Stroke in Young Adults: The Role of Paradoxical Embolism

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Venous to arterial circulation shunt, foramen ovale, transcranial doppler, ischaemic stroke

Summary
Stroke in young adults may be devastating and frequently no cause can be found. However, there is ample literature to suggest an association between cryptogenic stroke in young people and paradoxical embolisation via a venous to arterial circulation shunt (v-aCS), commonly due to patent foramen ovale (PFO). Although paradoxical embolisation is assumed to be a rare event, this review suggests that it is an important or even dominant cause of stroke in young people and that a transcranial Doppler (TCD) technique may be the investigation of choice to identify v-aCS.

Methods

Introduction
The reported annual incidence of stroke in women of reproductive age in California is 10.7 per 100,000, in young people of both sexes in Sweden and the Netherlands this incidence is 11.3 per 100,000 and 6.6 per 100,000 respectively (1-3). No aetiology can be identified in up to 40% of these young patients and these strokes are referred to as “cryptogenic” (4). Even when a cause is identified, how can we be confident that a stroke is caused by migraine in a young woman with a history of headache or related to smoking in a young smoker? Investigation for PFO has not been routine in stroke patients and until recently paradoxical embolism has been considered to be a rare curiosity. Although stroke in the young is rare, the implications to both the patient and society are immense. With the increasing availability of techniques to both identify and close PFO to prevent paradoxical embolism, the importance of v-aCS in young adults with stroke is now obvious.

Four criteria for the confident diagnosis of paradoxical embolism are frequently cited (10, 11):
1. Arterial embolism with no evidence of a source in the left heart or arterial circulation.
2. Evidence of an abnormal communication between the right and left circulations.
3. Confirmation of venous thrombosis or embolism; either deep vein thrombosis (DVT) or pulmonary embolism.
4. A pressure gradient that favours right-to-left shunting, although this may be transient e.g. during the Valsalva manoeuvre or coughing.

The first three of these criteria comprise Johnson’s triad (12, 13). Although logical, these criteria are usually unhelpful in confirming paradoxical embolism as criteria 3 is rarely fulfilled and 4 almost never measured.

Paradoxical Embolism

Paradoxical embolism, the transmission of a venous embolus to the arterial circulation via a defect in the cardiac septum or a pulmonary arterio-venous malformation, was originally thought to be a rare curiosity. Consequently, a number of case reports have been published which even include the remarkable circumstance of thrombus actually found within the PFO either on post mortem or during echocardiography (Appendices I and II). One of these reports refers to 52 verified cases of a blood clot trapped within a PFO (5). Although these demonstrate “publication bias” with only special or interesting cases being reported; their frequency suggests that paradoxical embolism may occur more often than previously realised.

Congenital Cardiac Abnormalities Causing Right to Left Shunt

Congenital heart disease occurs in 8-10/1,000 live births (6). Many are major and lead to reduced life expectancy, yet most patients with isolated septal defects enjoy a good quality of life. Atrial septal defects are considerably more frequent than ventricular defects and PFO is by far the most common (6). The valve like nature of a PFO only permits right to left shunting whereas a true atrial septal defect allows bi-directional blood flow (7). A PFO therefore has little or no influence on normal cardiac function and has been assumed to have no clinical significance. However, although a large embolus is required to cause a clinically significant pulmonary embolus, emboli as small as 1 mm in diameter may pass through a PFO to enter the cerebral circulation causing stroke (8, 9).

Criteria for Diagnosing Paradoxical Embolism

Deep venous thrombosis. Even in patients with proven pulmonary embolism, a DVT is often not found despite appropriate investigations (14, 15). In stroke caused by paradoxical embolism, this picture is
Further complicated by the frequency of DVT in legs paralysed by stroke, so that it may be difficult to identify whether a DVT was the cause or the result of the stroke (16). In an observational study of PFO in patients presenting with a variety of suspected paradoxical emboli, Stollberger et al demonstrated that only 24 out of 42 patients had venographically proven DVT (17). As venography was performed after the stroke, there was a risk that DVT developed following the stroke. Even when such patients were given DVT prophylaxis, the rate of thrombosis was between 4 and 13 percent (18, 19). Failure to document a DVT does not exclude the possibility of paradoxical embolism any more than it would exclude the diagnosis of pulmonary embolism (18).

**Elevated right atrial pressure.** Left atrial pressure is normally higher than the pressure in the right atrium so that the valve mechanism of a PFO is closed and no shunting occurs. However during coughing or Valsalva manoeuvres, right atrial pressure rises allowing a transient v-aCS. It is possible that the increased risk of stroke in patients with pulmonary disease is explained by the higher pulmonary artery and right heart pressures found in these patients and to transient increases in right heart pressures during coughing (21).

**Pulmonary Embolism**

Right heart pressure may also increase following pulmonary embolism and in a prospective study of 139 patients with pulmonary embolism, the presence of a PFO in 48 patients (35%) increased the risk of stroke from 2.2% to 13% (22). Although this rise is statistically insignificant, the overall risk of a complicated hospital stay was increased by a factor of 5.2 (p <0.001) (22).

**Detection of PFO**

**Post mortem Studies**

Hagen et al reported a PFO prevalence of 34% in those dying in the first three decades of life but a lower prevalence in later adult life at 24% (23). He did not consider the possibility that these PFOs may have increased the risk of death in young adults and that his study group may have been selected by virtue of their premature deaths. Most similar studies report a high prevalence of PFO in adults who die young and a decreasing frequency with increasing age (24, 25). Hagen suggested that this relationship might be explained by closure of smaller PFOs during adult life (23). When transoesophageal echo was performed in 581 random subjects over the age of 45, the prevalence of PFO was 25.6% and was not influenced by age (26). It is perhaps more likely that the prevalence of 22-26 percent in late adult life more truly represents the population prevalence and that there is an association between PFO and death in young adults.

**In Patients**

**Ultrasound with contrast media.** There are several ultrasound methods for the detection of PFO. An air-saline microbubble contrast medium is frequently used; inexpensive and simple to prepare by agitation of 0.5 ml of air in a 5 ml syringe of saline to produce an emulsion of microbubbles that are easily detected by ultrasound (25). Bubble stability may be improved by adding 0.5 ml of the patient’s blood as an emulsifier (27). Commercially available contrast media are based on galactose or oxypolygelatin suspensions (28, 29). In a randomised study in 54 patients, Droste et al found that agitated saline was as sensitive as galactose for the detection of v-aCS (30).

**Provocation tests.** Most PFOs do not shunt under resting conditions. A provocation test is usually necessary to reverse the pressure gradient across the inter-atrial septum. This can be either by coughing or by performing a Valsalva manoeuvre. There is no general agreement on the optimum timing; but most advise a provocation test during or immediately following the injection of contrast. Significantly more microbubbles were detected entering the cerebral circulation on transcranial Doppler (TCD) when injected immediately prior to a standardised Valsalva manoeuvre (31). Similarly Schwarze et al. found that sensitivity for TCD detected emboli was greatest when the Valsalva manoeuvre was performed five seconds following injection of contrast (32).

A cough or repeated coughing may also induce a transient v-aCS, but the two studies comparing coughing with the Valsalva manoeuvre reported conflicting results on the relative sensitivity (31, 33). This debate is of little importance as both are effective and both may be used in the same patient by repeating microbubble injections. Coughing may be the only option in patients where stroke impairs the ability to perform a Valsalva manoeuvre.

**Echocardiography**

Transthoracic echocardiography (TTE) is widely available and non-invasive but less sensitive than transoesophageal echocardiography (TOE) for the detection of atrial septal defects (4). Furthermore, image quality is lost during coughing or a Valsalva manoeuvre making it more difficult to detect a v-aCS (28). TOE, with repeated injection of an air-saline emulsion of microbubbles, is perhaps the most sensitive technique for the detection of PFO (34-37). Both atria can be directly imaged with injected contrast entirely opacifying the right atrium and, in the presence of a PFO, microbubbles can be seen entering the left atrium. A further advantage is that other cardiac pathologies, such as atrial septal aneurysm found in 10-20% of patients with cryptogenic stroke (38) mural thrombi, and valve abnormalities may also be more clearly visualised. The disadvantages are that TOE is costly, invasive and uncomfortable for many patients – especially those with swallowing difficulties following a stroke. De Rook et al suggested an algorithm for the investigation of patients where the cause of stroke is uncertain (37). They recommended TOE for all patients under the age of 45 and limiting TOE to those over this age where TTE had not identified a diagnosis (37). In a study of 824 stroke patients, Leung et al concluded that TOE was useful in patients with an abnormal initial TTE and in all young patients where detecting a PFO may contribute to patient management (39). The development of second harmonic imaging for TTE may improve sensitivity sufficiently to make TOE unnecessary in most cases (40).

**Transcranial Doppler (TCD)**

The TCD technique involves ionising blood flowing in the middle cerebral artery to detect air micro-emboli entering the cerebral circulation. TCD may also be used to detect emboli in the basilar artery, in patients with posterior circulation infarcts but it is likely that microbubbles would also be detected in the middle cerebral artery (41). Small numbers of emboli are counted individually ‘on line’ whilst information from larger numbers of emboli or ‘showers’ can be stored for later analysis. This technique is comfortable for patients and volunteers, inexpensive and requires little technical expertise.

TCD does not distinguish PFO from other causes of v-aCS such as pulmonary artery-venous fistulas. It would therefore be necessary to
confirm that a v-aCS detected by TCD was due to a PFO before invasive treatment could be considered. Anzola et al. injected contrast via antecubital veins in a series of patients with PFOs and found that the arm to brain time was consistent at 4.3 (+/- 1.8 sd) sec (42). Signals detected after this time were attributed to other sources such as intrapulmonary shunts and it may be possible to improve sensitivity by using a time limit for the arrival of emboli in the cerebral circulation. Using a longer time interval of 20–25 sec for microbubbles to appear in the MCA, Droste et al found that TCD detected TOE proven PFO with a sensitivity of 100% (43). TCD has been found to have a remarkable specificity for PFO when compared with TOE, however sensitivity ranges from 68 to 91.3 % and probably relates to the technique used (29, 32, 44, 45).

Severity of v-aCS

Post mortem studies yield little information about PFO function as the mere presence of a PFO is no guide to the functional severity of v-aCS; although it is likely that larger defects conduct higher flow volumes and allow the passage of larger and/or more emboli. TOE is the most sensitive, picking up even minor defects. TCD and TTE are less sensitive detecting only more severe right to left shunting, which may even be an advantage as only these more severe v-aCS would be likely to precipitate paradoxical embolism. In 54 stroke patients, only one patient had a v-aCS detected by TOE that could not also be detected by TCD; this being a small PFO with minimal shunting (30). There are a number of other studies suggesting that TCD may be the ideal technique to screen for v-aCS in stroke patients (27, 28, 46, 47).

In a relatively small study of strokes of all age groups, Itoh et al used only TCD as a means of detecting v-aCS and demonstrated a shunt in 50% of cryptogenic strokes. When they selected those patients with a sudden onset of cryptogenic stroke (arguing that these were the most likely to be embolic), 77 % were found to have v-aCS (48). Cryptogenic stroke was more frequently associated with medium sized (2–3.9 mm diameter) and large (greater than 4 mm diameter) PFO’s (52).

TCD has been used to measure the severity of v-aCS by counting microbubbles in the middle cerebral artery. By dividing shunts into ‘small’ (less than 10 bubbles), ‘intermediate’ (10 to 50 bubbles) and ‘massive’ (greater than 50 bubbles), Job et al found that 64% of patients with cryptogenic stroke had massive shunts (29). Similarly, Serena et al. classified transcardiac shunts into ‘normal’ (no bubbles detected), ‘small’ (with less than ten bubbles after each injection) and ‘large’ when more than ten were detected (53). The latter ‘large’ group was further subdivided into those with ‘showers’ (more than 25) or a ‘curtain’ of emboli too numerous to count. In patients with cryptogenic stroke, a right to left shunt was identified very much more frequently than in healthy controls with an odds ratio of 12.4 (95% CI = 4.08-38.09) (53). It seems that TOE may be too sensitive as even minor and probably clinically insignificant PFOs were detected. Where a patient was found to have a v-aCS by TCD, the association with stroke was more striking.

PFO in Stroke

In autopsy studies (all causes of death), the prevalence of PFO was 34.4% in the first three decades, 25.4% in the fourth to eighth decade and 20.2% during the ninth and tenth decades (23). The prevalence of PFO in healthy adults on TOE is only 22% (54, 55). A substantial number of studies have compared the frequency of PFO in patients with cryptogenic stroke with that in either patients where an alternative cause for stroke was identified or in age-matched healthy controls (Tables 1 and 2). PFO was consistently more frequent in those patients who suffered cryptogenic ischaemic stroke than it was either in patients with a known cause for stroke or in healthy controls. A persistent theme in these publications was that the prevalence of PFO was highest in patients who have no other risk factors for stroke (56).

Increasing age is perhaps even more important than a history of smoking or hypertension as an indicator for developing atherosclerosis. Many studies emphasise the higher prevalence of PFO in younger stroke patients. We examined the prevalence of PFO in stroke patients in two age ranges: Table 1 includes only patients aged under 50 years or where the data was sub-analysed to look at PFO in the young. Table 2 includes studies of all ages or those with an upper age limit of 55 or 60 years. The odds ratio for PFO in patients with cryptogenic stroke when compared with normal controls is consistently greater than 1.45 and ranges up to 8. The significance of these high odds ratios is that cryptogenic stroke in young adults aged under 50 years may be predominantly due to PFO, especially when there were no risk factors for arterial disease. Although tables I and II consistently demonstrated odds ratios in favour of an association between cryptogenic stroke and PFO, these studies were relatively small, of cross sectional design and often uncontrolled. Comparisons are difficult as some use patients with stroke of known aetiology and others use healthy controls to compare frequency of PFO with cryptogenic stroke patients. The pooling of data for a meta-analysis or formal overview is clearly impossible.

Risk of Recurrence in Patients with PFO

If a patient has suffered stroke due to paradoxical embolism, then the risk of recurrent stroke would be expected to be higher in patients

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age years</th>
<th>Test</th>
<th>Number of patients with cryptogenic stroke</th>
<th>Cryptogenic stroke with PFO</th>
<th>Stroke controls (known cause)</th>
<th>Stroke controls with PFO</th>
<th>Healthy controls with PFO</th>
<th>Odds ratio (95%CI) for studies with stroke controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hausmann et al 1995 (47)</td>
<td>&lt;40</td>
<td>TOE</td>
<td>18</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>18</td>
<td>2 NA</td>
</tr>
<tr>
<td>Jones 1994 (29)</td>
<td>&lt;50</td>
<td>TOE</td>
<td>14</td>
<td>4</td>
<td>12</td>
<td>3</td>
<td>19</td>
<td>2 1.2(0.2-6.9)</td>
</tr>
<tr>
<td>Job et al 1994 (28)</td>
<td>38 mean</td>
<td>TOE</td>
<td>41</td>
<td>27</td>
<td>33</td>
<td>11</td>
<td>63</td>
<td>27 3.6(1.10-10.2)</td>
</tr>
<tr>
<td>Harvey et al 1986 (80)</td>
<td>38 mean</td>
<td>TCD</td>
<td>41</td>
<td>22</td>
<td>33</td>
<td>11</td>
<td>63</td>
<td>28 2.3(0.9-6.0)</td>
</tr>
<tr>
<td>Webster et al 1995 (81)</td>
<td>32 mean</td>
<td>TEE</td>
<td>11</td>
<td>8</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>NA</td>
</tr>
<tr>
<td>Bosson et al 1994 (75)</td>
<td>36 mean</td>
<td>TEE</td>
<td>40</td>
<td>20</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>6 NA</td>
</tr>
</tbody>
</table>

INC = No controls used
(NA = Not applicable)
(CI = Confidence interval)
with a substantial v-aCS. The French study group on PFO and atrial septal aneurysm identified 132 patients under the age of 60 years with unexplained stroke or transient ischaemic attack who also had a PFO. The average annual rates of recurrence were 1.2 % for stroke and 3.4 % for stroke or transient ischaemic attack (TIA) (57). In patients with both PFO and atrial septal aneurysm (where the right to left shunt tends to be larger) the stroke recurrence rate was 4.5 % per year despite prophylactic antithrombotic therapy with either aspirin or full anticoagulation.

The Lausanne Stroke with Paradoxical Embolism Group undertook a similar study in 140 consecutive patients under the age of 60 years with cryptogenic stroke and PFO (58). The rate of recurrent stroke was remarkably similar; 1.9% per year, with 3.8% of patients suffering either stroke or TIA each year. Again, many of these patients were on antithrombotic therapy. These patients were divided into groups according to the severity of v-aCS and 31% of patients with a severe shunt suffered stroke or TIA in under two years (58). Studies on surgical or transcatheter closure of PFO were encouraging, but the numbers of patients were too small to influence current practice (59-66). We agree with the conclusion that major clinical trials are now required to address this issue (67). Unfortunately, there is increasing evidence that transcatheter closure may prove incomplete in up to 15% of patients, particularly if they have an atrial septal defect (63, 65, 66).

To avoid the problems of small sample numbers, Nendaz et al used a hypothetical model to estimate the relative risks and benefit of various treatments. They conclude that when the risk of stroke recurrence is greater than 0.8% per year, active therapy is advised (68). This does not help in the clinical decision on which patients require treatment and whether anticoagulation or closing the defect is most appropriate. Even anticoagulation carries a risk: 1-2% of patients on long-term anticoagulation will suffer a bleed each year (69). Adequate studies on the epidemiology of v-aCS in stroke patients are needed. Only then can clinical trials on anticoagulation or closure techniques be properly designed.

Confounding Variables

If v-aCS causes stroke, then conditions leading to an increased incidence of venous thromboembolism would be expected to increase the risk of stroke in patients with v-aCS.

**Oral contraceptive pill.** The World Health Organisation Scientific Group Meeting on Cardiovascular Disease and Steroid Hormone Contraception concluded that in women who do not smoke and are not hypertensive, the risk of ischaemic stroke is increased by a factor of 1.5 in women taking combined oral contraceptive pills (70). Furthermore, in epidemiology studies on stroke associated with PFO or ASD, the frequency of oral contraceptive pill usage was consistently high (71,72,73).

**Pregnancy and the puerperium.** Cross et al estimated in 1968 that the incidence of cerebral infarction during or following pregnancy was 5 per 100 000 births (74). Of 31 cases, 16 occurred in pregnancy and 15 within 16 days post partum suggesting that the risk was highest in the puerperium. The Baltimore-Washington Cooperative Young Stroke Study also demonstrated a marked increase in risk in the six weeks post partum when the risk of DVT is also high.

**Thrombophilia.** Several hereditary and acquired defects of coagulation have been demonstrated to increase the risk of venous thrombosis and would therefore be expected to increase the risk of stroke in the presence of v-aCS. However the low prevalence of the thrombophilias makes the detection of any association difficult. This is perhaps why only a weak association was found between stroke and the presence of Factor V Leiden mutation. In children, 6 of 33 (18%) suffering stroke were found to be carrying the Factor V Leiden mutation, compared with a population prevalence of 4.6% in Austria (77).

**Conclusion**

The available evidence suggests that when no ‘conventional’ cause can be found to explain cerebral infarction in a young adult, paradoxical embolisation is a possible or even likely cause, especially in patients with a predisposition to thrombosis. The TCD technique for detecting v-aCS is non invasive, cheap and reliable for the detection of moderate-severe shunting of the type associated with ischaemic stroke. This investigation may be the most appropriate for all young adults suffering ischaemic stroke when the cause is not obvious.

As yet there is not enough persuasive evidence to safely guide the management of v-aCS in stroke patients. Although stroke in the young is rare, it has considerable costs both to the patients and to society. The
increasing realisation of the importance of v-aCS in this patient group argues for large multicentre trials to address the question of long term stroke prophylaxis.

Appendix I

Case Reports – Paradoxical Embolism
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Appendix II

Case Reports – Thrombus in situ in PFO

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Direct evidence of patent foramen ovale as a route for paradoxical embolism

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