Diagnostic Value of Somatosensory Evoked Potential Changes During Carotid Endarterectomy
A Systematic Review and Meta-analysis

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IMPORTANCE Perioperative stroke is a persistent complication of carotid endarterectomy (CEA) for patients with symptomatic carotid stenosis (CS).

OBJECTIVE To evaluate whether changes in somatosensory evoked potential (SSEP) during CEA are diagnostic of perioperative stroke in patients with symptomatic CS.

DESIGN, SETTING, AND PARTICIPANTS We searched PubMed and the World Science Database for reference lists of retrieved studies and/or experiments on SSEP use in postoperative outcomes following CEA in patients with symptomatic CS from January 1, 1950, through January 1, 2013. We independently screened all titles and abstracts to identify studies that met the inclusion criteria and extracted relevant articles in a uniform manner. Inclusion criteria included randomized clinical trials, prospective studies, or retrospective cohort reviews; population of symptomatic CS; use of intraoperative SSEP monitoring during CEA; immediate postoperative assessment and/or as long as a 3-month follow-up; a total sample size of 50 or more patients; studies with adult humans 18 years or older; and studies published in English.

MAIN OUTCOME AND MEASURE Whether intraoperative SSEP changes were diagnostic of perioperative stroke indicated by postoperative neurological examination.

RESULTS Four-hundred sixty-four articles were retrieved, and 15 prospective and retrospective cohort studies were included in the data analysis. A 4557-patient cohort composed the total sample population for all the studies, 3899 of whom had symptomatic CS. A change in SSEP exhibited a strong pooled mean specificity of 91% (95% CI, 86-94) but a weaker pooled mean sensitivity of 58% (95% CI, 49-68). A pooled diagnostic odds ratio for individual studies of patients with neurological deficit with changes in SSEPs was 14.39 (95% CI, 8.34-24.82), indicating that the odds of observing an SSEP change among those with neurologic deficits were 14 times higher than in individuals without neurologic deficit.

CONCLUSIONS AND RELEVANCE Intraoperative SSEP is a highly specific test in predicting neurological outcome following CEA. Patients with perioperative neurological deficits are 14 times more likely to have had changes in SSEPs during the procedure. The use of SSEPs to design prevention strategies is valuable in reducing perioperative cerebral infarctions during CEA.

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Carotid endarterectomy (CEA) is the gold-standard treatment for patients with symptomatic carotid stenosis (CS) to reduce the risk of stroke. There is a clear benefit for CEA in symptomatic patients (usually with CS ≥70%) when compared with medical management alone. At the 5-year mark, 85% to 90% of patients treated with CEA are stroke free in comparison with medical treatment, which has a rate of 75% to 80%. However, studies have shown 2% to 3% of CEA cases result in ischemic insult to the patient. These are mainly thought to be a result of thromboembolic events from the operative and/or distal site as a result of atherosclerotic plaque disruption or from cerebral hypoperfusion owing to cross-clamping of the internal carotid artery in conjunction with inadequate collateral circulation. Stroke after CEA is associated with significant morbidity and a nearly 3-fold increase in future mortality in these patients.

Intraoperative intraluminal shunting has been used during CEA to prevent cerebral hypoperfusion and impending ischemia during the cross-clamping of the carotid artery. In conjunction, intraoperative neurophysiological monitoring with somatosensory evoked potential (SSEP) has been shown to be a valuable technique for determining the need for selective intraoperative shunting in place of routine shunting in all patients. Somatosensory evoked potential monitoring allows for adequate assessment of collateral circulation and the need for shunt insertion.

A shunt is generally inserted if there is a significant change in response to the SSEP waveform, which is usually defined as a decrease greater than 50% in the amplitude of the cortical N20-P25 complex and/or a 10% increase in latency of cortical wave after the cross-clamping of the carotid artery. However, strokes still occur despite these preventive measures. Moreover, the predictive value of the neurologic outcome of SSEP changes that persist following the placement shunt remains unclear. Such information could offer assistance during the CEA procedure to detect shunt malfunction, as well other events of hypoperfusion, which can lead to perioperative stroke. Furthermore, the predictive values of SSEP changes can help effectively test newer mechanical and pharmacological targets of neuroprotective strategies during CEA to reduce stroke. Additionally, SSEP intraoperative monitoring holds great potential in its ability to allow for proper decision making and stratification to permit aggressive perioperative management for at-risk patients in efforts to prevent neurological deficits. To our knowledge, such level of neurosurgical care is currently unavailable for patients undergoing CEA. Somatosensory evoked potential can be the vital tool to rectify such a dilemma.

Our primary aim was to perform a systematic review of the scientific literature to evaluate whether changes in SSEPs during CEA are diagnostic for perioperative strokes (neurological deficits). The goal of this review was to ascertain the sensitivity, specificity, diagnostic odds ratio, and area under receiver operating characteristic (ROC) curves of intraoperative SSEP changes in relation to neurological outcome in patients undergoing CEA for symptomatic CS.

Methods

Search Criteria and Strategy
We searched PubMed and the World Science Database for reference lists of retrieved reports and/or experiments from January 1, 1950, through January 1, 2013, for studies on SSEP use for postoperative outcome after CEA in patients with symptomatic CS. To execute the search, the following terms were used: cerebrovascular diseases, carotid stenosis, carotid artery diseases, transient ischemic attack, intraoperative monitoring, somatosensory evoked potentials, N20 cortical potential, carotid endarterectomy, postoperative complications, neurologic deficits, stroke, paralysis, and paresis.

Study Selection
The inclusion criteria included the following: (1) randomized clinical trials and prospective or retrospective cohort reviews; (2) population of symptomatic CS; (3) use of intraoperative SSEP-monitoring during CEA; (4) immediate postoperative assessment and/or as long as a 3-month follow-up; (5) a total sample size of 50 or more patients; (6) studies with adult humans 18 years or older; and (7) studies published in English.

Data Extraction
The authors (E.L.N. and P.D.T.) independently screened all titles and abstracts to identify studies that met the inclusion criteria and extracted relevant articles in a uniform manner. Subsequently, each author constructed an Excel spreadsheet outlining the articles to be eliminated; a reason for the elimination was dictated by a number corresponding to 1 of the inclusion criteria. After elimination disagreements were reconciled, a final list of articles was assembled. The number of true-positives, false-negatives, false-positives, and true-negatives in patients with symptomatic CS who underwent CEA were extracted and tabulated for each study in a 2 × 2 table (see eMethods in the Supplement for more detail).

Statistical Analyses
The data synthesis used a bivariate normal model for the logit-transformed pairs of sensitivities and false-positive rates prior to the fitting of a linear mixed model. This model preserved the bivariate nature of the data by taking into account any correlation between sensitivity and specificity. In the absence of covariates, it was equivalent to the hierarchical summary ROC model. The mean logit sensitivity, specificity, and covariance were estimated from this model. Forest plots and a summary ROC with a 95% contour ellipsoid were constructed. As a secondary analysis, we also fitted fixed and random effects models for log-diagnostic odds ratios. Unlike the bivariate normal model, this converted the bivariate nature of the data to a univariate problem.

We assessed heterogeneity in sensitivities and specificities via univariate I² or the estimated variance coefficients. Heterogeneity was also examined visually through forest and summary ROC plots. Potential sources of heterogeneity were examined by meta-regression. Covariates that were
considered included reversibility rate or shunt rate. As a sensitivity analysis, models were fitted with potential outlying studies deleted. To investigate publication bias, we constructed funnel plots of log-diagnostic odds ratios vs the inverse square roots of the effective sample size and tested for funnel plot asymmetry using the Deeks et al\(^\text{38}\) method, an approach that has been recommended in the literature.\(^\text{37}\) Additionally, the QUADAS 2 checklist was used to evaluate for bias and applicability of the studies.\(^\text{39}\) All statistical analyses were carried out in R (version 3.1) using the MADA package.\(^\text{40}\)

### Results

There were 464 articles retrieved based on title and abstract from a literary database search (Figure 1). However, 47 articles remained after full assessment by the authors. Further evaluation based on study inclusion criteria led to 15 studies that were included for study analyses. These 15 studies consisted of prospective and retrospective cohort studies.

All of the studies used SSEP as a mode of intraoperative neuromonitoring during CEA. Baseline SSEPs were recorded in all patients either before or after induction of anesthesia. Each study constructed alarm criteria needed for intraluminal shunt placement during significant SSEP change, which were classified in all studies as complete or 50% decrease in N20-P25 cortical waveforms. Furthermore, in these studies neurological clinical evaluation ranged from immediately to 3 months postoperatively (Table 1).

A 4557-patient cohort composed the total sample population for all the studies, of which 3899 had symptomatic CS characterized by recurrent transient ischemic attacks or cerebral vascular accident. The mean age for the patient population from all the studies was approximately 61 years.

Of the total patient population, 514 (11.3%) exhibited significant SSEP change during surgical manipulation, indicating an ischemic event. Furthermore, the significant SSEP change group was subdivided into reversible and irreversible change. Of this subgroup, 480 patients (93.4%) were reversible, with 34 patients (6.6%) who were irreversible. A moderate proportion, 1194 (26.2%) of the patient population, were shunted either routinely as a result of significant SSEP change or at the surgeon’s discretion. In patients with SSEP changes, the incidence of neurological deficit was 65 of 514 (12.6%). In patients without SSEP changes, the incidence of neurological deficit was 43 of 4043 (1.1%). There were 2 studies in which most patients underwent shunting irrespective of changes in SSEPs.

Postoperative neurological deficit was observed in 108 patients (2.4%) in the patient sample. Of the minor subgroup of patients with neurological deficit, 65 (60.2%) had intraoperative SSEP change while 43 (39.8%) did not. Additionally, the incidence of neurological deficit in the reversible and irreversible SSEP subgroup was 6.6% and 97%, respectively. In the entire study sample, there was a mortality rate of 0.22% (Table 2).

Figure 2 shows a forest plot of sensitivities and specificities of the ability of SSEP change to predict postoperative neurological outcomes for each study. Study sensitivities ranged from 25% to 93%, while specificities ranged from 67% to 98%. Combining data from all studies without accounting for possible covariates explaining heterogeneity and using the bivariate normal mixed effects model, SSEP change exhibited strong specificity (mean, 91%; 95% CI, 86%-94%) but weaker sensitivity (mean, 58%; 95% CI, 49-68). The model-based pooled area under the ROC curve was estimated to be 67%. The hierarchical summary ROC curve presented a global summary of test performance and showed the trade-off between sensitivity and specificity. A graph of the estimated hierarchical summary ROC along with the summary point, 95% confidence ellipse, and prediction ellipse for SSEP is shown in Figure 3.

A pooled random effects estimate of the diagnostic odds ratios for individual studies of patients with neurological deficit with changes in SSEPs was 14.39 (95% CI, 8.34-24.82). This indicated that the odds of observing an SSEP change among those with neurologic deficit were 14 times higher than those without neurologic deficit. To account for the wide variation in the confidence interval in individual studies, a forest plot of log-diagnostic odds ratios for the individual studies was obtained (Figure 4). Log-diagnostic odds ratios ranged from 0.52 to 5.0. A significant pooled average estimate of 2.67 (95% CI, 2.12-3.21) was based on a random effects model.
Specificities (I) and sensitivities (I) of 0.91 but a weak sensitivity of 0.58 to detect neurological deficits during CEA. The higher specificity of neurological deficits in patients with SSEP changes indicates that, in some patients, reversal of SSEPs is desirable but not always achievable. We believe that low sensitivity is a result of clinical interventions, such as intraluminal shunts and mean arterial pressure elevation, implemented once ischemia is detected with SSEPs following the cross-clamping of the carotid artery. In our study, this resulted in reversible increase in the cerebral blood flow (CBF), thus preventing infarction. Cerebral blood flow is normally 50 mL/100 g/min, with higher flow to the metabolically active cortical regions compared with subcortical regions. Animal studies have indicated that a drop in CBF below 16 to 20 mL/100 g/min causes a reversible decrease in the amplitude of cortical SSEP responses. More over, CBF values between 12 and 15 mL/100 mg/min result in complete disappearance of SSEP responses resulting in electrical failure. Further animal studies have shown that loss of SSEP responses is a precursor of ion pump failure at the cellular level. In addition, human studies have shown that when CBF decreases below 14 mL/100 g/min, persistent reduction in SSEP amplitude by 50% is usually observed. Infarction of the tissue or ion pump failure occurs at CBF of 10 to 12 mL/100 mg/min. Hence, in this narrow hemodynamic window where loss of cortical SSEP responses does not imply loss of

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Modality</th>
<th>Alarm Criteria</th>
<th>Reason for Shunt</th>
<th>Baseline SSEP</th>
<th>Length of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beese et al,17 1998</td>
<td>Prospective cohort</td>
<td>SSEP</td>
<td>Yes</td>
<td>50% Decrease in N20-P25</td>
<td>Yes (after anesthesia)</td>
<td>Immediately postoperatively and on discharge</td>
</tr>
<tr>
<td>Dinkel et al,28 1992</td>
<td>Prospective cohort</td>
<td>SSEP</td>
<td>Yes</td>
<td>100% Decrease in N20-P25</td>
<td>Yes (after anesthesia)</td>
<td>Immediately postoperatively</td>
</tr>
<tr>
<td>Fava et al,29 1992</td>
<td>Retrospective cohort</td>
<td>EEG, SSEP</td>
<td>Yes</td>
<td>50% Decrease in N20-P25</td>
<td>Yes (after anesthesia)</td>
<td>Immediately postoperatively</td>
</tr>
<tr>
<td>Guerin et al,31 1997</td>
<td>Retrospective cohort</td>
<td>SSEP</td>
<td>Yes</td>
<td>50% Decrease in N20-P25</td>
<td>Yes (after anesthesia)</td>
<td>Immediately postoperatively and on discharge</td>
</tr>
<tr>
<td>Haupt and Horsch,35 1992</td>
<td>Retrospective cohort</td>
<td>SSEP</td>
<td>Yes</td>
<td>50% Decrease in N20-P25</td>
<td>Yes (before anesthesia)</td>
<td>Immediately and up to 2 wk postoperatively</td>
</tr>
<tr>
<td>Horsch et al,32 1990</td>
<td>Prospective cohort</td>
<td>SSEP</td>
<td>Yes</td>
<td>50% Decrease in N20-P25</td>
<td>Yes (before anesthesia)</td>
<td>Immediately postoperatively</td>
</tr>
<tr>
<td>Linstedt et al,24 1998</td>
<td>Retrospective cohort</td>
<td>SSEP</td>
<td>Yes</td>
<td>50% Decrease in N20-P25 and surgeon discretion</td>
<td>Yes (after anesthesia)</td>
<td>Immediately postoperatively</td>
</tr>
<tr>
<td>Manninen et al,26 2001</td>
<td>Retrospective cohort</td>
<td>SSEP</td>
<td>Yes</td>
<td>50% Decrease in N20-P25</td>
<td>Yes (after anesthesia)</td>
<td>Immediately postoperatively</td>
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<tr>
<td>Manninen et al,25 2004</td>
<td>Prospective cohort</td>
<td>SSEP</td>
<td>Yes</td>
<td>50% Decrease in N20-P25</td>
<td>Yes (after anesthesia)</td>
<td>Immediately postoperatively</td>
</tr>
<tr>
<td>Pedrini et al,33 1998</td>
<td>Retrospective cohort</td>
<td>SSEP</td>
<td>Yes</td>
<td>50% Decrease in N20-P25</td>
<td>Yes (before anesthesia)</td>
<td>Immediately postoperatively</td>
</tr>
<tr>
<td>Prokop et al,32 1996</td>
<td>Prospective cohort</td>
<td>SSEP</td>
<td>Yes</td>
<td>50% Decrease in N20-P25 and preoperative contralateral occlusion</td>
<td>Yes (after anesthesia)</td>
<td>Immediately postoperatively</td>
</tr>
<tr>
<td>Rowe et al,10 2004</td>
<td>Prospective cohort</td>
<td>EEG, SSEP, TCD</td>
<td>Yes</td>
<td>50% Decrease in N20-P25</td>
<td>Yes (after anesthesia)</td>
<td>Immediately postoperatively to discharge</td>
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<tr>
<td>Schweiger et al,16 1991</td>
<td>Prospective cohort</td>
<td>SSEP</td>
<td>Yes</td>
<td>50% Decrease in N20-P25</td>
<td>Yes (after anesthesia)</td>
<td>Immediately to 4 d postoperatively</td>
</tr>
<tr>
<td>Stejskal et al,12 2007</td>
<td>Retrospective cohort</td>
<td>EEG, SSEP, TCD</td>
<td>Yes</td>
<td>50% Decrease in N20-P25</td>
<td>Yes (after anesthesia)</td>
<td>Immediately to 3-7 d postoperatively and 3 mo</td>
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<tr>
<td>De Vleeschauwer et al,33 1988</td>
<td>Prospective cohort</td>
<td>SSEP</td>
<td>Yes</td>
<td>50% Decrease in N20-P25</td>
<td>Yes (before anesthesia)</td>
<td>Immediately and up to 2 wk postoperatively</td>
</tr>
</tbody>
</table>

Abbreviations: EEG, electroencephalogram; SSEP, somatosensory evoked potential; TCD, transcranial doppler.

Univariate heterogeneity analysis indicated homogeneity in sensitivities (P<0.01%) but substantial heterogeneity in specificities (P<0.01). Subsequently, SSEP change reversibility rate or shunt rate was used as a covariate in bivariate normal mixed effects meta-regression models. The reversibility rate was found to be significant in explaining heterogeneity in specificity (I<0.01%) but substantial heterogeneity in specificity (I<0.01%). Subsequently, SSEP change reversibility rate was found to be significant in explaining heterogeneity in specificity (I<0.01%). Reanalysis of data excluding 2 studies,13,33 which appear to have outlying specificities, yielded similar estimates as the original analysis.

Discussion

Our results indicated that SSEP changes possess a strong specificity of 0.91 but a weak sensitivity of 0.58 to detect neurological deficits during CEA. The higher specificity of neurological deficits in patients with SSEP changes indicates that, in some patients, reversal of SSEPs is desirable but not always achievable. We believe that low sensitivity is a result of clinical interventions, such as intraluminal shunts and mean arterial pressure elevation, implemented once ischemia is detected with SSEPs following the cross-clamping of the carotid artery. In our study, this resulted in reversible increase in the cerebral blood flow (CBF), thus preventing infarction. Cerebral blood flow is normally 50 mL/100 g/min, with higher flow to the metabolically active cortical regions compared with subcortical regions. Animal studies have indicated that a drop in CBF below 16 to 20 mL/100 g/min causes a reversible decrease in the amplitude of cortical SSEP responses. Moreover, CBF values between 12 and 15 mL/100 mg/min result in complete disappearance of SSEP responses resulting in electrical failure. Further animal studies have shown that loss of SSEP responses is a precursor of ion pump failure at the cellular level. In addition, human studies have shown that when CBF decreases below 14 mL/100 g/min, persistent reduction in SSEP amplitude by 50% is usually observed. Infarction of the tissue or ion pump failure occurs at CBF of 10 to 12 mL/100 mg/min. Hence, in this narrow hemodynamic window where loss of cortical SSEP responses does not imply loss of
neuronal viability, reversing CBF changes quickly changes the course of iatrogenic cellular ionic changes.45

As previously shown in the literature, our study supports evidence that perioperative stroke is a major complication of surgery for CS. The result from our data revealed an incidence of 2.4%, which is congruent with rates in the current literature. Additionally, diagnostic odds ratios estimated that when individuals experienced a significant ischemic event perioperatively, SSEPs were approximately 14 times more likely to have changed during CEA. More importantly, patients who had...
Patients identified a new lesion in 17% of the patients. Intraoperative neuromonitoring with the use of SSEPs based on the current study appears to be a specific indicator of a perioperative neurological deficit.

Based on the literature, false-negative SSEP results appear to be a common problem, with ranges of 0% to 3.5%. Our study demonstrated a false negative rate of 0.96%. Again, false-negatives were seen in patients who experienced postoperative neurological deficit but in whom there were no significant SSEP changes. One particular hypothesis is that these neurological deficits could have occurred postoperatively from thromboemboli and, in that case, it would be unrealistic for the SSEP to recognize them intraoperatively. Additionally, technical errors could also be a factor that leads to false-negative SSEP results in particular patients.

Although the current study showed strengths based on comprehensive literature review, with quality assessment using the QUADAS-2, there are several limitations that must be addressed. Most importantly, it is crucial to acknowledge the fact that a search bias may have existed owing to the difficulty associated with acquiring every possible study assessing use of SSEP during CEA. Also, owing to the study design, our analysis is at risk of publication bias because of the dependence on currently published data on the topic of investigation; however, our analysis via funnel plot (eFigure in the Supplement) provides no evidence of such bias in the current study. Statistically significant heterogeneity was observed among the averaged specificity of the studies. Owing to the design of this study, it was difficult to assess every possible factor for such a result because of data pooling from diverse sources. However, we assessed 2 critical variables (rate of shunt and SSEP reversibility) for the study in a meta-regression. The reversibility of SSEP accounted for some of the heterogeneity seen in the averaged specificity.

Somatosensory evoked potentials are not the only modality used during CEA to determine the need for intraluminal shunt placement. Electroencephalography, transcranial Doppler, stump pressure, and cerebral oximetry have been used to identify hypoperfusion during cross-clamping of the carotid artery. Our study did not evaluate the diagnostic accuracy of such studies; it is unclear if these tests provide similar prognostic information.

Conclusions

Intraoperative SSEP is a highly specific test in predicting neurological outcome following CEA. Low sensitivity could be related to interventions performed after a change in SSEPs. Patients with postoperative neurological deficits are 14 times more likely to have had changes in SSEPs during the procedure. Perioperative stroke is almost guaranteed in a patient who demonstrates irreversible SSEP during CEA. Thus, these results are clinically relevant both for surgical approach and patient education in regards to postoperative expectations. Ultimately, understanding the etiologies of perioperative strokes and further using SSEPs to design prevention strategies can prove valuable in reducing perioperative cerebral infarctions during CEA.
Somatosensory-Evoked Potential Changes in Carotid Endarterectomy

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Study concept and design: Balzer.
Acquisition, analysis, or interpretation of data: Nwachuku, Yabes, Habeych, Crandall, Thirumala.
Drafting of the manuscript: Nwachuku, Yabes.

Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Yabes.
Obtained funding: Nwachuku.
Administrative, technical, or material support: Nwachuku.
Study supervision: Balzer, Habeych, Thirumala.

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REFERENCES
27. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test


