Influence of transoesophageal echocardiography on therapy and prognosis in young patients with TIA or ischaemic stroke

T.C.D. Rettig, B.J. Bouma, R.B.A. van den Brink

Objective. To determine the influence of transoesophageal echocardiography (TEE) on therapy and prognosis in patients with cryptogenic transient ischaemic attack (TIA) or ischaemic stroke under the age of 50 years.

Methods and results. We evaluated all patients aged 50 and under who were referred to our university hospital for cryptogenic TIA or ischaemic stroke during the period 1 January 1996 to 31 December 2004. All patients underwent both transthoracic echocardiography (TTE) and TEE. Patients with known pre-existent heart disease, such as atrial fibrillation, were excluded. Eighty-three patients with TIA (22) and ischaemic stroke (61) were enrolled. Mean age was 39 ± 8 years (range 18 to 50). In 30% of the patients TEE detected one or more potential cardioembolic source, compared with 10% for TTE ($p=0.003$). Standard treatment (aspirin 38 mg daily) was changed in 7% of the patients due to the TEE findings. Complete follow-up was obtained in 93% with an average of 5 ± 3 years. Twelve recurrences occurred; two out of six patients (33%) with therapy change and ten out of 71 (14%) of the patients without therapy change had a recurrent TIA or ischaemic stroke.

Conclusion. In patients with cryptogenic TIA or ischaemic stroke, TEE is superior to TTE in the detection of a potential cardiac source of embolism.

However, findings obtained by TEE only influence the already initiated treatment in a small percentage of patients. The recurrence rate both in the group with and without therapy change is high. (Neth Heart J 2009;17:373-7.)

Keywords: cardioembolism, transient ischaemic attack (TIA), stroke, echocardiography

At a glance, in approximately 50% of young patients (≤ 50 years) with a transient ischaemic attack (TIA) or ischaemic stroke an identifiable cause is apparent, such as large vessel disease, small vessel disease, coagulopathy or arterial dissection.^{1,2} Embolism of cardiac origin is another main cause of TIA and ischaemic stroke in young patients. It has been estimated that 15 to 30% of all TIAs and ischaemic strokes are due to a cardioembolic source (CES).^{3,4} Echocardiography is the tool of choice to identify high- and low-risk cardioembolic sources.

Transoesophageal echocardiography (TEE) is known to be superior to transthoracic echocardiography (TTE) in visualising potential CES. Large studies showed that in an older population TEE strongly influenced secondary prevention and led to oral anticoagulation in one third of the patients with a stroke of undetermined aetiology.^{5,6} However, in the young patient the prevalence of findings for which oral anticoagulation is indicated is much lower. Moreover, TEE is a diagnostic tool that, although semi-invasive, can cause considerable discomfort especially in the young. Image quality of TTE has improved over the years and there are conflicting data about the additional therapeutic benefit of TEE.⁷⁻¹⁴

We evaluated the additional value of TEE in the determination of a potential CES requiring treatment other than the standard dose of antiplatelet therapy in patients less than 50 years of age with a TIA or stroke. We also investigated the recurrence rate of TIA or ischaemic stroke during follow-up in patients in whom treatment was changed because of the TEE.

T.C.D. Rettig

Department of Cardiology, Sint Lucas Andreas Hospital, the Netherlands

B.J. Bouma

R.B.A. van den Brink

Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Correspondence to: T.C.D. Rettig

Department of Cardiology, Sint Lucas Andreas Hospital, PO Box 9423, 1006 AE Amsterdam, the Netherlands
E-mail: threttig@hotmail.com

Methods

Study protocol

We investigated all patients aged 50 years and under who underwent TTE and TEE because of an unexplained TIA or ischaemic stroke, while admitted at our university hospital in the period between 1 January 1996 and 31 December 2004. Patients were excluded if the stroke aetiology could be classified on routine diagnostic information, e.g. a dissection, vasculitis or severe stenosis (>70%) of the corresponding cerebral vessel responsible for the TIA or ischaemic stroke. Diagnoses of TIA and ischaemic stroke were based on standard criteria. Clinical symptoms in combination with cerebral computed tomography and/or magnetic resonance imaging of the brain were used to determine the diagnosis. Patients with known valvular heart disease, prosthetic heart valve, (paroxysmal) atrial fibrillation, myocardial infarction, angina pectoris, congestive heart failure and other arrhythmias were excluded. Medical records of all patients were reviewed.

Echocardiography

According to the SSS-TOAST classification 'cardio-aortic embolism' as a causative mechanism for stroke was considered 'evident' in case of a 'high risk' cardio-embolic source (CES), 'probable' in case of evidence of systemic embolism or multiple acute cerebral infarctions that have occurred closely related in time within both right and left anterior or both anterior and posterior circulations and 'possible' in case of a 'low risk' CES.¹⁵

The following echocardiographic abnormalities were considered to be high-risk CES: left atrial thrombus, left ventricular thrombus, severely impaired left ventricular function (ejection fraction <30%), aortic and/or mitral valve vegetations, left atrial myxoma, atrial appendage flow <20 cm/sec, protruding thrombus or atheroma in the ascending aorta or aortic arch. Echocardiographic abnormalities that were considered to be 'low or uncertain risk' CES were: patent foramen ovale (PFO), atrial septal aneurysm (ASA), combined PFO and ASA, isolated left atrial spontaneous echo contrast (SEC), mitral valve prolapse, calcification or thickening of the aortic or mitral valve. A General Electric Vivid 7, and Philips ATL 3000 were used to perform the investigations.

Follow-up

Follow-up ended on 30 June 2005. From the treating physician and general physician we obtained information on recurrence of TIA or ischaemic stroke and therapy at the end of follow-up. At the time of our study, standard therapy after a TIA or ischaemic stroke in the Netherlands was aspirin 38 mg daily. A change of therapy was defined as a change caused by the additional information obtained by TEE, such as an increase in dosage, a switch to another medication, i.e. warfarin, or surgical or catheter intervention.

Statistical analysis

SPSS 16.0 (SPSS Inc., Chicago, US) was used for analysis. Continuous variables are reported as means and standard deviation. We analysed the association of the clinical characteristics with the presence of a cardiac source of the embolism with the χ^2 test. The recurrence rate during follow-up was estimated with the Kaplan-Meier method. Patients were censored if they were free of recurrence at the end of follow-up. The association between recurrence and the clinical characteristics was analysed with Cox proportional hazard analysis. A *p* value of <0.05 was considered significant.

Results

Patients

We studied 83 patients (37 male). Mean age was 39±8 (range 18 to 50). Prior TIA or ischaemic stroke was present in 6% (5/83). Baseline characteristics are summarised in table 1. Patients with a CES were more likely to have hypercholesterolaemia (*p*=0.04).

Echocardiographic findings

In 30% (25/83) of all patients one or more CES was identified by TTE and/or TEE (table 2). TTE identified a CES in 10% (8/83) of all patients, compared with 30% (25/83) with TEE (*p*=0.003). All CES on TTE were also seen on TEE. Four patients had more than one potential CES.

A high embolic risk source was found with TTE in one patient. TEE identified six patients with a high embolic risk source (table 2). Two patients had an echo dense structure at the mitral valve. One patient had an abnormality of the mitral valve leaflet suggesting a Libman-Sacks endocarditis although laboratory studies did not support the diagnosis of systemic lupus erythematosus (SLE). The other patient had a mobile structure on the left ventricular side of the mitral valve.

In the group of low or uncertain embolic risk source patent foramen ovale (PFO) in nine (*p*=0.003) and atrial septum aneurysm (ASA) in five (*p*=0.02) were the most common missed abnormalities by TTE (table 2).

Therapy change

Findings obtained by TEE led to therapy change in 7% (6/83) of all patients (table 3). Therapy change consisted of an increase of aspirin dosage from 38 to 100 mg (*n*=1) or substitution of aspirin by warfarin (*n*=5). No catheter interventions or surgery was performed based on echocardiographic findings.

Follow-up

A total of 93% (77/83) of the questionnaires were returned. The average follow-up period was 5±3 years (range 0.02 to 9.2). Twelve recurrences occurred during this period: five TIAs and seven ischaemic strokes. Mean recurrence rate was 6.5% in 0 to 1 year and 2% in 2 to 5 years. Recurrence of TIA or ischaemic

Table 1. Baseline characteristics of the patients, according to the presence of a cardioembolic source (CES).

Characteristics	All	Patients with a CES at echocardiography	
		N	%
Patients	84	25	30
Mean age (years)	40		
Female	47	17	44
Diagnosed as TIA	21	7	33
Diagnosed as CVA	63	18	29
Risk factors for atherosclerosis			
Known hypertension*	18	7	39
Current smoking	40	8	20
Known hypercholesterolaemia*	4	3	75
Known diabetes mellitus	7	2	29
Positive family history†	26	6	23
Clinical characteristics			
Use of antiplatelets	6	2	33
Prior TIA or ischaemic stroke	5	2	40

* $p < 0.05$. There were no significant differences in the other characteristics. † Family history for TIA and ischaemic stroke only. At the time of presentation none of the patients were in atrial fibrillation.

Table 2. Echocardiographic findings according to high and low/uncertain embolic risk.

	TTE findings (n)	TEE findings (n)
High embolic risk		
Left atrial (appendage) thrombus	0	1
Valve vegetation	0	1
Aortic atherosclerotic plaques	0	2
Structure at mitral valve	1	2
Low/uncertain embolic risk		
PFO †*	1	10
ASA †*	2	7
Spontaneous echo contrast	0	1
Mitral valve prolaps	4	4
Thickening of the mitral valve	1	1

† $p < 0.05$. There were no significant differences for the other findings. *Injection of agitated saline during TTE was only performed during the last years of this study. In 59 patients TTE and TEE did not reveal a potential CES. PFO=patent foramen ovale, ASA=atrial septal aneurysm.

Table 3. Findings that changed therapy.

Findings at echocardiography	Number of patients	Original therapy	New therapy
ASA	1	Aspirin 38 mg	Aspirin 100 mg
Thrombus in left atrial appendage	1	Aspirin 38 mg	Warfarin
Spontaneous echocardiographic contrast in the left atrial appendage	1	Aspirin 38 mg	Warfarin
Structure at the mitral valve*	1	Aspirin 38 mg	Warfarin
PFO and aortic atherosclerotic plaques	1	Aspirin 38 mg	Warfarin
PFO and ASA	1	Aspirin 38 mg	Warfarin

*Libmann Sacks endocarditis-like abnormality. PFO=patent foramen ovale, ASA=atrial septal aneurysm.

stroke in patients with standard therapy (aspirin 38 mg) occurred in ten out of 71 patients (14%) and in two out of six in patients with therapy change. A recurrent TIA or ischaemic stroke occurred in four out of 23 patients (17%) with a CES at echocardiography, and eight out of 54 patients (15%) without a CES ($p=ns$).

Discussion

Main findings

TEE detected far more CES than TTE, 30 and 10% respectively. However, additional information obtained by TEE led to therapy change in only 7%. Patients had a high risk of recurrent TIA or ischaemic stroke, irrespective of the therapy change that was made.

Echocardiographic findings

Of all patients, 30% had one or more possible cardio-aortic embolic sources (CES) identified by TTE and/or TEE. This result corresponds with the literature review done by the Cerebral Embolism Task Force, which showed that approximately 30% (range 22 to 39%) of all patients with TIA or ischaemic stroke had one or more possible cardiac embolic sources at echocardiography.³

In our study the main difference between the detection of CES with TTE and TEE was present in the detection of PFOs and atrial septal aneurysms. TTE missed these potential CES in nine and five patients, respectively. This rather large difference is probably due to the fact that intravenous injection of agitated saline was only performed during TTE during the last years of our study.

Therapeutic consequences of echocardiograph findings

Echocardiographic evaluation is aimed at detecting a CES that would require something other than standard antiplatelet therapy (i.e. aspirin 38 mg), such as anti-coagulants, endovascular intervention, surgery, antibiotics or immunosuppressive therapy.

In the group of patients with a high-risk CES, the standard therapy of aspirin was changed into warfarin in three patients. The first patient had a complex aortic plaque and a PFO. The SPAF III trial has shown that in patients with complex aortic plaques recurrence rate of stroke with aspirin is significantly higher than with warfarin.¹⁶ The second patient had a thrombus in the left atrial appendage and the third had an echo-dense structure at the mitral valve.

In the present study population, 50% of the therapy changes based on the echocardiographic findings occurred in patients with a CES with a low or uncertain embolic risk (ASA, PFO and SEC) for which there is no evidence-based superior treatment.¹⁷ Currently, randomised trials are ongoing, which compare percutaneous closure of the PFO versus medical therapy (either aspirin or warfarin). None of our patients received surgical or catheter intervention.

The impact of TEE on therapy in our study population (therapy change in 7%) is consistent with the results from Cujec et al. and Hata et al.^{18,19} In their studies TEE altered management in 5 and 10% of the patients, respectively.

Recurrence rate of TIA or ischaemic stroke

A total of 12 patients had a recurrence of a TIA or ischaemic stroke. Mean recurrence was 5.2% in 0 to 1 year and 4.5% in 2 to 5 years. Our results did not confirm the favourable prognosis in young patients in other studies.²⁰⁻²² The percentage of recurrence was remarkably high, both in patients with and without therapy change, 33 and 14% respectively. However, the two patients with recurrence and a change in therapy had risk factors for atherosclerosis, i.e. diabetes mellitus in one and end-stage renal failure in the other.

Limitations

Our study is rather small, although it has an interesting long follow-up. Moreover, the available data in the literature about the effect of therapy change on the recurrence of TIA or ischaemic stroke based on echocardiographic findings is limited.

In our study a PFO was visualised in only 11% of all patients. This is substantially less than in the literature and can be explained by the fact that injection of agitated saline was not performed during the first years of this study.²³⁻²⁵ The statistically significant difference between TTE and TEE in the detection of a CES in the present study was almost entirely due to the failure to detect PFOs by TTE, for which evidence-based treatment is not yet available. This sublineates our doubts about the usefulness of TEE in young patients with stroke.

Six patients were lost to follow-up, what means we cannot exclude a small underestimation of recurrent TIA, ischaemic stroke and death in our study group.

Conclusion

In young patients with cryptogenic TIA or ischaemic stroke, TEE is superior in finding a cardiac source of embolism. However, these findings hardly influence the already initiated treatment. In addition, more than half of the treatment changes in our study population were done in patients with an echocardiographic CES that establishes a low or uncertain embolic risk, i.e. PFO and ASA, for which optimal treatment is still uncertain. Annual recurrence of TIA or ischaemic stroke proved to be remarkably high irrespective of change of therapy based on echocardiographic findings. ■

References

- 1 Yonemura K, Kimura K, Hasegawa Y, Yokota C, Minematsu K, Yamaguchi T. Analysis of ischemic stroke in patients aged up to 50 years. *Rinsho Shinkeigaku*. 2000;40:881-6.
- 2 Cerrato P, Grasso M, Imperiale D, Priano L, Baima C, Giraudo M, et al. Stroke in young patients: etiopathogenesis and risk factors in different age classes. *Cerebrovasc Dis*. 2004;18:154-9.

- 3 Asinger RW, Dyken ML, Fisher M, Harrison MJG, Hart RG, Sherman DG. Cardiogenic brain embolism. The second report of the Cerebral Embolism Task Force. *Arch Neurol*. 1989;46:727-43.
- 4 Flemming KD, Brown RD, Pety GW, Huston J 3rd, Kallmes DF, Piepgrad DG. Evaluation and Management of Transient Ischemic Attack. *Mayo Clin Proc*. 2004;79:1071-86.
- 5 Harloff A, Handke M, Reinhard M, Geibel A, Hetzel A. Therapeutic Strategies After Examination by Transesophageal Echocardiography in 503 Patients With Ischemic Stroke. *Stroke*. 2006;37:859-64.
- 6 Ward RP, Don CW, Furlong KT, Lang RM. Predictors of Long-Term Mortality in Patients With Ischemic Stroke Referred for Transesophageal Echocardiography. *Stroke*. 2006;37:204-8.
- 7 Kapral MK, Silver FL. Preventive health care, 1999 update: 2. Echocardiography for the detection of a cardiac source of embolus in patients with stroke. Canadian Task Force on Preventive Health Care. *CMAJ*. 1999;161:989-96.
- 8 Leung DY, Black IW, Cranney GB, Walsh WF, Grimm RA, Stewart WJ, et al. Selection of patients for transesophageal echocardiography after stroke and systemic embolic events. Role of transthoracic echocardiography. *Stroke*. 1995;26:1820-4.
- 9 Warner MF, Momah KI. Routine transesophageal echocardiography for cerebral ischemia. Is it really necessary? *Arch Intern Med*. 1996;156:1719-23.
- 10 Cujec B, Polasek P, Voll C, Shuaib A. Transesophageal echocardiography in the detection of potential cardiac source of embolism in stroke patients. *Stroke*. 1991;22:727-33.
- 11 Rauh R, Fischereder M, Spengel FA. Transesophageal echocardiography in patients with focal cerebral ischemia of unknown cause. *Stroke*. 1996;27:691-4.
- 12 Kizer JR, Devereux RB. Patent foramen ovale in young adults with unexplained stroke. *N Engl J Med*. 2005;353:2361-72.
- 13 Rabinstein AA, Chirinos JA, Fernandez FR, Zambrano JP. Is TEE useful in patients with small subcortical strokes?. *Eur J Neurol*. 2006;13:522-7.
- 14 DeRook FA, Comess KA, Albers GW, Popp RL. Transesophageal echocardiography in the evaluation of stroke. *Ann Intern Med*. 1992;117:922-32.
- 15 Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol*. 2005;58:688-97.
- 16 Blackshear JL, Baker VS, Rubino F, Safford R, Lane G, Flipse T, et al. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet*. 1996;348:633-8.
- 17 Khairy P, O'Donnell CP, Landzberg MJ. Transcatheter Closure versus Medical Therapy of Patent Foramen Ovale and Presumed Paradoxical Thromboemboli. A Systematic Review. *Ann Intern Med*. 2003;139:753-60.
- 18 Cujec B, Polasek P, Voll C, Shuaib A. Transesophageal echocardiography in the detection of potential cardiac source of embolism in stroke patients. *Stroke*. 1991;22:727-33.
- 19 Hata JS, Ayres RW, Biller J, Adam HP Jr, Stuhlmuller JE, Burns TL et al. Impact of transesophageal echocardiography on the anticoagulation management of patients admitted with focal cerebral ischemia. *Am J Cardiol*. 1993;72:707-10.
- 20 Marini C, Totaro R, Carolei A. Long-term prognosis of cerebral ischemia in young adults. National Research Council Study Group on Stroke in the Young. *Stroke*. 1999;30:2320-5.
- 21 Varona JF, Bermejo F, Guerra JM, Molina JA. Long-term prognosis of ischemic stroke in young adults. Study of 272 cases. *J Neurol*. 2004;251:1507-1.
- 22 Leys D, Bandu L, Henon H, Lucas C, Mounier-Vehier F, Rondepierre P, et al. Clinical outcome in 287 consecutive young adults (15 to 45 years) with ischemic stroke. *Neurology*. 2002;59:26-33.
- 23 Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation*. 2002;105:2625-31.
- 24 Ranoux D, Cohen A, Cabanes L, Amarenco P, Bousser MG, Mas JL. Patent foramen ovale: is stroke due to paradoxical embolism? *Stroke*. 1993;24:31-4.
- 25 Nighoghossian N, Perinetti M, Barthelet M, Adeleine P, Trouillas P. Potential cardioembolic sources of stroke in patients less than 60 years of age. *Eur Heart J*. 1996;17:590-4.