, ephedrine, NE, and phenylephrine. These agents caused either tachycardia or low cardiac outputs with MAP of 50 to 60 mm Hg and were difficult to manage. Finally, we studied LDE by early 1987, and a case series was published in 1990.[32] It demonstrated that at zero epinephrine with MAP of less than 60 mm Hg there was a 30% reduction in cardiac index (CI), and when CI was 1.8 L/m^2 or less, patients developed signs of central nervous system impairment, namely, nausea, yawning, and lightheadedness, often with bradycardia. With LDE, CI increased in a dose-dependent fashion. Similar observation had been made by John Bonica et al[33] (the first Gaston Labat awardee) 20 years earlier.

What is HEA? It is an extensive neuraxial blockade with preserved filling pressures utilizing an LDE intravenous infusion. The circulatory effects of LDE include arterial vasodilatation of large and small vessels, venoconstriction, an augmentation of systolic function (inotropic effect), and diastolic relaxation (lusitropic effect). Epinephrine in low physiological doses is designed to increase cardiac output and redistribute blood flow to the brain, heart, and skeletal muscle.

We have studied the physiological effects of HEA in a number of studies—first by comparing LDE with phenylephrine.[34] Low-dose epinephrine is associated with a preservation of heart rate, CI, and, importantly, pulmonary artery pressure. Stroke volume is increased by 10%. By contrast, phenylephrine is associated with a reduction in CI, heart rate, and pulmonary artery (filling) pressure. As mentioned earlier, we demonstrated an augmentation of calf blood flow with HEA.[21] Studies of renal function were conducted demonstrating a preservation of renal blood flow but a diminution in urine output.[35]

We have performed a number of cohort studies verifying the safety of HEA in elderly patients with hypertension and ischemic heart disease,[36] patients with chronic renal insufficiency,[37] and those with aortic stenosis.[38]

Studies of cognitive function have been performed as it was assumed that if cerebral blood flow were diminished, evidence of ischemia would be apparent on cognitive function testing. In a large randomized trial of 2 blood pressure groups of 45 to 55 mm Hg versus 60 to 70 mm Hg, there was no evidence of impairment in cognitive function in the hypotensive group.[39] Subsequently, we assessed short-term changes in cognitive function by repeatedly measuring the Stroop Color Test (preoperatively and 1 and 2 hours following surgery).[40] There was no decline in

cognitive function from the preoperative value when the lowest recorded MAPs were in the 30- to 40-mm Hg range.

The other test of safety of the technique in brain function is to measure cerebral blood flow. We performed an observational study of cerebral blood flow velocity (CBFV) during HEA on a cohort of 52 patients.[41] Mean arterial blood pressure was maintained at 50 mm Hg throughout. Peak CBFV increased 20%, and mean CBFV was preserved at 50 mm Hg. To determine whether there was a blood pressure at which mean CBFV began to decline, mean CBFV was plotted against MAP. There was no evidence for a lower limit of cerebral autoregulation with MAP of 40 mm Hg (Fig. 4).

The final safety question is: What is the rate of stroke with HEA? Conventional wisdom is that it would be increased, but our research suggests that it may not be. As the thrombogenic risk is reduced on the venous side, perhaps it is also reduced on the arterial side of the circulatory system. We had the opportunity to assess the in-hospital rate of stroke following total joint arthroplasty as part of a surveillance of inpatient strokes at HSS. All patients who had symptoms of stroke had computed tomography scans ± magnetic resonance imaging to characterize the stroke. All in-hospital patients who had THA and TKA with evidence of stroke on magnetic resonance imaging or computed tomography scan were included. We then compared the rates of both THA and TKA with rates from 2 national database studies conducted during the same time period.[15,42] At HSS, HEA is used in THA but not in TKA. We assume HEA was not used elsewhere in the United States in hips. The results are shown in Figure 5.

The rate of stroke following TKA is slightly lower at HSS than elsewhere, but the rate of stroke following THA at HSS is one-third of the national rate. Furthermore, in a follow-up of 4060 of my (N.E.S.) patients, none have had a stroke, whereas 6 would have been expected assuming the national average. These data suggest that HEA is associated with less risk of thrombogenicity within the arterial system.

Thus, in summary, what are the benefits of HEA? They fall into 2 categories: less blood loss and less thrombogenicity. In a carefully conducted study of blood loss during THA, we randomized 40 patients to have a MAP of 45 to 55 mm Hg or 55 to 65 mm Hg during surgery.[43] Blood loss was 179 mL in the 45- to 55-mm Hg group and 263 mL in the 55- to 65-mm Hg group, a 30% increase in blood loss with only a 10-mm Hg increase in pressure. With the surgeons blinded to the pressure, they were consistently able to predict which pressure group the patients were in. Surgeons appreciate a dry surgical field.

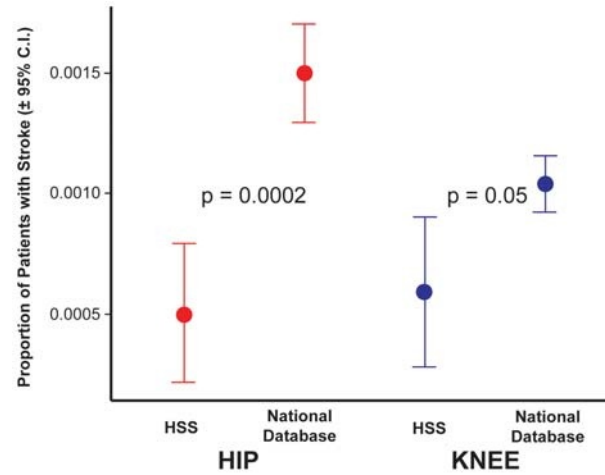

FIGURE 5. The proportion of patients with stroke following total hip and knee arthroplasty from national databases and HSS studies. At HSS, rates of stroke are slightly lower for total knee ($P = 0.05$) but one-third of the national database rate for total hips ($P = 0.0002$).

Second, less thrombogenicity. The low rate of DVT, especially proximal DVT, has been well documented with venographic studies. The low rate of stroke suggests that there is also less risk of arterial thrombosis.

The whole discussion of lowering blood pressure during surgery on the supine position may be best represented by a quote from St Augustine: "Right is right even if no one is doing it; wrong is wrong even if everyone is doing it."

Thank you.

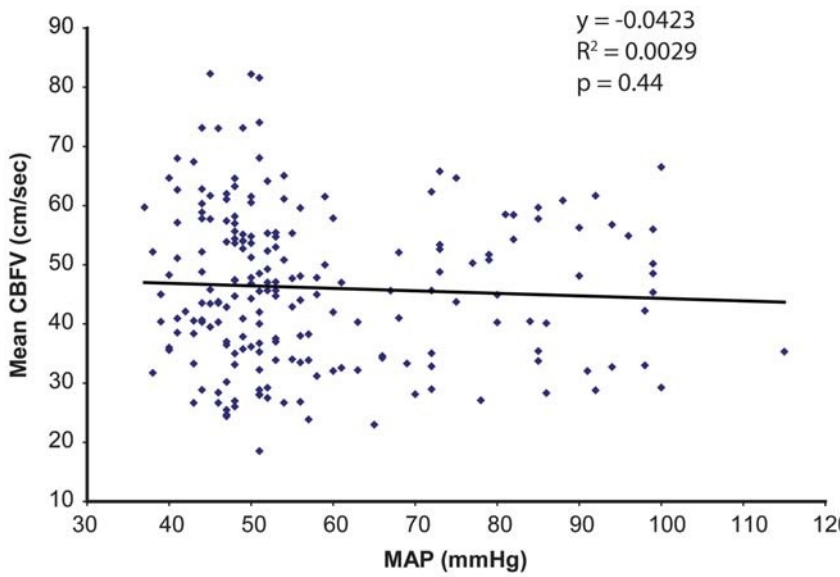

FIGURE 4. Scatter plot of the lowest mean CBFV observed in the 52 patients at any of the 3 HEA intervals plotted against the simultaneous MAP. Reprinted with permission from Bombardieri et al.[41]

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