Transcranial Doppler ultrasonography in the detection of venous to arterial shunting in acute stroke and transient ischaemic attacks

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Abstract

Objectives—To prospectively evaluate the prevalence of venous to arterial shunting in patients with acute stroke and transient ischaemic attacks (TIAs) using transcranial Doppler ultrasonography (TCD) with saline contrast.

Methods—A consecutive series of patients with stroke or TIA underwent contrast TCD. Patients were subsequently divided into groups according to causative factors for stroke or TIA. The prevalence of right to left shunt was assessed within these groups.

Results—A total of 210 patients underwent contrast TCD. A right to left shunt was detected in 28.6% of patients (60 of 210). Among the patients with cryptogenic stroke or TIA, 37.1% (43 of 116) had a positive contrast TCD whereas only 18% (17 of 94) with another identifiable cause had a positive test ($P = 0.0024$). When age was used to further classify those patients with cryptogenic stroke, TCD was positive in 59.3% patients (16 of 27) of ≤ 50 years of age versus 30.3% of patients (27 of 89) > 50 years of age ($P = 0.0058$).

Conclusions—There was a significantly higher prevalence of venous to arterial shunting in patients with stroke or TIA of undetermined cause than in stroke patients with identifiable aetiologies, as detected by contrast TCD. The prevalence of a venous to arterial shunt was significantly higher in the younger group with cryptogenic stroke. Saline contrast TCD is a relatively non-invasive bedside procedure useful in the detection of venous to arterial shunting.

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Even after extensive investigations, the cause of ischaemic stroke remains undetermined in as many as 35%–40% of patients, especially in younger adults.¹⁻⁴ Young people may display mitral valve prolapse or venous to arterial shunting (patent foramen ovale or atrial septal defect) as a probable cause for stroke.²⁻⁵ A right to left shunt may allow paradoxical embolisation of peripheral venous thromboemboli into the arterial circulation causing stroke or transient ischaemic attacks (TIAs), even in the absence of the usual clinical fea-

tures of deep vein thrombosis and pulmonary hypertension.^{3,4,6-10} Paradoxical emboli could also be an important cause of strokes in the older patient population as clinically silent venous thromboses are common^{4,11,12} and a patent foramen ovale has been detected in up to 24% of elderly subjects.^{2,4,7,13,14} The identification of a patent foramen ovale as an important risk factor for stroke would have major implications for stroke prevention and management.

Previous studies, using transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE) with saline contrast, have reported that paradoxical embolism through a patent foramen ovale may be a cause for stroke in 40%–50% of young patients in whom there is no other obvious identifiable cause.^{2,4,14,15}

Transcranial Doppler ultrasonography (TCD) with saline contrast is a sensitive technique for the detection of right to left interatrial shunting and potential direct involvement of the cerebral target organ.^{8,17,18} It is a relatively simple bedside procedure and well tolerated by most patients when compared with transoesophageal echocardiography (TEE), the current reference standard used to differentiate interatrial shunting from pulmonary vasculature shunting.¹⁷ In addition, TEE is relatively invasive, more expensive, and may not be appropriate in acute stroke patients in whom sedation may be contraindicated. We prospectively evaluated the prevalence of venous to arterial shunting in patients with acute stroke and TIA using TCD with saline contrast.

Methods

PATIENTS WITH STROKE OR TIA

The study population consisted of consecutive patients admitted to the Royal University Hospital at the University of Saskatchewan with a diagnosis of stroke or TIA between 1 April 1994 and 31 March 1995. The clinical diagnosis was made by an attending neurologist. Stroke was defined as an acute focal ischaemic neurological deficit that persisted for at least 24 hours. A TIA was defined as a focal ischaemic neurological deficit that resolved within 24 hours. All patients underwent a diagnostic investigation which included general medical and neurological examinations, general blood chemistry, chest radiograph, 12 lead ECG, head CT or MRI, carotid duplex (B mode and Doppler) scanning, and transcranial Doppler examinations.

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Transthoracic and transoesophageal echocardiography were performed in selected cases. Patients were excluded if there was: impaired consciousness for more than five days; respiratory failure; haemorrhage on CT; inability to perform a Valsalva manoeuvre; inability or refusal to give informed consent; and technical failure of insonation of the middle cerebral artery by TCD. All clinical data were collected prospectively. Informed consent was obtained from all patients. The research protocol was approved by our institutional review board.

After these studies had been performed, the patients were divided into four groups as previously described by Amarenco *et al.*¹⁹ Assignments were made without knowledge of the TCD findings. Group A comprised patients with stroke likely to have been caused by > 70% stenosis of the ipsilateral internal carotid artery, a definite cardiac source of embolism (acute anterior myocardial infarction, atrial fibrillation with left atrial thrombus or spontaneous echo contrast, mural thrombus in left heart cavities, mitral stenosis, a prosthetic heart valve, or endocarditis), or arterial dissection. Group B comprised patients with infarcts that may have been caused by 31% to 69% stenosis of the ipsilateral carotid artery, isolated atrial fibrillation, or atrial fibrillation occurring after the brain infarction. The third group, group C, was presumed to have lacunar infarcts due to thrombosis of small penetrating intracranial arteries, with one of the four major lacunar syndromes (pure motor hemiplegia, pure sensory loss, ataxic hemiparesis, or sensorimotor impairment) and with infarcts that were small (< 15 mm) and deep or not demonstrable with CT or MRI in the absence of a cardiac or carotid source of embolism. Patients in the fourth group, group D, had no detectable lesions or no definitive cause for stroke such as ipsilateral carotid stenosis of $\leq 30\%$, or mitral valve prolapse.

DETECTION OF RIGHT TO LEFT ARTERIAL SHUNTS

All eligible patients underwent transcranial Doppler (TCD) examination with agitated saline injection; TCD examinations were performed within seven days of the patient's admission using an EME TC/2000 (Eden Medizinische Elektronik, Uberlingen, Germany) with a 2 MHz hand-held pulsed Doppler transducer. Signals were recorded for analysis on videotape linked to an IBM compatible microcomputer. The middle cerebral artery was insonated via the temporal window.²⁰

Microcavitation saline contrast was generated by agitating a mixture of 9 ml normal saline and 1 ml air between two 12 ml syringes connected by a three way stopcock.²⁴⁵ Once the contrast was prepared, it was injected directly into a cubital vein which had previously been cannulated with an 18 gauge indwelling intravenous catheter. Appearance of microbubbles in the cerebral circulation was indicated by a characteristic "chirping" or "popping" sound in the Doppler signals from the middle cerebral artery and a corresponding

video spike.^{15 17 18 21 22} These signals were of much higher intensity than the background Doppler flow signal and subjectively correlated in intensity with the quantity of bubbles shunting right to left.

A five minute baseline TCD recording of the middle cerebral artery was performed followed by two saline contrast injections given during normal respiration. This was then repeated during performance of the Valsalva manoeuvre for five seconds. The Valsalva manoeuvre has been reported to detect the presence of a patent foramen ovale with a sensitivity of 60% and a specificity of 78%.⁴ When at least one spike appeared less than 20 seconds after injection, we considered the TCD positive and assumed direct passage through a patent foramen ovale; when the onset of the bubble signature was later than 20 seconds, pulmonary passage was assumed.¹⁸ A repeat five minute TCD recording was performed after the contrast injections.

STATISTICAL ANALYSIS

The significance of the prevalence of a right to left shunt in stroke patients was determined by the Mantel-Haenszel χ^2 test.

Results

A total of 428 patients were admitted with the diagnosis of acute stroke or TIA between 1 April 1994 and 31 March 1995. After excluding ineligible patients, 210 patients (49%) had TCD with saline contrast examinations. There were 148 patients with stroke (33 had lacunar syndromes), and 62 patients with TIA. There were 134 men (mean age 65, range 12–86 years) and 76 women (mean age 63, range 23–86 years).

A right to left shunt was detected by TCD contrast studies in 60 patients (28%), 33 (24.6%) in men and 27 (35.5%) in women; mean age was 61 (range 12–86) years. The appearance of the high intensity transient signals on TCD occurred within 20 seconds in all patients. The venous to arterial shunt was detected spontaneously in 44 patients, whereas the Valsalva manoeuvre was required to show its presence in 16 patients. The TCD procedure was well tolerated by all patients.

Of the 60 patients with a positive TCD, 16 underwent transoesophageal echocardiography with saline contrast. Fourteen had confirmation of a patent foramen ovale (87.5% correlation); one patient had a large pulmonary arteriovenous malformation (6.5%), and one patient had a normal TEE (6.5%). This TEE was an inadequate study as the Valsalva manoeuvre was not performed and the TCD had been positive only during the Valsalva manoeuvre.

GROUP A

This group comprised 37 patients (17.6% of 210 patients). Carotid stenosis $\geq 70\%$ occurred in 22. Two had ipsilateral carotid artery dissection. Six had new onset atrial fibrillation or atrial flutter. Aortic thrombus was found in one patient, and three had a left ven-

Figure 1 Prevalence of positive TCD with saline contrast studies in patients with stroke or TIA. Prevalence in group A (patients with stroke likely to have been caused by $\geq 70\%$ stenosis of ipsilateral internal carotid artery, a definite cardiac source of embolism, or arterial dissection) was 24.3%; in group B (patients with infarcts caused by 31% to 69% stenosis of ipsilateral carotid artery, isolated fibrillation, or atrial fibrillation occurring after stroke), 3.8%; in group C (lacunar infarctions), 22.6%; and in group D (stroke of undetermined origin), 37.1% ($P = 0.0024$).

tricular mural thrombus. Mitral stenosis, a prosthetic mitral valve, and a pulmonary arteriovenous malformation was present in one patient each.

Contrast TCD was positive in nine patients in this group (24.3%). Four patients had carotid atherosclerosis, four had new onset of atrial fibrillation, and one had a large pulmonary arteriovenous malformation associated with hereditary haemorrhagic telangiectasia.

Five patients (13.5%) in this group were 50 years of age or less; none had a positive TCD.

GROUP B

This group comprised 26 patients (12.4% of 210 patients) with moderate (31%–69%) carotid stenosis, isolated atrial fibrillation, or left ventricular dysfunction with no evidence of mural thrombus. Of these patients, 13 had chronic isolated atrial fibrillation, five had moderate ipsilateral carotid stenosis, four had previous myocardial infarctions with mild to moderate left ventricular dysfunction and no evidence of mural thrombus on transthoracic echocardiography, two had chronic atrial fibrillation and a previous myocardial infarction, and two had cardiomyopathy.

Contrast TCD was positive in one patient with chronic atrial fibrillation (3.8%).

Five patients (19.2%) were 50 years of age or younger; none had a positive TCD.

GROUP C

Thirty one patients (14.8%) had lacunar syndromes. TCD was positive in seven patients (22.6%). Five patients (16.1%) were 50 years old or younger; none had a positive TCD.

GROUP D

This group comprised 116 patients (55.2%). Four patients had an ipsilateral carotid stenosis $\leq 30\%$, one patient had mitral valve pro-

Figure 2 Prevalence of positive TCD with saline contrast within group D (stroke or TIA of undetermined origin) according to age. In patients ≤ 50 years of age, prevalence was 59.3%; in the older age group, prevalence was 30.3% ($P = 0.0058$).

lapse, and one patient had an interatrial septal aneurysm. The remainder (110 patients, 94.8%) had no associated coagulopathy, arterial problem, or cardiac abnormality detected.

Contrast TCD was positive in 43 (37.1%) of these patients, two of whom had a non-significant ipsilateral carotid stenosis.

When patients with cryptogenic stroke or TIA and a positive TCD (43 positive TCDs in 116 patients) were compared with patients with stroke or TIA of other probable origin and a positive TCD (groups A+B+C: 17 positive TCDs in 94 patients), a significant difference was found ($P = 0.0024$; fig 1).

Group D was further divided according to age—27 patients (23.1%) were 50 years of age or less, and 89 patients (76.7%) were older than 50. Contrast TCD was positive in 16 patients (59.3%) in the younger age group, and in 27 (30.3%) in the older age group ($P = 0.0058$; fig 2). When these two age groups were further divided into age ranges < 36 years, 36–50 years, 51–65 years, and ≥ 66 years, prevalences of a positive TCD study were 66.7%, 55.6%, 21.4%, and 33.9% respectively.

Within groups A, B, and C, a total of 15 patients were ≤ 50 years of age; TCD was negative in this age group. Contrast TCD was positive only in the 17 older patients (20.7% of 82 patients).

Discussion

Saline contrast TCD detected a 28% prevalence of venous to arterial shunting in our overall patient population. This correlates well with the 25 to 35% prevalence of patent foramen ovale reported in necropsy series.¹³

Group B showed a very low prevalence of right to left shunting. This may be related to patient selection or the low numbers within this group.

In group D, in which patients had no discernible cause of stroke, the prevalence of a venous to arterial shunt as detected by TCD

saline contrast studies was significantly higher than in the other three groups (36.8% *v* 17.9%). This became even more significant when age was taken into consideration—the prevalence of a right to left shunt in patients with no cause found for their stroke who were ≤ 50 years of age was 59% *v* 30.3% in the older group (fig 2). This high prevalence was also higher than in the general population.^{13 23}

Lechat *et al*, using transthoracic contrast echocardiography (TTE), have shown a 40% prevalence of patent foramen ovale in young patients with stroke compared with 10% prevalence in control subjects; furthermore, the prevalence of patent foramen ovale was 21% in patients with an identifiable cause for their stroke, 40% in patients with no identifiable cause but with risk factors for stroke, and 54% in patients with no identifiable cause or risk factors for stroke.⁴ Other studies have shown a similar high prevalence of patent foramen ovale (42%–54%) in patients with cryptogenic stroke.^{2 4 7 24}

An increased prevalence of patent foramen ovale in patients with cryptogenic stroke has been found both in patients younger than 55 years (48% compared with 4% in patients with stroke of determined cause) and in the older population (38% *v* 8%).^{2 21} These findings would suggest that a patent foramen ovale may be a risk factor for cryptogenic stroke regardless of age of the patients.

Several reports have shown that transthoracic echocardiography is the least sensitive technique for detecting a patent foramen ovale when compared with TEE and TCD.^{7 25–33} The sensitivity of TCD for detection of patent foramen ovale ranges from 87% to 100%, with a specificity of 100%,^{25 26} using TEE as the reference standard. Overall, TCD seems to be very sensitive in detecting large or moderate shunts, but less sensitive for smaller ones.²⁷ In our study, all 15 patients who underwent technically complete (both with and without Valsalva) TEE with saline contrast had confirmation of right to left shunting, with a patent foramen ovale confirmed in 14 patients and a pulmonary arteriovenous malformation in one. In addition, because of a positive contrast TCD study, one of these patients underwent several contrast injections during TEE before a small patent foramen ovale was eventually detected. Corroborative confirmation of right to left shunting by TEE in the remaining 45 patients was not obtainable due to logistical difficulties.

Detection of patent foramen ovale by contrast echocardiography or TCD implies a reversal of the normal interatrial pressure gradient, either spontaneously or during provocative manoeuvres; this may not be valid as contrast echocardiography has demonstrated that microcavitation contrast can cross a patent foramen ovale in the absence of high pulmonary pressure.⁴ Our study would tend to confirm this, as most of our positive TCD contrast studies occurred during normal respiration, and not during the Valsalva manoeuvre.

Our results suggest that paradoxical

embolism through a patent foramen ovale could be a major risk factor for stroke, especially in the younger population with cryptogenic stroke. Paradoxical embolism is considered an infrequent event, accounting for fewer than 2% of all arterial emboli.¹¹ Loscalzo found that a patent foramen ovale was the most commonly detected intracardiac shunt (72%) in cases of presumed or established paradoxical embolus.³⁴ A clinical diagnosis of paradoxical embolism can be made using the following criteria: arterial embolism without a left sided circulation source; potential for right to left shunting; previous venous thrombosis or pulmonary embolism; and increase in right heart pressure.^{9 11 35 36}

Ranoux *et al*³⁷ found a 57% incidence of patent foramen ovale in patients with strokes of undetermined aetiology. However, they were unable to confirm the presence of a deep venous thrombosis, their main criterion for paradoxical emboli. Deep vein thromboses may be difficult to confirm as the source of embolism because less than 50% of patients with them have clinical symptoms and signs.^{11 12 35} Therefore, it is possible that systemic embolism could be of paradoxical origin in the presence of a patent foramen ovale when there is no clinical evidence of thrombophlebitis.^{9 12} In a recent report, patients with cryptogenic stroke and an established patent foramen ovale were examined for venous thrombosis with Duplex sonography and phlebography; potential embolic sources were present in 31% of patients.³⁸ Further studies are needed to characterise the relation between stroke associated with a patent foramen ovale and latent venous thrombosis.

The diameter of a patent foramen ovale tends to increase with increasing age.¹³ The prevalence of venous thrombosis is also increased in elderly people.^{35 36} These two factors might make elderly people more susceptible to paradoxical embolism, especially after manoeuvres that increase right heart pressures, such as cough or defecation.² However, Vella *et al*¹⁴ and Jones *et al*³⁹ found a low prevalence of haemodynamically significant patent foramen ovale in elderly people who had cryptogenic stroke. They suggested that most patent foramen ovals in older people were physiologically unimportant. Our results would tend to agree that a right to left shunt as a risk factor in stroke of undetermined aetiology is higher in the younger (≤ 50 years) age group; however, we also noted that the prevalence was higher in the age group ≥ 66 years.

Other authors have noted the association of atrial septal aneurysm and patent foramen ovale as significant synergistic risk factors for stroke.^{15 40 42} Lone atrial septal aneurysm is associated with cardiogenic embolism, but when accompanied by interatrial shunts, this association is even more significant. In the Lausanne study,⁴³ only 25% of 140 patients with known patent foramen ovale had an associated atrial septal aneurysm; the interatrial communication was a significant risk factor for recurrent stroke whereas the associated atrial septal aneurysm was not.

How aggressively a right to left shunt should be sought in patients with stroke depends on the therapeutic interventions that would be introduced on the basis of its detection.²⁷ No evidence is presently available to suggest that any treatment for a patent foramen ovale will affect the prognosis of a patient who has had a true paradoxical embolus. In most cases, the treatment of choice in acute stroke and an associated patent foramen ovale is unclear.

We have shown that there is a significantly higher association of venous to arterial shunting in patients with acute stroke or TIA of unknown cause than in patients with identifiable aetiologies, using transcranial TCD with saline contrast. Although TEE may define the pathology of the shunt,²⁷ TCD provides evidence of potential direct involvement of the cerebral arterial circulation.¹⁷ It is a relatively non-invasive, bedside procedure that is well tolerated by most patients. We recommend that TCD with saline contrast should be an early investigative tool in ascertaining the cause of stroke, especially in the younger stroke population, in whom aetiology is often undetermined. A positive contrast TCD may warrant an extensive search for venous sources of emboli.

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