Computer-assisted detection of tardus parvus waveforms on Doppler ultrasound

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Abstract

Objective: To determine if a novel computer-generated metric, effective acceleration time, improves accuracy for detecting tardus parvus waveforms on spectral Doppler ultrasound.

Methods: Patients with echocardiography-confirmed aortic valve stenosis ($n = 132$; 60 mild, 44 moderate, 28 severe) and matched controls ($n = 48$) who underwent carotid Doppler ultrasound were identified through an imaging database search at a single medical center. A custom-built spectral analysis computer program generated effective acceleration time values for spectral Doppler waveforms in the carotid arteries and a receiver operating characteristic analysis was performed to determine the optimal median effective acceleration time cutoff value to detect tardus parvus waveforms. Two radiologists, blinded to subject disease status, reviewed and rated all carotid sonograms for presence of tardus parvus waveforms. Inter-rater variability was measured, and the accuracy of aortic valve stenosis detection with and without use of the effective acceleration time cutoff was calculated.

Results: Receiver operating characteristic analysis revealed an optimal effective acceleration time cutoff of ≥ 48 ms with a corresponding area under the curve of 0.77 (95% CI: 0.70–0.84). Use of the effAT cutoff demonstrated an accuracy of 74%. Accuracy of visual waveform interpretation by raters ranged from 43% to 61%. Inter-rater agreement in detection of tardus parvus waveforms was 76% (136/180 cases, $K = 0.44$, $p < 0.001$).

Conclusions: Detection of tardus parvus waveforms through visual interpretation of spectral Doppler waveform morphology is limited by low accuracy and moderate inter-rater variability. Use of a computer-generated median effective acceleration time cutoff value markedly improves diagnostic accuracy and avoids observer variability.

Keywords

Computer-aided diagnosis, tardus parvus waveform, spectral analysis, aortic stenosis

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Introduction

Doppler ultrasound is often the imaging modality of choice for evaluating vascular pathologies throughout the body, including carotid and renal artery stenoses, post-transplantation stenoses in the hepatic and renal arteries, peripheral vascular disease, and cerebral vasospasm induced by subarachnoid hemorrhage. In view of the growing utility and frequency of the use of ultrasound in vascular medicine, technologies that increase its diagnostic accuracy and reduce reader variability

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have the potential to improve the evaluation of a wide range of diseases.

The tardus parvus (TP) waveform is a sonographic sign frequently observed in spectral Doppler of arteries distal to a stenosis or reconstituted arteries distal to an occlusion.¹ TP waveforms are characterized by a delayed or slow rising (“tardus”) systolic upstroke and a diminished (“parvus”) systolic amplitude creating a rounded systolic peak.² Stenosis severity directly correlates with the degree of observed TP waveform changes,^{3–5} although trans-stenotic pressure gradient and post-stenotic vessel wall compliance also have some influence.^{6,7}

In recent years there has been renewed interest in the development of measures to better analyze and quantify TP changes.^{8–10} Technical limitations of measures conventionally used in clinical practice, including qualitative assessment, peak systolic velocity, resistive index, pulsatility index, acceleration index and acceleration time are well known, and listed in Table 1. Our group developed a novel computer-generated metric for spectral Doppler waveform analysis called effective acceleration time (effAT) in an effort to more effectively capture and quantify TP waveform changes. The purpose of this study was to investigate the use of effAT for detecting tardus parvus waveforms by using carotid Doppler ultrasound of patients with aortic valve stenosis as an *in vivo* model. We hypothesized that use of an effAT cutoff value would have superior accuracy for detecting aortic valve stenosis compared with both qualitative Doppler waveform assessment and conventional Doppler metrics.

Methods

Subject recruitment and screening

Institutional Review Board approval was obtained and the requirement for informed consent was waived for this retrospective case-control study. An exam code search of our medical center’s diagnostic imaging database was performed to identify all patients at our institution who underwent carotid ultrasound and echocardiography between 1 July 2000 and 1 July 2010. Patients who underwent both studies were subsequently identified by cross-matching patient medical record numbers. This cross-matched list was then filtered by exam date to identify only those patients who underwent both studies within a 90-day time period. For patients with multiple studies within 90 days, paired exams with the smallest number of interval days were preferentially selected for subsequent analysis. The most recent pair of studies was selected for patients with multiple pairs of qualifying exams.

Table 1. Technical limitations of measures used to assess tardus parvus waveforms

Measure	Limitations
Qualitative waveform assessment	Inter-observer variation Dependent upon observer expertise
Peak systolic velocity (PSV)	Must measure near stenosis Multiple peaks may cause inaccurate measurement Dependent upon angle of insonation Intra- and inter-vessel variation Inter-observer variation in measurement Varies with cardiac function
Resistive index (RI)	Inter-wave and inter-vessel variation Varies with patient age, etiology of stenosis, peripheral vascular resistance, and end diastolic velocity
Pulsatility index (PI)	Varies with patient age, etiology of stenosis, and peripheral vascular resistance
Acceleration index (AI)	Difficult to measure Influenced by variations in waveform morphology Inter-observer variation in measurement Dependent upon flow regimen and angle of insonation
Acceleration time (AT)	Inter-observer variation in measurement Varies with cardiac function

A keyword search of our medical center’s echocardiography report database was then performed to identify all patients diagnosed with aortic stenosis as well as those without valvular heart disease during the study time period. These patients were subsequently cross-matched by medical record number with the list of patients who underwent both studies within 90 days to yield a final list of potential subjects.

Imaging reports and electronic medical records for all potential subjects were then screened for the presence of exclusion criteria (Table 2). 132 aortic stenosis patients met all study criteria. Qualifying controls were matched to cases by sex and age (≤ 10 year difference) until all cases had been matched, for a total of 48 controls. A flow chart of subject recruitment and screening is provided in Figure 1.

Table 2. Subject exclusion criteria

Patient age ≤ 18 years
Missing imaging, limited imaging (incomplete study), or poor image quality
Carotid ultrasound not performed on a Philips IU22 or HDI 5000 machine ^a
$\geq 50\%$ stenosis of any carotid artery
Tortuous carotid arteries
Significant aortic regurgitation ($>$ mild)
Presence of a prosthetic cardiac valve
Evidence of left ventricular outflow tract obstruction
Presence of a ventricular septal defect
Presence of an intra-aortic balloon pump or atrioventricular assist device
Evidence of aortic dissection

^aImages from other machines were incompatible with the custom built spectral analysis software.

Data collection

Data of interest were extracted from carotid ultrasound and echocardiogram reports for all subjects. In instances where data were absent, patient charts were reviewed for alternative sources of information (such as provider notes) from the same exam date. Missing echocardiographic data were retrieved via review of archived images. All information was entered into data management software (Microsoft Excel for Mac 2008; Microsoft, Redmond, WA, USA) prior to statistical analysis.

Stenosis grade classification

Echocardiographic data were reviewed to classify cases into three grades of stenosis (mild, moderate, or severe), which we modified from published guidelines as follows: the 2008 published guidelines¹¹ provide three indicators (peak aortic jet velocity, mean pressure gradient across the aortic valve, and aortic valve cross-sectional area) by which aortic stenosis may be classified. To minimize the possibility of an outlying value for one indicator causing an erroneous grade

Figure 1. Flow chart of subject recruitment and screening.

ACC/AHA: American College of Cardiology/American Heart Association; AS: aortic stenosis.

classification, and to better take into account the overall impression of the study by the cardiologist who performed the original clinical reading, we used a best-fit approach whereby at least two indicators per subject were required to fit within a given grade range for classification into that grade. A case was classified as moderate if all three indicators fit into three separate grade ranges. A total of 60 mild, 44 moderate, and 32 severe cases of aortic stenosis were identified (Figure 1).

Review of carotid ultrasounds

All carotid sonograms were performed in accordance with published practice guidelines¹² using HDI 5000 or IU22 ultrasound machines (Philips Healthcare, Bothell, WA, USA). Spectral Doppler images for each subject were downloaded from our institution's Picture Archiving and Communication System directly onto a Health Insurance Portability and Accountability Act-compliant computer hard drive. Each complete study included images from fourteen artery sites: the right and left proximal common carotid artery (CCA), distal CCA, proximal internal carotid artery (ICA), mid ICA, distal ICA, external carotid artery and vertebral arteries. All images were cleared of personally identifiable information using a custom-built image anonymization program created with MATLAB (Version 2010b SP1, The MathWorks, Inc., Natick, MA, USA). Completely anonymized studies containing all fourteen images per subject were then assigned numeric codes and randomized prior to radiologist evaluation.

Next, two attending radiologists (26 and 6 years of post-residency experience) evaluated all images for the presence or absence of TP waveforms. Waveform changes were characterized in accordance with previous studies^{2,13,14} and rater expertise. Normal waveforms were defined as having a brisk systolic upstroke with a uniform slope and a sharp systolic peak. TP waveforms were defined as having a delayed systolic upstroke, a diminished systolic peak, and a rounded systolic contour. During evaluation, each image was assigned a score from 0 to 3 based on the severity of the waveform changes. Scores of 0 (clearly normal) and 1 (equivocal or mild waveform changes) were classified as normal while scores of 2 (moderate waveform changes) and 3 (severe waveform changes) were classified as TP. Each rater also assigned an overall impression for each complete study using the same scale. Prior to image evaluation, each radiologist reviewed a series of 10 test studies unrelated to the subject population that included controls and all grades of aortic stenosis. These test studies were first evaluated independently and then in consensus conference to facilitate

standardization of waveform interpretation. Once a consensus on test case scores was established, the radiologists were blinded to each other and to the disease status of all subjects and evaluated all study images using randomly sorted subject lists.

Spectral analysis

Effective acceleration time (effAT) was defined as the time elapsed in milliseconds from the end diastolic velocity (EDV) to the peak systolic velocity (PSV) assuming a constant upslope of the velocity curve as measured from 30% to 70% of the systolic upstroke (Figure 2a and 2b). Similar to acceleration time, effAT uses the time-based criterion of delayed systolic upstroke ("tardus"), and is independent of the angle of insonation and varies minimally with changes in peripheral vascular resistance.^{15,16} We used the 30% to

Figure 2. (a) 65 year old woman with severe aortic valve stenosis on echocardiography. Spectral Doppler ultrasound of the right proximal internal carotid artery shows tardus parvus waveforms. (b) Effective acceleration time (effAT) measurement. effAT is defined as the time elapsed in milliseconds from the end-diastolic velocity to the peak systolic velocity points assuming a constant slope of the velocity curve as measured from 30% to 70% of the systolic upstroke. A computer program generates effAT values from spectral Doppler waveforms for each systolic upstroke and uses the median measurements of the different waves on the image.

70% segment of the systolic upstroke, as this avoids the subjectivity introduced when the observer (or computer) has to identify the early systolic peak. Unlike conventional metrics that require technician input, computerized analysis avoids error introduced by manual measurements,^{10,17} and also samples all available waves in an image to minimize errors due to inter-wave variability.^{18,19}

effATs for all spectral Doppler images were generated retrospectively using a custom-built spectral analysis program created with MATLAB (Version 2010b SP1, The MathWorks, Inc., Natick, MA, USA). This custom-built program uses edge-detection and scale optical character recognition technologies to convert a spectral Doppler tracing to velocity values. Once velocities are generated for a given tracing, the program detects EDV and PSV for each sequential spectral wave cycle. The slope of the velocity curve from 30% to 70% of the systolic upstroke (in cm/s^2) is then computed for each systolic upstroke. Finally, the effAT for each systolic upstroke is calculated. The effAT generated by the spectral analysis software is the median effAT across all spectral Doppler waves in a given tracing. The effAT for each of the fourteen artery sites per subject, as well as the median effAT across all available artery sites for each subject, were recorded. For subjects where the software program was able to analyze images from some but not all artery sites, the median effective AT is the median of only the analyzed artery sites.

The resistive index (RI) for each artery site was also calculated from values generated by the spectral analysis program. RIs were computed according to the formula $(\text{PSV}-\text{EDV})/\text{PSV}$, where PSV represents the median peak systolic velocity and EDV represents the median end diastolic velocity of a given spectral Doppler tracing. The median RI across all artery sites for each subject was also recorded.

In instances where the spectral analysis software failed to generate values for a given image, the missing values were excluded from statistical analysis.

Statistical analysis

All statistical analyses were performed using version 3.3.0 of the statistical programming language R (The R Foundation, Vienna, Austria), the epiDisplay package for interobserver variability assessment, and the pROC package for receiver operating characteristic analysis. Unpaired *t*-tests were used to compare anthropometric and physiologic characteristics between cases and controls. A one-way analysis of variance (ANOVA) test of equality of means was used to analyze inter-group differences between different diagnostic classes (control, mild, moderate, and severe aortic stenosis) for key characteristics (age, body mass index, and

ejection fraction). Pearson's Chi-squared test for independence was used to test inter-group differences in sex across diagnosis classes.

To measure the accuracy of TP waveform identification for detecting aortic stenosis, raters were evaluated individually using sensitivity, specificity, and accuracy. These parameters were calculated across all stenosis grades, as well as for separate stenosis grades (mild, moderate, and severe). Inter-observer variability was measured by comparing the observed and expected agreement between raters for both individual images and overall impressions. The inter-rater agreement statistic, kappa, and its standard error and *p*-value were calculated for these comparisons.

Unpaired *t*-tests were used to compare carotid artery Doppler ultrasound parameters between cases and controls. A logistic regression analysis was then performed to identify anthropometric and Doppler ultrasound features that best predict the presence of aortic stenosis. Stenosis classification (stenosis or control) was used as the gold standard. Regression coefficient estimates, *z*-values, odds ratios, 95% confidence intervals, and *p*-values were calculated for each variable. Numeric parameters were normalized to have a mean of zero and standard deviation of 1 to facilitate comparison between regression coefficient estimates. Stepwise logistic regression analysis was then performed to select the most parsimonious model and to exclude covariates with little explanatory power.

Receiver operating characteristic (ROC) analysis was then performed to determine the diagnostic accuracy of the measure found to be most predictive of aortic stenosis from the regression analysis (median effAT). The area under the ROC curve (AUC) was calculated and 95% confidence intervals were computed using bootstrap resampling. The optimal cutoff value, defined as the point on the curve closest to the point (sensitivity=1, 1-specificity=0), was calculated to determine the optimal median effAT cutoff to detect aortic stenosis. The sensitivity, specificity, and accuracy of this cutoff value were then calculated across all stenosis grades as well as for separate stenosis grades (mild, moderate, and severe) for comparison to both raters.

Statistically significant findings were defined as those with a *p*-value less than 0.05. Results are reported as mean $\pm$ standard deviation or estimate $\pm$ standard error unless otherwise noted.

Results

Subject characteristics are reported in Table 3. Cases included 69 males (52%) and 63 females (48%). The control group included 24 males (50%) and 24 females (50%). There were no significant differences between cases and controls in regards to age, body mass index,

Table 3. Subject characteristics

Characteristic	Aortic stenosis (<i>n</i> = 132)	Control (<i>n</i> = 48)	<i>p</i> -Value
Age (years)	75.3 ± 12.6	74.4 ± 12.9	0.68
Sex (%)			
Female	48	50	
Male	52	50	
Body mass index (kg/m ²)	28.2 ± 6.6	29.8 ± 8.9	0.28
Body surface area (m ²)	1.9 ± 0.2	1.9 ± 0.3	0.15
Indexed left ventricular end diastolic diameter (cm/m ²)	2.5 ± 0.4	2.3 ± 0.4	0.06
Average left ventricular wall thickness (cm)	1.1 ± 0.2	1.0 ± 0.2	<0.001
Indexed aortic root diameter (cm/m ²)	1.7 ± 0.3	1.7 ± 0.3	0.72
Ejection fraction (%)	58.3 ± 11.8	61.0 ± 7.7	0.14

Values containing ± reported as mean ± standard deviation.

body surface area, indexed left ventricular end diastolic diameter, indexed aortic root diameter, or ejection fraction. A significant difference between cases and controls was detected for average left ventricular wall thickness (1.1 vs. 1.0 cm, $p < 0.001$).

ANOVA test for equality of means did not find significant differences between diagnostic classes in regards to age ($F = 1.22$, $df_1 = 3$, $df_2 = 85.1$, $p = 0.31$), body mass index ($F = 0.83$, $df_1 = 3$, $df_2 = 78.6$, $p = 0.48$), or ejection fraction ($F = 1.19$, $df_1 = 3$, $df_2 = 82.3$, $p = 0.32$). Pearson's chi-squared test for independence of sex between diagnostic classes was not significant ($\chi^2 = 0.61$, $df = 3$, $p = 0.89$).

When single images were considered, inter-rater agreement in the detection of TP waveforms was 77% (1893/2450 cases, $\kappa = 0.43 \pm 0.02$, $p < 0.001$). When overall impressions for all 14 images per subject were compared between raters, inter-rater agreement was 76% (136/180 cases, $\kappa = 0.44 \pm 0.06$, $p < 0.001$).

The software was able to analyze 2212 of 2520 (88%) images. In two of 180 (1%) patients (one each with moderate and severe stenosis), the software was unable to analyze all the images of the patients and, therefore, could not return a median effective AT value for that patient. These two patients were excluded from the analysis comparing the blinded readers and the computer aided diagnosis software.

When carotid artery Doppler ultrasound parameters were analyzed, significant differences were detected between cases and controls only for PSV in the left and right common carotid arteries ($p = 0.004$ and 0.002 , respectively), and effAT in the

left proximal common carotid artery ($p = 0.002$), right proximal internal carotid artery ($p = 0.02$), and the median value across all artery sites ($p < 0.0001$). A summary of the analysis of all carotid artery Doppler ultrasound parameters is provided in Table 4.

Logistic regression analysis of anthropometric and Doppler ultrasound factors (Table 5) demonstrated that only median effAT across all artery sites was significantly related to the presence of proximal aortic stenosis (OR = 10.17, 95% CI = 3.35–30.85, $p < 0.0001$). Subsequent stepwise logistic regression analysis included PSV in the left proximal common carotid artery, RI in the left proximal common carotid artery, effAT in the left proximal common carotid artery, and median effAT across all artery sites in the most parsimonious model. Only PSV in the left proximal common carotid artery (OR = 0.48, 95% CI = 0.29–0.74, $p = 0.002$) and median effAT across all artery sites (OR = 10.15, 95% CI = 3.85–32.00, $p < 0.0001$) were statistically significant predictors in the model obtained by stepwise logistic regression.

ROC analysis of median effAT for detecting aortic stenosis demonstrated an area under the curve of 0.77 (95% CI = 0.70–0.84). The optimal cutoff was calculated to be 48 ms (Figure 3). The sensitivity, specificity, and accuracy of an effAT cutoff of ≥ 48 ms to detect any grade of aortic stenosis was 72%, 81%, and 74%, respectively. In comparison, the ranges of sensitivity, specificity, and accuracy of radiologist detection of aortic stenosis through TP waveform identification by overall impression were 23–50%, 90–96%, and 43–61%, respectively.

Table 4. Carotid artery Doppler ultrasound parameters

Parameter (by site)	Aortic stenosis (<i>n</i> = 132)	Control (<i>n</i> = 48)	<i>p</i> -Value
Peak systolic velocity (cm/s)			
Common carotid artery, proximal			
Left	79 ± 21	89 ± 21	0.004
Right	75 ± 20	87 ± 28	0.002
Internal carotid artery, proximal			
Left	67 ± 24	68 ± 18	0.75
Right	65 ± 26	63 ± 23	0.65
Median value across all sites	71 ± 15	76 ± 16	0.06
Resistive index			
Common carotid artery, proximal			
Left	0.84 ± 0.09	0.84 ± 0.06	0.63
Right	0.85 ± 0.08	0.86 ± 0.06	0.29
Internal carotid artery, proximal			
Left	0.78 ± 0.11	0.79 ± 0.09	0.38
Right	0.77 ± 0.11	0.76 ± 0.09	0.54
Median value across all sites	0.82 ± 0.08	0.82 ± 0.05	0.63
Effective acceleration time (ms)			
Common carotid artery, proximal			
Left	56 ± 33	44 ± 16	0.002
Right	157 ± 973	64 ± 169	0.31
Internal carotid artery, proximal			
Left	149 ± 187	397 ± 1894	0.40
Right	219 ± 592	88 ± 92	0.02
Median value across all sites	66 ± 32	45 ± 16	<0.0001

Values containing ± reported as mean ± standard deviation.

Comparisons between diagnostic parameters for all stenosis grades are reported in Table 6.

Discussion

We investigated the use of a novel computer-generated metric, effAT for the detection of tardus parvus

waveforms in spectral Doppler of carotid arteries in patients with aortic valve stenosis. We found that use of a median effAT cutoff of ≥ 48 ms (computer-assisted detection) has superior accuracy compared with qualitative waveform assessment for the detection of any grade of aortic stenosis on carotid Doppler ultrasound. When different grades of stenosis were considered

Table 5. Multivariate logistic regression analysis to determine factors that predict aortic stenosis ($n = 148$)

Factor	Estimate	Z-value	OR	95% CI	p-Value
Age (years)	-0.30 ± 0.29	-1.04	0.74	0.42–1.31	0.30
Male sex	-0.08 ± 0.49	-0.16	0.92	0.35–2.43	0.87
Body mass index (kg/m^2)	-0.21 ± 0.23	-0.88	0.81	0.51–1.29	0.38
Peak systolic velocity (m/s)					
Common carotid artery, left proximal	-0.57 ± 0.38	-1.51	0.56	0.27–1.18	0.13
Common carotid artery, right proximal	-0.36 ± 0.30	-1.18	0.70	0.38–1.27	0.24
Median value across all sites	0.01 ± 0.33	0.04	1.01	0.53–1.93	0.97
Resistive index					
Common carotid artery, left proximal	0.68 ± 0.44	1.55	1.97	0.84–4.63	0.12
Common carotid artery, right proximal	0.16 ± 0.36	0.44	1.17	0.58–2.35	0.66
Median value across all sites	-0.25 ± 0.43	-0.59	0.78	0.34–1.79	0.55
Effective acceleration time (ms)					
Common carotid artery, left proximal	-0.61 ± 0.36	-1.71	0.54	0.27–1.09	0.09
Common carotid artery, right proximal	0.09 ± 0.37	0.23	1.09	0.52–2.27	0.82
Median value across all sites	2.32 ± 0.57	4.10	10.17	3.35–30.85	<0.0001

Estimates reported as estimate $\pm$ standard error. Only cases with complete values across all factors were included in the regression. CI: confidence interval (for odds ratio); OR: odds ratio.

alone, computer-assisted detection was superior in accuracy to qualitative waveform assessment for mild and moderate stenosis and equivalent in accuracy to qualitative waveform assessment in cases of severe stenosis. Both qualitative waveform assessment and computer-assisted detection demonstrated improved sensitivity, specificity, and accuracy as stenosis severity increased.

Previous studies comparing the performance of qualitative waveform analysis with quantitative measures have demonstrated inconsistent results,^{13,14,20–22} which may be attributed in part to technical variations in how quantitative parameters are measured,^{16,21,23} the classification schemes used to define and interpret qualitative waveform changes,^{13,14} the degree of stenosis used for disease determination, as well as the sample size and unique population under investigation.²² In clinical practice, the use of quantitative measures like PSV, RI, AI, and AT are preferred due to the significant inter-observer variability inherent in qualitative waveform assessment.^{13,23} However, the most commonly used manufacturer implementation requires

technician input to measure these parameters,¹⁰ which introduces manual error. Our study provides additional evidence that visual assessment of TP waveforms has a low accuracy and a high inter-observer variability, negating its use as a stand-alone diagnostic test. Furthermore, multivariate analysis demonstrated that median effAT is superior to conventionally used Doppler parameters (PSV and RI) in the detection of proximal stenosis. Regardless of their comparative accuracies, a computer-generated measure that incorporates whole-waveform analysis may have an advantage over operator-dependent metrics by insuring greater reliability of measurement.

To our knowledge, this is the largest study to date of aortic stenosis-related TP changes and the first to use age and sex-matched controls for comparison.^{3,24,25} When Doppler parameters were analyzed, small but significant differences between cases and controls (10–15 cm/s) were observed only in the PSVs of the left and right proximal common carotid arteries. Similar findings were reported in previous studies,^{3,24} although the mean PSVs observed in this study were

Figure 3. Receiver operating characteristic curve for median effAT in determining mild, moderate, severe and all grades of proximal stenosis ($n=178$). The area under the curve (AUC) and its 95% confidence interval (in parentheses) is displayed. The optimal cutoff value is labeled and marked with a red diamond. Green diamonds represent the sensitivity and specificity of raters A and B. A dashed reference line representing an AUC of 0.50 is provided. Note that the AUC is higher with an increasing grade of aortic stenosis severity.

between 20 and 40 cm/s higher than in other reports. It is unclear why PSV measurements were higher in this study. Difference in sample sizes as well as variation in image acquisition, measurement technique, measurement location, or in the imaging equipment used may have played a role. Nonetheless, a 10–15 cm/s difference in PSV is within manual measurement error and unlikely to be of clinical significance. PSV was not found to be predictive of aortic stenosis during multivariate regression analysis and PSV in the left proximal common carotid artery made only a minor (but statistically significant) contribution to the most parsimonious predictive model. Thus, the impact of aortic stenosis on PSVs in the carotid arteries is minor, and small reductions in values are observed only in the most proximal vessels.

RI measurements at all artery sites, as well as the median value across all sites, were not significantly different between cases and controls. Since previous studies do not seem to have reported RI measurements in the carotid arteries of patients with aortic stenosis, no

comparisons to other studies can be made. It is unclear as to why no differences were observed. One possible explanation is that because of the relatively advanced age of all subjects, age-related loss of arterial compliance and atherosclerosis may have obscured any difference in RIs caused by aortic stenosis.^{16,26} Coexisting aortic regurgitation in some of the patients may have further eliminated RI differences between groups,²⁷ although all cases with greater than mild aortic regurgitation were excluded. Finally, RI may simply be a poor measure of stenosis-related TP changes in proximal, medium-sized vessels like the extra-cranial carotid arteries.

effAT values at single artery sites generally exhibited wide ranges in means and large standard deviations. It is possible that because the spectral analysis software used for effAT measurements relies on edge detection, Doppler images with insufficiently darkened backgrounds may have caused erroneous measurements. Additionally, patients with arrhythmias were not

Table 6. Diagnostic parameters by stenosis grade

		Rater A	Rater B	Computer assisted ^a
Mild stenosis (<i>n</i> = 60)	Sensitivity	8	32	53
	Specificity ^b	96	90	81
	Accuracy	47	57	66
Moderate stenosis (<i>n</i> = 43) ^c	Sensitivity	28	58	84
	Specificity ^b	96	90	81
	Accuracy	64	75	82
Severe stenosis (<i>n</i> = 27) ^c	Sensitivity	48	78	93
	Specificity ^b	96	90	81
	Accuracy	79	85	85
Any stenosis (<i>n</i> = 130) ^c	Sensitivity	23	50	72
	Specificity ^b	96	90	81
	Accuracy	43	61	74

All values reported as percentages (%).

^aAs determined by a median effAT (effAT) of ≥ 48 ms.

^bSpecificity remains constant through all grades of stenosis because the total number of controls (i.e. the true negatives plus false positives) for comparison is the same at all stenosis grades.

^cThe computer-aided diagnosis program was unable to analyze the images of one patient each with moderate and severe stenosis, so these values are excluded from the comparative analysis.

excluded from the study, which may have also contributed to waveform variability and measurement noise. The median effAT across all artery sites was calculated to help eliminate such noise and to obtain an aggregate measure that included all post-stenosis artery sites. Median effAT values thus generally exhibited much smaller standard deviations across patients compared to effATs at individual artery sites.

ROC analysis of median effAT indicated fair to good accuracy across all stenosis grades. In comparison, studies of renal and hepatic artery stenoses have generally reported higher accuracies and larger areas under the curve for Doppler measures like AT and AI.^{9,14,15,28–30} However, it is important to note that in these other studies, positive cases are considered to have at least 50–60% stenosis. Inclusion of more mild degrees of stenosis, such as in the present study, would have likely decreased the reported predictive accuracy of these Doppler measures. Unfortunately, AT and AI measurements could not be included in the analysis for comparison because they could not be measured once images were removed from the ultrasound unit. The

spectral analysis program could not be programmed to detect these parameters due to waveform heterogeneity that obscured automated identification of the early systolic peak.⁹

This study has several limitations in addition to those already discussed. The retrospective design precluded control over image acquisition. However, all images were acquired by experienced vascular technologists who followed a standardized imaging protocol in an accredited medical facility. Carotid arteries are also relatively easy to image with ultrasound and, thus, image acquisition is less subject to technical error.⁶ As with all chart reviews, information extracted from imaging reports was dependent on completeness and accuracy of reporting; missing data restricted sample sizes during some statistical analyses. During image analysis by the radiologists, differences in the ultrasound machines used, as well as the unique settings employed to acquire each image, may have influenced visual waveform interpretation. However, variation in equipment and image settings is routine in clinical practice and a more restrictive design would have limited

generalizability of our results. Since patients with tortuous carotid arteries, hemodynamically significant carotid stenoses, moderate or severe aortic regurgitation, or various pathologies of the heart and aorta were excluded from the study, our results apply only to individuals with isolated aortic stenosis and normal carotid arteries. However, such exclusions were necessary to eliminate confounding factors that can influence spectral Doppler waveforms in the carotid circulation. We used a “best-fit approach” partly based on the 2008 American Heart Association/American College of Cardiology criteria¹¹ for grading aortic stenosis, whereby at least two of three indicators (mean pressure gradient, peak velocity, and aortic valve area) per subject were required to fit within a given grade range for classification into that grade. In 2017, the European Association of Cardiovascular Imaging and the American Society of Echocardiography published a focused update³¹ emphasizing the aortic valve area, given that it is independent of ventricular load, unlike mean pressure gradient and peak velocity. However, considering that (a) the echocardiograms were acquired between 2000 and 2010 for this retrospective study, (b) clinical cardiologists at that time measured all three parameters, and only “saved” the measurements that most closely correlated to their overall impression of the aortic valve on the echocardiogram, and (c) the available echocardiography literature at the time of image acquisition did not emphasize aortic valve area over the other parameters, we felt that a “best-fit approach” would be more appropriate. Finally, our software program was unable to return a value for effective AT in 308 of 2520 (12%) images and median effective AT in 2 of 180 (1%) patients.

Computer-assisted technologies that employ automated quantitative measures in the assessment of spectral Doppler waveforms can avoid measurement variability while improving diagnostic accuracy. The image processing steps performed by our software program on the saved ultrasound images such as edge detection are quite standard. Therefore, effective AT computation could be implemented in any medical image software viewing program. In our research software implementation of waveform detection and effective AT computation, it took less than a second to calculate effective AT per image on a regular laptop computer.

To be sure, the detection of tardus parvus waveforms on carotid Doppler ultrasound is not a substitute for an echocardiogram in grading aortic stenosis. Instead, tardus parvus waveforms are known to occur distal to a significant stenosis in a wide range of arterial territories, including renal artery stenosis and transplant-related arterial stenosis, and therefore, computer aided computation of effective AT may be useful in a

wide range of organ systems. Prospective validation studies comparing effective AT and other spectral Doppler parameters in the carotid artery as well as other organ systems may be warranted.

Declaration of Conflicting Interests

The author(s) declared following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: LMS is an Educational Consultant for Philips Healthcare, unrelated to this work. The remaining author(s) declared no other potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics approval

Approval was obtained from the Human Investigation Committee of Yale University, protocol number 1106008656. Waiver for informed consent was granted for this retrospective study.

Guarantor

GG

Contributors

GG, JDM, and LMS researched literature and conceived the study. GG, JDM, ES, RLM, and LMS collected the data and performed image analysis. JDM and FWC performed the statistical analysis of data. JDM wrote the first draft of the manuscript. JDM and GG wrote the final version of the manuscript. All authors reviewed and approved the final version of the manuscript.

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