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Young Adult Myocardial Infarction and Ischemic Stroke

The Role of Paradoxical Embolism and Thrombophilia (The YAMIS Study)

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OBJECTIVES We aimed to investigate the frequency of venous-to-arterial circulation shunts (v-aCS), usually caused by patent foramen ovale (PFO), and thrombophilia in young adults suffering myocardial infarction (MI) and ischemic stroke (IS) and matched healthy control subjects.

BACKGROUND The cause of MI and IS in young adults is often uncertain, and paradoxical embolism might be more frequent than previously thought.

METHODS Young adults (ages 16 to 39 years) surviving MI (n = 101) and IS (n = 101) between 1993 and 1998 were matched by age and gender to 202 control subjects from the same general practitioner practices. The v-aCS were detected by transcranial Doppler after intravenous microbubble ultrasound contrast; "significant" v-aCS (≥15 microbubble emboli) correlated with PFO on transesophageal echocardiography. A "major" v-aCS was >50 microbubbles spontaneously or >10 microbubbles spontaneously with >80 after provocation. Venous blood was taken for a thrombophilia screen.

RESULTS Myocardial infarction, more frequent in men, was associated with the usual cardiovascular risk factors. More women suffered IS, which was associated only with migraine and hypertension. Neither "significant" nor "major" v-aCS were associated with MI. "Major" v-aCS was found in 24 (25%) IS cases compared with 12 (12%) control subjects (odds ratio 2.80, 95% confidence interval 1.21 to 6.84; p = 0.016). Thrombophilia was not significantly associated with either MI or IS.

CONCLUSIONS Only "major" v-aCS were associated with stroke in young adults. Closure of smaller v-aCS might not be justified. (J Am Coll Cardiol 2006;48:686–91) © 2006 by the American College of Cardiology Foundation

Myocardial infarction (MI) and ischemic stroke (IS) are rare in young adults and the etiology is often uncertain, with no cause found in 30% to 40% of cases (1,2). Many of these cryptogenic strokes in young adults might be caused by paradoxical embolism, and a higher prevalence of patent foramen ovale (PFO) has been reported in young adults suffering IS (3,4). A meta-analysis of these case-control studies, which were often small and poorly designed, confirmed a significant association between PFO and IS in adults below 55 years of age (5). Because paradoxical embolism might also occur through septal defects and pulmonary arterio-venous malformations, we prefer the term venous-arterial circulation shunt (v-aCS) to right to left cardiac shunting.

A PFO was identified on postmortem in 35% of all adults dying under 30 years of age but in only 22% of older persons (6). The authors concluded that PFO might close in adult life, but we wondered whether PFO might be a cause of premature deaths due to paradoxical embolism. We investigated the role of paradoxical embolism through v-aCS in young adults surviving both MI and IS. If paradoxical embolism of venous thrombus causes either MI or IS, then there might also be an association with the thrombophilias, known risk factors for venous thromboembolism (7). We conducted a case-control study to investigate the frequency of v-aCS and thrombophilia in young adults surviving MI or IS—the first adequately powered study, on the basis of sound epidemiological principles, to explore these associations and to include only adults 16 to 39 years of age in whom the prevalence of atherosclerosis is low.

METHODS

This case-control study was designed to answer the following research questions:

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Abbreviations and Acronyms

APCr = activated protein C resistance
CI = confidence interval
GP = general practitioner
ICD = International Classification of Diseases
IS = ischemic stroke
MI = myocardial infarction
OR = odds ratio
PFO = patent foramen ovale
TCD = transcranial Doppler
TOE = transesophageal echocardiography
v-aCS = venous-to-arterial circulation shunt

1. Is the frequency of v-aCS in young adults who have suffered: 1) MI, or 2) IS higher than in similar young adults without either condition?
2. Is the frequency of thrombophilia in young adults who have suffered: 1) MI, or 2) IS higher than in similar young adults without either condition?
3. Is the association between either v-aCS or thrombophilia and: 1) MI, or 2) IS independent of other cardiovascular risk factors, and is any association still significant after adjustment for such potential confounding?

Case recruitment. Young adults ages 16 to 39 years surviving their first MI (International Classification of Diseases [ICD]-9: 410; ICD-10: I21, I22) or first IS (ICD-9: 433, 434, 436, 437.1; ICD-10: I63, I64, I67.2, I67.8, I67.9) between October 1, 1993, and December 31, 1998, were identified from all acute hospitals in the North West and Mersey Regions. Ethical approval was obtained from the North West Multi-Centre Research Ethics Committee. Cases of MI and stroke were confirmed on World Health Organization criteria (8,9). The diagnosis in every case was reviewed by diagnostic committee, including consultants in cardiology and stroke medicine.

All eligible subjects were approached by asking the relevant general practitioner (GP) to contact cases and control subjects by letter. All consenting subjects were invited to participate, and the first 101 cases and their matched control subjects for each diagnosis were included.

Control recruitment. Six potential control subjects of the same gender and most closely matched to each case by age were drawn from the local community, using the same GP list as the case. The first to agree was included. All cases and potential control subjects were recruited with strict inclusion and exclusion criteria.

Inclusion criteria. For inclusion, young adults surviving MI and IS and matched population control subjects were:

- 16 to 39 years old at the time of the event
- Currently residing within a 70-mile radius of Manchester city center
- A "district of residence" code within the study area at the time of the event

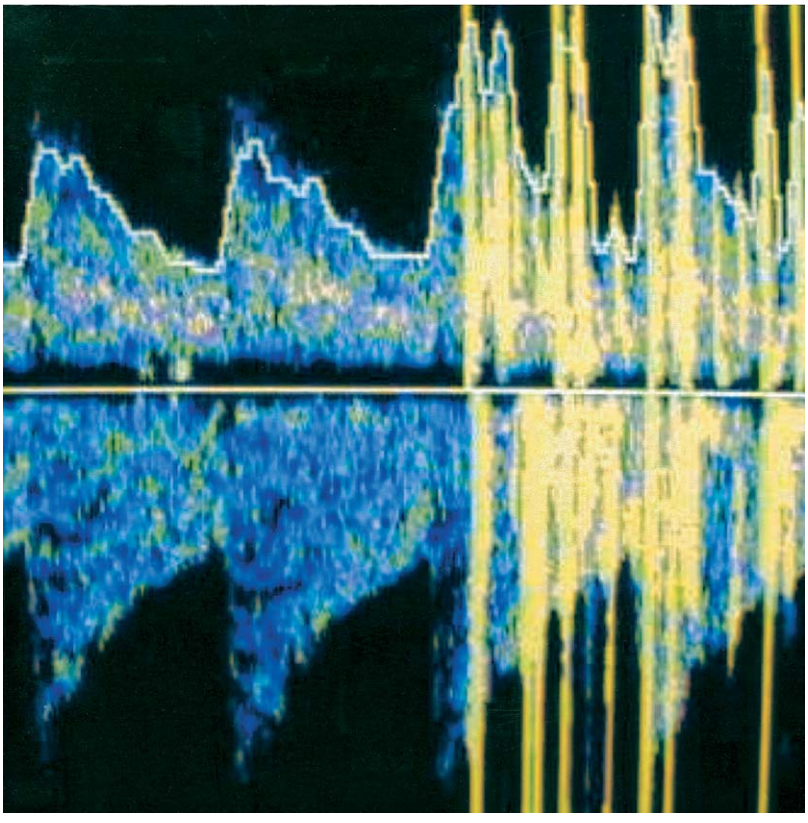

Figure 1. Characteristic appearance of microbubbles on a middle cerebral artery Doppler trace in a patient with a venous-to-arterial circulation shunt.

Table 1. Univariate Analysis of Cardiovascular Risk Factors in MI

	MI Cases (n = 101)	MI Control Subjects (n = 101)	Odds Ratio (95% CI)	p Value
Age (yrs), mean (range)	35.3 (19–39)	35.3 (19–39)		
Gender, male/female	69/32	69/32		
Smoking	83	47	8.2 (3.24–20.75)	**<0.001**
Hypertension	20	9	3.00 (1.09–8.25)	**0.033**
Cholesterol, mean (SD)	5.48 (1.08)	5.37 (0.96)	1.09 (0.81–1.46)	0.56
Diabetes mellitus	4	0		0.12
Body mass index, mean (SD)	28.7 (5.6)	26.0 (3.7)	1.13 (1.05–1.21)	**0.001**
Oral contraceptive pill	5	6	0.75 (0.17–3.35)	0.71
Migraine	34	38	1.24 (0.65–2.34)	0.52

Bold p values indicate statistically significant results.
CI = confidence interval; MI = myocardial infarction.

Exclusion criteria. Cases were excluded who had:

- Surgery or injury requiring overnight hospital stay in the 10 weeks before the event.
- Malignant disease diagnosed at any time.

Control subjects were excluded if there was a medical history of cardiovascular disease defined as MI, angina, transient cerebral ischemia, stroke, or any arterial thrombosis.

Data collection. Full medical history, including cardiovascular events and risk factors, were documented at a face-to-face interview with a structured questionnaire. Information was referenced to the date of the case's event for both cases and control subjects. The accuracy of this interview data was validated by examination of the GP notes in all subjects. There was excellent concordance.

Investigation for v-aCS. We developed a standardized transcranial Doppler (TCD) technique using intravenous ultrasound contrast. The advantages over transesophageal echocardiography (TOE) are that TCD: 1) is minimally invasive and comfortable for research patients; 2) detects both intracardiac and pulmonary arterio-venous shunts; and 3) measures the functional significance of a v-aCS by counting the number of microbubble emboli entering the middle cerebral arteries. The TCD criteria (see the following text) were sensitive and specific to the detection of PFO when compared with TOE (10).

Both middle cerebral arteries were insonated by a Neuroguard (Medasonics, Fremont, California) TCD system with 2-MHz probes over the temporal windows set at 50- to 60-mm depth secured by a headband with the patient sitting upright. The Doppler signal was recorded onto digital audio tape for blind analysis by a panel of 3 observers. An emulsion of microbubbles as an ultrasound contrast was prepared by agitating a mixture of 8 ml saline, 1 ml air, and 0.5 ml of the patient's blood as an emulsificant between 2 10-ml syringes, 6 times through a 3-way tap. This emulsion was then immediately injected via an 18-gauge cannula in an antecubital vein. Our standardized protocol involved 2 injections under each of the following conditions: at rest, after vigorous coughing for 5 s, and after a standardized Valsalva maneuver (patients blew into a manometer to maintain 40 mm Hg for 5 s).

In our validation study comparing our standardized TCD technique with TOE in 40 patients, ≥15 microbubble emboli on TCD, defined as "significant" v-aCS, was 100% specific for PFO on TOE (Fig. 1) (10). A "major" shunt (>50 microbubbles spontaneously or >10 microbubbles spontaneously with >80 after provocation) identified patients with moderate or large shunts on TOE with 80% sensitivity and 100% specificity. The TCD reproducibility was also good with kappa results in excess of 0.8 for both "significant" and "major" shunts (11).

Thrombophilia testing. Venous blood was taken for a thrombophilia screen and lipid assays. Functional assays were used to test for activated protein C resistance (APCr); lupus anticoagulant; proteins C and S; antithrombin III; fibrinogen; and Factors II, VII, VIII, and IX. Enzyme-

Table 2. Univariate Analysis of Cardiovascular Risk Factors in IS Cases and Control Subjects

	IS Cases (n = 101)	IS Control Subjects (n = 101)	Odds Ratio (95% CI)	p Value
Age (yrs), mean (range)	33.2 (17–39)	33.2 (21–39)		
Gender, male/female	43/58	43/58		
Smoking	47	41	1.32 (0.72–2.39)	0.37
Hypertension	21	8	2.86 (1.21–6.76)	**0.017**
Cholesterol, mean (SD)	5.18 (0.90)	5.16 (0.92)	1.05 (0.77–1.45)	0.74
Diabetes mellitus	3	1	3.0 (0.31–28.8)	0.34
Body mass index, mean (SD)	25.8 (5.3)	25.3 (4.0)	1.02 (0.96–1.08)	0.54
Oral contraceptive pill	16	16	1.08 (0.49–2.37)	0.84
Migraine	63	34	3.64 (1.86–7.09)	**<0.001**

Bold p values indicate statistically significant results.
CI = confidence interval; IS = ischemic stroke.

Table 3. Univariate and Multivariate Analysis of v-aCS in MI Cases and Control Subjects

	MI Cases	MI Control Subjects	Unadjusted Odds Ratio (95% CI)	p Value	Adjusted* Odds Ratio (95% CI)	p Value
Significant v-aCS	22	36	0.52 (0.28–0.96)	**0.038**	0.61 (0.28–1.36)	0.23
Major v-aCS	11	16	0.67 (0.30–1.48)	0.32	1.19 (0.45–3.13)	0.73

*Adjusted for hypertension, smoking, cholesterol, and diabetes.
CI = confidence interval; MI = myocardial infarction; v-aCS = venous-to-arterial circulation shunt.

linked immunosorbent assay was used for anticardiolipin antibodies. Patients with APCr deficiency were investigated for Factor V Leiden mutation, and those with raised Factor II levels were investigated for prothrombin gene G20210A mutation. Patients on long-term warfarin therapy (5 MI cases and 15 IS cases), which interferes with the functional assays, were tested only for Factor V Leiden and prothrombin gene G20210A mutations.

Statistical analysis and study power. Odds ratios (ORs) between the pairwise matched cases and control subjects for v-aCS and thrombophilia were computed with conditional logistic regression for MI and IS separately, adjusting for confounding factors where appropriate. For continuous variables, the ORs refer to the increased risk related to a 1-U increase in the variable.

Assuming a frequency of v-aCS of 25% in control subjects and a frequency of thrombophilia of 5% in control subjects, 100 matched cases and control subjects would detect an OR relating to v-aCS of 2.5 with a power of 80% and of 3.0 with a power of 95% and an OR relating to thrombophilia of 3.0 with a power of 80% and of 4.0 with a power of 95%.

RESULTS

Lists of patients with the relevant ICD codes were received from 22 hospitals identifying 741 potential cases (298 MI; 434 IS), of whom 227 met the diagnostic criteria for MI and 219 for IS. Of the 227 MI cases, 169 were contacted by their GP, 110 agreed to participate, and the first 101 were included. General practitioners contacted 173 of the 219 IS cases, 110 agreed to participate, and the first 101 were included.

Individually matched control subjects were recruited for 95 MI and 90 IS cases. Six control subjects for MI and 11 for IS were successfully matched by gender and age but not by GP list. Matching within 1 year of age was achieved in 98% of MI pairs and 97% of IS pairs.

Case and control characteristics. Nearly 70% of MI cases were men (Table 1) compared with only 43% of IS patients (Table 2). Risk factors for atherosclerosis, such as smoking and raised body mass index were more frequent in MI cases than in either control subjects or IS cases. Hypertension was significantly more frequent in both MI and IS cases than their control subjects. Migraine was associated with IS but not MI.

MI cases and control subjects. FREQUENCY OF v-aCS. A "significant" v-aCS in was found in 22 (23%) MI patients compared with 36 (38%) matched control subjects with an OR of 0.52 (95% confidence interval [CI] 0.28 to 0.96, p = 0.038) (Table 3). After adjustment for confounding factors, this OR was 0.61 (95% CI 0.28 to 1.36, p = 0.23). "Major" v-aCS were found in 11 (12%) of MI cases and 16 (17%) control subjects (unadjusted OR 0.67 [95% CI 0.30 to 1.48], p = 0.32; adjusted OR 1.19 [95% CI 0.45 to 3.13], p = 0.73).

THROMBOPHILIA RESULTS. There were no differences between MI cases and control subjects for APCr, antithrombin III, protein C, protein S, lupus anticoagulant, anticardiolipin antibodies, Factor V Leiden gene, and prothrombin variant gene (Table 4). Fibrinogen and Factors

Table 4. Univariate Analysis of Thrombophilia Results in MI Cases and Control Subjects

	MI Cases	MI Control Subjects	Odds Ratio (95% CI)	p Value
Activated protein C resistance	5	8	0.62 (0.20–1.91)	0.41
Antithrombin III deficiency	0	1		
Protein C deficiency	0	1		
Protein S deficiency	0	1		
Factor V Leiden	5	8	0.62 (0.20–1.91)	0.41
Prothrombin gene variant	4	3	1.33 (0.30–5.96)	0.71
Lupus anticoagulant	17	11	1.60 (0.73–3.52)	0.24
IgG anticardiolipin antibodies	3	9	0.33 (0.09–1.23)	0.1
IgM anticardiolipin antibodies	8	5	1.60 (0.52–4.89)	0.41
Fibrinogen assay, mean (SD)	3.39 (0.63)	3.02 (0.54)	2.86 (1.60–5.24)	**<0.001**
Fibrinogen screen, mean (SD)	4.51 (1.06)	3.97 (0.89)	1.8 (1.26–2.56)	**0.001**
Factor II, mean (SD)	104.7 (12.0)	98.7 (12.3)	1.04 (1.01–1.07)	**0.002**
Factor VII, mean (SD)	113.0 (21.1)	105.5 (21.0)	1.02 (1.00–1.03)	**0.019**
Factor VIII, mean (SD)	143.8 (47.5)	111.7 (31.2)	1.02 (1.01–1.03)	**<0.001**
Factor IX, mean (SD)	137.9 (34.7)	122.5 (30.5)	1.02 (1.00–1.03)	**0.004**

Bold p values indicate statistically significant results.
CI = confidence interval; Ig = immunoglobulin; MI = myocardial infarction.

Table 5. Univariate and Multivariate Analysis of v-aCS in IS Cases and Control Subjects

	IS Cases	IS Control Subjects	Unadjusted Odds Ratio (95% CI)	p Value	Adjusted* Odds Ratio (95% CI)	p Value
Significant v-aCS	43	38	1.22 (0.70–2.11)	0.48	1.34 (0.74–2.42)	0.33
Major v-aCS	24	12	2.20 (1.04–4.64)	**0.039**	2.80 (1.21–6.48)	**0.016**

*Adjusted for hypertension, smoking, cholesterol, and diabetes. **Bold** p values indicate statistically significant results.
CI = confidence interval; IS = ischemic stroke; v-aCS = venus-to-arterial circulation shunt.

II, VII, VIII, and IX were significantly elevated in MI cases compared with their control subjects.

Stroke cases and control subjects. FREQUENCY OF v-aCS. A "significant" v-aCS was found in 43 (45%) IS patients compared with 38 (40%) control subjects, giving a nonsignificant OR of 1.22 (95% CI 0.70 to 2.11; p = 0.48) (Table 5). This OR was increased only marginally by adjustment for confounding factors to 1.34 (95% CI 0.74 to 2.42; p = 0.33). However, "major" v-aCS were found in 24 (25%) IS cases compared with only 12 (12%) control subjects giving an OR of 2.20 (95% CI 1.04 to 4.64; p = 0.039). After adjustment for confounding factors, this OR remained significant at 2.80 (95% CI 1.21 to 6.48; p = 0.016).

THROMBOPHILIA RESULTS. Levels of Factors VII and VIII were significantly higher in IS cases than control subjects, but there were no differences in the frequency of APCr, antithrombin III, protein C, protein S, lupus anticoagulant, anticardiolipin antibodies, Factor V Leiden gene, and prothrombin variant gene (Table 6).

DISCUSSION

This is the first adequately powered case-control study of appropriate epidemiological standards to explore definitively the association between v-aCS and both MI and IS in young adults. No relationship was found between v-aCS and MI, consistent with a previous smaller study on frequency of PFO in patients with MI and normal coronary arteries (12). In IS, only "major" v-aCS was significantly more common than in control subjects. Previous studies have also suggested that only large shunts were associated with stroke in the young (13). Current clinical trials that randomize all IS patients with a PFO to medical therapy or transvenous closure of the PFO might prove insensitive to the therapeutic effect of these treatments, because it will be diluted by smaller PFOs where therapeutic benefit is unlikely.

Contrast TCD proved to be a simple and effective way to detect v-aCS. If used as the initial investigation for v-aCS in young patients suffering IS, only those with "significant" if not a "major" v-aCS would require TOE to distinguish PFO from other causes of v-aCS and assess anatomical suitability for closure. Otherwise only patients with an inadequate temporal window for TCD would require TOE.

The expected strong association between MI and risk factors for atherosclerosis was not found in IS cases (14). The association between migraine and IS was again confirmed (15). Data on smoking, migraine, and the patient's weight was based on their memory of circumstances at the time of the case's event up to 7 years previously. There is no reason to believe that errors in recollection would differ between cases and control subjects.

Factor V Leiden, antithrombin III, protein C or protein S deficiency, and prothrombin gene variant—all known to be associated with venous thromboembolism—were not associated significantly with either MI or IS. Elevated fibrinogen levels, well-recognized in atherosclerosis, were found in MI but not in IS cases (16). The raised fibrinogen levels and atherosclerotic risk factors found in MI but not IS

Table 6. Univariate Analysis of Thrombophilia Results in IS Cases and Control Subjects

	IS Cases	IS Control Subjects	Odds Ratio (95% CI)	p Value
Activated protein C resistance	3	8	0.43 (0.11–1.67)	0.22
Antithrombin III deficiency	3	0		
Protein C deficiency	1	0		
Protein S deficiency	1	1		
Factor V Leiden	4	8	0.50 (0.15–1.66)	0.26
Prothrombin gene variant	2	0		
Lupus anticoagulant	9	7	1.60 (0.52–4.89)	0.41
IgG anticardiolipin antibodies	9	4	4.00 (0.85–18.8)	0.08
IgM anticardiolipin antibodies	1	5	0.20 (0.02–1.71)	0.14
Fibrinogen assay, mean (SD)	3.06 (0.63)	3.00 (0.59)	1.20 (0.70–2.07)	0.51
Fibrinogen screen, mean (SD)	4.02 (1.10)	3.91 (1.02)	1.12 (0.82–1.52)	0.48
Factor II, mean (SD)	98.3 (11.1)	96.3 (9.4)	1.02 (0.99–1.05)	0.20
Factor VII, mean (SD)	105.8 (22.2)	96.0 (22.1)	1.02 (1.00–1.04)	**0.013**
Factor VIII, mean (SD)	128.0 (42.5)	113.6 (27.4)	1.01 (1.00–1.03)	**0.019**
Factor IX, mean (SD)	129.6 (35.2)	119.9 (34.3)	1.01 (1.00–1.02)	0.08

Bold p values indicate statistically significant results.
CI = confidence interval; Ig = immunoglobulin; IS = ischemic stroke.

cases suggest a different etiology for MI and IS in young adults.

Conclusions. Risk factors for atherosclerosis were associated with MI but not with IS. There was no association between v-aCS and MI, but the increased frequency of "major" v-aCS in IS argues for appropriate TCD or TOE investigation of young IS patients, with a view to anticoagulation or transvenous closure in those with a "major" v-aCS due to PFO. There is no evidence to justify closure of insignificant or moderate v-aCS. Clinical trials on anticoagulation or PFO closure should focus on patients with "major" v-aCS.

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REFERENCES

1. Hart RG, Miller VT. Cerebral infarction in young adults: a practical approach. Stroke 1983;14:110–4.
2. Kittner SJ, Stern BJ, Wozniak M, et al. Cerebral infarction in young adults: the Baltimore-Washington Cooperative Young Stroke Study. Neurology 1998;50:890–4.
3. Webster MW, Chancellor AM, Smith HJ, et al. Patent foramen ovale in young stroke patients. Lancet 1988;2:11–2.
4. Di Tullio M, Sacco RL, Gopal A, Mohr JP, Homma S. Patent foramen ovale as a risk factor for cryptogenic stroke. Ann Intern Med 1992;117:461–5.
5. Overell JR, Lees KR, Bone I. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism. Circulation 2001;103: E56.
6. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc 1984;59:17–20.
7. Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet 1999;353:1167–73.
8. WHO MONICA Project. MONICA Manual. Geneva, Switzerland: World Health Organization, 1990:11–32.
9. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. Lancet 1996;348:498–505.
10. Sastry S, MacNab A, Daly K, Ray SG, McCollum CN. Transcranial Doppler or transoesophageal echocardiography for the detection of venous-to-arterial circulation shunts. Eur J Echocardiogr 2003;4 Suppl 1:S105.
11. Sastry S, Daly KJ, Chengodu T, McCollum CN. Is the contrast transcranial Doppler test for venous-to-arterial circulation shunts reproducible? Cerebrovasc Dis 2002;13 Suppl 4:6.
12. Crump R, Shandling AH, Van Natta B, Ellestad M. Prevalence of patent foramen ovale in patients with acute myocardial infarction and angiographically normal coronary arteries. Am J Cardiol 2000;85: 1368–70.
13. Serena J, Segura T, Perez-Ayuso MJ, Bassaganyas J, Molins A, Davalos A. The need to quantify right-to-left shunt in acute ischemic stroke: a case-control study. Stroke 1998;29:1322–8.
14. Choudhury L, Marsh JD. Myocardial infarction in young patients. Am J Med 1999;107:254–61.
15. Tzourio C, Kittner SJ, Bousser MG, Alperovitch A. Migraine and stroke in young women. Cephalalgia 2000;20:190–9.
16. Yarnell JW, Baker IA, Sweetnam PM, et al. Fibrinogen, viscosity, and white blood cell count are major risk factors for ischemic heart disease. The Caerphilly and Speedwell collaborative heart disease studies. Circulation 1991;83:836–44.