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Carotid Stenoses Assessed with a 4D Semi-Automated Doppler System

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Abstract

Objective: To compare peak systolic velocities (PSVs) and degree of stenoses obtained with a real-time three-dimensional (i.e., 4D) Doppler ultrasound (US) scanner (the Encore PV; Vuesonix Sensors, Wayne, PA) to conventional Doppler US of the carotids (common=CCA; internal=ICA; external=ECA). Also to assess Encore volume flow measurements.

Methods: Seventy subjects, referred for clinical carotid US, participated in this pilot study. PSVs of the CCA, ECA and ICA were obtained bilaterally. The degree of stenosis in the ICA was calculated based on the ICA PSV and the ICA/CCA PSV ratio. The Encore detects all 3D blood flow velocity vectors within 10s longitudinal volumes of the ICA, ECA and CCA. On the Encore, a reader determined the center line of the vessels. PSV and volume flow were then automatically calculated. The flow measurement error was obtained by comparing the CCA flow to the ICA and ECA flow. Data were compared using linear regression, intraclass correlation coefficients (*icc*) and Bland-Altman analysis.

Results: Due to technical difficulties only 59 subjects (323 vessel segments) were available for analysis. There was good agreement between methods for assessing the degree of stenosis based on the ICA PSV (*icc*=0.83; *p*<0.0001) and, to a lesser degree, on the ICA/CCA PSV ratio (*icc*=0.65; *p*<0.0001). PSV measurements obtained with US and the Encore correlated in all vessels (*r*≥0.32; *p*<0.002) and the Bland-Altman analysis showed reasonable variations. Encore mean volume flow error was $-4.1 \pm 66.4\%$ and was not biased (*p*=0.57).

Conclusion: A new semi-automated 4D Doppler device is comparable to conventional Doppler US for assessment of carotid stenoses.

Keywords

Carotid disease; real-time 3D Doppler imaging; 4D color Doppler; volume flow measurements

Introduction

Non-invasive, Doppler ultrasound (US) imaging is the most common imaging examination performed world-wide for the diagnosis of carotid stenosis.¹⁻³ Hemodynamics and blood volume flow can also be studied utilizing different US techniques,³⁻¹² which could potentially expand the role of US imaging in monitoring response to endovascular treatment. However,

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achieving consistent peak velocity measurements with spectral Doppler US across different scanning platforms and laboratories can be difficult^{1, 13-14} and this is undoubtedly one reason why volume flow estimation using conventional Doppler US has been shown to be highly variable.^{4, 15} Other, potentially more accurate, US methods for measuring volume flow impose assumptions of a circular vessel with an axisymmetric velocity distribution.⁵⁻¹² This assumption can be removed through the use of a real time, three-dimensional (3D) US imaging system (also referred to as a 4D US system).¹⁶⁻¹⁸

The Encore PV system (Vuesonix Sensors, Wayne, PA) is one such 4D US scanner that can detect all the blood flow velocity vectors (in cm/s) within a volume and from those can calculate blood volume flow (in ml/min). An initial validation study was conducted comparing volume flow measurements obtained with the Encore scanner (*in vitro* and *in vivo*) to those from an invasive transit-time flowmeter.¹⁸ Based on the encouraging results from the animal studies, we hypothesized that accurate 4D Doppler measurements could be performed in the carotid arteries of humans and that such measurements would enable the diagnosis of carotid stenoses. Thus, the purpose of our study was to prospectively compare 4D Doppler measurements of stenoses in the internal carotid artery (ICA) using the Encore scanner to those obtained with clinical Doppler US. A secondary goal was to validate the reproducibility of performing volume flow measurements with the Encore system in the human, carotid circulation.

Materials and Methods

The study was approved by the Thomas Jefferson University's Institutional Review Board and was compliant with the Health Insurance Portability and Accountability Act. All subjects who met the inclusion criteria over the study period and who were willing to participate gave written informed consent prior to enrollment in the study. While this pilot study was sponsored by the NIH, the Encore scanner was provided by VueSonix Sensors, Inc. The authors of this article (except ADS and DH as employees of VueSonix Sensors) had sole control of the data generated by this trial and the information provided for publication.

Subjects

Seventy subjects were enrolled in this prospective study over a 6 months period. The subjects were over 21 years of age and scheduled for a clinically indicated carotid US evaluation. There were no other inclusion or exclusion criteria for this study. The mean age was 67 years with a range from 31 to 85 years. Demographic characteristics were recorded (i.e., gender and age).

Clinical Examinations

As part of their clinical care, all patients underwent a standard bilateral carotid US examination in the accredited Vascular Laboratory of Thomas Jefferson University. One of seven certified sonographers performed the examination using one of four high-end commercial US scanners. Image parameters such as gain, pulse repetition frequency and filter settings were adjusted for each individual patient to optimize flow detection in accordance with clinical practice. The common carotid artery (CCA), ICA and external carotid artery (ECA) were interrogated at 3 different sites using pulsed Doppler and the peak-systolic and end-diastolic velocities (PSV and EDV, respectively) were measured. In each vessel, the highest PSV and EDV (out of 3 measurements) were recorded as the final results of the examination.

4D Doppler Studies

Following the clinical US examination, the subjects underwent a 4D Doppler examination performed by one of two experienced sonographers (DAM & KJL blinded to the clinical Doppler study) using the Encore scanner. This system employs a 2D matrix array transducer with 1008 elements over an 8 cm² footprint (operating at 6 MHz center frequency) to acquire

Doppler data within a volume. The unit does not use elevation or lateral beam steering, but rather relies on the disperse location of the receive beams (by emitting a broad transmit beam with 16:1 parallel receive beamforming) and one pixel beam steering (which is not significant enough to effect the Doppler measurements) to provide information on Doppler velocity and flow directivity. Volumes of Doppler information are encoded in color and displayed in 3 windows: a real time 3D color display at frame rates up to 25 volumes/s, 24 long axis 2D real time sagittal images across the entire volume, and a three paned view of the sagittal, coronal and axial planes (Fig 1). One side of the 3D volume is color coded blue to denote the location of the transmit beam. Further technical details on the Encore scanner can be found elsewhere. 18-20

Image parameters such as gain, pulse repetition frequency (PRF) and filter settings were adjusted for each individual patient to optimize flow visualization. An initial dual-mode acquisition (color flow and rudimentary grayscale US) was performed to facilitate manual gain adjustment. High gain settings were used to obtain Doppler signals close to the vessel walls, while the PRF was kept as low as possible without introducing aliasing. Bilateral 10 s data volumes of the CCA, ICA and ECA, respectively, were acquired followed by a second acquisition of the ICA to allow the reproducibility of volume flow and PSV measurements to be assessed (i.e., a total of 8 volumes were acquired per subject).

Data Assessments

Evaluation of the 10 s 4D volumes were performed off-line by an independent observer (FF) blinded to the clinical US findings. For each volume a region of interest (depicted as a red box) was manually positioned on both the 3D display and the sagittal, coronal and axial panes to mark the sub-volume that was used for analysis. In order to minimize variability due to hemodynamic effects, straight vessel regions (away from any stenosis) were chosen for analysis, while more tortuous regions were avoided. Vessels were displayed with a superimposed center line (i.e., green dots) through the inside of the vessel (cf., Fig 1). This was calculated automatically based on a center-of-mass calculation with a spline interpolation algorithm based on the detection of peak flow velocity in the volume of color and using all the Doppler voxels within the volume. The position of the center line was modified by the operator (i.e., semi-automated processing) by setting the vessel's appearance to different amounts of transparency and adjusting the spline parameters for constructing the center line based on the 3D, sagittal, coronal, and axial images until the position of the line was deemed acceptable by the operator (on average this procedure took 30 s to complete).

Next, the 3D vector velocity was obtained, as the radial velocity (measured at every voxel) multiplied by the ratio of the length of a segment of the centerline to the length of that segment's component along the line of sight from the transducer (i.e., the radial velocity measurement was compensated for the Doppler angle). This resulted in the true 3D velocity at every point in space and time and the PSV was recorded. Finally, the mean volume flow was calculated (in ml/min over a 3 s segment) from the entire volume by multiplying the 3D velocity of each voxel with the cross sectional vessel area. This area was calculated as the vessel cross sectional area in a plane parallel to the probe surface multiplied by the cosine of the angle that the centerline subtended with the probe normal. It should be noted that results from this algorithm will be directly influenced by processing parameters such as gain, PRF and wall filter settings.

The error in the flow measurements (E_{VF}) was calculated in percent as:

$$E_{VF} = \frac{VF_{CCA} - (VF_{ICA} + VF_{ECA})}{VF_{CCA}} \times 100 \quad (1)$$

assuming that all the volume flow (denoted VF) in the CCA was distributed between the ICA and the ECA. To avoid any bias, the operator calculated the flow in the CCA and one of the two ICA data sets in one session and the flow in the ECA and the other ICA data set in another session. The sessions were spaced at least 3 weeks apart. Moreover, two observers (ADS and DAM) graded all Encore volumes for data quality in consensus using a scale from 1 to 5 (poor, fairly poor, analyzable, fairly good, and good) based on the presence or absence of aliasing, image noise and data drop-out as well as the ability to visualize all three carotid vessels clearly. The highest scored data set was used for analysis, when more than one acquisition had been made (except for the reproducibility assessments). Data volumes graded 1 or 2 were excluded from the analysis.

The degree of stenosis in the ICA (denoted Ψ) was assessed with both US techniques on a four-point scale: 1) $\Psi < 50\%$, 2) $50\% < \Psi < 69\%$, 3) $70\% < \Psi < 99\%$, and 4) $\Psi = 100\%$. For the clinical US assessments this scale is based on standard ICA velocity criteria¹ where PSV < 125 cm/s indicates $\Psi < 50\%$, PSV > 125 cm/s and EDV < 100 cm/s equals a stenosis between 50 and 69%, while PSV > 125 cm/s and EDV > 100 cm/s indicates $70\% < \Psi < 99\%$. Only subjects with no flow in their ICA were categorized as occlusive (i.e., a score of 4). For the Encore system the degree of stenosis was calculated automatically as the ratio between the smallest and the largest area of flow within the ICA. Finally, the degree of stenosis was also assessed based on the ICA/CCA PSV ratio (R_{psv}) employing a three-point scale: 1) $0 < R_{psv} < 2$, 2) $2 < R_{psv} < 4$, and 3) $R_{psv} > 4$ or $R_{psv} = 0$, which has been reported to be equivalent to $\Psi < 50\%$, $50\% < \Psi < 69\%$ and $70\% < \Psi$, respectively.¹

Statistical Analysis

Since this was a pilot study, no statistical power analysis could be performed *a priori*. The error and reproducibility (in percent) of the Encore volume flow and PSV measurements were assessed using a two-way student's t-test and by calculating the intraclass correlation coefficient (*icc*).^{21, 22} The analyses were conducted using Stata 8.0 (Stata Corporation, College Station, TX) and considering *p*-values less than 0.05 to indicate significance. The degree of stenosis in the ICA calculated using the Encore and the clinical US scanners (based on the ICA PSV as well as the ICA/CCA PSV ratio) were compared using the *icc*. The comparison was conducted per vessel as well as per patient (to ensure statistical independence). In the latter case, the vessel with the highest degree of stenosis in each subject (as determined by the clinical US examination) was selected for analysis.

For each carotid vessel the Encore PSV measurements were compared to the subjects' age and to clinical US results using linear regression analysis. However, in the latter case the Encore and the clinical US scanners measure the same parameter in the same vessel. Hence, statistical independence cannot be assumed and the additional analysis of agreement suggested by Bland and Altman²³ was therefore carried out. In brief it consists of plotting the difference between corresponding Encore PV and US velocity measurements as a function of their mean values.

Results

Patient Characteristics

A total of 132 patients were screened for enrollment over a 6 month period, out of which 62 refused to participate. The 70 subjects enrolled in this study included 42 men and 28 women. The men were on average older than the women (69 ± 10 years vs. 64 ± 14 years; $p = 0.049$).

US Findings

Due to technical difficulties with the Encore scanner (mainly some initial data transfer problems) only data from 59 subjects were available for analysis. Among these 59 subjects,

data from 7 vessel segments (i.e., data volumes) were not acquired (due to either anatomical inaccessibility or time constraints on behalf of the subject being studied) leaving 465 vessel segments (59 subjects $\times$ 8 volumes/subject – 7 volumes). There were 53 volumes, graded as 1 or 2 in the consensus reads, which were excluded from further assessments, resulting in a total of 412 vessel segments being available in this study. Finally, 89 volumes were repeat ICA acquisitions (obtained for the reproducibility analysis) leaving 4D data from 323 different vessels for analysis.

Comparison of Imaging Modalities

There were 109 ICAs where corresponding measurements were acquired with the 4D Encore scanner and the clinical US systems. In 95 out of the 109 vessels (i.e., 87.2 %) the two US techniques were in agreement on the degree of stenosis present (Table 1) indicating good concurrence between the standard 2D and the new 4D US technique ($icc = 0.83$; $p < 0.0001$). Only in 2 subjects did the disagreement reach two scores (from 1 to 3 and from 3 to 1). Similar results were obtained when the data was analyzed on a per subject basis (Table 2). Among the 55 subjects with matching measurements, there was good agreement between the two US techniques in 78.2 % of cases (43 out of 55 subjects) corresponding to an icc of 0.82 ($p < 0.0001$).

When the ICA/CCA PSV ratio was employed to determine the degree of stenosis, there was agreement between the measurements of the 4D Encore scanner and the clinical US scanners in 92 out of 104 vessels (88.5 %; Table 3). However, even though the concurrence between the two US techniques was still good, the actual value of the icc declined to 0.65 ($p < 0.0001$). This was due to 3 vessels in which the Encore scanner assigned a score of 1 and the clinical US examination produced a score of 3 (using a scale from 1 to 3 to diagnose the degree of stenosis). The icc obtained based on the ICA PSV was significantly higher than the one obtained based on the PSV ratio (0.83 vs. 0.65; $p = 0.0085$).

The linear regression analysis (Table 4) showed that the PSV measured with the 4D Encore system and with standard clinical spectral Doppler correlated significantly, but not strongly, in all 3 carotid vessels ($r \geq 0.32$; $p < 0.002$). Not surprisingly, the larger the vessel being investigated the better the agreement between the two techniques with the best results being obtained in the CCA (Fig 2a; although it should be noted that if the outlier in the data is eliminated the r^2 value for the CCA will drop from 0.53 to 0.32). The agreement between the two techniques was further elucidated with the Bland-Altman analysis (Table 5; Fig 2b) and it was found to be somewhat reasonable with mean differences of 10 to 25 cm/s and 2 standard deviations ranging from 76 to 109 cm/s.

Assessment of the 4D US Measurements

There were 88 complete 4D data sets acquired with the Encore scanner (i.e., where volume flow measurements were available from all 3 carotid vessels). The mean volume flow error calculated was -4.1 ± 66.4 % (Fig 3). The volume flow error was not significantly biased (i.e., the absolute errors were not significantly different from zero; $p = 0.57$). Likewise, when pairwise comparisons of the 83 corresponding pairs of volume flow and pairs of PSV measurements (acquired in the ICA) were performed, differences of 2.7 ± 52.5 % and 0.8 ± 32.6 % for volume flow and for PSV pairs, respectively, were obtained. These differences resulted in icc -values of 0.67 and 0.64 for volume flow and PSV measurements indicating reasonably good reproducibility for the Encore scanner ($p < 0.0001$). Finally, the volume flow in the CCA and ICA (but not in the ECA) was found to decrease significantly with age ($r \geq 0.32$; $p < 0.03$).

Discussion

In this pilot study, 59 subjects with 323 carotid vessel segments were evaluated with the 4D Encore system and with standard, clinical 2D US. The two US techniques were in good agreement on the degree of stenosis present in the ICA when the data was analyzed on a per vessel basis based on ICA PSV and EDV measurements ($icc = 0.83$; $p < 0.0001$) and, to a lesser degree, based on the ICA/CCA PSV ratio ($icc = 0.65$). Similar results were obtained when the data was analyzed based on ICA PSV and EDV values on a per subject basis ($icc = 0.82$; $p < 0.0001$). Moreover, there was reasonably good reproducibility for the Encore ICA PSV measurements ($icc \geq 0.64$). These results indicate that 4D imaging with the Encore is comparable to standard, clinical Doppler US for assessing the carotid circulation (albeit based on a somewhat limited number of subjects).

The volume flow measured with the Encore scanner was not significantly biased and the mean volume flow error (the difference between the flow in the CCA and the combined flow in the ICA and ECA) was low ($-4.1 \pm 66.4\%$). Likewise, when corresponding pairs of ICA volume flow measurements were compared a mean difference of $2.7 \pm 52.5\%$ was obtained. This difference corresponded to an icc of 0.67 ($p < 0.0001$), which demonstrates reasonably good reproducibility of the Encore volume flow measurements. Very similar results were obtained for the PSV measurements (a smaller mean difference of $0.8 \pm 32.6\%$ but a slightly lower icc of 0.64).

Given the well-known variability of volume flow estimation using conventional Doppler US, 4, 15 time-domain correlation combined with a color M-mode technique⁵⁻⁸ as well as a new dual-beam, angle-independent Doppler device⁹⁻¹² have been suggested as alternatives. While both methods (somewhat unrealistically) assume a circular symmetric velocity distribution, initial patient studies (involving 10 – 71 subjects) have been encouraging and have demonstrated the complex hemodynamic effects of carotid disease.^{7-8, 11-12} Studies of healthy volunteers to determine normal values on volume flow in the CCA and ICA have involved more subjects (205 and 77, respectively) and have shown an age-related decrease in flow. These results were confirmed by the findings of this study.

The assumption of circular symmetric blood velocities can be removed through the use of a 2D array transducer (such as in the Encore scanner), which enables the 3D velocity field within a vessel to be calculated. Results from another scanner with a 2D array found excellent correlation ($r \geq 0.92$) between US and MRI for assessing flow through the mitral valve in children.²⁴ This is also in agreement with our results in animals comparing Encore volume flow measurements to transit time flowmetry ($r = 0.93$).¹⁸ In the current study, no independent reference standard was employed, but the degree of stenosis present in the ICA determined by the Encore scanner and by clinical US systems (based on PSV measurements) were in good agreement ($icc > 0.82$; $p < 0.0001$). These results indicate that the 4D Encore scanner is comparable to the current imaging mode of choice for assessment of carotid stenoses, conventional Doppler US.

It is important to note the limitations of our study. A relatively small number of subjects participated in this initial trial of 4D carotid US imaging (in particular too few subjects with a high grade stenosis were assessed), which limits the statistical power of the study and, therefore, the clinical conclusions which can be made. Too many different sonographers and US scanners (7 and 5, respectively) were used in the clinical evaluations introducing additional variability into the data; although this also reflects the reality of clinical practice in a busy vascular laboratory. There was no independent reference standard employed in this study making it impossible to assess if the standard deviations obtained in the Bland-Altman analysis (Table 5) are due to the Encore or the clinical scanners. Moreover, the lack of state-of-the-art grayscale

US on the Encore scanner made it difficult to optimize flow imaging parameters (such as wall filter settings, PRF and overall gain) to avoid issues like partial volume averaging. Although great care was taken to produce good flow images within the linear vessel regions chosen for analysis (and problematic volumes were eliminated in the consensus reads), the processing strategy of the Encore scanner will introduce uncertainty into correctly determining the Doppler velocity and vessel area needed when obtaining volume flow data. Finally, the current engineering prototype Encore system suffered from some initial data transfer problems (which reduced the number of subjects available for analysis to 59). We expect that the final commercial version of the Encore scanner will overcome these stability problems.

Thus, in this pilot study the use of 4D US imaging has been investigated for *in vivo* carotid imaging and appears to be comparable to conventional, clinical 2D US for the diagnosis of carotid disease. The new semi-automated 4D Doppler device studied here also provides access to reproducible volume flow measurements. However, these results were obtained in a limited number of subjects and further studies are, therefore, required to substantiate this investigation in a larger patient population.

Acknowledgments

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Figure 1.
Example of 4D flow image of the ICA obtained with the Encore PV. The blue box (2.5×3.2 cm) denotes the location of the transmit beam, while the red box sets the volume for analysis. The green dots within the vessel mark the center line.

Figure 2.

PSV in the CCA measured with the Encore system and with clinical US (a) along with the best linear fit (solid line) and line of identity (dashed line) as well as the corresponding Bland-Altman plot (b) showing mean $\pm$ 2 standard deviations as solid and dashed lines, respectively.

Figure 3.
The mean Encore volume flow obtained in the CCA versus the sum of the volume flow measured in the corresponding ICA and ECA along with the line of identity (dashed line).

Table 1
The degree of stenosis in the ICA calculated with the Encore PV and with clinical US based on the ICA PSV and EDV (i.e., on a 1-4 scale).

	Score	Encore PV			
		1	2	3	4
Clinical US	1	84	4	1	0
	2	7	4	0	0
	3	1	1	0	0
	4	0	0	0	7

Table 2
The degree of stenosis in the ICA calculated on a per subject basis based on the ICA PSV and EDV.

		<u>Encore PV</u>			
Score		1	2	3	4
Clinical US	1	33	3	1	0
	2	6	3	0	0
	3	1	1	0	0
	4	0	0	0	7

Table 3

The degree of stenosis in the ICA calculated with the Encore PV and clinical US based on the ICA/CCA PSV ratio (i.e., on a 1-3 scale).

		<u>Encore PV</u>		
	Score	1	2	3
Clinical US	1	86	2	0
	2	6	0	0
	3	3	1	6

Table 4

Linear regression analyses between the Encore PV and the clinical US measurements for each vessel.

vessel	r-value	p-value
CCA	0.53	<0.0001
ICA	0.53	<0.0001
ECA	0.32	0.0012

Table 5

Bland-Altman analysis of the Encore PV and clinical US measurements showing the mean of the differences ± 2 standard deviations (SD) per vessel.

vessel	Mean velocity [cm/s]	± 2 SD [cm/s]
CCA	-11.5	75.75
ICA	-25.7	108.98
ECA	-18.4	98.12