European Heart Journal Supplements (2023) **25** (Supplement C), C212–C217
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad022

ESC
European Society
of Cardiology

Echocardiography in cardioembolic stroke prevention

Emanuele Canali*, Marco Serani, Pierpaolo Tarzia, Pellegrino Ciampi, Stefano Canestrelli, and Leonardo Calò

Department of Cardiology, Policlinico Casilino, Via Casilina 1049, 00169 Rome, Italy

KEYWORDS
Cardioembolic stroke;
ESUS;
Echocardiography;
Left atrial thrombus;
PFO;
Thrombosis prosthetic valve;
Endocarditis;
Myxoma

Stroke is a leading cause of mortality and disability, and cardiac embolism accounts for one-third of all ischaemic strokes. Thirty per cent of strokes are cryptogenic. In this setting, echocardiography is essential in the diagnosis, treatment, and prevention of embolic stroke of undetermined source since it is a widely available, safe, and inexpensive tool. Transthoracic echocardiography and transoesophageal echocardiography, furthermore, are proven to change therapeutic management leading to initiation of anti-coagulation, anti-microbial therapy, patent foramen ovale (PFO) closure, or cardiac tumour resection. The most common cardioembolic sources include left atrial appendage thrombus, left ventricular thrombus, vegetations in endocarditis, paradoxical embolization in PFO, prosthesis thrombosis, and intracardiac tumours. Although the presence of a cardioembolic source only represents a risk factor for an ischaemic stroke, it could not assure the certain or the unique cause of the event. The purpose of this review is to underline the importance of echocardiography and overview the main sources of cardiac embolism and the echocardiographic features.

Introduction

Stroke is a major source of morbidity and mortality, accounting for the second cause of death and an important cause of adult disability in the European Union. It affects around 1.1 million people in Europe every year and causes 440.000 deaths, with a huge cost of care and loss of productivity according to epidemiologic data. Cardioembolic stroke represents 15–30% of all ischaemic strokes. Approximately 30% of strokes are cryptogenic and remain without an established cause. Most cryptogenic strokes, however, appear to be embolic and are defined as 'ESUS' (Embolic Strokes of Undetermined Source). Considering the clinical importance of a correct aetiological diagnosis, the role of transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE) is essential for the evaluation of potential causes of cardiac embolism and for recurrency prevention addressing, also, a correct therapeutic management. Taking into account the EACVI recommendations on cardiovascular imaging for the detection of embolic sources, these can be divided into two categories: major cardiac sources of cerebral embolism and minor or unclear cardiac sources of cerebral embolism.[1]

It may be challenging to distinguish cardioembolic stroke from other types of ischaemic stroke since there is no gold standard for certain diagnosis. Most important characteristics to diagnose a cardioembolic stroke are the evidence of a potential source of cardiac embolism and the absence of arterial disease.

Cardioembolic strokes are usually localized in cortical territory and may involve multiple arterial territories. Due to the size of the emboli, the area of infarction may be very large and is usually located in the middle cerebral artery. Lacunar stroke, instead, affects subcortical areas and the extension is $\leq$1.5 cm ($\leq$ 2.0 cm on MRI diffusion images).

ESUS definition was introduced in 2014 by Hart et al. and identified as non-lacunar ischaemic stroke detected by CT or MRI in absence of atherosclerosis (extra- or intracranial) causing >50% luminal stenosis in arteries supplying the ischaemic area. In addition, there must not be present a major risk cardioembolic source and no other specific cause of stroke (arteritis, dissection, migrain/vasospasm, drug abuse).[2]

*Corresponding author. Tel: +39 3473067059, Fax: +39 0623188305, Email: emanuele.canali@gmail.com

Based on a systematic review, the reported frequency of ESUS ranged from 9% to 25% of ischaemic strokes, averaging 17%. Moreover, it was found that patients affected by ESUS tend to be younger and present less often cardiovascular risk factors than non-ESUS patients with ischaemic stroke. The risk of stroke recurrence after ESUS was higher, ~4.5% per year in patients on anti-platelet therapy.[3] Importantly, the two randomized trials NAVIGATE-ESUS (7213 participants) and RESPECT-ESUS (5390 participants) failed to prove benefit of anti-thrombotic therapy with rivaroxaban and dabigatran over aspirin for the prevention of recurrent stroke in patients with ESUS.[4,5]

Role of the echocardiography

The main goal of TTE in stroke is the detection of the embolic event's cause. TTE should be preferentially performed within the first days after admission in the Stroke Unit but can be also done in the Emergency Department, in case of strong suspicion of embolic stroke when the risk of recurrence is high.

TEE is a semi-invasive exam widely performed in patients with ischaemic stroke. It is consistently superior to TTE in terms of imaging detection, especially when the patients present without clinical signs suggestive of heart disease. TEE superiority seems to be higher in younger patients. Therefore age, history, the risks of recurrence and consequences of treatment must be considered when in presence of an embolic event. When a cardioembolic cause is suspected, it is recommended to consider both TTE and/or TEE according to clinical context: for instance, emergent indications of TEE are, usually, limited (e.g. fever, prosthesis).

A systematic review and meta-analysis of 27 studies that aimed to assess the clinical utility of routine TEE for patients with unexplained ischaemic stroke found that TEE-detected findings let to the introduction of anticoagulant therapy in up to one-third of patients, although the examinations were performed mostly not for established guideline-based indications leading the authors concluding that it is unclear whether routine use of TEE is indicated or not.[6] In a retrospective single-center study of 1458 patients hospitalized for stroke or transient ischaemic attack with a suspected cardioembolic cause, TEE changed the management in 243 patients (16.7%); a significant change was evident in patients aged less than 40 years of age, decreasing in frequency with older age, while 71% of patients with change in management underwent PFO closure.[7] We will discuss the main cardioembolic sources where echocardiography has an undoubted role in the identification (major and minor sources of ischaemic stroke are listed in *Table 1*).

Table 1 Major and minor or unclear cardioembolic sources

Major cardioembolic sources	Minor or unclear cardioembolic sources
• Atrial fibrillation • Recent or previous myocardial infarction • Cardiomyopathies • Intracardiac masses (thrombus, tumours) • Mitral stenosis • Aortich atheromatous plagues • Endocarditis • Prostethic valve	• Mitral valve prolapse • Mitral anulus calcification • Spontaneous echo contrast • Calcified aortic stenosis • Valvular strands and Lambl's excrescences • Atrial septal aneurysm • Patent foramen ovale

Left atrial thrombus

Atrial fibrillation (AF) is the most frequent source of cardioembolic stroke. It affects 5% of adults aged 65 and rises to 10% over 75 years. Of all ischaemic strokes, 20–30% and 10% of cryptogenic stroke can be attributed to AF. A dilated left atrium (LA) and reduced LA and left atrial appendage (LAA) blood flow on echocardiogram are independent risk factors for thromboembolism and are more likely to have stasis of blood as demonstrated by the presence of spontaneous echo contrast (SEC) or 'smoke' on trans- oesophageal echocardiography.[8] SEC has been related to haemodynamic and haemostatic abnormalities and an increased risk of stroke and thromboembolism.[9] Nearly all patients with their first episode of AF or who are referred for radiofrequency pulmonary vein antral isolation will benefit from transthoracic echocardiographic evaluation to identify an LA thrombus, although sensitivity is low. TEE is much more sensitive for identifying the presence of LA thrombi (*Figure 1*) and for quantifying the risk of thrombus formation through the study of LAA anatomy and function: the loss of LAA contractility in AF and the lower emptying velocity (< 20 cm/s) promote thrombus formation; moreover, multilobate anatomy and 'chicken wing' shape in this setting are also predisposing to cardioembolism.[10] Furthermore, TEE is considered the gold standard for detection of LA/LAA thrombus in patients with AF who are selected for undergoing electrocardioversion or pulmonary vein isolation.[11] It is important to underline also the clinical relevance of TEE, rather than TTE, for accurate detection and risk stratification of intracardiac thrombi, confirming a different impact of TEE in terms of cumulative mortality prevention and recurrent events (thrombus-associated ischaemic stroke overall risk was high in patients underwent

Figure 1 LAA thrombosis on TEE.

to TEE—aHR: 3.13; 95% CI: 1.17–8.35—but not in those who performed TTE alone—aHR,:0.89; 95% CI: 0.12–6.51).[12] Finally, TEE is also the preferred imaging modality to guide transcatheter left atrial appendage closure (LAAC). Although several observational studies have shown similar success rates and perioperative complications between TEE and the less invasive intracardiac echocardiography (ICE) for LAAC, a recent retrospective analysis shows that the incidence of major adverse events were significantly lower for TEE-guided LAAC.[13] Lastly, it is known that 3D TEE is a useful and reliable tool as proved in experimental studies and shows an excellent correlation between full-volume or zoom-mode and reference data; indeed, in this context, it could be advantageous for some purposes: the evaluation of LAA geometry and features such as LAA orifice diameters, LAA depth, mean volume and number of lobes are surely better characterized with 3D TEE than 2D echocardiography also for surgical intentions.[14]

PFO

It is already known that observational studies and meta-analysis show a strong relative association of patent foramen ovale (PFO) with cryptogenic stroke in patients <55 years old as compared to older patients. In patients with otherwise cryptogenic stroke, approximately one-third of discovered PFOs are likely to be incidental and hence not benefit from closure.[15] This probability is sensitive to patient characteristics and to the presence of some echocardiographic markers, suggesting the importance of patient selection in therapeutic decision-making.

The last European position paper on the management of patients with PFO explicates an algorithm for the diagnosis of PFO, recommending initial execution of saline contrast-enhanced TTE or (if negative or equivocal) contrast-enhanced transcranial Doppler for the evidence of right-to-left shunt and reporting as last step contrast-enhanced TEE.[16] At present, grounded on the accrued low-quality evidence, no technique can be considered a gold standard for diagnosis and, in most cases, a precise diagnosis of PFO needs the combined use of different techniques, prescribed according to their different characteristics.[16]

For our purposes, a low-risk stroke PFO is characterized by the absence of aneurysmal changes of the interatrial septum with limited motion and separation of the septum primum and the secundum, resulting in a small PFO size and shunt during the Valsalva manoeuver. High-risk stroke PFO is characterized by PFO size of >3 mm or the presence of atrial septal aneurysm with hypermobility of the septum during the Valsalva manoeuver resulting in a large PFO size. In addition, some patients without a characteristic atrial septal aneurysm may show exaggerated motion of the atrial septum during the Valsalva manoeuver, resulting in septal excursion >10 mm and a large PFO size and at high risk for cardioembolic stroke.[16] The presence of Eustachian valve, Chiari network or a long PFO tunnel were suggested to be linked to PFO-associated strokes but only in retrospective studies. Other studies have failed to detect one or more of these associations, however, underlining the heterogeneity of phenotypes and the need to identify them. Hence, it is important to remark that no single clinical, anatomical or imaging characteristics are sufficient to make a quantitative estimation of the probability of a PFO causal role but when a PFO is considered to play a pathogenic role in an embolism, the episode should not be classified as cryptogenic anymore.

Left ventricular thrombus

Left ventricular thrombus (LVT) formation can result from several risk factors: recent myocardial infarction, dilated, restrictive and hypertrophic cardiomyopathy, Tako-Tsubo syndrome, non compaction cardiomyopathy, heart failure. Since the introduction of reperfusion therapy after acute MI, LVT has significantly reduced. According to data it is believed to occur in up to 19.2% of patients with anterior STEMI and LVEF < 50%. The role of echocardiography is essential as the first imaging modality for detection of LVT since it is widely used in all patients with myocardial infarction. However, sensitivity of TTE is only 29% when compared to Cardiac Magnetic Resonance (CMR), whereas specificity is 98%. CMR is the optimal or gold standard imaging modality to detect LVT since the sensitivity ranges from 82% to 88% and the specificity is almost 100%. Beyond its diagnostic capabilities, CMR has also demonstrated value in identifying structural risk factors for LV thrombus formation, particularly myocardial scar burden or infarct size. Given the poor sensitivity of TTE in thrombus detection, it's already known that the addition of an intravenous ultrasound contrast agent improves both the specificity (99%) and sensitivity (64%) of TTE, particularly in patients with anterior MI, by enhancing the endocardial border definition. Recently, some authors proposed an algorithmic approach to the diagnosis and management of LVT following acute myocardial infarction that begins with TTE with contrast within 24 h of index myocardial infarction.[17] TEE has limited added utility to TTE in diagnosing LV thrombus because the LV apex, particularly in patients with a dilated left ventricle and apical dyskinesis, is typically foreshortened and may be poorly visualized from either the transoesophageal or transgastric views.

Prosthesis thrombosis

Thrombus formation is the most common cause of obstruction of mechanical prosthesis (0.3% to 8% per patient-year). Although less frequent and more insidious, it can also be observed in bioprosthesis. The incidence of pannus formation causing prosthesis obstruction is, instead, similar in biological and mechanical prosthesis. Mitral and tricuspid prosthesis are associated with, respectively, 7.5- and 11.7-times higher hazard risk of thrombosis and the risk of pannus formation is three times larger in the mitral position. Large prosthesis size (>27 mm), tilting disk, and bileaflet prostheses are associated with, respective, 67, 69, and 83% risk reduction of thrombosis.[18] Generally, the left/right atrial (LA/RA) side of a prosthetic mitral/tricuspid valve is obscured by acoustic shadowing from the TTE approach, resulting in a low sensitivity for detection of prosthetic mitral or tricuspid regurgitation (MR, TR), thrombus, pannus, or vegetation. So, TEE provides superior images of the LA/RA side of the mitral/tricuspid prosthesis. Differentiation between thrombosis and pannus overgrowth remains challenging. Direct signs of prosthesis valve thrombosis include immobility or

reduced leaflet mobility and the presence of thrombus on either side of the prosthesis, with or without obstruction. Pannus formation is more frequent on mitral prostheses and is usually annular in location. When observed on mitral prosthetic valves, it most often occurs on the atrial side of the prosthesis. At echocardiography, the thrombus tends to be mobile and globular with a soft echo density (similar to that of the myocardium) and may be attached to the valve occluder or sewing ring or both. Pannus is firmly fixed, has a bright echo density (small dense mass with the same echo intensity as the valve housing), and is attached to the valve apparatus. Bioprosthetic valve thrombosis (BPVT) is an important cause of prosthetic valve dysfunction (PVD), and guidelines do not recommend routine TTE during the first 5 years after valve implantation.[19] Most patients with PVD due to BPVT were asymptomatic at initial diagnosis, which was made based on routine surveillance TTE, often performed before 5 years. BPVT, an acute disease process, requires timely diagnosis because patient conditions rapidly deteriorate. Further studies are needed to determine whether routine surveillance TTE should be considered for patients with bioprosthetic valves to identify pre-symptomatic features of BPVT in order to provide effective and appropriate therapy. The presence and localization of thrombus formation, pannus, and prosthetic valve dehiscence can be evaluated better by 3D echocardiography. This is especially useful for the assessment of mechanical mitral and aortic valves where 2D images are often of poor quality due to acoustic shadowing. With 3D imaging, the ventricular side of mitral prosthetic valves, which is consistently prevented with 2D imaging, can be often visualized.[19] No study has reported on the evaluation of pannus or thrombus using CMR.

Endocarditis

Currently, the imaging methods used to assess infective endocarditis (IE) primarily include echocardiography with a growing role of MRI, CT, and PET-CT for undiagnosed cases. Prosthetic valves, drug abuse, cardiac implanted electronic devices, congenital heart diseases are predisposing or known risk factors for IE. Embolic events are common complications (16–46% of patients in literature—25% of patients at time of diagnosis) and are of prognostic importance, especially for patients candidates to surgery, with a mortality rate of up to 30% at 30 days. The brain is the most common site of embolization, followed by solid organs, including the spleen, kidney, and lung. Less common sites of embolization included peripheral arteries, coronary circulation, and eyes. So, patients with high embolic risk (ER) should be identified early to allow for best decision-making: the embolic risk French Calculator is the most utilized calculator and employs six parameters, including age, presence of diabetes, atrial fibrillation, previous EE, vegetation length, and S. aureus infection. The high-risk designation on the ER French Calculator (defined as a probability greater than 8% on the 28th day) predicted EE independently of other candidate predictors in patients with IE, as it has been recently remarked.[20] Based on existing literature, it is already known that Staphylococcus aureus aetiology, a globular shape of vegetation at echocardiography, its mobility, mitral involvement and vegetation size > 10 mm are associated with an increased risk of embolism. In left-sided endocarditis (*Figure 2*) it has also been proposed a simple scoring system, which combines aetiology and vegetation size with time on anti-microbials and might contribute to a better assessment of the risk of embolism and to a more individualized early surgery treatment.[21] An underestimated form of endocarditis is non-bacterial thrombotic one, sometimes referred to as thrombotic, marantic, verrucous, or Libman-Sacks endocarditis: a non-infective endocarditis that develops in patients (especially females) with autoimmune disorders or malignancies associated with a poor prognosis. The true incidence of non-bacterial thrombotic endocarditis is still unknown, and much of the available evidence regarding its prevalence is derived from case reports or autopsy series. Patients with non-bacterial thrombotic endocarditis are often asymptomatic but can present with systemic cardioembolic stroke as first manifestation, a phenomenon that occurs in up to 50% of patients. At our best knowledge, only a contemporary 20-year cohort retrospective study has shown the superior role of TEE in diagnosis underlying the needing of anti-coagulant therapy and confirming the high mortality.[22]

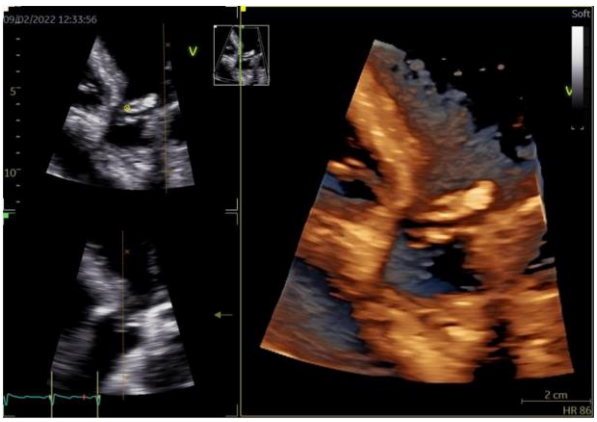

Figure 2 Aortic endocarditis on 3D TEE.

Intracardiac tumours

Intracardiac tumours may be associated with embolic manifestations and stroke. The frequency of primary cardiac tumours is 0.02%. Among benign cardiac tumours, myxoma and papillary fibroelastoma represent the most frequent, accounting for almost 40% of all primary cardiac tumours.

Myxomas are more frequent in young women (30–60 yrs) and are located approximately in 75% of cases in the left atrium, 23% in right atrium and present in one-third of the time with embolism. Symptoms of myxoma depend on the localization and morphology and are represented by constitutional (fever, arthralgias, weight loss, fatigue), obstruction (dyspnoea, orthopnoea, syncope) and arterial embolization manifestations.[23] In about 25–45% of cases, myxomas present with neurological manifestations and the more frequent are ischaemic stroke or transient ischaemic attack (82%), syncope (28%), psychiatric presentations (23%), headache (13%), intracerebral haemorrhage (12%) and seizures (12%). Echocardiography is essential in detecting the mass that is more frequently located in the

left atrium and attached to the fossa ovalis of the interatrial septum, though it can be located in any endocardial surface. It is usually a single mass and the morphology is round or ovoid with smooth or lobular regular borders. Pedunculated myxoma tends to be greater in size and cause transvalvular obstruction.[24] Myxomas have variable mobility depending on size and implantation. Transoesophageal echocardiography may be needed to visualize the implantation site and the potential extension into the pulmonary or caval veins. Though imaging suggests the diagnosis, this must be confirmed histologically and echocardiographic follow up is recommended for a minimum of 4 years after the resection.[24] Although fibroelastoma are often diagnosed incidentally and clinical manifestations are not well described, embolic events such as stroke, sudden death, acute myocardial infarction, pulmonary emboli and retinal artery embolism have been reported. In a study, among 45 patients who had prospectively diagnosed papillary fibroelastoma, stroke occurred in one patient and transient ischaemic attack in two patients in young age and no other cardiovascular disease (incidence 6.6%). Papillary fibroelastoma derives from the endocardium and is more frequently located on the surface of cardiac valves (90%) and the aortic valve is the most affected. For the aortic tumours, no predilection for the aortic or ventricular side has been observed. Papillary fibroelastoma typical echocardiographic features are round, oval or irregular appearance, well demarcated borders and homogenous texture, small dimensions (mostly < 20 mm), no valvular destruction. Differential diagnosis includes valvular calcifications, thrombi, vegetations, strands and Lambl's excrescences and TEE may be an essential examination to lead to the correct diagnosis.[25]

Conclusions

Cardioembolic stroke is a major cause of disability and mortality world-wide. Identifying potential cardiac sources of embolism is a fundamental objective, also in terms of treatment and medical management: since stroke recurrences in patients on anti-aggregation therapy and considering that DOAC routinary employment in cardioembolic stroke do not reach a superiority evidence, it is mandatory to make a correct diagnosis by using echocardiography. Transthoracic echocardiography as first line and transoesophageal echocardiography may help to recognize the underlying cause, despite up to 30% of ischaemic strokes remaining 'cryptogenic'. TTE and TEE should be performed according to the clinical context, considering CT and MRI as complementary techniques or, sometimes, as gold standard reference. This review encourages a multi-modality imaging approach, also combining 3D reconstruction when feasible, for diagnosis and management of cardioembolic stroke.

Funding

None declared.

Conflict of interest: None declared.

Data availability

No new data were generated or analysed in support of this research.

References

1. Cohen A, Donal E, Delgado V, Pepi M, Tsang T, Gerber B *et al.* Reviewers: this document was reviewed by members of the 2018-2020 EACVI scientific documents committee; chair of the 2018-2020 EACVI scientific documents committee. EACVI recommendations on cardiovascular imaging for the detection of embolic sources: endorsed by the Canadian society of echocardiography. *Eur Heart J Cardiovasc Imaging* 2021;**22**:e24-e57.
2. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ *et al.* Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;**13**:429-438.
3. Hart RG, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic stroke of undetermined source: a systematic review and clinical update. *Stroke* 2017;**48**:867-872.
4. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD *et al.* Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018;**378**:2191-2201.
5. Diener HC, Easton JD, Granger CB, Cronin L, Duffy C, Cotton D *et al.* Design of randomized, double-blind, evaluation in secondary stroke prevention comparing the EfficaCy and safety of the oral thrombin inhibitor dabigatran etexilate vs. Acetylsalicylic acid in patients with embolic stroke of undetermined source (RE-SPECT ESUS). *Int J Stroke* 2015;**10**:1309-1312.
6. McGrath ER, Paikin JS, Motlagh B, Salehian O, Kapral MK, O'Donnell MJ. Transesophageal echocardiography in patients with cryptogenic ischemic stroke: a systematic review. *Am Heart J* 2014;**168**:706-712.
7. Khariton Y, House JA, Comer L, Coggins TR, Magalski A, Skolnick DG *et al.* Impact of transesophageal echocardiography on management in patients with suspected cardioembolic stroke. *Am J Cardiol* 2014;**114**:1912-1916.
8. Black IW, Hopkins AP, Lee LC, Walsh WF. Left atrial spontaneous echo contrast: a clinical and echocardiographic analysis. *J Am Coll Cardiol* 1991;**18**:398-404.
9. Bernhardt P, Schmidt H, Hammerstingl C, Lüderitz B, Omran H. Patients with atrial fibrillation and dense spontaneous echo contrast at high risk a prospective and serial follow-up over 12 months with transesophageal echocardiography and cerebral magnetic resonance imaging. *J Am Coll Cardiol* 2005;**45**:1807-1812.
10. Beigel R, Wunderlich NC, Ho SY, Arsanjani R, Siegel RJ. The left atrial appendage: anatomy, function, and noninvasive evaluation. *JACC Cardiovasc Imaging* 2014;**7**:1251-1265.
11. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA *et al.* 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *J Interv Card Electrophysiol* 2012;**33**:171-257.
12. Tanaka K, Koga M, Lee KJ, Kim BJ, Mizoguchi T, Park EL *et al.* Transesophageal echocardiography in ischemic stroke with atrial fibrillation. *J Am Heart Assoc* 2021;**10**:e022242.
13. Morcos R, Megaly M, Saad M, Barakat AF, Rubens M, Saxena A *et al.* In-hospital outcomes of transesophageal versus intracardiac echocardiography guided left atrial appendage closure. *Catheter Cardiovasc Interv* 2022;**99**:1572-1581.
14. Nakajima H, Seo Y, Ishizu T, Yamamoto M, Machino T, Harimura Y *et al.* Analysis of the left atrial appendage by three-dimensional transesophageal echocardiography. *Am J Cardiol* 2010;**106**:885-892.
15. Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke: incidental or pathogenic? *Stroke* 2009;**40**:2349-2355.
16. Pristipino C, Sievert H, D'Ascenzo F, Louis Mas J, Meier B, Scacciatella P *et al.* European Position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. *Eur Heart J* 2019;**40**:3182-3195.
17. Camaj A, Fuster V, Giustino G, Bienstock SW, Sternheim D, Mehran R *et al.* Left ventricular thrombus following acute myocardial infarction: JACC state-of-the-art review. *J Am Coll Cardiol* 2022;**79**:1010-1022.
18. Rizzoli G, Guglielmi C, Toscano G, Pistorio V, Vendramin I, Bottio T *et al.* Reoperations for acute prosthetic thrombosis and pannus: an assessment of rates, relationship and risk. *Eur J Cardiothorac Surg* 1999;**16**:74-80.
19. Lancellotti P, Pibarot P, Chambers J, Edvardsen T, Delgado V, Dulgheru R *et al.* Recommendations for the imaging assessment of prosthetic heart valves: a report from the European association of

cardiovascular imaging endorsed by the Chinese society of echocardiography, the inter-American society of echocardiography, and the Brazilian department of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging* 2016;**17**:589–590.
20. Hu W, Wang X, Su G. Infective endocarditis complicated by embolic events: pathogenesis and predictors. *Clin Cardiol* 2021;**44**:307–315.
21. Rizzi M, Ravasio V, Carobbio A, Mattucci I, Crapis M, Stellini R *et al*. Predicting the occurrence of embolic events: an analysis of 1456 episodes of infective endocarditis from the Italian study on endocarditis (SEI). *BMC Infect Dis* 2014;**14**:230.
22. Zmaili MA, Alzubi JM, Kocyigit D, Bansal A, Samra GS, Grimm R *et al*. A contemporary 20-year Cleveland clinic experience of nonbacterial thrombotic endocarditis: etiology, echocardiographic imaging, management, and outcomes. *Am J Med* 2021;**134**:361–369.
23. Sarjeant JM, Butany J, Cusimano RJ. Cancer of the heart: epidemiology and management of primary tumors and metastases. *Am J Cardiovasc Drugs* 2003;**3**:407–421.
24. Gil J, Marmelo B, Abreu L, Antunes H, Dos Santos LF, Cabral JC. Silent cardiac tumor with neurological manifestations. *J Cardiol Cases* 2017; **15**:132–135.
25. Sun JP, Asher CR, Yang XS, Cheng GG, Scalia GM, Massed AG *et al*. Clinical and echocardiographic characteristics of papillary fibroelastomas: a retrospective and prospective study in 162 patients. *Circulation* 2001;**103**:2687–2693.