Ultrasound in Med. & Biol., Vol. 40, No. 11, pp. 2637–2641, 2014

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2014.06.017

● *Original Contribution*

ADDING BLOOD TO AGITATED SALINE SIGNIFICANTLY IMPROVES DETECTION OF RIGHT-TO-LEFT SHUNT BY CONTRAST-TRANSCRANIAL COLOR-CODED DUPLEX SONOGRAPHY

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(*Received* 29 *July* 2013; *revised* 14 *June* 2014; *in final form* 30 *June* 2014)

Abstract—Contrast-transcranial Doppler and contrast-transcranial color-coded duplex sonography (c-TCCD) have been reported to have high sensitivity in detecting patent foramen ovale as compared with transesophageal echocardiography. An international consensus meeting (Jauss and Zanette 2000) recommended that the contrast agent for right-to left-shunt (RLS) detection using contrast-transcranial Doppler be prepared by mixing 9 mL of isotonic saline solution and 1 mL of air. The aim of our study was to determine whether adding blood to the contrast agent results in improved detection of RLS. We enrolled all consecutive patients admitted to our neurosonology laboratory for RLS diagnosis. For each patient, we performed c-TCCD both at rest and during the Valsalva maneuver using two different contrast agents: ANSs (1 mL of air mixed with 9 mL of normal saline) and ANSHBs (1 mL of air mixed with 8 mL of normal saline and 1 mL of the patient's blood). To classify RLS, we used a four-level visual categorization: (i) no occurrence of micro-embolic signals; (ii) grade I, 1–10 signals; (iii) grade II, >10 signals but no curtain; grade III, curtain pattern. We included 80 patients, 33 men and 47 women. RLS was detected in 18.8% at rest and in 35% during the Valsalva maneuver using ANSs, and in 31.3% and in 46.3% using ANSHBs, respectively ($p < 0.0001$). There was a statistically significant increase in the number of micro-embolic signals with the use of ANSHBs. The use of blood mixed with saline solution and air as a c-TCCD contrast agent produced an increase in positive tests and a higher grade of RLS compared with normal saline and air alone, either with or without the Valsalva maneuver. (E-mail: mauro.gentile@unife.it) © **2014 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Contrast-transcranial color-coded duplex sonography, Right-to-left shunt diagnosis, Contrast-transcranial color-coded duplex sonography contrast agent.**

INTRODUCTION

Patent foramen ovale (PFO) is a component of normal fetal circulation. At birth during neonatal circulatory transition, pulmonary pressure falls after lung oxygenation, while systemic pressure acutely increases after cord clamping and placental exclusion. Increased left atrial pressure promotes compression of the septum secundum by the septum primum, inducing functional closure of PFO. Anatomic PFO closure occurs later in infancy in the majority of the population, but autopsy (Hagen et al. 1984) and echocardiography studies have revealed that anatomic closure is incomplete in approximately one of four adults. Therefore, PFO should be considered a normal anatomic variant in the absence of paradoxical embolism or other specific clinical conditions.

The association between PFO and cryptogenic stroke (CS) was first reported by Lechat et al. (1988). In that study, the prevalence of PFO, as detected by contrast echocardiography, was significantly higher in patients with stroke (40%) than in controls (10%). Among those with no identifiable stroke cause, the prevalence of PFO was 56%. Taken together, the existing retrospective studies suggest that PFO is more common in patients who have had a CS than in the general population (approximately 50%–60% vs. 20%–25%) or in patients with stroke of defined etiology. Today, the routine diagnostic workup of CS in young patients should exclude the presence of PFO or right-to-left shunt (RLS).

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Contrast-transesophageal echocardiography (c-TEE) is currently considered the diagnostic gold standard for detection of PFO. However, compared with c-TEE, contrast-transcranial Doppler (c-TCD) and contrast-transcranial color-coded duplex Sonography (c-TCCD) have been reported to have high sensitivity in detecting PFO (Chen et al. 1992; Nemec at al 1991; Pearson et al. 1991; Stendel et al. 1998). Both c-TCD and c-TCCD are less invasive and less dependent on patient cooperation than c-TEE. Moreover, the Valsalva maneuver (VM) can be performed more comfortably and more reliably during Doppler examination than during transesophageal echocardiography. Furthermore, the results are more quantifiable, and only c-TCD and c-TCCD can detect RLS occurring at levels other than the atria. In current clinical stroke management, these techniques are considered first-choice screening tools (Zito et al. 2009).

Previous studies on the diagnostic properties of different contrast agents for RLS detection, (Droste et al. 2002; Uzuner et al. 2004) found the sensitivity of shunt diagnosis to be higher when a contrast agent rather than agitated saline was used. However, commercial contrast agents are more expensive and not broadly available compared with normal saline. In contrast, agitated saline is a simple and cheap medium without side effects (Tsivgoulis et al. 2011).

An international consensus meeting (Jauss and Zanette 2000) recommended that in the detection of RLS using c-TCD, the contrast agent should be prepared by mixing 9 mL isotonic saline solution and 1 mL air using a three-way stopcock and exchanging the saline/air mixture between two syringes before injection of this mixture as a bolus into the cubital vein. The examination is performed at rest (basal condition) and, in case of detection of few or no microbubbles, is repeated during the VM, which should start 5 s after the injection and last 10 s. The strength of the VM can be controlled by peak flow velocity of the Doppler curve.

In the literature there are anecdotal reports on use of a mixture of agitated saline solution and blood as a contrast agent in diagnosis of RLS (Teague and Sharma 1991), but there are much fewer data on direct comparisons between this mixture and the saline–air only solution. Two previous studies (Lange et al. 2012; Shariat et al. 2011) compared agitated saline alone with agitated saline + blood for detection of RLS using c-TCD with inconclusive results. The aim of our study was to determine whether addition of blood to the contrast agent results in improved detection of RLS in the same patient.

METHODS

We enrolled all consecutive patients admitted to the Laboratory of Neurosonology for right-to-left shunt diagnosis. Exclusion criteria were age <18, absence of temporal window for c-TCCD and undetectable cubital venous access. Informed consent was obtained from all patients. The study was approved by the local ethics committee.

Contrast-transcranial color-coded duplex sonography was performed by three trained examiners (C.A., A.D., M.G.) with a Philips IU22 (Philips Electronics, Amsterdam, Netherlands) ultrasound machine using a multifrequency transcranial probe (1–5 MHz). For bubble detection, we used a small sample volume 5–8 mm in length and a low gain (Droste at al. 1999). The probe was hand-held by the examiner.

We insonated the right middle cerebral artery in the axial plane through the temporal window with the patient lying supine; the arm used for injection was in the horizontal position. The contrast agent was injected through a previously cannulated cubital superficial vein, during c-TCCD recording. The contrast agents tested were ANSs (air/normal saline solution), prepared by mixing 1 mL of air with 9 mL of normal saline, and ANSHBs (air/normal saline/homologous blood solution), prepared by mixing 1 mL of air, 8 mL of normal saline and 1 mL of the patient's blood. To create a well-agitated solution, according to the international consensus meeting, we connected two 10-mL syringes through a three-way stopcock and vigorously exchanged the solution between the syringes at least 10 times. Finally, we injected the solution as a bolus as rapidly as possible to prevent the formation of larger air bubbles and clots (Jauss and Zanette 2000).

We recorded c-TCCD in four different experimental conditions for each patient: (i) at rest using ANSs, (ii) at rest using ANSHBs, (iii) during a VM using ANSs, (iv) during a VM using ANSHBs. Tests were consecutively performed in each patient with a minimum interval of 5 min between tests; the contrast solution used first (ANSs or ANSHBs) was randomly chosen for each patient. We trained patients in performance of the VM before the tests. The efficacy of the VM was evaluated by verifying a minimum 25% decrease in peak flow velocity of the Doppler spectrum. The Valsalva maneuver began 5 s after the contrast agent injection and lasted 10 s. We defined the micro-embolic signal as a transient, short (<0.01–0.03 s), unidirectional increase in the flow Doppler spectrum with a typical visible and audible pattern (whistle, chirping or clicking) (Babikian 1995; Ringelstein et al. 1998). According to Ringlestein et al. (1998), because embolic signals may only occasionally produce bidirectional signals and most of the bidirectional signals are artifacts, we decided to consider only unidirectional signals so as not to include artifacts. Diagnosis of right-to-left shunt was based on the recording of at least one micro-embolic signal on c-TCCD.