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### **Clinical Research**

# Transcranial Doppler is Complementary to Echocardiography for Detection and Risk Stratification of Patent Foramen Ovale

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#### **ABSTRACT**

**Background:** In patients with patent foramen ovale (PFO), strategies are needed to identify patients at higher risk, who might benefit from PFO closure.

Methods: We studied the frequency of detection of a right-to-left shunt (RLS) using transesophageal echocardiography (TEE) among patients with cryptogenic stroke and transcranial Doppler (TCD) to detect RLS, and analyzed the prediction of recurrent stroke according to TCD shunt grade, by detection of RLS on TEE, and by atrial septal aneurysm or mobility.

**Results:** Among 334 patients with TCD, 69.8% were female, with a mean (SD) age of 53 (14) years, with a median follow-up of 420 days. There were 284 cases with TCD and TEE; 54 (19%) had atrial septal aneurysm or mobility. Echocardiography failed to show a RLS in 43 (15.1%) of the patients who had TCD and TEE, even in some patients with high-grade shunts on TCD: 18 (42%) were grade 3 or higher on TCD. Survival free of stroke or transient ischemic attack was predicted significantly by TCD shunt grade < 2 (P = 0.028), shunt grade < 3

#### RÉSUMÉ

Introduction: Chez les patients présentant un foramen ovale perméable (FOP), il faut établir des stratégies afin d'identifier ceux qui présentent un risque plus élevé et qui pourraient bénéficier d'une fermeture du FOP.

Méthodes: Nous avons étudié la fréquence de détection d'un shunt droite-gauche (SDG) à l'aide d'une échocardiographie transcesophagienne (ETO) chez les patients ayant subi un accident vasculaire cérébral (AVC) cryptogénique et un Doppler transcrânien (DTC) visant à déceler un SDG. Nous avons ensuite analysé la prédiction de survenue d'un autre AVC d'après le grade du shunt déterminé par le DTC, la détection du SDG à l'aide de l'ETO et la présence d'un anévrisme du septum interauriculaire ou de la mobilité de ce dernier. Résultats: Parmi les 334 patients ayant subi un DTC, 69,8 % étaient des femmes âgées en moyenne (écart-type) de 53 (14) ans, le suivi médian s'établissant à 420 jours pour les 284 cas ayant subi un DTC et une ETO; 54 patients (19 %) présentaient un anévrisme du septum interauriculaire ou une mobilité de ce dernier. Il n'a pas été possible de

Management of paradoxical embolism is a difficult clinical problem. Approximately 25% of the population have a patent foramen ovale (PFO), and a small percentage have additional passages from the pulmonary to the systemic circulation (right-to-left shunt [RLS]) such as pulmonary arteriovenous fistula, atrial septal defect, or ventricular septal defect. Approximately 2% of ischemic strokes in young people are due to pulmonary arteriovenous fistulae. However, only

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See page 986.e15 for disclosure information.

4%<sup>3</sup>-5.5%<sup>4</sup> of ischemic strokes are due to paradoxical embolism. Kent and Thaler<sup>5</sup> calculated that among patients with cryptogenic stroke, half of PFO's are incidental. This poses a major problem for statistical power in trials randomizing patients with PFO and stroke or transient ischemic attack (TIA) to percutaneous closure vs medical therapy, as well as a challenge for management decisions in patients.

Indeed, despite rather widespread use of percutaneous closure outside of trials,<sup>6</sup> the randomized trials,<sup>7,8</sup> have failed to show in intention-to-treat analyses that percutaneous closure of PFO reduced the risk of recurrent stroke or TIA, although per-protocol or subgroup analyses suggested benefit. Similar results were obtained in a trial of percutaneous closure of PFO in migraine.<sup>9</sup> The decision to deploy percutaneous closure devices is made difficult by complications, including a greater risk of atrial fibrillation with some of the devices; it has

(P=0.03), and shunt grade <4 (P<0.0001); this was attenuated by adjustment for risk factors in Cox regression (P=0.08). Neither RLS on TEE (P=0.47), or atrial septal aneurysm or mobility (P=0.08), predicted events.

Conclusions: Our findings suggest that TCD might be more sensitive than TEE for detection of RLS, which misses some cases with substantial RLS, and might be valuable for prediction of recurrent stroke or transient ischemic attack in patients with PFO. TCD complements TEE for management of suspected paradoxical embolism.

been suggested<sup>8</sup> that percutaneous closure might do more harm than good. A meta-analysis suggested a benefit in the time-to-event analysis, but the greater risk of atrial fibrillation in patients who underwent percutaneous closure might limit the potential benefit of such procedures.<sup>10</sup>

Some early small studies suggested 11,12 that high-risk features of PFO such as degree of shunting, atrial septal aneurysm, or septal mobility could be identified using echocardiography, but the recent results of the Risk of Paradoxical Embolism (RoPE) study 13 and the Northern Manhattan Study 4 suggest otherwise. The authors of the latter study concluded 14 that "Additional tools to describe PFOs might be useful in helping to determine whether an observed PFO is incidental or pathogenically related to (cryptogenic stroke)."

One such tool might be transcranial Doppler (TCD) saline studies. Some authors have suggested <sup>15,16</sup> that TCD might be more sensitive than echocardiography for detection of PFO. One likely reason is that sedation for transesophageal echocardiography (TEE) might prevent an adequate Valsalva manoeuvre. <sup>17</sup> Another is the striking sound of the bubbles on TCD (see Videos 1 and 2 with view videos online). One study in 59 patients indicated that larger RLS detected using TCD predicted risk of stroke.

The main objectives of the present study were to assess the frequency of RLS detected using TEE saline study with sedation in patients with RLS on TCD, and to compare the prediction of recurrent stroke according TCD shunt grade, by detection of RLS on TEE, and by the presence of atrial septal aneurysm or atrial septal mobility.

#### **Methods**

#### Study population

All patients referred to J.D.S., an experienced stroke neurologist, at the Urgent TIA Clinic at University Hospital, London, Canada, between its inception in 2000 and the closure of the database in October 2013 were considered for inclusion in the analyses if they had complete data and a TCD

détecter un SDG par échocardiographie chez 43 des patients (15,1 %) qui avaient subi un DTC et une ETO, et ce, même chez certains patients qui montraient un SDG de grade élevé au DTC: en effet, 18 patients (42 %) affichaient un grade 3 ou plus élevé au DTC. La survie sans AVC ni ischémie cérébrale transitoire a été prédite de façon significative en fonction d'un grade de shunt déterminé par un DTC < 2 (p=0,028), d'un grade de shunt < 3 (p=0,03) et d'un grade de shunt < 4 (p<0,0001); ces valeurs ont été ajustées en fonction des facteurs de risque du modèle de régression de Cox (p=0,08). Ni la présence d'un SDG détecté par ETO (p=0,47) ni celle d'un anévrisme du septum interauriculaire ou de la mobilité de ce dernier (p=0,08) n'ont permis de prédire les événements.

Conclusions: Nos résultats donnent à penser que le DTC pourrait s'avérer plus sensible que l'ETO dans la détection du SDG, puisque certains cas pourtant considérables de SDG n'ont pas été détectés, et pourrait être utile dans la prédiction des AVC ou d'ischémies cérébrales transitoires récurrents chez les patients atteints d'un FOP. Notons enfin que le DTC est un complément à l'ETO dans la prise en charge des cas soupçonnés d'embolie paradoxale.

or TEE examination. The reason for performing TCD and TEE was that patients had cryptogenic stroke (ie, no other apparent cause of stroke found in their other investigations including history, neurological examination, carotid ultrasound examination, assessment of intracranial stenosis using TCD, magnetic resonance imaging, or computed tomography, 48-hour Holter recording, or blood tests). Furthermore, in many cases, the reason for performing TCD embolus detection was that clues to paradoxical embolism, discussed in the *Discussion* section, were present in the history. Patients with atrial fibrillation, and other apparent cardiac sources of emboli were excluded, as were patients with lacunar infarction and large artery disease. Tests for coagulation disorders were not available in some cases (they are rationed in our hospital by the Hematology division). The protocol was approved by the Western University Health Sciences Research Ethics Board (review number 12107E).

Cases were first identified from the clinic database, and then their paper files and the hospital medical record were searched for any missing data. Recurrent stroke or TIA was ascertained at clinic follow-up visits and confirmed from hospital medical records.

#### TCD saline bubble studies

In most cases the TCD examination was performed before the TEE (usually the same day as the initial clinic visit). Assessment of RLS grade was performed using Spencer Technologies ST3 Power M-mode Transcranial Doppler, with bitemporal 2-MHz probes. Initially, all patients were assessed for the presence of temporal windows on both sides for right and left middle cerebral artery (MCA) monitoring. When the temporal access of at least 1 MCA was confirmed, a head frame was placed on the head to maintain the 2 TCD probes in place for monitoring; insonation was focused at a depth of 40-60 mm.

Patients were placed in a semirecumbent position and a 21-gauge butterfly needle was inserted in an antecubital vein of the most convenient forearm. The catheter of the butterfly needle was connected with a 3-way stopcock system to 2

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