Diagnostic Performance of Duplex Ultrasound in Patients Suspected of Carotid Artery Disease
The Ipsilateral Versus Contralateral Artery

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Background and Purpose—To evaluate duplex ultrasonographic thresholds for the determination of 70% to 99% stenosis of the ipsilateral and contralateral internal carotid artery in patients with symptoms of amaurosis fugax, transient ischemic attack (TIA), or minor stroke based on 2 criteria: maximizing accuracy and optimizing cost-effectiveness and to compare these with current recommendations.

Methods—From January 1997 to January 2000, a prospective multicenter study was conducted including 350 consecutive patients with symptoms of amaurosis fugax, TIA, or minor stroke who underwent bilateral duplex ultrasonography and digital subtraction angiography. A linear regression analysis was performed to estimate the degree of angiographic stenosis as a function of the peak systolic velocity (PSV). PSV thresholds were calculated for the ipsilateral and contralateral carotid arteries based on maximizing accuracy and optimizing cost-effectiveness.

Results—The PSV measurements significantly overestimated the angiographic stenosis in the contralateral artery (9.5%; 95% CI, 6.3% to 12.7%) compared with the ipsilateral carotid artery. The recommended PSV threshold for the diagnosis of 70% to 99% stenosis is 230 cm/s. Maximizing accuracy, the optimal PSV threshold for the ipsilateral artery was 280 cm/s, and for the contralateral artery, 370 cm/s for diagnosing a 70% to 99% stenosis. Optimizing cost-effectiveness, the optimal PSV threshold was 220 cm/s for ipsilateral and 290 cm/s for contralateral carotid arteries.

Conclusions—PSV measurements overestimate the degree of angiographic stenosis in the contralateral carotid artery in patients with symptoms of amaurosis fugax, TIA, or minor stroke. Separate PSV thresholds should be used for the ipsilateral and contralateral carotid artery. PSV thresholds that optimize cost-effectiveness differ from the recommended thresholds and from thresholds that maximize accuracy. (Stroke. 2005;36:2105-2109.)

Key Words: carotid arteries • carotid stenosis • ultrasonography

Duplex ultrasonography is currently the principal noninvasive test for evaluating carotid artery disease. Screening for this disease in symptomatic patients has become particularly important since publication of the results from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST).1-4 These large randomized trials demonstrated that carotid endarterectomy is beneficial in symptomatic patients with severe stenosis (70% to 99%) and in subgroups of patients with moderate stenosis (50% to 69%).

The reference standard for detection of significant carotid artery stenosis is digital subtraction angiography (DSA). Because of the risks and costs associated with this invasive procedure, there is a trend toward relying more on noninvasive imaging techniques. Duplex ultrasonography (DUS) is often used as initial test. Since the publication of the NASCET and ECST results, many studies aimed at determining optimal ultrasonographic criteria for identifying angiographic carotid artery stenosis. However, different optimal threshold values of the peak systolic velocity (PSV) have been reported, for example, 175, 200, and 230 cm/s for diagnosing a 70% to 99% stenosis.5-7 Based on a literature review, a recent consensus study recommended the use of 230 cm/s as the optimal PSV threshold.8 However, potential differences between thresholds for the ipsilateral and contralateral side in symptomatic patients were not evaluated. Furthermore, various criteria were used in the reviewed studies to determine the optimal threshold. Most studies maximized diagnostic accuracy. However, the consequences of a false-negative test are probably more harmful and more expensive than the consequences of a false-positive test or vice versa. Therefore, it is more clinically relevant to use

Received February 22, 2005; final revision received June 21, 2005; accepted July 12, 2005.

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Stroke is available at http://www.strokeaha.org

DOI: 10.1161/01.STR.0000181753.40455.07

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clinical outcome and costs as criteria for the determination of the optimal threshold to identify a significant stenosis. In a previous study, we calculated the optimal PSV threshold based on a cost-effectiveness analysis for the ipsilateral carotid artery.9

The aim of this study was to evaluate potential differences in duplex ultrasonographic thresholds between the ipsilateral and contralateral internal carotid artery for the determination of 70% to 99% stenosis in patients with symptoms of amaurosis fugax, transient ischemic attack (TIA), or minor stroke based on 2 criteria: maximizing accuracy and optimizing cost-effectiveness and to compare these thresholds with current recommendations.

Materials and Methods

Study Population

A prospective study was performed in 2 academic hospitals and 1 nonacademic hospital from January 1997 to January 2000.10 After giving informed consent, patients with symptoms of amaurosis fugax, TIA, or minor stroke in the previous 6 months underwent bilateral carotid DUS and carotid DSA within a time frame of 4 weeks. Patients were enrolled in the University Medical Center Utrecht, Erasmus University Medical Center Rotterdam, and Medical Spectrum Twente. The medical ethical committee approved the study for each hospital.

Carotid DUS

The PSV was measured bilaterally in the proximal part of the internal carotid artery using an ATL machine (Ultramark 9 HDI or HDI 3000) in 89% of the patients and a Diasonics Master in the rest. PSV measurements were performed by qualified vascular technologists in the vascular laboratory of each hospital. The Doppler angle was kept at <60 degrees. A carotid artery was recorded as ipsilateral if its perfusion territory was associated with the symptoms of amaurosis fugax, TIA, or minor stroke. If no detectable flow was present, arteries were classified as occluded (100% stenosis). Slow flow (<150 cm/s) in combination with a visualized severe stenosis was defined as a near occlusion. Arteries with an (near) occlusion on DUS were excluded because the PSV is absent or not reliably measurable in these arteries. The hospital in which the patient was tested was recorded because the results of DUS may depend on the equipment used, local imaging protocols, and the image-processing software used.

Digital Subtraction Angiography

DSA was performed by selective positioning of an intra-arterial catheter sequentially in each common carotid artery. Each carotid bifurcation was imaged in 3 projections (lateral, posteroanterior, and oblique).

The DSA results were read by 1 observer in each hospital. Observers were blinded for clinical information and for the duplex results. Printed hard copies were used to read the DSA images. The percentage stenosis was determined according to the NASCET criteria.1 The degree of stenosis was defined as the percentage reduction in lumen diameter comparing the narrowest diameter of the residual lumen at the site of the stenosis with the normal lumen distal to the stenosis. The maximum degree of stenosis on the 3 projections was used in the analysis. DSA was considered the standard of reference.

Linear Regression Analysis

The absolute PSV values obtained with DUS were compared with the percentage stenosis measured with DSA, the reference standard, using linear regression analysis. Because the relationship between the absolute PSV and the percentage angiographic stenosis was nonlinear, the PSV was transformed to its natural logarithm (ln). Three linear models were assessed. First, the degree of angiographic stenosis was modeled as a function of the ln(PSV). In the second model, a dummy variable was added to evaluate potential differences between the ipsilateral and contralateral artery.

In the formula angiographic stenosis = β₀ + β₁ ln(PSV) + β₂ S, the angiographic degree of stenosis is the dependent variable, β₀ is the intercept, β₁ and β₂ are regression coefficients, ln(PSV) is the ln of the PSV, and S is the dummy variable that takes value 1 for ipsilateral and 0 for contralateral arteries.

In the third model, variables were added to adjust for potential confounders such as hospital, age, and sex. Variables were kept in the model if the model performance improved significantly, which was assessed by testing the change in R² (F test) and if the regression coefficient of the added variable had a significance level of P<0.05.

To study the effect of the association between the ipsilateral and contralateral PSV measurements within patients, we also analyzed our data using a repeated-measurements analysis.

Receiver Operating Characteristic Analysis

Receiver operating characteristic (ROC) analysis was performed to calculate sensitivities and specificities associated with each observed PSV result using DSA as the reference standard. Separate ROC curves were drawn for the ipsilateral and contralateral arteries. The statistical package SPSS 11.0 was used for all calculations.

PSV Thresholds

The recommended PSV threshold of 230 cm/s for diagnosing a 70% to 99% stenosis was applied to our data.8 We calculated the associated sensitivity, specificity, and accuracy for the ipsilateral and contralateral carotid arteries separately.

We subsequently calculated our own PSV thresholds using 2 approaches: maximizing overall accuracy and optimizing outcome in terms of cost-effectiveness. The first approach assumes that a false-positive test is equally important as a false-negative test. In the second approach, we used outcomes from a previous study in which we calculated the optimal threshold PSV based on the prevalence of disease, the consequences of false-positive results relative to true-negative results, and the consequences of false-negative results relative to true-positive results in terms of costs and quality-adjusted life years saved.9 The consequences of the test results were based on a cost-effectiveness analysis that modeled lifetime outcome as a result of diagnostic testing and subsequent treatment of the ipsilateral carotid artery in patients with amaurosis fugax, TIA, or minor stroke.11 Our previous analysis resulted in an optimal threshold PSV of 220 cm/s for diagnosing a 70% to 99% stenosis for ipsilateral arteries.8 In the current study, we calculated the optimal threshold PSV for contralateral arteries by first substituting the optimal PSV of 220 cm/s in the formula above. We assumed that the angiographic thresholds for ipsilateral and contralateral arteries were equivalent. Subsequently, we derived the optimal PSV threshold for the contralateral arteries by rearranging the formula: Threshold PSV_{contralateral artery} = \exp((\text{Angiographic stenosis} \cdot \beta_0)/\beta_1).

The sensitivities, specificities, and accuracy associated with the threshold PSV value were derived from the ROC analysis. The outcomes were compared with the recommended threshold PSV.

Results

Study Population

In the prospective study, 350 patients were included (mean age 67 years [range 39 to 88]; 76% male; 24% female).10 The carotid arteries could be imaged in 323 patients with DSA and in 330 with DUS. Both tests were available for 621 arteries.

DUS identified 99 occlusions. The sensitivity and specificity of diagnosing an occlusion by DUS were 95% and 99%, respectively. Near occlusions were found in 18 arteries. The analysis was performed on all arteries without (near) occlusions on DUS (n=504). Angiographic stenosis of 0% to 49%
was found in 44 ipsilateral and 195 contralateral arteries, 50% to 69% stenosis in 60 ipsilateral and 35 contralateral arteries, 70% to 99% in 131 ipsilateral and 38 contralateral arteries, and 100% stenosis in 1 ipsilateral artery. Bilateral angiographic severe stenosis (>70%) was found in 25 patients, including 8 patients with ipsilateral occlusions.

Linear Regression Analysis

Figure 1 demonstrates the nonlinear distribution of the angiographic stenosis as a function of the PSV. The ln of the PSV showed a good linear relationship with angiographic stenosis ($R^2=0.76$). In the second model, the angiographic stenosis was significantly more severe in the ipsilateral than the contralateral artery for a given PSV (regression coefficient $[r]=0.095$; 95% CI, 0.063 to 0.127). In other words, the PSV was significantly higher in contralateral arteries than in ipsilateral arteries for a given degree of angiographic stenosis (Figure 2). In the third model, the variables hospital ($r=0.093$; 95% CI, 0.049 to 0.137), age ($r=0.0015$; 95% CI, 0.000 to 0.003), and sex ($r=0.031$; 95% CI, 0.001 to 0.061) significantly influenced the degree of angiographic stenosis. However, the difference between ipsilateral and contralateral arteries remained the same ($r=0.091$; 95% CI, 0.060 to 0.122). The intraindividual association between the ipsilateral and contralateral PSV measurements was negligible ($r=0.12$). Therefore, we used model 2 to determine the optimal PSV thresholds for ipsilateral and contralateral arteries.

ROC Analysis

In Figure 3, the ROC curves are presented for the ipsilateral and contralateral arteries. Figure 3 demonstrates that the area under the ROC curves is larger for the contralateral arteries, indicating a higher diagnostic performance of DUS in contralateral than in ipsilateral arteries. This is a result of the large error range in PSV measurements in high-grade stenosis, which is primarily found in the ipsilateral arteries, compared with the relatively small error range in low-grade stenosis, which is mainly found in the contralateral arteries (Figure 1).

PSV Threshold Analysis

In the Table, the results of the threshold analyses are presented. The recommended PSV threshold (230 cm/s) is highly sensitive and less specific for the ipsilateral and contralateral arteries. If accuracy is maximized, then specificity becomes more important than sensitivity in contralateral arteries. The accuracy increased with 7 percentage points using a higher threshold for contralateral arteries than for ipsilateral arteries (370 cm/s versus 280 cm/s).

Maximizing cost-effectiveness resulted in a high sensitivity in ipsilateral arteries and a high specificity in contralateral arteries. For the ipsilateral arteries, the optimal threshold was a PSV of 220 cm/s, and for the contralateral side, it was 290 cm/s.

Discussion

This study shows that the estimated angiographic stenosis in contralateral carotid arteries is overestimated if criteria are
Thresholds of the PSV and Corresponding Sensitivity, Specificity, and Accuracy for the Diagnosis of 70% to 99% Stenosis

<table>
<thead>
<tr>
<th>Threshold Definition</th>
<th>PSV Threshold, cm/s</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Accuracy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended threshold$^8$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral artery</td>
<td>230</td>
<td>95.4</td>
<td>51.4</td>
<td>75.8</td>
</tr>
<tr>
<td>Contralateral artery</td>
<td>230</td>
<td>92.1</td>
<td>86.5</td>
<td>87.3</td>
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<tr>
<td>Maximum accuracy</td>
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<tr>
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<td>280</td>
<td>84.7</td>
<td>69.5</td>
<td>78.0</td>
</tr>
<tr>
<td>Contralateral artery</td>
<td>370</td>
<td>71.1</td>
<td>97.8</td>
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<tr>
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<tr>
<td>Contralateral artery</td>
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<td>91.4</td>
<td>90.3</td>
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used based on the PSV measurements of ipsilateral arteries. For a given degree of angiographic stenosis, the PSV measurements were consistently higher in contralateral arteries than in ipsilateral arteries. As a result, we found that the optimal PSV threshold for identifying 70% to 99% angiographic stenosis in contralateral carotid arteries was higher than in ipsilateral arteries (290 cm/s versus 220 cm/s). Similar observations were made for the peak systolic frequency in arteries with contralateral severe stenosis or occlusions.$^{12,13}$

The physiological mechanism for this observation has been referred to as the compensatory flow phenomenon, which explains that flow would have to be increased in the contralateral artery to maintain the same level of blood volume to the brain as before the stenosis emerged.$^{14}$ Because this increased volume of blood must pass through a vessel with a relatively fixed cross-sectional area, the velocity of the blood must increase. The higher volume load might arise from crossover flow via collateral pathways. This phenomenon has been illustrated in studies that evaluated changes in PSV in contralateral arteries before and after carotid endarterectomy$^{14–16}$ and carotid stenting.$^{17}$

In these studies, the PSV measured in the contralateral artery significantly decreased after revascularization, which often led to reclassification of stenosis in the contralateral artery. These findings suggested that when severe bilateral carotid stenosis is found on initial duplex testing, more careful evaluation of the exact degree of stenosis in the contralateral artery is necessary.$^{14}$

Our study suggests that it is more accurate and cost-effective to use a higher PSV threshold for the diagnosis of significant stenosis in contralateral than in ipsilateral arteries in symptomatic patients. Application of separate thresholds in clinical practice will reduce the number of patients diagnosed with bilateral severe stenosis based on ultrasonography alone.

There are several limitations of our study. First, we focused on the presence or absence of symptoms of amaurosis fugax, TIA, or minor stroke in the perfusion territory of the carotid artery to define the ipsilateral artery. In the calculation of the PSV threshold on the contralateral side, we did not take into account the severity of disease or the presence of actual stenosis on the ipsilateral side. Several studies have shown that the hemodynamic effect is more pronounced if the contralateral artery is severely stenosed or occluded.$^{12,13,15}$

However, adjustment for the severity of stenosis would make the clinical application of different PSV thresholds very complex. Application of our PSV thresholds in clinical practice only requires information about the side of symptoms.

Second, we assumed that the angiographic thresholds for the ipsilateral and contralateral arteries were the same, implying that the indication for carotid endarterectomy (70% to 99% stenosis) was the same for both arteries. However, indications for staged or simultaneous bilateral carotid endarterectomy may vary. For example, bilateral symptomatic stenosis >70% or ipsilateral symptomatic stenosis >70% and a contralateral asymptomatic stenosis of 80% to 99% have been suggested as indications for bilateral endarterectomy.$^{18}$

Moreover, our threshold for the contralateral asymptomatic side should not be used for unilateral stenosis estimation in completely asymptomatic patients because these patients were not included in our study.

Third, verification bias may have influenced our results. Verification bias may exist if patients are referred to the reference test based on the results of the test under investigation. Sensitivity may be inflated and specificity deflated if selection takes place. This may have been the case in our study for the ipsilateral arteries: only patients with a clinical indication for carotid endarterectomy and a high PSV were included in the study. Indeed, we did see a high sensitivity and low specificity in the ipsilateral arteries. By including both carotid arteries of each patient in our analysis, representing the whole spectrum of arterial stenoses, we partially corrected for verification bias. We showed that sensitivity decreased and specificity increased, which is equal to the effect of mathematically correcting for verification bias based on the probability of verification.$^{19}$ However, our results may not apply for patients without a clinical indication for carotid endarterectomy because these patients were not included in this study. Moreover, to evaluate the effect of verification bias, our results should be validated in an independent patient population.

Fourth, we did not take into account other velocity parameters than the PSV value. In several studies, it was shown that the PSV in the internal carotid artery is the best single velocity parameter for quantifying a stenosis.$^{20,21}$ In clinical practice, multiple clinical parameters could be combined to account for differences in patients and to decide which patients should receive carotid endarterectomy.

Finally, several studies have shown that different laboratories should establish their own thresholds.$^{22,23}$ PSV measurements tend to differ because of differences in manufacturers or technologists. We also observed that 1 hospital measured consistently higher PSV values than the other 2 hospitals. However, when corrected for type of hospital, the difference between ipsilateral and contralateral arteries remained significant. Therefore, our results show that if labo-
ratories establish their own laboratory-specific duplex criteria, the side of carotid disease should be taken into account.

The recently published recommendations by the Society of Radiologists in Ultrasound advocate the use of a PSV threshold of 230 cm/s for diagnosing a 70% to 99% stenosis. Application of this threshold to our data resulted in a high sensitivity, a moderate specificity, and good overall diagnostic accuracy. We used 2 criteria for selecting the optimal threshold for the PSV: maximization of diagnostic accuracy and optimization of outcome in terms of cost-effectiveness. The second approach balances the clinical consequences of missed diagnoses and unnecessary endarterectomies, which is clinically more relevant than maximizing accuracy. Because the majority of contralateral arteries have a nonsignificant stenosis, a highly specific threshold is advantageous for contralateral arteries, whereas a highly sensitive threshold is desirable for ipsilateral arteries.

In conclusion, PSV measurements overestimate the degree of angiographic stenosis in the contralateral carotid artery in patients with symptoms of amaurosis fugax, TIA, or minor stroke. Therefore, separate PSV thresholds should be used for the evaluation of the ipsilateral and contralateral carotid arteries by DUS. Optimal PSV thresholds, based on cost-effectiveness criteria, for diagnosing a 70% to 99% stenosis are 220 cm/s for ipsilateral arteries and 290 cm/s for contralateral arteries.

Acknowledgments

Financial support for this study was provided by a program grant (nr. 904-66-091) from the Netherlands Organization for Scientific Research.

References

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Stroke. 2005;36:2105-2109; originally published online September 8, 2005; doi: 10.1161/01.STR.0000181753.40455.07
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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