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Fully Automated Transcranial Doppler Ultrasound for Middle Cerebral Artery Insonation

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Background: Transcranial Doppler ultrasound (TCD) is utilized in the assessment of neurological conditions in clinical environments such as the intensive care unit and emergency department. However, obstacles for widespread use of TCD include a lack of trained registered vascular technologists (RVT) and operator variability. We present a study comparing RVT and a fully automated robotic TCD system (NovaGuide rTCD) for insonation of the middle cerebral artery (MCA).
Methods: A trained RVT and rTCD sequentially collected bilateral MCA cerebral blood flow velocity (CBFV) from 86 healthy subjects. Mean CBFV (mCBFV) and the signal quality assessment (SQA) acquired manually by RVT and autonomously via rTCD were compared. Comparison metrics evaluated include mean accuracy ratio (MAR), and Bland-Altman mean-difference (MD) between rTCD and RVT with paired *t*-Test for significance. Bootstrapping was used in the accuracy ratio and mean-time to best signal computations to establish 95% confidence intervals.
Results: The mCBFVs and SQAs found by rTCD compared to RVT had MAR of 99.7% (97.7-101.7%) and 102.7% (101.1-104.8%), respectively. The rTCD mean-time to best-quality signal was 0.87 min (0.71-1.05) (RVT was not timed). The mean-difference scores for mCBFV and SQA were MD=-0.43cm/s (p=0.053) and MD=-0.36 (p=0.61), respectively. The rTCD had a 3.5% no-window failure rate compared to RVT no-window rate of 4.1%.
Conclusion: Comparison of bilateral TCD signals collected by rTCD and RVT demonstrated equivalence in mCBFV and signal quality, suggesting rTCD's potential to expand utility of TCD in clinical settings that are resource-limited.
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INTRODUCTION

Transcranial insonation of the cerebral circulation presents a method of real-time evaluation of cerebral blood flow velocity (CBFV) and direction, known as transcranial Doppler (TCD) ultrasound.[1] TCD measures time dependent CBFV waveforms demonstrating flow throughout the major arteries and veins of the head and neck from which pathology may be evaluated. Features extracted from these waveforms, including mean CBFV and Pulsatility Index, have been shown to be influenced by vessel status and pathology.[2-4]

Information provided by TCD in the clinical setting has been tested and indicated in a number of different pathologies, including large vessel occlusion,[4,5] elevated intracranial pressure,[6] traumatic brain injury,[3] and dementia,[7] among others. In addition to its experimental validation, TCD has been acknowledged as valuable and recommended for use in the clinical setting by a number of professional guidelines. The American Academy of Neurology and the American Society of Neuroimaging acknowledge that TCD provides relevant information in sickle cell disease, cerebral ischemia (stroke, TIA), carotid artery stenosis and occlusion, vasospasm after subarachnoid hemorrhage, brain death, and periprocedural monitoring.[8,9]

Despite the utility of information provided by TCD, its diagnostic and prognostic value in vascular assessment remains limited by stringent training requirements necessary to reliably obtain these waveforms and meaningfully interpret the associated morphology. The procedure of TCD signal acquisition is a challenging interactive process requiring interpretation and response by a trained sonographer as they encounter the real-time CBFV data. Recent works have shown that the validity of TCD examination is highly dependent on the training and experience of the sonographer.[10,11] Thorough training of TCD operators has tremendous impact on its clinical value, and can also work to lessen the amount of intra and inter-operator variability associated with TCD.[11]

In addition to its inherent limitations by user dependence, analysis of the actual CBFV waveform data has historically relied on expert evaluation for application in diagnosis.[4] Recent work has been done to present and evaluate possible solutions to these limitations of TCD, ranging from semi-autonomous insonation of healthy control subjects to fully-autonomous evaluation and indication of angiographic vasospasm after SAH.[12,13] For TCD to become more widely utilized, the limitations of both operation and analysis must be addressed. Here we sought to evaluate the performance of a novel, fully autonomous robotic TCD (rTCD) system, NovaGuide (NovaSignal Corp., Los Angeles, CA, USA). We tested the agreement and quality of CBFV data collected by both NovaGuide and a human expert from each subject.

SUBJECTS AND METHODS

1. Protocol

Subjects were recruited on a voluntary basis from a cohort of healthy adults of 18 years and older. The protocol was exercised by a registered vascular technician (RVT). The protocol specified that the RVT manually acquires the best MCA signal possible through each of the left and right temporal windows without regard to time restrictions and records the measured mCBFV. The RVT then performed the exam utilizing the NovaGuide Robotic TCD Ultrasound System (rTCD). This order was specified to eliminate any potential bias from the RVT observing the robotic exam. Each signal found during the exam was recorded as a 10 seconds segment. This length was chosen to minimize the potential confounding effect of RVT fatigue, and to maintain the comparability of both the robotic and manual TCD data. A single RVT with TCD experience (2,000 studies) was selected due to the increased training requirements and to reduce person to person variability.

Immediately after the RVT completed the manual TCD examination, the NovaGuide rTCD was set up on the subject while still in supine position (Fig. 1). For conducting a NovaGuide exam, two fiducial stickers are placed on each side of the subject's head, one on the corner of the eye and the other on the tragus of the ear. Following placement of the fiducials, the subject is placed within the NovaGuide head cradle in the supine position. Consistent with manual TCD examinations, TCD gel is applied to the temporal region before the exam is initiated. The NovaGuide software then automatically registers the fiducials placed on the subject using image processing techniques from images captured by the system's bilateral cameras located adjacent to the probes. The system user then starts the examination by pushing a "start button" on the exam screen. The NovaGuide will concurrently search bilaterally, providing multiple signals for consideration as it optimizes for the highest quality signal. The evaluation determination is made automatically by a previously presented method which incorporates several relevant metrics for signal quality.[14,15] Each candidate signal is evaluated/recorded for 10 seconds. The NovaGuide system was restricted to 10 minutes total time to conduct the bilateral TCD examination. All data processing and analysis were performed using Python (v2.7) with major data science libraries, such as scipy, pandas, matplotlib, and scikit-learn.[16-18]

FIG. 1. (A) The NovaGuide cart system, including a transcranial Doppler ultrasound display screen (left) and NovaGuide (NovaSignal Corp, Los Angeles, CA, USA) display screen demonstrating search progress. (B) The NovaGuide (NovaSignal Corp) head cradle showing probe pods positioned on both sides of a subject in the supine position for an exam.

2. NovaGuide rTCD system

The NovaGuide system is a five degree of freedom, autonomous robotic TCD system that identifies the acoustic window and optimizes the CBFV signal. The robotic probe pods are independently controlled so that the user can conduct autonomous simultaneous bilateral insonation of the patient. The NovaGuide system uses an optical registration system to align the robotic search space with the patient's temporal region.

Once the patient head unit is in place, the user begins the autonomous TCD examination. During the examination, the NovaGuide system progresses through a temporal window search protocol looking for an acoustic access window within the patient's temporal region. Once the acoustic access window is located, the NovaGuide system begins a signal optimization protocol evaluating MCA signals for quality. Each signal acquired that meets sufficient quality standards is recorded within the NovaGuide signal database and displayed on the graphical user interface. For this study protocol, the user was prohibited from interacting with the control system to allow for a direct comparison of the autonomous insonation system with the results from manual sonography.

3. Analysis

Two metrics were used to evaluate the TCD signals—mean cerebral flow velocity (mCBFV) and signal quality assessment (SQA). Two different metrics are used because mCBFV is typically the clinically reported metric; however, there are many scenarios in which the velocity of the signal is high, but the acquired signal is of very poor quality. SQA is a metric that assesses the overall quality of a CBFV signal and was validated with a panel of 11 TCD experts.[14,15] SQA is a mathematical summative statistic that optimizes for a balance between TCD signal velocity, smoothness, depth range, power, and signal-to-noise ratio, and assess the signal quality in real-time over a short data segment of 500 ms, which is smaller than ~1 sec typical TCD beat length. Evaluation of agreement of SQA with TCD experts has demonstrated strong agreement (Kendall-tau-rank-correlation-coefficient, T_k=0.76).[15]

We enumerate the unilateral patient scan regions by an index set denoted by j in the following equations. Note that a single subject has two scan regions corresponding to their left and right temporal regions, so each subject contributes two indices to the analysis (e.g. j=1 and j=2). For each scan region j, denote the signals acquired by the RVT can be defined as $RVT^j=\{S^i_{rvt}\}_j$ and the signals acquired by NovaGuide rTCD as $rTCD_j=\{S^i_{rtcd}\}_j$. We define $mCBFV^j_{rvt}=max(\{mCBFV(S):for\ S\ in\ RVT^j\})$ and $SQA^j_{rvt}=max(\{SQA(S)\ for\ S\ in\ RVT^j\})$. Note that argmax($\{mCBFV(S)\ for\ S\ in\ RVT^j\}$) may not be equal to argmax($\{SQA(S)\ for\ S\ in\ RVTj\}$) that is the highest velocity signal may not be the same signal that has the highest signal quality assessment. Similarly, we define $mCBFV^j_{rtcd}$ and SQA^j_{rtcd} for the rTCD system. For each scan region j, we consider the signal pairs ($mCBFV^j_{rtcd}$, $mCBFV^j_{rvt}$) and (SQA^j_{rtcd}, SQA^j_{rvt}) for which we report the mean accuracy ratio (MAR) and Bland-Altman mean difference (MD) defined as:

$$MAR^j_{mCBFV} = \frac{mCBFV^j_{rtcd}}{mCBFV^j_{rvt}}$$

$$MAR^j_{SQA} = \frac{SQA^j_{rtcd}}{SQA^j_{rvt}}$$

$$MD^j_{mCBFV} = \frac{(mCBFV^j_{rtcd} - mCBFV^j_{rvt})}{mean(mCBFV^j_{rtcd} - mCBFV^j_{rvt})}$$

$$MD^j_{SQA} = \frac{(SQA^j_{rtcd} - SQA^j_{rvt})}{mean(SQA^j_{rtcd} - SQA^j_{rvt})}$$

For the results, we report the population mean of each of these values over the subjects indexed by j. We also conduct at 10,000 case bootstrap to establish 95% CIs on the population mean values for MAR and a paired t-test for establishing statistical significance in the NovaGuide rTCD vs RVT measurement distributions.

These metrics are conditioned on $rTCD^j \neq \emptyset$ and $RVT^j \neq \emptyset$, that indicates subject should have measurable signal via rTCD and RVT If either set is empty, that means either the RVT or rTCD was not able to record a signal in that region, hence then the above calculations are not performed, and scan region j is left out of the population analysis.

RESULTS

The study population evaluated included 86 healthy volunteers, average age 37.5 years (±11.5), 34% identified as female. 66% were white, 25% Asian, 6% other/not reported, 2% Black/African American, and 1% Pacific Islander. The no-window-found rate was not signifi-

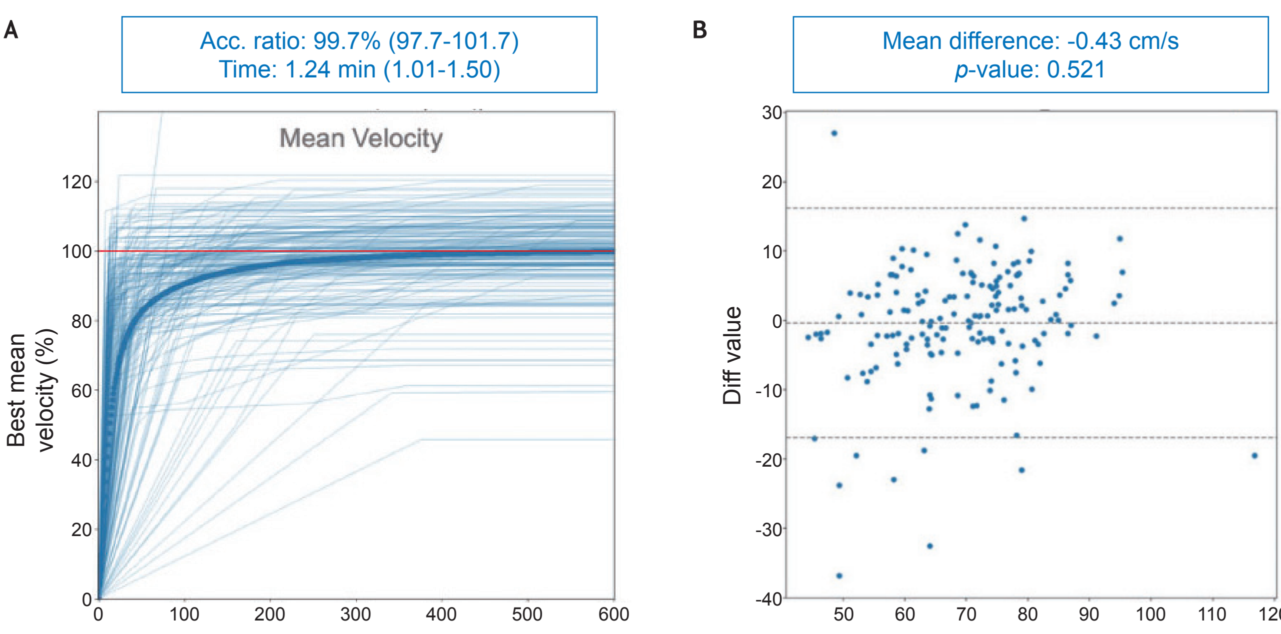

FIG. 2. Mean accuracy ratio and Bland-Altman results of NovaGuide (NovaSignal Corp, Los Angeles, CA, USA) vs. expert for mean cerebral blood flow velocity insonation.

cantly different between NovaGuide and RVT (3.5% vs. 4.1%, *p*=0.53).

In our comparison of NovaGuide and RVT, we first estimate the population mean MAR_{mCBFV} trend over time (Fig. 2); the population mean MAR_{mCBFV} was 99.7% at 10 minutes (95% CI, 97.7-101.7%). The Bland-Altman mean difference for mCBFV of the MCA (MDmCBFV) is -0.43 cm/s as shown in Fig. 1 with the paired *t*-test not statistically significant (*p*=0.521). The NovaGuide mean time to highest-velocity signal was 1.24 min (range, 1.01-1.50).

Next, we compared the quality of the signal obtained by NovaGuide and RVT for the bilateral MCA (Fig. 3); the population mean MAR_{SQA} was 102.7% at 10 minutes (95% CI, 101.1-104.8%). Bland-Altman mean difference for signal quality (MDSQA) was -0.36 in Fig. 2, with the paired *t*-test not statistically significant (*p*=0.611). The NovaGuide time to highest-quality signal acquisition was 0.87 min (0.71-1.05). The results of the NovaGuide system compared to RVT are summarized in Table 1.

DISCUSSION

The mCBFV values collected by the NovaGuide rTCD fell within range of those collected by a human expert sonographer for the same subject, demonstrated by the non-significant Bland-Altman mean differences.

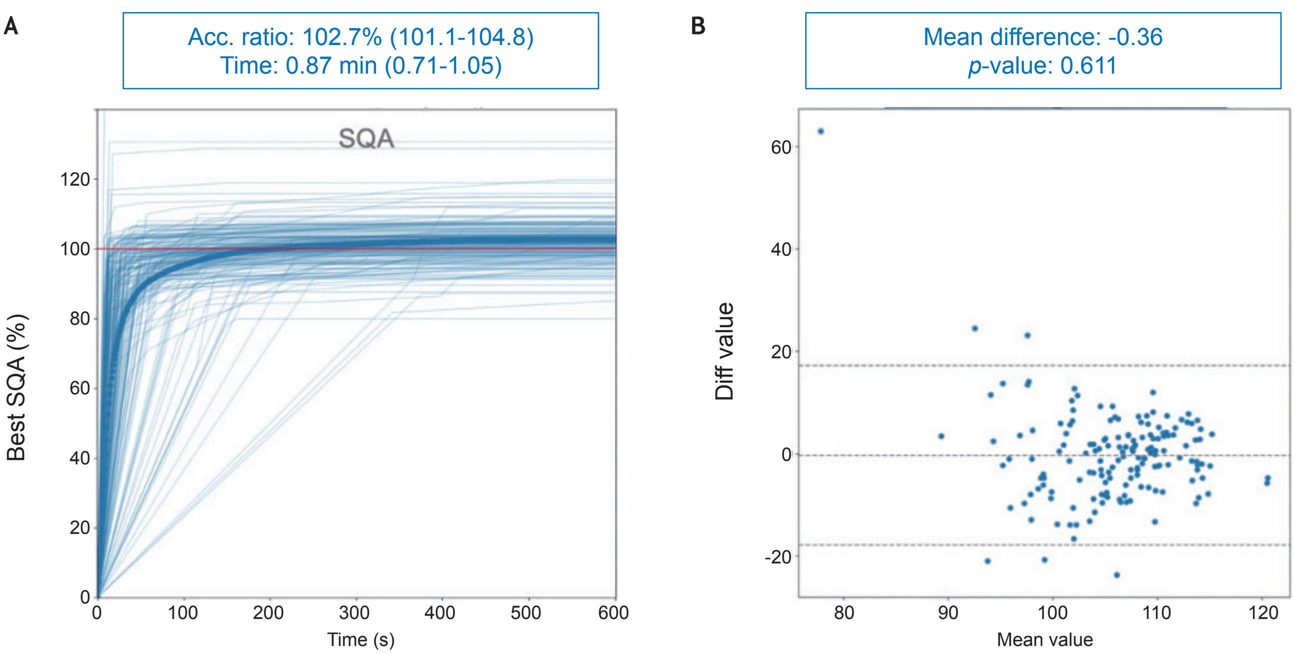

FIG. 3. Mean accuracy ratio and Bland-Altman results of NovaGuide (NovaSignal Corp, Los Angeles, CA, USA) vs. expert for signal quality of middle cerebral artery insonation. SQA; signal quality assessment.

TABLE 1. NovaGuide (NovaSignal Corp, Los Angeles, CA, USA) per formance metrics and comparison to RVT

Metric	Value	Confidence
MAR_{mCBFV}	99.7%	95% CI, 97.7-101.7
MAR_{SQA}	102.7%	95% CI, 101.1-104.8
MDmCBFV	-0.43 cm/s	*p*=0.521
MDSQA	-0.36	*p*=0.611
No-window failure rate	3.5% (4.1% RVT)	N/A

RVT; registered vascular technologist, MAR; mean accuracy ratio, mCBFV; mean cerebral blood flow velocity, MD; mean-difference, SQA; signal quality assessment, CI; confidence interval.

Furthermore, the values collected also were within the normal range of MCA mCBFV values observed in previously-published studies of TCD metrics.[19-21] The results of this study demonstrate that the NovaGuide autonomous ultrasound system is comparable to expert sonographer in acquisition of bilateral data including mCBFV and signal quality in bilateral MCA.

The findings of this work align well with previous investigations of variability in TCD measurements between expert sonographers. Inter-rater agreement of mCBFV measurements between two human operators has been studied previously, with varying levels of agreement depending on the level of training and experience.[10,11,22] For example, a comparison of mCBFV measurements between an expert and untrained sonographer revealed a large and significant difference in these values (-26.0±27.4 cm/s, $p<0.001$).[10] Also noted by Bhuiyan et al. was a significant difference in sensitivity of TCD measurements by trained operators (100%) compared to untrained operators (40%).[10] These findings further underscore the importance of precise TCD exam execution. Despite developments in the automation of TCD operation, inter-rater variability is an obstacle that will persist while human involvement is required. In a comparison of mCBFV measurements between an expert sonographer (ES, defined as subjective TCD expert that may/may not be licensed RVT) and semi-autonomous TCD device (required manual manipulation of probes), the Bland-Altman mean difference was significant (-12.3±19.5 cm/s, $p=0.004$).[12] Even the manipulation and orientation of the transducers requires some knowledge of TCD and cerebrovascular anatomy and therefore presents an obstacle for accessibility of TCD in the clinical setting. The results of this fully automated NovaGuide rTCD study as compared to other studies is summarized in Table 2.

In addition to work on the utility of automated TCD acquisition, there has been recent work focused on novel morphological analysis of the TCD waveform ranging from ischemic stroke to traumatic brain injury.[5,23-26] These methods use objective features of the TCD waveform to create powerful and consistent metrics that are clinically useful. Conversely, although the presentation of an automated method of TCD examination makes this technology more valid and useful for the non-expert, it fails to fully address the operator dependency issue associated with TCD by continuing to require operator interaction during the exam.[12] To the best of our knowledge, this is the first work describing fully-automated search, acquisition, and assessment of healthy control TCD signals, and its comparability to human ES.

The clinical implications of utilization of NovaGuide are highlighted by the recently published results in which this technology is compared with an ES for the indication of vasospasm after SAH.[14] This case study found that the MCA mCBFV insonated by NovaGuide were comparable to those measured via an expert; in the evaluation of a patient with angiographically-confirmed vasospasm (concordance correlation coefficient, 0.83; 95% CI, 0.42-0.96; $p=0.001$).[13] This work is an important compliment to this study, showing equivalence in a pathological population.

Limitations of this study include a sample population with limited variability in demographics, which may be partially responsible for the low rate of temporal win-

Table 2. Comparison of this study's results, with previously-published relevant works

Published results	Reference (no window rate)	Experimental (no window rate)	mCBFV Bland-Altman mean-difference±standard
rTCD vs. RVT	ES (4.1%)	rTCD (3.5%)	-0.4±8.4 cm/s ($p=0.53$)
Venturelli et al.[22] (2017)	ES (2.0%)	ES (2.0%)	2.0±9.0 cm/s ($p>0.05$)
McMahon et al.[11] (2007)	ES (3.7%)	ES (3.7%)	1.8±11.3 cm/s (N/A)
McMahon et al.[11] (2007)	ES (3.7%)	Inexperienced sonographer (6.5%)	-5.6±20.5 cm/s (N/A)
Bhuiyan et al.[10] (2012)	ES (N/A)	Untrained sonographer (N/A)	-26.0±27.4 cm/s ($p<0.001$)
Han et al.[12] (2015)	ES (8.7%)	Presto 1000 (17.4%)	-12.3±19.5 cm/s ($p=0.004$)

mCBFV; mean cerebral blood flow velocity, rTCD; NovaGuide Intelligent Ultrasound System, RVT; registered vascular technologist, ES; expert sonographer (may/may not be RVT), Presto 1000; semiautonomous TCD device.

dow absence in our study. Since the data collected and analyzed was only for the MCA, more work is needed to evaluate the applicability of these findings to other cerebral vessels.

In conclusion, the findings of this study show that metrics collected using a fully-autonomous ultrasound system are within normative ranges expected of inter-operator TCD mCBFV variance and therefore comparable to an ES for evaluation of the MCA. More work is needed to evaluate the consistency of these results when applied to other vessels. The NovaGuide Intelligent Ultrasound presents a user-independent method of TCD evaluation of the MCA which produces highly accurate and reliable results.

Ethics Statement

This study was approved by the Advarra Institutional Review Board (CIRBI: CR00246755). Subjects were recruited voluntarily and informed of the relevant details and risks associated with their participation. Informed consent was received from all subjects prior to their participation in a study scan.

Availability of Data and Material

Data can be made available upon reasonable request.

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Sources of Funding

None.

Conflicts of Interest

At the time of this study, all authors were employees of NovaSignal Corporation, and hold either stock or stock options in the company.

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