PROTOCOL TITLE: Continuous Cerebral Autoregulation Monitoring to Reduce Brain Injury from Cardiac Surgery

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Abstract Summary

Brain injury during cardiac surgery results primarily from cerebral embolism and/or reduced cerebral blood flow (CBF). The latter is of particular concern for the growing number of surgical patients who are aged and/or who have cerebral vascular disease. Normally, CBF is physiologically autoregulated (or kept constant) within a range of blood pressures allowing for stable cerebral O_2 supply commensurate with metabolic demands. Cerebral autoregulation is impaired in patients undergoing cardiac surgery who have cerebral vascular disease and in many others due to other conditions. This could lead to brain injury since current practices of targeting low mean arterial blood pressure empirically (usually 50-70 mmHg) during cardiopulmonary bypass may expose patients with impaired cerebral autoregulation to cerebral hypoperfusion. *The hypothesis of this proposal is that targeting mean arterial pressure during cardiopulmonary bypass to a level above an individual's lower autoregulatory threshold reduces the risk for brain injury in patients undergoing cardiac surgery compared with the current standard of care of empiric blood pressure management.* Monitoring of cerebral autoregulation will be performed in real time using software that continuously compares the relation between arterial blood pressure and CBF velocity of the middle cerebral artery measured with transcranial Doppler and with cerebral oximetry measured with near infrared spectroscopy. *The primary end-point of the study will be a comprehensive composite outcome of clinical stroke, cognitive decline, and/or new ischemic brain lesions detected with diffusion weighted magnetic resonance (MR) imaging.* Autoregulation is mediated by reactivity of cerebral resistance vessels. A secondary aim of this proposal is to evaluate whether near infrared reflectance spectroscopy can be used to trend changes in cerebral blood volume and provide a reliable monitor of vascular reactivity (the hemoglobin volume index). Assessments for extra-cranial and intra-cranial arterial stenosis will be performed using MR angiography to control for this potential confounding variable in the analysis. An additional aim of the study will be to assess whether perioperative transcranial Doppler examination of major cerebral arteries can identify patients who are prone to the composite neurological end-point. Near infrared oximetry is non-invasive, continuous, requires little care-giver intervention and, thus, could be widely used to individualize patient blood pressure management during surgery. The role of p16 in PBTLs will be

evaluated as a predictor of outcomes after cardiac surgical procedures. Finally, pilot data will be obtained on whether two novel risk factors (frailty and depth of anesthesia) might be associated with postoperative delirium. Brain injury from cardiac surgery is an important source of operative mortality, prolonged hospitalization, increased health care expenditure, and impaired quality of life. Developing strategies to reduce the burden of this complication has wide public health implications and is within the mission of the NHLBI.

OBJECTIVES:

The specific aims of this proposal are:

Aim 1: To determine whether targeting blood pressure to a level above an individual's lower CBF autoregulatory threshold during CPB (cardiopulmonary bypass) reduces the frequency of the composite end-point of clinical stroke, or a diffusion-weighted MRI brain lesion, or postoperative cognitive decline 4 to 6 weeks after surgery, compared with patients who receive standard empiric blood pressure management. **Hypothesis:** Targeting mean arterial pressure during CPB to a level above an individual's lower autoregulatory threshold reduces the risk for brain injury in patients undergoing cardiac surgery.

Aim 1a: To assess whether extracranial and/or intracranial arterial stenosis (detected by MR angiography), or other patient characteristics such as age, gender, hypertension, diabetes, or prior stroke, modify the effect of maintaining blood pressure above an individual's lower CBF autoregulatory threshold on the risk for the above composite neurological outcome. **Hypothesis:** Targeting blood pressure during CPB to a level above an individual's lower autoregulatory threshold reduces the risk for brain injury in patients undergoing cardiac surgery who have extra- and/or intra-cranial arterial stenosis.
Aim 1b: To assess whether targeting MAP to a level above an individual's lower CBF autoregulatory threshold during CPB reduces the frequency of cognitive decline 1 year after surgery compared with the use of standard blood pressure management.

Aim 2: To compare three methods of continuous monitoring of CBF autoregulation derived from the linear regression correlation between cerebral oximetry O2 saturation and blood pressure (oximetry index), near infrared-derived relative total hemoglobin and blood pressure (hemoglobin volume index), and transcranial Doppler measured CBF velocity and blood pressure (mean velocity index). **Hypothesis:** Mean velocity index, cerebral oximetry index, and hemoglobin volume index provide complimentary data on detecting the lower limit of CBF autoregulation.

Aim 2 has been satisfactorily addressed and will no longer be an aim of this project.

Aim 3: To evaluate whether perioperative transcranial Doppler measurements of major cerebral artery blood flow velocity can identify patients prone to the composite neurological end-point. **Hypothesis:** Perioperative transcranial Doppler examination can

identify patients with cerebral arterial stenosis who are at risk for the composite neurological outcome.
At this point we feel we have enough data to answer this question when the analysis is to be performed. Therefore, we will not be doing the formal TCD study on subjects going forward.

Aim 4: To assess whether targeting MAP during CPB to a level above an individual's lower CBF autoregulatory threshold during CPB reduces the frequency of postoperative delirium, as assessed with a structured examination, compared with the use of standard blood pressure management.

Aim 5: To determine whether baseline frailty is independently associated with delirium or functional decline after cardiac surgery. **Hypothesis:** Baseline frailty assessments will identify patients at high risk for delirium or functional decline.

BACKGROUND:

A pervasive contemporary view is that cerebral embolism is the dominant cause of brain injury during CPB and that cerebral hypoperfusion is a minor precipitant.[5,7-12] This view has shaped current CPB management practices that include tolerating conditions that would be unacceptable in other medical settings. Such conditions include: a) reduced brain O_2 delivery (hematocrit often <21%); b) low mean arterial blood pressure, typically between 50 and 60 mmHg; and c) CBF that is reduced by 40%–50% from baseline.[9,10,50,51] Understanding the mechanisms of brain injury is important because strategies to increase CBF during CPB (e.g., by raising blood pressure and/or $PaCO_2$) might paradoxically worsen injury by increasing cerebral embolic load.[5,52] Moreover, embolism and hypoperfusion might interact synergistically to exacerbate injury from impaired embolic clearance ("washout").[5,11,21,53] Cerebral hypoperfusion likely has a larger role in current practices than it has in the past due to a growing prevalence of patients with cerebrovascular disease. Multiple series using brain MRI have revealed cerebral infarction in 40%–50% of patients before surgery.[14-20,23] These lesions are usually clinically asymptomatic, are associated with cerebral arterial stenosis, and increase the risk for new perioperative brain injury. Using SPECT imaging, Moraca et al.[22] found that 75% of 82 patients had abnormal regional cerebral perfusion (defined as >2 SD below age-matched controls) before CABG surgery, even though patients with prior stroke or transient ischemic attack had been excluded from the study.

Postoperative stroke occurred in 5% of patients and only in those with a preoperative regional perfusion defect. Our group has further reported on the high proportion of watershed strokes after cardiac surgery (see Effect of Mean Arterial Pressure on CPB and Watershed Stroke) and the relationship of this hypoperfusion-associated injury with decreases in mean arterial pressure >10 mmHg from baseline on CPB.[54] Importantly, preoperative brain imaging is not routine; therefore, patients with cerebral vascular disease receive the same empiric management during CPB as do patients without this disease. Reports showing jugular O_2 desaturation in 17%–23% of patients during CPB

document that, for some patients, CBF resulting from current practices is inadequate to meet cerebral O2 demands during at least portions of surgery.[14,55,56]

Cerebral Blood Flow Autoregulation

During CPB, systemic blood flow is calculated based on body surface area and body temperature and is then adjusted, depending on indicators of adequate global tissue perfusion (SvO2, pH, etc.). *Currently, there are no widely accepted clinical monitoring procedures to ensure adequate cerebral perfusion.* Thus, CBF is assumed to be sufficient based mostly on older data showing that CBF–arterial pressure autoregulation remains intact with CPB flows between 1.6 and 2.4 L/min/m2 (using α-stat pH management).[9,10] Supported by these data, a mean arterial pressure of 50 mmHg is widely considered to be the minimal acceptable blood pressure during CPB. This practice fails to consider that CBF–blood pressure autoregulation has wide individual variation, is altered in many common conditions (e.g., hypertension, diabetes, stroke), and is derived using statistical methods that have been questioned.[24,25,57-62] Moreover, rewarming from hypothermia could potentially lead to disruption of cerebrovascular reactivity, leading to CBF dysregulation.[30] Data supporting a mean arterial pressure of 50 mmHg (or lower) during CPB are inconsistent and are mostly from older studies that have included few patients at high risk for brain injury.[10,11,63] Indeed, Gold et al.[64] found that combined myocardial and neurologic adverse events were less frequent when mean arterial pressure during CPB was maintained at between 80 and 100 mmHg, rather than between 50 and 70 mmHg. These data are corroborated by retrospective analysis showing beneficial effects of higher mean arterial pressure for patients at risk for neurologic injury.[65,66]

Individualizing blood pressure targets to be above a patient's lower autoregulatory threshold might provide a means to avoid cerebral hypoperfusion during and after CPB. Monitoring of cerebral autoregulation with a moving linear regression correlation coefficient between cerebral perfusion pressure and middle cerebral artery TCD measured blood flow velocity (mean velocity index) has been validated in volunteers and in patients with head trauma, carotid artery stenosis, acute ischemic stroke, and subarachnoid hemorrhage.[31-37, 39, 67] When autoregulation is lost, flow velocity has a correlation of 1 with cerebral perfusion pressure at low frequencies. This method provides a way to monitor autoregulation continuously at the bedside in contrast to the intermittent ("snap shot") measurements provided by other methods (e.g., PET, inert gas washout). This feature allows for assessment of CBF autoregulation in individual patients rather than estimating a patient's autoregulatory threshold based on summary data obtained from a group of patients. This ability is important in surgical patients, as CBF autoregulation is dynamic and potentially influenced by many perioperative perturbations, including rewarming from hypothermia, volatile anesthetics (dose dependently), and anemia.[30, 68, 69] These methods have been applied in several clinical situations, and measurement of mean velocity index correlated with the degree of carotid artery stenosis and improvement of cerebral dysautoregulation after carotid recanalization.[34, 35]

No gold standard exists for measuring CBF to determine autoregulation.[68] TCD monitoring of CBF velocity is a commonly used surrogate of CBF that assumes that small changes in middle cerebral artery diameter have minimal influence on CBF measurement.[70] In most instances, these assumptions have minimal clinical impact. Monitors of brain oxygenation, such as direct tissue O_2 tension measurement, jugular bulb O_2 saturation measurement, and transcranial near-infrared spectroscopy have been used as surrogates of CBF for measuring autoregulation.[68,71] Clinical monitoring of near-infrared spectroscopy can be performed with two FDA-approved devices.[72,73] The INVOS device (Somenetics Corp, Troy, MI) uses light-emitting diodes in two channels to provide a continuous-wave spectrometer that measures relative changes in regional O_2 saturation of the frontal lobe. The Fore-Sight device (CAS Medical Systems, Branford, CT) uses fiberoptic light in four channels to monitor phase shifts at 754 nm, 785 nm, and 816 nm in reference to 780 nm to accurately measure brain tissue oxygenation. The spacing of the light source and receivers determines the depth of sampling. A shallow receiver subtracts O_2 saturation derived from extracranial tissue. Near-infrared spectroscopy provides an estimate of oxyhemoglobin saturation in the underlying frontal lobe that is weighted toward venous blood, thus indicating the adequacy of regional cerebral O_2 supply versus demand. Our group has demonstrated that cerebral oximetry provides a clinically acceptable surrogate of CBF for experimental and clinical autoregulation monitoring (see Cerebral Autoregulation Monitoring).[38] Using nearinfrared spectroscopy a variable, cerebral oximetry index was generated to describe the moving linear correlation between cerebral O_2 saturation and cerebral perfusion pressure. Monitoring CBF autoregulation with the cerebral oximetry index has many clinically attractive features: it is noninvasive, its output is continuous and updated every 60 sec, monitoring requires little caregiver intervention, and it has sufficient resolution to discriminate the lower autoregulatory threshold. Unlike TCD, the use of cerebral oximetry as a proxy for CBF does not require a trained technician and, thus, can be widely applied in a broad range of clinical settings and locations.

Autoregulation is mediated by reactivity of cerebral resistance vessels (vascular reactivity), which consists of dynamic, low-frequency vessel diameter changes in response to changes in arterial blood pressure. *In most physiologic instances, limits of pressure reactivity are wider than limits of autoregulation.*[74] Assessing vascular reactivity involves measuring the relationship between blood pressure change and a measure of cerebral blood volume.[39,40] Low-frequency oscillations in cerebral blood volume are attributed to changes in the dynamic collective vascular radius. In health, vascular diameter changes to oppose changes in arterial blood pressure (decreased diameter for increased blood pressure). Vascular reactivity is measured clinically using the pressure reactive index, which is the moving linear correlation between slow waves of intracranial pressure and blood pressure.[39] A positive-pressure reactive index, indicating pressure passivity, is associated with death in adults with traumatic brain injury.[75] A negative-pressure reactive index, indicating pressure reactivity, is associated with survival in adults with traumatic brain injury. The pressure reactive index can delineate a range of perfusion pressure with maximal vascular reactivity in most patients with traumatic brain injury, and deviation from this optimal perfusion pressure is associated with death and persistent

vegetative state.[33] The strength of these data led to a citation in the guidelines for the management of severe traumatic brain injury from The Brain Trauma Foundation, with a new option for autoregulation monitoring to optimize cerebral perfusion pressure goals.[76] Invasive intracranial pressure monitoring is a prerequisite for pressure reactive index monitoring. Cardiac surgery patients cannot have invasive intracranial pressure monitoring but may benefit from precise blood pressure management using this index. Our preliminary data (*see Cerebrovascular Reactivity Measured by Near-infrared Spectroscopy*) suggest that near-infrared reflectance spectroscopy can be used to trend changes in cerebral blood volume (relative total hemoglobin in the reflectance arc) and provide a reliable monitor of vascular reactivity (the hemoglobin volume index).

Regional brain areas in a vascular territory of a flow-limiting arterial stenosis would likely have impaired autoregulation.[28,34,77-79] Blood flow to these brain areas would, thus, be pressure dependent. Intra- and extra-cranial vascular stenosis could influence the effectiveness of targeting blood pressure during CPB, based on a global measurement of CBF autoregulation. However, maintaining blood pressure above the lower CBF autoregulatory threshold, even if estimated from vascular territories with functional autoregulation, would likely ensure an adequate cerebral perfusion to pressure dependent brain regions. On the other hand, compensatory vasodilation in response to lowered blood pressure during CPB to these same brain areas with intact autoregulation could potentially lead to a “steal phenomenon,” whereby CBF is directed away from the pressure-dependent vascular territories.[77-79] Interpretation of the effectiveness of a strategy of basing blood pressure management during CPB on CBF autoregulation measurement requires knowledge on the extent of cerebral vascular disease.

Detection of Brain Injury

Brain injury after cardiac surgery has a range of clinical manifestations, including clinical stroke (detected in ~2%–5% of patients) and cognitive decline (reported in 18%–40% of patients, depending on statistical criteria and timing of testing).[5] Cognitive testing has methodologic limitations that lower its sensitivity and specificity for detecting neurologic injury (as opposed to its use for studying the effects of surgery on cognition), including difficulty with distinguishing the confounding effects of preexisting cerebral vascular disease.[41-43] Moreover, preexisting brain infarction is associated with cognitive impairment, regardless of surgery, thus lowering the likelihood of being able to diagnose further cognitive decrement from new injury or “basement effect.” [41-44] Nonetheless, our data indicate that cardiac surgery results in changes in cognition indicative of brain injury. Cognitive decline, though, appears to be a transient phenomenon, with most individuals returning to near baseline by 3–6 months after surgery.[41,80] More controversial is the relationship between perioperative cognitive decline and long-term cognitive decline. Data from our colleagues suggest that the rate of long-term cognitive decline is not different for patients undergoing CABG surgery than it is for patients with documented coronary artery disease undergoing medical management.[41] These findings suggest that the natural progression of cerebral vascular disease, as opposed to the use of CPB per se, is a major determinant of longitudinal decline in cognition after cardiac surgery.

Understanding the impact of interventions aimed at reducing brain injury from cardiac surgery on long-term cognition may help assess their overall benefit for patient outcome.

Advanced MRI techniques such as diffusion-weighted imaging allow for the detection of early ischemic changes in the brain.[45-49] Diffusion-weighted imaging is an MRI sequence capable of demonstrating changes within minutes of experimental ischemia.[47-49] It is believed that ischemia-induced energy depletion increases the influx of water from the extracellular to the intracellular space, restricting water motion and resulting in a bright signal and low calculated apparent diffusion coefficient.[81,82] Although there is wide individual variability, the apparent diffusion coefficient signal remains low for 4 days, pseudonormalizes at 5–10 days, and increases thereafter. This temporal evolution of the diffusion-weighted imaging signal allows one to determine the age of a stroke and differentiate acute from chronic ischemia. Investigations combining conventional MRI with diffusion-weighted imaging have revealed new small lesions after cardiac surgery in 26%–50% of patients.[19,20,23,83-85] In our own series, we found DWI lesions after surgery in 56% of patients. The lesions are broadly distributed in the brain and often have a watershed distribution with/without an embolic signature. Watershed strokes (i.e., lesions in end-vascular territories) in the general population are usually secondary to focal hypoperfusion, although the mechanism in cardiac surgical patients is not as certain.[86] Most diffusion-weighted imaging lesions that are seen after cardiac surgery are not associated with clinically detected stroke, and preliminary analysis suggests that they may occur without detectable short-term cognitive decline. However, in these studies, patient follow-up might have been too short to detect a relationship between “silent” MRI cerebral infarctions and cognitive decline, [87] or the cognitive battery might not have been sensitive to the functions of the actual injured brain regions. Regardless, new diffusion-weighted imaging lesions do represent ischemic brain injury, as they can become brain infarction when re-examined with conventional MRI 1–2 weeks later.[88] Furthermore, in the general population, clinically “silent” infarction detected with brain imaging is increasingly recognized to be associated with cognitive decline, depression, and reduced functional capacity.[89] Combined diffusion-weighted imaging and perfusion-weighted imaging (PWI) will enable us to determine whether lesions detected by the former method occur in relatively hypoperfused brain areas. Although diffusion-weighted imaging is sensitive for detecting ischemic brain injury, post-cardiac surgery lesions may occur in brain areas not involved with higher cognitive function. Thus, combining detection of lesions by diffusion-weighted imaging with clinical neurologic end points (including cognitive deficits) will provide a highly sensitive evaluation of perioperative brain injury. The findings will be especially important for examining mechanisms and/or prevention of brain injury related to cardiac surgery.

Frailty

Frailty is commonly used to characterize the most vulnerable subset of older adults, with decreased physiologic reserve across multiple organ systems.[181] Using data from the Cardiovascular Health Study, a frailty phenotype was derived by Fried et al.[188] and includes: unintentional weight loss, low grip strength, self-reported exhaustion, gait

speed, and low physical activity. In community-based cohort studies, frailty has been associated with new falls, decreased mobility, disability, hospitalization, and death.[190] However, the impact of frailty on outcomes after surgery has not been well studied. In non-cardiac surgery, measures of frailty have been independently associated with postoperative complications and length of stay,[180] institutionalization,[191] and mortality.[192] In cardiac surgery, frailty has similarly been associated with mortality and institutionalization,[182] and the addition of frailty to existing risk models can slightly improve prediction of mortality.[183] However, the measurement of frailty in the surgical literature has been inconsistent,[180,183,191] and there have been no studies which have examined important patient-centered outcomes, including delirium and functional status. Delirium and functional status-decline are important patient-centered outcomes that are hypothesized to occur more in frail vs. non-frail patients after cardiac surgery, given the reduced physiologic reserve of frail patients to recover from stressors. The incidence of delirium after cardiac surgery has been estimated to occur in up to 52% of patients (consistent with our data), [193] and the consequences of postoperative delirium in older adults can be profound. Delirium after cardiac surgery is independently associated with reduced functional capacity, [194] and mortality.[153] Although a small study in non-cardiac surgery demonstrated an increased risk of delirium among frail patients, [195] the association between frailty and delirium in cardiac surgery patients has not been studied, nor has the ability of frailty to improve current prediction models of delirium been examined. Similarly, change in functional status after cardiac surgery has not been well studied among frail older adults, with evidence suggesting that physical function might improve[196] or decline[194] after cardiac surgery, depending on the measure of functional status and the baseline function of the population assessed. Thus, the impact of baseline frailty on change in functional status after cardiac surgery is not known.

Depth of Anesthesia

Depth of anesthesia may represent a modifiable target to improve outcomes after surgery in frail adults. In both cardiac and non-cardiac surgery, greater depth of anesthesia (as measured by the Bispectral Index [BIS], a processed encephalogram) has been associated with mortality.[184, 185] In current practice, depth of anesthesia as reflected by BIS values has been shown to vary widely,[197] and importantly, older adults may experience greater depth of anesthesia at the same drug dose because of increased susceptibility to anesthetic agents,[198] potentially resulting in relative anesthetic overdose. In order to determine whether actively reducing depth of anesthesia could reduce postoperative delirium, a collaborator at Johns Hopkins Bayview (Dr. Frederick Sieber) randomized 114 patients undergoing hip fracture repair under spinal anesthesia to light vs. deep intraoperative sedation and found a 50% reduction in delirium in the light sedation group.[186] In a separate trial of non-cardiac surgery patients undergoing general anesthesia, a BIS-guided protocol for depth of anesthesia was reported to reduce postoperative delirium from 24.1% to 15.6% (P=0.001).[187] However, these results in spinal anesthesia or non-cardiac general anesthesia may not be generalizable to patients undergoing cardiac surgery, because of different patient populations and perioperative insults (e.g. cardiopulmonary bypass).

In addition, the range of BIS values during cardiac surgery is unknown. These data motivate our current proposal to examine the range of depth of anesthesia (BIS values) during cardiac surgery for both frail and non-frail patients. We anticipate that frail patients will spend a significant amount of time with BIS values less than cutoffs for general anesthesia (BIS 45-60), and time of BIS<45 will be greater in frail vs. non-frail patients. These results would support the future development of a protocol to maintain BIS values at higher ranges (45-60) while reducing total anesthetic dose, particularly in frail patients.

Preliminary Studies

The team comprises highly experienced researchers who have performed seminal investigations into the frequency, causes, and consequences of neurologic complications after cardiac surgery. The group is a multidisciplinary team that encompasses the specialties of anesthesiology, neurology, neuroradiology, cardiac surgery, neuropsychology, and biostatistics organized to study perioperative neurologic injury with the intent of developing strategies to reduce its frequency. The experiences of the team members provide evidence of a track record in conducting neurologic outcomes research in cardiac surgical patients. The researchers are experienced with all of the proposed measurements.

Neurologic Outcomes after Cardiac Surgery

Our neurologic team has been studying the cognitive and neurologic outcomes after both conventional and off-pump CABG surgery.[41, 90-92] Our current cohort, which is being followed up to 6 years after surgery, was recruited to determine if CABG is associated with late or delayed cognitive impairment. To control for the effect of coexisting cerebrovascular disease in an aging population, we included a control group with similar risk factors for cerebrovascular disease as the surgical group and a group of healthy subjects. Our studies and those of others have shown that a significant proportion of candidates for CABG surgery have abnormal cognitive performance even before surgery. Our data do not support disproportionate decline among CABG patients compared to nonsurgical controls, although both groups performed lower than healthy controls lacking risk factors for cerebrovascular disease. In addition to highlighting the importance of including control groups, our studies also illustrate the importance of the choice of statistical criteria for defining postoperative cognitive decline. Some commonly used criteria, such as 20% decline on 20% of tests, will result in significantly inflated estimates of postoperative cognitive decline. We have proposed more powerful and appropriate analyses using random effects regression models, which can account for practice effects and for heterogeneity among subjects in the levels and trends of their test scores. Additionally, we have assembled a multi-disciplinary team to assess delirium in the postoperative period using rigorous assessment with the Confusion Assessment Method. We have successfully assessed delirium in over 70 patients undergoing cardiac surgery at Johns Hopkins, thus demonstrating the feasibility of our aims.

Effect of Mean Arterial Pressure on CPB and Watershed Stroke

In a study of 98 patients with clinically detected stroke after cardiac surgery (between 1998 and 2003), we found, based on diffusion-weighted imaging, that 68% had at least unilateral watershed strokes and 48% had bilateral watershed strokes (Fig. 1).[54] This prevalence of watershed stroke suggests that the frequency of infarction due to cerebral hypoperfusion is higher than in the general stroke population. We sought to determine the role of change in mean arterial pressure from baseline during CPB in the development of watershed strokes. Patients with a drop from baseline in mean arterial pressure of ≥10 mmHg during CPB were 3.25 times more likely to have a watershed infarct than those who had a smaller drop in mean arterial pressure. The odds ratio for a watershed infarct after adjustment for preoperative mean arterial pressure, history of hypertension, CPB time, and circulatory arrest was 4.1 (95% CI, 1.03–15.90).

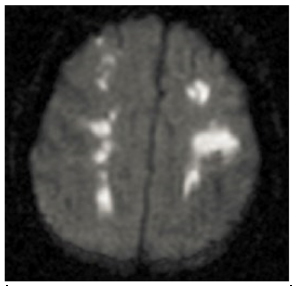


Fig 1. MR diffusionweighted imaging of a patient with bilateral watershed stroke after cardiac surgery.

Patients with a drop in mean arterial pressure ≥10 mmHg also were 3.2 times more likely to have a larger infarct volume (95% CI, 1.1–10.7). Operative mortality was higher for patients with bilateral watershed strokes than for those with other types of cerebral infarctions (17% vs. 4%, p=0.04).

These preliminary data suggest that an important factor in the development of watershed strokes is change from baseline in mean arterial pressure during CPB, not the absolute intraoperative mean arterial pressure. As the studied patients represented only those with symptomatic stroke, it is likely that the frequency of watershed injury might be even higher. Regardless, these data support the hypothesis that reduced CBF during CPB is an important contributor to neurologic complications. The data further suggest that low CBF-associated brain injury is related to an individual's baseline blood pressure. Therefore, it is plausible that affected patients might have their autoregulatory threshold shifted to the right, thus exposing them to cerebral hypoperfusion by current blood pressure management practices.

Cerebral Autoregulation Monitoring

We have performed preliminary laboratory and clinical investigations of CBF blood pressure autoregulation reactivity. In these studies, analog signals from arterial pressure and surrogates of CBF measurements are digitally converted, stored in a laptop computer, and then processed by ICM+ software (Cambridge University; Cambridge, UK).31-37 CBF autoregulation can be monitored with a moving linear regression correlation coefficient between cerebral perfusion pressure and TCDmeasured middle cerebral artery (MCA) blood flow velocity (mean velocity index or Mx).25-33When autoregulation is functional, there is no correlation between CBF velocity and MAP, but when MAP is outside the autoregulation limits, Mx approaches 1, meaning that flow is

pressure-dependent. No gold standard exists for measuring CBF to determine autoregulation.[35] Near infrared spectroscopy-measured regional cerebral oxygen saturation ($rScO_2$) is weighted toward venous blood, thus indicating the adequacy of O_2 supply versus demand. Our group has demonstrated that $rScO_2$ provides a clinically acceptable surrogate of CBF for clinical autoregulation monitoring.[38,134,135] The variable COx is generated as the correlation coefficient between cerebral perfusion pressure and $rScO_2$.Similar to Mx, when CBF is outside the limits of autoregulation COx approaches 1, but it approaches zero or is negative when autoregulation is functional (no correlation between CBF and MAP). Monitoring CBF autoregulation with COx has many clinically attractive features: it is noninvasive, monitoring requires little caregiver intervention, and it has sufficient resolution to discriminate the lower autoregulatory threshold. In a laboratory study of 3- to 8-day-old piglets, we evaluated autoregulatory reactivity by comparing laser-Doppler–derived red cell flux in the frontoparietal cortex with perfusion pressure.[38] These studies were used to evaluate whether near-infrared cerebral oximetry might serve as surrogate for CBF. If so, it would provide a clinically feasible means for measuring CBF autoregulation in real time across a wide array of clinical practices. Hypotension was induced by inflation of a balloon catheter in the inferior vena cava. The autoregulatory breakpoint was determined by plotting CBF (flux) as a function of perfusion pressure and intersecting the two best-fit lines with the lowest combined squared error. Cerebral oximetry was performed, and the waveform plotted as a function of perfusion pressure, but an autoregulatory plateau was not seen. Two time-domain indices of autoregulation were measured during these experiments: the laser-Doppler index (velocity index), which correlates laser-Doppler flux with blood pressure, and the oximetry index (Fig. 2). Note, when perfusion pressure is <LLA, CBF and perfusion pressure become correlated, indicated by increasing laser Doppler index (LDx) and COx (arrows). Data combined from multiple experiments in piglets show that a cerebral oximetry value of ≥0.3 has a sensitivity of 89%, specificity 64%, and likelihood ratio 2.5 for detecting the lower limit of autoregulation.

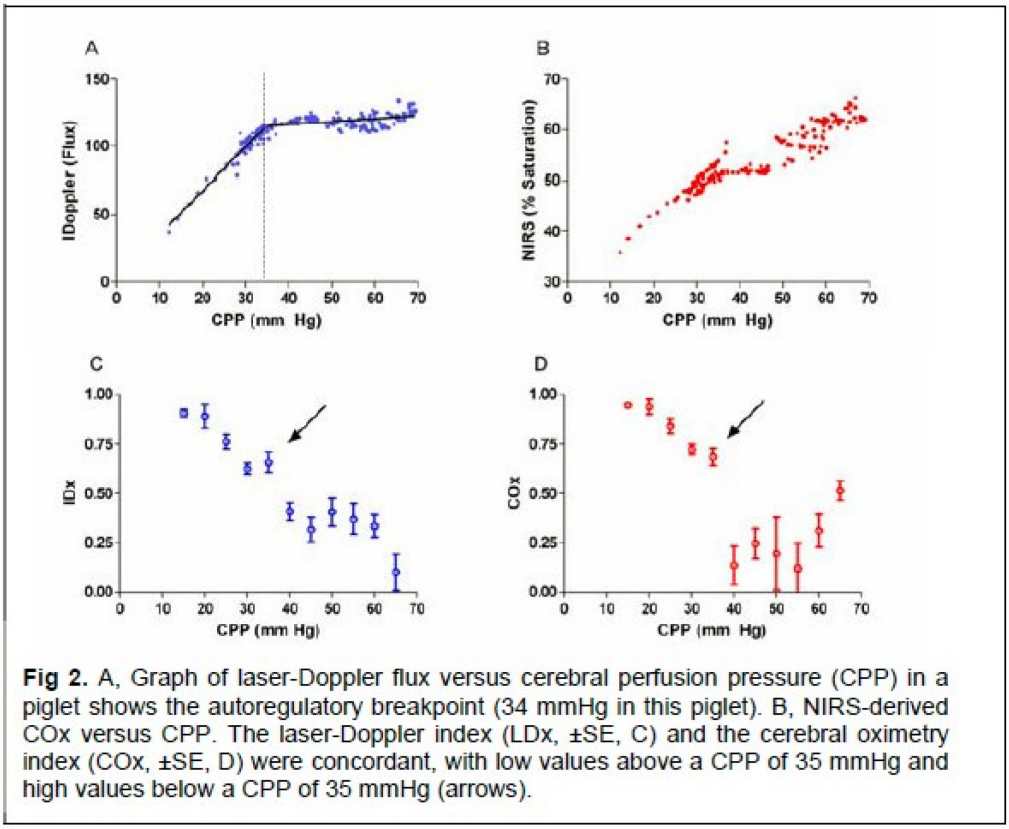


Fig 2. A, Graph of laser-Doppler flux versus cerebral perfusion pressure (CPP) in a piglet shows the autoregulatory breakpoint (34 mmHg in this piglet). B, NIRS-derived COx versus CPP. The laser-Doppler index (LDx, ±SE, C) and the cerebral oximetry index (COx, ±SE, D) were concordant, with low values above a CPP of 35 mmHg and high values below a CPP of 35 mmHg (arrows).

Our group has experience with TCD monitoring in patients undergoing cardiac surgery.[97] In pilot studies, TCD monitoring of the right and left middle cerebral arteries was performed in patients; the data were combined with arterial signals, digitally converted at 58 Hz, and stored in a laptop computer for processing by methodology similar to that described above. In these studies, CBF autoregulation was defined as the relationship between CBF velocity and mean arterial pressure (mean velocity index). Of note, mean arterial pressure—not cerebral perfusion pressure—is measured because we have found that central venous pressure measurements (needed for calculating cerebral perfusion pressure) are not reliable during CPB. The reason is that vacuumassisted venous drainage during CPB collapses the right atrium and vena cava, resulting in highly negative central venous pressure measurements. As described above, a correlation between CBF velocity and mean arterial pressure (rising velocity and oximetry indices) indicates that CBF is pressure dependent, or not autoregulated, and vice versa.

We initially assessed CBF autoregulation in nearly 150 patients undergoing cardiac surgery using the methods and equipment proposed for this study. Data from 60 patients with complete transcranial Doppler and NIRS data were analyzed. There was a significant correlation (r=0.55, p<0.0001) and good agreement (bias=0.082±0.18, 95% CI, -0.327 to 0.43) between COx and Mx for the timeaveraged data during CPB. Coherence between slow waves (20 s to 2 min) from NIRS and TCD signals was high (0.74) suggesting that NIRS can be substituted for TCD for monitoring CBF autoregulation. *The mean lower autoregulatory threshold determined by Mx (mean±SD) in our early data was 61±15 mmHg and by COx, 60±15 mmHg. The range of mean arterial blood pressures at the autoregulatory threshold was 40–80 mmHg.* We have subsequently validated COx versus Mx in adult patients undergoing CPB.[135] In our studies that have included >450 patients thus far, rScO2 remained >50% in two-thirds of patients when MAP was below the LLA, indicating that COx might provide indication of low perfusion pressure earlier than rScO2. An example of Mx and COx monitoring in a patient during CPB is shown in **Fig. 3**.

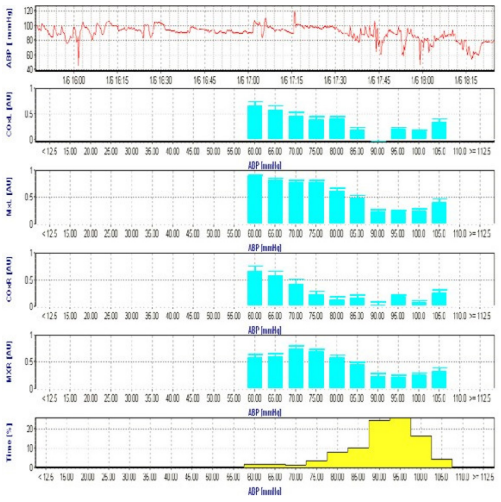


Fig 3. Arterial pressure, Mx, and COx values in 5 mmHg bins, and the percent time at each MAP. Increasing Mx and COx with declining MAP indicates threshold of autoregulation (arrow).

Cerebrovascular Reactivity Measured by Near-infrared Spectroscopy

The prototype index of vascular reactivity is the pressure reactivity index. The pressurereactivity index describes cerebral vessel activity by correlation of slow waves of intracranial pressure and arterial blood pressure. The pressure reactivity index analysis assumes that slow waves (Lundberg B waves) of intracranial pressure are caused by vascular diameter changes. We reasoned that slow changes in the relative total hemoglobin (rTHb) measured by transcranial near-infrared reflectance spectroscopy would also reflect vascular diameter changes (i.e., increases in rTHb results from increased vessel diameter and vice versa). We hypothesized that the hemoglobin volume index correlates with the pressure reactivity index using the Fore-Sight device, as proposed in this submission. The latter monitor is a continuous-wave reflectance spectrophotometer that uses 4 laser-bandwidth wavelengths of light in the near-infrared spectrum to quantify the percentage of saturated hemoglobin in cortical tissue. Transcranial near-infrared light transmittance is inversely proportional to the concentration of absorbing chromophores in the tissue. Oxyhemoglobin and deoxyhemoglobin have different absorption spectra between wavelengths of 600 and 1000 nm, but an isobestic wavelength for these two chromophores is near 800 nm. These relationships form the basis of oximetry, which reports the ratio of oxygenated-tototal hemoglobin concentration in the light path as a percentage of total hemoglobin concentration. The tissue concentration of hemoglobin determined in this way is a function of both the hematocrit and the blood volume in the tissue. Oximetric methods

cancel the effect of changes in blood volume by reporting the percentage of oxygenated hemoglobin. The intensity of light detected at the point of the reflected arc by the sensing optode, (I), is inversely proportional to the concentration (c) of the chromophore being measured when the intensity of the light source (Is) is held constant. We were able to use 1/I from a nearly isobestic wavelength (805 nm) of infrared light to derive an index of autoregulation. Because the relative change in total hemoglobin is a small fraction of the absolute hemoglobin during autoregulation, a logarithmic transformation may not be necessary. Moreover, the phase of the blood volume waveform is more important than the power when describing vascular reactivity. The hemoglobin volume index was continuously recorded as a moving linear correlation between slow waves (20–300 sec) of arterial blood pressure and rTHb. The pressure reactive index was similarly continuously recorded. Autoregulation curves were constructed by averaging values of the pressure reactivity index and hemoglobin volume index in 5 mmHg bins according to the cerebral perfusion pressure at which they were recorded.

The lower limit of autoregulation as determined by laser-Doppler flow velocity was 29.4±6.7 mmHg (±SD). Relative total hemoglobin displayed a high degree of lowfrequency coherence with ICP. Using all 2242 paired measurements, hemoglobin volume index was linearly correlated with pressure reactivity index (Spearman r=0.73). The pressure reactivity index and hemoglobin volume index were both accurate measures of vascular reactivity, showing higher values below the lower limit of autoregulation and lower values above this limit. Receiver operating characteristics (ROC) of the autoregulation curves derived by hemoglobin volume index and pressure reactivity index were delineated using the individually derived lower limits of autoregulation as standards. Areas under the ROC curves were 0.88 for the pressure reactivity index (95% CI, 0.82–0.96) and 0.85 for the hemoglobin volume index (95% CI, 0.75–0.94). The demonstrated coherence between the relative total hemoglobin and intracranial pressure waveforms at the frequency of slow waves (Fig. 4) suggest that slow waves of intracranial pressure are the result of blood volume changes. The hemoglobin volume index has potential for further development as a noninvasive alternative to the pressure reactivity index for patients at risk of neurologic compromise.

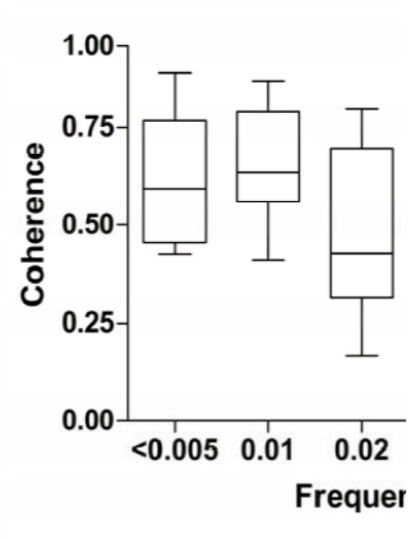


Fig 4. Intracranial pressure and relative total hemoglobin (rTHb) coherence averaged for 8 animals. Coherence scores between the intracranial pressure and relative total hemoglobin waveforms are high at frequencies corresponding to the observed slow waves of intracranial pressure, ≤0.02 Hz.

An example of hemoglobin volume index compared with mean velocity and cerebral oximetry indices in a patient during nearly 90 min of CPB is shown in Fig 5.

Together, our preliminary data support our ability to carry out the measurements necessary to address our specific aims and suggest the immense potential clinical utility of these noninvasive brain monitors.

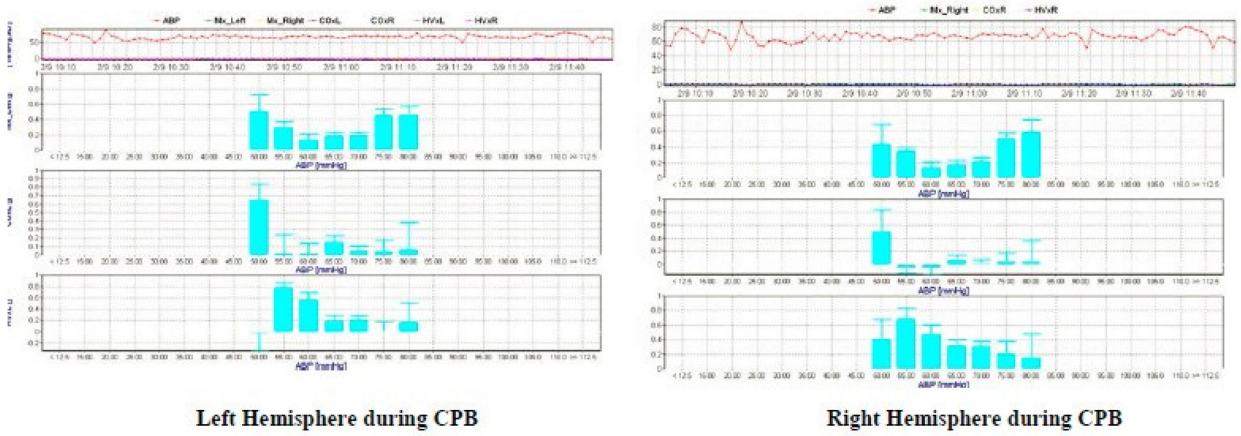


Fig 5. An example of CBF autoregulation monitoring in a 62 year old patient undergoing cardiac surgery. In this patient the autoregulatory threshold based on TCD-derived mean velocity index (>0.2) was 55 mmHg in both hemispheres. There was a 5 mmHg lag in detection of this threshold based on cerebral oximetry index (>0.3). In contrast, hemoglobin volume index demonstrated changes that correlated with lowering blood pressure 5 mmHg higher than mean velocity index in the left and right hemispheres. This example demonstrates the potential value of noninvasive monitoring of the CBF autoregulation with cerebral oximetry and hemoglobin volume index.

COx and Clinical Outcomes

We have found that there is a wide inter-individual range of MAPs at the LLA during CPB (40 to 90 mmHg) and that these limits are difficult to predict based on clinical information.[137] These data indicate that monitoring autoregulation is a more precise means for determining individual MAP targets during CPB than empirically choosing targets, as is the current standard of care. Moreover, our results show that patients experience MAP below the LLA for varying durations of time when MAP targets are empirically determined. Acute kidney injury (AKI) increases the risk for mortality after cardiac surgery.[6-8] To assess whether MAP below the LLA has any meaningful consequences for patient outcome, we monitored COx in 349 patients during CPB.[41] Based on the RIFLE criteria,[8,10,42] AKI developed within 7 days of surgery in 121 (34.7%) patients. Excursions of MAP below the LLA (mmHg × min/h of CPB) (relative risk, 1.02; 95% CI, 1.01 to 1.03; p<0.0001) were independently associated with AKI. Each 5 mmHg x min/h of MAP below the LLA increased the risk for AKI by 10%. In an analysis of 450 patients, we found that the duration of MAP < LLA was higher in patients (n=83) with major organ morbidity or mortality (stroke, renal failure requiring dialysis or increase > 2 mg/dL, mechanical lung ventilation > 48 h, operative mortality, inotrope use > 24 h or new requirement for IABP insertion) than in those without this complication (odds ratio, 2.21; 95% CI, 1.32 to 3.71; p=0.003).43 These data support the premise that individualizing MAP during CPB based on physiologic endpoints such as COx monitoring, rather than empiric targets, may provide a means for modifying the risk for AKI and major organ morbidity and possibly mortality.

<u>COx and Neurologic Complications:</u> Our group has been investigating CBF autoregulation for a number of years. Interim analysis has shown a relationship between MAP < LLA as detected with COx (i.e., independent of TCD metrics), and neurologic dysfunction (ND), defined as postoperative DWI lesions, or clinical stroke, or transient ischemic attack, or clinically detected delirium (Table 1).

These data are from 176 patients of a planned enrollment of 254 patients. The limit of autoregulation was defined as that MAP at which COx increases to >0.3.136 Excursions were defined as mmHg × min/h of CPB of MAP below the LLA. MRI was available from 82 patients. Obtaining MRI after cardiac surgery is not possible in all patients because of retained pacemaker wires (i.e., temporary pacing wires left in place rather than having them removed postoperatively as is the usual practice), unavailability of research MRI scanners, patient's level of illness, or death. These factors are only known after surgery, not during screening. As a result, some enrolled patients later are found not to be eligible for MRI scanning. Thus, the primary impetus of this renewal, to continue enrollment until an adequate number of patients have been studied with MRI. Regardless, our preliminary results show that patients with ND had a larger magnitude and duration of time with MAP < LLA. Delirium was diagnosed based on clinical observations as previously described.[23] Clinical assessments underestimate the frequency of delirium compared with structured instruments, particularly hypoactive variants that may go unrecognized clinically.[146]

The etiology of perioperative delirium is likely multifactorial. Contributing factors include pharmacologic and other perturbations in individuals with preexisting vulnerability. Whether perioperative hypotension contributes to the etiology of delirium has not been extensively examined. The small number of studies that have addressed this issue produced conflicting findings, did not use structured assessments for delirium, varied in the timing of blood pressure recordings (i.e., every 5 min in some studies), had small numbers of patients, and were associated with other limitations. Based on our findings of a wide inter-individual variability of MAP at the LLA, we believe that examining the relationship between hypotension and delirium using a priori blood pressure cutoffs, rather than individualized definitions based on autoregulation monitoring, is imprecise. We have performed a retrospective analysis of our data obtained from several trials of patients undergoing CPB. Of 496 patients monitored with COx, 10% developed delirium based on clinical criteria. In a multivariate logistic regression model, the magnitudeduration of MAP < LLA during CPB determined with COx was associated with postoperative clinical delirium (odds ratio, 1.10, 95% CI, 1.10-1.11, p=0.0203) after adjusting for age, history of hypertension, stroke, and duration of CPB. We have also obtained preliminary delirium data in our current randomized trial comparing MAP management with autoregulation monitoring to standard of care in patients during CPB. In this latter analysis, Drs. Brown and Neufeld carefully assessed for the presence of delirium using structured instruments as proposed in this submission (see Delirium Assessment). In that preliminary analysis, the frequency of delirium (19 of 37 [51%] patients) tended to be lower in patients who were randomized to have MAP managed during CPB based on real-time autoregulation monitoring than in patients who received standard of care (33% vs. 66%, p=0.134). **Acknowledging the limitations of the preliminary analysis, our early results provide evidence of a relationship between MAP < LLA and ND including delirium. Our methods would challenge current standard practice of empirically determining MAP targets during CPB and support COx monitoring as a clinically feasible approach for improving patient outcomes from cardiac surgery.**

Table 1. Mean arterial pressure below autoregulation limits detected with COx in relation to neurologic dysfunction (ND) after cardiac surgery.

	Negative ND (n=110) Mean±SD	Positive ND (n=66) Mean±SD	p-value
MAP at autoregulation threshold	65.7±13.1	74.9±13.4	0.0004
Excursion ≤ lower threshold	6.6±8.0	13.7±12.4	0.0421

HOW PATIENTS WILL BE SCREENED FOR ELIGIBILTY: Authorized research personnel will screen for eligible participants during cardiac preoperative visits scheduled at the surgeons office. Potential participants will be introduced to the study by authorized research personnel at this time.

INCLUSION AND EXCLUSION CRITERIA:

Inclusion criteria will be male or female patients, ≥55 years old, undergoing primary or re-operative CABG, aortic root replacement and/or valvular surgery that requires CPB (but not undergoing circulatory arrest) who are at high risk for neurologic complications (stroke or encephalopathy) as determined by a Johns Hopkins Encephalopathy Risk score of >0.05, or Stroke Risk > 0.02.[132] This prediction algorithm, devised from data analysis by the investigative team, identifies probability of an adverse neurologic outcome based on five patient-related factors: age, prior stroke, diabetes, hypertension, or the presence of a carotid bruit. Women of childbearing potential will have a urine pregnancy test done prior to surgery to insure that they are not pregnant.

Patients will be ineligible for this study if they have any of the following **exclusion criteria:**

1. Contraindication to MRI imaging (e.g., permanent pacemaker, cerebral arterial vascular clips);
2. AST, ALT and Alkaline phosphatase obtained before surgery which is more than twice the upper limit of institutional normal value and which, in the opinion of the principal investigator, is believed to be related to hepatic dysfunction;
3. Chronic renal failure requiring renal dialysis. (Subjects with an estimated glomerular filtration rate ≤60 mL/min who do not require dialysis may be included in the study. However, these subjects will not receive gadolinium during their MRI/MRA.);
4. Emergency surgery;
5. Inability to attend outpatient visits;
6. Visual impairment or inability to speak and read English; or
7. Female of child bearing capacity with a positive pregnancy test.
8. Individual adults less than 54 years old
9. Prisoners

The patient will be excluded from further study if an adequate temporal window for TCD monitoring cannot be identified before surgery.

STUDY-WIDE NUMBER OF PARTICIPANTS: Initially we are conducting a 5-year study that includes a 1-month interval for investigator training and start-up, 56 months for enrollment of 280 patients (~5 patients/month), and 3 months for final patient followup testing, data analysis, manuscript preparation, and dissemination of the results (see Rapid Dissemination of Clinical Research). The initial study time line is schematically summarized in Table 2.

STUDY TIMELINES:

Table 2. Summary of Study Timeline During the Initial Phase of the Project

	Year 1	Year 2	Year 3	Year 4	Year 5
Start Up	One month				
Enrollment	56 Months				
Close-out, analyses manuscripts					3 months

Table 2. Summary of Study Timeline During the Initial Phase of the Project

We will continue this study for an additional 5-years that will enroll 350 new patients (in addition to the 280 patients of the initial study) over a 45-month period (~8 patients/month) with the remaining duration of the proposed funding used for patient follow-up testing, data analysis, manuscript preparation, and dissemination of the results. As of June 2016, we have enrolled 280 patients in the first five years and 244 patients in the second five year study. We need approximately 150 patients to complete enrollment.

Patient Randomization

Patients will be prospectively randomized after anesthesia induction, but before CPB, using a computer generated randomization program into one of two single-blinded groups:

1) Blood pressure intervention group (Intervention Group) in which mean arterial pressure during surgery is targeted to be kept above the patient's lower CBF autoregulatory threshold based on continuous monitoring of mean velocity index or cerebral oximetry index ***(see CBF Autoregulation Measurements)*** or

2) Control Group in which mean arterial pressure is maintained during surgery, including CPB, using institutional standard of care.

Blinding: Clinicians caring for the patients will participate in managing blood pressure in the Intervention Group and, thus, cannot be blinded. Individuals making the neurologic assessments and performing data analysis will be blinded to the intraoperative management group, providing effective double blinding.

Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.The algorithm for the management of mean arterial pressure during cardiopulmonary bypass as detailed in *Appendix A* which reflects the current standard of care for the institution. The difference between the two randomized groups is when that intervention will take place. For the Control group, the algorhythm will be followed as per routine standard of care. For the Blood Pressure Intervention Group, the algorhythm will be instituted when the blood pressure is below the lower autoregulatory limits as determined by mean velocity index or cerebral oximetry index.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed. N/A

c. Justification and safety information if non-FDA approved drugs without an IND will be administered. *N/A*

Perioperative Management

Preoperative Variables: Preoperative demographics, medical history (including euroScore[131] calculated based upon the medical history), and medications will be recorded. A history of prior stroke or transient ischemic attack will be made by review of medical records, the results of prior brain imaging studies, or by contacting the patient's primary care physician. Preoperative left ventricular function as assessed by ventriculography or echocardiography will be recorded as normal, mildly depressed (ejection fraction ≥40% but <50%), moderately depressed (ejection fraction ≥35% but <40%), or severely depressed (ejection fraction <35%). The results of carotid artery ultrasound imaging studies obtained before surgery will be recorded.

Anesthesia and Patient Monitoring: To avoid hypotension during surgery, patients will not be given angiotensin converting enzyme inhibitors on the day of surgery. The patients will be connected to the NIRS monitor (Invos, Covidien, Boulder, CO) with two self-adhesive probes attached to the forehead, according to manufacturer guidelines. Arterial blood pressure will be measured via a cannula inserted into the radial or femoral artery placed for clinical purposes. Anesthetic drugs will be standardized and will consist of midazolam, propofol, fentanyl, isoflurane, and skeletal muscle relaxants. During CPB, isoflurane will be administered via the membrane oxygenator. Sedation after surgery will be started when sternal wires are placed and will consist of propofol. Propofol will be titrated off when the patient meets institutional standards for tracheal extubation. Postoperative pain will be managed per hospital standard.

A deficiency of current clinical practice is that urine output is measured crudely and intermittently, and it is not precisely recorded. For this study, the patient's urine flow will be measured every 1 min with automatic gravimetric sensing device connected to the urinary catheter collection bag (RenAdapter: Urine Flowmeter and Multiparameter Monitor). The urine bag will hang on the Renalert device intraoperatively to monitor urine output during surgery. At the conclusion of the surgery the device will be removed before the patient is transferred to the intensive care unit.

Assessment of Depth of Anesthesia through BIS monitoring
We will measure depth of anesthesia during surgery using the Bispectral Index Monitor (BIS), which is an FDA-approved device to measure processed electroencephalogram signals. Two adhesive pads will be placed on the patient's forehead during surgery for this monitoring.

Cardiopulmonary Bypass: A 40-μm or smaller filter will be placed in the CPB circuit. Blood flow during CPB will be maintained between 2.0 and 2.4 L/min/m2 using nonpulsatile flow.

Nasopharyngeal temperature will be measured during surgery and the temperature nadir recorded. In addition to continuous in-line monitoring, arterial blood gases will be recorded 30 min after the start of CPB and every 60 min thereafter. The patients will be managed using α-stat pH management. Hemoglobin will kept >8.0 g/dL with transfusion of packed red blood cells. Blood glucose will be measured at the onset of CPB and at least every 60 min thereafter. Blood glucose will be managed per routine standard of care. Rewarming will be at an arterial inflow temperature of ≤37°C. Nasopharyngeal temperature will not exceed 36°C. Surgical field CO_2 insufflation will be performed. Cardiotomy suction will be returned to the CPB circuit after being processed with a cell saver device for patients undergoing CABG surgery or directly to the CPB circuit for open chamber procedures, as is our usual practice.

Perioperative Blood Pressure Monitoring and Recording: A decrease in arterial blood pressure that occurs any time preoperatively could confound analysis of the data. Blood pressure will be monitored using standard operating room and ICU monitors. Transducers will be placed level with the right atrium and zeroed to atmospheric pressure before the start of anesthesia, before the start of CPB, and after separating from CPB. Blood pressure will be recorded continuously during surgery and recorded on a computer interfaced with the operating room hemodynamic monitor (using ICM+ software, see Cerebral Autoregulation Monitoring and CBF Autoregulation Measurements). Computerized medical record systems will record arterial pressure every 15 min in the ICU. Study personnel will review these medical records daily for the duration of the ICU admission. The number of hypotensive episodes (mean arterial pressure <70 mmHg) will be recorded to adjust for the effect of this potential confounding variable on the primary outcomes. The dose and duration of any vasoconstrictor or vasodilator drugs given during surgery and in the ICU will be recorded.

The patients will be visited on the postoperative ward daily by members of the surgical team to evaluate for adverse events, cardiac arrhythmias, and other events necessitating medical intervention, including hypotension or other complications.

Perioperative Variables: The patients will receive routine institutional perioperative care that includes continuous arrhythmia monitoring with telemetric ECG after surgery. Postoperative variables, including complications that affect organ systems, will be collected during the hospitalization. Patients will undergo 12-lead ECGs before surgery and on arrival to the ICU after surgery as well as for the first 3 postoperative days. The definition of myocardial infarction will be a new Q-wave >0.04 sec and/or >1/3 the height of the R-wave. Data sheets for each patient will be completed to denote no myocardial infarction or Q-wave myocardial infarction. The data will then be entered into the study database.

Autoregulation Monitoring

CBF autoregulation will be monitored continuously by members of the investigative team. The patient's forehead will be cleansed with the supplied alcohol sponge and wiped dry. Then, two Foresight monitoring electrodes will be calibrated, as specified by the manufacturer, and placed on the patient's forehead. The electrodes will be attached to a Fore-Sight cerebral oximeter (CasMed, Branford, CTI) specially equipped with an output signal for this project. We will perform TCD monitoring (DWL, Compumedics DWL, El Paso, TX) of the right and left middle cerebral arteries using two 2.5-MHz transducers fitted on a headband and positioned over the temporal bone windows to obtain bilateral continuous measurement of baseline velocity. Depth of insonation will be varied between 35 and 52 mm until representative spectral middle cerebral artery flow is identified.

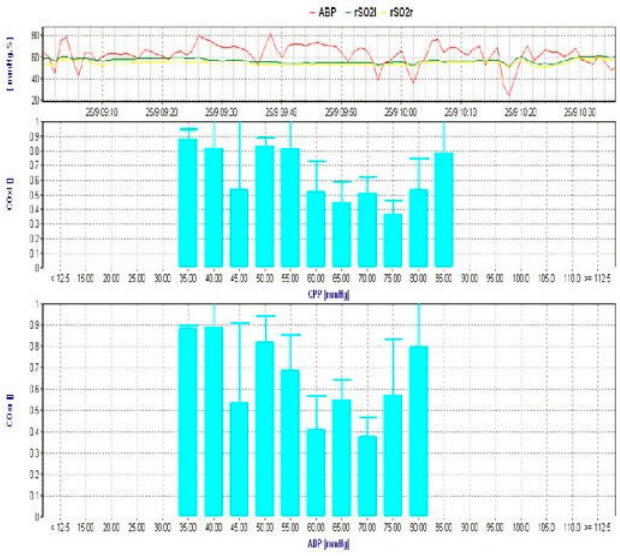


Fig 6. Dysregulated pattern when COx is >0.3 at all MAPs. In this patient optimal MAP is 70-75 mmHg. Note, the top panel is the MAP time series. The y-axis on the remaining graphs is left and right COx, respectively, on a scale of 0 to 1.0. The xaxis is MAP in 5 mmHg bins.

Arterial pressure from an indwelling cannula (started for clinical indication), along with TCD signals from the middle cerebral arteries and the near-infrared spectroscopy signals, will be sampled with an analog-to-digital converter using ICM+ software at 58 Hz.31-37 Digital rScO2 signals from the NIRS monitor will be transferred directly to a laptop computer. Blood pressure, TCD, and rScO2 signals will then be time integrated as non-overlapping 10-sec mean values, equivalent to applying a moving average filter with a 10-sec time window and re-sampling at 0.1 Hz. This operation eliminates high-frequency noise from the respiratory and pulse frequencies, according to the Nyquist theorem, allowing detection of oscillations and transients that occur below 0.05 Hz. A continuous, moving Pearson correlation coefficient will be calculated between mean arterial pressure and TCD CBF velocity of the middle cerebral arteries, rendering the variable mean velocity index (Mx). Similar methods will be performed to calculate the Pearson correlation coefficient between mean arterial pressure and cerebral oximetry signals, rendering the variable cerebral oximetry index, and between mean arterial pressure and relative total hemoglobin signals, generating the hemoglobin volume index (see Cerebrovascular Reactivity Measured by Nearinfrared Spectroscopy). Consecutive, paired, 10-sec averaged values from 300-sec duration will be used for each calculation, incorporating 30 data points for each index.35,37 Mx and COx values for each patient will be placed into 5 mmHg MAP bins and displayed on the laptop computer (**Figs. 3 and 6**). When MAP is within the limits of CBF autoregulation, Mx and COx approach zero, but when MAP is

outside the limits of autoregulation, Mx and COx approach 1, indicating that CBF is blood pressure dependent. Based on our prior studies, we designate the LLA as the highest MAP associated with Mx ≥ 0.2 or Cox ≥ 0.3. These values are within the range found to be associated with poor outcome after traumatic brain injury and adverse outcomes after cardiac surgery.[17,40,151,152] In about 20% of patients, impaired autoregulation is observed when Mx and COx are ≥0.3 at all MAPs during CPB (Fig. 6). An attenuated autoregulation plateau is usually observed. Thus, the "optimal" MAP, defined as the MAP with the lowest Mx, will be the blood pressure target during CPB, as this point is observed in patients with functional and impaired autoregulation. As blood pressure varies during the usual course of surgery, including during the initiation of CPB, no specific interventions are needed to establish autoregulation indices. Clinicians will have access to COx data only for patients randomized to the Intervention Group.

The autoregulatory threshold will be defined as the mean arterial pressure at which the mean velocity index increases to ≥0.2 or cerebral oximetry index increases ≥0.3.

Information regarding the mean arterial pressure at which the lower CBF autoregulatory threshold is detected will be made available to the anesthesiologist, perfusionist, and critical care doctors who are caring for the patients in the Intervention Group before and after surgery. Physicians and perfusionists will be told specifically that a patient has been randomized to the Intervention Group and that his/her mean arterial pressure should be kept higher than that value associated with a mean velocity index ≥0.2 or cerebral oximetry index ≥0.3. During surgery, the mean velocity index will be monitored continuously by the investigative team to confirm that treatments are instituted if mean arterial pressure falls below these limits. These same data will be collected in the Control Group but no specific measures for treating blood pressure will be advised.

At the conclusion of surgery, patient steaming data files will be stored on a portable computer in the ICM+ file. The data files will be transferred to a departmental server with a password-protected file folder specifically designed for this study. Data on the server is backed up daily. The data from each patient will be copied to an excel spread sheet. This data will include the mean arterial pressure from a range of 0 to 115 mmHg and the corresponding mean velocity index and cerebral oximetry index as well as the percentage of time at each blood pressure.

Blood Pressure Management

To avoid hypotension during surgery, angiotensin converting enzyme inhibitors will not be given on the day of surgery. Patients randomized to the blood pressure Intervention Group will have their mean arterial pressure treated according to the protocol outlined in *Appendix A* when it is below the lower autoregulatory limits as determined by mean velocity index or cerebral oximetry index. Patients in the Control Group will receive the same treatment, but the lower threshold for treatment will be based on institutional practices and not mean velocity index or cerebral oximetry data. The threshold for treating high blood pressure is not specified and will be based on institutional practices. A

treatment algorithm for treating high blood pressure is provided to ensure consistency in treatments between patients. To avoid a precipitous drop in mean arterial pressure on initiation of CPB, a 100-µg bolus dose of phenylephrine will be given intravenously immediately before drainage of blood from the patient to the CPB reservoir. Initiation of CPB will be begun gradually, at no more than 2 L/min, to allow slow equilibration. CPB will be increased by 0.5 L/min increments to the calculated full CPB flow. Phenylephrine boluses (50–100 µg) can be given when mean arterial pressure is below the lower limit, until it is stabilized.

Hypotension for periods other than during CPB will be treated by first ensuring adequate cardiac preload with crystalloid or colloid. The decision will be dictated by examination of left and right ventricular end-diastolic areas with transesophageal echocardiography or based on central venous pressure or pulmonary capillary wedge pressure when a pulmonary artery catheter is in place and transesophageal echocardiography is not used. If cardiac filling is normal, as described above, and systemic vascular resistance is low, hypotension will be treated using the same algorithm as that for treating hypotension on CPB. If cardiac preload is adequate but cardiac function is poor (or cardiac index of <2.0 L/min/m2), epinephrine will be started per hospital standard care. If cardiac function/cardiac index remains depressed, milrinone and dobutamine will be used per hospital standard care. Persistent low cardiac function/cardiac index, including that resulting from right ventricular dysfunction, will be treated according to institutional treatment guidelines.

Patients will be evaluated at screening and sometime between postoperative day 5 and 7 or at hospital discharge (whichever occurs first) with the National Institutes of Health Stroke Scale (NIHSS). The NIHSS is a standardized, validated neurologic examination used in clinical trials to evaluate change in neurologic status.[105] The test quantifies neurologic deficits in 11 categories using a 42-point scale. This testing will be performed by a trained research nurse. Research personnel will be certified for performing the NIHSS using the American Stroke Association's Online NIH Stroke Scale Training Program (http://asa.trainingcampus.net/uas/modules/ trees/windex.aspx). Patients with a change from baseline in their NIHSS will be referred for evaluation by a neurologist per hospital standard of care by their medical team. An MRI of the brain will be obtained when stroke is likely based on the neurologist’s examination. Brain CT imaging will be substituted for MRI when MRI is viewed as clinically contraindicated. Central nervous system infarction will be defined based on the Expert Consensus Statement of the American Heart and Stroke Associations as ischemic injury to the brain, spinal cord, or retina based on pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting for ≥24 h or until death, and other etiologies have been excluded.[36]A stroke will be defined as an episode of neurologic dysfunction caused by focal cerebral infarction. An intracerebral hemorrhage will be defined as a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma. A transient ischemic

attack is defined as focal arterial ischemia with transient symptoms lasting < 24 h without evidence of infarction by pathology or imaging.

Delirium Assessment: Delirium is characterized by an acute-onset, fluctuating disorder in level of consciousness associated with changes in cognition, attention, and perception not explained by pre-existing or evolving dementia.[156] Trained examiners can diagnose delirium and quantify its severity with structured instruments (Appendix C). Examinations are followed by case-by-case adjudication.[146] A Mini Mental Status Exam and Abbreviated Digit Span will be done preoperatively to establish a baseline. Delirium assessments will be made on three of the first four postoperative days using the following tools:

a. *Confusion Assessment Method (CAM)* is a standardized method that is designed to allow trained non-psychiatrists to diagnose delirium. It shows high inter-rater reliability, sensitivity (94–100%), and specificity (90–95%) when compared to the gold standard of psychiatric diagnosis.[142] The CAM diagnostic algorithm is based on assessing the four cardinal features of delirium: 1) acute onset and fluctuating course, 2) inattention, 3) disorganized thinking, and 4) altered level of consciousness.

b. *Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)* is a validated instrument used to diagnose delirium in critically ill intubated patients in the ICU, including those who are non-verbal due to mechanical ventilation. Inter-rater reliability is high (kappa 0.79–0.95), and it has high sensitivity (95–100%) and specificity (89–93%) when compared to the gold standard of psychiatric diagnosis. This test will be used for intubated patients in the ICU.

c. *Delirium Rating Scale-Revised-1998 (DRS-R-98)* is a 16-item scale that has been validated as a measure of delirium severity. Inter-rater reliability is high (interclass correlation coefficient = 0.99), and the scale is one of the few that has been validated against a dementia group.[39]

Trained delirium assessors (authorized research members) will obtain a history of current symptoms from the patient, care providers, and family; review medical records; and perform a mental status exam and cognitive screens that will include the Mini Mental State Exam (MMSE) and abbreviated digit span.[68] This information will be used to rate the CAM, producing a binary outcome for the presence or absence of delirium in the past 24 h. The DRS-R-98, which yields a delirium severity rating, will also be completed. If a patient is unable to respond verbally to questions because of intubation and mechanical ventilation, the CAM-ICU version will be administered. This instrument has sensitivities of 76%–80% and a pooled specificity of 96% in the ICU.[157,158]

Neurocognitive Function: A component of the endpoint of this study is cognitive decline after surgery compared with the patient's baseline. Cognitive testing will be performed within two weeks before surgery, 4–6 weeks after surgery, and 1 year after surgery. Most elective cardiac surgical procedures are performed on patients admitted to the hospital the day of surgery. Assessing baseline cognitive status in patients during an outpatient visit is confounded by time constraints and anxiety that might bias the data and affect enrollment. Nonetheless, we have extensive experience in performing cognitive testing

on the day before cardiac surgery. For patients already admitted to the hospital, cognitive testing and other preoperative assessments will be performed on the ward. For patients who will be admitted the day of surgery, testing will occur either after their preoperative visit with their surgeon or by a separate visit specifically for the purposes of the study. For outpatients, testing before surgery will be at NMH.

Postoperative cognitive testing will be performed at the patient's postoperative surgical clinic visit, in NMH which usually occurs 4–6 weeks after surgery, and again at 1 year after surgery.

Our goal for cognitive testing is not to test hypotheses about specific types of cognitive decline or about injury to specific brain regions. We have selected neuropsychologic tests that assess a number of cognitive domains known to be affected by cardiac surgery.[81-83,159] They have the advantage of being standardized. They are also brief and easy to administer and score; the total administration time is approximately 35–45 min. Based on our previous experience, this focused approach is highly feasible for testing surgical patients. The battery is listed in Appendix B and consists of the Rey Auditory Verbal Learning Test,[87,160] a test of verbal learning and memory; Rey Complex Figure Test[121], an assessment of visual memory; Controlled Oral Word Association Test,[87] a test of executive functions; Symbol Digits Modalities Test,[162] a test of psychomotor speed and attention control; Trail Making A and B,[163] tests of visuomotor speed, attention, and executive functions; Grooved Pegboard Test,[34,164] a measurement of fine motor dexterity and speed; Beck Depression Inventory,[105,165] a self-reported scale of depression symptom severity; and the State-Trait Anxiety Inventory,[162] a measurement of anxiety symptoms. The patients are also evaluated with the SF-36 short form of the RAND Medical Outcomes Study (MOS) health-related quality of life questionnaire.[166] This questionnaire is a multi-item scale that measures 8 health-related concepts: physical function, social function, physical role, emotional role, mental health, energy, pain, and general health perceptions.[166,167] The standardized scores for each of the 8 quality-of-life domains range from 0 (worst) to 100 (best). The SF-36 has been used in previous studies to assess quality of life in cardiac patients and chronically ill populations. Cognitive decline will be defined as a decrement in performance from baseline to postoperative testing of at least 1 standard deviation (SD) in two or more tests, or 2 SD in one test. It has been shown that this definition is unlikely to classify random test-retest variability as decline but is nonetheless sensitive enough to detect actual postoperative change in cognitive performance.[46]

Magnetic Resonance Imaging

Brain ischemic lesions detected with diffusion-weighted imaging are a component of the primary outcome of this study. Brain MRI will be performed between postoperative days 3 and 14. The imaging sequences will include oblique axial diffusion-weighted images from which apparent diffusion coefficient (ADC) maps will be calculated, perfusionweighted images, T2, FLAIR, and 3D spoiled gradient-echo (SPGR; which allows 3dimensional reconstruction, comparable to MPRAGE) scans. These data will be acquired on an instrument TBD.[106] Diffusion-weighted trace images are obtained using a

multi-slice, isotropic, single-shot EPI sequence, with bmax = 1000 s/mm2 and TR/TE = 10,000/120 msec. Corresponding ADC maps will be used to identify infarcted tissue. For perfusion-weighted imaging, single-shot gradient echo EPI perfusion images (TR/TE = 2000/60 msec) are obtained with a 20 mL Gd-DTPA (Gadolinium) bolus power injected at 5 mL/sec at the start of the scan. These scans are used to generate maps of the time-to-peak arrival of contrast across voxels in the region of interest, relative to the homologous region of interest in the unaffected hemisphere. Given concerns about the potential for nephrogenic systemic fibrosis from gadolinium contrast in subjects with renal failure, the creatinine level of all patients will be measured before the MRI. Gadolinium will not be given to individuals with an estimated glomerular filtration rate ≤60 mL/min or to those who need dialysis after surgery (by FDA).[107] In such patients, only diffusion-weighted imaging without gadolinium administration will be performed as needed for determining the primary outcome. The FDA Web site states that "there are no reports received of individuals with normal or even moderately impaired renal function developing NSF http://www.fda.gov/cder/drug/infopage/gcca/qa_200705.htm.

In previous work by members of the investigative team, inter-observer point-to-point agreement for analysis of the time-to-peak delay in each area for 12 scans was 83% for calculating the delay to the nearest 0.1 sec and 100% for calculating the delay within 0.2 sec. We will register each image (first registering the corresponding SPGR scans) to a spatial standard, a digital form of the Montreal Neurological Institute atlas, using local registration methods or image warping, in which each voxel is individually displaced.[108] This technique results in better registration to an atlas than do global methods.[109] Registered images are first read by a neuroradiologist and reported in the patient's medical record as part of standard Department of Radiology policy at Northwestern Memorial Hospital. Any subject who enrolls in this study with a history of retained metal in their head and/or eye(s) will have an x-ray of the head done in order to determine if it will be safe to proceed with the MRI. If it is deemed safe for the subject the MRI will be obtained.

Additionally, stored images will be independently analyzed by one of two investigators (TBD) blinded to patient outcomes. The images will be assessed for nonischemic pathology, the presence and location of prior cerebrovascular disease, new acute ischemic lesions, global cerebral edema, and hemorrhages. Acute ischemic lesions will be depicted as a hyperintense signal on the diffusion-weighted images and hypointense signal on the ADC map. ADC can be calculated on a pixel-by-pixel basis. Based on the location, size, and pattern of distribution, the ischemic infarct will be classified into one of four categories: small subcortical infarction (lesion that is <1 cm in diameter located in the basal ganglia, thalamus, or brainstem); territorial infarction (lesion located in a vascular distribution, usually resulting from large vessel occlusion); watershed infarction (lesion located in the border zone between vascular territories); or multiple emboli (multiple lesions in one or several different vascular territories). The number of acute lesions detected by diffusion-weighted imaging will be counted, and the total infarct volume will be traced and measured volumetrically by a technician using the Image J software.110 The sum of infarcts and infarct volume will be recorded in addition to the categorization

of the infarcts as described above. *The primary MRI outcome will be a comparison of the number of diffusion-weighted imaging lesions for patients in the blood pressure Intervention Group with that of the Control Group*.

Secondary analysis will include total infarct volume, location in cortical or subcortical regions, and the ratio of diffusion-weighted imaging lesion size to perfusion-weighted imaging defect size.

MRA will be obtained by contrast-enhanced MRA (CE MRA), using IV contrast at the time of brain MRI. In the event that gadolinium is not administered, MRA of the neck will be carried out with 2D time of flight (TOF) imaging. When gadolinium is administered, neck MRA will be 3D TOF of the neck. MRA of the head will be 3D TOF regardless of use of gadolinium. Measurements of arterial stenosis on MRA will vary depending on the location of the vessel; standard measurements are made by a neuroradiologist, and these will be replicated by one of the investigators (TBD). For extracranial carotid stenosis, the technique is that used in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (Fig 7).

Intracranial arterial stenosis of the most clinically important major vessels (middle cerebral artery, basilar artery, intracranial internal carotid artery) and the extracranial vertebral arteries, will be measured based on the methods used in the Warfarin- Aspirin Symptomatic Intracranial Disease study.111

The percent stenosis of a major intracranial artery will be defined as [(1 (Dstenosis/Dnormal))] x 100, where
stenosis = the diameter of the artery at the site of the most severe degree of stenosis and normal= the diameter of the proximal normal artery.

For the middle cerebral, intracranial vertebral, and basilar arteries, normal will be defined as the diameter of the widest part of a normal segment of the proximal part of the artery. If this portion of the artery is not normal, then normal will be defined as the diameter of widest part of the distal portion of the artery. When the entire intracranial artery has atherosclerotic narrowing, the most distal part of the normal segment of the artery supplying the vessel will be used for determining normal.

Brain imaging might result in the detection of an unexpected condition, such as a brain mass, aneurysm, or vascular malformation. In the event of such findings, the patient, and his/her family and clinical physicians will be notified, and the patient will be referred for clinical management.

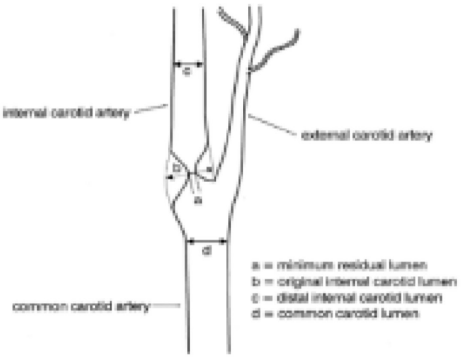


Fig 7. Position of measurements to be recorded from neck MRA for degree of internal carotid artery stenosis.
[(1 – (a/c)) · 100] gives the result as calculated in the NASCET trial. Adapted from Young et al., 1996.[112, 113]

Frailty Assessments:

We will evaluate frailty based on a validated scoring system[1] that characterizes frailty as an age-associated decline in 5 domains: shrinking, weakness, exhaustion, low physical activity, and slowed walking speed.

These measurements are described below based on the original paper.

Each domain will yield a dichotomous score of 0 or 1. We will classify patients scoring 3 to 5 as frail, 1 to 2 as intermediately frail (pre-fail), and 0 as nonfrail. We will also measure the Instrumental Activities of Daily Living scale as part of the frailty assessment. Research staff will undergo frailty screen training to allow consistent measurements of frailty domains in the study population. Frailty assessment will be held in clinic during the patient's preoperative and postoperative visits, and again at the time of the 1 year follow-up visit.

Weight loss: "In the last year, have you lost more than 10 pounds unintentionally (i.e., not due to dieting or exercise)?" If yes, then frail for weight loss criterion.

Exhaustion:
Using the CES–D Depression Scale, the following question and the accompanying two statements are read:
"How often in the last week did you feel this way?" (a) I felt that everything I did was an effort (b) I could not get going.

The subject will respond to these questions using the following scale:
0 = rarely or none of the time (1 day);
1 = some or a little of the time (1–2 days);
2 = a moderate amount of the time (3–4 days); or

3 = most of the time.

Subjects answering “2” or “3” to either of these questions are categorized as frail by the exhaustion criterion.

Physical Activity:

Based on the short version of the Minnesota Leisure Time Activity questionnaire, asking about walking, chores (moderately strenuous), mowing the lawn, raking, gardening, hiking, jogging, biking, exercise cycling, dancing, aerobics, bowling, golf, singles tennis, doubles tennis, racquetball, calisthenics, swimming. Kcals per week expended are calculated using standardized algorithm. This variable is stratified by gender:

Men: Those with Kcals of physical activity per week <383 are frail. *Women:* Those with Kcals per week < 270 are frail.

Walk Time: Table 3 (below) will be used to stratify Walk Time by gender and height (gender-specific cutoff a medium height).

Table 3. Walk Time criteria for frailty

Gender	Cutoff time to walk 15 feet criteria for frailty
Men	
Height ≤ 173 cm	≥ 7 seconds
Height > 173 cm	≥ 6 seconds
Women	
Height ≤ 159 cm	≥ 7 seconds
Height > 159 cm	≥ 6 seconds

Grip Strength: Table 4(below) will be used to stratify Grip Strength by gender and body mass index (BMI) quartiles

Table 4. Grip Strength criteria for frailty

Gender	Cutoff for grip strength (Kg) criterion for frailty
Men	
BMI ≤ 24	≤ 29
BMI 24.1–26	≤ 30
BMI 26.1–28	≤ 31
BMI > 28	≤ 32
Women	
BMI ≤ 23	≤ 17
BMI 23.1–26	≤ 17.3
BMI 26.1–29	≤ 18
BMI > 29	≤ 21

Instrumental Activities of Daily Living Scale will be used to provide additional information on functional status in the frailty assessment. Seven questions are asked to gauge participant difficulty with using the telephone, walking, preparing meals, managing money, shopping, doing housework, and taking medicines.

Each study subject will participate in the study for approximately 1 year.

Consent will be obtained before any study related events occur. Cognitive and quality of life testing, medical history, TCD measurements (to determine subject eligibility), National Institutes of Health Stroke Scale (NIHSS), ECG and psychomotor testing and Brief Smell Identification Test[133]will be performed within 1- 2 weeks before surgery. We plan to perform this testing in the outpatient center for most patients. Patients who are in-patients prior to surgery will have testing performed on the hospital ward.

On the day of surgery after anesthesia induction the patients will be connected to a transcranial Doppler to monitor middle cerebral artery blood flow velocity and to a near infra-red spectroscopy machine to monitor cerebral oxygenation. Doppler probes are held in place with a fitted head band. The NIRS electrodes will be placed using manufacturer guidelines. Both devices are FDA approved. Transcranial Doppler and NIRS are used to monitor cerebral blood flow autoregulation. Subject randomization will also be done at this time.

Before cardiopulmonary bypass is initiated (after sternotomy and pericardiotomy) the patients will undergo epiaortic ultrasound examination of the ascending aorta to examine for atherosclerotic changes. In many centers epiaortic ultrasound has replaced the traditional palpations by the surgeon of the aorta for the detection of atherosclerosis of the ascending aorta.

The day of surgery during cardiopulmonary bypass the patients will undergo cerebral blood flow autoregulation monitoring using methods described in the preliminary data section. For individuals in the intervention arm, blood pressure targets during cardiopulmonary bypass will be determined by this monitoring and will be the blood pressure where the mean velocity index (Mx) is <0.2 or the cerebral oximetry index (COx) is< 0.3. This information will be communicated to the perfusionist, anesthesiologist and surgeon by the investigative team. In the control arm, cerebral blood flow autoregulation information will be monitored and saved but the data will not be provided to the surgical team.

After surgery, visits will all be done in the ICU or postoperative unit. The patients will have an ECG which is to be done upon the subject's arrival in the ICU after surgery. This procedure is routine care and only a copy of the ECG will be obtained for the study case report form.

Each patient will be evaluated daily by the attending and resident physicians. Data will be collected from the patient record by a member of the study team. Every patient will have an ECG done each day postoperative days 1 through 3, per standard of care. An MRI will be done at some point between postoperative day three and postoperative day 14 or at hospital discharge (whichever occurs first). In addition, all patients will be evaluated between postoperative days 5 and 7 or at hospital discharge (whichever occurs first) with the National Institutes of Health Stroke Scale (NIHSS) And Brief Smell Identification Test.

Cognitive testing and the Brief Smell Identification Test will be repeated at the time the patient returns for follow-up with the cardiac surgeon, about 4 to 6 weeks postoperatively.

Cognitive testing will be repeated at 1 year postoperative.

Assessment Schedule

The schemata of study procedures are listed in Table 5.

Assessment Schedule	PRE-OP	DOS before CPB	DOS CPB	DOS after CPB	ICU	POD 1	POD 2	POD 3	POD 4	POD 5-7	4-6 wks POST-OP	1 YEAR POST-OP
Informed consent	X											
Medical history/PE	X											
NIH Stroke Scale	X									X	X	X
Smell Test	X									X	X	
Psychometric and quality of life testing	X										X	X
Frailty testing	X										X	X
Urine pregnancy test	X											
SAEs/AEs	----------X----------											
Randomization		X										
Mx and C02 monitoring		X	X	X								
Bispectral Index Monitoring		X	X	X								
Urine Flow		X	X	X								
Brain MRI								X_1				
MMSE and Abbreviated Digit Span	X											
Delirium assessments						X	X	X	X			
Electrocardiogram	X				X	X	X	X				

PRE-OP = preoperatively (up to 2 weeks before surgery); **DOS** = day of surgery; **POD** = postoperative day; **POST-OP** = postoperatively; **SAE** = serious adverse event; **AE** = adverse event; 1 = MRI will be done once between post-op day 3 and post-op day 14; 2 = blood drawn for standard of care ACT measurements that would normally have been discarded will be used for these samples; 3 = a 3mL lavender top vaccutainer tube will be drawn in the morning of POD1 at the same time standard of care bloods are drawn; 4 = urine pregnancy test will be done on women of childbearing potential only; 6 = Delirium assessments will be done on 3 of the first 4 postoperative days; 7 = urine flow will be monitored during surgery.

Clinicians caring for the patients will participate in managing blood pressure in the Blood Pressure Intervention Group and, thus, cannot be blinded. Individuals making the neurologic assessments and performing data analysis will be blinded to the intraoperative management group, providing effective double blinding.

Participation in this study will not require discontinuation of a subject's current therapy any more than would be required if the subject were to undergo CABG and/or valve surgery outside of the study. The Control Group will receive standard care practiced here at Northwestern Memorial Hospital. The Blood Pressure Intervention Group will be receiving investigational care. Blood pressure targets during surgery will be at least those of the standard care group or higher based on the individualized autoregulation measurements.

Justification for inclusion of a placebo or non-treatment group.
There will be a Control Group in which mean arterial pressure is maintained during surgery, including CPB, using institutional standard of care. This is being done in order to allow direct comparison of the current standard of care with the Blood Pressure Intervention Group.

Definition of treatment failure or participant removal criteria.
There is no definition for treatment failure. The subject will be excluded from further study if an adequate temporal window for TCD monitoring cannot be identified before surgery.

Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.
If a subject's participation in the study were to end prematurely then that subject would be treated according to current standard of care.

Study Statistics
a. Primary outcome variable.
Aim 1: *To determine whether targeting blood pressure to a level above an individual's lower CBF autoregulatory threshold during CPB reduces the frequency of the composite end point of clinical stroke, a diffusion-weighted MRI brain lesion, or postoperative cognitive decline 4 to 6 weeks after surgery, compared with patients who receive standard blood pressure management.*

Aim 1a: *To assess whether extracranial and/or intracranial arterial stenosis (detected by MR angiography), or other patient characteristics such as age, gender, hypertension, diabetes, or prior stroke, modify the effect of maintaining blood pressure above an*

individual's lower CBF autoregulatory threshold on the risk for the above composite neurological outcome.

Aim 1b: *To assess whether targeting MAP to a level above an individual's lower CBF autoregulatory threshold during CPB reduces the frequency of cognitive decline 1 year after surgery compared with the use of standard blood pressure management.* In Aim 1, we will test whether the Intervention and Control groups have the same risk of the primary composite neurologic endpoint of stroke, DWI lesion, or cognitive decline 4 to 6 weeks after surgery (i.e., null hypothesis). This will be done using a two-sided test of proportions at 5% significance level. We will first calculate and report the relative risk (RR) of composite neurologic outcome by comparing the Intervention and Control groups without adjusting for any potential confounders (i.e., the unadjusted RR). In addition, we will construct an adjusted estimate of RR using a generalized linear model (GLM) with Poisson distribution and robust standard errors.100 The candidate models will include study group as the primary independent variable as well as extra- or intracranial arterial stenosis determined by MRA, patient age, gender, and baseline risk factors that are assumed to be highly predictive of the outcome, such as history of hypertension, diabetes, or prior stroke. To assess potential effect modification by cerebral arterial stenosis, age, gender, hypertension, diabetes, or prior stroke (Aim 1a), we will calculate the unadjusted RR stratified by these variables. We will use a test of homogeneity to compare stratum-specific estimates of RR.101 Finally, we will use the model developed in Aim 1 to report stratum-specific adjusted estimates of RR by introducing appropriate interaction terms of these variables and study group in the GLM model. We will compute the Z-score for the cognitive tests to normalize the distribution to the control data. The individual Z-scores will be combined into an average score and re-normalized.102 To assess postoperative change in cognitive function for up to 1 year (Aim 1b), we will use population-average marginal models estimated using generalized estimating equations (GEE) with exchangeable working correlation structure. The model will include assessment time with 2 indicator variables for 1 year and 4 to 6 weeks postoperation and baseline as the reference group as well as Intervention Group, and their interaction to test whether postoperative trajectory of cognitive function differs by group.

As a secondary analysis, we will develop logistic regression models on the binary outcome of the composite neurologic outcome and the time spent below the CBF autoregulatory threshold regardless of treatment assignment (i.e., data combined from both groups), while adjusting for other statistically and scientifically important covariates. This will allow for the development of a "dose-response" relationship between blood pressure below the CBF autoregulatory threshold and outcome, whereby we can estimate the probability of an adverse neurologic event as a function of time spent in suboptimal perioperative conditions. In this analysis, we will consider the time spent below the CBF autoregulatory threshold as both an absolute time in minutes and as a percent of the total time on bypass, thereby allowing us to determine which measure of time below optimal threshold is more predictive of an adverse outcome. Note, the lower graph in **Figure 6 *(above),*** depicts the data from a single patient showing the percent time at each blood pressure epoch. The program saves the data in a spreadsheet format.

As an additional set of analyses for the multivariable logistic regression models, we will look whether there are interactions (e.g., effect modification) between gender or extra- and intra-cranial arterial stenosis on the composite neurologic outcome. In considering patient sex, we are particular interested in whether or not the effectiveness of the intervention applies equally to women as well as men. Similarly, we are interested in determining whether the association between the intervention and the neurologic end point differs in the presence or absence of clinically significant narrowing in the arteries of the neck and head. In considering the modifying effect of carotid arterial stenosis, we will dichotomize this variable with the cut point of <70% versus ≥70% narrowing based on the NASCET criteria, using the methods for measurement described in ***Magnetic Resonance Imaging***.113 For intracranial arterial stenosis, we will dichotomize the stenosis as ≥50% or <50%. As a second step, we will also consider three categories of arterial stenosis (<50%, 50%–70%, and >70%), which considers the clinically important stenosis definition as defined by the Warfarin-Aspirin Symptomatic Intracranial Disease criteria.111 Interaction terms for both the binary definition of stenosis and the three categories of stenosis will be incorporated into the regression model, and any statistically significant effect modifications will be determined via standard Wald tests. Finally, we will also consider arterial stenosis in the multivariable logistic regression model as a continuous variable if the inter-rater reliability is high for this variable. Considering arterial stenosis as a continuous variable will allow us to consider possible thresholds of risk for the neurologic end point as a function of a continuous measure of stenosis. We will look for inflection points in the risk of stenosis on the outcome by incorporating linear (e.g., broken arrow regression) and cubic spline terms in the model. If the inter-rater reliability for the continuous measures of stenosis is low, we will consider only the above categories of mild, moderate, and severe stenosis in the regression models.

Aim 2: *To compare the accuracy of CBF autoregulation as determined by monitoring of the linear regression correlation between blood pressure and cerebral O2 saturation (cerebral oximetry index) and near-infrared reflectance spectroscopy (hemoglobin volume index) with the accuracy of that determined by TCD-measured CBF velocity (mean velocity index).*

We expect that the estimated lower CBF autoregulatory thresholds based on the cerebral oximetry index will be similar to those measured with both the mean velocity index and the hemoglobin volume index. Nevertheless, to quantify variance, we will first calculate the pair-wise differences in each of these estimate threshold levels per patient. Graphically, we will quantify these differences using histograms to assess the distribution of the discrepancy. In addition, we will create Bland-Altman plots to investigate if these differences are related to the absolute values of the threshold estimate. In other words, does this difference in estimates using either the hemoglobin value and cerebral oximetry or the mean velocity index and the cerebral oximetry increase (decrease) as one's autoregulatory threshold increases (decreases)? We will also investigate whether the discrepancies in threshold estimates differ by the demographic or clinical variables in our patient sample using both univariate methods and linear regression modeling to examine the effect of these covariates on discrepancies in threshold estimates.

This hypothesis has already been adequately addressed and will no longer be an aim of this study as we move forward.

Aim 3: *To perform secondary analysis to determine whether an association exists between abnormal perioperative TCD findings indicative of intracranial arterial stenosis and the risk for the composite neurologic outcome.*
Under this aim, we will assess whether perioperative TCD findings indicative of arterial stenosis of major cerebral vessels (**see *Transcranial Doppler Evaluation***) are predictive of the composite adverse postoperative neurologic outcome. We will test for this possible association by considering - in the multivariable logistic regression model described under Specific Aim 1 - a dummy variable indicative for a positive finding for stenosis preoperatively. Results from this model in conjunction with determination of any potential effect modifications of stenosis on the outcome as described under **Aim 1a** will serve as a valuable tool for assessing the benefits and risks of this CBF-targeted intervention during CPB on patients found to have clinically significant narrowing of the intracranial arteries, as determined by either MRA or TCD examination before surgery.

Aim 4: *To assess whether targeting MAP during CPB to a level above an individual's lower CBF autoregulatory threshold during CPB reduces the frequency of postoperative delirium, as assessed with a structured examination, compared with the use of standard blood pressure management.*
In **Aim 4**, we will compare Intervention and Control groups for proportion of patients with delirium. For the analysis, we will include only those patients who have undergone the more extensive delirium assessments as described in this proposal. This same structure assessment for delirium was initiated in year 4 of the prior grant and is consistent with other delirium studies performed by co-investigators (R01 AGO33615). We will estimate the unadjusted (without any other variable in the model) and adjusted RR of delirium by comparing the two study groups. We will adjust for potential confounders using a generalized linear regression model with Poisson distribution and robust standard errors.119

Aim 5: *To determine whether baseline frailty is independently associated with delirium or functional decline after cardiac surgery*.
In **Aim 5**, we will test the hypothesis that frailty is associated with postoperative delirium. The primary outcome will be the development of delirium at any time, as measured by CAM or CAM-ICU and coded as a binary variable. Secondary outcomes will be delirium severity from the DRS-R-98 scale. Bivariable and multivariable logistic regression analysis will be used to determine if frailty is associated with postoperative delirium. We will also test the hypothesis that frailty is associated with decreased function after cardiac surgery. The primary outcome will be proportion of patients with >1 IADL decline. Secondary outcomes will be change in gait speed and grip strength. Bivariable and multivariable linear and logistic regression analyses will be used. For each of these analysis, covariates to include in the model will be selected using a priori evidence, and may include age, gender, race, baseline cognitive status, education, medications, and

type of surgery. We will also consider propensity score analysis to account for important confounding.

Aim 6: *To determine whether depth of anesthesia in frail patients is a modifiable risk factor for delirium and functional decline after cardiac surgery.*
In **Aim 6**, we will compare cumulative time of BIS<45 in frail vs. non-frail patients using bivariable and multivariable linear regression. The cumulative time of BIS<45 will also estimate the amount of potential anesthetic overdose in all patients.

Rapid Dissemination of Clinical Research
A major objective of this study is to disseminate new information to the medical and lay communities. We propose to fulfill this aim by presentations at national and international meetings and conventional publications in the medical literature. Full results of the study will be published as soon as possible, consistent with principles of peer-reviewed publication. National meetings of the AHA, American Stroke Association, Society of Thoracic Surgeons, and the Society of Cardiovascular Anesthesiologists are excellent venues for presenting clinical study results. We will continue to use MedDium, LLC (Silver Springs, MD) for a Web portal that provides the NIH and public with visibility into program activities and major scientific discoveries. Finally, the media relations department at Northwestern University will be utilized to coordinate press releases of study trial results as they become available.

Secondary outcome variables.
Included in Primary outcome variables (above).

Statistical plan including sample size justification and interim data analysis.

Sample size calculations are based on detecting differences in the proportion of patients with an adverse neurologic outcome (DWI lesion, stroke, or cognitive decline 4 to 6 weeks after surgery) between the Control and Intervention groups. We expect that approximately 45% of subjects in the Control Group will experience an adverse neurologic outcome after surgery based on the preliminary data analysis of outcomes of 176 patients. In comparison, we expect that the proportion of the Intervention Group that experiences adverse neurologic outcomes will be reduced by 40-45% (e.g. The frequency of neurologic adverse events will be between 25% and 27%). This magnitude of reduction in the frequency of the composite outcome is within the range that is considered to be clinically important effect (20% to 45% reduction from control frequency) based on prior trials that have evaluated temperature manipulations, pH management, transfusion triggers, and pharmacologic strategies for improving neurologic complications of cardiac surgery [116-118]. Postoperative MRI is not always feasible for reasons already discussed. According to our calculations, we will need to obtain MRI data on a total of 122 patients in each study arm (244 patients in total) to have 80% power to detect 40% reduction in the composite outcome of stroke, DWI lesion, or cognitive decline 4 to 6 weeks after surgery, assuming that 45% of Control Group patients experience adverse neurologic events. The Type I error is 5%.

Our current enrollment trajectory suggests that at least 277 patients will have undergone the protocol of our study before the end of the funding period for the initial grant. At that point we would expect to have 101 patients who have undergone MRI for evaluation of DWI lesions. An additional143 patients with complete MRI, stroke, and cognitive endpoint data are needed to reach the target of 244 patients with the primary, complete endpoint data. To reach this target, we will need to enroll an additional 350 patients in this renewal. Our recruitment projections for our initial funded study are a conservative estimate, as we have enrolled 277 patients to our study (101 have MRI data). On average, 5 to 8 patients are enrolled per month. These projections confirm that the plan for this submission of studying 350 additional patients (a total of 630 patients) will ensure completion of the study with 244 patients having all study assessments, including MRI, at the completion of the proposed study funding period.

In addition, we calculated the minimal sample size required to detect 0.2 SD difference in combined Z-score for cognitive tests normalized to the control group's data between the Intervention and Control groups with 80% power [47]. We assume 2 follow-up points (4 to 6 weeks and 1 year after surgery) and an average within-patient correlation of 0.7 (observed in our preliminary data). The calculations indicate that we will need 177 observations per group, or 354 patients in total, to detect 0.2 SD difference with 80% power (assuming 5% Type I error). The study (first and second funding periods) will recruit a total of 489 patients to meet the MRI endpoint. Therefore, we will meet our goal of having 354 patients to detect the expected 0.2 SD difference in combined cognitive score seven with a 1-year drop-out rates high as 27%.Historically, the drop-out rate for cognitive testing at 1 year in similar populations has been between 3% and 24% [47].

For Specific Aim 4, we assessed the level of statistical power to detect clinically meaningful differences in proportion of patients with postoperative delirium based on the sample size for Aim 1. Our preliminary data indicate a 50% reduction in this outcome when a structured instrument for delirium assessment is used (frequency of 33% vs. 66% in Intervention vs. Control Group). This marked decrease was based on n = 37 patients. Therefore, in the power assessment for this aim we conservatively assumed 50% frequency of delirium in the Control Group. We will expect to see a 40% reduction in frequency of this condition in the Intervention Group. Our calculations indicate that having a minimum of 122 patients in each group with thorough delirium assessments (not performed in all patients in the first cohort) will allow us to detect a 40% decrease in proportion of patients who develop delirium in the Intervention Group with 87% power, assuming a 5% level of statistical significance for the two-sided test. We have instituted careful delirium assessments in our current. Postoperative MRI is not always feasible for reasons already discussed. According to our calculations, we will need to obtain MRI data on a total of 122 patients in each study arm (244 patients in total) to have 80% power to detect 40% reduction in the composite outcome of stroke, DWI lesion, or cognitive decline 4 to 6 weeks after surgery, assuming that 45% of Control Group patients experience adverse neurologic events. The Type I error is 5%.

Our current enrollment trajectory suggests that at least 277 patients will have undergone the protocol of our study before the end of the funding period for the initial grant. At that point we would expect to have 101 patients who have undergone MRI for evaluation of DWI lesions. An additional 143 patients with complete MRI, stroke, and cognitive endpoint data are needed to reach the target of 244 patients with the primary, complete endpoint data. Our recruitment projections for our initial funded study are a conservative estimate, as we have enrolled 277 patients to our study (101 have MRI data). On average, 5 to 8 patients are enrolled per month. These projections confirm that the plan for this submission of studying 350 additional patients (a total of 630 patients) will ensure completion of the study with 244 patients having all study assessments, including MRI, at the completion of the proposed study funding period.

As of June 2016, we have enrolled 280 patients in the first five years and 244 patients in the second five year study. We need approximately 150 patients to complete enrollment.

In addition, we calculated the minimal sample size required to detect 0.2 SD difference in combined Z-score for cognitive tests normalized to the control group's data between the Intervention and Control groups with 80% power.[47] We assume 2 follow-up points (4 to 6 weeks and 1 year after surgery) and an average within-patient correlation of 0.7 (observed in our preliminary data). The calculations indicate that we will need 177 observations per group, or 354 patients in total, to detect 0.2 SD difference with 80% power (assuming 5% Type I error). The study (first and second funding periods) will recruit a total of 489 patients to meet the MRI endpoint. Therefore, we will meet our goal of having 354 patients to detect the expected 0.2 SD difference in combined cognitive scores even with a 1-year drop-out rate as high as 27%. Historically, the drop-out rate for cognitive testing at 1 year in similar populations has been between 3% and 24%.[47]

For Specific Aim 4, we assessed the level of statistical power to detect clinically meaningful differences in proportion of patients with postoperative delirium based on the sample size for Aim 1. Our preliminary data indicate a 50% reduction in this outcome when a structured instrument for delirium assessment is used (frequency of 33% vs. 66% in Intervention vs. Control Group). This marked decrease was based on n = 37 patients. Therefore, in the power assessment for this aim we conservatively assumed 50% frequency of delirium in the Control Group. We will expect to see a 40% reduction in frequency of this condition in the Intervention Group. Our calculations indicate that having a minimum of 122 patients in each group with thorough delirium assessments (not performed in all patients in the first cohort) will allow us to detect a 40% decrease in proportion of patients who develop delirium in the Intervention Group with 87% power, assuming a 5% level of statistical significance for the two-sided test. We have instituted careful delirium assessments in our current protocol. Thus, our sample size projections are conservative estimates, as we will have at least 60 patients in each group with careful delirium assessments by the completion of the first 5 years of the study. At the completion of the second 5 years, we are likely to have 180 patients in each study treatment arm with careful delirium assessments.

Missing data

Two sources of missing data are anticipated: missing data on predictors and missing data on the primary outcome. The strategy of dealing with missing data on predictors will depend on the amount of missing data. If the overall number of observations with missing predictors is under 5%, a complete-case analysis will be performed by dropping observations with missing data. The pattern of missingness will be examined. If the amount of missing data is between 5% and 20%, we will calculate the main results based on the complete-case analysis, but we will perform a sensitivity analysis using multiple imputation strategy. No attempt will be made to impute variables that have more than 20% data missing. Missing data on outcomes and the drop-out pattern will be assessed. No imputation of the outcome variables will be attempted. In addition to the primary analysis with the GEE approach, random-effects models have been shown to be a useful strategy in cases of non-equal number of measurements across individuals if missing data mechanism can be assumed to be ignorable. Therefore, the primary analysis will be supplemented by the random-effects approach. In addition, we will explore random-effects pattern mixture models to assess the influence of missing data in these analyses.[122]

Feasibility of Recruitment and Retention

The investigative team has a track record of high enrollment in industry-sponsored and extramurally funded clinical trials in patients undergoing cardiac surgery. The original study end point of 280 patients over a 56-month enrollment period required approximately 5 to be enrolled each month. The study endpoint of 350 patients in the second phase of the study requires enrollment of approximately 8 patients/month, a rate that we feel is attainable based on our success in the first phase of the study. The volume of surgical procedures performed at Northwestern Memorial Hospital (Table 6) will allow for the study to be completed in the planned timeframe. Procedures for retention of patients in the study will include visits by the nurse coordinators to the patients during hospitalization to reinforce the importance of the study. The patients will be contacted by phone before the 4-to-6–week postoperative visit to confirm their testing session.

Table 6: Number of Cardiac Procedures at Northwestern Memorial Hospital

Type of procedure	2014	2015
Coronary artery bypass graft surgery	177	144
Mitral valve procedure	134	119
Aortic valve procedure	286	264
Multiple procedures	198	186
Other CV (VAD, ECMO, Heart transplant)	88	124

This surgical volume and the track record of the PI and other investigators in enrolling patients in clinical trials involving cardiac surgical patients ensures that an adequate number of patients will be enrolled to complete this trial in the funding period.

Statistical Analysis Plan

Tabular and graphical methods of data exploration will be used to evaluate variable distributions over the perioperative time period. When conducting modeling, we will determine the influence of the outliers on model fit. If the influence is high, we will consider excluding the outlier/s. We will explore the extent to which CBF autoregulation changes over the perioperative period. Univariate distributions for all study variables will be evaluated. We will explore potential confounders as variables strongly predictive of the outcomes (a priori and in the data) and differentially distributed between the study arms. Results of these analyses will be used to refine the analyses and guide model building and selection.

The cognitive outcome will be assessed as change from baseline in a composite cognitive Z score 4 to 6 weeks after surgery. The Z score will be calculated for individual tests at each testing time point with the mean and SD of baseline tests of all patients. Timed tests will be multiplied by '-1' so that higher scores represent better performance. Individual Z scores will be combined into an average Z-score, calculated from the average of the non-missing individual test Z-scores. These will then be renormalized using the mean and standard deviation at baseline. A difference between pre- and post-test > 0.3 is considered cognitive decline.

Early stopping rules: N/A

Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Experimental Problems

Hemodynamic perturbations are frequent preoperatively. Such events could potentially confound the results of this study if a patient suffers cerebral ischemia from hypotension postoperatively. To adjust for hypotension, patient clinical data will be reviewed daily by research staff, and episodes that meet the criteria for hypotension will be recorded in the case report form. Use of vasoconstrictive or inotropic medications will be recorded. One strength of the protocol is that blood pressure will be measured continuously via the IMx+ software during surgery rather being recorded by an observer.

The use of gadolinium in subjects with renal failure has been implicated in the etiology of a rare condition called nephrogenic systemic fibrosis (NSF). As we state in Magnetic Resonance Imaging, a creatinine level will be measured in all patients before the MRI, and gadolinium will not be given to individuals with an estimated glomerular filtration rate of ≤60 mL/min or to those needing dialysis after surgery (by FDA and hospital recommendations).[107] Diffusion-weighted MRI will still be performed as part the

assessment of our primary end point. MRA will also be obtained of the head and neck; the neck MRA will be performed with gadolinium in individuals with adequate renal function and without other contraindications for gadolinium, but otherwise will be done without gadolinium. No cases have been reported to the FDA of NSF in individuals with normal renal function or with only mild renal insufficiency. Thus, we do not anticipate an increased risk in our study protocol.

One challenge in this study will be the transport of patients who remain in the postoperative ICU to the MRI scanner, particularly those who require continued mechanical lung ventilation and infusion of vasoactive drugs. The PI or a critical care physician will accompany such patients to the scanner, along with the critical care patient transport team of The Northwestern Memorial Hospital.

AEs will be reviewed by the investigative team at bi-monthly meetings and by the IRB to ensure that these safeguards are adequate to protect the safety of the enrolled patients.

Patients will be excluded if a TCD trans-temporal window cannot be identified before surgery, as the primary intervention is dependent upon detecting the lower CBF autoregulatory threshold using this method. Regardless, monitoring with TCD in surgical patients is challenging for many reasons. Maintaining continuous monitoring is particularly difficult during certain portions of the procedures, such as during tracheal intubation, central venous line placement, transesophageal echocardiography examination, and especially during dissection of the left internal mammary artery, when frequent changes in the patient's body position and the sternal retractor can lead to displacement of the transducers. Intermittent loss of the temporal window during surgery might lead to bias if blood pressure reductions below the autoregulatory threshold are not detected as such. Defining the lower autoregulatory threshold based on mean velocity index or oximetry index should minimize this bias, as the latter will be a continuous measurement not subject to intermittent loss of signal.

Many factors can influence a surgical patient's CBF, including anemia, temperature fluctuations, and volatile (but not intravenous) anesthetics.[69] The effects of many of these variables on CBF autoregulation in this setting have not been examined extensively. Further, the effect of volatile anesthetics on CBF autoregulation is dose dependent. In low to moderate doses, as used clinically, the CBF autoregulatory plateau might be slightly attenuated and minimally shifted to the left. These clinical considerations emphasize the dynamic nature of CBF autoregulation and the need to monitor this parameter continuously when targeting blood pressure management to remain above the point at which CBF is pressure passive. The conditions of this study will enhance the external validity of the findings.

The monitoring of the CBF autoregulatory threshold by a moving linear regression correlation (mean velocity index) requires first ensuring the fidelity of the TCD-derived measurements of middle cerebral artery CBF velocity. Intraoperative TCD monitoring will be performed by individuals with extensive experience in obtaining these measurements,

including in cardiac surgical patients. Our experience is that the demarcation of the lower CBF autoregulatory threshold via mean velocity index is clearly indicated by the error bar graphing, as shown in Figures 3 and 5.

Undergoing an MRI can lead to anxiety in some patients. The investigative team will take measures to reassure the patients during the MRI procedure. Image acquisition will be stopped at frequent intervals to query the patients about distress. A “panic button” will also be available to the patients to notify radiology and study personnel about distress. Some patients may have temporary cardiac pacemaker leads placed after surgery. Coiled pacemaker wires on the surface of the patient could potentially serve as antennae during MRI that might generate heat or induce premature cardiac beats. However, brain MRI will be obtained between postoperative days 1 and 5 or within the first 14 days after the procedure (whatever the patient is more comfortable with), usually after the patient has had the pacemaker wires removed. When necessary, brain MRI can be performed safely in patients with retained metallic materials[128] by taping the pacemaker wires straight to the skin to avoid coiling.

The location and extent of abnormality in perfusion-weighted imaging, diffusion weighted imaging, and conventional MRI are subject to inter-observer discrepancy. However, we have found a high degree of inter-judge reliability in evaluating volume and sites of abnormalities on diffusion-weighted imaging and perfusion-weighted imaging, calculating the number of seconds of delay in perfusion, and determining the affected regions of interest, as described above. We will evaluate effects of cerebral edema on both T2- and perfusion-weighted imaging. Edema is usually significant only in large strokes, is greatest at day 3–10, and is most visible on T2 images. Edema contributes to the hypoperfused region. Patients in whom edema is observed on T2 beyond regions of hypoperfusion on perfusion-weighted imaging will be excluded.

We will obtain only postoperative brain MRI imaging rather than paired pre- and postoperative imaging. The logistics of obtaining preoperative MRI in surgical patients would be a major impediment to recruitment. In some patients, small, clinically undetected diffusion-weighted imaging lesions might result from cardiac catheterization performed before surgery. Such lesions would be mistaken to have occurred during surgery. Therefore, a careful neurologic examination using the NIHSS will be performed before surgery but after cardiac catheterization to ensure that there are no new major deficits. Acute strokes that may have occurred 1–2 weeks before surgery should no longer appear acute at the time of a postoperative DWI MRI (they will no longer be bright on DWI and dark on ADC, as occurs with new strokes).

The significance of new diffusion-weighted imaging lesions to brain regions not involved with higher cerebral function might be debated. However, it is increasingly appreciated that the cumulative impact of a small area of injury on cognitive or other neurologic end points might only be manifest after long-term follow-up. Even if the impact of some diffusion-weighted imaging lesions is minor, development of strategies to improve

neurologic outcomes after cardiac surgery should aim to detect all forms of injury using sensitive means.

The use of 2D TOF MRA in the subset of individuals who cannot receive gadolinium will limit the resolution of this vascular imaging in this subset; however, we anticipate that we should still be able to make global measurements of stenoses. In addition, MRA may suggest stenoses that are not as narrow as they appear, because it measures flow.

Unfortunately, alternative technologies that might give better vascular imaging (such as CT angiography or conventional angiography) expose patients unnecessarily to iodinated dye and, in the case of angiography, an invasive procedure.

Although perfusion-weighted imaging provides an indication of whether a brain area is relatively hypoperfused, it cannot necessarily distinguish whether a brain infarct results from embolism and/or hypoperfusion. Small emboli in well-perfused areas might be transient, but those in areas of hypoperfusion might persist (slow “washout”). In this study, we will count the number of TCD-detected microembolic signals to adjust statistically for the number of emboli in patients with and without diffusion-weighted imaging lesions. Although this study will provide only inferential data on the mechanism of brain injury, the combination of MRI indices and our determination of duration during CPB that mean arterial pressure is below the individual’s CBF autoregulatory threshold, combined with emboli monitoring with TCD, will provide important clinical mechanistic insights.

Failure to obtain study data after a patient is discharged from the hospital (i.e., at the 4- to 6-week postoperative testing sessions) could confound analysis of the secondary cognitive end points of the trial. Multiple reasons might cause patients not to comply with follow-up testing, including death, severe stroke, and discharge to a secondary care facility. Postoperative testing is coordinated to occur during the patient’s postoperative clinic visit with his/her surgeon.

Off-pump CABG surgery is performed in <10% of patients at our institution but is not performed in patients undergoing combined CABG and valve surgery. Although performance of CABG surgery “on-” versus “off-pump” has not been shown to impact neurologic outcomes remarkably based on prospectively randomized trials, it is possible that new data may become available during this trial that might support the decision to perform more surgeries without CPB. Such a decision could conceivably influence recruitment. However, the number of procedures performed at our hospital and the number of patients projected for this study suggest that a sufficient number of patients will be recruited during the planned period of study.

Providing additional information about functional capacity including performance of instrumental ADLs, as well as about ability to drive. This carries minimal additional medical risk to the participant beyond routinely held structured preoperative interview – increased anxiety due to extension of regular pre-operative interview time.

Frailty testing which includes 15 feet walk and performance of hand grip strength. Performance of handgrip strength test using the dynamometer is associated with minimal risks including muscle strain (<1%), discomfort with muscle exertion (~1%), and elevated blood pressure as a response to physical exertion (~5%).

Informed Consent

Before the start of any study-related procedure, a signed and dated IRB-approved informed consent form (ICF) will be obtained and documented in the patient's medical record. The investigator must 1) inform each patient accordingly and allow each patient sufficient time to decide whether or not to participate in the study; 2) give patients and relatives the opportunity to inquire about details of the study and to answer any questions regarding the study; and 3) ensure that the ICF is approved by the IRB when an amendment to the study protocol is made.

A patient is free to withdraw consent for participation in the study at any time, without prejudice to further treatment. Every effort will be made to obtain complete follow-up information on subjects who discontinue from the study prematurely. The reason(s) for a subject's discontinuation must be clearly documented in the subject's medical records and in the case report form (CRF). A patient's participation in the study may be discontinued at any time at the discretion of the PI.

Data Management Methods

Patient information relevant to this study will be recorded on case report forms customized for this study. Only the PI and authorized research staff according to the list of Authorized Study Personnel are entitled to make entries on the case report form. Completed case report forms will be dated and signed by the PI or Sub-PI. Personal patient data will be kept confidential. Case report forms or other documents will identify a patient by initials and study number only. The PI or authorized research personnel will keep the Patient Identification and Enrollment List separately. To allow compliance with GCP principles, each patient will be asked for consent regarding the access to source documents for monitoring, audits, and inspections. The agreement, also covering the use of the data for analyses, must be documented in writing, together with the written ICF for study participation. Data will be transferred from the case report form to a study database (Redcap). This database will include only the patient study number and will be devoid of patient identifying information. All information obtained during the conduct of this study will be regarded as confidential.

Quality Assurance

Before the start of the study, a training session will be conducted to familiarize team members with the protocol and case reporting processes. The protocol and all testing, including the cognitive tools, the NIHSS, and the process for reporting AEs, will be reviewed in detail.

Quality control procedures for the cognitive testing include multilayered training of examiners, review of practice protocols by a board-certified neuropsychologist, and

random selection and review of actual patient testing by a board-certified neuropsychologist during the study period. An initial training session with detailed discussion and demonstration of each test in the battery will be performed led by a member of the research team. All examiners will practice administration of the battery with colleagues. Next, all examiners will practice administration of the battery on three volunteers at the site. The same procedure will be followed if new examiners are added after the study period has begun. During the study period, similar quality control procedures will be in place. Research personnel will be certified for performing the NIHSS using the American Stroke Association's Online NIH Stroke Scale Training Program (http://asa.trainingcampus.net/uas/modules/trees/windex.aspx).

All members of the team who assess delirium will undergo rigorous training prior to study enrollment. During the course of the study, team members will meet every two weeks to discuss the diagnosis and evaluation of individual cases of delirium.

Data and Safety Monitoring Plan

At the start of the study, a Data and Safety Monitoring Board (DSMB) will be appointed and will consist of a cardiac surgeon, two neurologist, an anesthesiologist/critical care physician, a statistician (Dr. McCarthy), an independent member from an outside institution and a member from the NIH all with expertise in the area of neurological complications after cardiac surgery. The DSMB members will not be direct participants in the study and they must attest to not having any conflicts of interest with the study or any of its investigators. A team member (TBD) will participate in the DSMB meetings as non-voting member. The DSMB will be charged with oversight of the study's safety and integrity and assessing the risk versus benefits of continuing the study if such questions arise. The DSMB will meet at least bi-annually in person or by conference call or more often, if necessary, based on the progression of the study, including any arising events as communicated by the PI. The DSMB will continue to meet until the completion of the study.

The DSMB will review patient recruitment and patient follow-up, compliance with the protocol including protocol violations, timeliness and completeness of data entry, compliance with patient confidentiality and HIPPA regulations, and communications of adverse events to the IRB. The DSMB members should immediately review the data in order to make any requests for additional information or analysis in a time frame that can allow for such requests to be completed before the scheduled DSMB meeting. Members of the DSMB must maintain confidentiality of the study data until otherwise instructed. An interim analysis of the data looking at safety will be conducted by the DSMB when results from the first 140 subjects are available. If we are given continued funding a meeting of the investigative team will be held to discuss the validity of an additional interim analysis.

Plan for reporting unanticipated problems or study deviations.

Adverse Events

For this study, an adverse event (AE) is any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness, or abnormal laboratory finding) that

emerges or worsens relative to baseline during the study periods, regardless of the suspected cause. Untoward medical events that occur from the time the subject signs the ICF to the time of surgery are not considered AEs and should be recorded under medical history. AEs encountered during or after surgery will be recorded on the appropriate AE section of the CRF. All AEs will be evaluated by the PI for their intensity, frequency, relationship to study, and outcome. The intensity of both serious and nonserious AEs will be graded as mild, moderate, or severe. The definitions are as follows: 1) mild, transient event—does not require medical intervention; the normal clinical course for a subject undergoing cardiac surgery is not changed; AND/OR the subject experiences discomfort, but no disruption of normal daily activity; 2) moderate—event may require medical intervention; induces moderate deviation from the normal clinical course for a subject undergoing cardiac surgery; AND/OR the subject experiences sufficient discomfort to reduce or affect normal daily activity; and 3) severe—event requires significant medical intervention and constitutes a marked deviation from the normal clinical course for a subject undergoing cardiac surgery AND/OR the subject is incapacitated and unable to perform normal daily activities.

An AE should be classified as SERIOUS if: 1) it resulted in death (i.e., the AE caused or led to death); 2) it was life threatening (i.e., the AE placed the subject at immediate risk of death); 3) it required or prolonged inpatient hospitalization (i.e., the AE required at least a 24 h inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay); 4) it was disabling (i.e., the AE resulted in a substantial disruption of the patient's ability to carry out normal life functions); or 5) it did not meet any of the serious criteria listed above but potentially jeopardized the patient or required medical or surgical intervention to prevent one of the outcomes listed above. Adverse events will be reported to the IRB, recorded in the study database, and reviewed at the weekly investigators' meeting. Adverse events also will be reviewed at the quarterly Data Safety and Monitoring Board meeting. Serious AEs will be reported to NIH personnel. As soon as the research team notices that an enrolled patient has died or suffered as an adverse event the research team will report it within 24 h and within 72 h respectively.

Financial risks to the participants.
The only foreseeable financial risk for the study participant would be in the event that a referral was needed for something found on MRI scan. The study related MRI scan will be paid for by the study sponsor. However, since MRI scanning of the brain is not routinely done for cardiac surgery there is the potential that a pre-existing condition may be diagnosed that would not have ordinarily been found. In that case, the study participant's insurance would need to cover the cost of further diagnostics and/or treatment.

Benefits
Description of the probable benefits for the participant and for society.
Brain imaging might result in the detection of an unexpected condition, such as a brain mass, aneurysm, or vascular malformation. In the event of such findings, the patient, and his/her family and clinical physicians will be notified, and the patient will be referred for clinical management.

Brain injury from cardiac surgery is an important source of operative mortality, prolonged hospitalization, increased health care expenditure, and impaired quality of life. Developing strategies to reduce the burden of this complication has wide public health implications.

Brain imaging might result in the detection of an unexpected condition, such as a brain mass, aneurysm, or vascular malformation. In the event of such findings, the patient, and his/her family and clinical physicians will be notified, and the patient will be referred for clinical management.

Payment and Remuneration
The patients will receive a $100 stipend for participation at the time of their 4-6 week visit. Patients who return for the 1 year follow-up visit will receive an additional $100 stipend. Patients will also receive a $300 if the finish the MRI component of the study. These are meant to help defray the cost of parking and meals associated with the postoperative visit.

Costs
The subjects will not be charged for study procedures including TCD monitoring, blood pressure management, MRI/MRA (and x-ray of the head, where indicated), neurocognitive testing. In the event something is found on MRI and a referral to a specialist is made, that referral would need to be covered by the subject's insurance.

RESOURCES AVAILABLE:
The research team includes personnel with vast experience in clinical research studies and some have been involved with other NIH funded projects and have published numerous papers in peer review journals. Dr Sorond is a neurologist with many years of experience with clinical trials. Dr. Nemeth is a neuroradiologist who has participated in a several clinical trials. Dr. Schrift is a neuropsychiatrist who has participated in clinical trials. Research staff have over 15+ years of clinical research, GCP, and data analysis experience.

PRIOR APPROVALS:
Department of Anesthesiology Research
Committee John Hopkins Institutional Review Board

NUMBER OF LOCAL PARTICIPANTS:
150 participants

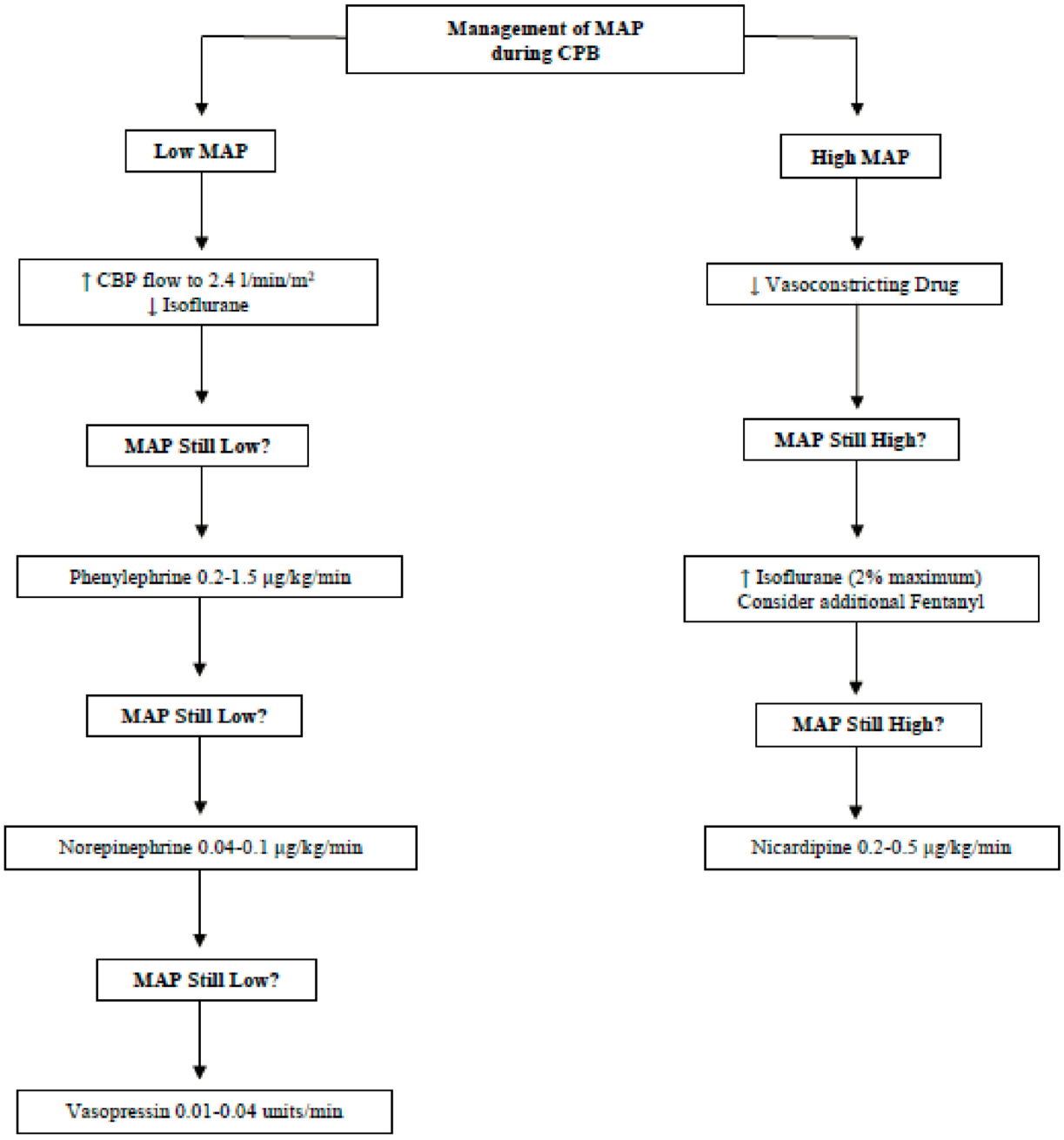
PROCESS TO DOCUMENT CONSENT IN WRITING:
(*Review "SOP: Written Documentation of Consent (HRP-091)." If you will not be following HRP-091, describe whether and how consent of the participant will be documented in writing*.)

We will be using documentation of consent checklist.

DRUGS OR DEVICES:

A near infrared spectroscopy machines (INVOS 5100, Covidien, Inc, Boulder, CO) with digital signal output capability, A/D converter for digitizing blood pressure data from OR hemodynamic monitors, and a laptop computer all on a mobile cart for acquisition and analysis of cerebral blood flow autoregulation data. The mobile cart will be stored at the 5th floor or 7th floor of Feinberg pavilion in the anesthesia block room which is locked and requires key entry. It will only be used for research purposes.

Appendix A


Management of MAP during CPB
Low MAP
↑ CBP flow to 2.4 l/min/m²
↓ Isoflurane
MAP Still Low?
Phenylephrine 0.2-1.5 µg/kg/min
MAP Still Low?
Norepinephrine 0.04-0.1 µg/kg/min
MAP Still Low?
Vasopressin 0.01-0.04 units/min
High MAP
↓ Vasoconstricting Drug
MAP Still High?
↑ Isoflurane (2% maximum)
Consider additional Fentanyl
MAP Still High?
Nicardipine 0.2-0.5 µg/kg/min

Appendix B

Neuropsychological Test Battery

MEMORY
- Rey Auditory Memory Test
  - New Learning Score (sum of trials 1 – 5)
  - Delayed Recall Score
  - Delayed Recognition Score
- Rey Complex Figure Test

EXECUTIVE FUNCTIONS
- Controlled Oral Word Association
  - Total correct responses (F, A and S)
- Trail Making test A and Trail Making test B
  - Time (seconds) to complete

PSYCHOMOTOR/MOTOR SPEED
- Grooved Pegboard
  - Time to complete (dominant hand)
  - Time to complete (non-dominant hand)
- Trail Making test A and Trail Making test B
  - Time (seconds) to complete
- Symbol Digit Modalities test
  - Number of correct responses in 90 seconds

MOOD/ANXIETY
- Beck Depression Inventory – II
- State Trait Anxiety Inventory

HEALTH STATUS/MEDICAL OUTCOMES
- SF-36 Short Form

Appendix C

Delirium Test Battery

PREOPERATIVE TESTING
- Mini Mental Status Exam (MMSE)
- Abbreviated Digit Span

POSTOPERATIVE TESTING
- Mini Mental Status Exam (MMSE)
- Abbreviated Digit Span
- Confusion Assessment Method (CAM)
- Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)
- Delirium Rating Scale-Revised-1998 (DRS-R-98)

Appendix D

Frailty Assessments and Scoring

TOTAL SCORE
Total score = Exhaustion Score + Walk Score + Grip Score + Weight Score + Activity Score

FRAILTY LEVEL
If total score = 0, then non-frail
If total score = 1 or 2, then prefrail
If total score = 3 – 5, then frail

EXHAUSTION SCORE
Ask the subject the following questions:
"How often in the last week did you feel this way?"
(a) I felt that everything I did was an effort. ***(Effort)***
"How often in the last week did you feel this way?"
(b) I could not get going. ***(Motivation)***
The subject will respond to these questions using the following scale:
0 = rarely or none of the time (1 day);
1 = some or a little of the time (1–2 days);
2 = a moderate amount of the time (3–4 days); or
3 = most of the time.
An answer of "2" or "3" to either of these questions = 1
An answer of "0" or "1" to either of these questions = 0

If Effort + Motivation = 0, then non-frail
If Effort + Motivation ≥ 1, then frail

WALK SCORE

Gender	Height (cm)	Cutoff time to walk 15 feet criteria for frailty
Men	≤ 173	≥ 7 seconds
	> 173	≥ 6 seconds
Women	≤ 159	≥ 7 seconds
	> 159	≥ 6 seconds

Subject will be timed while he/she walks 15 feet at his/her usual pace. This will be done a total of three times.
If average Walk Time is at or above the cutoff for height, then 1 (frail)
If average Walk Time is below the cutoff for height, then 0 (non-frail)

GRIP SCORE

Gender	BMI	Cutoff for grip strength (Kg) criterion for frailty
Men	≤ 24	≤ 29
	24.1–26	≤ 30
	26.1–28	≤ 31
	> 28	≤ 32
Women	≤ 23	≤ 17
	23.1–26	≤ 17.3
	26.1–29	≤ 18
	> 29	≤ 21

Subject will squeeze the dynamometer with his/her dominant hand and the result will be recorded. This will be done a total of three times with the dominant hand and then an additional three times with the non-dominant hand.

If average Grip Strength is at or below the cutoff for BMI, then 1 (frail)
If average Grip Strength is above the cutoff for BMI, then 0 (non-frail)

Weight Score
Ask the subject if they have lost > 10 pounds in the last year *unintentionally*.
If > 10 lbs unintentional weight loss in the last year, then 1 (frail)
If < 10 lbs unintentional weight loss in the last year, then 0 (non-frail)

ACTIVITY SCORE
Activity Score = (kcals Walk for exercise per week) + (kcals Moderately strenuous household chores per week) + (kcals Moderately strenuous outdoor chores per week) + (kcals Dancing per week) + (kcals Bowling per week) + (kcals Regular exercise program per week)

Gender	Cutoff for physical activity kcals per week criteria for frailty
Men	< 383
Women	< 270

If Activity Score is below the cutoff for BMI, then 1 (frail)
If Activity Score is above the cutoff for BMI, then 0 (non-frail)

Calculating kcals for Activity Score:
Walk for exercise
(Walk frequency per week) X (minutes per walked) X 3.5 = kcals walked per week
Moderately strenuous household chores
(Chores frequency per week) X (Minutes per chores) X 4.5 = kcals chores per week
Moderately strenuous outdoor chores
Moderately strenuous outdoor chores = (kcals mow per week) + (kcals rake per week) + (kcal garden per week) + (kcals hike per week) + (kcals jog per week) + (kcals bike per week) + (kcals exercycle per week)
(Mow frequency per week) X (Minutes per mow) X 4.5 = kcals mow per week
(Rake frequency per week) X (Minutes per rake) X 4 = kcals rake per week

(Garden frequency per week) X (Minutes per garden) X 4.5 = kcal garden per week
(Hike frequency per week) X (Minutes per hike) X 6 = kcals hike per week
(Jog frequency per week) X (Minutes per jog) X 6 = kcals jog per week
(Bike frequency per week) X (Minutes per bike) X 3.5 = kcals bike per week
(Exercycle frequency per week) X (Minutes per exercycle) X 5 = kcals exercycle per week

Dancing

Dancing = (kcals Dance per week) + (kcals aerobic dance per week)
(Dance frequency per week) X (Minutes per dance) X 5.5 = kcals dance per week
(Aerobic dance frequency per week) X (Minutes per aerobic dance) X 6 = kcals aerobic dance per week

Bowling

(Bowl frequency per week) X (Minutes per bowl) X 3 = kcals bowl per week

Regular exercise program

Regular exercise program = (kcals golf per week) + (kcals tennis per week) + (kcals doubles tennis per week) + (kcals racquet ball per week) + (kcals calisthenics per week) + (kcals swim per week)
(Golf frequency per week) X (Minutes per golf) X 4.5 = kcals golf per week
(Tennis frequency per week) X (Minutes per tennis) X 8 = kcals tennis per week
(Doubles tennis frequency per week) X (Minutes per doubles tennis) X 6 = kcals doubles tennis per week
(Racquet ball frequency per week) X (Minutes per racquet ball) X 7 = kcals racquet ball per week
(Calisthenics frequency per week) X (Minutes per calisthenics) X 4.5 = kcals calisthenics per week
(Swim frequency per week) X (Minutes per swim) X 6 = kcals swim per week

Appendix E

IADL Assessment[199,200]

1. Can you use the telephone …

   - ☐ 2 without help, including looking up numbers and dialing?
   - ☐ 1 with some help (can answer phone or dial operator in an emergency, but need a special phone or help in getting the number or dialing); or
   - ☐ 0 are you completely unable to use the telephone?

2. Can you get to places out of walking distance …

   - ☐ 2 without help (drive your own car, or travel alone on buses, or taxis);
   - ☐ 1 with some help (need someone to help you or go with you when traveling); or
   - ☐ 0 are you unable to travel unless emergency arrangements are made for a specialized vehicle like an ambulance?

3. Can you go shopping for groceries or clothes [ASSUMING HAS TRANSPORTATION] …

   - ☐ 2 without help (taking care of all shopping needs yourself, assuming you had transportation);
   - ☐ 1 with some help (need someone to go with you on all shopping trips); or
   - ☐ 0 are you completely unable to do any shopping?

4. Can you prepare your own meals …

   - ☐ 2 without help (plan and cook full meals yourself);
   - ☐ 1 with some help (can prepare some things but unable to cook full meals yourself); or
   - ☐ 0 are you completely unable to prepare any meals?

5. Can you do your housework …

   - ☐ 2 without help (can clean floors, etc.);
   - ☐ 1 with some help (can do light housework but need help with heavy work); or
   - ☐ 0 are you completely unable to do any housework?

6. Can you take your own medicine …

   - ☐ 2 without help (in the right doses at the right time);
   - ☐ 1 with some help (able to take medicine if someone prepares it for you and/or reminds you to take it); or
   - ☐ 0 are you completely unable to take your medicines?

7. Can you handle your own money …

   - ☐ 2 without help (write checks, pay bills, etc.);
   - ☐ 1 with some help (manage day-to-day buying but need help with managing your checkbook and paying your bills); or
   - ☐ 0 are you completely unable to handle money?

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