Lumen Reduction Measurements of the Internal Carotid Artery Before and After Levovist Enhancement: Reproducibility and Agreement with Angiography

Otto E.H. Elgersma, MD, Maarten S. van Leeuwen, MD, PhD, Rudy Meijer, Bert C. Eikelboom, MD, PhD, Yolanda van der Graaf, MD, PhD

Our aim was to assess reproducibility of three different lumen reduction measuring methods—North American Symptomatic Carotid Endarterectomy Trial, European Carotid Surgery Trial, and common carotid—using power Doppler and color Doppler sonography before and after Levovist enhancement.

We included 20 symptomatic patients with mild or severe carotid disease. North American Symptomatic Carotid Endarterectomy Trial, European Carotid Surgery Trial, and common carotid measurements on longitudinal views and European Carotid Surgery Trial measurements on transverse views were performed. Examinations were repeated and the results compared to assess reproducibility of measurements. Correlation with angiography was obtained by calculating Pearson correlation coefficients.

Reproducibility was significantly better ($P < 0.05$) for European Carotid Surgery Trial and common carotid measurements (95% limits of agreement between −10% to 10% and −19% to 17%) as compared to North American Symptomatic Carotid Endarterectomy Trial measurements (95% limits of agreement between −11% to 21% and −21% to 23%). Variability of measurements after enhancement increased slightly (not significant) for both power and color Doppler sonography. Additionally, European Carotid Surgery Trial measurements, using nonenhanced power Doppler or color Doppler sonography, did not correlate significantly with angiography, whereas North American Symptomatic Carotid Endarterectomy Trial and common carotid measurements correlated well with angiography, particularly in power Doppler mode after enhancement ($r = 0.88$ and $r = 0.82$, respectively).

We conclude that for lumen reduction measurements of the internal carotid artery with power and color Doppler sonography, the common carotid method is the only method that is reproducible and has good correlation with angiography, which slightly improves after Levovist enhancement.

KEYWORDS: Carotid arteries; Ultrasonography; Contrast media; Angiography.
The NASCET and the ECST both established that carotid endarterectomy is beneficial to patients with cerebrovascular symptoms and a severe ICA stenosis. In these trials the percentage of ICA stenosis was established by angiography, though the method of assessment of the percentage of stenosis was different. NASCET assessed lumen reduction by dividing the minimal lumen diameter at the level of the stenosis by the distal ICA lumen diameter. Conversely, ECST related the minimal lumen diameter to the estimated former normal lumen of the carotid bulb. A third method of quantifying ICA stenosis is the CC method. This method relates the minimal lumen diameter to the diameter of the distal CCA.

With the risk of stroke or death for selective angiography ranging from 1 to 4% in patients with atherosclerosis, continuous efforts have been directed toward the design of an optimal diagnostic strategy with less invasive methods for patient selection. Ultrasonography and, more specifically, hemodynamic parameters obtained with pulsed Doppler sonography have been extensively studied for noninvasive quantification of ICA stenosis. A good correlation between PSV values and angiographic findings has been reported in many studies. However, in a nonselected population of 1011 symptomatic patients from the NASCET, sensitivity and specificity for detecting 70 to 99% carotid stenosis were only 0.68 and 0.67, respectively, and even more important, PSV values did not correlate with the risk of stroke. This indicates that patient selection cannot be performed on PSV values alone. Therefore, if ultrasonography is used for patient selection, additional means for quantifying lumen reduction seem required.

PD and CD sonography both visualize flowing blood and display vascular structures with high spatial resolution, allowing measurements of lumen reduction similar to measurements on angiograms. However, in case of calcifications or severe plaque fibrosis, Doppler signals can be weak and the visualization of minimal residual lumen may be hampered. The intravenous contrast agent SHU 508A (Leovist, Schering AG, Berlin, Germany) increases the echogenicity of blood, which results in an increased signal-to-noise ratio for Doppler signals. Application of Leovist should thereby improve visualization of minimal residual lumen and show better delineation of vessel walls. However, before ultrasonographically derived lumen reduction measurements can be applied clinically, the optimal ultrasonographic technique, lumen reduction measuring method, and the possible benefit of Leovist enhancement have to be defined. Therefore, we undertook a study to assess the reproducibility of three different methods of linear ICA lumen reduction measurements using PD and CD sonography, both before and after Leovist enhancement. Additionally, we compared the ultrasonographically derived measurements with similar measurements on corresponding angiograms.

SUBJECTS AND METHODS

Twenty patients with symptoms of carotid disease (transient ischemic attack, stroke, or amaurosis fugax) in the past 6 months were included. Fifteen patients were men and five were women. The mean age was 69 years (range, 55–80 years). The study was approved by the hospital ethical committee, and informed consent was obtained in all patients.

Symptomatic patients were first screened by carotid duplex sonography. If PSV values in the ICA were 150 cm/s or more, carotid disease was suspected, and patients were subsequently referred for angiography. Further selection for inclusion in this study was based on the availability of two experienced technicians and the supervising medical doctor as well as the availability of an ultrasonography machine within 24 h before or after the angiography.

An ATL HDI 3000 ultrasonography machine (Advanced Technology Laboratories, Bothell, WA) with an L 7–4 MHz linear array transducer was used to visualize the carotid bifurcation. Patients sequentially underwent two identical PD and CD examinations by different experienced technicians. The technicians were blinded to findings of each other and to the results of the angiography. Blinding for the ultrasonographic technique used and the application of Leovist was not possible, because these were always recognizable to the technician. Each technician performed the nonenhanced PD and CD examinations first. The order in which the PD and CD examinations were performed was established by random allocation.

In PD mode the receiver gain was raised to the point at which noise became visible. In CD mode gain settings were set high enough to detect all flow within the lumen, displaying the complete presumed lumen, and low enough to avoid color bleeding into surrounding tissue. PRF was generally set at the preset of high velocity (6000 Hz) to visualize ICA stenoses and at the preset of medium or low velocity (3000 or 1500 Hz, respectively) to visualize normal lumen. For each enhanced examination in either PD or CD mode, an 11 ml Leovist suspension with a
concentration of 200 mg/ml, containing micrometer-sized microparticles of α-D-galactose (99.9%) and palmitic acid (0.1%) with adsorbed microscopic gaseous bubbles, was administered at a rate of 1 ml/s into the cubital vein. After injection, gain settings were adjusted to obtain optimal image quality. PRFs and all other parameters were identical to the settings used before enhancement. Again, the order in which the PD and CD examinations were performed was randomized.

The affected ICA segment, the normal ICA distal to the bulb, and the CCA 1 cm proximal to the beginning of the bulb were visualized using longitudinal views, because these gave an adequate anatomic overview and allowed good definition and visualization of the different carotid sections. Minimal residual lumen diameter, former bulb diameter (i.e., the distance of the adventitia of the near wall to the adventitia of the far wall), distal ICA lumen diameter, and CCA lumen diameter were measured using the standard caliper of the ultrasonography machine (resolution, 0.1 mm). On transverse views the affected ICA segment was displayed very well. However, the deeply situated distal ICA and the distal CCA were not suitable for lumen diameter measurements because the precise longitudinal location and perpendicular orientation with respect to the long axis of the vessel could not be defined adequately using transverse views. Therefore, only minimal residual lumen diameter and former bulb diameter were measured on transverse views.

Lumen reduction measurements according to the ECST method were performed on both transverse and longitudinal images (stenosis = [1 – (minimal residual lumen/former bulb diameter)] × 100%). Lumen reduction measurements according to the NASCET and CC methods were only performed on longitudinal images (NASCET stenosis = [1 – (minimal residual lumen/distal ICA lumen diameter)] × 100% and CC stenosis = [1 – (minimal residual lumen/CCA lumen diameter)] × 100%) (Figs. 1, 2).

Selective angiography was performed in all patients within 24 h before or after the ultrasonographic lumen reduction measurements. The carotid bifurcation was imaged in at least three different directions (lateral, posteroanterior, and oblique). Measurements with NASCET, ECST, and CC methods were performed on the hard copy using a PAV electronic caliper (Prezition Apparatenbau, Vaduz, Liechtenstein) with a resolution of 0.01 mm. The view showing the most severe lumen reduction was used for correlation with ultrasonography.

Reproducibility of measurements using the different combinations of ultrasonographic techniques and lumen reduction measuring methods were presented as 95% limits of agreement (i.e., the mean difference between measurements of both technicians ± 1.96 times the SD of the mean difference). 95% limits of agreement represent the range of values in which, for a given measurement, one would expect 95% of the differences in results of a second measurement to lie.26 To compare reproducibility of measurements using the different combinations of ultrasonographic techniques and lumen reduction measuring methods, differences between measurements of both technicians were first adjusted for the fact that measurements were not performed independently (each technician performed a series of measurements on the same patient). Subsequently, SDs of the mean adjusted differences between measurements were calculated. Differing SDs were tested for significant differences (P < 0.05) with the F-test using the Bonferroni correction, adjusting the observed significance level for the fact that multiple comparisons are being made. Additionally, the lumen reduction measurements using the different measuring methods and ultrasonographic techniques were correlated with measurements on corresponding angiograms and expressed as Pearson correlation coefficients with 95% confidence intervals.

Figure 1 A schematic view of the linear lumen reduction measuring methods used for the ICA. ECST stenosis = 1 – (A/B) × 100%), NASCET stenosis = 1 – (A/C) × 100%, CC stenosis = 1 – (A/D) × 100%.
Figure 2 An example of lumen reduction measurements of the ICA with the ECST method. A, A transverse view of the affected carotid segment in CD mode before Levovist enhancement. B, The same segment in PD mode. C, A longitudinal view of the affected segment in CD mode. The short arrow marks the diameter of the residual lumen. The long arrow marks the presumed former lumen diameter (adventitia–adventitia diameter). Note on longitudinal images how the echogenicity of the adventitia (the media–adventitia interface) is visualized easier as compared to transverse views. D, The same view after Levovist injection and reduction of the gain shows increased color signal in the carotid lumen. E, The same segment in PD mode. The CCA and part of the ICA distal to the stenosis were not visualized with PD sonography. F, The same view after Levovist injection, which shows a typical striped pattern artifact and color blooming in the distal part of the ICA. Because of the increased echogenicity of blood, the CCA and entire ICA lumen could be visualized well with PD sonography. G, The corresponding angiogram.
RESULTS

PSV values could be derived from all 20 examined symptomatic ICAs at the point of greatest mean frequency shift on the color map. However, visualization of the minimal residual lumen was considered insufficient for performing lumen reduction measurements in two carotid arteries in PD as well as in CD mode by both technicians due to extensive plaque calcifications. Additional Levovist enhancement did not improve visualization of the residual lumen in these patients. Therefore, measurements of 18 carotid arteries remained for analysis (Tables 1a and 1b).

The mean differences in measured lumen reduction did not reveal consistent differences between measurements of both technicians for any combination of ultrasonographic technique and lumen reduction measuring method. In nonenhanced PD and CD mode 95% limits of agreement for ECST measurements were between −10% to 10% and −8% to 12%, and for CC measurements between −8% to 12% and −16% to 12%. After enhancement, 95% limits of agreement for ECST and CC measurements in both PD and CD mode increased slightly. The 95% limits of agreement for NASCET measurements in both PD and CD mode were about twice as high as for ECST measurements. After adjusting for the fact that measurements were not performed independently, SDs of the mean adjusted differences between NASCET measurements of both technicians were compared with SDs of the mean adjusted differences between ECST measurements of both technicians and CC measurements of both technicians. Reproducibility of all NASCET measurements (in nonenhanced as well as in enhanced PD and CD mode) was significantly worse (P < 0.05) as compared to reproducibility of ECST or CC measurements.

Figure 3 shows the scatterplots of angiographic lumen reduction measurements versus the ultrasonographically derived lumen reduction measurements of technician 1. All ultrasonographically derived measurements tended to underestimate the amount of ICA stenosis with an average 5% (ECST measurements) to 9% (NASCET measurements) compared to angiographic measurements. The amount of lumen reduction measured with the ECST method was an average 5% higher than measurements with the CC method and an average 16% higher than measurements with the NASCET method. ECST measurements using nonenhanced PD or CD sonography did not correlate significantly with angiography (r = 0.32 to r = 0.56). NASCET and
CC measurements showed a better correlation with angiography ($r = 0.54$ to $r = 0.79$). After enhancement, correlation with angiography improved substantially for measurements performed by technician 1, particularly when performed in PD mode ($r = 0.88$ and $r = 0.82$ for NASCET and CC measurements, respectively), whereas correlation with angiography of measurements performed by technician 2 only slightly improved.

**DISCUSSION**

This study showed that ICA lumen reduction measurements can be reproducibly obtained with both PD and CD sonography using ECST and CC methods. Measurements with the ECST method showed the least interobserver variability. Interobserver variability was significantly higher for all measurements with the NASCET method. After Levovist enhancement, variability in lumen reduction measurements increased slightly. Measurements with CC and NASCET methods in both PD and CD mode showed the best correlation with angiographic measurements and improved further for one technician after enhancement. For reliable lumen reduction measurements, variability in measurements should be as low as possible and correlation with the gold standard as high as possible. The CC method appeared to be the only method that is reproducible and has good correlation with angiography.

Griewing and associates measured lumen reduction with the longitudinal ECST method and by cross-sectional area reduction in PD and in CD mode, using angiography as the gold standard. They found that PD sonography was better in detecting mild and severe stenoses than CD sonography. Our findings, however, did not suggest major differences between PD and CD sonography in quantifying ICA stenosis, although measurements

| US Derived Stenosis, % | Reproducibility, 95% Limits of Agreement | Correlation Coefficients |  |  |
|-----------------------|------------------------------------------|--------------------------|--------------------------|
| **US Derived Stenosis, %** | **Reproducibility, 95% Limits of Agreement** | **Correlation Coefficients** | **Technician 1 95% CI** | **Technician 2 95% CI** |
| ECST transverse | 73 | 54–90 | 0.34 | 0.34–0.71 | 0.44 | 0.44–0.76 |
| After Levovist | 72 | 51–87 | 0.52 | 0.07–0.79 | 0.48 | 0.00–0.77 |
| ECST longitudinal | 78 | 54–91 | 0.32 | 0.18–0.83 | 0.47 | 0.00–0.77 |
| After Levovist | 76 | 51–87 | 0.59 | 0.22–0.85 | 0.63 | 0.24–0.88 |
| CC | 73 | 44–90 | 0.63 | 0.22–0.85 | 0.63 | 0.24–0.88 |
| After Levovist | 70 | 49–86 | 0.73 | 0.39–0.89 | 0.79 | 0.52–0.92 |
| NASCET | 62 | 25–80 | 0.54 | 0.10–0.81 | 0.60 | 0.19–0.84 |
| After Levovist | 59 | 27–75 | 0.72 | 0.38–0.89 | 0.79 | 0.50–0.92 |

**Table 1a**: Characteristics of CD Derived Carotid Lumen Reduction Measurements*

| US Derived Stenosis, % | Reproducibility, 95% Limits of Agreement | Correlation Coefficients |  |  |
|-----------------------|------------------------------------------|--------------------------|--------------------------|
| **US Derived Stenosis, %** | **Reproducibility, 95% Limits of Agreement** | **Correlation Coefficients** | **Technician 1 95% CI** | **Technician 2 95% CI** |
| ECST transverse | 72 | 53–85 | 0.45 | 0.21–0.84 | 0.48 | 0.03–0.78 |
| After Levovist | 72 | 53–85 | 0.61 | 0.21–0.84 | 0.48 | 0.00–0.77 |
| ECST longitudinal | 77 | 54–88 | 0.34 | 0.13–0.81 | 0.46 | 0.35–0.77 |
| After Levovist | 75 | 54–89 | 0.69 | 0.33–0.87 | 0.45 | 0.04–0.75 |
| CC | 72 | 38–89 | 0.63 | 0.22–0.86 | 0.79 | 0.50–0.92 |
| After Levovist | 70 | 44–90 | 0.82 | 0.58–0.93 | 0.80 | 0.53–0.93 |
| NASCET | 61 | 35–82 | 0.56 | 0.13–0.81 | 0.70 | 0.34–0.88 |
| After Levovist | 59 | 28–83 | 0.88 | 0.70–0.95 | 0.69 | 0.33–0.85 |

**Table 1b**: Characteristics of PD Derived Carotid Lumen Reduction Measurements*

*The mean and range of percentage of ICA stenosis, obtained with the different measuring methods, using CD sonography before and after Levovist enhancement, the 95% limits of agreement, and correlation with angiography. Correlation with angiography for measurements of both technicians is expressed as Pearson correlation coefficients, with 95% confidence intervals.

US, Ultrasonographically; CI, Confidence interval.

*The mean and range of percentage of ICA stenosis, obtained with the different measuring methods, using PD sonography before and after Levovist enhancement, the 95% limits of agreement, and correlation with angiography. Correlation with angiography for measurements of both technicians is expressed as Pearson correlation coefficients, with 95% confidence intervals.

US, Ultrasonographically; CI, Confidence interval.
in PD mode of one technician showed a slightly higher correlation with angiographic measurements than measurements in CD mode. Steinke and colleagues found a high correlation between CD and PD mode for measurements of cross-sectional area reduction and a moderate correlation between CD and PD mode for longitudinal ECST measurements. In addition, PD sonography visualized residual ICA lumen and characterized plaque surface better. Although not remarkably, PD sonography sometimes visualized the carotid lumen better than CD sonography did in our study population. However, except for two bifurcations, in which minimal residual lumen could not be visualized with either PD or CD mode due to extensive plaque calcifications, lumen reduction measurements could be performed in all carotid bifurcations in PD as well as in CD mode. Sitzer and coworkers compared duplex examinations (including CD examinations) of high-grade ICA stenoses before and after Levovist enhancement and found a significantly improved visualization of the residual intrastenotic lumen and a higher percentage of irregular and ulcerative plaques after enhancement. Furthermore, a very high correlation was found between cross-sectional area reduction before and after enhancement (r > 0.90) and between plaque length measurements before and after enhancement. However, they did not assess reproducibility of lumen reduction measurements and did not compare their findings with a gold standard.

Which lumen reduction measuring method to use for grading ICA stenosis and subsequent patient selection is a matter of controversy. Recently, different measuring methods have been compared on angiograms. Vanninen and colleagues compared ECST and NASCET methods and found the greatest interobserver variability with NASCET measurements. Their findings are in agreement with those of Bladin and associates who also found NASCET to be the least reproducible method. Rothwell and coworkers, Eliasziw and associates, and Young and colleagues compared reproducibility of ECST, NASCET, and CC methods. Rothwell and coworkers recommended the CC method, because it showed the best reproducibility, particularly for lumen reduction in the clinically important range of 50 to 90%. Conversely, Eliasziw and associates and Young and colleagues reported no consistent differences between the measuring methods. Therefore, Eliasziw and associates recommended the NASCET method, because criteria for identifying patients who benefit from carotid endarterectomy are based on this method. We compared different measuring methods on ultrasonographic images and found ECST and CC methods to be the most reproducible methods for determining lumen reduction. Variability in measurements with the NASCET method was significantly higher, primarily because visualization of the deeply situated ICA distal to the carotid bulb was not adequate, also after enhancement.

The tendency of ultrasonographically derived measurements to underestimate ICA lumen reduction with an average 5% using the ECST method to 9% using the NASCET method compared to angiographic measurements has to be taken into account. A reason could be that ultrasonographically derived lumen reduction on longitudinal views is measured in only one direction, while on angiography lumen reduction is measured on the view showing the most severe lumen reduction (from the three views available). In case the residual stenotic lumen is not circular, ultrasonographic images in one direction may not reveal the minimal residual lumen. The difference in calipers used for measuring lumen reduction on ultrasonographic images and on the hard copies of the angiography is unlikely to be of influence on the differences in lumen reduction between measurements on ultrasonographic images and angiography, since we compared ratios (i.e., the percentage of lumen reduction) and not the absolute measurements of lumen diameters. In our selected population with predominantly severe ICA stenoses, differences between the amount of ultrasonographically derived lumen reduction, measured with the different methods (ECST measurements were an average 5% higher than CC measurements and 16% higher than NASCET measurements) were in agreement with the differences found by Eliasziw and associates who performed the same measurements on selective angiograms of severely stenosed ICAs (ECST measurements were 5.5% higher than CC measurements and 21% higher than NASCET measurements). Variability of measurements in both PD and CD mode increased slightly, though not significantly, after enhancement as compared to measurements before enhancement. The reason for this may be the occurrence of spectral bubble noise and color blooming, partly obscuring the vessel walls, after enhancement (Fig. 2F). The color blooming effect occurred immediately after the bolus of contrast arrived and was eliminated by reducing color gain. Hereafter, color gain needed frequent adjustments because of the continuously diminishing contrast enhancement, making measurements on enhanced images more operator dependent. Furthermore, one technician
appeared to benefit from enhancement, particularly when measurements were performed in PD mode. This may be a result of PD mode using the amplitude of the echo signal reflected from scatterers (red blood cells and, in case of enhancement, microbubbles) within the flowing blood, whereas CD mode maps the Doppler frequency. PD mode essentially depends on the density of scatterers within the sample volume and might therefore benefit most from contrast enhancement.24

Several limitations of this study have to be taken into account. We only examined symptomatic carotid arteries that showed a certain degree of ICA stenosis with duplex sonography, because for those it is essential to differentiate between more or less than 70% stenosis in order to choose between carotid endarterectomy in combination with the best medical treatment and the best medical treatment alone. Because of this approach, we did not include low-grade stenoses in the study and, hence, do not know how the different techniques for measuring

Figure 3 The scatterplots of angiographic lumen reduction measurements against ultrasonographically derived lumen reduction measurements. The solid diamonds represent the measurements on nonenhanced images. The open squares represent the measurements on enhanced images.
ICA lumen reduction perform in the entire range of ICA stenoses. In addition, this study had a small number of patients, enough to estimate reproducibility of measurements but not enough to obtain a very valid estimation of correlation of ultrasonographically derived measurements with angiographic measurements (large 95% confidence intervals of Pearson correlation coefficients).

What could eventually be the value of ultrasonographically derived lumen reduction measurements in a diagnostic strategy for patient selection? The ultimate aim is to adopt a noninvasive strategy that is approximately as accurate as the standard strategy used in most clinics today: screening of symptomatic patients with duplex sonography (i.e., PSV values in the ICA) and subsequent selection for carotid endarterectomy by means of lumen reduction measurements using selective angiography. When duplex sonography is used as a screening tool, a high sensitivity is required in order to not miss any patient. However, using PSV values alone, this can be obtained only at the cost of a relatively low speci-
ficiency.\textsuperscript{12,31} Therefore, additional tests are required in order to refrain from carotid endarterectomy in patients who do not meet the criteria. These tests should be based preferably on linear lumen reduction measurements.\textsuperscript{32} When a larger study proves that ultrasonographically derived lumen reduction measurements, except for being reproducible, also have a high accuracy compared with selective angiography, an extensive ultrasonographic examination, using lumen reduction measurements as an adjunct to hemodynamic parameters, could possibly provide all information needed to select patients eligible for carotid endarterectomy.

REFERENCES


