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Exploring variability in the causal link of HITS and cognitive decline

James L. Rudolph, MD, SM^a, Kristen K Martin, DO, MS^b, Val E. Pochay^c, and Michael D. Crittenden, MD^d

^aGeriatric Research, Education, and Clinical Center, VA Boston Healthcare System, Boston, MA

^bDepartment of Family Medicine, University of Arkansas for Medical Sciences, Pine Bluff, AR

^cDepartment of Neurology, VA Boston Healthcare System, Boston, MA

^dDivision of Cardiac Surgery, VA Boston Healthcare System, Boston, MA

We thank Dr. Whitaker and associates for their comments and appreciate the opportunity to respond. The purpose of this study was to objectively review the evidence related to high-intensity transient signals (HITS) and cognitive function after surgery. We agree with the biological plausibility where a microembolism occludes a small arteriole resulting in cognitive decline.[1] A causal link would establish definitively that increased microembolic load would result in a detectable cognitive decline. Table 1 reviews Hill's Criteria for causality as applied to HITS and cognitive function.[2] In our opinion, the literature to date does not establish a causal link.

In agreement with Dr. Whitaker and associates, there is substantial variability in the studies presented. This variability limits the establishment of a causal link between HITS and cognitive decline after surgery. The variability limiting the causal link can be divided into five broad categories: 1) measurement of microemboli, 2) measurement of cognitive function, 3) patient factors, 4) operative, perioperative, and postoperative factors, and 5) study design. Each of these categories will be detailed below.

Dr. Whitaker and associates accurately describe the technical, recording, storage, and counting factors which can influence TCD measurement of the HITS exposure. The studies presented have variable HITS measurement. As a result, HITS from one study may be different than HITS from another study. Thus, our ability to draw a causal link is limited.

Another source of variability is the measurement of preoperative and postoperative cognitive function. From our analysis and other reviews[1,3], it is clear that numerous methods for assessing cognitive function and defining cognitive decline are utilized in the literature. As a result, cognitive decline is not consistent across studies. Efforts to standardize assessment of cognitive decline have been undertaken.[4] However, until a standard cognitive battery and definition of cognitive decline is adopted and utilized, a causal link is unlikely to be established.

Corresponding Author: James L. Rudolph, M.D., VA Boston Healthcare System GRECC, 150 South Huntington Avenue, Boston, MA 02130, Tel: 857-364-6812, Fax: 857-364-4544, jrudolph@partners.org.

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Each patient presenting for surgery has a heterogeneous combination of: demographic characteristics (age, gender, education, ethnicity), physical attributes (temporal bone thickness, atherosclerosis), comorbidities (underlying medical, surgical, neurological, and psychiatric disorders), and functional levels (occupation, social and family support). These factors can influence HITS (ascending aortic plaque or temporal bone thickness) and/or cognitive decline (age, education, atherosclerosis). Variability in patient factors is innate to human research. However, a causal link would be expected to manifest despite these factors (Table 1 - Consistency).

The patient experience between HITS exposure and outcome measurement including the operative, perioperative, and postoperative course can influence HITS and/or cognitive function. While a few factors can be experimentally controlled (i.e. type of surgery, perfusion protocol, etc), most (i.e. pain, environment, sleep, complications, social support, cognitive activity, etc.) cannot be controlled. For example, a patient who develops delirium after surgery related to medications, environment, sleep deprivation, and/or iatrogenic complications is at increased risk of cognitive decline after surgery which may not be related to HITS. Because of the large number of factors involved in this period, the strength of association and dose-response (Table 1) factors would need to be stronger than observed in the current literature.

Finally, we agree with Dr. Whitaker and associates that the type of study is important in interpreting a causal link. Consistency across study design could provide strong evidence of a causal relationship. We would also argue that the statistical management of HITS is a critical factor. HITS counts tend to be skewed. If this skew is not taken into account, the study will be under-powered further limiting our ability to draw a causal link (Table 1 – strength of association, biological gradient).

Ultimately, we are still left with the clinical question: Do HITS cause cognitive decline after surgery? Based on the current literature, we remain unable to provide a definitive answer.

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Table 1**Application of Hill's Causality Criteria to HITS and Cognitive Decline After surgery**

Causality Criteria	Clinical Interpretation	Current Evidence
Strength of association	Is there a strong correlation between HITS and NP performance?	Most studies do not show a significant correlation
Consistency of association	Is the association seen in different populations and operations?	Different studies have different associations – most studies found no association.
Specificity	Does eliminating HITS eliminate cognitive decline?	This is not a useful criteria, because HITS are not the sole cause of cognitive decline after surgery.
Temporal relationship	Do HITS precede cognitive decline?	HITS are not monitored prior to surgery, but the cognitive decline happens afterward.
Biological gradient	Do more HITS result in more/worse cognitive decline?	There are some secondary analyses to support this, but others which do not support.
Biological Plausibility	Does the theory of 'HITS occluding small arterioles resulting in cognitive decline' make sense?	The theory is logical. There is variability in the measurements.
Coherence	Are HITS causing cognitive decline compatible with existing theory and knowledge?	While the theory is logical, there are numerous factors which can influence the exposure and outcome.
Experimental Evidence	Does efforts to reduce HITS also reduce cognitive decline?	Randomized studies which have reduce HITS via use of CPB or arterial line filters have not consistently shown reduction in cognitive decline.
Reasoning by analogy	Are there other explanations for cognitive decline not related to HITS?	There is significant variability with respect to measurement of HITS and cognitive decline, as well as, patient, operative, and study design factors.

CPB – Cardiopulmonary bypass; HITS – High intensity transient signals; NP- neuropsychological