Ultrasound in Med. & Biol., Vol. 41, No. 7, pp. 1827–1834, 2015

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2015.03.018

● *Original Contribution*

DELAYED TRANSCRANIAL ECHO-CONTRAST BOLUS ARRIVAL IN UNILATERAL INTERNAL CAROTID ARTERY STENOSIS AND OCCLUSION

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(*Received* 27 *October* 2014; *revised* 11 *February* 2015; *in final form* 12 *March* 2015)

Abstract—Some patients with internal carotid artery (ICA) occlusion or stenosis are at risk of developing a hemodynamic stroke. Transcranial ultrasonography using an echo-contrast bolus technique might be able to assess the extent of hemodynamic compromise. We describe a transcranial Doppler sonographic method that analyzes the differences in echo-contrast bolus arrival between both middle cerebral arteries after intravenous echo-contrast application. Ten patients with 50%–79% ICA stenosis, 10 patients with 80%–99% ICA stenosis and 22 patients with ICA occlusion were studied and compared with 15 age-matched controls. There were significant increases in delayed filling of the middle cerebral artery in both 80%–99% stenoses and occlusions compared with controls. The extent of the observed delays did not correlate with vasomotor reactivity. Echo-contrast bolus arrival time can be used to gain additional information on the intracranial hemodynamic effects of extracranial carotid artery disease that seems to be independent of the established ultrasound indices. (E-mail: jose.valdueza@segebergerkliniken.de) © **2015 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Doppler ultrasound, Echo contrast, Carotid stenosis, Stroke.**

INTRODUCTION

ICA disease is a common cause of ischemic stroke. The predominant pathophysiologic mechanism is thought to be thromboembolism. However, in 10% to 40% of cases with high-grade ICA stenosis or occlusion, stroke can also occur as a result of impaired hemodynamics (Szabo et al. 2001; Tsiskaridze et al. 2001; Wodarz 1980). Carotid endarterectomy has been proven beneficial in patients with symptomatic ICA stenosis >70% to 80% and in a selected group with high-grade asymptomatic stenosis (European Carotid Surgery Trialists' Collaborative Group 1998; Mayberg et al. 1991; North American Symptomatic Carotid Endarterectomy Trial [NASCET] Collaborators 1991; Walker et al. 1995). Although extra-intracranial bypass surgery can improve brain blood supply (Neff et al. 2004) in patients with ICA occlusion, it has failed to reduce the number of ischemic strokes, and almost exclusively conservative clinical management has subsequently been recommended (EC/IC Bypass Study Group 1985; Fluri et al. 2010), even in patients with confirmed cerebral hemodynamic impairment (Mendelowitsch et al. 2004; Powers et al. 2011).

Because of this dual embolic–hemodynamic role of carotid stenosis, different methods have been proposed to estimate the risk of stroke that relies on embolic (King and Markus 2009) or hemodynamic (King et al. 2011; Markus and Cullinane 2001) mechanisms. The hemodynamic effect of either high-grade carotid stenosis or occlusion has already been visualized in early angiographic studies that revealed ipsilateral delayed filling of the middle cerebral artery (MCA) (Fig. 1) (Boczko and Caplan 1967; Krayenbühl and Yasargil 1982) and in single-photon-emission computed tomography (SPECT) studies (Love et al. 1961; Oldendorf et al. 1960; Tolonen 1981). Today, non-invasive neuroimaging studies, especially magnetic resonance imaging (MRI), can offer similar information about cerebral hemodynamic status. Whereas classic time-of-flight (TOF) or arterial spin labeling (ASL)-based MR angiographic studies can indicate the pattern of collaterals at the circle of Willis (Anzola et al. 1995; Hoksbergen et al. 2003;

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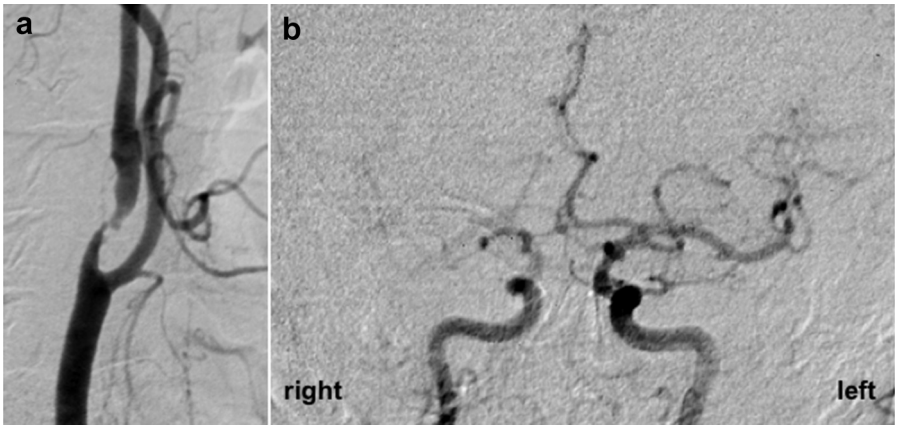

Fig. 1. Digital subtraction angiograms of a 75-y-old male patient with 80%–99% right internal carotid artery stenosis. (a) Selective right common carotid artery filling, lateral projection. (b) Aortic arch filling, anteroposterior projection. Contrast on the left side has already reached the M2 branches of the middle cerebral artery. On the right side, only the proximal M1 segment is visible, filling *via* retrograde flow in the hypoplastic right A1 segment of the anterior cerebral artery; the posterior circulation does not contribute to collateral supply (not shown). The ultrasonographic delayed echo-contrast bolus arrival (dMCA) in this patient was 1.08 s. Reprinted from Valdueza et al.: "Neurosonology and Neuroimaging of Stroke, 2008" with permission from Thieme Medical Publishers, Stuttgart, Germany.

Sallustio et al. 2008; Warmuth et al. 2005), perfusion studies either with gadolinium (Kajimoto et al. 2003) or based on ASL, have been able to disclose those cerebral areas with impaired blood flow in patients with severe carotid artery disease (Bokkers et al. 2008, 2009; MacIntosh et al. 2011). In ASL, magnetically labeled endogenous blood is used as a tracer for MRI sequences (Robson et al. 2010).

Classic ultrasonographic parameters used to evaluate hemodynamic status are the intra- and extracranial evaluation of collaterals, flow velocity, pulsatility index (PI) and the delay in systolic flow acceleration of the ipsilateral MCA, as well as the assessment of cerebral vasomotor reactivity (VMR) (Hartmann et al. 2000; Kelley et al. 1990; Kleiser and Widder 1992; Markus and Cullinane 2001; Ringelstein et al. 1988; Wilterdink et al. 1997).

The present study describes a new ultrasonographic technique used to analyze the differences in echo-contrast bolus arrival between both MCAs after intravenous administration of an echo-contrast agent. Intravascular ultrasound signal enhancer—initially designed to improve the signal-to-noise ratio in cases of insufficient transcranial insonation conditions (Zunker et al. 2002)—is used here in analogy to angiographic and MRI perfusion studies in patients with ICA stenosis and occlusion. The detected delays are compared with conventional ultrasonographic measures of impaired hemodynamics.

METHODS

Patients and controls

After giving informed consent, patients were included if they had a unilateral ICA stenosis >50% or occlusion determined with duplex ultrasound and a transcranial bone window suitable for transcranial Doppler (TCD) investigation. We excluded patients with dementia or aphasia so that we would have full cooperation during the study; we also excluded persons who had an acute stroke within the last 6 wk, additional contralateral stenoses >50% (stenoses defined by NASCET criteria) or intracranial stenoses detected by TCD. In addition, the contraindications to use of the echo signal enhancer Levovist (galactose intolerance, severe heart failure: New York Heart Association grades III and IV) were considered in controls and patients. Controls were included if no ultrasonographic signs of atherosclerotic artery disease could be found. Patients and controls were recruited from the routine diagnostic program of the neurologic ultrasound laboratory of the University Hospital Berlin Charité, Germany. The study protocol was approved by the local ethics committee.

Ultrasound protocol

All tests were performed with patients in a comfortable supine position. For extracranial duplex sonography a Toshiba Powervision 6000 system was used (7.5- to 9-MHz longitudinal transducer, SSA-370 A, Toshiba, Tokyo, Japan). The degree of stenosis was assessed using peak-systolic velocity, end-diastolic velocity and the ICA/common carotid artery (ACA) ratio, according to established duplex sonographic criteria adapted to NASCET criteria (Valdueza et al. 2008). Occlusion was assumed in cases of missing ICA flow (duplex setting: lowest pulse repetition frequency and high gain) and a concomitant clearly reduced diastolic flow in the distal