

## Comparison of ultrasonography, CT angiography, and digital subtraction angiography in severe carotid stenoses

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Digital subtraction angiography (DSA) is considered to be the ‘gold standard’ for confirmation of severe (70–99%) stenoses of internal carotid arteries (ICAs). However, it is associated with a risk of complications. The aim of this study was to assess the accuracy of ultrasonography (US), computed tomographic angiography (CTA), and their combined use for the detection and quantification of severe carotid stenoses, when compared with DSA. Severe ICA stenoses were diagnosed by US in a set of 29 patients. All patients also underwent CTA and DSA. Sensitivity, specificity, positive (PPV), negative predictive values (NPV), and Pearson’s correlation coefficient were used in the evaluation of the percentage of stenosis results. Homogeneity  $\chi^2$  test was applied when assessing statistical significance. Severe stenosis was diagnosed in 34 ICAs. Two ICAs with uninterpretable CTA finding were excluded. The number of ICAs with stenoses 70–99% / < 70% – US 32/0; CTA 29/3; US + CTA 29/3; DSA 24/8. Pearson’s correlation coefficient – US 0.601; CTA 0.725; US + CTA 0.773. Sensitivity/specificity/PPV/NPV – US 1.0/0.75/0.75/xxx; CTA 1.0/0.844/0.828/1.0; US + CTA 1.0/0.844/0.828/1.0. Homogeneity  $\chi^2$  test results – US,  $P = 0.002$ ; CTA,  $P = 0.098$ ; US + CTAG,  $P = 0.098$ . US in combination with CTA can be used for relatively secure diagnostics of severe ICA stenoses. Thus, invasive DSA can be avoided in a substantial number of patients.

### Introduction

Arteriosclerotic stenoses of extracranial carotid arteries are an important risk factor for an ischemic stroke, and transient ischemic attack (TIA). Previous studies proved a significant benefit of carotid endarterectomy (CEA) in the prevention of ischemic stroke in patients with severe (70–99%) symptomatic stenoses of internal carotid arteries (ICAs) (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991; European Carotid Surgery Trialists’ Collaborative Group, 1998). The results reported in other papers suggest the indication of CEA also in asymptomatic severe ICA stenoses (Norris *et al.*, 1991; Executive Committee for the Asymptomatic Carotid Atherosclerosis Study, 1995; The European Carotid Surgery Trialists Collaborative Group, 1995; Barnett *et al.*, 1996; Findlay *et al.*, 1997; Mintz and Hobson, 2000).

Duplex color-coded Doppler ultrasonography (US) is a non-invasive, quick technique, used in the screening of these stenoses. It has a relatively high sensitivity in comparison with digital subtraction angiography (DSA) (Demarin *et al.*, 1989; Steinke *et al.*, 1990, 1997;

Moneta *et al.*, 1993; Faught *et al.*, 1994; Neale *et al.*, 1994; Browman *et al.*, 1995; Hood *et al.*, 1996; Back *et al.*, 2000; Huston *et al.*, 2000; Lovrenčić-Huzjan *et al.*, 2000; Dinkel *et al.*, 2001; Eckstein *et al.*, 2001; Keberle *et al.*, 2001; Rotstein *et al.*, 2002), and even in the planimetric measurements of the arteries specimens (Eckstein *et al.*, 2001; Schulte-Altdorneburg *et al.*, 2002). However, Qureshi *et al.* (2001) in their recent study concluded that the present accuracy of carotid Doppler US in general practice did not justify its use as the sole basis of selecting appropriate patients for carotid intervention.

Digital subtraction angiography is considered to be a ‘gold standard’ in the arterial imaging, including the confirmation of severe ICA stenoses; however, this invasive examination is associated with a risk of complications (Hessel *et al.*, 1981; Waugh and Sacharias, 1992; Warnock *et al.*, 1993; Heiserman *et al.*, 1994; Pryor *et al.*, 1996; Rolland *et al.*, 1996; Hagen, 1997; Link *et al.*, 1997; Guo *et al.*, 2000; Dinkel *et al.*, 2001). Heiserman *et al.* (1994) reported 1% overall incidence of neurologic deficit and 0.5% incidence of persistent deficit, and Warnock *et al.* (1993) 3.89% overall incidence of neurologic deficit and 0.52% incidence of persistent deficit in cerebral angiography. Other authors described permanent stroke in up to 0.5%, but total number of complications (including systemic complications) in up to 5% of patients undergoing DSA

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(Waugh and Sacharias, 1992; Pryor *et al.*, 1996; Link *et al.*, 1997). This led to the search for less invasive methods for the evaluation of carotid artery stenosis.

Computed tomographic angiography (CTA) is a relatively new and minimally invasive method of visualizing both intracranial and extracranial blood vessels. The use of contrast-infused CT scanning in the examination of carotid artery bifurcation was reported for the first time in the late 1980s. It can be also used alone, or in combination with US in the diagnostics of ICA stenoses (Castillo, 1993; Cumming and Morrow, 1994; Heiserman *et al.*, 1994; Leclerc *et al.*, 1995; Link *et al.*, 1997; Mildenberger *et al.*, 1997; Simeone *et al.*, 1997; Magarelli *et al.*, 1998; Sugahara *et al.*, 1998; Cinat *et al.*, 1999; Marcus *et al.*, 1999; Sameshima *et al.*, 1999; Binaghi *et al.*, 2001; Randoux *et al.*, 2001; Patel *et al.*, 2002; Alvarez-Linera *et al.*, 2003). According to some authors, it is more accurate than US (Link *et al.*, 1997; Simeone *et al.*, 1997; Magarelli *et al.*, 1998; Sugahara *et al.*, 1998; Cinat *et al.*, 1999; Sameshima *et al.*, 1999; Binaghi *et al.*, 2001) and its findings are consistent with DSA examination results (Castillo, 1993; Cumming and Morrow, 1994; Heiserman *et al.*, 1994; Link *et al.*, 1997; Mildenberger *et al.*, 1997; Simeone *et al.*, 1997; Magarelli *et al.*, 1998; Sugahara *et al.*, 1998; Marcus *et al.*, 1999; Sameshima *et al.*, 1999; Binaghi *et al.*, 2001; Randoux *et al.*, 2001; Patel *et al.*, 2002; Alvarez-Linera *et al.*, 2003). However, CTA cannot replace DSA (Castillo, 1993); moreover, there is an inaccuracy of CTA in the discrimination of the degree of stenosis within the 50–99% range (Anderson *et al.*, 2000), which is crucial in the indication of CEA. Moll and Dinkel (2001) suggested the use of CTA in the case of inconclusive US during the pre- and postoperative phase, and as a third modality in the case of disagreement between DSA and US.

Therefore, the aim of our study was to evaluate the reliability of US, CTA, and their combined use (US + CTA) in the detection and quantification of severe ICA stenoses, when compared with the current 'gold standard' of DSA.

## Subjects and methods

Patients with severe ICA stenosis (70–99%) diagnosed by US were included in a prospective study. Indication for CEA was considered in all these patients for confirmation of the degree of stenosis by angiography.

A total of 29 patients, who underwent duplex color-coded Doppler US examination in the Neurosonological Laboratory, Stroke Center, Department of Neurology, University Hospital, Olomouc, Czech Republic between August 1999 and October 2000, also underwent CTA and DSA. The set consisted of 24

males (aged 48–83 years; mean  $66.4 \pm 8.4$  years) and five females (aged 47–74 years; mean  $66.2 \pm 9.9$  years). None of the patients had contraindications to the administration of iodine contrast material.

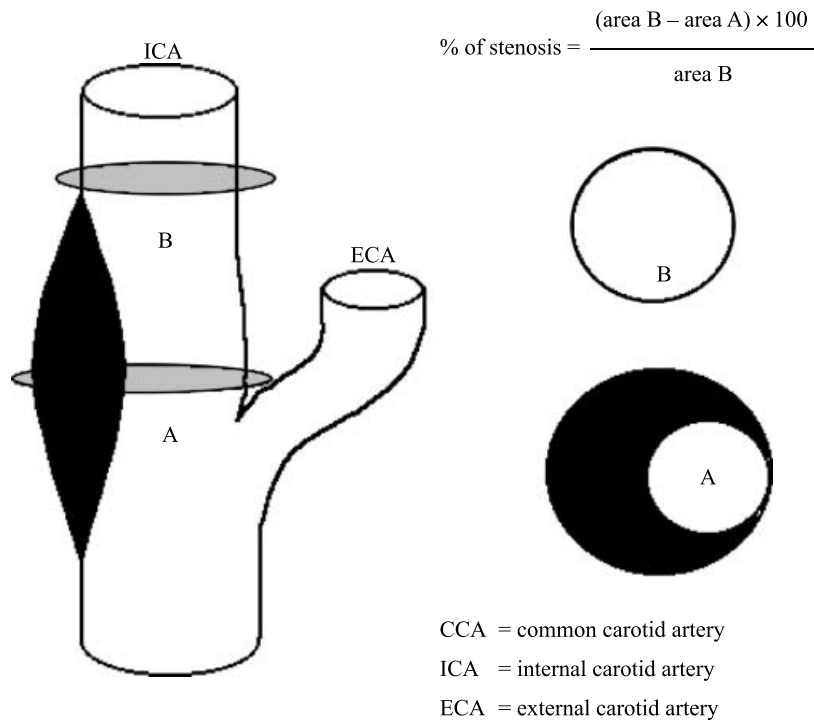
The time between the first (US) and the last (angiographic) examination varied between 1 and 26 (mean 8.5) days.

Ultrasonographic examination was performed with a Hewlett Packard Sonos 2000 apparatus (Hewlett Packard, Andover, MA, USA). A 7.5/5.5 MHz probe was used for duplex color-coded Doppler US. The percentage of stenosis was evaluated by the use of the modified NASCET (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991) criteria. The stenosis value was counted from the residual area (measured in the location of maximal atherosclerotic plaque), and from the true area (measured beyond the ICA bulb, and beyond the atherosclerotic plaque) (Fig. 1) – both measured in B-mode imaging. ICA peak systolic velocities identified by the Doppler examination (Fig. 2) correlated with the degree of severe ICA stenosis in our patients.

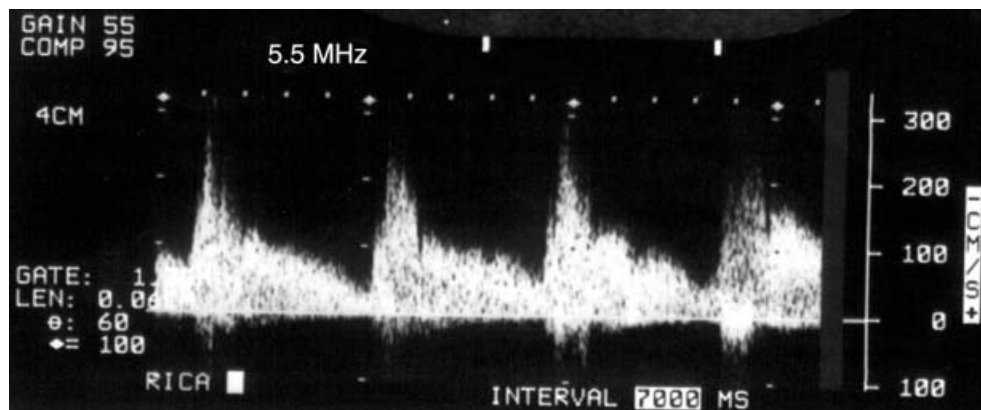
Computed tomographic angiography examination was performed with a GE HiSpeed CT/i helical scanner (General Electric, Milwaukee, WI, USA). A total volume of 80–100 ml of non-ionic contrast iohexol (Omnipaque 300; Nycomed Imaging A/S, Oslo, Norway) was infused at a 3.5 ml/s via a peripheral intravenous cannula placed in the upper extremity. The percentage of stenosis was evaluated by the use of both axial (Fig. 3a) and coronary (Fig. 3b) maximum intensity projection (MIP), and shaded-surface display (SSD, Fig. 3c) imaging.

An Angio Star (Siemens, Erlangen, Germany) apparatus was used for DSA examination. Non-ionic contrast iohexol (Omnipaque 240, Nycomed Imaging A/S, Oslo, Norway) was administered in a total volume of 20 ml at 20 ml/s for the examination of the aortic arcus, and in a total volume of 6 ml at 6 ml/s for the examination of carotid artery via the intra-arterial catheter introduced using the transfemoral Seldinger technique in most of the patients. Transbrachial approach was used only in two patients – due to the appearance of technical problems during transfemoral approach in the first, and the previous history of aortic-bifemoral by-pass in the second one. Common carotid arteries were selectively catheterized for the examination of carotid arteries territory. The percentage of stenosis was evaluated using longitudinal projection imaging (Fig. 4).

The US, CTA and DSA images were reviewed and the degree of stenosis was quantified using all three diagnostic modalities with an accuracy precision of 5%. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) were used in the evaluation of percentage of stenosis measured by US and CTA, as



**Figure 1** Evaluation of the percentage of stenosis using the modified NASCET criteria.



**Figure 2** Severe (>90%) ICA stenosis shown on a Doppler examination.

well as for the evaluation of the average percentage of stenosis counted from the values gained from both US and CTA. Pearson's correlation coefficient was used to assess the correlation between the percentage of stenosis measured by (i) US and DSA; (ii) by CTA and DSA; and (iii) between the average percentage of stenosis counted from the values gained from both US and CTA, and the percentage of stenosis measured by DSA. Homogeneity  $\chi^2$  test was applied to the frequency tables when assessing statistical significance.

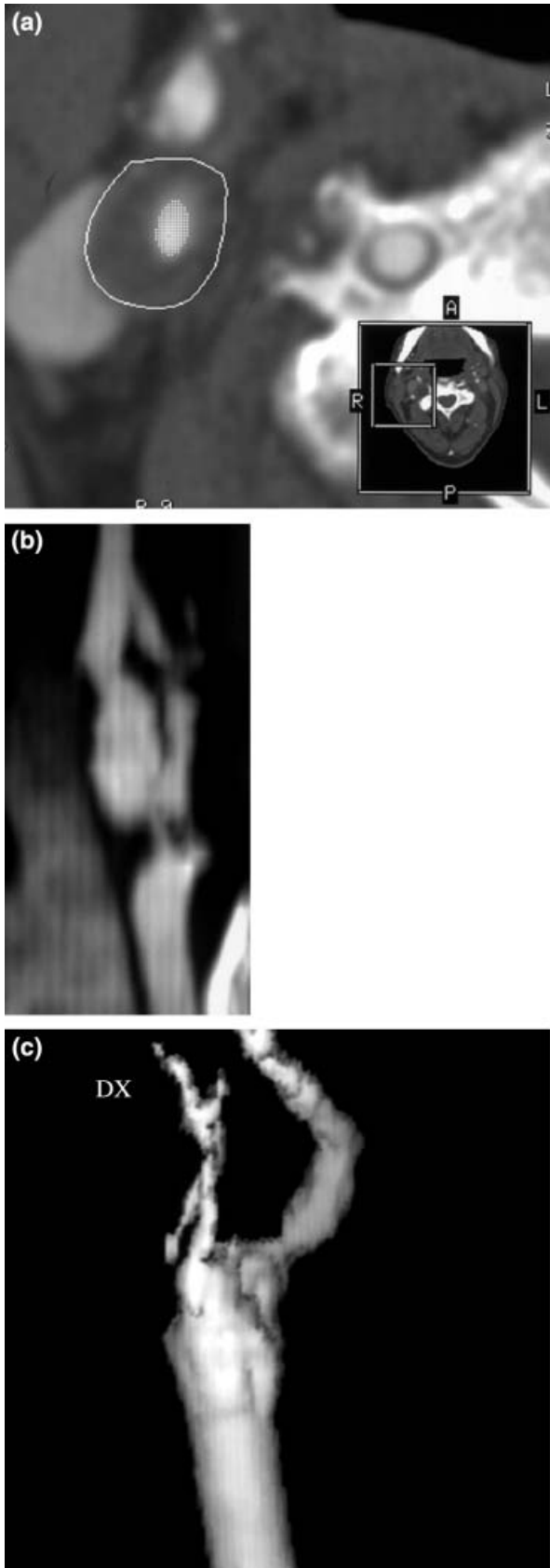
The whole study was conducted in accordance with the Helsinki Declaration of 1975 (as revised in 1983) and it was approved by the local ethics committee of our hospital. Informed consent was obtained from all patients.

## Results

Table 1 shows the relationship between neurologic symptomatology and the side of severe ICA stenosis in our set of patients. TIA/stroke or transient monocular blindness was present in the territory of the stenosed ICA in 18 of the 29 (62.1%) patients, neurologic symptomatology occurred in another territory in nine (31.0%) patients, and two (6.9%) patients were asymptomatic.

In total, US revealed severe (70–99%) stenosis in 34 ICAs in 29 patients.

Computed tomographic angiography images in two (both in the first patient being examined by CTA) ICAs (5.9%) were uninterpretable due to a poor quality images caused by technical artifacts. These were



**Figure 3** Severe (>90%) ICA stenosis shown on CTA: axial MIP (a), coronary MIP (b), SSD (c) images.

excluded from the study as, their quality made it possible only to assess the degree of ICA stenosis as a 'severe' one, however, not to quantify it with an accuracy precision of 5%. Remaining 32 examined ICAs in 28 patients were included in the study.

Computed tomographic angiography showed severe stenosis in 29 of the 32 ICAs (90.6%); the degree of stenosis according to CTA was 40, 50 and 60% in the three remaining cases. DSA confirmed severe stenosis in 24 ICAs (75%). The degree of stenosis diagnosed by DSA was 50% in two, 55% in one, 60% in four and 65% in one of the remaining cases. Both US and CTA tended to overestimate the degree of stenosis when compared with DSA, in 25.0 and 15.6%, respectively.

The overall correlation between the CTA and DSA (Pearson's correlation coefficient 0.725) was better than the correlation between the US and DSA (Pearson's correlation coefficient 0.601). However, the best correlation (Pearson's correlation coefficient 0.773) was achieved when counting the average percentage of stenosis from the values gained from the US and CTA, and comparing them with the percentage of stenosis measured by the DSA.

Comparison of sensitivity, specificity, PPV and NPV in the identification of severe ICA stenosis by US, CTA, and the average percentage of stenosis counted from US and CTA values, with DSA are shown in Table 2.

Homogeneity  $\chi^2$  test (applied to the frequency tables, describing the ability of the US, CTA and US + CTA to detect and correctly identify severe ICA stenosis in the comparison with DSA) reached the statistically significant value ( $P = 0.002$ ) only in the case of US, whilst the values for CTA and US + CTA ( $P = 0.098$ ) were not statistically significant.

Computed tomographic angiography was not associated with any complications. However, DSA transfemoral Seldinger technique was associated with technical problems (leading to the use of transbrachial approach) in one patient (3.4%). The use of transaxillary approach in another patient with a previous history of aortic-bifemoral bypass was planned and there was no attempt to use the transfemoral approach in this patient. DSA was associated with TIA in two patients (6.9%). Besides, mild groin hematomas were present as a local complication of DSA in several patients.

## Discussion

Sensitivity for the detection of severe (70–99%) ICA stenosis was 100% in all methods used. This is a very



**Figure 4** Severe (>90%) ICA stenosis shown on a DSA longitudinal projection image.

**Table 1** Characteristics of the set of patients – relationship between neurologic symptomatology and the side of severe ICA stenosis

	Number of patients
Ipsilateral TIA/stroke	17
Ipsilateral transient monocular blindness	1
Contralateral TIA/stroke	4
Vertebrobasilar territory symptomatology	5
Asymptomatic patient	2

TIA, transient ischemic attack.

**Table 2** Comparison of sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of the identification of severe ICA stenosis by US and CTA with DSA

Method	Sensitivity	Specificity	PPV	NPV
Duplex color-coded Doppler US	1.0	0.750	0.750	xxx
CT angiography	1.0	0.844	0.828	1.0
Duplex color-coded Doppler US + CT angiography	1.0	0.844	0.828	1.0

good result, when compared with some other studies, which focused on the diagnostics of such stenoses. The values of the US sensitivity reported in the literature ranged from 65 to 98% (Moneta *et al.*, 1993; Faught *et al.*, 1994; Neale *et al.*, 1994; Browman *et al.*, 1995; Barnett *et al.*, 1996; Hood *et al.*, 1996; Anderson *et al.*, 2000; Back *et al.*, 2000; Guo *et al.*, 2000; Huston *et al.*, 2000; Lovrenčić-Huzjan *et al.*, 2000; Dinkel *et al.*, 2001; Johnston and Goldstein, 2001; New *et al.*, 2001; Patel *et al.*, 2002); Demarin *et al.* (1989), Steinke *et al.* (1990, 1997), Keberle *et al.* (2001) and Rotstein *et al.* (2002)

also reported 100% US sensitivity in their studies. Our 100% CTA sensitivity was superior to the results in most of the studies, in which the values ranged from 65 to 95% in severe stenoses (Cumming and Morrow, 1994; Mildemberger *et al.*, 1997; Simeone *et al.*, 1997; Magarelli *et al.*, 1998; Sugahara *et al.*, 1998; Marcus *et al.*, 1999; Sameshima *et al.*, 1999; Anderson *et al.*, 2000; Patel *et al.*, 2002; Alvarez-Linera *et al.*, 2003); only Leclerc *et al.* (1999) and Randoux *et al.* (2001) also reported 100% sensitivity.

Specificity was low in the US (75%); higher specificity was obtained in the CTA and the combined US + CTA examination (84.4%). Still, our value of the CTA specificity was lower, when compared with that reported by other authors – Anderson *et al.* (2000) (up to 92%), Leclerc *et al.* (1999) and Marcus *et al.* (1999) (up to 96%), Mildemberger *et al.* (1997) and Alvarez-Linera *et al.* (2003) (up to 98%) and 100% published by Simeone *et al.* (1997), Sameshima *et al.* (1999), Randoux *et al.* (2001) and Patel *et al.* (2002). Our low US specificity was worse than the results of the majority of other studies (83–98%; Steinke *et al.*, 1990; Moneta *et al.*, 1993; Faught *et al.*, 1994; Neale *et al.*, 1994; Barnett *et al.*, 1996; Hood *et al.*, 1996; Guo *et al.*, 2000; Huston *et al.*, 2000; Lovrenčić-Huzjan *et al.*, 2000; Dinkel *et al.*, 2001; Keberle *et al.*, 2001; Rotstein *et al.*, 2002), however, it was better when compared with the other ones (46–74% – Browman *et al.*, 1995; Steinke *et al.*, 1997; Anderson *et al.*, 2000; Back *et al.*, 2000; Johnston and Goldstein, 2001; New *et al.*, 2001; Patel *et al.*, 2002).

Positive predictive value was higher in the CTA, and the US + CTA examination (0.828), than in the

separate US (0.75). A lower PPV value is connected with a higher portion of false-positive results. The PPV value found in our US was better (Anderson *et al.*, 2000; Back *et al.*, 2000; New *et al.*, 2001; Qureshi *et al.*, 2001), similar (Moneta *et al.*, 1993; Johnston and Goldstein, 2001), but also worse (Faught *et al.*, 1994; Hood *et al.*, 1996; Huston *et al.*, 2000; Lovrenčić-Huzjan *et al.*, 2000), when compared with other literary results. Our CTA PPV value was better than other reported results (Leclerc *et al.*, 1999; Anderson *et al.*, 2000).

Our NPV values were excellent and again, they were better when compared with the results reported by other authors (Moneta *et al.*, 1993; Faught *et al.*, 1994; Hood *et al.*, 1996; Anderson *et al.*, 2000; Back *et al.*, 2000; Huston *et al.*, 2000; Lovrenčić-Huzjan *et al.*, 2000; Johnston and Goldstein, 2001). However, Leclerc *et al.* (1999) also reported an NPV value of 1.0.

The value of the homogeneity  $\chi^2$  test for the US ( $P = 0.002$ ) means that only the results gained by the isolated use of the US differed significantly statistically from the results obtained using a 'gold standard' DSA. The differences found between the CTA and the US + CTA respectively, versus the DSA results were not statistically significant.

The total number of five (15.6%) ICAs would be indicated for CEA incorrectly (stenoses 50–69% according to the DSA) in the set of our patients, if they were examined only by the US and CTA. This result is similar to the value of 13% of such patients reported by Anderson *et al.* (2000). However, there would be no wrongfully denied surgery in severe ICA stenoses diagnosed by the means of the US and CTA in our patients; Anderson *et al.* (2000) reported 8% of such cases examined by CTA in their study.

There were no complications present after the CTA in our study. The incidence of neurologic deficit following the DSA (6.9%) was higher, but the absence of permanent neurologic deficit in our patients was better when compared with the results reported by other authors (Waugh and Sacharias, 1992; Warnock *et al.*, 1993; Heiserman *et al.*, 1994; Pryor *et al.*, 1996; Link *et al.*, 1997). However, local complications were present in several patients after the DSA.

We have to mention that examining only the patients with severe ICA stenoses, as detected by US, causes some selection bias and thus represents a certain limitation of our study.

Ultrasonography in combination with CTA can be used for a relatively sure diagnosis of severe (70–99%) ICA stenoses, in which CEA is considered, at our Stroke Center. These techniques can be employed if the result of transcranial color-coded ultrasonography

(TCCS) is interpretable for the exclusion of relevant tandem stenosis in the intracranial arteries (CTA can be used for the examination of intracranial vessels in the case, when TCCS gives uninterpretable finding even with the use of the US contrast). Elimination of the invasive DSA, which is connected with a higher risk of complications than the used examinations, is an advantage. CTA has another advantage – it allows visualization of the carotid artery wall and lumen rather than just the lumen showed by DSA (Leclerc *et al.*, 1995), and also US provides some additional information, such as plaque characteristics, content and surface (Middleton *et al.*, 1988; Demarin *et al.*, 1989; Steinke *et al.*, 1996; Tranquart *et al.*, 2000).

There are no risks of false-negative results in our patients; however, we are not able to avoid certain percentage of false-positive results, when CEA can be indicated in patients with moderate ICA stenosis (50–69%). In total, we think the advantage of the combined use of the US and the CTA in the identification and quantification of ICA stenoses is in our conditions higher, than its risk of false-positive results – especially, when the 60% (or even 50%) ICA stenoses are being discussed as the indication for CEA (Mayberg *et al.*, 1991; Hobson *et al.*, 1993; Executive Committee for the Asymptomatic Carotid Atherosclerosis Study, 1995; Barnett *et al.*, 1998; Mintz and Hobson, 2000; European Stroke Initiative Executive Committee and the EUSI Writing Committee, 2003).

In conclusion, the combination of US and CTA is an acceptable method for the quantification of severe carotid artery stenoses in a substantial number of patients thus avoiding DSA as an invasive and potentially harmful procedure.

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