Carotid Duplex Ultrasound Velocity Measurements Versus Intravascular Ultrasound in Detecting Carotid In-Stent Restenosis

Bryan P. Yan, MBBS; David J. Clark, MBBS; Michael R. Jaff, DO; Thomas J. Kiernan, MD; Robert M. Schainfeld, DO; Sara Lessio, MD†; Kenneth Rosenfield, MD

Background—Duplex ultrasonography criteria for assessing the severity of carotid artery (CA) in-stent restenosis are not well established.

Methods and Results—We analyzed 39 patients (40 CAs) who underwent CA stenting with baseline and 6-month follow-up carotid duplex ultrasonography and intravascular ultrasound. Intravascular ultrasound measurements included minimum luminal diameter, percent diameter, and lumen area stenosis. Duplex ultrasonography measurements included peak systolic velocity (PSV), percentage change in PSV, end-diastolic velocity (EDV), and internal-to-common CA PSV ratio (ICA/CCA). Receiver operating characteristic curves assessed each duplex measurement to detect ≥50% diameter, ≥75% lumen area stenosis, and minimum luminal diameter <3 mm at follow-up. At 6-month intravascular ultrasound follow-up, ≥50% diameter and ≥75% lumen area CA in-stent restenosis occurred in 20% and 25%, respectively; minimum luminal diameter <3 cm occurred in 48%. Area under receiver operating characteristic curves for PSV, EDV, and ICA/CCA were 0.85, 0.96, and 0.89 for ≥50% diameter stenosis and 0.89, 0.93, and 0.88 for ≥75% lumen area stenosis, respectively. Optimal PSV, EDV, and ICA/CCA criteria to detect ≥50% diameter and ≥75% lumen area CA in-stent restenosis were greater compared with those for native CA. A 98% increase in PSV had the highest specificity, whereas the combination of EDV ≥41 cm/s and ICA/CCA ≥2 had the highest sensitivity in detecting ≥75% lumen area CA in-stent restenosis.

Conclusions—PSV, EDV, and ICA/CCA PSV ratio were good discriminators for detecting significant diameter and lumen area greater compared with those for native CA. The combination of duplex velocity criteria increases diagnostic accuracy. (Circ Cardiovasc Intervent. 2009;2:00-00.)

Key Words: carotid artery stenting ■ in-stent restenosis ■ duplex ultrasonography ■ intravascular ultrasound ■ restenosis

Restenosis rates after carotid artery stenting (CAS) range from 2% to 22% as early as 1 year after stenting depending on the diagnostic testing methods and interpretation criteria.1–3 These patients require regular surveillance to monitor stent patency and to identify in-stent restenosis (ISR).

Clinical Perspective on p ●●●

Duplex ultrasonography (DUS) is the current modality used to follow-up patients with native CA stenosis and those who have undergone CEA. Peak systolic velocity (PSV), end-diastolic velocity (EDV), and the ratio between the PSV of the internal CA compared with the common CA 2 cm proximal to the flow divider (ICA/CCA) have been validated with angiographic percent stenosis in nonstented CAs.4,5 However, native artery DUS velocity criteria are thought to be less accurate in patients who have undergone CAS. Stent implantation may result in changes in the vessel wall compliance and blood flow velocities.2,3,6 Although studies have shown that stented CAs are associated with increased velocities, reliable diagnostic criteria have recently been proposed in determining the degree of hemodynamically significant ISR and require further validation.7–9

Intravascular ultrasound (IVUS) allows a detailed assessment of the carotid lumen, vessel wall, atherosclerotic plaque, stent dimensions, and expansion as well as its apposition to the vessel wall in 3 dimensions.10 We found IVUS was an invaluable tool in assessing the mechanisms of carotid stent
remodeling and restenosis. Theoretically, lumen area stenosis is a better representation of the severity of carotid restenosis than diameter, especially in stenoses with noncircular lumen. Supporting this, we have previously reported that the mean ICA stent expansion after deployment was only 75% by IVUS, and the minimum in-stent diameter was less by IVUS compared with quantitative carotid angiography (QCA).

Therefore, IVUS measurements of carotid ISR should be ideal to evaluate the accuracy of DUS.

The aim of this study is to assess the accuracy of DUS to detect CA ISR by comparing DUS velocity criteria to the percent diameter and lumen area ISR as determined by IVUS.

**Methods**

**Study Population**

We retrospectively analyzed 40 consecutive CAs in 39 patients who underwent CAS with pre-, postprocedural, and follow-up carotid DUS and IVUS. All patients underwent routine repeat carotid angiography and IVUS at 6-month follow-up. The study protocol was approved by the Institutional Review Board, and all patients provided written informed consent.

**Carotid Stent Procedure and IVUS Imaging Protocol**

CAS and IVUS were performed by one experienced operator. All patients received 325 mg of aspirin and a loading dose of either 500 mg of ticlopidine or 300 mg of clopidogrel on the day of the procedure. Dual antiplatelet therapy was continued for a minimum of 4 weeks after the procedure. Intravenous heparin was administrated to maintain the activated clotting time between 200 and 250 seconds. Intra-arterial nitroglycerine (100 to 200 μg) was administered directly into the CA before IVUS. CAS was performed in accordance with techniques previously described.11 The Wallstent (Boston Scientific Corporation, Natick, Mass) was used in most cases.

IVUS was performed using a 2.6F to 3.5F 20- to 40-MHz transducer (Boston Scientific Corporation). A motorized transducer pullback was used at a speed of 0.5 mm/s before and after stent deployment. The transducer was positioned in the nontapered distal segment of the ICA and systematically pulled back through the stented portion of the ICA and CCA and into the guiding catheter or sheath. Studies were recorded and analyzed off-line. QCA was performed at similar anatomic locations, as previously described.

Before intervention, the distal nontapered reference of the ICA, the lesion site, and the proximal reference of the CCA were studied with IVUS and QCA. After stent deployment, measurements were made within the stent, which included the minimum lumen diameter (MLD) and minimum lumen area as well as at the reference sites within the ICA and CCA and the site of the original lesion.

**IVUS Analysis**

All IVUS measurements follow current American College of Cardiology guidelines.2-12 Analysis was performed by an independent interventional cardiologist not involved in the stent procedure. At all the designated sites, MLD and minimum lumen area were measured using computer planimetry (Tape Measure Indec Systems, Palo Alto, Cali). Identification of the lesion site pre- and postprocedure and then at follow-up was achieved by measuring its distance from the origin of the external CA.

Percentage ICA stent restenosis at follow-up was defined by IVUS measurements using the North American Symptomatic Carotid Endarterectomy Trial criteria as:

1. Percent diameter stenosis = \((1 - \text{follow-up ICA MLD/reference distal ICA MLD}) \times 100\).
2. Percent lumen area stenosis = \((1 - \text{follow-up ICA minimum lumen area/reference distal ICA minimum lumen area}) \times 100\).

**Duplex Ultrasound Analysis**

Carotid DUS examination was performed (i) before, (ii) within 48 hours, and (iii) 6 months after CAS. All examinations were performed in the same vascular laboratory with the same ultrasound equipment (Sonoline Elegra, Siemens, Malvern, Pa) using high-resolution, 7.5-MHz ultrasound transducers. Image optimization was achieved with appropriate pulse repetition frequencies and Doppler angle correction. All spectral Doppler measurements of PSV, EDV, and ICA/CCA were obtained with a small sample volume and a Doppler angle of \(\leq 60^\circ\) in the center stream of flow or within the area of greatest velocity shift.

Velocity in the ICA was determined at distal, middle, and proximal portion of the stent as well as just proximal and distal to the stent. Velocity in the CCA was determined in the proximal and distal segments. The highest values for PSV, EDV, and ICA/CCA were recorded in our study in all DUS examinations. The percentage change in PSV (%ΔPSV) was derived from the difference in PSV between immediately post-CAS and follow-up measurements (%ΔPSV = (1 - [follow-up ICA PSV/baseline ICA PSV]) × 100).

Analysis was performed off-line by an independent operator not involved in the stent procedure and blinded to the results of the QCA and IVUS.

**Statistical Analysis**

Continuous variables were expressed as mean±SD, and categorical data expressed as percentages. Mean MLD measured by QCA and IVUS was compared using Student t test. The variables analyzed were PSV, EDV, and ICA/CCA PSV ratios versus carotid in-stent percent diameter and lumen area stenosis as determined by IVUS. These variables were compared with the Pearson coefficient of correlation (R) and the relative P value. An R coefficient for any velocity criteria was considered significant in cases of percent stenosis with a \(P = 0.0001\). The percentages of lumen area stenosis and their corresponding PSV, %ΔPSV, EDV, and ICA/CCA observed at DUS were grouped into 3 classes: (1) stenosis < 50%, (2) stenosis 50% to 74%, and (3) stenosis ≥ 75% using box plots and scatter plots. Receiver operating characteristic (ROC) curves were computed.
used to compare IVUS data and velocity measurements to determine the optimal velocity criteria for restenosis. Sensitivity and specificity were calculated to determine the optimal threshold for PSV, %ΔPSV, EDV, and ICA/CCA PSV ratio in determining ≥50% diameter and ≥75% lumen area stenosis. All calculated P values were 2 sided and P<0.05 was considered statistically significant. A statistical analysis was performed using SPSS version 16.0 for Windows (SPSS Inc, Chicago, Ill) and graphs using MedCalc for Windows, version 9.2.0.0 (MedCalc Software, Mariakerke, Belgium).

Results
Thirty-nine patients underwent CAS in 40 ICAs. Baseline clinical and procedural characteristics are shown in Table 1. At follow-up IVUS, in-stent lumen area stenosis ≥50% and ≥75% were detected in 30 (75%) and 10 arteries (25%) of 40 arteries, respectively (Table 2). In-stent diameter stenosis ≥50% was detected in 8 arteries (20%) using IVUS. In-stent diameter stenosis ≥75% was not detected in any artery at follow-up IVUS.

The scatter plots of PSV, %ΔPSV, EDV, and ICA/CCA PSV ratio as a function of IVUS-derived lumen area stenosis are shown in Figure 1 with R=0.65, 0.65, 0.56, and 0.69 compared with R=0.70, 0.57, 0.62, and 0.74 for diameter stenosis, respectively. Correlation between PSV, %ΔPSV, EDV, and ICA/CCA and percent stenosis by QCA were 0.60, 0.62, 0.55, and 0.56, respectively. There was no significant difference in mean MLD measured by QCA (3.01±1.05 mm) compared with IVUS (3.02±0.93 mm, P=0.75) and the correlation between IVUS and QCA MLD was high (r=0.95).

The distribution of the velocities corresponding to <50%, 50% to 74%, and ≥75% area stenosis are shown in Figure 2. Intervals for PSV, %ΔPSV, EDV, and ICA/CCA overlap significantly for stenosis <50% and 50% to 74% and therefore cannot be used reliably to distinguish between these 2 classes of stenosis severity. However, PSV, %ΔPSV, EDV, and ICA/CCA could be used to obtain potential thresholds in predicting ≥75% lumen area stenosis.

The ROC curves of PSV, %ΔPSV, EDV, and ICA/CCA for ≥50% diameter, ≥50%, and ≥75% lumen area stenosis

<table>
<thead>
<tr>
<th>Table 2. Six-Month Follow-Up IVUS and QCA</th>
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<tr>
<td>Diameter stenosis, %</td>
</tr>
<tr>
<td>≥50%</td>
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<tr>
<td>≥70%</td>
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<tr>
<td>Lumen area stenosis, %</td>
</tr>
<tr>
<td>≥50%</td>
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<tr>
<td>≥75%</td>
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</table>

Data are presented as mean±SD or n (%).

Figure 1. Scatter plot with regression line (solid line) and 95% CI (dotted line) of PSV (A), EDV (B), ICA/CCA (C), and %ΔPSV (D) as a function of percentage lumen area stenosis by IVUS. PSV stenosis, R=0.65; EDV stenosis, R=0.56; ICA/CCA, R=0.69; %ΔPSV stenosis, R=0.65; all P values <0.001.
are shown in Figure 3. All variables demonstrated excellent discriminating capacity for \( \geq 50\% \) diameter and \( \geq 75\% \) lumen area stenosis (Table 3). A comparison of ROC curves did not show any significant differences between each criterion for various degrees of diameter or lumen area stenosis.

Optimal PSV, \( \% \Delta \text{PSV} \), EDV, and ICA/CCA values to detect diameter stenosis \( \geq 50\% \) and lumen area stenosis \( \geq 75\% \) are shown in Table 4. Used independently in detecting \( \geq 75\% \) lumen area stenosis, a PSV \( > 197 \text{ cm/s} \) yielded a sensitivity of 75\% and a specificity of 93\%; a \( > 98\% \) increase in PSV had a low sensitivity of 50\% but a high specificity of 100\%; an EDV \( > 41 \text{ cm/s} \) had a sensitivity of 100\% and a specificity of 71.9\%; and an ICA/CCA \( > 2 \) had a sensitivity of 100\% and a specificity of 71.9\%. Only the combination of EDV \( > 41 \text{ cm/s} \) and ICA/CCA \( > 2 \) improved the accuracy of detecting in-stent area restenosis \( \geq 75\% \) with a sensitivity of 100\% and a specificity of 84.4\% (Table 5).

**Discussion**

In this study, we demonstrated that (i) the relationship between increasing severity of carotid ISR by IVUS measurements and increasing Doppler velocities was preserved in the stented CA; (ii) significant ISR defined as \( \geq 50\% \) diameter or \( \geq 75\% \) lumen area stenosis occurred in 20\% and 25\% of...
Carotid ISR

PSV, cm/s 0.85 (0.71–0.95) 0.68 (0.52–0.82) 0.89 (0.75–0.97)
DPSV, % 0.77 (0.59–0.90) 0.71 (0.52–0.86) 0.80 (0.62–0.92)
EDV, cm/s 0.96 (0.84–0.99) 0.65 (0.49–0.80) 0.93 (0.80–0.99)
ICA/CCA 0.89 (0.75–0.96) 0.77 (0.61–0.96) 0.88 (0.74–0.96)

They defined velocity criteria for grading carotid ISR as for detecting ≥50% diameter and 75% lumen area stenosis ISR and MLD <3 mm; (iv) optimal duplex ultrasound velocities to detect significant stenosis in stented CAs were greater compared with those for native CAs; and (v) the combination of PSV and %ΔPSV increased specificity, whereas EDV and ICA/CCA PSV ratio improved sensitivity in detecting ≥75% lumen area ISR.

The utility of native artery DUS criteria developed for nonstented CAs to evaluate stented CA is not well established. Recent reports have suggested that DUS was less accurate for determining ISR, and velocity thresholds for carotid ISR need to be modified.2,3 In a recent study by Lal et al, PSV, EDV, and ICA/CCA ratio increased compared with native CAs.14 The pattern of carotid ISR may predict the long-term prognosis of patients after CA stenting.13 Therefore, reliable methods of determining ISR are critical.

Some investigators have suggested that stent deployment alters wall compliance, producing a stiffer conduit and theoretically an increase in PSV within the stented segment.2,3 In a recent study by Lal et al, PSV, EDV, and ICA/CCA ratio increased to a greater degree. Similarly, the largest published to date comparing DUS versus QCA in >800 patients over 6 years demonstrated that in-stent velocities were increased compared with native carotid vessels.14 They defined velocity criteria for grading carotid ISR as PSV >104 cm/s, if <30% stenosis; PSV 105 to 174 cm/s if 30% to 50% stenosis; PSV 175 to 299 cm/s if 50% to 70% stenosis; and PSV >300 cm/s, EDV >140 cm/s, and ICA/CCA >3.8 if >70% stenosis achieved excellent ROC for ISR >70%.

Our findings using IVUS support these studies; DUS was accurate in determining ISR once new velocity criteria for grading severity of ISR were developed based on ROC analysis. Although our study is smaller in number than the above studies, it is valuable because we have validated DUS against area stenosis using IVUS, which is more representative of the severity of carotid restenosis than diameter, because we have previously shown that stent expansion is asymmetrical, particularly if the vessel is calcified.10

Table 3. Area Under the Receiver Operating Curve (95% CI) of Velocity Parameters for Diagnosis of Carotid ISR

<table>
<thead>
<tr>
<th>Stenosis Type</th>
<th>PSV</th>
<th>DPSV</th>
<th>EDV</th>
<th>ICA/CCA</th>
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<tbody>
<tr>
<td>≥50% Diameter</td>
<td>0.85</td>
<td>0.68</td>
<td>0.96</td>
<td>0.89</td>
</tr>
<tr>
<td>≥50% Area</td>
<td>0.77</td>
<td>0.71</td>
<td>0.65</td>
<td>0.77</td>
</tr>
<tr>
<td>≥75% Area</td>
<td>0.96</td>
<td>0.65</td>
<td>0.93</td>
<td>0.88</td>
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</table>

Table 4. Suggested DUS Velocity Criteria in Predicting Carotid ISR

<table>
<thead>
<tr>
<th>Stenosis Type</th>
<th>PSV cm/s</th>
<th>EDV cm/s</th>
<th>ICA/CCA</th>
<th>%ΔPSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50% diameter stenosis</td>
<td>232</td>
<td>49</td>
<td>3.4</td>
<td>98</td>
</tr>
<tr>
<td>≥75% lumen area stenosis</td>
<td>197</td>
<td>41</td>
<td>2</td>
<td>98</td>
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</table>

Another strength of our study was that we analyzed paired observations obtained at the completion of CAS and at follow-up in all patients, whereas previous studies only performed angiography when ISR was predicted by DUS. This approach allowed us to develop paired observations for a range of severity of restenosis and minimize bias toward higher or lower velocities, thus providing valid data on false-negative and false-positive results.

Two considerations went into selecting optimal velocity criteria: the first was to maximize overall sensitivity and specificity; and the second was to emphasize that post-CAS DUS was primarily a screening tool. The clinical relevance of identifying ≥50% diameter stenosis (ie, ≥75% lumen area stenosis) is to initiate a more intense surveillance program. Therefore, criteria with high sensitivity and negative predictive values were selected to minimize false negatives.

PSV is generally the most reliable parameter for detecting and quantifying native CA stenosis. PSV increases with progressive stenosis of the artery and is useful for grading carotid stenosis. PSV may be less reliable under certain circumstances, such as the presence of tandem lesions, contralateral high-grade stenosis, elevated CCA velocity, hyperdynamic cardiac state, or low cardiac output. In our study, PSV and %ΔPSV had a higher specificity than sensitivity in detecting significant ISR. This may be due to increased spread of PSV seen in stented CAs and the absence of associated high-grade >70% diameter ISR (ie, >91% lumen area stenosis) in our cohort.

A standard criterion for grading carotid ISR does not exist. Even when laboratories use the same method for identifying ICA stenosis, DUS criteria developed for a given degree of stenosis may differ. Differences may be due to variability in carotid angiogram measurements, scanning techniques, or US equipment. As a result, Doppler spectral velocities recorded in one laboratory may differ significantly from those recorded in another laboratory. Therefore, it is recommended that each noninvasive vascular laboratory validate its results and develop its own criteria based on published experience.1,15,16 Establishing a baseline value after CAS is important to reduce the number of potential false-positive examinations. Immediate poststenting DUS provides a valuable baseline value for future follow-up comparisons.
Limitations
This study included retrospectively collected data in a small sample from one institution and is therefore subject to limitations associated with such an analysis. No patients had high-grade ISR and therefore our findings may not be generalizable to this group. Further, confirmatory studies should be done. However, it is unlikely that IVUS will be routinely performed following CAS procedures, despite the fact that no complications resulted directly from the addition of IVUS in our patient cohort.

Conclusions
PSV, EDV, and ICA/CCA PSV ratio were reliable in detecting diameter and area carotid ISR. Optimal duplex ultrasound velocities to detect significant stenosis in stented CAs were greater compared with those for native CAs. The diagnostic accuracy in detecting significant ISR on IVUS was increased using a combination of duplex velocity criteria. Carotid DUS is the ideal noninvasive diagnostic modality to evaluate the long-term patency of carotid stents.

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Disclosures
Dr Jaff has served on the advisory board for and received research support from Abbott Vascular; has served as a consultant for Neoxen Medical; has served as a board member for VIVA Physicians; and has an Icon Interventional equity ownership. Dr Rosenfield has served as a consultant and advisory board member for and received research support from Abbott Vascular; has served as a consultant for Cordis Endovascular; has received research support from Bard Peripheral Vascular, Boston Scientific, EV3 Inc, and Invatec Inc; has served as a board member for VIVA Physicians; has equity in Lumen Biomedical; receives deferred payments from AngioGuard (cordis); and is on the medical advisory board to ICON.

References

CLINICAL PERSPECTIVE
Duplex ultrasound criteria for assessing the severity of carotid in-stent restenosis remain poorly defined. We aimed to compare the accuracy of Duplex ultrasound with intravascular ultrasound, which provides a precise assessment of lumen area stenosis and cross-sectional area. Our investigation differs from previous observational studies, in that we were able to analyze “matched” intravascular ultrasound and Duplex images obtained, both at the completion of initial carotid artery stenting and again at follow-up, in all patients. This approach allowed us to develop paired observations for the full spectrum of severity of restenosis and minimize bias toward higher or lower velocities. Our main findings included (i) Duplex ultrasound velocities were good discriminators for detecting significant diameter and lumen area in-stent restenosis; (ii) optimal duplex ultrasound velocities to detect significant stenosis in stented carotid arteries were greater compared with those for native carotid arteries; and (iii) the combination of duplex velocity criteria increases diagnostic accuracy. Carotid duplex ultrasonography is the ideal noninvasive diagnostic modality to evaluate the long-term patency of carotid stents.
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