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TRANSESOPHAGEAL ECHOCARDIOGRAPHY DISCLOSES UNEXPECTED CARDIAC SOURCES OF EMBOLUS IN STROKE PATIENTS AGED MORE THAN 45 YEARS

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ABSTRACT - Cerebral embolism from cardiac source is an important cause of stroke, specially in patients younger than 45 years old. *Objective:* To describe the transesophageal echocardiography (TEE) findings in young and non-young stroke patients without any prior evidence of cardiac source for cerebral embolism. *Method:* Transversal study: 523 patients (267 men and 256 women) with ischemic stroke, without any evidence of cardiac abnormality, underwent to TEE. Results: Ten percent were aged 45 years; or less. Left ventricle hypertrophy, left atrial enlargement, spontaneous contrast in aorta, interatrial septum aneurysm, mitral and aortic valve calcification, aortic valve regurgitation, and atherosclerotic plaques in aorta were significantly more frequent in patients aged more than 45 years; 2.8% of non-young patients had thrombus in left heart. *Conclusion:* TEE is widely used to diagnose cardiac source of cerebral embolism in young patients, but it seems to be as useful for older ones, in whom cerebral embolism risk is underestimated; atherogenic and cardioembolic causes may actually coexist, and both should be treated.

KEY WORDS: stroke, cardiac embolism, transesophageal echocardiogram.

Ecocardiograma transesofágico revela fonte cardíaca de embolia cerebral em pacientes com AVC e mais que 45 anos

RESUMO - Embolia cerebral de fonte cardíaca é frequentemente relacionada a acidente vascular cerebral (AVC) em jovem. *Objetivo:* Descrever achados ecocardiográficos em jovens e não jovens com AVC isquêmico, sem suspeita de fonte cardíaca. *Método:* Estudo transversal; 523 pacientes (267 homens e 256 mulheres) com AVC isquêmico sem evidência de fonte cardíaca submeteram-se ao ecocardiograma transesofágico (ECOTE). *Resultados:* 10% dos pacientes tinha 45 anos; ou menos. Hipertrofia do ventrículo esquerdo, aumento do átrio esquerdo, contraste espontâneo na aorta, aneurisma do septo interatrial, calcificação da válvula mitral e aórtica, insuficiência aórtica e placas de ateroma na aorta foram significantemente mais frequentes nos pacientes com mais que 45 anos; 2.8% dos não-jovens apresentaram trombo nas câmaras esquerdas. *Conclusão:* ECOTE é amplamente sugerido na investigação de embolia em pacientes jovens, porém parece ser tão importante também no grupo de pacientes mais velhos, nos quais o risco de embolia cerebral é subestimado; etiologia cardioembólica e aterosclerótica coexistem, e ambas devem ser identificadas e tratadas para melhor prognóstico.

PALAVRAS-CHAVE: acidente vascular cerebral, embolia cardíaca, ecocardiograma transesofágico.

Cerebral embolism from cardiac source (CECS) is considered the cause of 15 to 45% of all strokes, and many studies suggest that it is more prevalent in patients younger than 45 years old[1-3]. The absence of qualitatively valid criteria for the clinical diagnosis of CECS, and the frequent coexistence of a potential cardiac source of emboli and cerebral atherosclerosis, make the diagnosis presumptive in

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many situations. There is neither consensus nor guidelines for diagnosis of CECS. About one third of all stroke patients have some clinical evidence of potential cardiac source of embolism by physical examination, chest roentgenogram or electrocardiogram[2]. The classical cardiac conditions associated with CECS are nonvalvular atrial fibrillation, acute myocardial infarction, ventricular aneurysm, rheumatic heart disease, and prosthetic valves, and some studies have correlated specific entities to less common potential cardiac source of cerebral embolism: mitral valve prolapse, mitral annulus calcification, nonbacterial thrombotic endocarditis, calcified aortic valve stenosis, myxoma, paradoxical embolism and congenital heart disease, nonischemic dilated cardiomyopathy, and infective endocarditis[1]. Aging produces major cardiovascular changes, including decreased elasticity and compliance of the aorta and other arteries, that leads to higher systolic arterial pressure and increased impedance to left ventricle ejection, and subsequent left ventricle hypertrophy. Heart valves thicken and calcification results at the basis of aortic valve and mitral annulus causing valve dysfunction. Aortic valve calcification is associated with atherosclerotic disease, specially coronary artery disease. Various types of arrhythmia are associated with cell degeneration, and occur preferentially in the elderly[4].

The transesophageal echocardiography (TEE) was first used in 1971, and has been very useful in the diagnosis of many cardiac abnormalities, some of them associated to unsuspected ethiology for stroke, as follows: patent foramen ovale, atrial communication, atrial septal aneurysm, aortic atheromatous plaques, echocardiographic spontaneous contrast, mitral valve strands, intracardiac thrombus specially in left appendage[5-7]. The TEE has been more widely used since the eighties when technical improvements mostly regarding transducers, and topic anesthetic procedures were achieved[3,8]. It is well known the superiority of TEE compared to transthoracic echocardiography to detect the above mentioned abnormalities[3,8-12], but even so, it is not widely used in the stroke investigation[13].

Some algorithms for cardiac evaluation, until last decade, included TEE for young stroke patients, and for older only if there was some evidence of cardiac disease[9,14-17]. A recent guideline recommend echocardiography for young stroke patients and for older patients (typically more than 45 years) only with neurological events without evidence of cerebrovascular disease or other obvious cause[18].

The objective of this study was to describe the TEE findings in young and non-young stroke patients without any prior evidence of cardiac source for cerebral embolism. Our hypothesis is that we are underestimating cerebral embolism risk in an older population and therefore it would be useful to submit every patient with acute stroke to TEE in order to diagnose unsuspected sources of embolism.

METHOD

Patients and design – Transversal study with consecutive inclusion of 523 adult patients between November 1998 and March 2004. Patients were admitted to the Division of Neurological Emergencies of São Paulo Hospital at Federal University of São Paulo, and were enrolled if they fulfilled the entry criteria, and signed the consent form. The diagnosis of ischemic stroke were performed by neurologists following a standard protocol including clinical examination and brain CT scan. The selected patients underwent TEE up to 15 days after stroke.

Exclusion criteria – Patients bearing any clinical suspicion of cardioembolism like atrial fibrillation, recent myocardial infarction (in the last 6 months), prosthetic cardiac valves, severe impairment of cardiac function, formal contraindication for TEE, critical care required or those hospitalized for more than 14 days were excluded from the study.

Group assignment – Based on current criteria patients aged 45 or less were considered young, and those aged more than 45 years were considered non-young[19]. To analyze clinical data we split our sample into male and female groups because known epidemiological differences among them.

TEE – Multplane transesophageal echocardiography with a 5mHz transesophageal probe (Vingmed echocardiography System V) were performed to the selected patients. Images were recorded on videotape for later review by two observers. TEE examinations were performed after administration of topical anesthesia with an aerosolized 10% solution of lydocaine and intravenous sedation with midazolan (1.5mg/ml) and meperidine (50mg/ml). Contrast studies were performed through rapid injection of microbubble solution (6ml of isotonic saline 0.9%, 4ml of glucosis 50%, and 1ml of air) in the peripheral vein at rest, during coughing, and Valsalva maneuver. A comprehensive TEE examination was performed with standardized scan planes. The following abnormalities were evaluated: left atrium enlargement, presence of masses, thrombi, or spontaneous contrast either inside the atrium or at the atrial appendage or left ventricle, interatrial septum aneurysm; patent foramen ovale, or any interatrial septal communication; fibrosis, mitral valve strands, calcifications, myxomatous

degeneration, significant stenosis, or regurgitation of the mitral or aortic valve; enlargement, hypertrophy, left ventricle segmental or global dysfunction; and also atherosclerotic plaques or thrombi in the thoracic aorta. Patent foramen ovale was diagnosed if more than three microbubbles were detected in the left atrium within 5 cardiac cycles, following the opacification in the right atrium. Interatrial septal aneurysm was diagnosed when excessive expansion was observed. Spontaneous echo contrast was characterized by smooth echoes with circular or spiral movement inside cardiac chambers. Mitral valve strands were defined as a thin mobile filamentous projections attached to the atrial surface of mitral leaflets or subvalvar apparatus. The left atrium was considered enlarged when it was >40mm. The left ventricle was considered enlarged when diastolic diameter was >50mm and hypertrophic when diastolic thickness was ≥12mm; atherosclerotic plaques in the ascending aorta, aortic arch, and descending aorta had their maximum thickness measured and were classified into 2 groups: those <4mm and those ≥4mm.

Statistical analysis – Proportions and 95% confidence interval were computed for echocardiographic findings. Qui-square tests were performed to compare the proportions of each group. A p value < 0.05 was considered significant. Calculations were performed with SPSS 12 (SPSS Inc., U.S.A.) statistical package.

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RESULTS

There were 523 patients included in the study (267 men and 256 women); the ages ranged from 26 to 92 years (mean = 62.8; SD=12.47). Fifty-four patients (10.3%) were aged 45 years or less (23 man and 31 women) and 469 patients (89.7%) were aged more than 45 years (244 men and 225 women).

No complications occurred during the echocardiography exam. One patient could not be submitted to TEE because of esophagitis diagnosed during the procedure.

The women of non-young group presented a higher proportion of hypertension and diabetes, and lower proportion of cigarette smoking. The men of non-young group had lower proportion of cigarette smoking (Table 1).

Left ventricle hypertrophy, left atrial enlargement, spontaneous contrast in aorta, interatrial septum aneurysm, mitral valve calcification, aortic valve calcification, aortic valve regurgitation, and atherosclerotic plaques in aorta were more frequent in patients aged more than 45 years. Echocardiographic findings are presented in Table 2. Neither mass in left atrium or ventricle nor strands in mitral valve were found.

Four patients had intermittent atrial fibrillation not present during emergency management, all of them were aged more than 45 years old. Four patients presented aortic aneurysms with signs of dissection (43 years old woman, 46 years old woman, 59 years old woman, and 58 years old man). In 1 patient of young group, who had aortic aneurysm dissection and also thrombus, and in 17 patients of non-young group (atrial fibrillation, aortic aneurysm dissection, mitral stenosis, aortic stenosis, or thrombus) the treatment change was mandatory, and was performed immediately after TEE.

Six TEE were considered normal (14.3%) in the group of young patients, and 5 (1.4%) amongst older patients (p<0.0001).

DISCUSSION

The proportion of young patients with stroke in the present study (10.8%) was similar to that previously reported in Brazil (10.6% of cerebral infarct)[20], and in other countries[21], showing that stroke is not rare in young people. Considering that cardioembolism is an important ethiology of stroke in young people (12 to 35% of the cases)[2,19,22,23], and that patients with any suspected cardiac source of embolism were excluded from our study, the

Table 1. Atherosclerotic risk factors of male and female stroke patients distributed by ages.

	Women (n=256)			Men (n=267)		
	≤ 45 years (n=31)	>45 years (n=225)	p	≤ 45 years (n=23)	>45 years (n=224)	p
Hypertension	18	192	0.0002	14	189	0.0748
Diabetes mellitus	4	69	0.0400	2	60	0.0844
Previous stroke	5	53	0.3544	5	60	0.7607
Coronary disease	2	26	0.3933	4	42	0.9827
Cigarette smoking	20	49	<0.0001	16	107	0.0180

Qui-square test.

Table 2. Echocardiography findings in patients younger and older than 45 years.

Echocardiographic findings	≤ 45 years (N=54)			> 45 years (N=469)			p
	N	proportion	95%Confidence interval	N	proportion	95%Confidence interval	
Left ventricle hypertrophy	8	0.1481	0.0662 - 0.2712	200	0.4264	0.3812 - 0.4726	**0.0001**
Left atrium enlargement	3	0.0556	0.0116 - 0.1539	128	0.2729	0.2331 - 0.3157	**0.0005**
Left ventricle enlargement	6	0.1111	0.0419 - 0.2263	101	0.2154	0.1790 - 0.2554	0.0721
Spontaneous contrast in left atrium	4	0.0741	0.0206 - 0.1789	77	0.1642	0.1318 - 0.2009	0.0831
Spontaneous contrast in left ventricle	0	0		21	0.0448	0.0279 - 0.0676	0.1125
Spontaneous contrast in aorta	0	0		45	0.0959	0.0708 - 0.1263	**0.0173**
Thrombus in left atrium	0	0		5	0.0107	0.0035 - 0.0247	0.4458
Thrombus in left ventricle	0	0		3	0.0064	0.0013 - 0.0186	0.5556
Thrombus in aorta	1	0.0185	0.0005 - 0.0989	5	0.0107	0.0035 - 0.0247	0.6076
Interatrial septum aneurysm	0	0		38	0.0810	0.0580 - 0.1095	**0.0298**
Patent foramen ovale	15	0.2778	0.1646 - 0.4164	111	0.2367	0.1989 - 0.2778	0.5036
Mitral valve calcification	0	0		91	0.1940	0.1592 - 0.2328	**0.0004**
Aortic valve calcification	1	0.0185	0.0005 - 0.0989	155	0.3305	0.2880 - 0.3751	**<0.0001**
Mitral valve regurgitation	34	0.6296	0.4874 - 0.7571	349	0.7441	0.7021 - 0.7830	0.0719
Aortic valve regurgitation	7	0.1296	0.0537 - 0.2490	193	0.4115	0.3666 - 0.4576	**0.0001**
Atherosclerotic plaque <4mm in aorta	12	0.2222	0.1204 - 0.3560	239	0.5096	0.4633 - 0.5557	**0.0001**
Atherosclerotic plaque >4mm in aorta	2	0.0370	0.0045 - 0.1275	125	0.2665	0.2270 - 0.3090	**0.0002**
Myxomatous valve degeneration	0	0		4	0.0085	0.0023 - 0.0217	0.4957
Mitral stenosis	1	0.0185	0.0005 - 0.0989	3	0.0064	0.0013 - 0.0186	0.3329
0Aortic stenosis	0	0		3	0.0064	0.0013 - 0.0186	0.5556

Qui-square test

actual proportion is likely to be even greater. Because of the low prevalence of atherosclesosis in the young, the cardiac conditions are more frequently related to the ethiology of stroke[2,21,24].

Left ventricular hypertrophy, left atrial enlargement, left ventricle enlargement, spontaneous contrast in aorta, mitral valve calcification, aortic valve calcification, aortic valve regurgitation, and atherosclerotic plaques in aorta are related to aging, and were more prevalent in the older group as expected. PFO occurred in the older group in same proportion as younger group. PFO and atrial septal aneurysm are typically related to cryptogenic stroke[25].

Atrial fibrillation and myocardial infarction are more prevalent in older patients, and are considered main sources of emboli[1]. However, in this study patients with some cardiac source of embolism were previously excluded, so the TEE findings were unexpected. Cabral et al. studied a similar population, without cardiac source of embolism, and found also more abnormalities in older group[26]. We have previously reported that 16% of patients had their treatments changed after TEE, leading to significant clinical impact[27].

In current guideline for clinical application of echocardiography, it is recommended for younger patients, typically less than 45 years, with cerebrovascular events and for older patients, typically more than 45 years, with neurological events without evidence of cerebrovascular disease or other obvious cause. As aging is frequently related to obvious cause of ischemic stroke, considered athe-

rothrombotic event, other etiologies are not systematically investigated[14]. Last Brazilian echocardiography guideline also states as class I recommendation echocardiography for young patients (<45 years) with acute stroke, for patients older than 45 years without evidence of cerebrovascular disease, and for stroke with preexisting cerebrovascular disease with suspicion of embolus; also makes class II recommendations for echocardiography after acute neurological symptoms in patients with preexisting cerebrovascular disease, and for patients with stroke in whom echocardiography would not interfere in diagnosis or management[28].

Clinical[29], or review studies[9,17,30] recommend echocardiography with the same restrictions of current guidelines, i.e., only for patients with stroke and atrial fibrillation, coronary artery disease, and other cardiac diseases. Few studies recommend echocardography for patients without clinical suspicion of cardiac source of embolism[5].

In our study we found in the group of non-young patients, 13 individuals (2.8%) with some thrombus, 6 (1.3%) with mitral or aortic valve stenosis, 4 (0.9%) with thoracic aorta dissection, 4 (0.9%) with intermittent atrial fibrillation. Those patients demanded proper management, as well as some patients with other TEE abnormalities needed specific care. In the group of young patients 54 TEE were performed and we found one case of thrombus, while in the non-young group a change in management was mandatory at each 21 TEE.

TEE is widely used to diagnose cardiac source of cerebral embolism in young patients, but it seems to be as useful for older ones, in whom atherogenic and cardioembolic causes may actually coexist. In these patients the ethiological diagnosis of stroke is even more difficult, and it might be multifactorial. Each cause should be promptly identified and treated, reducing recurrence.

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