Intraoperative Changes in Somatosensory Evoked Potentials as Predictors of Perioperative Stroke in Carotid Endarterectomy

by

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Intro: Perioperative stroke is a known but severe neurological complication that can occur after carotid endarterectomy (CEA). Perioperative stroke has been shown to increase the risk of morbidity and mortality in the short and long term. Intraoperative neurophysiological monitoring with somatosensory evoked potentials (SSEPs) is utilized to warn the surgical team of impending neurological deficits. Our goal for this study is to quantitatively evaluate the diagnostic value of SSEP changes in predicting perioperative stroke during CEA.

Method: We identified all perioperative strokes during the hospital stay. We further classified them into major and minor strokes. To quantitatively assess SSEP changes, amplitudes and latencies of the cortical SSEP responses were measured during various critical and consistent times during CEA.

Results: There is a significant difference in amplitude between controls and perioperative strokes at all time points after pre-incision, not including the end of the surgery. Patients with perioperative strokes had significantly decreased amplitude from all four baselines. The area under the curve for ROC curve analysis of pre-incision amplitude change was greater than incision, heparin, and pre-clamp. A decrease greater than 50% of amplitude was predictive of perioperative stroke and major strokes alone from all baselines.

Discussion: It should be considered that the purpose of an alarm is to present a warning in which an intervention is still possible to prevent the occurrence of a perioperative stroke. It should be recommended that a pre-incision baseline is used during CEA. The alarm criteria should be moved to provide an appropriate cushion to allow intervention. Latency changes were very specific but have limited sensitivity, and do not appear to be very useful, especially at the current alarm criteria of a 10% increase.

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PREFACE

I would like to extend a special thank you to those that were an integral part of helping me complete this thesis: Dr. Partha Thirumala for being an excellent mentor and giving me the responsibility, encouragement, and guidance to complete all of the necessary research, Dr. Jeff Balzer for providing additional support and guidance, Dr. Eyad Saca for all of his assistance in designing the study and feedback on the manuscript, and my family for helping me get to where I am. Thank you to the members of my defense committee for taking time out of their very busy schedules to participate and give constructive feedback to help solidify my thesis.

1.0 INTRODUCTION

Carotid endarterectomy (CEA) has been shown to be helpful in patients with symptomatic and asymptomatic carotid stenosis.[15] Perioperative stroke is a known but severe neurological complication that can occur after CEA, and has been shown to increase the risk of morbidity and mortality in the short term, immediately after CEA, and long term, up to 10 years after CEA.[2] Risk factors for perioperative stroke after CEA include advanced age, previous stroke, coronary artery disease, renal disease, atrial fibrillation, perioperative beta blocker use, and substantial cardiovascular manipulation.[14] The primary causes for perioperative stroke include small and large vessel thrombosis, cardioembolism, hypoxia, and hemorrhage with hypoperfusion and embolism seeming to have a synergistic effect [143].

Intraoperative neurophysiological monitoring (IOM) with somatosensory evoked potentials (SSEPs) is utilized to warn the surgical team of impending neurological deficits during CEA.[5] Further, significant SSEP changes have been shown to correlate with cerebral blood flow and predict perioperative stroke.[11] Changes in cerebral blood flow in the setting of constant emboli, might be one of the causative factors for stroke.[3] In fact, SSEP changes seem to predict the risk of stroke even in the long term, ten years or longer.[5] This could be secondary to the fact that patients who have SSEP changes have decreased cerebrovascular reserve leading to decreased perfusion after cross-clamping.[57] The current American Clinical Neurophysiology Society (ACNS) and the American Society of Neurophysiological Monitoring (ASNM)

guidelines define a significant SSEP change as a 50% drop in amplitude or a 10% increase in latency.[113] However, the guidelines have suggested that these are empirical, are the result of data from spinal procedures, and have not been robustly evaluated within the context of vascular surgeries.

Our goal for this study is to quantitatively evaluate the diagnostic value of various SSEP changes during CEA in predicting perioperative stroke. Further, we aim to evaluate the sensitivity and specificity of the current alarm criteria in terms of predicting stroke. We believe the results of this paper would serve in determining if the current criteria are appropriate or if new criteria should be adopted. The results might support the use of SSEP changes as a biomarker for impending perioperative stroke during CEA and could lead to development of therapeutic interventions based on them.

2.0 METHODS

2.1 PARTICIPANTS

A retrospective chart review was performed to identify patients with carotid artery stenosis treated with carotid endarterectomy from 2010-2015 at UPMC (University of Pittsburgh Medical Center). Patients without intraoperative recording were excluded from the study. We identified all perioperative strokes that occurred during the hospital stay. We defined a stroke as a new onset or worsening of a neurological deficit. We further divided them into minor and major strokes, with a minor stroke defined as the absence of a persistent neurologic deficit that is potentially disabling. We considered a disabling deficit as any of the following: complete hemianopia, severe aphasia, visual or sensory extinction, weakness limiting sustained effort against gravity, any deficit that leads to a total National Institute of Health Stroke Scale (NIHSS) >5, and inability to walk.[9] There were a total of 148 subjects, 47 strokes and 101 controls. All identified strokes from 2010-2015 that met the criteria were included in the study. The controls were randomly selected using a random number generator.[6] This study was approved by the IRB (Institutional Review Board) for retrospective review of data on human subjects (MOD08120394-04 / PRO08120394).

2.2 NEUROPHYSIOLOGICAL MONITORING

Electrode placement and intraoperative monitoring were overseen by a neurophysiologist. Upper extremity SSEPs were obtained by bilateral stimulation of the median or ulnar nerve using subdermal electrodes placed at the wrists. Cortical potentials produced by peripheral nerve stimulation were recorded using subdermal electrodes placed on the patient's scalp. The stimuli were delivered at a current of 45-60 mA and a pulse duration of 0.2-.3ms with a frequency of 2.31-2.45 Hz. Baseline SSEPs were recorded for each patient after induction to compare to intraoperative responses. A significant SSEP change based on traditional criteria was considered to be a 50% decrease in amplitude or a 10% increase in latency of the N20-P30 complex, figure 1, for upper extremity SSEP. To eliminate electrical artifacts caused by signal interference only changes that were sustained over two consecutive averages were used. The surgeon was immediately informed if a significant change was reported.

2.3 QUANTITATIVE ANALYSIS

We measured the SSEP responses in the P3/Fz or P4/Fz cortical channels for all pateints at key surgical points. The points selected as baselines were pre-incision, incision, heparin administration time, before carotid cross clamping. An epoch that was representative of the average amplitude around that time point was measured. To assess SSEP changes, the amplitude and latency of

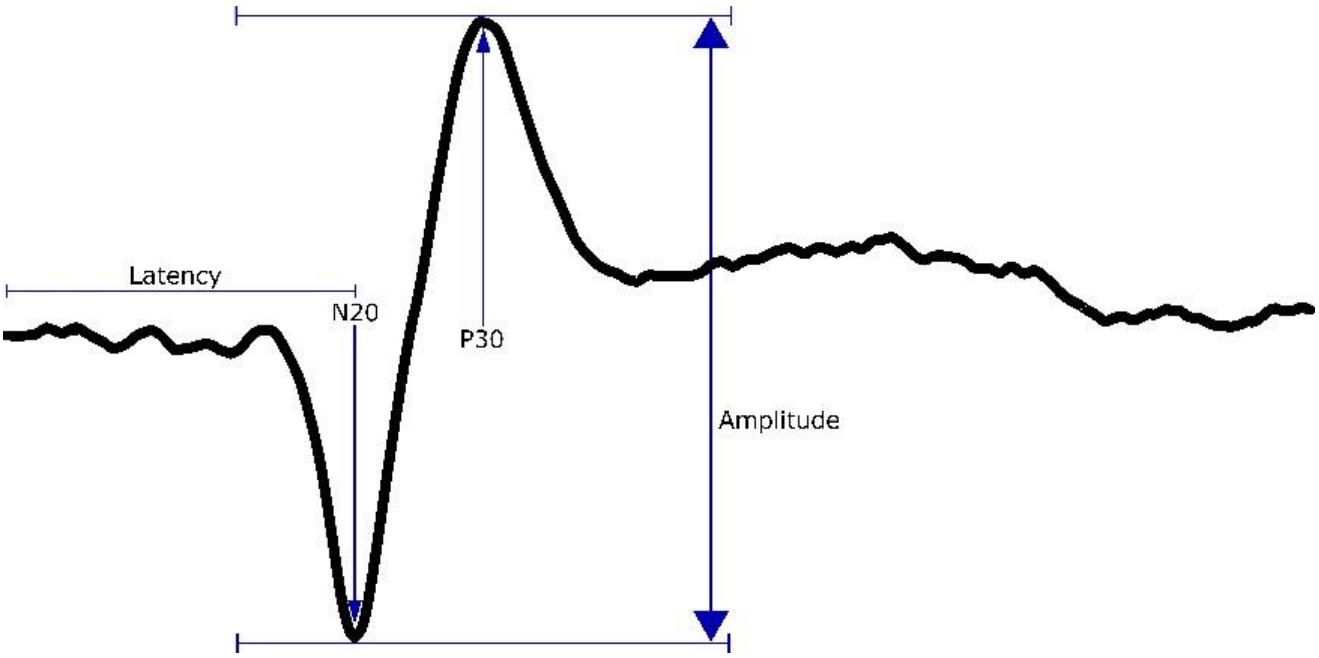

Figure 1. Example of epoch recording. Measuring the amplitude and latency of an upper extremity SSEP. This was taken from a patient in this study.

epochs were measured starting at five minutes after the clamp was placed because at this point hypoperfusion should start to show an effect on the SSEPs if present. Measurements followed at ten minutes, fifteen minutes, and the point with the worst amplitude after fifteen minutes until the clamp was removed; as well as, after clamp removal and a final measurement at the end of the operation. For each non-baseline point, the worst amplitude that was sustained over at least two epochs was taken. To measure a specific epoch, the first negative (N20) and positive (P30) peaks from baseline were identified, this can be seen in Figure 1. The amplitude was measured from the minimum of the N20 waveform to the maximum of the P30 waveform, and the latency was measured from the stimulation time to the time of the N20 minimum. Then the maximum change percentage for latency (LMC%) and amplitude (AMC%) from each baseline measurement was calculated for each SSEP as follows:

$$\text{LMC}\% = \frac{Longest\ latency - Baseline\ latency}{Baseline\ latency} \times 100 \qquad AMC\% = \frac{Baseline\ Amplitude - Smallest\ Amplitude}{Baseline\ Amplitude} \times 100.$$

2.4 STATISTCAL ANALYSIS

Welch two sample t-test or non-parametric Wilcoxon signed-rank test were utilized to compare continuous variables. Chi-squared test and Fischer's exact test were utilized to compare categorical variables, $p<0.05$ was considered significant. Receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC) was calculated using the pROC package,[12] AUC measures the ability of a test, SSEP Change percentage, in predicting perioperative neurological events. 95% confidence interval (CI) not crossing 0.5 was set as significant. Delong's test for two correlated ROC curves[4] was used to compare the AUC of two tests, $p<0.05$ was set as significant.

The OptimalCutpoints package[10] was utilized to calculate the optimal test threshold, the maximum value of Youden's index[16] was considered as the criterion for selecting the optimal cutoff point, the point that gives the greatest compromise between sensitivity and specificity. Sensitivity and specificity were calculated using the caret package.[8] Statistical analysis was performed using R statistical software v3.4.3 (Foundation for Statistical Computing, Vienna, Austria).

3.0 RESULTS

3.1 SUBJECT DEMOGRAPICS

We retrospectively reviewed 1508 consecutive CEA surgeries at our institution, University of Pittsburgh Medical Center, between 2010 and 2015. Forty-seven patients were identified as having a perioperative stroke (3.12%, age 69 $\pm$ 10 years) between 2010 and 2015. Of the forty-seven perioperative strokes, seventeen (36.2%) were classified as major strokes and thirty patients (63.8%) were classified as minor strokes. Age and gender were statistically similar between the two groups, table 1. We randomly identified 100 patients (age 68 $\pm$ 9 years) who did not incur a perioperative stroke as controls.

3.2 EVALUATING COMPARABILITY OF SSEPs

Prior to comparing the predictive value of SSEPs, the absolute amplitudes and latencies of all baseline recordings were evaluated for comparability. There were no significant differences between absolute amplitudes and latencies for all measures: pre-incision, incision, heparin, and pre-clamp baselines. Amplitude changes from each baseline followed a normal distribution. Patients with perioperative stroke had significantly decreased amplitude from all four baselines ($p < .001$), Figure 2. There was a significant difference in amplitude decrease between the two

Table 1. Patient characterizing information.

Variable	Stroke, n=47 (32%)	Controls, n=101 (68%)	p-value
	Mean ± SD		
Baseline			
Age, years	68.0 ± 9.41	69.6 ± 9.83	0.3434
Male:Female	:	:	0.5321
Amplitude			
Pre-incision	3.70 ± 2.60	3.59 ± 2.33	0.8126
Incision	3.16 ± 2.35	3.33 ± 2.14	0.6744
Heparin	2.58 ± 1.72	2.92 ± 1.89	0.2804
Pre-clamp	2.68 ± 1.86	2.97 ± 1.89	0.3803
Latency			
Pre-incision	23.8 ± 1.96	24.0 ± 2.12	0.6089
Incision	23.8 ± 1.97	23.9 ± 1.93	0.7375
Heparin	23.7 ± 1.93	24.2 ± 1.95	0.1158
Pre-clamp	23.8 ± 2.00	24.1 ± 1.93	0.3643

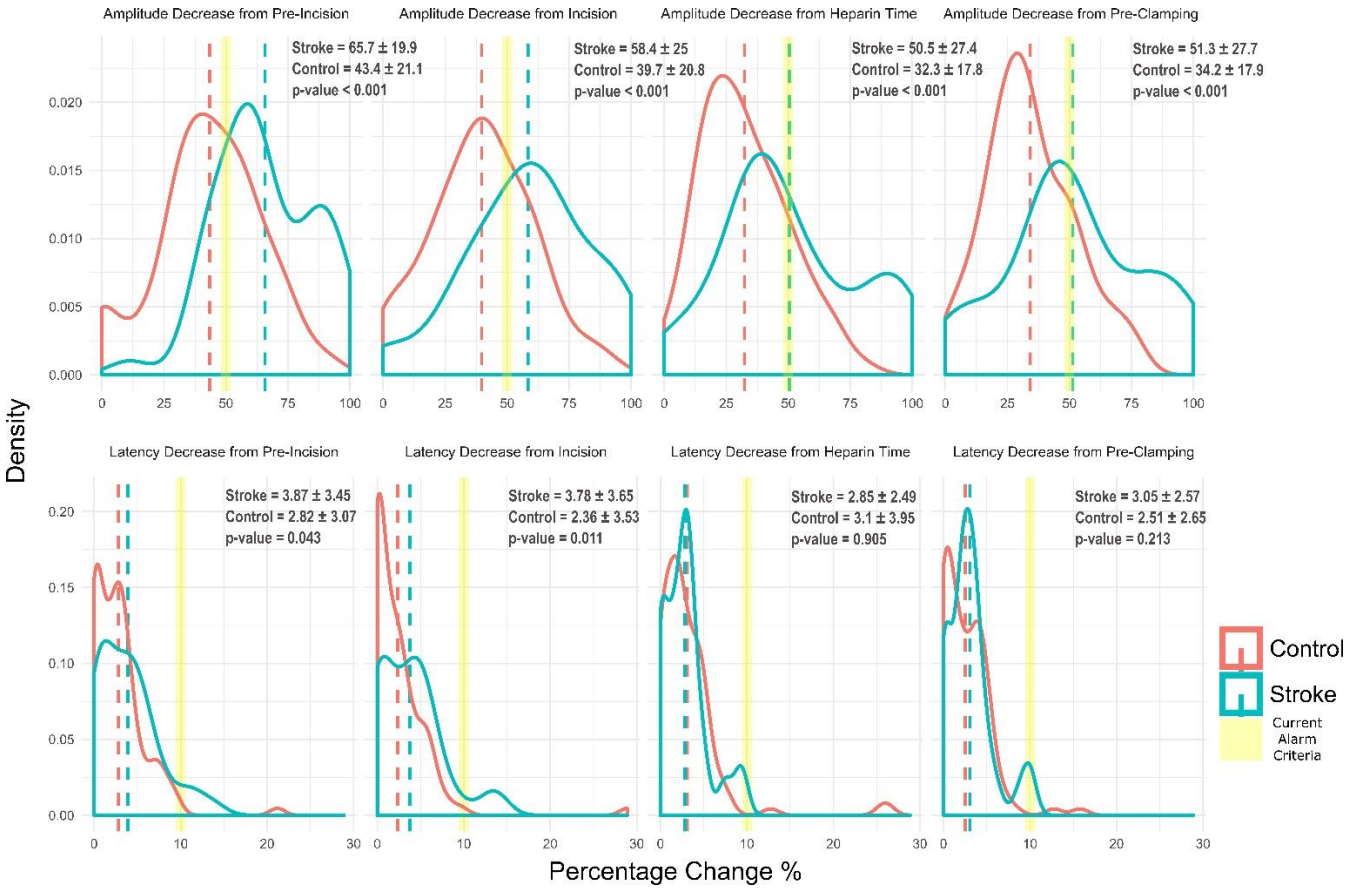

Figure 2. Density plots of mean amplitudes and latencies. Density plots showing the average maximum percentage changes amongst controls and strokes. The vertical dashed lines represent the means and the vertical solid line represents current alarm criteria.

groups at all time points proceeding pre-incision except the end of the surgery: incision ($p = .0141$), heparin ($p = .0167$), pre-clamp ($p = .025$), 5 minutes after clamp ($p = .0048$), 10 minutes after clamp ($p < .001$), 15 minutes after clamp ($p < .001$), any time longer than 15 minutes after clamp ($p < .001$), and after clamp removal ($P = .0269$), Figure 3. Latency changes were positively skewed. Comparing the latency percentage changes between the two groups revealed a significant difference when utilizing a pre-incision ($p = .048$) and incision ($p = .008$) baseline, but not heparin ($p = .9$) and pre-clamp baselines ($p = .213$).

3.3 PREDICTIVE VALUE OF SSEP CHANGES FOR PERIOPERATIVE STROKE:

Table 2

ROC curve analysis was employed, and the AUC was utilized to determine the diagnostic accuracy of SSEPs in predicting perioperative stroke, Figure 4. Maximal Youden's Index value decided the optimal cutoff for all four measures.[16] The AUC for pre-incision amplitude change (.778) was greater than incision (.723), heparin (.704), and pre-clamp (.703). The optimal cutoffs were a 55% decrease in amplitude from pre-incision, 50% from incision, and 31% and 38% from heparin and pre-clamp, respectively. The AUC for latency change from incision (.628) was greater than pre-incision (.603), and the optimal cutoffs were 3.8% for incision and 3.9% for pre-incision. Based on the 95% confidence intervals for AUC, latency changes from heparin (CI: .406-.607), and pre-clamp (CI: .467-.660) were not significant predictors of perioperative stroke. AUC was compared between all baseline measures for significant differences using DeLong's test for two correlated ROC curves. There was a significant difference from pre-incision in AUC

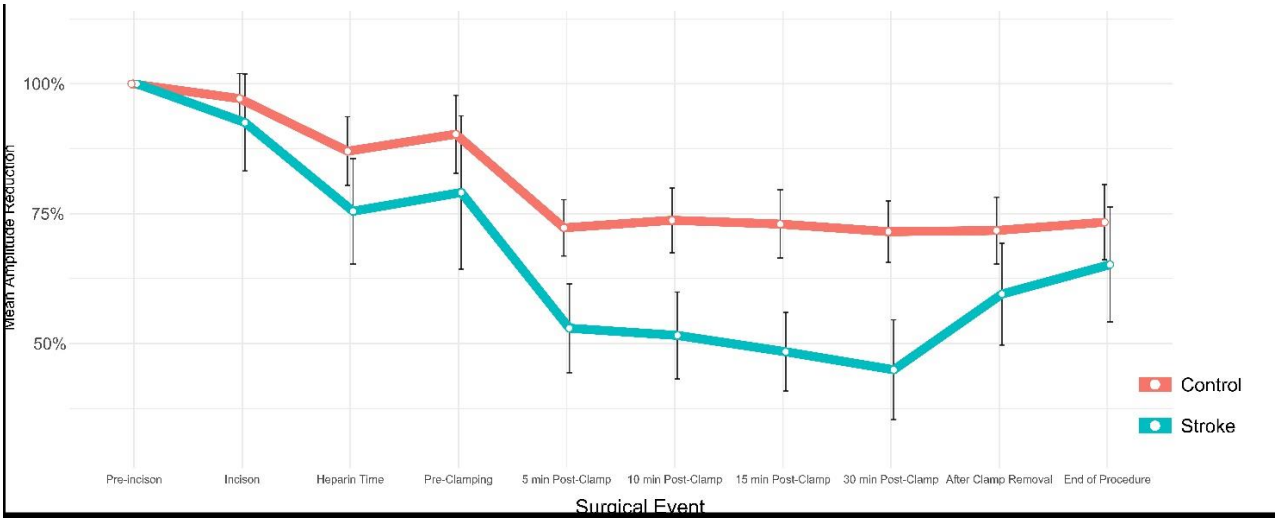

Figure 3. Mean percentage SSEP amplitude reduction at key surgical points. Error bars represent the 95% confidence interval. The x-axis represents each measured time point. The y-axis is the average percentage decrease from pre-incision.

Table 2. ROC analysis of each baseline in predicting stroke.

Significant Change Modality	Optimal Cutoff (%)	AUC	95% CI:	Sensitivity	Specificity
Amplitude changes as a predictor					
Pre-incision	55%	0.778	0.701-0.855	0.745	0.693
Incision	50%	0.723	0.631-0.816	0.702	0.683
Heparin	31%	0.704	0.610-0.798	0.829	0.515
Pre-clamp	38%	0.703	0.604-0.802	0.745	0.653
Latency changes as a predictor					
Pre-incision	3.8%	0.603	0.503-0.704	0.468	0.762
Incision	3.9%	0.628	0.528-0.728	0.511	0.782
Heparin	2.4%	0.506	0.406-0.607	0.574	0.535
Pre-clamp	2.1%	0.563	0.467-0.660	0.702	0.505

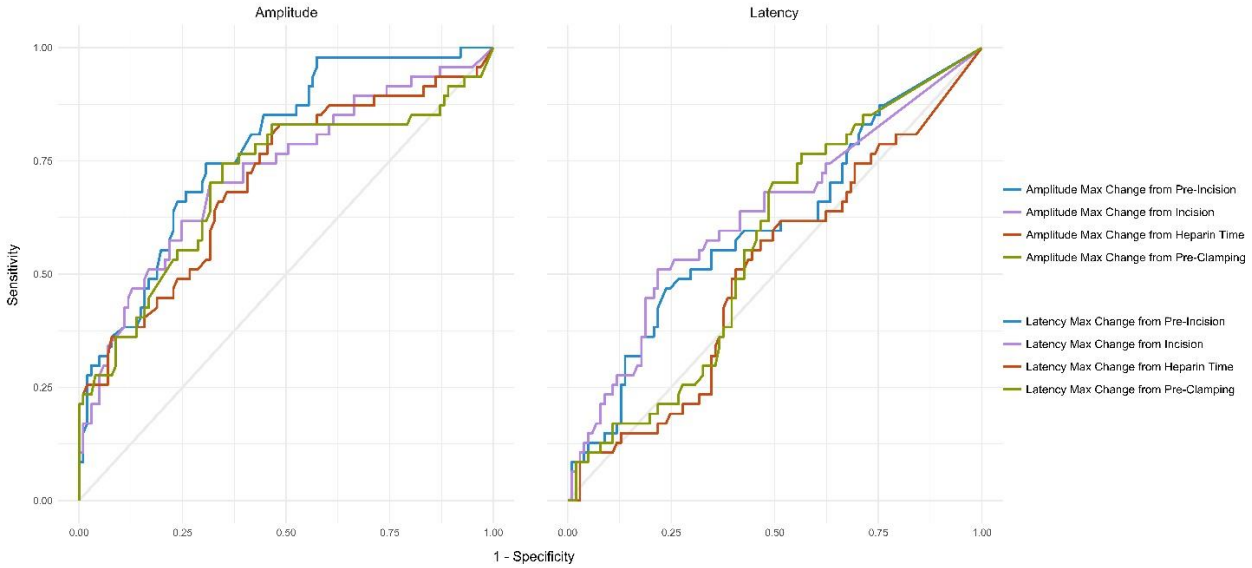

Figure 4. ROC curves for maximum amplitude and latency percentage changes. Each point is the sensitivity (x-axis) and 1 minus the specificity (y-axis) for every single percentage change, 0-100%. The optimal cutoff, determined by the Youden's Index, is the point that gives the greatest area under the curve. This point has the best compromise between sensitivity and specificity for that baseline measure.

when compared to incision ($p = .0208$) and heparin ($p = .0266$), and pre-clamp ($p = .0387$). There were no significant differences in AUC between all latency changes.

3.4 EVALUATING THE DIAGNOSTIC ACCURACY OF CURRENT ALARM CRITERIA IN PERIOPERATIVE STROKE: Table 3

Current alarm criteria are considered significant if there is a 50% decrease in amplitude and/or a 10% increase in latency. In our analysis a decrease greater than 50% of amplitude in SSEPs was predictive of stroke from all baselines. The sensitivity follows a decreasing trend from pre-incision (.745) to incision (.617), heparin (.404) and pre-clamp (.447). However, the specificity has an increasing trend from pre-incision (.624) to incision (.703), heparin (.842), and pre-clamp (.832). A 10% increase in latency was predictive of stroke at all baseline time points with very high specificity, the lowest being heparin (.970), but sensitivity was low with the highest being pre-incision and incision (.085). When including if a patient had a 50% decrease in amplitude or a 10% increase in latency, the criteria is predictive from all measures with a negatively correlated trend in sensitivity and specificity similar to a 50% decrease in amplitude. Patients with both a 50% decrease in amplitude and a 10% increase in latency was predictive regardless of baseline and followed the same trends in sensitivity and specificity as patients with a 10% latency increase.

Table 3. Evaluation of current alarm criteria in stroke.

Significant Change Modality	Accuracy	95% CI:	Sensitivity	Specificity
50% amplitude decrease from baseline				
Pre-incision	0.662	0.579-0.738	0.745	0.624
Incision	0.676	0.594-0.750	0.617	0.703
Heparin	0.703	0.622-0.775	0.404	0.842
Pre-clamp	0.71	0.629-0.781	0.447	0.832
10% latency increase from baseline				
Pre-incision	0.703	0.622-0.775	0.085	0.990
Incision	0.703	0.622-0.775	0.085	0.990
Heparin	0.662	0.580-0.738	0	0.970
Pre-clamp	0.676	0.594-0.750	0.021	0.980
50% amplitude decrease or 10% latency increase from baseline				
Pre-incision	0.655	0.573-0.732	0.745	0.614
Incision	0.669	0.587-0.744	0.617	0.693
Heparin	0.689	0.608-0.763	0.404	0.823
Pre-clamp	0.703	0.622-0.775	0.447	0.822
50% amplitude decrease and 10% latency increase from baseline				
Pre-incision	0.710	0.629-0.781	0.085	1.000
Incision	0.710	0.629-0.781	0.085	1.000
Heparin	0.676	0.594-0.750	0	0.990
Pre-clamp	0.682	0.601-0.756	0.021	0.990

3.5 CATEGORIZATION OF MAJOR AND MINOR STROKES

After separating the groups into controls, major strokes, and minor strokes, major strokes showed a greater percent amplitude decrease from all baselines than both minor strokes and controls. Minor strokes still showed a greater decrease in amplitude when compared to controls. Table 4 shows the means, standard deviations, and p-values for amplitude and latency between the two groups. There were no significant differences in the mean amplitude and latency changes at any point during surgery between major and minor stroke ($p > .05$). Changes in latency followed similar trends for both pre-incision and pre-clamp baselines, but minor strokes had a greater increase from incision and controls had a greater increase than both minor and major strokes from heparin.

3.6 PREDICTIVE VALUE OF SSEPs IN MAJOR STROKES AGAINST CONTROLS

Patients with perioperative major stroke had significantly decreased amplitude from all four baselines ($p < .001$). There is a significant difference in latency changes between the two groups from pre-incision ($p = .019$). Latency changes from incision, heparin and pre-clamp time points are not statistically significant.

ROC curve analysis was again utilized, and AUC was used to determine significance. Maximal Youden's Index value decided the optimal cutoff for all four measures. As shown in table 5, the AUC for pre-incision amplitude change (.829) was greater than incision (.804),

Table 4. Differences in major and minor stroke.

Variable	Major, n=17 (32%)	Minor, n=30 (32%)	p-value
	Mean ± SD		
Amplitude			
Pre-incision	67.7 ± 19.6	59.0 ± 18.8	0.1746
Incision	62.8 ± 25.5	48.8 ± 22.1	0.0846
Heparin	51.9 ± 30.6	43.3 ± 22.1	0.3397
Pre-clamp	52.7 ± 30.3	44.4 ± 24.0	0.3682
Latency			
Pre-incision	4.12 ± 3.76	3.35 ± 3.47	0.5241
Incision	3.23 ± 3.86	4.09 ± 3.48	0.4806
Heparin	2.56 ± 2.42	2.62± 2.28	0.9441
Pre-clamp	3.09 ± 2.58	2.70 ± 2.25	0.6280

Table 5. ROC analysis of each baseline in predicting major strokes.

Significant Change Modality	Optimal Cutoff (%)	AUC	95% CI:	Sensitivity	Specificity
Major stroke amplitude changes as a predictor					
Pre-incision	55%	0.829	0.747-0.911	0.846	0.693
Incision	50%	0.804	0.698-0.911	0.846	0.683
Heparin	38%	0.744	0.621-0.866	0.731	0.663
Pre-clamp	38%	0.744	0.619-0.868	0.808	0.653
Major stroke latency changes as a predictor					
Pre-incision	3.9%	0.649	0.527-0.770	0.500	0.772
Incision	3.9%	0.591	0.460-0.721	0.462	0.782
Heparin	2.5%	0.523	0.396-0.650	0.577	0.554
Pre-clamp	2.1%	0.585	0.466-0.703	0.769	0.505

heparin (.744), and pre-clamp (.744). The optimal cutoffs were a 55% decrease in amplitude from pre-incision, 50% from incision, and 38% from both heparin and pre-clamp. The AUC for latency change is only predictive from pre-incision (.649). Based on the 95% confidence intervals for AUC, latency changes from incision (CI: .460-.721), heparin (CI: .369-.650), and pre-clamp (CI: .466-.703) were not significant predictors. AUC was compared between all baseline measures for significant differences using DeLong's test for two correlated ROC curves. There was a significant difference from pre-incision in AUC when compared to heparin ($p = .0237$) and pre-clamp ($p = .0357$), but no significant difference from incision ($p = .324$). There were no significant differences in AUC between all latency changes.

3.7 EVALUATING THE DIAGNOSTIC ACCURACY OF CURRENT ALARM CRITERIA IN MAJOR STROKES: Table 6

A decrease of 50% or greater of amplitude is predictive of major stroke from all baselines. The sensitivity follows a decreasing trend from pre-incision (.846) to incision (.769), heparin (.500) and pre-clamp (.500). However, the specificity has an increasing trend from pre-incision (.624) to incision (.703), heparin (.841), and pre-clamp (.831). A 10% increase in latency was predictive of major stroke at all baseline time points with very high specificity, the lowest being heparin (.97) but almost no sensitivity, the highest being pre-incision and incision (.115). When including if a patient had a 50% decrease in amplitude or a 10% increase in latency, the criteria is predictive from all measures with a negatively correlated trend in sensitivity and specificity

similar to a 50% decrease in amplitude. Patients with both a 50% decrease in amplitude and a 10% increase in latency was predictive regardless of baseline and followed the same trends in sensitivity and specificity as patients with a 10% latency increase.

Table 6. Evaluation of current alarm criteria in major strokes.

Significant Change Modality	Accuracy	95% CI:	Sensitivity	Specificity
50% amplitude decrease from baseline				
Pre-incision	0.669	0.580-0.750	0.846	0.624
Incision	0.717	0.630-0.793	0.769	0.703
Heparin	0.772	0.689-0.841	0.500	0.842
Pre-clamp	0.764	0.680-0.835	0.500	0.832
10% latency increase from baseline				
Pre-incision	0.811	0.732-0.875	0.115	0.990
Incision	0.811	0.732-0.875	0.115	0.990
Heparin	0.772	0.689-0.841	0	0.970
Pre-clamp	0.787	0.706-0.855	0.038	0.980
50% amplitude decrease or 10% latency increase from baseline				
Pre-incision	0.661	0.572-0.743	0.846	0.614
Incision	0.709	0.622-0.786	0.769	0.693
Heparin	0.756	0.672-0.828	0.500	0.822
Pre-clamp	0.756	0.672-0.828	0.500	0.822
50% amplitude decrease and 10% latency increase from baseline				
Pre-incision	0.819	0.741-0.882	0.115	1.000
Incision	0.819	0.741-0.882	0.115	1.000
Heparin	0.787	0.706-0.855	0	0.990
Pre-clamp	0.795	0.715-0.862	0.038	0.990

4.0 DISCUSSION

SSEP recordings are used intraoperatively during CEA to detect changes in cerebral blood flow and act as an alarm for ischemia and impending perioperative stroke. We defined a stroke as a new onset or worsening of a neurological deficit. Having the proper alarm criteria is crucial to warn the surgical team and allow for necessary interventions to prevent any complications. Data from the current study show that amplitude changes are able to significantly predict perioperative stroke. However, an increase in latency does not seem to be useful, especially at a 10% increase, and should be reconsidered as a legitimate predictor of perioperative stroke in this patient population.

While past studies have shown the usefulness of changes in SSEPs in a clinical setting through correlation with poor postoperative neurological outcomes, few have presented a true quantitative analysis of how efficient they are in predicting perioperative stroke. The current alarm criterion is set at a 50% decrease in SSEP cortical amplitude. This is predictive of stroke from all baselines. The further along in the surgery that the baseline is taken before clamping, the less sensitive the measure is, but it becomes more specific. This makes sense because if a 50% decrease in amplitude from pre-clamp is detected using its baseline then it is very likely to have a 50% decrease in amplitude from pre-incision. It should be considered that the purpose of an alarm is to present a warning in which an intervention is still possible to prevent the occurrence of a stroke. With a 50% decrease in amplitude being predictive of perioperative stroke, it removes the ability for any intervention to be performed. The optimal cutoffs were determined to

range from 55% from pre-incision to 38% from pre-clamp. Patients who had perioperative stroke had a much faster decrease in amplitude from pre-incision which likely accounts for why there is an overall decreasing trend in optimal cutoffs as the baseline is taken later in the surgery. The slight increase in the optimal cutoff and predictive nature that is observed from the heparin baseline to the pre-clamp baseline is likely due to an increase in perfusion due to the thinning of the patient's blood. The two groups were not significantly different in absolute amplitude at the end of surgery. However, the average amplitude for the stroke group was still lower than controls. This return towards baseline is most likely from a combination of restored perfusion and the higher proportion of minor strokes. Latency changes were very specific but have limited sensitivity, and do not appear to be very useful, especially at the current alarm criteria of a 10% increase. The optimal cutoff from pre-incision was about 4%. An alarm set in advance of 4% would give minimal room for intervention and is questionable at best.

Categorizing strokes by major and minor strokes helped to increase the degree to which SSEPs were predictive. While the mean amplitude changes between both major and minor strokes were not statistically different, there still seems to be precedent to separate them. Not to downplay the importance of stopping any stroke from occurring, preventing major strokes should be of much higher priority. After excluding minor strokes, sensitivity and specificity of all baselines increased. The optimal cutoffs remained exactly the same. Removing minor strokes had no effect on the usefulness of latency changes as a predictor. Analysis of AUC shows there was no significant difference in pre-incision and incision baselines in major strokes, pre-incision was still different from heparin and pre-clamp time points. Furthermore, pre-incision is significantly different from incision, heparin, and pre-clamp when considering all stroke. It should be recommended that a pre-incision baseline is used during CEA. The alarm criteria

should be moved to provide an appropriate cushion to allow intervention. A possible suggestion would be to use the cutoff at which SSEP changes are no longer predictive of stroke in any capacity, but any shift in criteria must also consider the changes in sensitivity and specificity that are associated with it.

A major limitation to this study is that we did not control for shunting. A shunt is used to divert blood flow during the procedure to help try to restore perfusion after a significant change has occurred. Shunting does not come without its own complications and it does not guarantee that the patient will not have a stroke. Multiple cases in this study, both control and stroke, received shunts during their procedure. This could have an effect on the results because controls who had a 50% amplitude decrease and then received a shunt that successfully prevented significant ischemia, could have elevated the average change in the controls. Also, anyone who received a shunt and still had a stroke calls into question the ability for intervention to prevent stroke. Based on the data that we have presented, shunting after a 50% decrease is already too late because this decrease in amplitude is predictive of stroke. An earlier, more accurate alarm followed by shunting may have been effective in those cases. In order to fix this, future studies should assess this criterion by controlling for shunts as their own group or excluding them all together.

It is important to note that there are several other factors that limit this study. First, data collection was not blinded to which patients were strokes and which were controls. Future studies should consider this to remove any underlying biases. All data were collected from a single institution which raises questions about its generalizability. We did not control for changes in temperature, anesthesia, or blood pressure. This could have had an effect on both sensitivity and specificity because any cases that had a greater than 50% change but received an

intervention such as raising blood pressure or lowering anesthesia to restore the SSEPs and prevent stroke were not excluded from the controls. SSEPs only monitor activity of the primary somatosensory cortex so cerebral ischemia that occurred in other areas of the brain could go undetected. It is not possible to determine if the strokes actually occurred during surgery or post operation. Finally, the study was done retrospectively which may have some effect on reliability. In the future we plan to assess the contralateral changes as a stroke is not limited to the ipsilateral side.

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