

## Forbidden Word Entropy of Cerebral Oximetric Values Predicts Postoperative Neurocognitive Decline in Patients Undergoing Aortic Arch Surgery under Deep Hypothermic Circulatory Arrest

### Abstract

**Purpose:** Up to 53% of cardiac surgery patients experience postoperative neurocognitive decline. Cerebral oximetry is designed to detect changes in cerebral tissue saturation and therefore may be useful to predict which patients are at risk of developing neurocognitive decline. **Methods:** This is a retrospective analysis of a prospective study originally designed to determine if treatment of cerebral oximetry desaturation is associated with improvement in postoperative cognitive dysfunction in patients undergoing aortic reconstruction under deep hypothermic circulatory arrest. Cognitive function was measured, preoperatively and 3 months postoperatively, with 15 neuropsychologic tests administered by a psychologist; the individual test scores were summed and normalized. Bilateral cerebral oximetry data were stored and analyzed using measures of entropy. Cognitive decline was defined as any decrease in the summed normalized score from baseline to 3 months. **Results:** Seven of 17 (41%) patients suffered cognitive decline. There was no association between baseline cerebral oximetry and postoperative cognitive dysfunction. Nor were changes in oximetry values associated with cognitive decline. However, cognitive decline was associated with loss of forbidden word entropy (FwEn) (correlation: Rho  $\rho = 0.51$ ,  $P = 0.037$  for left cerebral oximetry FwEn and  $\rho = 0.54$ ,  $P = 0.025$  for right cerebral oximetry FwEn). **Conclusion:** Postoperative cognitive decline was associated with loss of complexity of the time series as shown by a decrease in FwEn from beginning to end of the case. This suggests that regulation of cerebral oximetry is different between those who do and those who do not develop cognitive decline.

**Keywords:** Cardiac surgery, cerebral oximetry, circulatory arrest, cognitive dysfunction, complexity, entropy

### Introduction

Neurological complications after cardiac surgery have been widely studied.<sup>[1-5]</sup> Complications range from stroke in 5% to 14% of patients to cognitive decline in up to 53% of patients. Although cognitive decline may be transient, in some patients, it persists and is present in up to 42% at 5-year postcoronary artery bypass surgery. Cognitive dysfunction contributes to loss of employment, loss of self-care efficacy, earlier death, and increased health care expenditures. Patients who recover from postoperative neurocognitive decline several months after their cardiac surgery are at a greater risk for further cognitive decline 5-year postsurgery.<sup>[1]</sup> The extent of perioperative injury also predicts a long-term neurocognitive decline.<sup>[6]</sup> The proposed mechanisms for cognitive dysfunction after cardiac surgery are cerebral

microembolism as well as hypoperfusion.<sup>[7]</sup> Patient and surgical factors that may affect postoperative neurocognitive decline are preexisting atherosclerotic disease and cerebrovascular disease, hyperthermia, hemodilution on cardiopulmonary bypass, maintenance of cerebral perfusion pressure, and number of embolic events.<sup>[6]</sup> Cerebral oxygen desaturation has been correlated with postoperative neuropsychological dysfunction in cardiac surgery patients.<sup>[7]</sup> Cerebral oximetry can be utilized to detect changes in cerebral tissue saturation, and anesthesiologists may be able to modify some of these factors to reduce the neurocognitive decline in cardiac surgery population.

Cerebral oximetry has been used to assess frontal cortex perfusion in multiple settings ranging from neonatal intensive care units

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to deep hypothermic circulatory arrest (DHCA) in adult cardiac surgery. Cerebral oximetry is based on the principle that biological material is transparent in near-infrared (NIR) light range. Commercially available cerebral oximeters emit light of two preset wavelengths: 730 nm to measure the ratio of oxygenated to deoxygenated hemoglobin and 800 nm, the isosbestic point, to estimate the concentration of hemoglobin independent of oxygen saturation. The Beer–Lambert law is applied to calculate relative oxygen saturation in tissues by linking the concentration and absorption of tissue chromophores to the path length of NIR light. A sustained drop in the regional oxygen saturation (rSO<sub>2</sub>) is closely related to the occurrence of neurological events following aortic surgery.<sup>[8]</sup> Smaller or transient changes in cerebral oxygenation may lead to cognitive dysfunction. Whether NIR spectroscopy (NIRS) can be used as a standard monitor to identify patients who will develop postoperative cognitive dysfunction remains unknown.

While traditional measures such as mean, median, and standard deviation, of a time series provide information about the global characteristics of the time series, they provide no information about the patterns within the time series. For this, newer descriptors of time series that measure the complexity of the patterns in the time series have shown promise of identifying pathology from normalcy by quantitating the entropy or information encoded within the time series.<sup>[9-11]</sup> Changes in complexity or entropy are felt to be related to changes in the regulatory control of the involved system.<sup>[10-13]</sup> For example, in Cheyne–Stokes respiration, the respiratory centers have a delayed response to the normal fluctuations in PaCO<sub>2</sub> between inspiration and expiration, and different spectral entropy compared to patients with obstructive sleep apnea or normal breathing.<sup>[14]</sup>

We hypothesized that changes in cognitive function will be associated with changes in the entropy of cerebral oximetry measures. We, therefore, conducted a study of cardiac surgery patients receiving formal pre- and postoperative cognitive testing to determine the association between cerebral oximetry measures and cognitive decline.

## Methods

This is a retrospective analysis of a prospective study originally designed to determine if treatment of cerebral oximetry desaturation was associated with lower incidence of postoperative cognitive dysfunction. Twenty-five patients were recruited for this study. Seven patients did not complete postoperative neurocognitive testing and one patient died intraoperatively; therefore, this report is the analysis of the remaining 17 patients. The original study was a prospective, randomized controlled study comparing the incidence of neurological dysfunction and neurocognitive impairment with and without the use of NIRS to monitor cerebral rSO<sub>2</sub> to guide interventions in patients undergoing aortic surgery requiring DHCA and antegrade selective

cerebral perfusion with or without retrograde cardioplegia. After Institutional Review Board approval, written informed consent, and in accordance with the Helsinki Declaration of 1975, revised 2000, patients undergoing aortic arch replacement under DHCA were prospectively randomized to a blinded control group (cerebral oximetry values not displayed to anesthesiologists, surgeons, and perfusionists) or an unblinded intervention group. To measure cerebral rSO<sub>2</sub>, patches were applied to the patient's forehead in the operating room, before preoxygenation and baselines were established (INVOS® Cerebral/Somatic Oximeter, Somanetics, Inc., Troy, MI, USA). The group that was randomized to have NIRS monitoring with rSO<sub>2</sub> values unblinded received an intraoperative algorithmic intervention if there was a decrease in rSO<sub>2</sub> >20% from the baseline reading on either the right or left side frontal sensors or declines in rSO<sub>2</sub> value below 50%.<sup>[15]</sup> The anesthesiologist or perfusionist as appropriate in consultation with the surgeon initiated an intervention. The surgeon, anesthesiologist, perfusionist, and all Operating Room (OR) personnel were blinded to rSO<sub>2</sub> values in the blinded control group. The rSO<sub>2</sub> results from both groups were stored by the monitor then downloaded to a computer for analysis. Both groups received standard pre-, intra-, and postoperative surgical and anesthetic protocols that are currently established at our university hospital. As there was no difference in outcome based on group assignment, the two groups were combined into one for this analysis. Cognitive function was assessed preoperatively within 28 days before the surgical procedure and 3 months postsurgery using a battery of standardized neurocognitive tests.

## Cognitive testing

Cognitive testing assessed areas of learning, memory, processing speed, and executive functioning using the following measures: Hopkins Verbal Learning Test (HVLT) - Total Learning, HVLT Delay, HVLT Discrimination Index, Controlled Oral Word Association - Verbal Fluency total, Brief Visual Memory Test (BVMT) - Total Recall, BVMT Delay, BVMT Recognition Discrimination, Letter Comparison, Pattern Comparison, and Letter–Number Sequencing scaled scores. The mean values of the two Letter Comparison pages and Pattern Comparison pages were used as the raw score for Letter Comparison and Pattern Comparison, respectively. Each test score was normalized by subtracting the mean and dividing by the standard deviation based on known means and standard deviations by age. Due to the small sample size, a summary cognitive score was computed by adding the normed scores on each test and then dividing by the number of tests to give an overall measure of global cognitive functioning. Scores were calculated for the baseline and 3-month cognitive test scores. Due to one missing BVMT Recognition Discrimination baseline score, one of the ten scores was missing for one patient. The

corresponding mean baseline score was calculated as the mean of the remaining nine scores. These summary scores allowed for a normalized score measuring the change between the baseline and 3-month scores.

### Complexity measures

For calculation of entropy, cerebral oximetry values for each patient were divided into epochs of 400 values and measure of central tendency (mean), two measures of variability (standard deviation and spikiness), and three measures of entropy (approximate entropy [ApEn], sample entropy [SampEn], and forbidden word entropy [FwEn]) were calculated for each epoch. Spikiness was defined as the ratio of the standard deviation of the first differenced (incremental) time series to the standard deviation of the original time series. Spikiness quantifies sharp, brief, staccato-like unpatterned fluctuations, which heighten the uncertainty of any single measurement.<sup>[16]</sup> Entropy measures differ from usual measures of variability, such as standard deviation, by considering the sequences of the numbers. For example, the series 0, 1, 0, 1, 0, 1, 0, 1, 0, 1, in which the 0's and 1's simply alternate, and 0, 1, 1, 0, 1, 0, 1, 1, 0, 0 have the same means and standard deviations, but the second series is more irregular and less predictable. Entropy measures aim to quantitate this irregularity. ApEn, SampEn, and FwEn were analyzed as previously described.<sup>[9]</sup> Briefly, ApEn and SampEn are the conditional probabilities that two sequences within a tolerance  $r$  for two points remain within  $r$  of each other at the next point. FwEn transforms a time signal to a symbol signal and denotes the uncertain occurrence of  $m$  consecutive points of the form  $\pi$ . FwEn predominantly differs from ApEn and SampEn in that FwEn evaluates only the local information contained in the  $m$  consecutive points, whereas ApEn and SampEn compare the local vectors with all vectors in the series. By restricting evaluations to only  $m$  consecutive points at a time, Li and Ning proposed that nonstationary data are better handled by FwEn than by ApEn and SpEn.<sup>[17]</sup>

To choose the appropriate tolerance,  $r$  (for ApEn and SampEn) and  $\alpha$  (for FwEn), we first randomized the individual data series by shuffling them and calculating ApEn and SampEn, with  $r = 1\%–300\%$  of the standard deviation for each data set and calculated FwEn for  $\alpha = 0.01–3$ .<sup>[11,18]</sup> We then chose the tolerances,  $r$  and  $\alpha$  that were in an area of stability. For final analysis, we chose  $r = 20\%$  of the standard deviation to calculate ApEn and SampEn and  $\alpha = 0.5$  to calculate FwEn. For ApEn and SampEn,  $m = 2$ , and for FwEn,  $m = 4$ . The computer program to calculate entropy values was written by one of the authors (ME) in EXCEL and is available upon request.

### Statistical analysis

Correlation was measured using Spearman's rho, rather than Pearson's  $r$ , because rho is more robust to outliers, and with few patients in the analyses, one outlier has a

very big effect on  $r$  (increased chance of Type I error).  $P < 0.05$  denoted statistical significance and SPSS software version 19.0 (IBM, Armonk, NY, USA) was used for all statistical analyses.

### Results

One patient in the intervention group died intraoperatively and seven did not complete postoperative neurocognitive testing and were excluded from analysis, leaving us 17 patients. Table 1 summarizes demographic, clinical, and operative characteristics of all patients who completed the study. The median summary cognitive score was  $-0.57$  preoperatively and  $-0.39$  postoperatively [Figure 1]. Based on neurocognitive testing, seven of these seventeen patients (41%) had postoperative cognitive decline after undergoing aortic surgery under DHCA [Figure 1]. There was no association between group assignment (intervention vs. control) and cognitive changes. We also found that while there was no association between baselines measures of cerebral oximetry and postoperative cognitive decline, there was a correlation between loss of complexity, as measured by FwEn, and loss of cognitive function [Tables 2 and 3] ( $\rho = 0.51$ ,  $P = 0.037$  for left cerebral oximetry FwEn and  $\rho = 0.54$ ,  $P = 0.025$  for right cerebral oximetry FwEn). Patients who had greater drops in FwEn had greater cognitive decline.

**Table 1: Patient demographics, operative course, and lengths of stay**

	Completed study ( $n=17$ ), $n$ (%)	
Intervention arm	9 (43)	
Female	8 (47)	
Left handed	2 (12)	
Smoker	9 (36)	
Depression	3 (18)	
Diabetes mellitus	1 (6)	
COPD	1 (6)	
Chronic kidney disease	0	
Hypertension	11 (65)	
Stroke	1 (6)	
Coronary artery disease	2 (12)	
	Median	IQR
Age (year)	62	56-65
Ejection fraction	0.60	0.55-0.65
Baseline cerebral oximetry left (%)	68	63-73
Baseline cerebral oximetry right (%)	69	62-70
Operative time (min)	565	495-720
Cardiopulmonary bypass (min)	191	162-235
Aortic cross clamp (min)	106	80-136
Circulatory arrest (min)	30	20-36
Lowest intraoperative hematocrit (%)	21	19-22
ICU length of stay (day)	3	3-5
Hospital length of stay (day)	9	5-12

COPD: Chronic obstructive pulmonary disease, ICU: Intensive Care Unit, IQR: Interquartile range

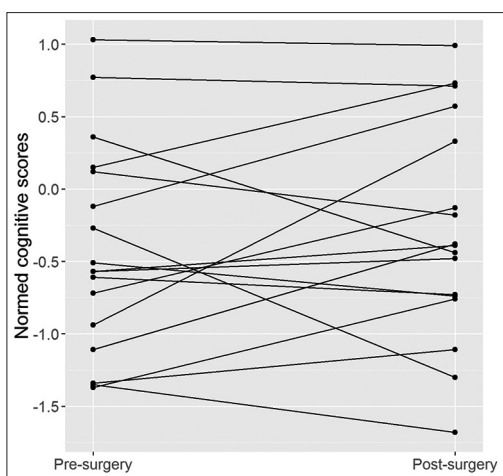


Figure 1: Normed cognitive scores showing the preoperative baseline and the 3-month postoperative results for each patient

### Discussion

We found that postoperative cognitive decline was associated with loss of complexity of the time series as shown by a decrease in FwEn values from the beginning to the end of the case. This is a novel finding. Our findings that loss of complexity is associated with postoperative cognitive decline are consistent with studies relating complexity of cerebral oxygenation in patients with cognitive impairment and dementia. Yang *et al.* using spontaneous fluctuations in blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) found that there was a loss of complexity in cerebral oxygenation in cognitively impaired elderly patients and this was most notable in the hippocampal cortex, cingulate cortex, superior and middle frontal gyrus, and middle temporal gyrus and that the amount of loss of complexity correlated with the amount of cognitive dysfunction.<sup>[19]</sup> Similarly, Liu *et al.* also using BOLD fMRI found loss of complexity of cerebral oxygenation in patients suffering from familial Alzheimer’s disease, but not in nonmutation carrying family members or in cognitively normal aged volunteers.<sup>[20]</sup> Notably, a study of the complexity of retinal vascularity found a loss in the complexity of the branching of retinal vessels in elderly patients with cognitive dysfunction.<sup>[21]</sup> Recently, one study showed that blood transfusion and organ dysfunction were associated with loss of cerebral oximetry complexity and suggested that this was related to loss of cerebral autoregulation.<sup>[22]</sup> These studies suggest that both blood distribution and oxygenation control are impaired in patients with cognitive dysfunction. Our study is limited in that it does not provide a mechanism for loss of complexity. Future studies will be needed to determine if our loss of FwEn was related to changes in vascular patterns, oxygen delivery, or oxygen utilization. Our findings are novel in that we extend these findings of loss of oxygenation complexity to acute cognitive decline in the perioperative period.

Table 2: Baseline cerebral oximetry (regional oxygen saturation) measurements and total cognitive change (n=17)

	Cerebral oximetry (rSO <sub>2</sub> )		Correlation (ρ)	P
	Median	IQR		
<b>Left</b>				
rSO <sub>2</sub> - mean	72	65-79	0.088	0.736
rSO <sub>2</sub> - SD	4.2	2.8-6.6	0.054	0.837
rSO <sub>2</sub> - ApEn	0.689	0.595-0.777	-0.130	0.619
rSO <sub>2</sub> - SampEn	0.672	0.361-0.899	0.010	0.970
rSO <sub>2</sub> - FwEn	45	43.5-51.5	0.278	0.280
rSO <sub>2</sub> - spikiness	0.171	0.140-0.235	-0.032	0.903
<b>Right</b>				
rSO <sub>2</sub> - mean	69	64-77	-0.108	0.680
rSO <sub>2</sub> - SD	4.0	3.0-5.8	0.243	0.348
rSO <sub>2</sub> - ApEn	0.772	0.662-0.818	-0.076	0.772
rSO <sub>2</sub> - SampEn	0.578	0.474-0.793	0.105	0.687
rSO <sub>2</sub> - FwEn	45	38.5-51	0.154	0.556
rSO <sub>2</sub> - spikiness	0.212	0.150-0.276	-0.012	0.963
L-R correlation	0.93	0.80-0.96	-0.221	0.312

L-R correlation: The correlation between the left rSO<sub>2</sub> and the right rSO<sub>2</sub> for each patient, Correlation (ρ): The correlation between baseline measurements (first 400 points) and the change in the cognitive scores for each patient, rSO<sub>2</sub>: Regional oxygen saturation, SD: Standard deviation, IQR: Interquartile range, ApEn: Approximate entropy, SampEn: Sample entropy, FwEn: Forbidden word entropy

Table 3: Differences between the baseline and last measurements (first minus last values) and cognitive change

	Cerebral oximetry (rSO <sub>2</sub> )		Correlation (ρ)	P
	Median	IQR		
<b>Left</b>				
rSO <sub>2</sub> - mean	1	-18-13	-0.034	0.896
rSO <sub>2</sub> - SD	0.3	-4.2-4.3	-0.088	0.736
rSO <sub>2</sub> - ApEn	0.154	-0.008-0.379	-0.245	0.343
rSO <sub>2</sub> - SampEn	0.097	-0.212-0.931	-0.078	0.765
rSO <sub>2</sub> - FwEn	9	-3.5-14.5	0.510	0.037
rSO <sub>2</sub> - spikiness	-0.006	-0.328-0.248	0.096	0.715
<b>Right</b>				
rSO <sub>2</sub> - mean	3	-7-12	-0.007	0.978
rSO <sub>2</sub> - SD	3.9	1.9-8.8	-0.208	0.422
rSO <sub>2</sub> - ApEn	0.129	-0.213-0.773	0.049	0.852
rSO <sub>2</sub> - SampEn	0.092	-0.369-0.853	0.127	0.626
rSO <sub>2</sub> - FwEn	8	3-14.5	0.540	0.025
rSO <sub>2</sub> - spikiness	0.000	-0.211-0.217	0.064	0.808
L-R correlation	0.01	-0.15-1.47	0.468	0.091

L-R correlation: The correlation between the left rSO<sub>2</sub> and the right rSO<sub>2</sub> for each patient, Correlation (ρ): The correlation between the change in rSO<sub>2</sub> and the change in the cognitive scores for each patient, IQR: Interquartile range, ApEn: Approximate entropy, SampEn: Sample entropy, FwEn: Forbidden word entropy, SD: Standard deviation, rSO<sub>2</sub>: Regional oxygen saturation

Mathematical models of physical systems suggest that complex patterns are formed by the interactions of various control systems, where through the interactions of oscillators, and positive and negative feedback loops that influence behavior, a quasi-stable outcome is achieved.<sup>[13,23]</sup> Disturbances in these control systems, such as of cerebral oxygenation, which are detectable through the changes in FwEn, we found, are indicative of an abnormal or at-risk system. Whether these changes are the cause of the postoperative dysfunction that can be prevented by better control of these interacting systems or these changes are an epiphenomenon related to some other systems that control both cognitive function and cerebral oxygenation regulation remain to be determined.

The advantages of cerebral oximetry are that it is a noninvasive method of measuring tissue oxygenation in the brain, it is easy to use, and it is cost effective when compared with transcranial Doppler and electroencephalogram modalities, where specialist technician support is required. Cerebral oximeters measure the average hemoglobin saturation along the various paths between the light source and sensor. This is a function of arterial, venous, capillary, and tissue oxygen saturation. Changes in the absolute value of any one of the arterial, venous, capillary, or tissue saturations or changes in the relative contributions of these four compartments will cause changes in the cerebral oximetry reading. Similar to other tissues, in the brain, there is a complex interplay between tissue metabolism, blood flow, and oxygen extraction to maintain neuronal homeostasis. Changes in blood flow or in edema will lead to changes in the relative contributions of the four compartments. During cardiac surgery, proper regulation of these factors is altered: the respiratory cycle, which is lost during cardiopulmonary bypass, controls PaCO<sub>2</sub> and pH; microemboli may impair cerebral blood flow; loss of acetylcholine-induced vasodilation; even drugs such as etomidate and phenylephrine affect vascular reactivity.<sup>[24-28]</sup> Our finding of loss of cerebral oximetry complexity associated with cognitive decline is in agreement with two studies that showed that altered vasoreactivity is associated with postoperative cognitive dysfunction and with late-onset depression.<sup>[25,29]</sup>

Our finding that FwEn but neither ApEn nor SampEn was associated with cognitive decline is not contradictory. They measure different types of complexity.<sup>[30]</sup> ApEn and SampEn compare every pair and triplet to every pair and triplet, respectively, in the time series, while FwEn compares every quadruple to the universe of possible quadruples. Since the absolute value of  $\alpha$  (based on the standard deviation of the four points determining each individual word) varies from each quadruple to the next, FwEn may better handle nonstationary time series data and be more resilient to trends in rSO<sub>2</sub> from global factors such as varying hemoglobin level.

The majority of cerebral oximetry limitations come from the assumptions built into the monitor. The algorithm programmed into the monitor assumes that the path length remains constant among patients; therefore, in patients with thick skull or skin or tissue edema 15 mm penetration may not be enough to reach frontal cortex. The algorithm also assumes that venous to arterial partitioning in the tissue is 70/30, when congestive heart failure or venous pooling may have altered that ratio and influenced saturation readings. Nonheme substances such as melanin and bilirubin can significantly attenuate light transmission and impede NIRS measurements. However, despite these limitations, our study and others have shown the utility of cerebral oximetry in association with postoperative problems.<sup>[7]</sup> Even though the returned oximeter light may not have penetrated the frontal cortex, the frontal cortex and the intervening skin, muscle, and bone are perfused from the same carotid circulation and are exposed to the same vasoactive substances; hence, changes in tissue oxygenation patterns may reflect changes in frontal cortex oxygenation patterns. Another limitation is that our study was a *post hoc* analysis of a study that did not achieve its enrollment goal. Thus, we are at increased risk of Type I and Type II errors.

Several studies have been done to evaluate the relationship between neuropsychological dysfunction and cerebral oximetry: some utilizing stroke as an outcome and others utilizing neurocognitive testing to detect deficits. Only a few studies employed comprehensive neuropsychologic evaluation, but all of them were coronary artery bypass grafting, single valve, or combined operations.<sup>[31]</sup> Even after those studies, the controversy continues on whether cerebral oximetry desaturation is linked to postoperative cognitive decline. In our study, we showed that a decrease in the FwEn is associated with more postoperative cognitive decline. FwEn is an easily computed statistic that could be computed in real time by the monitor and presented to the anesthesiologist. Future studies are needed to see if interventions that improve FwEn also improve postoperative cognition.

A major strength of our study is that we used comprehensive neurocognitive evaluation by a psychologist using well-validated quantitative tests that can be administered several times without a “learning effect.” These provided an objective measure of cognition.

## Conclusion

Using comprehensive neurocognitive evaluation, postoperative cognitive decline occurred in 41% of patients undergoing aortic surgery under DHCA. The amount of perioperative cognitive change was significantly correlated with changes in FwEn of the cerebral oximetry time series.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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