Published in final edited form as:

Am J Surg. 2009 January ; 197(1): 55–63. doi:10.1016/j.amjsurg.2007.12.060.

Intraoperative cerebral high intensity transient signals and postoperative cognitive function: a systematic review

Kristin K Martin, DO, MS[1,*], **Jeremy B. Wigginton, BS**[2,*], **Viken L Babikian, MD**[3,6], **Val E. Pochay**[3], **Michael D. Crittenden, MD**[4], and **James L. Rudolph, MD, SM**[5,7]

1*Plaza Medical Center, General Surgery Residency, Fort Worth TX, and University of North Texas Health Sciences Center, Fort Worth, TX*

2*University of Mississippi Medical School, Jackson, MS*

3*Department of Neurology, VA Boston Healthcare System, Boston, MA*

4*Division of Cardiac Surgery, VA Boston Healthcare System, Boston, MA*

5*Geriatric Research, Education, and Clinical Center, VA Boston Healthcare System, Boston, MA*

6*Boston University School of Medicine, Boston, MA*

7*Harvard Medical School, Boston, MA*

Summary

Microemboli during surgery have been hypothesized to cause postoperative cognitive changes. The purpose of this article was to systematically review the available literature related to intraoperative microemboli, measured with transcranial Doppler ultrasound and postoperative cognitive function. The literature remains largely undecided on the role of microemboli and cognitive impairment after surgery, because most studies underpowered to show a relationship.

Keywords

Embolism; Transcranial Doppler; Postoperative Cognitive dysfunction; Surgery; Cardiac surgery; Carotid endarterectomy; Orthopedic surgery; cognition

Introduction

Cognitive decline after cardiac surgery is a common complication and has been reported in approximately 50% of patients at discharge, 36% at 6 weeks, 26–33% at one year, and 42% at five years[1,2] postoperatively. Cerebral microemboli, due to gaseous, organic, or inorganic particles generated during the procedure, have been hypothesized to be a primary predictor of cognitive decline following cardiac surgery[3]. Transcranial Doppler Ultrasound (TCD) is a portable, non-invasive tool for the measurement of cerebral hemodynamics which has been used in the operative setting to measure the high intensity transient signals (HITS) which are felt to represent particulate or gaseous microembolic particles[4,5]. The focus of this paper was to systematically examine the evidence relating intraoperative HITS to cognitive decline postoperatively.

Corresponding Author: James L. Rudolph, MD, SM, VABHS GRECC (JP-182), 150 South Huntington Ave, Boston MA 02130, Email: jrudolph@partners.org, Fax: 857 364-4544, Phone 857 364-6812.

*Both authors have contributed significantly and agreed to share first authorship

During cardiac surgery, numerous embolic sources including pre-exisiting atherosclerotic plaque, thrombogenesis from the foreign surfaces of cardiopulmonary bypass, air from the cardiopulmonary bypass circuit, and pericardial fat globules are generated.[5] Macroemboli (>200μm) occlude larger arteries that supply focal vascular territories and produce a clinically apparent stroke. Microemboli may only occlude small arterioles and produce no or only subclinical findings with no apparent physiologic deficits. Within an artery, embolic material has different reflective properties than the surrounding red blood cells and produce distinct HITS from the background flow velocity pattern. These HITS are felt to represent microemboli.

Pathophysiologically, microemboli may cause neurological injury. Autopsy of patients who died after cardiac surgery found evidence of microemboli in all of the brains examined[6] Further, Aly-Omar, et al[7] used magnetic resonance imaging to demonstrate that HITS can result in acute or subacute brain infarction. However, the size of the microemboli make clinically evident stroke relatively infrequent after surgery[8]. Most studies have focused the relationship of HITS to more subtle, postoperative cognitive functioning.[9],[10] The purpose of this paper was to systematically review the literature to determine if intraoperative HITS were related to cognitive function after surgery. Because of the time commitment and resource commitment required to assess preoperative and postoperative cognitive function and to measure and quantify HITS, we predicted that most studies of intraoperative HITS and cognitive function would be small (<100 patients). We hypothesized that 1) operative procedures with direct connection to the cerebral vasculature (cardiac surgery and carotid endarterectomy) would be more studied and provide the best evidence, 2) the evidence would derive from smaller studies, which are less likely to demonstrate a significant change in cognitive function, and 3) the lack of a unified testing battery and common outcome limit the ability to combine the available studies into a meta-analysis.

Methods

A pubmed search of studies (1965-July 2007) was conducted. We combined 3 broad category searches (cognition, surgery, and TCD) to identify appropriate abstracts for review. The cognition search category combined the results of the following the medical subject headings (MeSH) and keywords: “cognition”, “dementia”, “postoperative cognitive dysfunction”, “delirium”, or “encephalopathy”. The surgery search category combined the following results “surgery”, “cardiac surgery” “carotid endarterectomy”, or “CABG”. The TCD category combined the following results: “transcranial Doppler”, “Doppler ultrasound”, “embolism”, “intracranial embolism”, “blood flow velocity”, or “microemboli”. The three categories were examined for intersection. Further, manual searches of references from relevant study articles and reviews were also conducted.

Selection of English language articles was performed by three authors (KKM, JBW, JLR). We included all surgical procedures, because the understanding of HITS in one surgical procedure may provide valuable evidence to the relationship in other studies. We selected prospective studies that used cerebral TCD to count HITS during the surgical procedure. Studies that performed neuropsychological evaluation before and after surgery were included. Randomized studies of interventions (stenting vs. surgery; different arterial filters for cardiopulmonary bypass) were included if they described the relationship of intraoperative HITS and neuropsychological performance.

Results

Our pubmed search identified 337 abstracts which were reviewed and 56 articles were identified for review. From these, we selected 14 cardiac surgery, 5 carotid endarterectomy (CEA) and 2 orthopedic surgery articles for presentation. Each subset of surgery is detailed below. In agreement with our hypothesis about smaller studies, 12 of 14 (86%) cardiac surgery studies, 2 of 5 (40%) CEA studies, and 2 of 2 (100%) orthopedic studies had fewer than 100 patients.

Cardiac Surgery

Table I describes the studies that examined intraoperative HITS and subsequent cognitive dysfunction after cardiac surgery. Several features of these studies warrant discussion. First, intraoperative HITS occur during nearly all cardiac surgical procedures,[9,11,12]. Among the fourteen studies identified, there is considerable heterogeneity with respect to the cognitive assessments and batteries, which limits the ability to make definitive conclusions about the relationship of HITS and cognitive deficits. For example, each study utilized a different number and combination of neuropsychological tests and the methodology used to define the outcome of cognitive decline is not consistent among the studies. Furthermore, the testing batteries were delivered at differing times postoperatively (range: 5 days – 5 years). Additionally, the statistical analysis of the HITS is variable between the studies. For example, three studies dichotomize HITS, which reduces statistical power, while others utilize nonparametric methods or correlations to examine HITS as a continuous variable. Further, the size of the cognitive battery and non-normal distribution of HITS result in challenges to the power of the smaller studies. Overall, HITS were associated with neuropsychological performance in 4 of 14 cardiac surgery studies.

The three largest studies (n>100) are mixed with the regard to the relationship of intraoperative HITS and cognitive outcomes. Motallebzadeh et al. found that off-pump coronary artery bypass grafting (CABG) was associated with significantly fewer median HITS compared to on-pump CABG (off-pump median 9; intraquartile range [IQR] 4, 28 vs. on-pump median 1,605; IQR 750, 2,475).[13] On-pump CABG was associated with significantly worse cognitive decline at discharge (−0.25 SD), but not at 6 weeks or 6-months. Upon adjustment for age, education, and pump-status, HITS were not associated with cognitive decline.[13] Whitaker, et al found no relationship between HITS and cognitive decline in 192 patients at 6–8 weeks and 3 months postoperatively. However, there were significant losses to follow-up and the primary focus of the study was to compare the effects of three arterial filters on HITS, not cognitive decline. Stygall et al. determined that intraoperative HITS were independently associated with cognitive decline 5-years postoperatively[9,14]. While the length and quality of follow-up were admirable, there was significant attrition and the data on HITS at the 6 days and 8 week timepoints are not presented. Because of the length of time between exposure (HITS) and follow-up, a major issue with the Stygall study is whether HITS, atherosclerosis predisposition, or other interim factor caused subjects to develop cognitive impairment. Atherosclerosis is associated with HITS and cognitive decline and thus, may confound the relationship of HITS and cognitive decline.

One of the larger studies (n=395) of microemboli and cognitive function during cardiac operations was not included in the table, because the study used a unilateral Doppler ultrasound on the carotid artery to measure HITS, not TCD[15]. The study found increased neuropsychological deficits in patients with more than 100 HITS.

Carotid Endarterectomy (CEA)

CEA is considered a high-risk procedure for stroke and cerebral HITS due to the direct connection to the cerebral vasculature[8,16]. Microembolism reportedly occurs during a majority of CEAs and has been associated with neurological sequelae from stroke and transient ischemic attacks[17–19] to more clinically subtle and silent lesions[19]. In addition to these studies, however, microembolism is seen as a major culprit in cognitive decline often witnessed post-carotid endarterectomy[20,21]. While, TCD has been established as a useful tool to monitor the occurrence of intraoperative HITS from microembolism during CEA[22,23], few studies have evaluated the interconnectedness of CEA, intraoperative HITS and post-operative cognitive decline. Table II describes five studies that have examined this relationship between intraoperative HITS and cognitive decline after CEA. One study was able to find an association with HITS and neuropsychological decline. In subgroup analysis, two studies found that higher intraoperative HITS (>10 HITS) were associated with some degree of cognitive decline. Another study comparing CEA and carotid angioplasty found no relationship between HITS and cognitive decline in either procedure[24]. Thus, conclusions about HITS and cognitive function are limited by the limited findings of an association, the low number of subjects in subgroup analysis, and the low number of intraoperative HITS relative to cardiac surgery.

Orthopedic Surgery

Although cardiac and carotid operations offer a more direct potential impact of circulating microemboli by their anatomical proximity and access to the cerebral arterial system, it has long been known that fat and thromboembolism occurs after long-bone fractures, total hip arthroplasty[25,26], knee athroplasty[27–29], and other skeletal surgical procedures[30–32]. Although previously believed to be captured by the lung, it has been shown that microemboli may transverse a patent foramen ovale and enter systemic circulation through right-to-left shunts in patients during orthopedic surgeries [33].

Microemboli that occur during orthopedic trauma and surgeries have been postulated to be a possible cause in the cognitive decline of 5%–41% of orthopedic patients[34,35], however, the exact etiologies are still unknown. As in cardiac and carotid procedures, TCD is an effective method of detecting intraoperative HITS.

Although several studies have confirmed intraoperative HITS during orthopedic surgery or documented cognitive decline post-orthopedic surgery, there are only two recent studies which have examined the possible interconnectedness of orthopedic surgeries, the intraoperative quantity of HITS and any clinically perceived neurocognitive decline (Table III). Compared to cardiac surgeries, the number of cerebral HITS from orthopedic surgeries was low (total HITS = 4–9)[35,36]. Both studies demonstrated higher number of HITS counts in subjects with right to left shunts which have bypassed the pulmonary vasculature. However, neither study was able to demonstrate a significant association between intraoperative HITS and cognitive function. Further discussion provided by these researchers hypothesized that their studies were limited by the decreased quantity of HITS in their particular subjects or that the study was diluted by their classification of “cognitively impaired”[36]. Interestingly, a study by Abraham et al.[37] reported that HITS from an operated leg persisted even a week following the operation. As such, potential HITS may occur and cause cognitive sequelae, yet would go undetected under the current methodology of most TCD and surgical studies.

Discussion

This systematic review examined the literature relating intraoperative HITS, measured with TCD, and their relationship to postoperative cognitive function. At this time, there is insufficient evidence to describe a causal link between intraoperative HITS and postoperative cognitive function. However, this systematic review was able to identify several important points. First, compared to cardiac surgeries (total HITS range= 0–5260), the number of cerebral HITS from orthopedic surgeries (total HITS range = 0–40) and CEA (total HITS range 0–700) was lower. Second, the studies use heterogeneous methods to analyze HITS and assess cognitive outcomes. For example, within each study a different battery of cognitive tests is utilized and a different methodology is used to define cognitive decline. Third, future work in populations at high risk for HITS and postoperative cognitive decline could address some of the limitations in the current literature. Finally, while cardiac surgery and CEA are high-risk for HITS because of the direct connection to the cerebral vasculature, there are many potential sources of HITS during surgery which may be modifiable.

The lack of a causal pathway does not mean that HITS do not contribute to postoperative cognitive function. The brain is a highly redundant and complex organ which may protect against our recognition of cognitive impairments caused by HITS. Clinical manifestation of HITS in one patient may not correlate well with symptoms of HITS in another patient despite similar load and location. As a result, a subclinical infarction from a microembolism may remain subclinical. However, it is still an infarction. Given the choice between a microembolism and no microembolism, we postulate that most patients would prefer no microembolism. With this postulate, we discuss implications for future studies of intraoperative TCD monitoring for HITS.

The basic pathophysiology (i.e. microembolism occludes a small arteriole resulting in cognitive decline) suggests that there should be a detectable cognitive decline with increased microembolic load. However, there may be differences in the composition of the HITS stemming from cardiopulmonary bypass, CEA, and orthopedic surgery. Embolic, air, and inorganic (calcium plaque) HITS are generally treated identically despite potential dissipation of the air emboli. HITS will have greater significance if established guidelines for microemboli detection are applied during studies.[38] Multifrequency TCD technology has been reported to accurately distinguish particulate from gaseous HITS[3] by comparing the reflected frequency of both blood and embolic material at two insonation frequencies [39], [40]. Additionally, functional magnetic resonance imaging (fMRI) cerebral intensity[41] and cerebral glucose metabolism measured with positron emission tomography (PET)[42] have been found to be correlated with number of HITS. While fMRI and PET are superior modalities for localizing microemboli and determining the alterations on cerebral function, use of these modalities in the immediate operative/postoperative setting is limited by patient acuity, the time to obtain the scan, and the physical requirements of the scanner. There is potential research and clinical value in validating the output of TCD, fMRI, and PET imaging modalities against each other to determine the functional implications and composition of HITS. Presently, *in vivo* data on the composition of the particles is limited.

The studies to date provide an excellent basis for a more comprehensive, prospective study to determine if HITS cause cognitive impairment related to cardiac surgery. TCD studies of HITS and cognitive function are resource intensive. As a result many of the studies reviewed are smaller (<100 patients). This poses statistical challenges to the power of these studies, because HITS during surgery is frequently a skewed variable with many cases having a relatively small number of HITS and fewer numbers of cases with larger HITS counts. As a result, there is a wide standard deviation in HITS counts, often greater than the mean. HITS rate (number of HITS / surgical duration) has been used for comparison of HITS counts between procedures of different duration, but still requires assessment of normality. To address the skew, many studies dichotomize HITS, which further reduces statistical power. Thus, studies with <100 patients would likely lack statistical power to detect a significant difference in HITS between those with and without cognitive decline. Smaller studies also limit our ability to adjust for multiple potential confounding patient variables such as age, prior history of stroke, baseline cognitive functioning, etc. While small studies may provide pertinent information about this evolving field, larger studies, which are still noticeably infrequent, will be necessary to formulate a conclusive opinion about the neurocognitive effects of intraoperative microemboli.

The heterogeneity of testing strategies and definitions of cognitive decline limit our ability to draw definitive conclusions about postoperative cognitive function. At present, there is not a single test for the assessment of cognitive function because of the complexity and redundancy of the brain; instead multiple neuropsychological tests are administered. However, each study has chosen a different battery for analysis of cognitive function. Further, the reduction of many continuously-scored neuropsychological tests into a single dichotomous variable removes important detail about domain-specific cognitive function, is statistically misleading, reduces study power, and lacks clinical validity.[43,44] As highlighted in a comprehensive review of cognitive function after non-cardiac surgery, these limitations are difficult to overcome until a consensus neuropsychological battery (with normative values) and scale for postoperative cognitive changes are validated.[45]

Future studies could target high-risk patients with a high burden of atherosclerotic disease who are more likely to be exposed to a larger HITS load. Atherosclerosis, especially in the ascending aorta and carotid arteries, has been shown to be associated with increased risk for negative cognitive sequelae and may benefit from monitoring[46,47]. Mackensen and colleagues demonstrated that microemboli are associated with atheromatous plaques of the ascending and arch portions of the aorta[48]. In a study of more than 900 CEA patients, the presence of fibrous aortic plaque was significantly associated an increase in HITS.[49] Crawley found that CEA was associated with fewer HITS than carotid artery angioplasty[24]. While further studies are needed to elucidate the neurocognitive impact of microemboli on patients with significant atherosclerotic disease, these patients remain an important study population for future TCD monitoring, because of their increased propensity to require the surgeries frequently associated with microemboli and to be more at risk for cognitive damage from HITS during surgery.

Another population that warrants further study is patients with pre-existing cognitive impairment who may be at increased risk for further decline following surgery. Patients with preoperative cognitive deficits lack reserve capacity to recover from cardiac surgery and have been shown to have a higher incidence of postoperative cognitive impairments[50]. Based on the diminished cognitive reserve, HITS can only serve to further impair cognitive function postoperatively in these patients with pre-existing cognitive impairment. As the incidence of the cognitive decline outcome increases, fewer subjects are needed to appropriately power such studies. If HITS are associated with cognitive impairment, using TCD to minimize HITS exposure in patients with cognitive impairment may be warranted.

A further consideration for use of TCD would include quality improvement among surgical teams. Working with the above postulate that no HITS are preferred to HITS, the use of TCD to measure HITS can inform the team members about the HITS consequences of routine procedures such as rapid injection, cross clamp removal, and CPB cannula insertion. For example, surgical teams have developed protocols to use TCD probes to count HITS occurring in the venous and arterial lines of the cardiopulmonary bypass. Termed ‘transpump Doppler’, this procedure can determine the effectiveness of cardiopulmonary bypass at filtering microembolic load and the effect of perfusionist interventions[51]. The combination of ‘transpump Doppler’ with TCD can accurately determine the source of the microemboli and can be used in quality improvement efforts to reduce microemboli.[52] Additionally, HITS associated with newer surgical procedures could be compared to HITS with traditional procedures. For example, no studies have compared HITS counts in carotid artery stenting vs. CEA. Finally, numerous embolic protective devices have been developed and studied in cardiac surgery, CEA, and carotid artery stenting. While most evaluation studies have focused on neurologic outcomes such as stroke, reduction in HITS could be an additional outcome of future studies.[53]. While the clinical consequences of improving technique may not be immediately appreciated, the long term impact may be significant to the patient[9].

Conclusions

In this systematic literature review, we were unable to demonstrate the causal link between intraoperative HITS, felt to represent microemboli, and postoperative cognitive decline. While some studies have reported an association, most studies have not. As a result, intraoperative HITS may only be a small contributing factor to a multifactorial problem. However, TCD could be used in high risk patients and to improve the technique of the surgical team. Large, multi-site studies are needed to further identify the cognitive and functional sequelae of HITS in a variety of operative settings.

Acknowledgements

This work was supported by grant AG026781 (JBW, JLR) and the American Foundation for Aging Research MSTAR Program (JBW, KKM, JLR). Dr Rudolph is supported by a VA Rehabilitation Career Development Award

References

1. Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 2001;344:395–402. [PubMed: 11172175]
2. van Dijk D, Jansen EW, Hijman R, et al. Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: a randomized trial. JAMA 2002;287:1405–1412. [PubMed: 11903027]
3. Russell D. Cerebral microemboli and cognitive impairment. J Neurol Sci 2002;203–204:211–214.
4. Borger MA, Peniston CM, Weisel RD, et al. Neuropsychologic impairment after coronary bypass surgery: effect of gaseous microemboli during perfusionist interventions. J Thorac Cardiovasc Surg 2001;121:743–749. [PubMed: 11279417]
5. Blauth CI. Macroemboli and microemboli during cardiopulmonary bypass. Ann Thorac Surg 1995;59:1300–1303. [PubMed: 7733756]
6. Newman SP, Harrison MJ. Coronary-artery bypass surgery and the brain: persisting concerns. Lancet Neurol 2002;1:119–125. [PubMed: 12849516]
7. Aly A, Babikian VL, Barest G, et al. Brain microembolism. J Neuroimaging 2003;13:140–146. [PubMed: 12722496]
8. Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 2008;242:326–341. [PubMed: 16135919]discussion 41–3
9. Stygall J, Newman SP, Fitzgerald G, et al. Cognitive change 5 years after coronary artery bypass surgery. Health Psychol 2003;22:579–586. [PubMed: 14640854]
10. Diegeler A, Hirsch R, Schneider F, et al. Neuromonitoring and neurocognitive outcome in off-pump versus conventional coronary bypass operation. Ann Thorac Surg 2000;69:1162–1166. [PubMed: 10800812]
11. Bowles BJ, Lee JD, Dang CR, et al. Coronary artery bypass performed without the use of cardiopulmonary bypass is associated with reduced cerebral microemboli and improved clinical results. Chest 2001;119:25–30. [PubMed: 11157580]
12. Wang D, Wu X, Li J, et al. The effect of lidocaine on early po stoperative cognitive dysfunction after coronary artery bypass surgery. Anesth Analg 2002;95:1134–1141. [PubMed: 12401580]table of contents
13. Motallebzadeh R, Bland JM, Markus HS, et al. Neurocognitive function and cerebral emboli: randomized study of on-pump versus off-pump coronary artery bypass surgery. Ann Thorac Surg 2007;83:475–482. [PubMed: 17257972]
14. Selnes OA, Royall RM, Grega MA, et al. Cognitive changes 5 years after coronary artery bypass grafting: is there evidence of late decline? Arch Neurol 2001;58:598–604. [PubMed: 11295990]
15. Hammon JW Jr, Stump DA, Kon ND, et al. Risk factors and solutions for the development of neurobehavioral changes after coronary artery bypass grafting. Ann Thorac Surg 1997;63:1613–1618. [PubMed: 9205158]
16. Gaunt ME, Martin PJ, Smith JL, et al. Clinical relevance of intraoperative embolization detected by transcranial Doppler ultrasonography during carotid endarterectomy: a prospective study of 100 patients. Br J Surg 1994;81:1435–1439. [PubMed: 7820463]
17. Spencer MP. Transcranial Doppler monitoring and causes of stroke from carotid endarterectomy. Stroke 1997;28:685–691. [PubMed: 9099179]

18. Ackerstaff RG, Moons KG, van de Vlasakker CJ, et al. Association of intraoperative transcranial doppler monitoring variables with stroke from carotid endarterectomy. Stroke 2000;31:1817–1823. [PubMed: 10926940]
19. Muller M, Reiche W, Langenscheidt P, et al. Ischemia after carotid endarterectomy: comparison between transcranial Doppler sonography and diffusion-weighted MR imaging. AJNR Am J Neuroradiol 2000;21:47–54. [PubMed: 10669224]
20. Heyer EJ, Sharma R, Rampersad A, et al. A controlled prospective study of neuropsychological dysfunction following carotid endarterectomy. Arch Neurol 2002;59:217–222. [PubMed: 11843692]
21. Heyer EJ, Adams DC, Solomon RA, et al. Neuropsychometric changes in patients after carotid endarterectomy. Stroke 1998;29:1110–1115. [PubMed: 9626280]
22. Babikian VL, Cantelmo NL. Cerebrovascular monitoring during carotid endarterectomy. Stroke 2000;31:1799–1801. [PubMed: 10926937]
23. Stork JL, Levi CR, Chambers BR, et al. Possible determinants of early microembolism after carotid endarterectomy. Stroke 2002;33:2082–2085. [PubMed: 12154267]
24. Crawley F, Stygall J, Lunn S, et al. Comparison of microembolism detected by transcranial Doppler and neuropsychological sequelae of carotid surgery and percutaneous transluminal angioplasty. Stroke 2000;31:1329–1334. [PubMed: 10835452]
25. Patterson BM, Healey JH, Cornell CN, Sharrock NE. Cardiac arrest during hip arthroplasty with a cemented long-stem component. A report of seven cases. J Bone Joint Surg Am 1991;73:271–277. [PubMed: 1993721]
26. Colonna DM, Kilgus D, Brown W, et al. Acute brain fat embolization occurring after total hip arthroplasty in the absence of a patent foramen ovale. Anesthesiology 2002;96:1027–1029. [PubMed: 11964616]
27. Yeon HB, Ramappa A, Landzberg MJ, Thornhill TS. Paradoxic cerebral embolism after cemented knee arthroplasty: a report of 2 cases and prophylactic option for subsequent arthroplasty. J Arthroplasty 2003;18:113–120. [PubMed: 12555195]
28. Weiss SJ, Cheung AT, Stecker MM, et al. Fatal paradoxical cerebral embolization during bilateral knee arthroplasty. Anesthesiology 1996;84:721–723. [PubMed: 8659801]
29. Sulek CA, Davies LK, Enneking FK, et al. Cerebral microembolism diagnosed by transcranial Doppler during total knee arthroplasty: correlation with transesophageal echocardiography. Anesthesiology 1999;91:672–676. [PubMed: 10485777]
30. Pell AC, Christie J, Keating JF, Sutherland GR. The detection of fat embolism by transoesophageal echocardiography during reamed intramedullary nailing. A study of 24 patients with femoral and tibial fractures. J Bone Joint Surg Br 1993;75:921–925. [PubMed: 8245083]
31. Christie J, Burnett R, Potts HR, Pell AC. Echocardiography of transatrial embolism during cemented and uncemented hemiarthroplasty of the hip. J Bone Joint Surg Br 1994;76:409–412. [PubMed: 8175843]
32. Rodriguez RA, Letts M, Jarvis J, et al. Cerebral microembolization during pediatric scoliosis surgery: a transcranial doppler study. J Pediatr Orthop 2001;21:532–536. [PubMed: 11433170]
33. Droste DW, Kuhne K, Schaefer RM, Ringelstein EB. Detection of microemboli in the subclavian vein of patients undergoing haemodialysis and haemodiafiltration using pulsed Doppler ultrasound. Nephrol Dial Transplant 2002;17:462–466. [PubMed: 11865093]
34. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet 1998;351:857–861. [PubMed: 9525362]
35. Rodriguez RA, Tellier A, Grabowski J, et al. Cognitive dysfunction after total knee arthroplasty: effects of intraoperative cerebral embolization and postoperative complications. J Arthroplasty 2005;20:763–771. [PubMed: 16139714]
36. Koch S, Forteza A, Lavernia C, et al. Cerebral fat microembolism and cognitive decline after hip and knee replacement. Stroke 2007;38:1079–1081. [PubMed: 17255544]
37. Abraham P, Carter D, Millot JR, et al. Prolonged asymptomatic micro-embolism after hip or knee arthroplasty. J Bone Joint Surg Br 1997;79:269–272. [PubMed: 9119855]

38. Ringelstein EB, Droste DW, Babikian VL, et al. Consensus on microembolus detection by TCD. International Consensus Group on Microembolus Detection. Stroke 1998;29:725–729. [PubMed: 9506619]
39. Russell D, Brucher R. Online automatic discrimination between solid and gaseous cerebral microemboli with the first multifrequency transcranial Doppler. Stroke 2002;33:1975–1980. [PubMed: 12154248]
40. Brucher R, Russell D. Automatic online embolus detection and artifact rejection with the first multifrequency transcranial Doppler. Stroke 2002;33:1969–1974. [PubMed: 12154247]
41. Abu-Omar Y, Cader S, Guerrieri Wolf L, et al. Short-term changes in cerebral activity in on-pump and off-pump cardiac surgery defined by functional magnetic resonance imaging and their relationship to microembolization. J Thorac Cardiovasc Surg 2006;132:1119–1125. [PubMed: 17059932]
42. Jacobs A, Neveling M, Horst M, et al. Alterations of neuropsychological function and cerebral glucose metabolism after cardiac surgery are not related only to intraoperative microembolic events. Stroke 1998;29:660–667. [PubMed: 9506609]
43. Barry SJ, Zeger SL, Selnes OA, et al. Quantitative methods for tracking cognitive change 3 years after coronary artery bypass surgery. Ann Thorac Surg 2005;79:1104–1109. [PubMed: 15797033]
44. Keith JR, Cohen DJ, Lecci LB. Why serial assessments of cardiac surgery patients' neurobehavioral performances are misleading. Ann Thorac Surg 2007;83:370–373. [PubMed: 17257950]
45. Newman S, Stygall J, Hirani S, et al. Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. Anesthesiology 2007;106:572–590. [PubMed: 17325517]
46. Rudolph JL, Babikian VL, Birjiniuk V, et al. Atherosclerosis is associated with delirium after coronary artery bypass graft surgery. J Am Geriatr Soc 2005;53:462–466. [PubMed: 15743290]
47. Vingerhoets G, Van Nooten G, Jannes C. Effect of asymptomatic carotid artery disease on cognitive outcome after cardiopulmonary bypass. J Int Neuropsychol Soc 1996;2:236–239. [PubMed: 9375189]
48. Mackensen GB, Ti LK, Phillips-Bute BG, et al. Cerebral embolization during cardiac surgery: impact of aortic atheroma burden. Br J Anaesth 2003;91:656–661. [PubMed: 14570786]
49. Verhoeven BA, de Vries JP, Pasterkamp G, et al. Carotid atherosclerotic plaque characteristics are associated with microembolization during carotid endarterectomy and procedural outcome. Stroke 2005;36:1735–1740. [PubMed: 16002764]
50. Newman MF, Croughwell ND, Blumenthal JA, et al. Predictors of cognitive decline after cardiac operation. Ann Thorac Surg 1995;59:1326–1330. [PubMed: 7733762]
51. Rudolph JL, Tilahun D, Treanor PR, et al. Use of a large bore syringe creates significantly fewer high intensity transient signals (HITS) into a cardiopulmonary bypass system than a small bore syringe. Perfusion 2006;21:67–71. [PubMed: 16485702]
52. Groom RC, Likosky DS, Forest RJ, et al. A model for cardiopulmonary bypass redesign. Perfusion 2004;19:257–261. [PubMed: 15376771]
53. Reimers B, Corvaja N, Moshiri S, et al. Cerebral protection with filter devices during carotid artery stenting. Circulation 2001;104:12–15. [PubMed: 11435330]
54. Bokeriia LA, Golukhova EZ, Breskina NY, et al. Asymmetric cerebral embolic load and postoperative cognitive dysfunction in cardiac surgery. Cerebrovasc Dis 2007;23:50–56. [PubMed: 16968987]
55. Stroobant N, Van Nooten G, Van Belleghem Y, Vingerhoets G. Relation between neurocognitive impairment, embolic load, and cerebrovascular reactivity following on- and off-pump coronary artery bypass grafting. Chest 2005;127:1967–1976. [PubMed: 15947309]
56. Whitaker DC, Newman SP, Stygall J, et al. The effect of leucocyte-depleting arterial line filters on cerebral microemboli and neuropsychological outcome following coronary artery bypass surgery. Eur J Cardiothorac Surg 2004;25:267–274. [PubMed: 14747125]
57. Whitaker D, Stygall J, Harrison M, Newman S. Relationship between white cell count, neuropsychologic outcome, and microemboli in 161 patients undergoing coronary artery bypass surgery. J Thorac Cardiovasc Surg 2006;131:1358–1363. [PubMed: 16733170]
58. Lund C, Hol PK, Lundblad R, et al. Comparison of cerebral embolization during off-pump and on-pump coronary artery bypass surgery. Ann Thorac Surg 2003;76:765–770. [PubMed: 12963195] discussion 70

59. Eifert S, Reichenspurner H, Pfefferkorn T, et al. Neurological and neuropsychological examination and outcome after use of an intra-aortic filter device during cardiac surgery. Perfusion 2003;18:55–60. [PubMed: 12708766]

60. Nadareishvili ZG, Beletsky V, Black SE, et al. Is cerebral microembolism in mechanical prosthetic heart valves clinically relevant? J Neuroimaging 2002;12:310–315. [PubMed: 12380477]

61. Browndyke JN, Moser DJ, Cohen RA, et al. Acute neuropsychological functioning following cardiosurgical interventions associated with the production of intraoperative cerebral microemboli. Clin Neuropsychol 2002;16:463–471. [PubMed: 12822055]

62. Fearn SJ, Pole R, Wesnes K, et al. Cerebral injury during cardiopulmonary bypass: emboli impair memory. J Thorac Cardiovasc Surg 2001;121:1150–1160. [PubMed: 11385383]

63. Braekken SK, Reinvang I, Russell D, et al. Association between intraoperative cerebral microembolic signals and postoperative neuropsychological deficit: comparison between patients with cardiac valve replacement and patients with coronary artery bypass grafting. J Neurol Neurosurg Psychiatry 1998;65:573–576. [PubMed: 9771790]

64. Clark RE, Brillman J, Davis DA, et al. Microemboli during coronary artery bypass grafting. Genesis and effect on outcome. J Thorac Cardiovasc Surg 1995;109:249–257. [PubMed: 7853878]discussion 57–8

65. Bossema ER, Brand N, Moll FL, et al. Perioperative microembolism is not associated with cognitive outcome three months after carotid endarterectomy. Eur J Vasc Endovasc Surg 2005;29:262–268. [PubMed: 15694799]

66. Lloyd AJ, Hayes PD, London NJ, et al. Does carotid endarterectomy lead to a decline in cognitive function or health related quality of life? J Clin Exp Neuropsychol 2004;26:817–825. [PubMed: 15370377]

67. Fearn SJ, Hutchinson S, Riding G, et al. Carotid endarterectomy improves cognitive function in patients with exhausted cerebrovascular reserve. Eur J Vasc Endovasc Surg 2003;26:529–536. [PubMed: 14532882]

Table I

TCD Studies Measuring HITS and Cognitive Function in Cardiac Surgery

Author & Year	Study Type	Surgical Procedure	n	Cognitive Assessments Definition of Decline	NP Time	Cognitive Findings in Relation to TCD
Motallebzadeh, 2007[13]	Randomized Prospective	CABG -on-pump -off-pump	212	8 NP tests Composite score	Preop; Postop discharge, 6 weeks, & 6 months	HITS: on-pump (1605) vs. off-pump (9) (p<.01) After adjustment for age, education, and on-pump status, HITS did not remain in the cognitive decline regression model
Bokeriia, 2007 [54]	Prospective	CABG Valve ± CABG	62	11 NP tests Z-scores on individual tests	Preop; Postop 2–4 weeks	HITS: CABG (463) vs. Valve ±ABG (881) (p<.01) Total HITS not associated with cognitive function Left ME may predict verbal memory performance (p=.07) Right ME may affect psychomotor function (p=.07)
Stroobant, 2006[55]	Prospective	CABG -on-pump -off-pump	50	7 NP tests 20% decline on 20% of tests	Preop; Postop 6 days and 6 months	HITS: on-pump (335) vs. off-pump (145) (p<.01) No correlation between number of HITS and NP tests
Abu-Omar, 2006[41]	Randomized Prospective	CABG -on-pump -off-pump	25	1 Verbal Memory Task	Preop; Postop 4 weeks	HITS: on-pump (254) vs. off-pump (35) (p<.01) No difference in preop and postop testing HITS negatively correlated with MRI prefrontal activation (r=−.61, p<.01)
Stygall, 2003[9]	Longitudinal Prospective	CABG	107	11 NP Tests Residualized change scores Simple change scores	Preop Postop 5 years	ME predicted of NP decline at 5 years (unadjusted)
Whitaker, 2003 & 2006 [56,57]	Randomized Prospective	CABG -3 arterial filters	192	9 NP tests ≥1 SD decline in ≥2 tests	Preop; Postop 6–8 weeks	Arterial filter decreases HITS HITS not correlated with NP change ≤35 HITS associated with better NP recovery
Lund, 2003[58]	Randomized Prospective	CABG -on-pump -off-pump	52	8 NP tests 20% decline on ≥2 tests	Preop; Postop 3 months	HITS: on-pump (90) vs. off-pump (16) (p<.01)

Author & Year	Study Type	Surgical Procedure	n	Cognitive Assessments Definition of Decline	NP Time	Cognitive Findings in Relation to TCD
						No correlation between HITS and NP impairment
Eifert 2003[59]	Prospective Randomized	CABG +/− Valve -Aortic filter	24	4 reaction time tests for attention and alertness	Preop; Postop 7 days	No difference between filter and non filter group with respect to HITS or NP function HITS were not correlated with NP performance
Nadareishvili, 2002 [60]	Prospective	Valve Replacement	36	4 Cognitive screening measures Measures analyzed individually	Postop 3 months	No correlation between HITS and cognitive decline ($p > 0.05$)
Browndyke 2002[61]	Prospective Controlled	CABG or Valve Controls	27 25	5 NP Measures Measures analyzed individually	Preop; Postop 10 days and 30 days	Surgical subjects perform worse than controls Surgical subjects performed worse at 10days than at 30 days No correlations between HITS and NP performance
Fearn, 2001 [62]	Prospective	CABG	65	Cognitive Drug Research Battery (4 tests)	Preop; Postop 1, 8, & 24 weeks	57% of patients had >200 HITS HITS correlated with decreased memory accuracy
Jacobs, 1998[42]	Prospective	CABG ± Valve	18	10 NP Tests	Preop; Postop 10 days, 3 months	12 patients with completed TCD PET scan uptake correlated with HITS No relationship of HITS and NP performance
Braekken, 1997[63]	Prospective	CABG and Valve Replacement;	40	10 NP Tests ≥1 SD decline in ≥1 test	Preop; Postop 2 months	Valve repair patients with cognitive deficits were more likely to have increased HITS counts. CABG patients had lower HITS counts
Clark, 1995 [64]	Randomized Prospective	CABG	41	Neurobehavioral Cognitive Status Examination	Preop Postop 5–10 days	Gradient effect of HITS with NP

Author & Year	Study Type	Surgical Procedure	n	Cognitive Assessments Definition of Decline	NP Time	Cognitive Findings in Relation to TCD
				Cognitive decline not defined		decline in 35% of those with >60 HITS

CABG - coronary artery bypass graft; + CABG - indicates with or without coronary artery bypass graft; HITS - high intensity transient signals; ME - microemboli; MRI - magnetic resonance imaging; NP-neuropsychological; On-Pump- utilizing the cardiopulmonary bypass machine/pump; Off-pump - surgery not requiring use of the cardio-pulmonary bypass machine/pump; Preop – preoperative; Postop- postoperative; SD- standard deviation

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table II

HITS and Cognitive Function after Carotid Endarterectomy

Author & Year	Study Type	Surgical Procedure	n	Cognitive Testing Definition of Decline	Testing Time	Cognition Findings in Relation to TCD
Bossema, 2005 [65]	Prospective	CEA	58	8 NP Tests >1SD decline from preop	Preop; Postop 3 months	No association between HITS and cognitive decline 3 months postop
Lloyd, 2004 [66]	Randomized Prospective	CEA	100	NP Battery of 7 cognitive domains	Preop; 6 months Post-op	Patients subjected to >10 HITS during carotid dissection had decline in at least two tests of cognition (p< 0.05; relative risk = 1.125)
Fearn, 2003[67]	Prospective Controlled	CEA	159	Cognitive Drug Research Battery (4 tests)	Preop; Postop 5 days and 2 months	Overall, no association with HITS Patients with >10 HITS prior to dissection (n=6) tended to be slower in memory
		Controls	20			
Crawley, 2000[24]	Prospective Matched	CEA	26	10 NP Tests ≥1 SD decline in ≥2 tests	Preop; Postop 6 weeks & 6 months	More HITS in PTCA No correlation between HITS and NP score
		Carotid PTCA	20			
Gaunt, 1994 [16]	Randomized Prospective	CEA	100	30-point NP Assessment	Pre-op; 5–7 days Post-op	>10 particulate embolic events detected by TCD correlated to post-operative cognitive decline (p<0.05)

CEA-Carotid endarterectomy; HITS – high intensity transient signals; NP-neuropsychological; On-Pump- utilizing the cardio-pulmonary bypass machine/pump ; Off-pump – surgery not requiring use of the cardio-pulmonary bypass machine/pump; Preop – preoperative; Postop- postoperative; PTCA – angioplasty; SD – standard deviation

NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table III

HITS and Cognitive Function after Orthopedic Surgery

Author & Year	Study Type	Surgical Procedure	n	Cognitive Testing	Testing Time	Cognition Findings in Relation to TCD
Koch, 2007[36]	Prospective A-V shunt matched	THA or TKA	24	11 NP tests 20% decline in ≥2 tests	Preop Postop 3 days & 2 months	All patients had HITS No correlation between HITS and cognitive performance
Rodriguez, 2005[35]	Prospective	TKA	37	13 NP tests 0.5 SD decline in ≥3 tests	Preop Postop 1 week and 3 months	22 of 37 patients had HITS No association between HITS and cognitive performance

A-V – arterial-venous; HITS- high intensity transient signals; NP – neuropsychological; Preop- preoperative; Postop- postoperative; SD- standard deviation; THA- total hip arthroplasty; TKA – total knee angioplasty;