Guidelines for the Use of Echocardiography in the Evaluation of a Cardiac Source of Embolism

Muhamed Saric, MD, PhD, FASE, Chair, Alicia C. Armour, MA, BS, RDCS, FASE, M. Samir Arnaout, MD, Farooq A. Chaudhry, MD, FASE, Richard A. Grimm, DO, FASE, Itzhak Kronzon, MD, FASE, Bruce F. Landeck, II, MD, FASE, Kameswari Maganti, MD, FASE, Hector I. Michelena, MD, FASE, and Kirsten Tolstrup, MD, FASE, *New York, New York; Durham, North Carolina; Beirut, Lebanon; Cleveland, Ohio; Aurora, Colorado; Chicago, Illinois; Rochester, Minnesota; and Albuquerque, New Mexico*

Embolism from the heart or the thoracic aorta often leads to clinically significant morbidity and mortality due to transient ischemic attack, stroke or occlusion of peripheral arteries. Transthoracic and transesophageal echocardiography are the key diagnostic modalities for evaluation, diagnosis, and management of stroke, systemic and pulmonary embolism. This document provides comprehensive American Society of Echocardiography guidelines on the use of echocardiography for evaluation of cardiac sources of embolism.

It describes general mechanisms of stroke and systemic embolism; the specific role of cardiac and aortic sources in stroke, and systemic and pulmonary embolism; the role of echocardiography in evaluation, diagnosis, and management of cardiac and aortic sources of emboli including the incremental value of contrast and 3D echocardiography; and a brief description of alternative imaging techniques and their role in the evaluation of cardiac sources of emboli.

Specific guidelines are provided for each category of embolic sources including the left atrium and left atrial appendage, left ventricle, heart valves, cardiac tumors, and thoracic aorta. In addition, there are recommendation regarding pulmonary embolism, and embolism related to cardiovascular surgery and percutaneous procedures. The guidelines also include a dedicated section on cardiac sources of embolism in pediatric populations. (J Am Soc Echocardiogr 2016;29:1-42.)

Keywords: Cardioembolism, Cryptogenic stroke, Cardiac mass, Cardiac tumor, Cardiac shunt, Vegetation, Prosthetic valve, Aortic atherosclerosis, Intracardiac thrombus

TABLE OF CONTENTS

From New York University Langone Medical Center, New York, New York (M.S.); Duke University Health System, Durham, North Carolina (A.C.A.); American University of Beirut Medical Center, Beirut, Lebanon (M.S.A.); Icahn School of Medicine at Mount Sinai Hospital, New York, New York (F.A.C.); Learner College of Medicine, Cleveland Clinic, Cleveland, Ohio (R.A.G.); Lenox Hill Hospital, New York, New York (I.K.); the University of Colorado School of Medicine, Aurora, Colorado (B.F.L.); Northwestern University, Chicago, Illinois (K.M.); Mayo Clinic, Rochester, Minnesota (H.I.M.); and the University of New Mexico Health Sciences Center, Albuquerque, New Mexico (K.T.).

The following authors reported no actual or potential conflicts of interest in relation to this document: Muhamed Saric, MD, PhD, FASE, Chair, Alicia Armour, MA, BS, RDCS, FASE, M. Samir Arnaout, MD, Richard A. Grimm, DO, FASE, Bruce F. Landeck, II, MD, FASE, Hector Michelena, MD, FASE, and Kirsten Tolstrup, MD, FASE. The following authors reported relationships with one or more commercial interests: Farooq Chaudhry, MD, FASE serves as a consultant for Lantheus Medical Imaging and received grant support from GE Healthcare and Bracco. Itzhak Kronzon, MD, FASE, serves as a consultant for Philips Healthcare; Kameswari Maganti, MD, FASE, received a research grant from GE Healthcare.

Reprint requests: American Society of Echocardiography, 2100 Gateway Centre Boulevard, Suite 310, Morrisville, NC 27560 (E-mail: *ase@asecho.org*).

0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2015.09.011

Abbreviations

2D = Two-dimensional

3D = Three-dimensional

ASA = Atrial septal aneurysm

ASD = Atrial septal defect

ASE = American Society of Echocardiography

ATS = Aortic thromboembolism syndrome

AVM = Arteriovenous malformation

CES = Cholesterol emboli syndrome

CT = Computed tomography

IE = Infective endocarditis

LA = Left atrium

LAA = Left atrial appendage

LV = Left ventricle

MAC = Mitral annular calcification

MRI = Magnetic resonance imaging

MV = Mitral valve

NBTE = Nonbacterial thrombotic endocarditis

PE = Pulmonary embolism

PFE = Papillary fibroelastoma

PFO = Patent foramen ovale

PLAX = Parasternal long-axis

PSAX = Parasternal short axis

RA = Right atrium

RV = Right ventricle

SEC = Spontaneous echocardiographic contrast

TAVR = Transcatheter aortic valve replacement

TCD = Transcranial Doppler

TEE = Transesophageal echocardiography

TIA = Transient ischemic attack

TTE = Transthoracic echocardiography

VSD = ventricular septal defect

INTRODUCTION

Embolism from the heart or the thoracic aorta often leads to clinically significant morbidity and mortality due to transient ischemic attacks (TIAs), strokes, or occlusions of peripheral arteries.

Stroke is the third leading cause of death in the United States and other industrialized countries. Echocardiography is essential for the evaluation, diagnosis, and management of stroke and systemic embolism.

Cardiac embolism accounts for approximately one third of all cases of ischemic stroke. Paradoxical embolism and embolism from the thoracic aorta, especially of its atheroma contents, are responsible for additional cases of stroke and systemic embolism.

This document provides the first set of guidelines of the American Society of Echocardiography (ASE) guidelines specific to this topic.

METHODOLOGY

These guidelines are based on an extensive literature review including all other relevant guidelines from the ASE and other national and international medical societies. They provide primarily expert consensus opinions, because randomized trial data are lacking for many topics discussed in these guidelines. Throughout these guidelines, recommendations are provided in the same format for all topics. There are three levels of recommendations: echocardiography recommended, echocardiography potentially useful, and echocardiography not recommended. It is hoped that these guidelines will provide standardization in the echocardiographic evaluation of patients with cardiac sources of embolism and lead to improved patient care.

GENERAL CONCEPTS OF STROKE AND SYSTEMIC EMBOLISM

Stroke, probably embolic in origin, was first described by the Greek physician Hippocrates (circa 460–370 BC). He also coined the term *apoplexy* (ἀποπληξία [apoplexia], "struck down with violence") which was used for centuries to describe what we now refer to as strokes or cerebrovascular accidents. In 1847, the German pathologist Rudolf Virchow (1821–1902) provided initial evidence for the thromboembolic nature of some strokes.

Each year, >795,000 people in the United States experience new or recurrent strokes; 610,000 are first attacks and 185,000 are recurrent strokes. It is estimated that 6.9 million American aged >20 years have had strokes, which represents 2.7% of all men and 2.6% of all women in the United States. The prevalence of silent cerebral infarction is higher, estimated to range from 6% to 28%. Stroke is the third leading cause of death in Western countries (after cancer and heart disease); it accounts for one of every 19 deaths in the United States. In 2009, the direct and indirect cost of stroke in the United States was $36.5 billion.[1]

Fifteen percent of all strokes are heralded by TIAs, defined as local neurologic deficits that last <24 hours.

Stroke Classification

It is estimated that 87% of all strokes are ischemic, and the remaining 13% are hemorrhagic. Using the Trial of Org 10172 in Acute Stroke Treatment criteria,[2] ischemic strokes may be further subdivided into following types:

1. Thrombosis or embolism associated with large vessel atherosclerosis
2. Embolism of cardiac origin (cardioembolic stroke)
3. Small blood vessel occlusion (lacunar stroke)
4. Other determined cause
5. Undetermined (cryptogenic) cause (no cause identified, more than one cause, or incomplete investigation)

The incidence of each cause is variable and depends on patient age, sex, race, geographic location, risk factors, clinical history, physical findings, and the results of various tests. This guidelines document deals primarily with cardioembolic strokes but also includes discussions of the role of echocardiography in evaluation of embolic strokes from the thoracic aorta (atheroembolism) and in cryptogenic strokes. Embolism of cardiac origin accounts for 15% to 40% of all ischemic strokes,[3] while undetermined (cryptogenic) causes are responsible for 30% to 40% of such strokes.[4]

Type and Relative Embolic Potential of Cardiac Sources of Embolism

In patients who are at risk for or have already had potentially embolic strokes, the primary role of echocardiography is to establish the existence of a source of embolism, determine the likelihood that such a source is a plausible cause of stroke or systemic embolism, and guide therapy in an individual patient.

Cardiac sources of embolism include blood clots, tumor fragments, infected and bland (noninfected) vegetations, calcified particles, and atherosclerotic debris. Conditions that are known to lead to systemic embolization are listed in Table 1 and subdivided into a high-risk and a low-risk risk group on the basis of their embolic potential. However, in

Table 1 Classification of cardiac sources of embolism

High embolic potential
1. Intracardiac thrombi
a. Atrial arrhythmias
i. Valvular atrial fibrillation
ii. Nonvalvular atrial fibrillation
iii. Atrial flutter
b. Ischemic heart disease
i. Recent myocardial infarction
ii. Chronic myocardial infarction, especially with LV aneurysm
c. Nonischemic cardiomyopathies
d. Prosthetic valves and devices
2. Intracardiac vegetations
a. Native valve endocarditis
b. Prosthetic valve endocarditis
c. Nonvalvular endocarditis
3. Intracardiac tumors
a. Myxoma
b. PFE
c. Other tumors
4. Aortic atheroma
a. Thromboembolism
b. Cholesterol crystal emboli
Low embolic potential
1. Potential precursors of intracardiac thrombi
a. SEC (in the absence of atrial fibrillation)
b. LV aneurysm without a clot
c. MV prolapse
2. Intracardiac calcifications
a. MAC
b. Calcific aortic stenosis
3. Valvular anomalies
a. Fibrin strands
b. Giant Lambl's excrescences
4. Septal defects and anomalies
a. PFO
b. ASA
c. ASD

many conditions more than one embolic source may be present (coexistence of embolic sources) or one cardioembolic condition may lead to another (interdependence of embolic sources). For instance, mitral stenosis is associated with spontaneous echocardiographic contrast (SEC), atrial fibrillation, left atrial (LA) clot, and even endocarditis.

Diagnostic Workup in Patients with Potential Cardiac Sources of Emboli

Evaluation of suspected cardiac source of embolism requires rapid diagnostic efforts, which should include detailed history, comprehensive physical examination, blood workup, and imaging of the heart and the organs damaged by the embolus. Echocardiography should be the primary form of cardiac imaging, supplemented by chest x-ray, computed tomography (CT), magnetic resonance imaging (MRI), and nuclear imaging when necessary. CT or MRI as well as angiography may be indispensable in the evaluation of organs and tissues affected by cardiac sources of embolism.

Prevention and Treatment

Echocardiography plays an important role not only in the diagnosis but also in the treatment and prevention of cardiac sources of embolism. This aspect of echocardiography is beyond the scope of this guidelines document; references to appropriate treatment and prevention guidelines are given in individual sections of this document.

ROLE OF ECHOCARDIOGRAPHY IN EVALUATION OF SOURCES OF EMBOLISM

Since its earliest days, echocardiography has been considered an important tool in the evaluation of possible cardiac source of embolism. Even the one-dimensional M-mode technique, which was first introduced in 1953 by Swedish cardiologist Inge Edler (1911–2001) and engineer Hellmuth Hertz (1920–1990), was capable of demonstrating conditions associated with embolic stroke and systemic emboli, such as mitral stenosis, LA dilatation, LA myxoma, and left ventricular (LV) systolic dysfunction.

The introduction of two-dimensional (2D) echocardiography in the early 1970's further expanded the diagnostic capability and accuracy of ultrasound imaging in the evaluation of cardiac sources of embolism; wall motion abnormalities could be better defined, and various normal and abnormal cardiac structures could be better assessed.

The introduction of Doppler techniques in the 1970's and transesophageal echocardiography (TEE) in the 1980's allowed more precise quantification of normal and abnormal intracardiac structures and blood flows. Finally, the advent of real-time three-dimensional (3D) echocardiography at the turn of the 21st century has provided unprecedented anatomic and functional details of many cardiac structures implicated as cardiac sources of embolism and allowed guidance of percutaneous treatments of sources of cardiac embolism (e.g., percutaneous closure of LA appendage (LAA) in patients with atrial fibrillation).

The overall use of echocardiography in the evaluation of cardiac sources of emboli should follow established appropriate use criteria.[5] Below is an excerpt from the appropriate use criteria guidelines, with entries relevant to cardiac sources of embolism.

Appropriate Use Criteria for Echocardiography in Evaluation of Cardiac Sources of Emboli

Appropriate Use: Transthoracic Echocardiography (TTE)

- Symptoms or conditions potentially related to suspected cardiac etiology, including but not limited to chest pain, shortness of breath, palpitations, TIA, stroke, or peripheral embolic event
- Suspected cardiac mass
- Suspected cardiovascular source of embolus
- Initial evaluation of suspected infective endocarditis (IE) with positive blood culture results or new murmur
- Reevaluation of IE at high risk for progression or complication or with a change in clinical status or cardiac examination results
- Known acute pulmonary embolism (PE) to guide therapy (e.g., thrombectomy and thrombolytic therapy)
- Reevaluation of known PE after thrombolysis or thrombectomy for assessment of change in right ventricular (RV) function and/or pulmonary artery pressure

Appropriate Use: TEE

- As initial or supplemental test for evaluation for cardiovascular source of embolus with no identified noncardiac source

- As initial or supplemental test to diagnose IE with a moderate or high pretest probability (e.g., staph bacteremia, fungemia, prosthetic heart valve, or intracardiac device)
- As initial test for evaluation to facilitate clinical decision making with regard to anticoagulation, cardioversion, and/or radiofrequency ablation

Uncertain Indication for Use: TEE

- Evaluation for cardiovascular source of embolus with a previously identified noncardiac source

Inappropriate Use: TTE

- Transient fever without evidence of bacteremia or new murmur
- Transient bacteremia with a pathogen not typically associated with IE and/or a documented nonendovascular source of infection
- Routine surveillance of uncomplicated IE when no change in management is contemplated
- Suspected PE to establish diagnosis
- Routine surveillance of prior PE with normal RV function and pulmonary artery systolic pressure

Inappropriate Use: TEE

- Evaluation for cardiovascular source of embolus with a known cardiac source in which TEE would not change management
- Routine use of TEE when diagnostic TTE is reasonably anticipated to resolve all diagnostic and management concerns
- Surveillance of prior transesophageal echocardiographic finding for interval change (e.g., resolution of thrombus after anticoagulation, resolution of vegetation after antibiotic therapy) when no change in therapy is anticipated
- To diagnose IE with low pretest probability (e.g., transient fever, known alternative source of infection, negative blood culture results or atypical pathogen for endocarditis)
- Evaluation when a decision has been made to anticoagulate and not to perform cardioversion

A Practical Perspective: Echocardiographic Techniques for Evaluation of Cardiac Sources of Embolism

Echocardiography plays an essential role in the evaluation, diagnosis, and management of cardiac and aortic sources of embolism.[6] Standard TTE and TEE are useful but yield to better results when additional imaging techniques are performed as a part of the examination.[7] These include, but are not limited to, high-frequency and fundamental imaging, off-axis and nonstandard views, thorough sweeps through chambers and multiple planes, multiplane and 3D imaging, and the use of contrast (both agitated saline and transpulmonary microbubble contrast agents). Such techniques are summarized in Table 2. When assessing specific structures of the heart using 3D imaging, acquisition should be focused on the structure as outlined in the European Association of Echocardiography and ASE recommendations.[8] Depending on the patient's presentation and history, most or some of the imaging techniques previously mentioned in this section should be applied. Examples of various echocardiographic imaging techniques, including still images and video clips, are provided throughout this document in sections dealing with individual cardiac sources of embolism.

Two-Dimensional High-Frequency and Fundamental Imaging. Most ultrasound systems are preset to image using harmonics, giving better endocardial definition while losing resolution on valvular structures and other structures compared with fundamental imaging. Tissue harmonics occur with transmission through tissue, so there is minimal harmonic effect in the near field. This is particularly important when evaluating for apical thrombus to differentiate the border of the thrombus from the endocardium. High-frequency and fundamental imaging, as mentioned in Table 2, should be applied to highlight structures without increasing the thickness of the structure. Figure 1 displays an akinetic apex from an apex-focused view on TTE with harmonics on the left side and fundamental imaging on the right side of the image.

Three-Dimensional and Multiplane Imaging. Three-dimensional and multiplane imaging has opened up echocardiography to new ways of interrogating and assessing cardiac structure and function. Although standard 2D imaging is still used for the majority of an examination, 3D and multiplane imaging can highlight areas often missed or overlooked as well as specify areas of interest when it comes to sources of cardiac, aortic, and pulmonary emboli. Figure 2 and Videos 1 and 2 display standard 2D apical four-chamber, biplane, and 3D images. With each image, more information is gathered regarding the extent, mobility, and number of thrombi in the left ventricle.

Figure 3 illustrates a transesophageal echocardiographic examination of a patient with an LA myxoma. In the standard 2D image, the myxoma is shown moving through the mitral valve (MV) orifice, while the 3D image shows not only the LA myxoma as it moves in the left atrium and MV but also the point of attachment on the interatrial septum.

Saline and Transpulmonary Contrast. The appropriateness and use of transpulmonary contrast for endocardial border definition as well as Doppler enhancement is well defined in the 2014 ASE contrast guidelines.[9] Additional uses of transpulmonary contrast can include border and structure definition of thrombi (Figure 4) and masses as well as showing if a structure is vascularized, much like cardiac MRI.

Although color Doppler can sometimes detect intracardiac communication, the use of agitated saline contrast yields higher results or incidence of findings (Figure 5).

Color Doppler, Off-Axis and Nonstandard Views and Sweeps. In addition to standard color Doppler imaging for valvular stenosis and regurgitation, routine imaging for intracardiac communication (with an appropriate Nyquist limit shift) should be performed in the setting of cardiac source of embolism. Color Doppler can illustrate new communication between cardiac chambers, paravalvular leaks, aneurysms and pseudoaneurysms, and abscesses. Figure 6 illustrates a prosthetic MV with endocarditis by 2D imaging, while the color Doppler image demonstrates the paravalvular leak from the infection.

As previously mentioned above in the section on 3D imaging, sources of cardiac, aortic, and pulmonary emboli can be missed or overlooked if only standard echocardiographic views are performed. The application of off-axis and nontraditional imaging can highlight pathology, enhance target definition by increasing specularity, and display regions of the heart in planes that are not appreciated by standard 2D images. The use of sweeps from multiple perspectives not only displays these additional planes of view but also highlights relational anatomy and gives spatial awareness of cardiac findings. Figure 7 shows an example of a sweep used to show an RV apical thrombus.

TTE versus TEE. The quality of TTE varies among patients and depends on body habitus, the size of the intercostal spaces, the presence of chest deformities, and lung disease such as emphysema. Even with the most advanced echocardiographic equipment, transthoracic imaging may still be suboptimal or even unobtainable.

Table 2 TTE and TEE: recommended techniques for visualization of sources of embolism

Cardioembolic source	TTE	TEE
Atrial arrhythmias	• Sweeps of atria and atrial appendages from multiple perspectives (PLAX, PSAX, apical views; two-chamber view for LAA) • Multiplane (biplane) imaging • 3D imaging, preferably from parasternal perspective for better resolution • High-frequency imaging • Transpulmonary contrast	• Sweeps of atria and atrial appendages from multiple perspectives • Multiplane (biplane) imaging • 3D imaging highlighting atrial anatomy and structures • Transpulmonary contrast • High-frequency imaging
Valvular disease: • Mechanical valve prosthesis • Rheumatic heart disease	• Fundamental imaging • Sweeps, anteriorly and posteriorly/ superiorly and inferiorly of valve(s) • 3D imaging may require nonstandard imaging windows for better resolution • Color Doppler (with sweeps)	• Fundamental imaging • Sweeps, anteriorly and posteriorly/ superiorly and inferiorly of valve(s) • 3D imaging to assess/better define valvular structure and related anatomy • Color Doppler (with sweeps)
Endocarditis	• High-frequency and fundamental imaging • Sweeps, anteriorly and posteriorly/ superiorly and inferiorly of valve(s) • 3D imaging, preferably from parasternal perspective for better resolution • Color Doppler	• High-frequency and fundamental imaging • Sweeps, anteriorly and posteriorly/ superiorly and inferiorly of valve(s) • 3D imaging (for point of attachment and sizing) • Color Doppler
Nonischemic and ischemic cardiomyopathies	• High-frequency and fundamental imaging (with sweeps) • Sweeps, anteriorly and posteriorly/ superiorly and inferiorly from multiple perspectives with and without harmonics • 3D and multiplane imaging • Transpulmonary contrast • Color Doppler (in aneurysmal wall cases and for VSD checks)	• Sweeps, anteriorly and posteriorly/ superiorly and inferiorly from multiple perspectives, especially gastric views for LV/RV focus • Transpulmonary contrast • 3D and multiplane imaging • Color Doppler (in aneurysmal wall cases and for VSD checks)
Cardiac masses		
Intracardiac thrombus, vegetations (marantic or infective)	• High-frequency and fundamental imaging (with sweeps) • Sweeps, anteriorly and posteriorly/ superiorly and inferiorly from multiple perspectives with and without harmonics • Off-axis/nonstandard views (to better show and define location) • 3D and multiplane imaging • Transpulmonary contrast	• High-frequency and fundamental imaging (with sweeps) • Sweeps, anteriorly and posteriorly/ superiorly and inferiorly from multiple perspectives • 3D and multiplane imaging • Transpulmonary contrast
Intracardiac tumors, fibroelastoma	• Sweeps, anteriorly and posteriorly/ superiorly and inferiorly from multiple perspectives with and without harmonics • 3D and multiplane imaging (for point of attachment, and for size and shape) • Transpulmonary contrast (to assist in border definition and check for vascularization)	• Sweeps, anteriorly and posteriorly/ superiorly and inferiorly from multiple perspectives • 3D and multiplane imaging (for point of attachment) • Transpulmonary contrast (to assist in border definition and check for vascularization)
Thromboembolism from the thoracic aorta	• Additional 2D views such as right parasternal and high left parasternal, short-axis perspective of suprasternal notch • Sweeps, anteriorly and posteriorly/ superiorly and inferiorly/lateral and medial with and without harmonics • 3D and multiplane imaging (for point of attachment) • Transpulmonary contrast	• Sweeps, anteriorly and posteriorly/ superiorly and inferiorly of aorta from multiple views with and without harmonics • 3D and multiplane imaging (for point of attachment) • Transpulmonary contrast
Aortic arch atheromatous plaque	• 3D and multiplane imaging • High-frequency and fundamental imaging	• 3D and multiplane imaging • High-frequency and fundamental imaging

(*Continued*)

Table 2 (*Continued*)

Cardioembolic source	TTE	TEE
Intracardiac shunt	• Color Doppler with appropriate Nyquist shift to show shunt (low for interatrial septal shunts and large VSDs, high for small VSDs) • Off-axis/nonstandard views • Agitated saline contrast study (as appropriate)	• Color Doppler with appropriate Nyquist shift to show shunt (low for interatrial septal shunts and large VSDs, high for small VSDs) • Agitated saline contrast study (as appropriate)
Intrapulmonary shunt	• Agitated saline contrast study (as appropriate)	• Agitated saline contrast study (as appropriate)
Transcatheter devices	• High-frequency and fundamental imaging (with sweeps) • Sweeps, anteriorly and posteriorly/superiorly and inferiorly from multiple perspectives with and without harmonics and color Doppler • 3D and multiplane imaging	• High-frequency and fundamental imaging (with sweeps) • Sweeps, anteriorly and posteriorly/superiorly and inferiorly from multiple perspectives with and without harmonics and color Doppler • 3D and multiplane imaging

PLAX, Parasternal long-axis; PSAX, parasternal short-axis; VSD, ventricular septal defect.

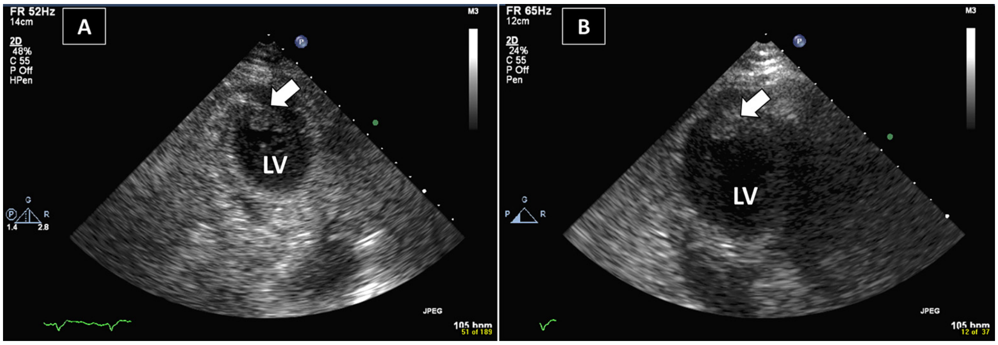

Figure 1 Two-dimensional TTE of LV apical thrombus with harmonic and fundamental imaging. **(A)** Apical focus of LV thrombus (*arrow*) with harmonics. **(B)** Apical focus of LV thrombus (*arrow*) without harmonics better displays extent of thrombus.

Because the ultrasound beam loses energy as it travels through tissue, structures that are far from the chest wall may not be well imaged by TTE. Lower transducer frequency improves penetration but decreases image resolution. As a result, structures that may be important sources of embolism, such as the posteriorly located left atrium and its appendage, the interatrial septum, and the thoracic aorta, may be suboptimally visualized by TTE.

With the transducer in the esophagus during TEE, there is close proximity between the transducer and the posterior aspect of the heart. This shorter distance enables the use of higher frequency transducers. With TEE, the heart is not masked by extracardiac structures such as bones and lung tissue. As a result, TEE can provide images of higher resolution and disclose findings that may be responsible for cardiac and aortic sources of embolism. In many echocardiography laboratories, evaluation for a source of embolism is the most common indication for TEE.

Although TEE is usually safe, it is still considered a semi-invasive procedure. Complications are rare, but the most serious one is esophageal perforation (with a reported incidence ranging from 0.01% to 0.09% of all studies performed).[10] Other complications include damage to the oral cavity, the teeth, the pharynx, and the trachea, as well as complications associated with topical anesthesia and sedation. Performance of TEE should follow appropriate ASE guidelines.[11]

Unless there are clinical findings that suggest conditions that explain the embolic event, such as atrial fibrillation, mitral stenosis, or endocarditis, the results of TTE are often negative. It had been therefore suggested that TTE may be unnecessary in patients with cryptogenic stroke and negative clinical evaluation. TTE may also be unnecessary when TEE is already planned (e.g., for evaluation of intracardiac masses, prosthetic valves, and the thoracic aorta or when TEE is used to guide a percutaneous procedure related to cardiac source of embolism). Others believe that TTE may occasionally provide information not well seen on TEE (such as LV apical thrombi) or may even eliminate the need for the more invasive and expensive TEE.

Efforts to determine the cost-effectiveness of echocardiography as applied to patients with acute neurologic deficits have yielded conflicting results depending on the assumptions used to conduct the analyses.[12,13] However, it is important to emphasize that these analyses do not take an individual patient into perspective but rather evaluate cost-effectiveness from a societal perspective.[3,14-19]

In summary, TTE excels in imaging of anterior cardiac structures using lower frequency probes. In contrast, TEE uses higher frequency

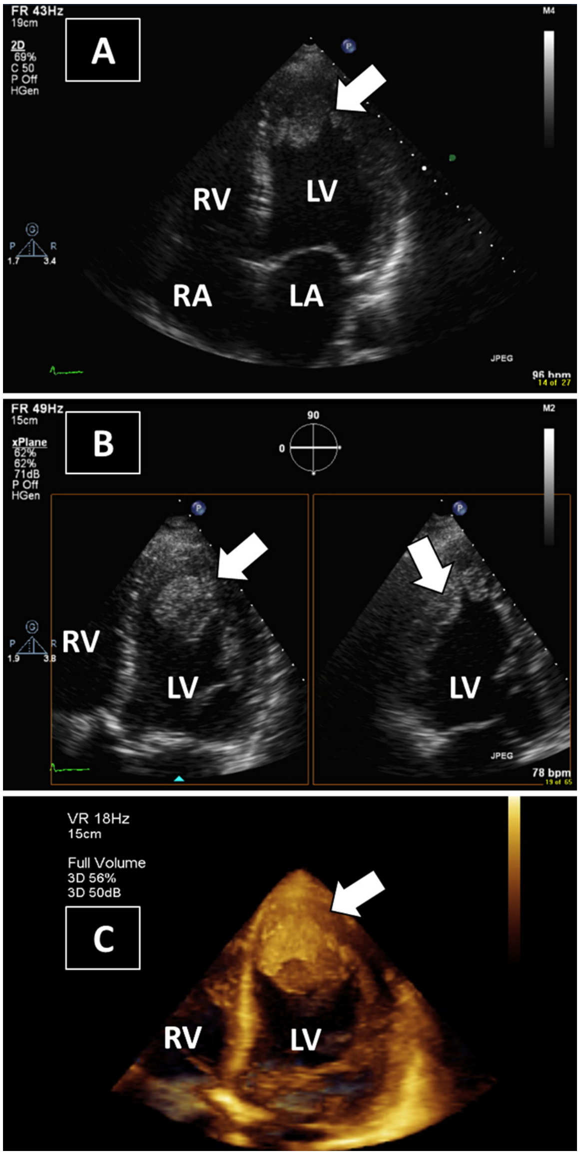

Figure 2 Two-dimensional and 3D TTE of LV apical thrombus. **(A)** Two-dimensional TTE, apical four-chamber view of the left ventricle displaying thrombus (*arrow*). **(B)** Three-dimensional TTE, biplane view of the left ventricle showing multiple LV thrombi. Video 1 corresponds to **(B)**. **(C)** Three-dimensional view of the left ventricle displaying the layers, location, and extent of the thrombi. Video 2 corresponds to **(C)**.

probes and excels in imaging of posterior cardiac structures and the thoracic aorta. In general, the sensitivity of TEE exceeds that of TTE.[20-22] TEE is likely to be helpful if TTE is of poor quality, in young patients with stroke, those with stroke of unknown etiology, and those with nonlacunar strokes.

Pros and cons of TTE and TEE are listed in Table 3.

Recommendations for Performance of Echocardiography in Patients with Potential Cardiac Source of Embolism

Echocardiography Recommended

- Echocardiography should be considered in all patients with suspected cardiac sources of embolism, especially in patients for whom clinical therapeutic decisions (such as anticoagulation or cardioversion) will depend on echocardiographic findings.

Echocardiography Potentially Useful

- Patients with neurologic events and concomitant intrinsic cerebrovascular disease.

Echocardiography Not Recommended

- Echocardiography is not recommended in patients for whom the results will not guide therapeutic decisions.

TTE versus TEE

- TEE is not indicated when transthoracic echocardiographic findings are diagnostic for a cardiac source of embolism.
- TTE may be unnecessary when TEE is already planned (e.g., for evaluation of intracardiac masses, prosthetic valves, and thoracic aorta or when TEE is used to guide a percutaneous procedure related to cardiac source of embolism).

ALTERNATIVES TO ECHOCARDIOGRAPHY IN IMAGING CARDIAC SOURCES OF EMBOLISM

Radiologic nonechocardiographic techniques are used in imaging target organs affected by cardioembolism (primarily the brain) as well as for visualization of sources of embolism in the heart and large vessels.

Computed Tomographic or Magnetic Resonance Neuroimaging

Computed tomographic or magnetic resonance neuroimaging is essential for differentiating ischemic from hemorrhagic strokes. Neuroimaging findings that support cardioembolic stroke include simultaneous or sequential strokes in different arterial territories (Figure 8). Because of their large size, cardiac emboli flow to the intracranial vessels in most cases and predominate in the distribution territories of the carotid and middle cerebral arteries.[7,23] These brain findings are distinct from nonembolic stokes such as watershed infarcts and lacunar strokes (Figure 9).

The presence of a potential major cardiac source of embolism in the absence of significant arterial disease remains the mainstay of clinical diagnosis of cardioembolic cerebral infarction.[23] When cardiac and carotid arterial disease coexist, determining the etiology of the ischemic stroke becomes more difficult.

Transcranial Doppler (TCD)

TCD may be used to detect cerebral microemboli, which may consist of cholesterol crystals, fat, air, or calcium.[24] TCD may also be used for the detection of intracranial emboli during surgical manipulation of the thoracic aorta. TCD may also allow noninvasive diagnosis of a right-to-left shunt caused by a patent foramen ovale (PFO) by detecting bubble signals in the middle cerebral artery after the injection of agitated saline in the antecubital vein.[25]

The most important limitation of contrast TCD is the absence of a temporal bone window in 10% of patients who have strokes, especially in the older population. The temporal bone window is located just above the zygomatic arch; suitability of this window is defined as the ability to measure Doppler flow in the middle cerebral artery.[23]

TCD also does not distinguish intracardiac shunts from extracardiac shunts, nor does it allow direct visualization of the shunt, as

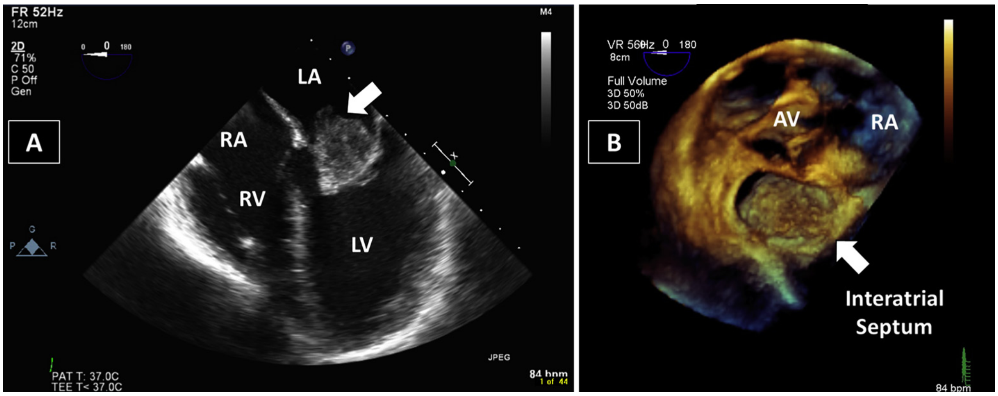

Figure 3 TEE of LA myxoma. **(A)** Two-dimensional TEE, four-chamber view at 0° showing LA myxoma (*arrow*) through the MV orifice. **(B)** Three-dimensional TEE, surgeon's perspective showing point of attachment (*arrow*) of the LA myxoma on the interatrial septum.

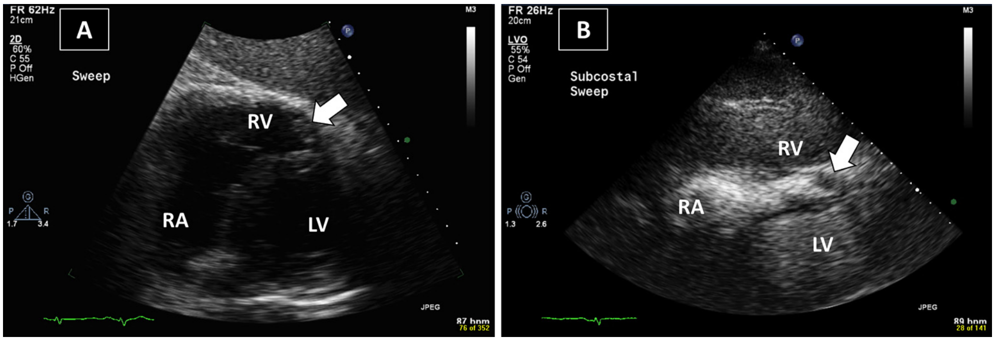

Figure 4 Imaging of RV apical thrombus with and without echocardiographic contrast. **(A)** TTE, subcostal image of the right ventricle with an apical thrombus (*arrow*). **(B)** TTE, subcostal image of the right ventricle with contrast better delineates the apical thrombus (*arrow*).

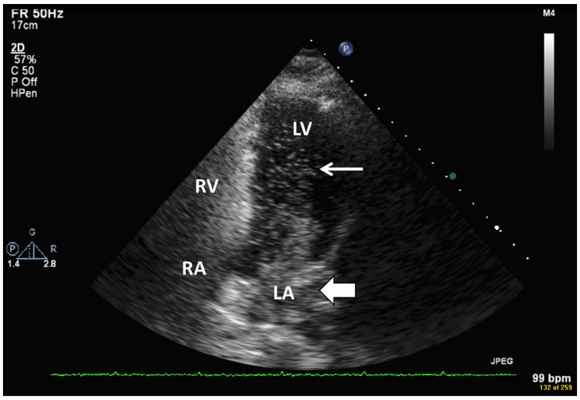

Figure 5 Intracardiac shunt detection using intravenous agitated saline injection. TTE, apical four-chamber view of an agitated saline contrast study demonstrates RA–to–LA shunting at rest. There is a large number of bubbles in the left atrium (*thick arrow*), and a smaller amount of bubbles is seen in the left ventricle (*thin arrow*).

does echocardiography.[26] TCD is a reliable, noninvasive alternative to TEE for the diagnosis of right-to-left shunting, with excellent sensitivity and specificity of 97% and 93%, respectively. Specificity can be further improved by increasing the bubble threshold for a positive result from one microbubble to 10 microbubbles, without compromising sensitivity.[27]

Nuclear Cardiology

Assessment of myocardial perfusion and ventricular function may be useful in selected patients (e.g., in patients with ischemic heart disease).[23]

Chest CT

Electrocardiographically gated multidetector CT can be used to study the left heart and great vessels in patients suspected to have cardioembolic strokes.[28] Multidetector CT allows extremely fast examination times combined with high spatial resolution (0.4–0.6 mm). Currently the main drawback is its relative lack of inherent soft-tissue contrast, which limits its assessment of the myocardium and identification of small thrombi. Other disadvantages are high radiation burden and exposure to potentially nephrotoxic iodinated contrast agents.

One advantage of chest CT and MRI compared with echocardiography is their ability to better visualize chest structures adjacent to the heart that may contribute to systemic embolism (e.g., cardiac invasion of a malignant tumor of a surrounding organ or tissue, visualization of the entire thoracic aorta).

Chest MRI

Routine cardiovascular MRI in the context of stroke does not currently form part of consensus guidelines, but there is an increasing body of literature to support its role, as an adjunct to echocardiography in selected cases (e.g., tissue characterization of cardiac tumors).[23]

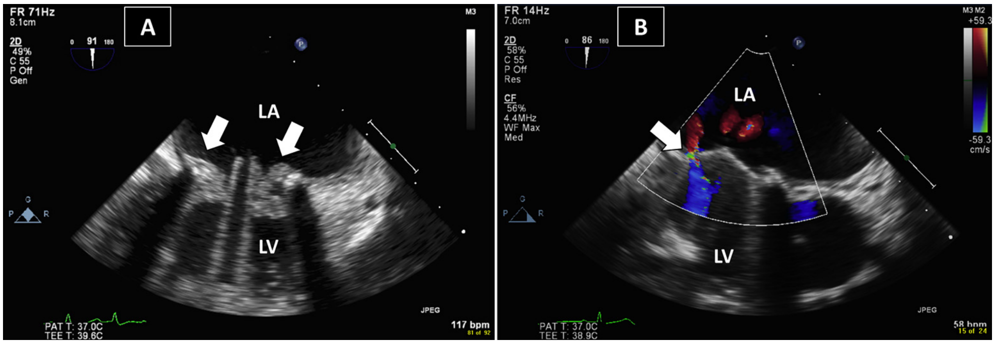

Figure 6 TEE of prosthetic valve endocarditis. Midesophageal two-chamber transesophageal echocardiographic view of mechanical MV with endocarditis. **(A)** B-mode imaging at 91° demonstrates vegetations (*arrows*) adherent to the prosthetic valve. **(B)** Color Doppler imaging demonstrates a perivalvular leak (*arrow*) near the infected area of the mechanical mitral prosthesis.

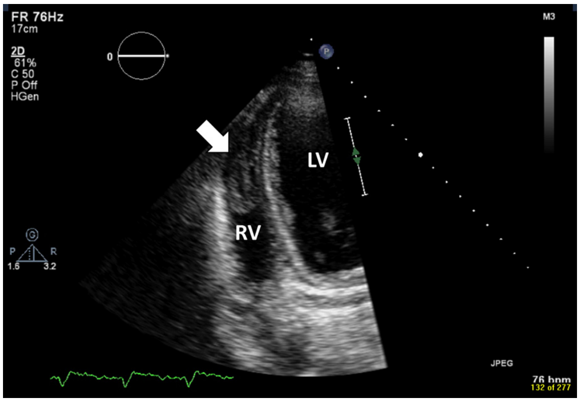

Figure 7 Transthoracic echocardiographic sweep used to visualize RV thrombus. RV focused apical view sweeping inferiorly displaying an apical thrombus (*arrow*).

Table 3 Relative benefit of TTE and TEE in evaluation of cardiac sources of embolism

	Potential source of embolism	TTE	TEE
Favors TEE	LA/LAA thrombus or SEC	–/+	++++
	Aortic atheroma	–/+	++++
	Prosthetic valve abnormalities	+	++++
	Native valve vegetation	++	++++
	Atrial septal anomalies	++	++++
	Cardiac tumors	+++	++++
Favors TTE	LV thrombus	++++	++

Based on data from Spencer KT. Cardiac source of emboli. In Lang R, Goldstein S, Kronzon I, Khandheria BK, eds. Dynamic Echocardiography. St. Louis, MO: Sanders/Elsevier; 2010:164–168.

Recommendation for Alternative Imaging Techniques in Evaluation of Cardiac Sources of Embolism

Alternative Imaging Recommended

- Computed tomographic and magnetic resonance neuroimaging is essential in the evaluation of patients with neurologic symptoms attributable to a cardiac source of emboli.
- CT, MRI, or other radiologic imaging of the heart and the great vessels may be useful in selected patients with cardiac sources of embolism.

Alternative Imaging Not Recommended

- Alternative imaging of the heart and great vessels is not recommended when echocardiographic findings are diagnostic.

THROMBOEMBOLISM FROM THE LEFT ATRIUM AND LAA

A thrombus located in the left atrium or, more precisely, the LAA is the most prevalent source of cardioembolic events and is typically associated with atrial arrhythmias such as atrial fibrillation and atrial flutter. TEE is the echocardiographic imaging modality of choice for the evaluation of LAA anatomy and function. The LAA may be unilobular or multilobular.[29] Four different morphologies have been used to categorize the LAA: cactus, chicken wing, windsock, and cauliflower. Patients with chicken-wing LAA morphology may be less likely to have thromboembolic events compared with those with other LAA morphologies.[30]

Pathogenesis of Atrial Thrombogenesis and Thromboembolism

Definite gaps remain in our knowledge regarding atrial thrombogenesis and thromboembolism and the most appropriate and clinically effective diagnostic and therapeutic options. The prevalence of atrial fibrillation is 0.4% to 1% of patients in the general population but increases to 9% in patients who are ≥80 years of age.[31] The risk for stroke or embolism in patients with atrial fibrillation ranges from a low-risk value of 1% per year to a high-risk value of 15%. It is estimated that in approximately 75% of patients with cardioembolic episodes, emboli arise from the LAA and are thus presumed to be caused by atrial fibrillation. However, many of these patients are >75 years of age, with concomitant hypertension, diabetes mellitus, and carotid disease, all of which are independent predictors of stroke.

Although the fundamentals of thrombogenesis were proposed >150 years ago by the report of Virchow's triad (blood stasis, endothelial injury, and hypercoagulability), the precise conditions under which thrombogenesis and thromboembolism occur in relation to the left atrium remain largely speculative. The tenets of this Virchow hypothesis have been extrapolated to the left atrium and atrial fibrillation. Thrombus formation occurs along a pathogenesis continuum that starts with SEC or "smoke" formation (erythrocyte rouleaux formation indicative of blood stasis), progresses to sludge

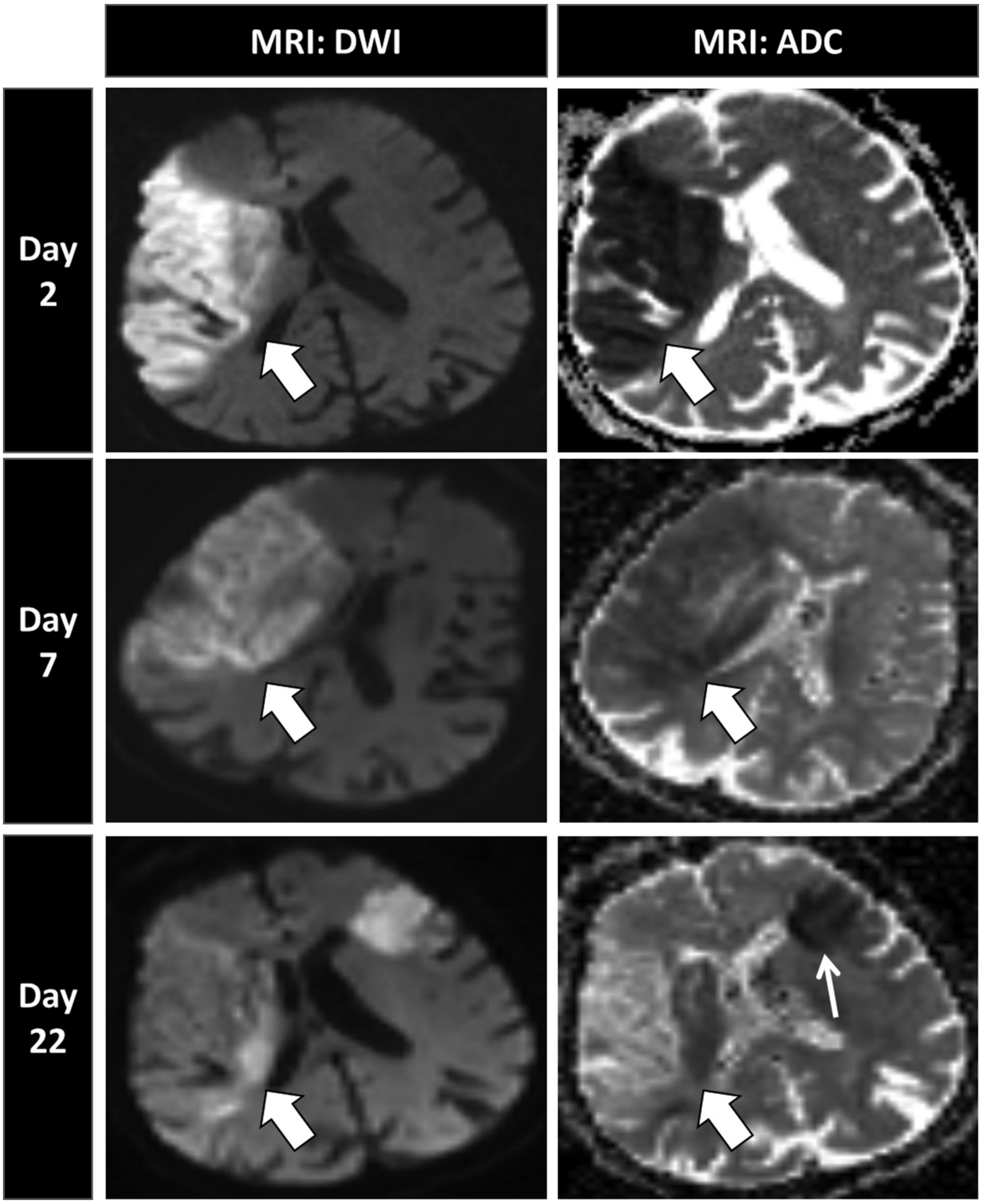

Figure 8 Brain MRI of embolic stroke. Brain MRI of a patient with atrial fibrillation demonstrates strokes in different territories occurring at different times, typical of an embolic etiology. The patient first had an embolic stroke to the right middle cerebral artery territory (*thick arrows*). Three weeks later, the patient had a new stroke in the territory of the left middle cerebral artery (*thin arrow*). *ADC*, apparent diffusion coefficient; *DWI*, Diffusion-weighted imaging. Courtesy of Dr Benjamin A. Cohen, Department of Radiology, New York University Langone Medical Center.

formation (very dense smoke) and ends with complete thrombus formation (Figure 10, and Videos 3, 4, and 5).[32] Persistent SEC in the left atrium on TEE has been associated with later thrombus formation and systemic embolization. Sludge has an echocardiographic appearance that is more viscid than smoke but less dense than thrombus.[33]

The anatomic structure of the LAA and acquired enlargement and stretch of the left atrium or LAA in valvular and nonvalvular heart disease provide the milieu for blood stasis.

Microscopic endocardial changes in the LAA have been reported in atrial fibrillation as compared with sinus rhythm and mitral stenosis as compared with mitral regurgitation. Edema, fibrinous transformation, and endothelial denudation have been described in the LA tissue in patients with atrial fibrillation and thromboembolism.[34] Additionally, impairment of extracellular matrix turnover has also been implicated as a factor contributing to structural changes that occur in the left atrium. Patients with LA fibrillation have abnormal amounts of collagen and degradation products as well as concentrations of matrix metalloproteinases.[35]

Stasis of flow in the left atrium can occur not only during atrial fibrillation (because of the reduction of effective atrial contractile function, as evidenced by the presence of SEC) but may also occur during sinus rhythm given the appropriate associated pathology (i.e., significant LA enlargement and/or mitral stenosis).[36]

Additional insights into the pathogenesis of thrombogenesis and thromboembolism have been obtained from studies that used TEE to study the effects of electrical cardioversion of atrial fibrillation to

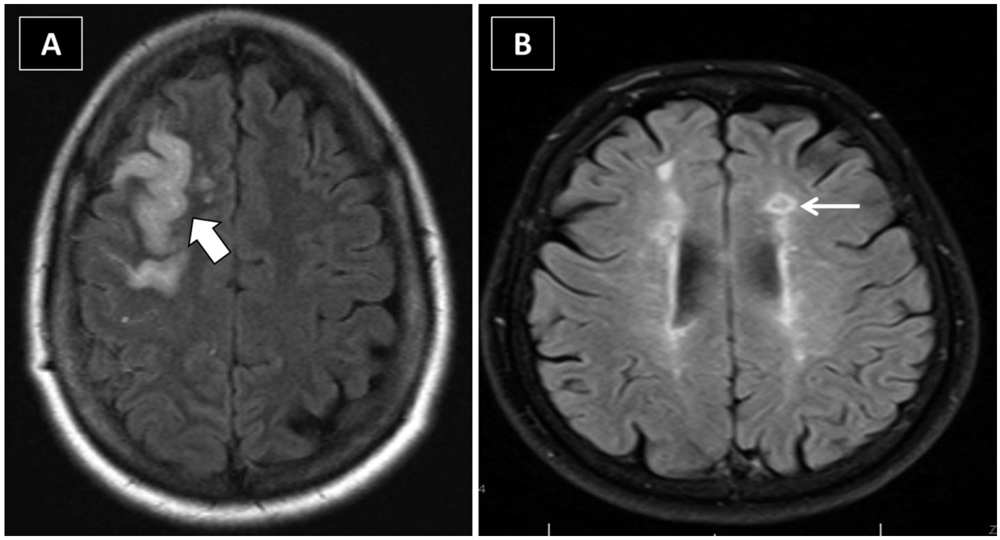

Figure 9 Brain MRI of nonembolic strokes. Brain MRI fluid-attenuated inversion recovery imaging demonstrates forms of nonembolic stroke. **(A)** *Thick arrow* points to a watershed infarct at the boundary of right anterior and right middle cerebral artery territories in a middle-aged woman with headache. **(B)** *Thin arrow* points to a lacunar infarcts in the left frontal paraventricular region of a patient with systemic hypertension. Courtesy of Dr Benjamin A. Cohen, Department of Radiology, New York University Langone Medical Center.

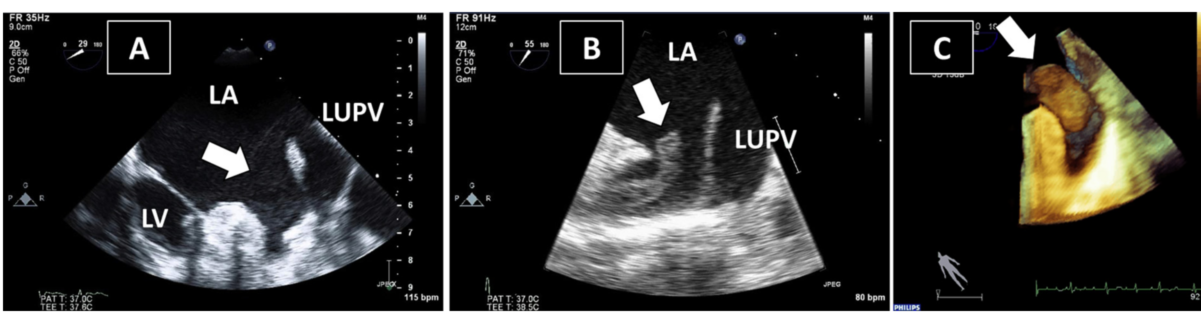

Figure 10 Two-dimensional and 3D TEE of LAA smoke and thrombus. **(A)** Two-dimensional midesophageal TEE of the left atrium, LAA, and left upper pulmonary vein (LUPV) in the midesophageal view demonstrating SEC (*arrow*) in a patient in atrial fibrillation. The SEC is continuous and present in the left atrium as well as in the LAA. Video 3 corresponds to **(A)**. **(B)** Two-dimensional midesophageal TEE of the left atrium, LAA, and LUPV in the midesophageal view at 55° demonstrating a prominent, mobile LAA thrombus (*arrow*) in a patient in atrial fibrillation. Video 4 corresponds to **(B)**. **(C)** Three-dimensional TEE of the LAA demonstrating a large mobile thrombus in the orifice of the LAA in a patient in atrial fibrillation. Video 5 corresponds to **(C)**.

sinus rhythm.[37,38] That thromboembolism could develop after electrical cardioversion of atrial fibrillation had been well described since the 1960's and before the advent of TEE. However, clues to the underlying mechanisms came only with the use of TEE in this patient population.[39,40]

The phenomenon of LAA "stunning" was demonstrated on TEE by an increase in the intensity of SEC (Figure 11) and the decrease in LAA Doppler flow velocities (Figure 12) immediately after cardioversion of atrial fibrillation to sinus rhythm.[37] Before this transesophageal echocardiographic observation, the prevailing theory was that stroke in the postcardioversion period resulted solely from dislodgement of a preexisting thrombus (present before cardioversion and due to the underlying atrial fibrillation).[41] Further evidence for the role of postcardioversion stunning in the genesis of thromboembolism came from a series of patients who had postcardioversion strokes despite the absence of LA or LAA thrombus on precardioversion TEE.[42] These transesophageal echocardiographic studies formed the basis and rationale for the TEE-guided anticoagulation strategy used today when managing patients with atrial fibrillation undergoing electrical cardioversion.

In addition to the anatomic and hemodynamic changes contributing to the propensity of the left atrium to thrombogenesis, abnormalities of coagulation cascade proteins and platelets may also play a role. Increased fibrin turnover and prothrombin fragments 1 and 2 have been associated with atrial fibrillation in patients with stroke.[43,44] Furthermore this prothrombotic state has been correlated with LAA dysfunction and SEC.[45] D-dimer levels also appear associated with thromboembolism events in patients with nonvalvular atrial fibrillation[46] and may be useful in determining hypercoagulability. Serum levels of von Willebrand factor, a marker of endothelial damage and dysfunction, have also been found to be elevated in the presence of LAA thrombus and atrial fibrillation.[47] Although many studies have suggested a potential role for platelets and thrombogenesis in atrial fibrillation, the precise involvement and link of platelet function to the hypercoagulable state have yet to be defined.[48]

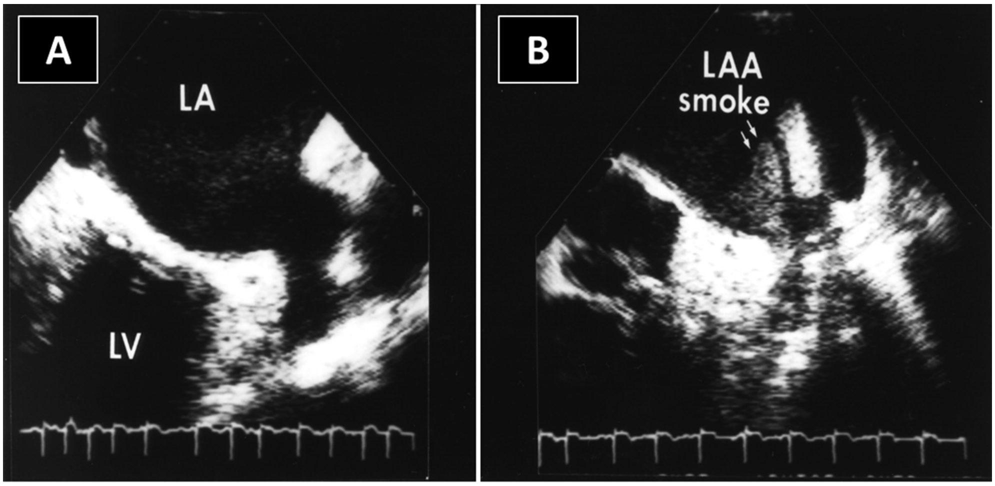

Figure 11 LAA smoke after cardioversion. Midesophageal TEE of LAA SEC before **(A)** and immediately after **(B)** electrical cardioversion of atrial fibrillation.

Echocardiographic Evaluation of the Left Atrium and LAA

The basis of imaging in atrial fibrillation centers on identifying one of the many underlying cardiac causes of atrial fibrillation, such as valvular heart disease, ventricular dysfunction, and hypertension. Once an associated etiology of atrial fibrillation has been identified or ruled out, attention turns to details of LA anatomy, specifically whether the left atrium is enlarged and, if so, how severely.

LA enlargement has significance relative to thromboembolic risk, maintenance of sinus rhythm, and prognosis.[49] Although thrombus can be identified by TTE and the specificity is high, the sensitivity of TTE is unacceptably low, in part because most atrial thrombi are located in the LAA rather than the main LA cavity. The LAA is best viewed by TEE.

LA size can be expressed as either the anterior-posterior LA diameter or LA area and measured according to the ASE guidelines on chamber quantification.[50] Investigation has demonstrated the superiority of LA volume measurements and more precisely LA volume indexed to body size as a more accurate measurement.[49] In addition, atrial volumes have significant prognostic value relative to stroke risk, mortality, atrial fibrillation recurrence after electrical cardioversion, ablation, and cardiac surgery. It is believed that LA volumes obtained by 3D echocardiography may provide the ultimate quantification. However, this has not been routinely adopted in clinical practice at this time.

Because of its portability, relatively low cost, and noninvasive nature, TTE is recommended for evaluation of the left atrium, cardiac structure, and function in atrial fibrillation by these guidelines as well as the European Association of Echocardiography consensus guidelines,[6] the American College of Cardiology, American Heart Association, and Heart Rhythm Society document on management of patients with atrial fibrillation,[51] and the American College of Cardiology, American Heart Association, and ASE appropriate use criteria for echocardiography.[5]

Because of its location immediately adjacent to the esophagus, the left atrium is the structure best suited to the strengths of TEE and its ability to visualize cardiac structures with high spatial resolution and good temporal resolution, all in real time. More specifically, TEE enables optimal visualization of LAA anatomy as well as interrogation of its function and physiology with Doppler interrogation. The introduction and addition of 3D imaging have added to our ability to interrogate the LAA, providing perspective relative to LAA anatomy as well as an added ability to visualize real or artifactual masses within the cavity.

Cardioversion. In a substudy of the Stroke Prevention in Atrial Fibrillation trial, in which patients with atrial fibrillation were randomized to warfarin versus aspirin for primary stroke prophylaxis, the LAA data obtained by TEE were found to be independent predictors of thromboembolism.[52] The presence of LAA clot (relative risk, 3.5), LAA peak flow velocity $\leq$ 27 cm/sec (relative risk, 1.7), and aortic plaque (relative risk, 2.1) were all associated with thromboembolic events.

In addition to evaluating patients with stroke and/or atrial fibrillation for the presence of thrombus, TEE is commonly used in the management of patients with atrial fibrillation in whom maintenance of sinus rhythm is desired either by using chemical or electrical cardioversion or pulmonary vein isolation. TEE has been demonstrated to be useful in guiding anticoagulation management around the time of cardioversion, such that if the results of TEE are negative for the presence of thrombus, one can proceed directly to cardioversion, provided the patient has been therapeutically anticoagulated before the procedure.[53]

The Assessment of Cardioversion Using Transesophageal Echocardiography trial was a prospective randomized multicenter trial that compared a conventional anticoagulation strategy with a TEE-guided anticoagulation management strategy in patients undergoing cardioversion for atrial fibrillation. Conventional anticoagulation management consisted of 3 weeks of therapeutic anticoagulation with warfarin before cardioversion and 4 weeks of anticoagulation after cardioversion. Patients randomized to the TEE-guided arm could proceed directly to cardioversion provided they were anticoagulated to therapeutic levels and had no evidence of thrombus on TEE. Low embolic event rates (0.65%) were found in both arms, with no difference between the conventional (0.5%) and TEE (0.8%) arms relative to embolic stroke as well as a composite end point that included mortality, embolic stroke, and bleeding. Bleeding was significantly lower in patients undergoing TEE-guided cardioversion, and the time to cardioversion was shorter compared with the conventional arm. Therefore, the primary advantage to the TEE-guided strategy is that a 3-week course of precardioversion

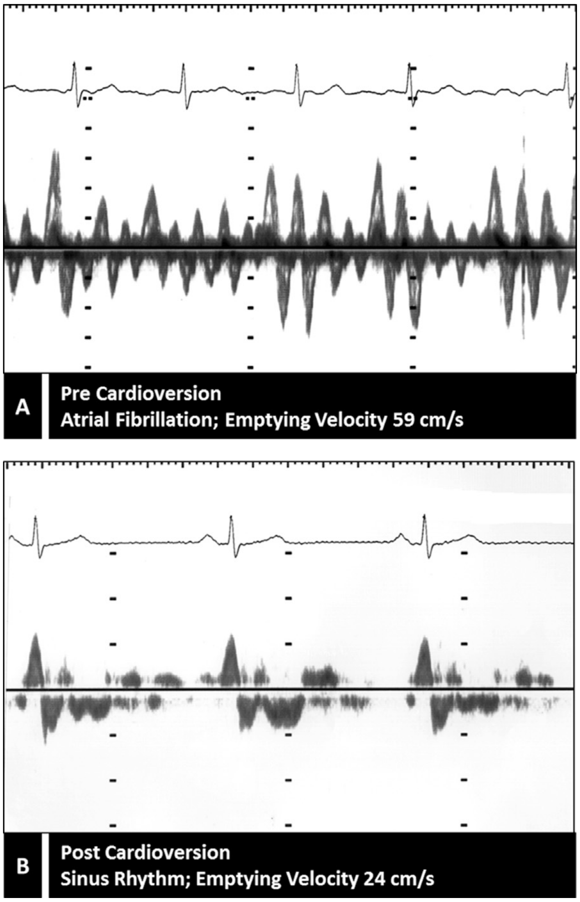

Figure 12 LAA emptying velocity. LAA spectral Doppler flow velocities. **(A)** Patient is in atrial fibrillation (LAA emptying velocity, 59 cm/sec). **(B)** Same patient as in **(A)** but now in sinus rhythm (LAA emptying velocity, 24 cm/sec) immediately after electrical cardioversion of atrial fibrillation. This tracing demonstrates the LAA stunning phenomenon believed to be related to post-cardioversion thrombogenesis and embolism.

anticoagulation can be avoided, provided the results of TEE are negative for thrombus.

Pulmonary Vein Isolation. Echocardiography, primarily TEE, has been studied and used in patients undergoing pulmonary vein isolation to assess for thrombus before instrumenting the left atrium.[54] Intracardiac echocardiography can also be useful in detecting atrial thrombus and is commonly used during the procedure by the electrophysiologist to assist in monitoring and guidance of the pulmonary vein isolation procedure.[55]

TTE has been reported to be useful in assessing return of LA function after pulmonary vein isolation,[56] while TEE can be useful in identifying pulmonary vein stenosis after the procedure.[57,58] The significant reduction in incidence of pulmonary vein stenosis as the procedure has matured as well as the excellent diagnostic accuracy of multidetector CT and cardiac MRI in this setting has reduced the prominence of TEE for this indication.

Guidance of LAA Percutaneous Procedures TEE in general and real-time 3D TEE in particular are useful for guiding percutaneous closure of the LAA using closure devices such as the recently US Food and Drug Administration–approved Watchman device (Boston Scientific, Marlborough, MA) or others still in investigational stages.

Recommendations for Performance of Echocardiography in Patients with Suspected LA and LAA Thrombus

Echocardiography Recommended

- TTE is recommended in patients with suspected LA or LAA thrombus to assess LA size and LV size and function, as well to assess for underlying etiologies of atrial fibrillation and additional risk factors for stroke.
- TEE is superior to TTE in assessment of anatomy and function of LAA in a variety of clinical contexts, such as before cardioversion, ablation of atrial arrhythmias, and percutaneous procedures for LAA closure.

Echocardiography Potentially Useful

- Contrast echocardiography using microbubble agents (such as perflutren) may aid in detecting LA and LAA thrombi and may help differentiate avascular thrombi from vascular tumors.
- Three-dimensional echocardiography may provide more precise assessment of LA and LAA size and morphology.

Echocardiography Not Recommended

- Echocardiography is not recommended in patients for whom the results will not guide therapeutic decisions.

THROMBOEMBOLISM FROM THE LEFT VENTRICLE

Acute Coronary Syndromes

Regional wall motion abnormalities along with subendocardial injury in the setting of an acute myocardial infarction result in blood stasis and nidus for LV thrombus formation. Furthermore, there is a hypercoagulable state with increased procoagulants and a decrease in concentration of physiologic anticoagulants during an acute coronary event, thus creating a perfect milieu for formation of LV thrombus. These thrombi, composed of fibrin, red blood cells, and platelets, can occur as early as 24 hours after an acute myocardial infarction, with the majority (90%) of thrombi forming within 14 days of a myocardial infarction.

The incidence of LV thrombus in the setting of an acute coronary event varies significantly depending on different studies, ranging from as low as 7% to as high as 46%.[59-61] Current reperfusion therapies such as thrombolysis and aggressive medical management, including aggressive use of antiplatelet and anticoagulant agents, have shown a trend toward reducing the incidence of LV thrombosis.[62] Patients with acute anterior myocardial infarction and/or apical infarction are more likely to have LV apical thrombus. The prevalence may be as high as 50% in chronic LV aneurysm.[63]

Data on the incidence of LV thrombus in the current era of aggressive interventions in the setting of acute myocardial infarction are limited and retrospective in nature; the incidence is reported to be about 5% to 15%.[64,65] These data are further compounded by many other factors, including time frame when the imaging study is done to identify an LV thrombus. Echocardiographic studies performed early are likely to miss the presence of LV thrombus.

The presence of LV thrombus from 2 to 11 days after myocardial infarction is reported to be as high as 40% in patients with acute anterior myocardial infarction. Despite the higher incidence of thrombus formation, the incidence of a thromboembolic event leading to stroke is relatively low.[63] The prevalence of LV thrombus is more likely to be present in patients with advanced systolic dysfunction, previous myocardial infarction, and large scar burden identified by delayed enhanced MRI.[66] In a study of 8,000 patients with ST-segment elevation myocardial infarction, LV thrombus was present in approximately 5% of cases.

Patients with anterior wall infarction were more likely to have LV thrombus (11.5% vs 2.3% in other regions). Furthermore, LV thrombus was more likely in patients with ejection fractions of <40% and anterior wall myocardial infarction (17.8%).[64] LV thrombus is not located exclusively within the LV apex; it can occur in other regions of the left ventricle, specifically the inferoposterior and septal walls in a small percentage of patients.[61]

Studies have consistently shown that LV thrombus is more likely to be present in the setting of large infarct size, anterior myocardial infarction, severe apical wall motion abnormality, and LV aneurysm.[59]

Cardiomyopathy

Patients with significant LV dilation and dysfunction, whether ischemic or nonischemic, are at increased risk for developing LV thrombus. It is unusual to have the presence of LV thrombus in the setting of normal wall motion, with the exception of endomyocardial fibrosis, in which thrombus can occur in either the left or right ventricle within normally contracting regions of the heart. The incidence of LV thrombus in patients with cardiomyopathies also varies depending on studies, which also are predominantly retrospective in nature. In patients with dilated cardiomyopathy, thromboembolic events are reported to be in the range of 1.7% to 18%.[67]

Risk factors that predispose patients with cardiomyopathies to thromboembolic events include extensive regional wall motion abnormalities, very dilated left ventricles, low cardiac output with the stagnation of blood within the ventricle, significant slow swirling streaks of blood within the left ventricle (SEC) and the presence of atrial fibrillation. Additionally, the presence of advanced apical hypertrophy cardiomyopathy with apical outpouching can also be a risk for clot formation.

LV Thrombus Morphology

There are three main types of thrombi that can be identified within the left ventricle:

1. Mural thrombus (only one surface exposed to the blood pool; flat and parallel to the endocardial surface)
2. Protruding thrombus (more than one surface exposed to the blood pool and protruding into the LV cavity)
3. Mobile thrombus with independent motion (either in parts of the thrombus or in its entirety)

Studies have shown that patients with LV thrombi that are mobile and/or protrude into the LV cavity have a higher incidence of embolization. However, 40% of embolic events occur in patients who do not have protruding and/or mobile thrombi.

The incidence of embolization is lowest for a mural thrombus and highest for a mobile thrombus.[68,69] However, serial echocardiographic studies have shown variability of thrombus morphology in the first several months after acute myocardial infarction, with 41% of thrombi changing shape and 29% changing mobility.[70] Other characteristics of thrombus that have been shown to be associated with increased risk for embolization include central lack of lucency, hyperkinesis of adjacent myocardial segments around the thrombus, and thrombus size (controversial).[69-71]

Patients at highest risk for embolization include patients with atrial fibrillation, severe congestive heart failure, markedly dilated left ventricles with severe systolic dysfunction, previous thromboembolic events, and advanced age. Thrombi within LV aneurysm are less likely to embolize, probably because of the absence of LV contraction in the aneurysm.

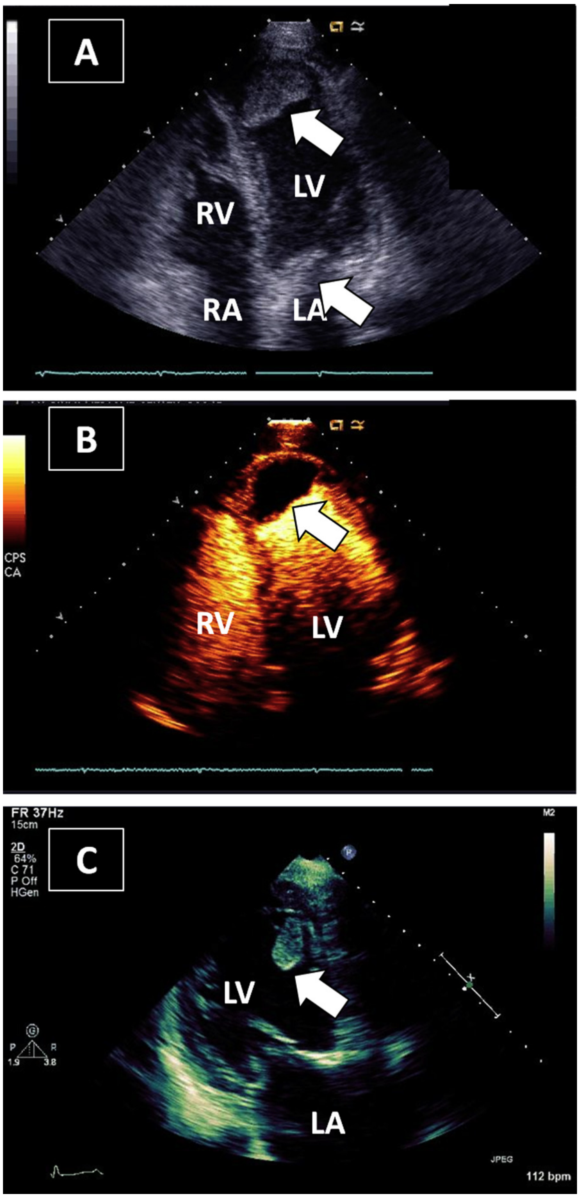

Figure 13 TTE of LV apical thrombus. **(A)** Apical four-chamber view of a noncontrast transthoracic echocardiographic study demonstrates a larger LV apical thrombus (*arrow*). Video 6 corresponds to **(A)**. **(B)** The same patient as in **(A)** was then imaged using transpulmonary microbubble echocardiographic contrast. The thrombus, lacking vascular supply, appears black (*arrow*) on contrast imaging. Video 7 corresponds to **(B)**. **(Panel C)** Apical three-chamber view demonstrates a mobile LV thrombus (*arrow*) attached to the apical portion of the anterior interventricular septum. Video 8 corresponds to **(C)**.

Role of Echocardiography in the Detection of LV Thrombus

TTE is the technique of choice and most widely used clinically for the evaluation of regional and global LV and RV function, assessment of valves, and LV thrombus. TTE has excellent sensitivity (95%) and specificity (85%–90%) in detecting LV thrombus.[61] Echocardiographically LV thrombus is identified as a discrete echocardiographic mass seen in the left ventricle with well-defined margins that are distinct from the endocardium and seen throughout systole and diastole in an area with corresponding significant LV, regional, or global wall motion abnormalities (Figure 13 and Videos 6, 7, and 8).

To confirm the diagnosis of a thrombus, it must be seen in at least two orthogonal (apical and short-axis) views. It is important to exclude artifacts, including near-field clutter, false tendons, LV trabeculations, and apical foreshortenings, to accurately diagnose a thrombus.[72,73] Simple steps can be used to overcome these artifacts, including moving the focal zone to the apex, using a higher frequency transducer, and using low-aliasing color flow velocities to define any filling defects. If the diagnosis is still uncertain, echocardiographic contrast agents should be used.

In technically limited studies (30%–35%), especially when the apex is not clearly visualized, the use of myocardial echocardiographic contrast agents has significantly affected the accurate diagnosis of ruling in or out an LV thrombus.[66,74,75]

TEE has a limited role in the detection of LV thrombus, because the apex is farthest from the transducer, and the apex is often foreshortened and/or not well visualized. In contrast, the transthoracic echocardiographic probe is in close proximity to the left ventricle and apex, making them easier to image in multiple planes.

Three-dimensional echocardiography may further enhance identification of LV thrombus by more detailed evaluation of the LV apex (more segments and regions evaluated). However, the limitations of 3D echocardiography remain, as it has low frame rates and poor resolution.

Recommendations for Performance of Echocardiography in Patients with Suspected LV Thrombus

Echocardiography Recommended

- TTE is recommended for the evaluation of patients with underlying cardiac disease known to predispose to LV thrombus formation (such as myocardial infarction or nonischemic cardiomyopathy).
- TTE is typically superior to TEE in the assessment of LV apical thrombus.

Echocardiography Potentially Useful

- Contrast echocardiography using microbubble agents (such as perflutren) may aid in detecting LV thrombi and may help differentiate avascular thrombi from vascular tumors.
- Three-dimensional echocardiography may provide more precise assessment of LV thrombus.

Echocardiography Not Recommended

- Echocardiography is not recommended in patients for whom the results will not guide therapeutic decisions.

VALVE DISEASE

Native cardiac valves can be a source of both systemic and PE in the form of thrombi, infective and noninfective vegetations, and calcific debris. In addition, both biologic and mechanical valvular prostheses may become embolic sources of thrombi and/or vegetations and also represent a common underlying substrate for cardioembolic stroke.[1] Both TTE and TEE play a central role in diagnosis, prognostication, and management and decision making for these patients.

Several specific valvular entities have been associated with embolism, including IE, nonbacterial thrombotic endocarditis (NBTE), valvular papillary fibroelastoma (PFE), mitral annular calcification (MAC), and biologic or mechanical prosthetic valve endocarditis and thrombosis. Other conditions remain controversial as embolic sources, including degenerative native valve strands and mechanical valve platelet thrombi. Each condition will be addressed separately with emphasis on its echocardiographic recognition, the diagnostic and prognostic value of echocardiography, as well as appropriate use and indications of each echocardiographic modality.

Infective Endocarditis

Diagnosis. In the great majority of cases, positive blood culture results and evidence of endocardial involvement constitute the definition of IE,[76] so echocardiographic exploration for endocardial infection is not only accepted but mandatory[5,77] in the evaluation of a patient with possible IE. Although a "valvular vegetation" is the hallmark of endocardial infection, cardiac abscess or fistula, new partial prosthetic valve dehiscence, and the presence of new valvular regurgitation all represent endocardial infection in the correct clinical setting, even in the absence of vegetation.

Knowledge of the patient's clinical history is critical because maximal diagnostic benefit of echocardiography will be obtained in those patients with intermediate pretest probability, and interpretation and reporting of imaging findings must be done in light of the clinical history because echocardiography does not provide substantial tissue characterization or pathologic information (Table 4).

Therefore, awareness of the echocardiographic features that characterize vegetations (Table 5, Figure 14 and Video 9) and paravalvular complications is key (Figure 15 and Video 10).[78] Native valvular findings that may be confused with infective vegetations are PFE, valvular strands and Lambl's excrescences, MAC with mobile components, redundant chordae tendineae, and NBTE.

Prosthetic findings that may be confused with vegetation include prosthetic strands, thrombosis, mitral subvalvular tissue remnants (Figure 16 and Videos 11 and 12), and microcavitations. An experienced echocardiographer should readily recognize microcavitations and their benign nature (Figure 17 and Video 13). Microcavitations are high-velocity, tiny, bright echoes that occur at the inflow zone of mechanical valves (both aortic and mitral, more frequent mitral) at the time of valve closure, when flow velocity and pressure drop abruptly. They represent a normal phenomenon and in fact may disappear with valve obstruction or thrombosis, only to return after thrombolysis.[79]

It is common knowledge that although the specificity of TTE for the diagnosis of vegetations is >90%, its limited spatial resolution renders it less sensitive, with reported meta-analyses' sensitivities ranging from 62% to 79%.[80,81] Indeed, vegetations <2 to 3 mm in size may be missed by TTE.[82] Conversely, both the sensitivity and specificity of TEE are >90%.[83,84] Even in modern times, with the advent of harmonic imaging, TTE remains at a significant diagnostic sensitivity disadvantage compared with TEE.[20]

The advantage of TEE becomes more significant when evaluating prosthetic valve endocarditis and complications such as leaflet perforations and abscesses. For prosthesis in the mitral and aortic positions, the sensitivity of TTE drops to approximately 20% to 40%, while for TEE it remains >80% to 90%.[80,85]

A mechanical prosthesis in the mitral position poses a special challenge, because it may shadow the entire left atrium on TTE, effectively concealing leaks (intra- and periprosthetic), as well as sewing ring dehiscence and vegetations, while direct imaging from behind the left atrium (TEE) eliminates this problem. Interestingly, the left ventricle is shadowed by the mitral prosthesis on TEE, at least in the

Table 4 Basic principles for echocardiographic evaluation of IE

- Be acquainted with patient's clinical history and pretest probability[2] for IE (low, intermediate, high), and interpret/report echocardiographic findings in light of that history
- Review previous echocardiograms to determine IE predisposing factors and confirm the presence of newly discovered periprosthetic leaks or native valve regurgitation
- Echocardiography has diagnostic and prognostic value in IE
- Echocardiography has postdiagnostic interval monitoring value in clinical decision making
- TTE exhibits low sensitivity but high specificity for IE diagnosis
- TTE determines the hemodynamic severity and hemodynamic consequences of IE-related valvular dysfunction, chamber size, and function and establishes a noninvasive baseline "fingerprint" of vegetations for future comparison
- TEE exhibits both high sensitivity and specificity for IE diagnosis
- TEE identifies anatomic detail of vegetations and thus may determine embolic risk; TEE identifies perivalvular complications
- TTE and TEE modalities are complementary
- Recognize echocardiographic features of vegetations
- Recognize echocardiographic features of perivalvular complications

Table 5 Echocardiographic features of infectious vegetations and abscesses

1. Vegetations
   - Echogenicity/echo texture: gray scale, myocardial texture, however, healed vegetations are more echogenic and often calcified
   - Size: highly variable
   - Aspect/shape: usually amorphous, shaggy, lobulated, less commonly linear or round
   - Location: atrial side of atrioventricular valves, ventricular side of the aortic valve, but may affect any side.
   - Motion: high-frequency flutter, oscillating, chaotic, orbiting, independent of valve motion; if large, prolapses into ventricles in diastole
   - Associations: valvular regurgitation, valvular mycotic aneurysms, valvular destruction, perivalvular abscess, prosthetic dehiscence
   - Differential diagnosis: native: noninfectious vegetations, PFE, valvular strands and Lambl's excrescences, MAC with mobile components, LVOT calcification with mobile components; prostheses: thrombosis, mitral subvalvular tissue remnants, platelet thrombi and microcavitations associated to mechanical prosthetic valves
   - "Healed vegetations": similar to any inflammatory process, once resolved, infective vegetations may scar and may appear as echogenic calcific nodules
2. Abscesses
   - Echolucent or echogenic-heterogeneous space or tissue thickening, which may or not "fill" with Doppler color signal, adjacent to valvular structure, usually paravalvular but may affect any myocardial region
   - Affects the aortic valve more commonly and may result in fistulous tract formation (i.e., aorta-ventricle, aorta-atrium) as well as pseudoaneurysm (typically of the aortic root).

LVOT, LV outflow tract.

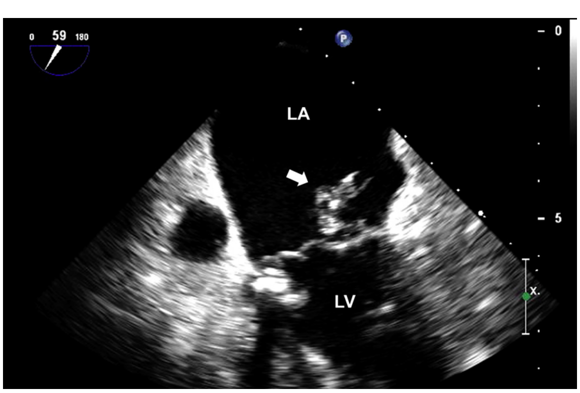

Figure 14 Native MV vegetation. On a midesophageal commissural transesophageal echocardiographic view, a systolic still frame at 59° demonstrates a large, amorphous, soft density (*arrow*) attached to the atrial surface of the MV, compatible with native MV vegetation. Video 9 corresponds to Figure 14 and demonstrates the high mobility and amorphous quality of this vegetation, as it prolapses into the left atrium in systole and left ventricle in diastole.

midesophageal four-chamber view, hence the complementary role of TTE for appropriate evaluation of LV size and function.

Aggressive microorganisms like staphylococci may cause paravalvular abscesses in both native and prosthetic valves, with a predilection for the aortic valve.[14] Sensitivity and specificity for abscess diagnosis have been estimated at 28% and 98%, respectively, for TTE and 87% and 95%, respectively, for TEE.[86]

Similarly, sensitivity and specificity for native leaflet or cusp perforation diagnosis have been estimated at 45% and 98%, respectively, for TTE and 95% and 98%, respectively, for TEE.[87] Therefore, TEE is considered a first-line modality when suspecting endocarditis complications (perforation, abscess), prosthetic valve endocarditis, *Staphylococcus aureus* bacteremia, intracardiac devices (i.e., pacemakers), and when transthoracic echocardiographic images are suboptimal. TTE is the first-line modality for all other situations and may be sufficient to suggest searching for another source of infection if the clinical suspicion for endocarditis is low and the test results are negative.

In the setting of intermediate or high clinical suspicion for endocarditis, negative results on TTE should always be followed by TEE. Furthermore, repeat TEE at an interval of approximately 7 days is

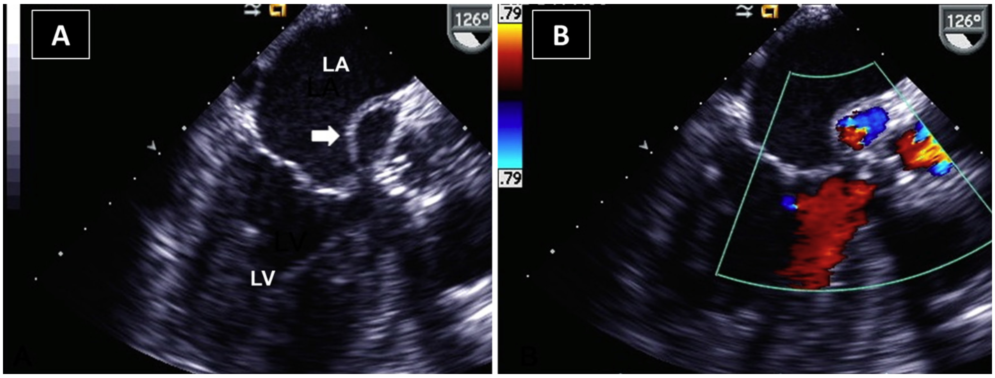

Figure 15 Native aortic valve endocarditis. **(A)** Midesophageal long-axis transesophageal echocardiographic systolic still frame at 126° shows a large posterior root cavity (*arrow*), compatible with root abscess/pseudoaneurysm complicating native aortic valve endocarditis. **(B)** Color Doppler on midesophageal long-axis TEE view in systole demonstrates communication between the left ventricle and abscess cavity in systole. Video 10 corresponds to **(B)** and depicts the pulsatile quality of this root abscess/pseudoaneurysm, as it fills with blood in systole and empties into the left ventricle in diastole.

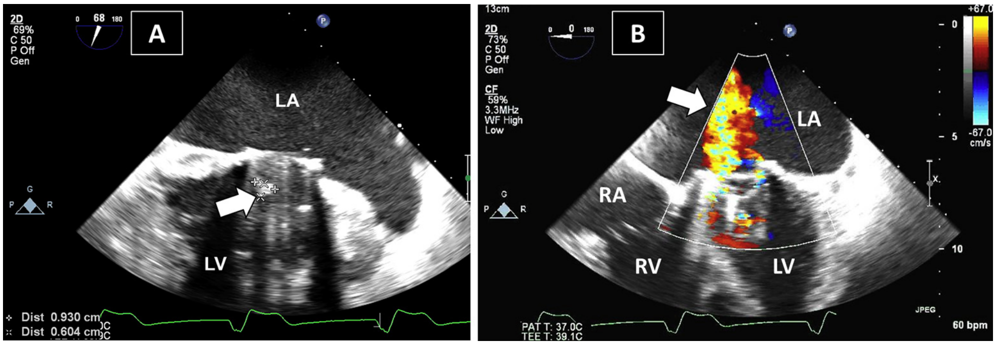

Figure 16 Remnant mitral subvalvular tissue versus vegetation. **(A)** Midesophageal transesophageal echocardiographic end-diastolic still frame at 68° shows an echogenic, rounded density within the mechanical mitral prosthesis subvalvular apparatus, measured at 0.9 × 0.6 cm, compatible with remnant subvalvular tissue versus vegetation. This patient was treated with antibiotics on the basis of echocardiographic findings and developed drug-related fever and thus continued to be treated as endocarditis. The absence of positive cultures and fever remission on stopping antibiotics, as well as surgical findings, confirmed this to be a native remnant of the MV. Video 11 corresponds to **(A)**. **(B)** Color Doppler demonstrates intermittent interference with occluder closure causing intermittent intraprosthetic mitral regurgitation. Video 12 corresponds to **(B)**.

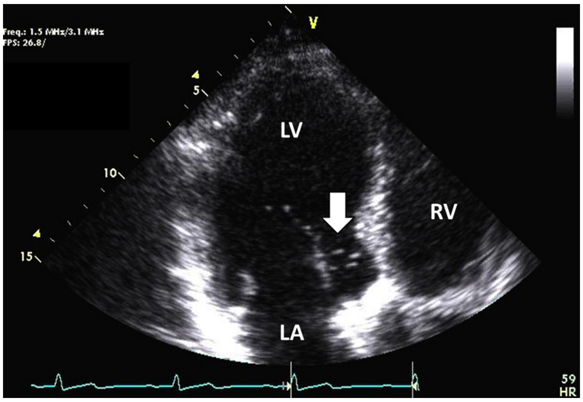

Figure 17 Microcavitations of a mechanical prosthesis. This transthoracic apical three-chamber view shows a significant amount of microcavitations arising from a large bileaflet mechanical prosthesis in the aortic position. Microcavitations appear as "bubbles" within the LV outflow tract. Video 13 corresponds to Figure 17.

reasonable if the clinical suspicion of IE remains high even after negative results on initial TEE.[80]

Prognosis. The variable reported incidence of systemic embolism (13%–49%) in IE reflects its heterogeneous nature.[88] Systemic embolism and thus stroke are seen mostly with left sided IE; however, right-sided endocarditis could potentially lead to stroke in the presence of a PFO or interatrial shunt. MRI-based studies have suggested that although a minority of patients present with clinical signs and symptoms of cerebral embolization (~20%–30%), a significant number of patients with IE have asymptomatic cerebral embolism and other IE-related cerebral lesions (~30%–50%).[89,90]

The highest risk for embolic events is observed before the diagnosis of IE is made. During the first 2 weeks after diagnosis and institution of antibiotic therapy, the embolic risk remains significant but decreases drastically after 2 weeks. The mere presence of vegetation in IE is a risk factor for embolization.[88] Although some series with limited use of TEE, retrospective designs, heterogeneous IE definitions, and limited patient numbers have suggested that vegetation size may not be predictive of embolism in IE, two large prospective studies support the contrary.[88,91]

Table 6 Echocardiographic and other predictors of systemic embolism and stroke

Echocardiographic predictors of systemic embolism and stroke
- Visible vegetations by both TTE and TEE
- Abscess formation
- Highly mobile vegetation
- Vegetation size > 10–15 mm
- MV endocarditis, particularly the anterior leaflet
- Bivalvular vegetation

Other predictors
- Fungal IE
- *S. aureus* IE
- *Streptococcus bovis* IE
- Antibiotic therapy, as risk for stroke decreases after 1–2 weeks of antibiotic therapy

A prospective study of 211 patients with left-sided IE showed embolic rates after the institution of antibiotics to be proportional to vegetation size and a significant increase in embolic risk was noted when vegetations were >10 mm in patients with staphylococcal infection and in patients with IE localized to the MV.[92] In a recent prospective multicenter European study of 384 consecutive patients with systematic TEE use and IE definition, vegetation size >10 mm and severe vegetation mobility were both independent predictors of new embolic events after antibiotic initiation.[91]

Therapeutic recommendations regarding IE are beyond the scope of this guidelines document; the reader is referred to appropriate treatment guidelines listed below. Briefly, vegetation size > 15 mm was an independent predictor of death. In addition, a transesophageal echocardiographic study of 178 consecutive patients with definitive IE suggested that patients with highly mobile vegetations >15 mm in size may benefit from early surgical intervention.[93] It is critical to recognize that vegetation characteristics in these studies were defined mostly by multiplane TEE, and "highly mobile" vegetations were defined as pedunculated vegetations prolapsing across the valve coaptation plane with the cardiac cycle (i.e., a mitral vegetation prolapsing into the left ventricle in diastole and left atrium in systole). Early surgery for IE has a class IIB recommendation for vegetations measuring >10 mm in current guidelines, regardless of the presence of clinical embolism. Echocardiographic predictors of embolization in IE are listed in Table 6.

Recurrent embolism with persistent vegetations as identified by echocardiography represents a class IIA indication for surgery.[94]

Recommendations for Performance of Echocardiography in Patients with Suspected IE

Echocardiography Recommended.
- TTE is recommended for the following:
  - Initial evaluation of suspected endocarditis with positive blood culture results or a new murmur.
  - Reevaluation of IE at high risk for progression or complication or with a change in clinical status or cardiac examination results.
  - Evaluation of hemodynamic consequences of IE (i.e., valvular regurgitation, shunts or fistulas, chamber enlargement, and function).
  - Repeat TTE at the end of antimicrobial therapy to serve as a baseline for future comparisons.
- TEE is recommended for the following:
  - To diagnose IE and its complications when clinical suspicion is intermediate or high, regardless of negative results on TTE.
  - As the first-line modality when complications of IE are suspected, such as abscesses, fistulas, or valve perforation, or when prosthetic valve endocarditis is clinically suspected.

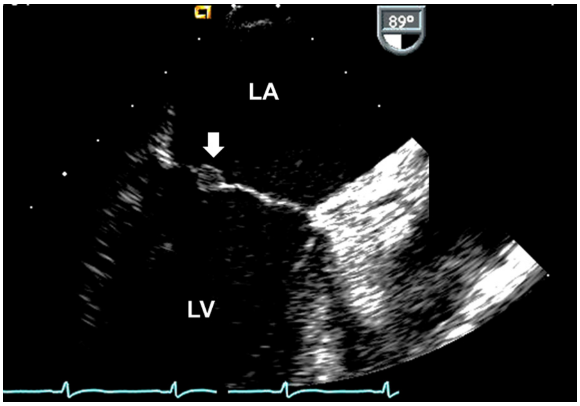

Figure 18 Antiphospholipid syndrome. TEE of a young adult woman with antiphospholipid syndrome, presenting with embolic stroke. Midesophageal two-chamber transesophageal echocardiographic systolic still frame at 89° shows a small rounded soft echogenic mass (*arrow*) on the anterior mitral leaflet edge. This was not visualized by TTE. Video 14 corresponds to Figure 18 and depicts a zoomed view of the MV showing a small rounded, not significantly mobile medium-echogenic mass attached to the free edge of the anterior leaflet and a tiny one attached to the free edge of the posterior leaflet. The patient was treated with warfarin, and these masses resolved.

  - Reevaluation of IE at high risk for progression or complication or with a change in clinical status or cardiac examination results (i.e., persistent fever and/or positive blood culture results, persistent embolic events, surgical planning, and suspected worsening valve function or heart failure).
  - Repeat TEE after a few days (~7 days) if clinical suspicion for IE remains high despite negative results on baseline TEE.

Echocardiography Not Recommended.
- Transient fever without bacteremia or a new murmur.
- Transient bacteremia with a nontypical organism and/or documented nonintravascular infection source.
- Routine surveillance of uncomplicated IE when imaging is not expected to change management.

Nonbacterial Thrombotic Endocarditis

Verrucous Endocarditis or Libman-Sacks Endocarditis. Described in 1924 by Libman and Sacks,[95] these usually small (1–4 mm) but sometimes very large verrucae are composed of granular material containing immune complexes, hematoxylin bodies, and platelet thrombi, without bacteria. Echocardiographically, despite the "echo texture" resembling IE (Table 5) and location not different from that of IE, they may appear less amorphous, more rounded, and not associated with valvular destruction. They are found in up to 43% of patients with systemic lupus erythematous when examined by TEE, affect typically the free edges of the mitral leaflets (high-flow area; Figure 18 and Video 14), but may affect any leaflet portion, as well as the aortic and tricuspid valves.[96]

These lesions are usually asymptomatic but can be complicated by IE, valve dysfunction (although not common), and systemic embolization. In a large transesophageal echocardiographic study, patients with lupus with valvular verrucae, valve thickening, or valvular dysfunction had a 22% combined incidence of stroke, peripheral embolism, heart failure, IE, and need for valve replacement, compared with 8% in patients without valvular defects.[24] Although it is likely that Libman-Sacks vegetations represent underlying valvulitis,[95] no association between clinical or laboratory markers of disease activity and these lesions has been found.

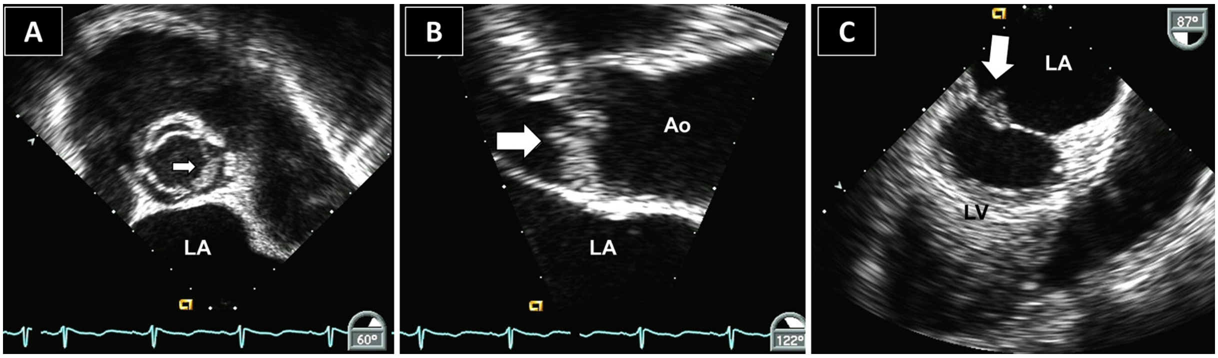

Figure 19 Marantic endocarditis. Images correspond to a male patient with bladder cancer and multivalvular marantic endocarditis. **(A)** Inverted midesophageal transesophageal echocardiographic systolic still frame of the aortic valve at 60° shows severe thickening of the left cusp edge (*arrow*). **(B)** It becomes apparent on the inverted midesophageal long-axis transesophageal echocardiographic view at 122° that there is a large soft mass attached to the left cusp (*arrow*). **(C)** A medium-echogenicity mass is also seen attached to the mitral leaflet (*arrow*) on midesophageal two-chamber transesophageal echocardiographic view. Video 15 corresponds to **(B)** and shows the left aortic cusp mass in inverted long-axis view. Note that it does not appear significantly mobile or amorphous, as a typical infective vegetation would appear.

Table 7 Recommendations for reporting valvular-associated masses

1. Careful echocardiographic description
   - Echogenicity/echo texture: attempt to differentiate "myocardial-like" echogenicity from more echogenic patterns and from strongly echogenic patterns with shadowing which likely represents calcification
   - Size: length and width in millimeters
   - Aspect/shape: sessile or pedunculated; amorphous, shaggy, lobulated, elongated, linear, rounded, hair-like, strand-like, sea anemone-like
   - Location: atrial or ventricular side of atrioventricular valves, aortic/vessel or ventricular side of the aortic valve, free edge of leaflet, "belly" of leaflet, base of leaflet, chordal attachments
   - Motion: dependent or independent of valvular motion; mild, moderate, or highly mobile (see text for definition)
   - Associations: valvular regurgitation, valvular stenosis, valvular mycotic aneurysms, valvular destruction, perivalvular abscess, perforation, prosthetic dehiscence
   - A description of prosthetic valve annular position (i.e., well seated), presence of rocking motion, and opening-closure of mechanical mechanisms (i.e., normal disk or leaflet diastolic excursion for a mitral prosthesis)
2. Differential diagnosis
   - Always attempt to answer the clinician's question/indication for the study
   - Usually two or three most likely explanations or differential diagnoses should be reported; if patient's clinical presentation is typical and echocardiographic characteristics are highly suggestive of pathology, may use terms as *suggestive of* or *likely represents*, *most consistent with*, followed by terms such as *less likely represents* or *unlikely to be*.
   - If clinical presentation unclear or noncontributory, and/or echocardiographic characteristics indistinct, report the most likely two or three differential diagnoses according to echocardiographic mass appearance, patient's age, predisposing factors, and epidemiology

Similar to "healed" IE vegetations (Table 5), healed verrucae may appear as echogenic calcific nodules and occasionally lead to residual valve dysfunction, particularly regurgitation. Routine echocardiography is not recommended for patients with lupus; however, the astute clinician will have a low threshold for performing it (i.e., fever, embolic phenomena, and new murmurs).

There are robust data suggesting that patients with lupus with antiphospholipid antibodies (both lupus anticoagulant and/or immunoglobulin G anticardiolipin antibodies) have a threefold risk for developing Libman-Sacks endocarditis, compared with those without antiphospholipid antibodies.[97] Therefore, routine transthoracic echocardiographic surveillance in patients with lupus with antiphospholipid antibodies is recommended. We also recommend routine echocardiography in patients with primary antiphospholipid syndrome, given the high prevalence (32%) of NBTE in these patients.[98]

Marantic Endocarditis or NBTE. Although the term *marantic* has been coined for lupus-associated verrucae,[95] it most commonly refers to noninfectious thrombotic endocarditis associated with malignancy, particularly related to solid metastatic carcinomas and lung, pancreatic, gastric, and unknown origin adenocarcinomas (Figure 19 and Video 15).[99] Interestingly, myelodysplastic syndromes have also been associated with NTBE with a high prevalence of marantic vegetations.[98] Fulminant states such as sepsis and burns may be associated with NBTE. Cancer is associated with a hypercoagulable state, such that 15% of patients with cancer experience thromboembolism during their disease, and postmortem studies identify deep venous thrombosis in up to 50% of patients.[100]

It is estimated that up to 50% of patients with NBTE may incur systemic embolic events. Marantic vegetations are composed of platelets and fibrin, uncommonly cause significant valvular dysfunction, and classically affect the atrial side of the MV and ventricular side of the aortic valve. Echo texture and location are not different from those of IE, and size can range from small to large. However, there is usually significant and diffuse thickening of the leaflets or cusps of the involved valve in NBTE, which may help differentiate between IE and NBTE.[98]

As with IE, TEE has significantly higher sensitivity for the identification of NBTE than TTE, so TEE must be performed in patients with negative results on TTE in whom clinical suspicion exists.[101,102] Given the lack of tissue characterization capability of echocardiography, it is recommended to first carefully describe the echocardiographic characteristics of the valvular-related mass and then suggest a differential diagnosis on the basis of the patient's clinical presentation (Table 7).

Recommendations for Performance of Echocardiography in Patients with Suspected Noninfective Endocarditis.

Echocardiography Recommended.

- Transthoracic echocardiographic surveillance in patients with primary antiphospholipid syndrome given the high prevalence of NBTE in these patients.
- Transthoracic echocardiographic surveillance in patients with lupus erythematosus with secondary antiphospholipid syndrome.

Echocardiography Not Recommended.

- Routine echocardiography is not recommended for patients with lupus in the absence of clinical signs such as fever, embolic phenomena, and new murmurs.

Papillary Fibroelastomas

PFEs are discussed separately in the "Cardiac Tumors" section of these guidelines.

Valvular Strands and Lambl's Excrescences

Valvular excrescences or strands are defined echocardiographically as filiform structures, with undulating motion, width ≤ 2 mm, and length between about 3 and 10 mm, localized to the line of leaflet closure (Figure 20 and Video 16).[103] They are usually multiple, affect the left-sided valves more commonly (the MV most commonly), and likely represent remnants of fenestrations (partially avulsed fenestrations). They are seen undulating on the atrial side of the MV and the ventricular side of the aortic valve. Lambl's excrescences (Video 10) are also localized to the closure line of leaflets or cusps, and the term is used interchangeably with *strands* and *excrescences*. However, it is likely that they are not histologically similar, because Lambl's excrescences appear to be hamartomatous growths with histologic similarities to PFEs, not avulsed fenestrations like strands. To our knowledge, there is no way of distinguishing strands and Lambl's excrescences by echocardiography.

In a prospective study, strands were found by TEE in 40% to 50% of all patients, regardless of age and gender, regardless of previous embolic events, did not change over time, and were not related to systemic embolism.[103] Other studies with retrospective design,[104] with unclear strand definitions,[101] which included prosthetic valves,[104] have found an association between strands and embolism. We believe these latter studies were significantly biased. An association between MV strands and prior embolic events has been described,[105] which does not imply causality, particularly because mitral strands are not independently associated with future embolic events.[106] The same association between TEE-detected strands and prior embolic events has been described for mechanical prosthetic valves in retrospective reviews.[107,108] In summary, there is currently no robust evidence that native or prosthetic valvular strands are causative of systemic embolism.

Mitral Annular Calcification

MAC is defined as calcific deposition in the mitral annulus, a C-shaped fibrous structure extending from fibrous trigone to fibrous trigone of the MV, thus sparing the anterior portion, which lacks fibrous annulus and is in continuation with the aortic valve (aortomitral curtain).[109]

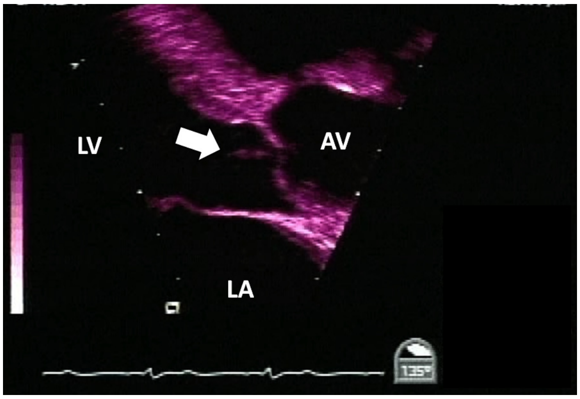

Figure 20 Lambl's excrescence. This inverted transesophageal echocardiographic long-axis view of the aortic valve shows the typical appearance of a Lambl's excrescence (*arrow*), as a linear echo density with undulating motion, arising from the coaptation interface of the valve. It is particularly well seen in diastole. Video 16 corresponds to Figure 20.

Severe MAC involves more than two thirds of the C-shaped annulus and is best seen on parasternal long-axis and short-axis views by TTE (Figure 21 and Videos 17 and 18). The parasternal short-axis view reveals a thick, lumpy, and highly echogenic rim that surrounds the external perimeter of the posterior mitral leaflet. Shadowing is also seen, particularly in the apical views by TTE and midesophageal long-axis LV views by TEE. The presence, extent, and severity of MAC are best evaluated by TTE. Furthermore, MAC can effectively conceal posterior annular abscesses in endocarditis when evaluated by TEE.[110]

When evaluating MAC, attention must be paid to low echogenic mobile components (vegetation, thrombus), as well as to highly echogenic (calcific) mobile components. MAC may serve as nidus for IE,[109,111] is related to significant carotid artery obstruction,[112] is an independent predictor of the presence of severe aortic atheroma,[113] and has been associated with stroke in population studies.[114,115] There are multiple possible mechanisms of stroke related to MAC, such as (1) IE-related vegetation embolization, (2) atherosclerotic risk marker for ischemic-thrombotic stroke, (3) ulcerated MAC with superimposed thrombus that embolizes, (4) MAC-associated calcific mobile components that embolize, and (5) an increase in transmitral gradient leading to LA dilation and atrial fibrillation.[116]

Recommendations for Performance of Echocardiography in Patients with MACs.

Echocardiography Potentially Useful.

- Echocardiography can establish the presence, extent, and severity of MACs.
- However, MACs are typically an incidental finding and unlikely to be an independent cause of a cardiac source of embolism.

Prosthetic Valve Thrombosis

Diagnosis. The annualized risk for mechanical prosthetic valve thrombosis is estimated to be 1% to 2%, and it affects the tricuspid and mitral positions more frequently than the aortic position, regardless of anticoagulation. Conversely, for bioprostheses, the yearly thrombosis risk is estimated at 0.5% to 1%. Prosthetic valve thrombosis may present with pulmonary (right-sided prostheses) or systemic (left-sided and rarely right-sided prostheses) embolism and/or

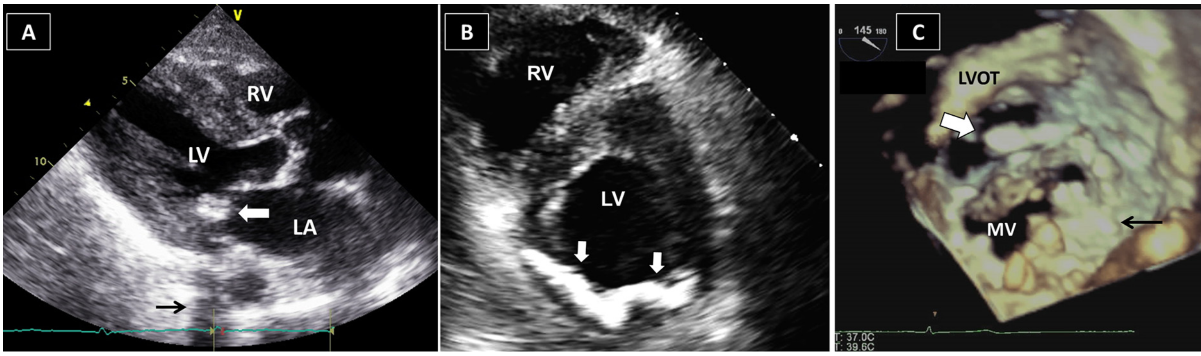

Figure 21 MAC. **(A)** Transthoracic parasternal long-axis diastolic still frame shows posterior mitral annular large echo density *(thick white arrow)* compatible with MAC. Also note shadowing artifact (*small black arrow*) by MAC. Video 17 corresponds to **(A)**. **(B)** Parasternal short-axis shows C-shaped dense echogenicity (*arrows*) corresponding to significant MAC. **(C)** A full-volume 3D transesophageal echocardiographic view of the MV and LV outflow tract (LVOT) from the LV perspective. Note the small mobile components associated to the posterior annulus (*small arrow*) and the large commissural mobile component that prolapses into the LVOT in systole (*large arrow*). The patient underwent surgical removal of all mobile components. The MV was preserved. Video 18 corresponds to **(C)**.

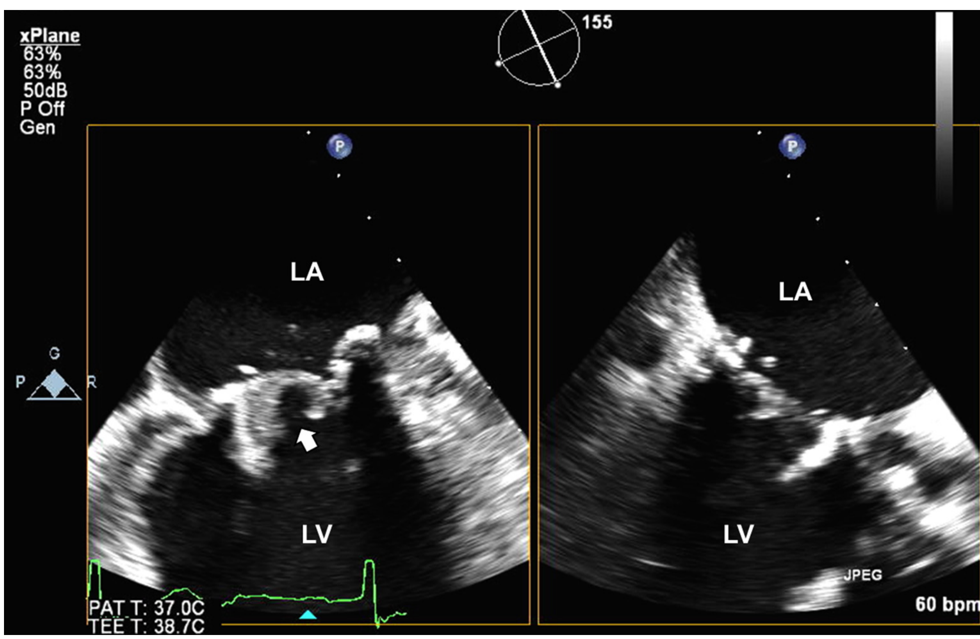

Figure 22 Prosthetic MV thrombus. Images are those of a woman 6 months after MV replacement who presented with dyspnea and increased mitral gradient. Midesophageal transesophageal echocardiographic biplane view of the MV shows layered thrombus underneath the entire ventricular aspect of the posterior prosthetic leaflet and strut (*arrow*). Video 19 corresponds to Figure 22. Note layered thrombus underlying the posterior leaflet and strut, rendering the leaflet fixed. The patient received anticoagulation, and thrombus resolved in 3 months.

symptoms of prosthetic obstruction or regurgitation, primarily shortness of breath, usually in the absence of fever.

Mechanical thrombosis often occurs in the setting of subtherapeutic anticoagulation, but not necessarily. Because it may be impossible to distinguish thrombus from vegetation echocardiographically, the patient's clinical background and associated imaging findings become critical. Both vegetations and fresh thrombi have a soft (medium echogenicity), myocardial-like texture (Table 5), vary in size, and are usually mobile; however, thrombi may be more shape defined and less mobile, as opposed to the amorphous, highly mobile vegetations. In bioprosthetic valves, thrombus may be layered on the biologic leaflet, rendering it fixed (Figure 22 and Video 19).

Similar to healed vegetations, "old thrombus" may acquire a rather echogenic and less mobile appearance. Hence, the echocardiographer must follow a systematic method of analysis and reporting, beginning with a careful echocardiographic description of findings (Table 7) and ending with a differential diagnosis in the report and a most likely diagnosis (if possible). Recognizing the presence and hemodynamic significance of prosthetic dysfunction is the first step of the evaluation when thrombosis is suspected, and the gold standard for this purpose is TTE. Nonetheless, the sensitivity for detecting the presence of thrombus (with or without prosthetic dysfunction) is exquisitely superior for TEE.[117] In addition, appropriate prosthetic occluder or leaflet motion is better ascertained by TEE.

Alternatively, gated cardiac CT (for both mechanical and bioprostheses) or fluoroscopy (for mechanical prostheses only) can effectively assess prosthetic components' motion. When elevated gradients across a prosthetic valve are due to obstruction rather

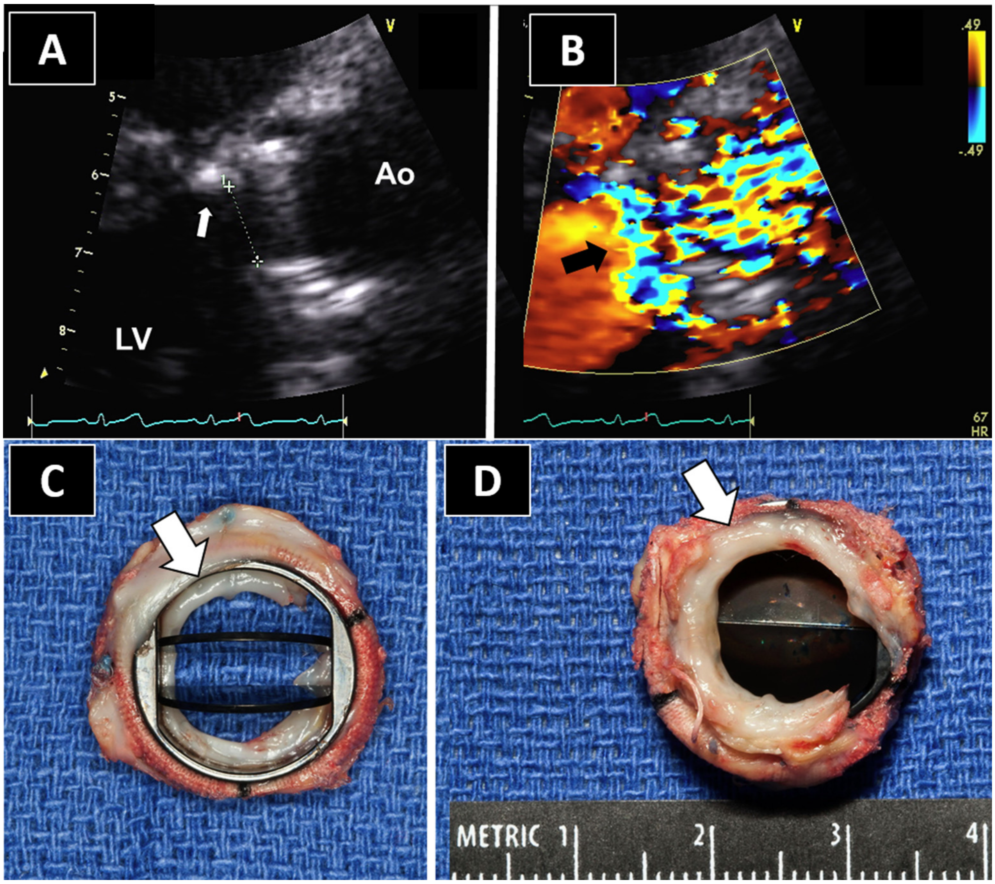

Figure 23 Aortic prosthesis pannus. Images are those of a patient with severe mechanical aortic valve obstruction. **(A)** Transthoracic parasternal long-axis systolic still frame shows nonmobile echo density (*arrow*) underneath the aortic valve, rendering the LV outflow tract (LVOT) stenotic just below the valve. **(B)** Color Doppler shows turbulent flow convergence (*arrow*) forming below the valve, just before the echo density shown in **(A)**. Video 20 corresponds to Figure 23; note turbulent flow convergence forming before the anterior subvalvular echo density. **(C)** Aortic side of explanted prosthesis shows pannus formation (*arrow*) on the superior aspect of the sewing ring. **(D)** Ventricular side of the explanted prosthesis shows severe, circumferential pannus formation (*arrow*).

Table 8 Echocardiographic evaluation of prosthetic valve obstruction mechanism

Favors pannus
• Mechanical prosthesis in the aortic position
• No significant decreased occluder motion
• Therapeutic anticoagulation
• Identified mass not significantly mobile
Favors thrombus
• Mechanical prosthesis in the tricuspid or mitral position
• Abnormal occluder motion with obstruction
• Attachment to the occluder itself
• Subtherapeutic anticoagulation
• Large and mobile identified mass

than patient-prosthetic mismatch, it may be difficult to distinguish thrombosis from pannus formation (chronic fibrous tissue ingrowth), which may occur in both mechanical and bioprosthesis (Figure 23 and Video 20), and from structural degenerative bioprosthesis stenosis.[118-120]

In addition, mixed pannus-thrombus pathology is not uncommon. Correct identification of the obstruction mechanism (compared with surgical findings) has been reported at 10% for TTE and 49% for TEE in mechanical aortic prostheses ($P<.0001$) and 63% for TTE and 81% for TEE in aortic bioprostheses ($P=.18$).[119] The superiority of TEE for mechanism identification is particularly notable for mechanical valves in the mitral position, for the same reasons discussed in the infectious endocarditis "Diagnosis" section. Clinical and echocardiographic features that help differentiate prosthetic obstruction mechanisms are depicted in Table 8.

Prosthetic thrombosis may also present with mixed obstruction or regurgitation or pure regurgitation, usually related to the thrombotic mass impeding prosthetic occluder closure (mechanical) or coaptation (bioprosthesis), but infectious vegetation may also present with regurgitation by impeding occluder closure or by bioprosthesis destruction. In addition, degenerative anatomic disruption (bioprosthetic torn leaflet or cusp) may mimic vegetation or thrombosis and usually presents with torrential regurgitation (Figure 24 and Video 21).[121] Yet again, the regurgitation severity is assessed by TTE and the mechanism of dysfunction refined by TEE. Therefore, both TTE and TEE are indicated when suspicion of prosthetic valve thrombosis arises. Furthermore, interval or repeat studies are also considered appropriate for the reevaluation of prosthetic valve thrombosis when it would change management or guide therapy.[5]

TEE-Guided Prosthetic Thrombosis Management. Transesophageal echocardiographic identification of the obstruction or regurgitation mechanism (Table 8) is critical because thrombosis is amenable to treatment with fibrinolysis or surgery

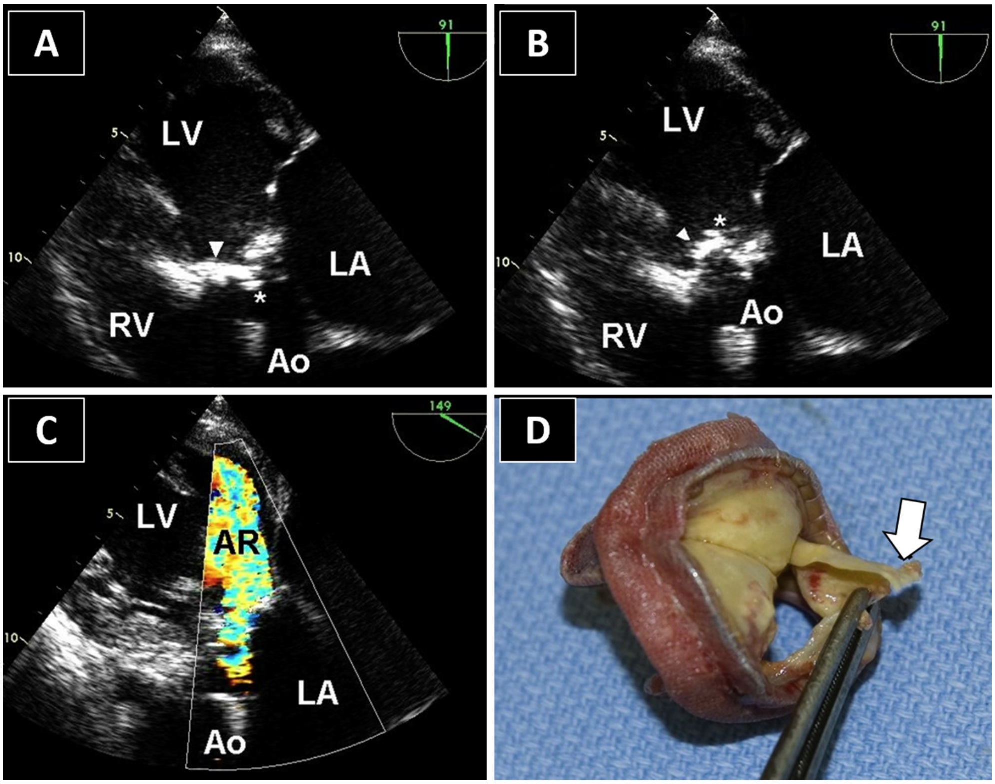

Figure 24 Degenerated torn aortic bioprosthetic cusp. Transesophageal echocardiographic images are those of a man with a degenerated torn aortic bioprosthetic cusp initially thought to have endocarditis. **(A)** Deep transgastric five-chamber transesophageal echocardiographic systolic still frame shows the torn cusp (*arrow*) with nodular tip (*asterisk*). **(B)** Diastolic still frame on deep transgastric five-chamber transesophageal echocardiographic view shows severe prolapse of the torn cusp (*arrow*) and nodular tip (*asterisk*). Video 21 corresponds to **(B)** and shows a deep transgastric view. Note significantly mobile structure (torn cusp) within the aortic valve, which may be mistaken for a vegetation. **(C)** Color Doppler shows severe aortic regurgitation. **(D)** Intraoperative photograph shows the torn cusp with nodular tip (*asterisk*).

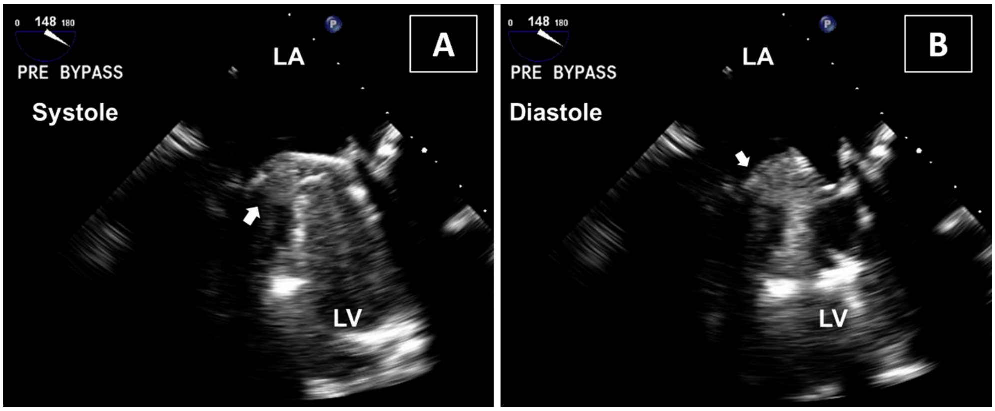

Figure 25 Prosthetic valve thrombosis. Prebypass intraoperative midesophageal long-axis transesophageal echocardiographic view shows a bileaflet mechanical valve in the mitral position. Note both occluders closed in systole **(A)** with a rounded, not significantly mobile soft echogenicity on the ventricular side of the posterior occluder (*arrow*). In diastole **(B)**, the anterior occluder opens and the posterior occluder remains closed. Video 22 corresponds to Figure 25 and shows the frozen posterior occluder embedded in thrombus. The patient underwent successful mitral re-replacement with a bioprosthesis.

(Figure 25 and Video 22). In addition, TEE can reliably identify patients with low thrombolysis-related embolization risk and facilitate the decision between thrombolysis and redo surgery. Mobile thrombi and those >5 to 10 mm in length are associated with greater risk for embolization with fibrinolysis.

A multicenter study of 107 patients with prosthetic thrombosis (~80% mechanical in the mitral position) showed a transesophageal echocardiographic thrombus area < 0.8 cm^2 to be an independent predictor of low complication risk for thrombolysis, regardless of symptom status.[122] The only independent predictors of thrombolysis complications were thrombus area by TEE (odds ratio, 2.4 per 1-cm^2 increment) and history of stroke (odds ratio, 4.5).

Both TTE and TEE can assess thrombolytic therapy success with improved valvular hemodynamics and thrombus resolution.

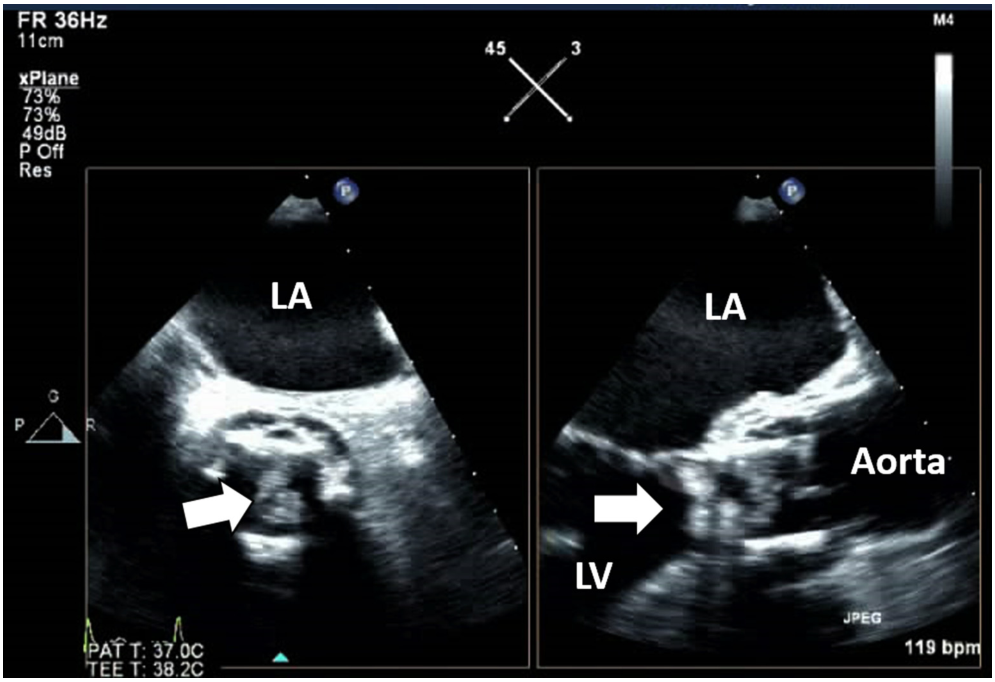

Figure 26 Thrombus on transcatheter aortic valve. Midesophageal biplane transesophageal echocardiographic view shows a recently deployed transcatheter aortic valve with acute substantial thrombosis. Note that this fresh thrombus is large and highly mobile. Differential diagnosis would include vegetation. Video 23 corresponds to Figure 26.

Embolic Complications in Interventional Procedures

The use of TEE has become, in combination with fluoroscopy, an integral part of the imaging armamentarium for guidance in percutaneous valvular interventions, which may include transcatheter aortic valve replacement (TAVR), mitral and aortic periprosthetic leak closure with vascular plugs, and the MitraClip (Abbott Vascular, Santa Clara, CA). During these procedures, it is critical to verify hardware position (i.e., guidewires and sheaths) and monitor constantly for the development of thrombus.[123]

Although rare, thrombus may form on the bioprosthesis after delivery into the LV outflow tract (Figure 26 and Video 23). Finally, careful preprocedural transesophageal echocardiographic evaluation of the native aortic valve is critical because it may uncover large mobile calcific debris associated with the valve (Figure 27 and Video 24), which could embolize during prosthetic valve deployment and thus represent a contraindication to the TAVR procedure.[123]

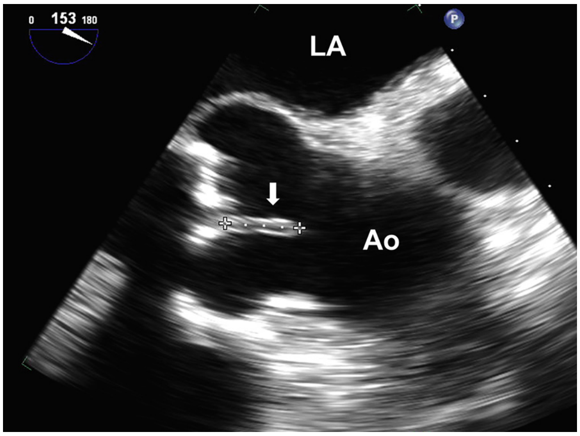

Figure 27 Aortic valve calcified debris. Pre-TAVR midesophageal long-axis transesophageal echocardiographic diastolic still frame of the aortic valve and proximal aorta reveals a 1.3-cm elongated, echogenic mass (*arrow*) attached to the aortic side of the calcified aortic valve. This likely represents calcific debris. The TAVR case was canceled as per protocol. Video 24 corresponds to Figure 27 and demonstrates a pre-TAVR transesophageal echocardiographic long-axis view shows a prominently calcified aortic valve with severely diminished systolic excursion and an elongated, echogenic continuation of the anterior cusp, which likely represents associated calcific debris. The TAVR procedure was canceled by protocol.

Recommendations for Performance of Echocardiography in Patients with Prosthetic Valve Thrombosis.

Echocardiography Recommended.

- Both TTE and TEE are indicated when suspicion of prosthetic valve thrombosis arises.
- Interval or repeat studies are considered appropriate for reevaluation of prosthetic valve thrombosis when it would change management or guide therapy.
- TTE and/or TEE are recommended for evaluation of thrombolysis therapy success as judged by improved valvular hemodynamics and thrombus resolution.

CARDIAC TUMORS

Primary cardiac tumors are very rare, with seven cases in >12,000 autopsies (a prevalence of 0.05%). Most primary cardiac tumors are histologically benign but may have malignant clinical course due to their often high embolic potential. The two most common primary cardiac tumors in adults are myxoma and PFE, both of which often present with stroke or other embolism. The strokes may occur because of embolism of the tumor itself or because of dislodgement of an associated thrombus. Primary malignant tumors of the heart are rare and are mostly sarcomas. Because they are located predominantly in the right heart, they may lead to pulmonary rather than systemic embolism.

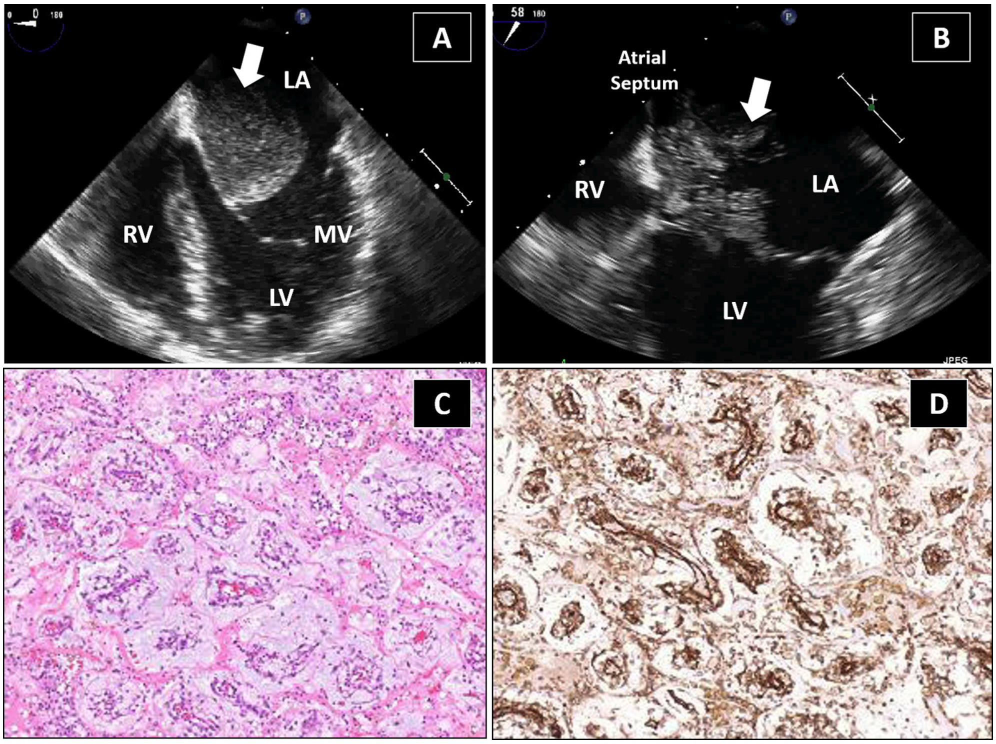

Figure 28 LA myxoma on TEE. **(A)** Midesophageal 2D transesophageal echocardiographic four-chamber view of large LA myxoma (*arrow*) in diastole. Video 25 corresponds to **(A)** and shows that the myxoma prolapses through the MV. **(B)** Midesophageal 2D transesophageal echocardiographic image of a friable LA myxoma with multiple frond-like structures located to the lower part of the interatrial septum. Video 26 corresponds to **(B)**. **(C,D)** Fibrotic and myxoid stroma with lepidic (myxoma) cells admixed with mononuclear cells, typical of myxoma. **(C)** Hematoxylin and eosin staining at 100× magnification. **(D)** Van Gieson's staining at 200× magnification.

Secondary tumors due to metastatic disease are 20 times more common (1% in autopsy series) than benign cardiac tumors but are infrequently implicated as a cardiac source of embolism. The most common malignant tumors of the heart include melanomas as well as metastases from lung, breast, colon, and stomach cancers.

Echocardiographic Evaluation of Cardiac Tumors

Echocardiography with color and Doppler should be considered in all patients with suspected cardiac tumors. Two-dimensional and 3D echocardiographic imaging can establish the location, appearance, size, and mobility of cardiac tumors.[124,125] Color and spectral Doppler is useful in determining the hemodynamic consequences of the tumors, such as the presence of mitral stenosis with large LA myxomas and any associated aortic valve abnormality with PFEs.[126] The use of perflutren contrast may aid in determining the vascular nature of the tumors, pointing to the diagnosis of tumor over thrombus or vegetation.[127] The administration of microbubble echocardiographic contrast may help differentiate low-vascularity structures (such as thrombi and vegetations, which have poor contrast uptake) from high-vascularity structures (such as malignant tumors, which often have marked contrast uptake), as discussed in guidelines on the use of echocardiographic contrast.[9] Echocardiographic imaging may aid in the description of the tumors, including the exact insertion of the stalk and the texture of the lesions, thereby improving diagnostic accuracy and aiding the surgeons in the surgical planning.[128]

Myxoma. Cardiac myxomas are seen in the left atrium in >75% of cases, predominantly attached with a stalk to the fossa ovalis (>90%). However, they can be seen in other locations (the left ventricle, the right atrium, and very infrequently the right ventricle). Myxomas may be multiple in up to 5%. Approximately 7% of all myxomas of the heart are associated with the Carney complex, an autosomal-dominant disease characterized by the presence of cardiac and skin myxomas, skin hyperpigmentation, and primary pigmented nodular adrenocortical disease leading to Cushing syndrome.

Myxomas are more common in women. They appear gelatinous and pedunculated with a smooth, villous, or friable surface. Histology show the typical scattered myxoma cells in a mucoid stroma, often associated with thrombus on the tumor surface (Figure 28). They may be more or less vascular and may contain necrotic areas or focal calcifications.

They may at times become very large, obstructing the MV orifice, causing mitral stenosis and associated symptoms such as dyspnea on exertion or with certain positions. Other times the tumors are very mobile, villous, and friable, with high risk for embolism. Examples of cardiac myxomas are given in Figure 28, Videos 25, and 26; and Figure 29, Videos 27, and 28.

In up to one third of cases of myxomas, there is evidence of distant embolism, including to the brain, which may be silent or cause neurologic symptoms. Neurologic deficits may often be the first presenting symptom of a cardiac myxoma. After surgical removal, myxomas may recur; wide excision of the tumor with adjacent cardiac tissue is necessary to prevent reoccurrence. Surgery is generally indicated when the diagnosis of cardiac myxoma is made and irrespective of whether systemic embolism has already occurred or not.[129-131]

Because myxomas are partly vascularized, they may be partly opacified on microbubble echocardiographic contrast imaging. This may help differentiate myxomas from thrombi (which are typically not opacified) and malignant tumors (which are often fully opacified).

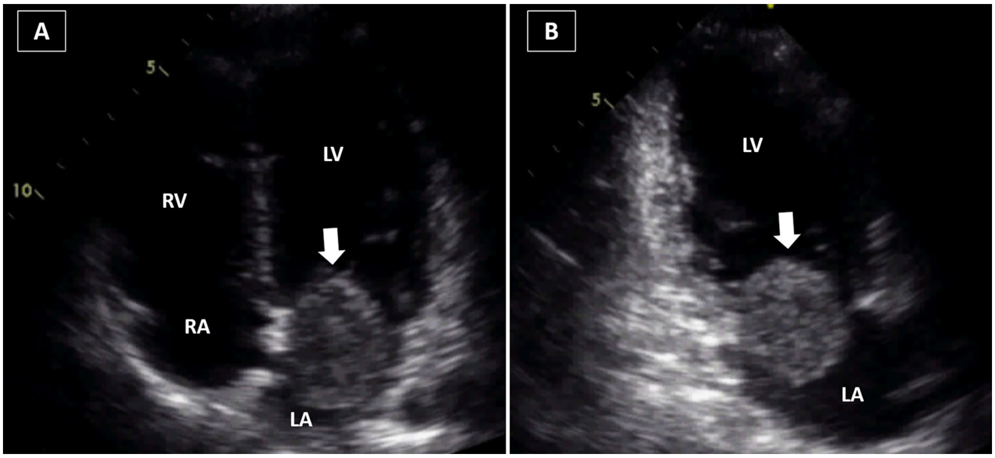

Figure 29 LA myxoma on TTE. **(A)** Two-dimensional transthoracic echocardiographic apical four-chamber view of LA myxoma occupying most of the left atrium (LA). *LV*, Left ventricle; *RA*, right atrium; *RV*, right ventricle. Video 27 corresponds to **(A)**. **(B)** Two-dimensional transthoracic echocardiographic apical two-chamber view of LA myxoma (*arrow*). Video 28 corresponds to **(B)** of Figure 29.

Papillary Fibroelastoma. PFE is the second most common primary cardiac tumor in adults. They are predominantly located on the cardiac valves (80%), with the highest prevalence on the aortic valve, followed by the MV. However, they may be seen on any endocardial surface. When located to the valves, they are typically on the aortic side of the aortic valve and on the ventricular side of the MV (downstream); this is exactly the opposite of the typical location of IE lesions. PFEs rarely cause significant valvular dysfunction.

They appear homogeneously textured, round, oval, or irregular,[132] with well-demarcated border, and are often mobile. These benign tumors have a dense central stalk with frond-like extensions in varying sizes (from a few millimeters to several centimeters, on average 1 cm), and the risk for embolism is very high. Because of their multiple frond-like projections, these endocardial-derived, avascular benign tumors resemble a sea anemone (Figure 30 and Videos 29-31).[133]

They may present as stroke, TIA, or cardiac infarct due to embolism of the coronary arteries. In about one third of cases, they are asymptomatic. Microscopy will reveal the papillary nature of the tumor. PFEs are usually <20 mm in size (mean, ∼8–9 mm) and are single (solitary lesion) in >90% of cases. Sensitivities of TTE and TEE for PFE detection have been estimated at about 62% and 77%, respectively.[132]

There is a strong association between left-sided mobile PFEs with stalks and future embolic phenomena.[134] Patients presenting with symptoms, large tumors, and very mobile tumors should undergo surgery upon diagnosis, while small sessile tumors in asymptomatic patients may warrant watchful waiting, especially if a patient is a high-risk surgical candidate.[132,134]

Recommendations regarding medical or surgical treatment of PFE are beyond the scope of this guidelines document. The echocardiographic differential diagnosis of PFEs includes myxoma, valvular strands, and Lambl's excrescences.

Recommendations for Echocardiographic Evaluation of Cardiac Tumors

Echocardiography Recommended

- Complete TTE is recommended in all patients suspected of having cardiac tumors.
- TEE may be superior to TTE in evaluating cardiac tumors, especially myxomas and PFEs.
- Echocardiography is recommended for surveillance after surgical removal of cardiac tumors with high recurrence potential (such as myxomas).

Echocardiography Potentially Useful

- Contrast echocardiography using microbubble agents (such as perflutren) may help differentiate vascular tumors from avascular masses such as vegetations and thrombi.
- Three-dimensional echocardiography may improve the diagnostic accuracy of cardiac tumors.

Echocardiography Not Recommended

- Echocardiography is not recommended in patients for whom the results will not guide therapeutic decisions.

EMBOLISM FROM THE THORACIC AORTA

Imaging of the aorta is an essential part of the evaluation of embolic stroke and peripheral embolization. By definition, the thoracic aorta is not a cardiac structure; however, embolism from the thoracic aorta is included in this report because of its geographic proximity to the heart and the fact that the aorta is routinely visualized during TTE and TEE. General aspects of imaging the thoracic aorta by echocardiography are addressed in a separate guidelines document.[135]

Atherosclerotic plaque is the most common source of embolism originating from the aorta. In rare instances, embolism can arise from aortic tumors.[136] Atherosclerotic plaques in the aorta may give rise to two different types of emboli (thromboemboli and cholesterol crystal emboli) and two different syndromes of arterioarterial embolism (aortic thromboembolism syndrome [ATS] and cholesterol emboli syndrome [CES]).

In ATS, a thrombus overlying an atheromatous plaque breaks off and travels distally to occlude large-caliber downstream arteries such as the carotid arteries and their branches.[137] In aortic thromboembolism, there is typically a sudden release of thrombi resulting in acute ischemia of a target organ. Clinical manifestations of ATS include stroke, TIA, renal infarcts, and infarcts in other arterial beds.

In CES, multiple small cholesterol crystal emboli are released from an atheromatous plaque over a period of time ("shower of emboli").[138] They embolize to small- or medium-caliber arteries, leading to end-organ damage due to either mechanical obstruction and/or

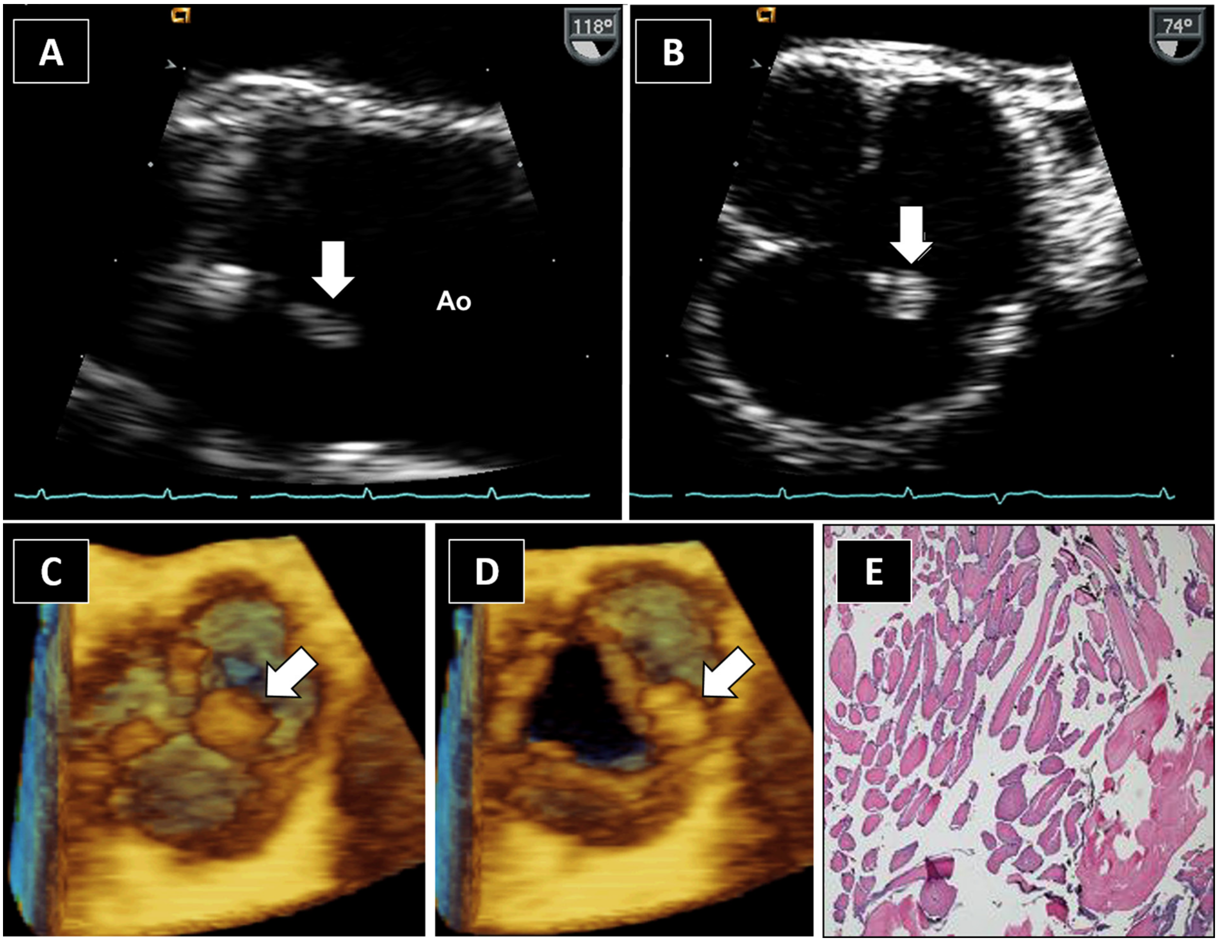

Figure 30 PFE. **(A)** Midesophageal long-axis 2D transesophageal echocardiographic diastolic still frame of the aortic valve at 118° shows PFE (*arrow*) attached with stalk to the aorta surface of the valve. Video 29: long-axis view depicts the mobile mass attached by a stalk to the aortic valve with the typical appearance of a PFE (anemone-like with stippling along the edges). This video corresponds to **(A)**. **(B)** Midesophageal short-axis 2D transesophageal echocardiographic diastolic still frame of the aortic valve at 74° shows the PFE (*arrow*). Video 30 corresponds to **(B)** and demonstrates the mobile PFE clearly attached to the free edge of the left coronary cusp. **(C,D)** Three-dimensional transesophageal echocardiographic image demonstrates an aortic valve PFE (*arrows*) from the ascending aorta side during diastole **(C)** and systole **(D)** in another patient. Video 31 corresponds to **(C,D)**. **(E)** Histopathology of PFE demonstrates numerous frond-like projections. Hematoxylin and eosin staining, 100× magnification.

inflammatory response.[139] Synonyms of *CES* include *atheroembolism*, *cholesterol crystal embolization*, and *atheromatous embolization syndrome*.[140] Clinical manifestations of CES include renal failure, blue-toe syndrome, hypereosinophilia, and diffuse rather than focal neurologic damage (e.g., mental confusion rather than stroke).

The pathophysiology of both ATS and CES involves six basic elements: the presence of an atherosclerotic plaque in the aorta, plaque rupture and/or thrombus formation, embolization of plaque content, lodging of emboli in distal arteries, and end-organ damage.

Atherosclerotic plaques are a manifestation of general atherosclerosis and are associated with known atherosclerosis risk factors such as hypertension, diabetes mellitus, advanced age, hypercholesterolemia, and tobacco smoking. Plaques reside within the aortic intima, and their development is a lifelong process (Table 9). In early stages, plaques contain intracellular and extracellular lipid deposits, are clinically silent, and typically start developing during childhood and early adulthood. In more advanced stages, plaques become more complex and undergo progressive changes from atheromas to fibroatheromas to complex plaques with hemorrhage, surface ulcerations, and formation of overlying thrombi.[141] In some advanced lesions, calcifications may develop within plaques. Advanced lesions are typically encountered in middle-aged and elderly individuals. It is these advanced atherosclerotic plaques that are the source of both thromboemboli and cholesterol crystal emboli.

The atheromas contain a necrotic core; when overlaid by a fibrous cap, they are called fibroatheromas. The necrotic core consists of foam cells, cell debris, and lipids. The cap consists of endothelial and smooth muscle cells as well as connective tissue. Rupture of this fibrous cap leads to in situ thrombus and an initial event that could lead to embolization that may result from forces from within the plaque itself (e.g., inflammation and hemorrhage) or from the luminal side of the plaque (e.g., shearing by the moving intraluminal blood or by mechanical disruption). Typically, the amount of plaque increases from the proximal to the distal segments of the aorta.[142] The risk for ATS and CES is directly correlated with the overall degree of atherosclerosis. As in other vascular beds, plaque rupture in the aorta may be spontaneous, traumatic, and/or possibly related to thrombolytic and anticoagulation therapy.

Table 9 Classification of atherosclerotic plaques

Onset	Stage	Clinical manifestations	Lesion name	Description
Early lesions	I	Typically silent	Initial lesion	Small amounts of intracellular lipid deposits
	II		fatty streak	Larger amounts of intracellular lipid deposits
	III		intermediate lesion	Small extracellular lipid deposits
Late lesions	IV	Silent or clinically overt	Atheroma	Extracellular lipid core
	V		Fibroatheroma	Lipid core with fibrotic changes
	VI		Complex plaque	Surface defects such as ulcerations, hemorrhage and thrombus; mobile plaque, a marker of severe atherosclerosis, is mostly made of thrombi

Role of Echocardiography in the Visualization of Aortic Plaques

The detection, characterization, and quantification of aortic plaques can be accomplished by TEE, CT, or MRI.[6,143] TEE together with CT and MRI is the primary means of aortic plaque visualization.[135] There are several plaque grading systems using a variety of parameters, such as plaque thickness, surface characteristics, and the presence or absence of mobile components. Details of plaque grading systems are presented in recent guidelines on aortic disease.[144]

The most important transesophageal echocardiographic views for visualization of plaque in the ascending aorta, aortic root, and aortic valve are the midesophageal long-axis (at 120°–150°) and short-axis (at 30°–60°) views. A small segment of the distal ascending aorta, just proximal to the takeoff of the innominate (brachiocephalic) artery is a 'blind spot' on TEE because of interposition of the air-filled right bronchus and trachea between the esophagus and the aorta. The aortic arch is visualized on upper esophageal TEE views. The descending aorta can be visualized from the subclavian artery to the superior mesenteric artery on short-axis (0°) and long-axis (90°) views. A major shortcoming of TEE is its inability to visualize the abdominal aorta distal to the ostium of the superior mesenteric artery.[145]

Plaque thickness ≥ 4 mm in the ascending aorta or aortic arch visualized by TEE is strongly correlated with cerebral embolization events.[146-148] Complex atheroma visualized by TEE has also been seen in patients with biopsy-proven cholesterol emboli to the kidneys and skin.[149,150] Three-dimensional TEE may provide incremental diagnostic information on aortic plaques (Figure 31 and Videos 32-34).

CT and MRI may also be used to visualize atherosclerotic plaques in the aorta.[151,152] Certain shortcomings of TEE (such as an inability to visualize the abdominal aorta or the arch because of a blind area created by air in the trachea interposed between the arch and esophagus) can be overcome by CT or MRI. Aortography lacks sensitivity for detection of plaques in the aorta.[153]

Recommendations for Echocardiographic Evaluation of Aortic Sources of Embolism

Echocardiography Recommended

- TEE is the preferred echocardiographic method for the evaluation of aortic sources of emboli.

Echocardiography Potentially Useful

- Aortic plaque may occasionally be seen on TTE. However, TTE has low sensitivity for the detection of aortic pathology, including aortic plaques, compared with TEE.

Echocardiography Not Recommended

- Echocardiography is not recommended in patients for whom the results will not guide therapeutic decisions

PARADOXICAL EMBOLISM

Paradoxical embolism occurs when there is embolic transit from the systemic venous circulation to the systemic arterial circulation through a right-to-left shunt, such as a PFO and atrial septal defect (ASD). A PFO is failure of the septum primum and septum secundum to fuse postpartum. The anatomy and physiology of PFO is provided in detail in a dedicated guidelines document.[154]

A PFO is an integral part of normal fetal circulation (Figure 32). It acts as a conduit for intrauterine blood flow, which allows oxygenated blood as the via sinistra leaving the umbilical vein through the ductus venosus to reach the foramen ovale, left ventricle and aorta, thus feeding the coronary and cerebral circuits.[155] Cardiac output and blood flow distribution in human fetal life demonstrate right-heart dominance. At midgestation, approximately 60% to 65% of blood is ejected by the right ventricle and 35% to 40% is ejected by the left ventricle. However, there is controversy whether this changes with increasing gestational age.[156]

A PFO is formed at the overlap of the septum secundum and the superior apical remnant of the septum primum. As has been well described, the septum primum forms early in intrauterine growth from the roof of the atrium and grows toward the endocardial cushions. After the septum primum fuses with the endocardial cushions, a series of fenestrations develop in the superior portion, creating the ostium secundum. The septum secundum forms from an invagination of the atrial wall later in gestation to the right of the superior remnants on the septum primum. The foramen ovale is the gap or tunnel between the inferior edge of the septum secundum and the superior edge of the septum primum.

Systemic vascular resistance that is low in utero because of the low-resistance placental circuit increases with birth and cord clamping.[157] This increase in afterload dramatically increases LV diastolic pressure and therefore LA pressure. This results in increased pulmonary venous return to the left atrium and decreased thoracic compliance that produce functional closure of the foramen ovale, typically within minutes after birth. Anatomic closure of the foramen ovale generally occurs by 9 to 30 months but may take longer.[158,159]

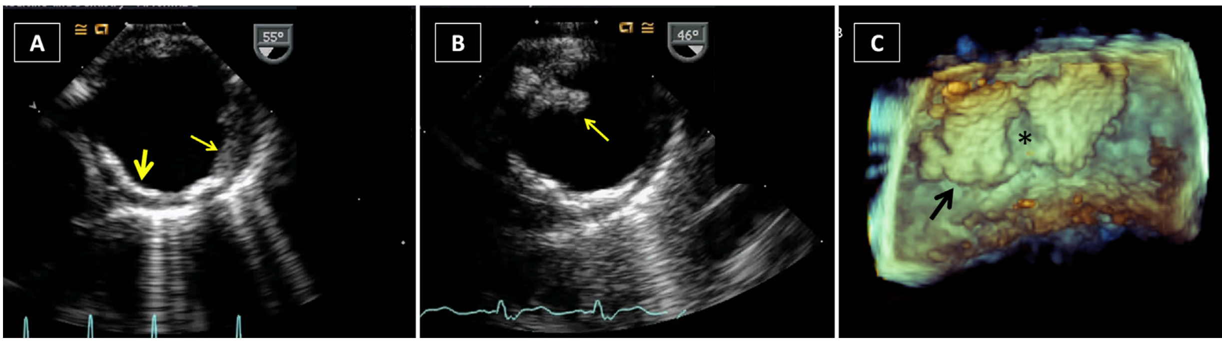

Figure 31 Aortic atheroma. **(A)** Upper esophageal 2D transesophageal echocardiographic view demonstrates severe nonmobile plaque (*thin arrow*) in the aortic arch that is partly calcified (*thick arrow*). Video 32 corresponds to **(A)**. **(B)** Upper esophageal 2D transesophageal echocardiographic view shows a mobile plaque (*arrow*) in the aortic arch; the mobile component represents an overlying thrombus. Video 33 corresponds to **(B)**. **(C)** Three-dimensional TEE reveals an en face view of a complex plaque (*arrow*) in the aortic arch with a large central ulceration (*asterisk*). Video 34 corresponds to **(C)**.

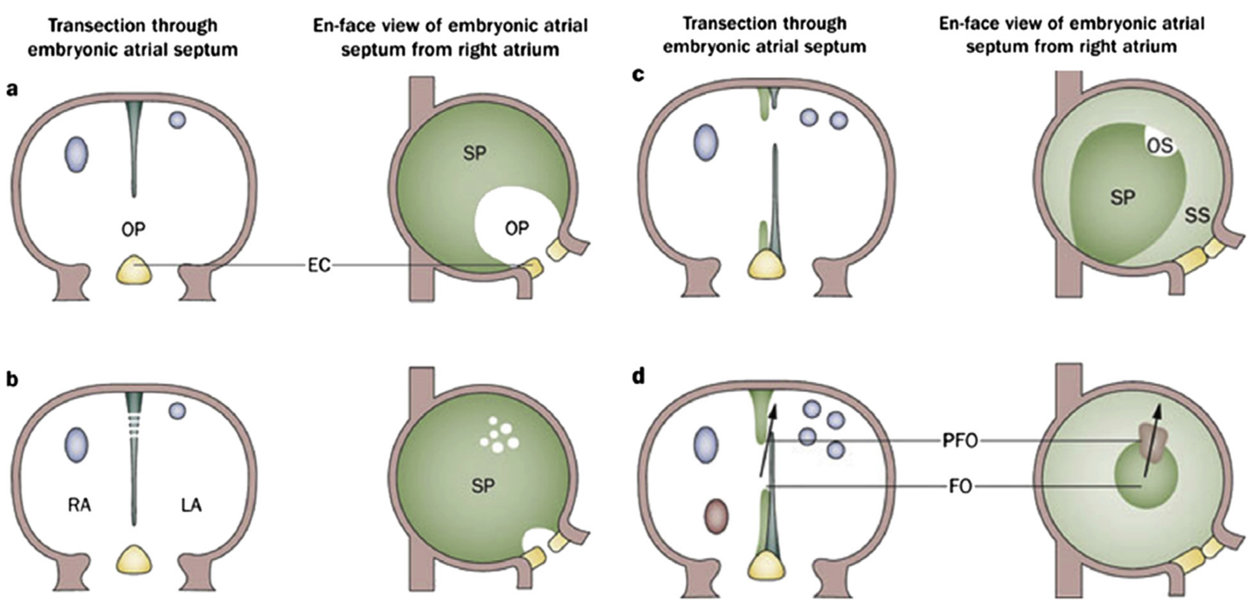

Figure 32 Embryology of atrial septum and PFO. **(A)** The septum primum grows from the roof of the atria. **(B)** Fenestrations develop within the septum primum. **(C)** The septum secundum develops by an in-folding of the atrial walls. The ostium secundum acts as a conduit for right-to-left shunting of oxygenated blood. **(D)** At the anterior superior edge of the fossa ovalis, the primum and secundum septa remain unfused, which constitutes a PFO. Arrow denotes blood flowing through the PFO from the embryonic right atrium to the left atrium. The *blue* and *pink dots* represent the development of the caval and pulmonary venous inflow to the atria. *EC*, Endocardial cushion; *FO*, fossa ovalis; *OP*, ostium primum; *OS*, ostium secundum; *SP*, septum primum; *SS*, septum secundum. Reproduced with permission from Calvert *et al*.[229] and the 2015 ASE guidelines for the echocardiographic assessment of ASD and PFO.[154]

A postmortem series of 965 patients showed that the prevalence of PFO decreased with age, from 34.3% in the group aged 0 to 30 years to 20.2% in the group aged 80 to 99 years.[160] Thus, the finding of a PFO should be considered a normal variant rather than a pathologic finding.

Typically, the PFO is closed because of the gradient between the left and right atria, and no left-to-right shunting is seen. Under certain hemodynamic conditions, when there is a transient pressure gradient from the right to left atrium such as elevated right atrial pressure seen with acute or chronic pulmonary hypertension or with a Valsalva maneuver, a right-to-left shunt can be seen.

The anatomy of PFOs is highly variable and can range from a tunnel valve with tightly opposed septa to a “wide-open PFO” due to a ridge on the LA side with resultant continuous left-to-right shunt. The presence of an atrial septal aneurysm (ASA) increases the likelihood of finding a PFO compared with the general population. An ASA is diagnosed if there is a fixed displacement or a mobile excursion of the fossa ovalis region of the primum atrial septum toward the right or left atria or a combined total excursion right and left of ≥15 mm from the midline.[154,161-164]

The mobile aneurysmal segment lies within the septum primum and can cause retraction of the septum primum, resulting in a large interatrial shunt. It is thought that an ASA may act like a net, capturing thrombi or debris and conveying them to the PFO. When present, a Eustachian valve, which is an embryological remnant of the inferior vena cava valve and the right valve of the sinus venosus, directs flow of blood from inferior vena cava toward the right atrial aspect of the PFO.

Although a PFO is present in approximately 25% of the general population, in some studies it was found in up to 40% of younger patients with cryptogenic stroke.[161,162,165-171]

A cryptogenic stroke is defined as a stroke of unknown etiology, despite extensive evaluation. Although a PFO is often implicated as a culprit in cryptogenic stroke, a clear-cut association is not often found. Given the frequent occurrence of PFO in the population, clinicians often assume that the PFO is the underlying etiology, though it may be an incidental finding. There may be a higher risk for stroke when PFO is associated with an ASA. It is felt that a PFO in combination with ASA behaves similar to atrial fibrillation with LA dysfunction, which promotes the milieu for thrombus formation.[172,173]

This phenomenon might be augmented in patients with procoagulation tendencies. However, this may just be the hallmark of PFOs capable of opening widely. A strong association between PFOs and ischemic stroke is noted in patients of all ages.[162,170] However, not all studies support the association between cryptogenic stroke and PFO. Despite circumstantial evidence, prospective studies have failed to demonstrate causality between recurrent stroke, the presence of PFO or ASA, or the size of right-to-left shunt.[174-177]

Role of Echocardiography in Evaluation of Suspected Paradoxical Embolism

To assess for the role of PFO in cryptogenic stroke, the presence of a right-to-left shunt needs to be established. If routine color Doppler imaging fails to detect a shunt across a PFO, this can be further assessed by lowering the Nyquist limit (caution is to be exercised so as not to decrease it too low) or performing an agitated saline contrast study. Agitated saline contrast is injected intravenously, as stated in previous ASE guidelines.[9] The injections should be performed at rest and with certain provocative maneuvers to increase the right atrial pressure, such as cough and the Valsalva maneuver. It is important to identify deviation of the interatrial septum to the LA side, confirming elevated right atrial pressure. The presence of PFO is presumed when agitated saline contrast is noted in the left atrium within three cardiac cycles after complete opacification of the right atrium (Figure 33 and Video 35).

If the agitated saline contrast is noted after five cardiac cycles after complete opacification of the right atrium, pulmonary arteriovenous malformations (AVMs) must be considered.[166,178] However, it is important to note that timing of contrast appearance is used as a rough guide and is not the most reliable discriminator of the location of shunting. Patients with tunnel PFOs, low right atrial pressure, and delayed coughing and Valsalva maneuvers may result in delayed appearance of contrast. Similarly, in patients with significant pulmonary AVMs resulting in high-output states, early appearance of contrast may be seen. The best discriminator to accurately predict the location of shunting is direct visualization of the shunt. A PFO can be held closed if persistent interatrial bowing is noted toward the right atrium, which can result in a false-negative finding. If suspicion for a PFO still exists after an adequate contrast study is performed, a repeat injection using a blood-saline-air mixture, a more appropriately timed Valsalva or cough maneuver, or TEE may be considered.[9]

It is important to perform the agitated saline contrast study with precision. An adequate number of beats needs to be captured to evaluate for the presence of PFO. The agitated saline contrast study may need to be repeated multiple times if necessary.

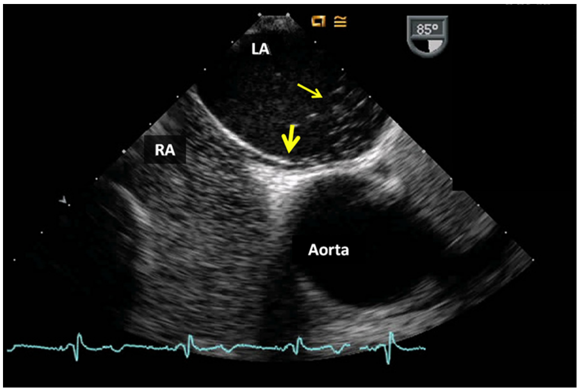

Figure 33 PFO visualization after intravenous injection of agitated saline. Two-dimensional TEE in midesophageal view at 85° demonstrates PFO (*thick arrow*) after intravenous administration of agitated saline. A large amount of saline bubbles (*thin arrow*) is seen in the left atrium, indicative of a right-to-left shunt. Video 35 corresponds to Figure 33.

Various classification schemes have been proposed to assess the sizes of shunts, though none have been universally accepted yet.[179]

However, >20 bubbles crossing the PFO from the right to left atrium is considered to be a large shunt. If the results of TTE are consistent with a right-to-left shunt, TEE is necessary to confirm the presence of the PFO and to exclude other shunts, such as secundum ASDs. Other shunts to exclude are pulmonary AVMs, primum ASDs, sinus and inferior venosus defects, and unroofed coronary sinus.

Given the highly variable anatomy of PFO, 3D TEE may be valuable to define the anatomy and evaluate for structural relationships (Figure 34). This has implications for successful therapeutic results if a closure device is ever considered.

The role of echocardiography in percutaneous or surgical closure of PFO is beyond the scope of this document; a detailed description on the role of echocardiography in such a setting can be found in separate PFO and ASD guidelines.[154]

Recommendations for Echocardiographic Evaluation of Suspected Paradoxical Embolism

Echocardiography Recommended

- TTE is recommended for the evaluation of a right-to-left shunt and atrial septal anatomy in a patient who presents with cryptogenic stroke, especially in the setting of elevated right atrial pressure with documented PE or deep venous thrombosis of lower extremities or pelvic veins.
- If the shunt could not be demonstrated by color Doppler, contrast echocardiography using intravenous injection of agitated saline should be performed at baseline and after provocative maneuvers (such as coughing or Valsalva maneuver).
- TEE may be performed if TTE fails to demonstrate a right-to-left shunt.

Echocardiography Potentially Useful

- Three-dimensional TEE may provide incremental value in assessing atrial septal anatomy.

Echocardiography Not Recommended

- Echocardiographic imaging to establish a right-to-left shunt is not recommended in patients (typically older ones) who have other probable causes of stroke or systemic embolism.

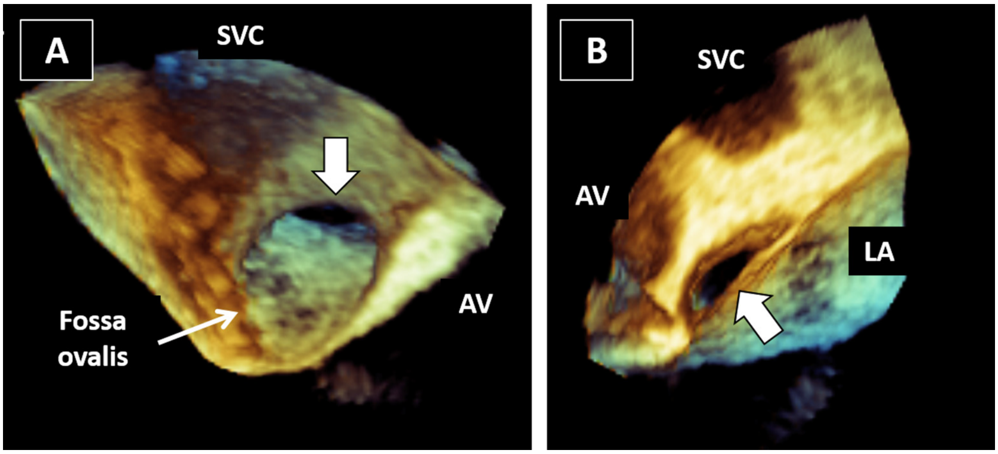

Figure 34 PFO on three-dimensional TEE. Three-dimensional TEE zoom view of a large PFO (*arrowhead*) seen from the right atrial side **(A)** and LA side **(B)**.

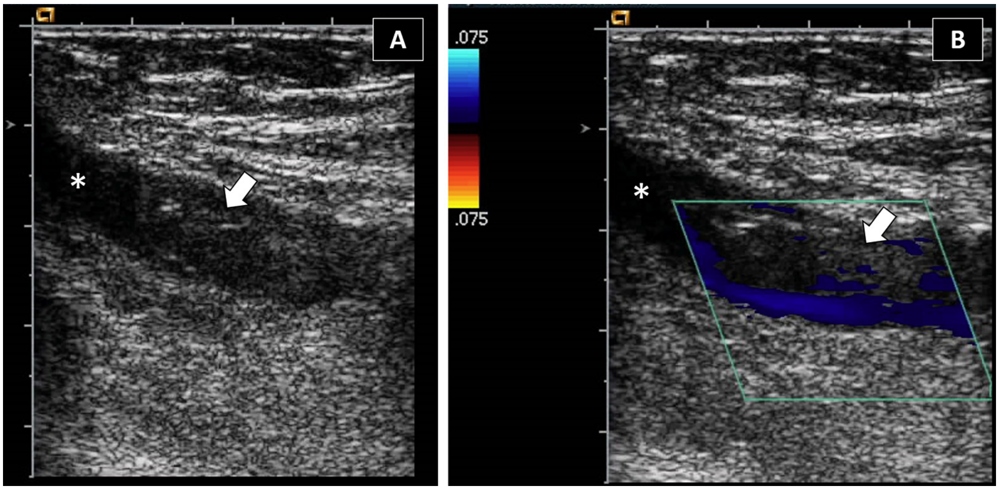

Figure 35 Deep vein thrombosis. Venous duplex ultrasound demonstrates a large thrombus (*arrow*) in the right femoral vein (*asterisk*) on B-mode imaging **(A)** and color Doppler **(B)**. Video 36 corresponds to **(A)**. Video 37 corresponds to **(B)**.

PULMONARY EMBOLISM

PE occurs in 250,000 patients annually, with significant morbidity and mortality, and poses an enormous health care burden.[180] The vast majority (90%–95%) of pulmonary emboli are a result of deep vein thrombosis, originating in the legs, with most involving the proximal (popliteal or more central) veins (Figure 35, and Videos 36 and 37).[181] Masses with mobile elements, endocarditis, thrombi attached to indwelling lines or leads, and thrombi or tumors originating anywhere in the right heart, such as the right atrium, right ventricle, tricuspid valve, pulmonary artery, or pulmonary valve, can also be a potential source of PE, though not as common as deep vein thrombosis as etiology for PE.[180,181]

PE is the third most common cause of vascular death after myocardial infarction and stroke and the leading preventable cause of death in hospital patients. Despite early diagnosis and treatment, clinical outcomes are quite variable, with mortality ranging widely.[182-185] About 10% or more of cases of symptomatic PE are thought to be rapidly fatal, and another 5% of patients die after starting treatment. About a third of patients are left with some residual symptoms, and 2% develop thromboembolic pulmonary hypertension due to unresolved PE.[186]

Distinction of high-risk from low-risk patients should be rapidly performed, so that further management strategies can be suitably tailored.[187-190] Echocardiography has been shown to be a good discriminator among the many prognostic markers that have been studied in this population.[191-195]

Role of Echocardiography in Evaluation of PE

Echocardiography is not a diagnostic modality of choice for the diagnosis of PE per se but is used for patient risk stratification. Both TTE and TEE provide noninvasive assessment of RV and LV size, systolic function, regional wall motion, valvular abnormalities, and hemodynamic assessment of filling pressure and right-heart pressures. Thrombi in transit are rare to see, and the appearance is typically that of a serpentine thrombus traversing the right-heart chambers (Figure 36, and Videos 38 and 39).

The typical echocardiographic pattern of hemodynamically significant PE (Figure 37, and Videos 40 and 41) shows the following features[196]:

- RV strain (RV dilatation and dysfunction)
- Interventricular septum bulging into the left ventricle
- Dilated proximal pulmonary arteries

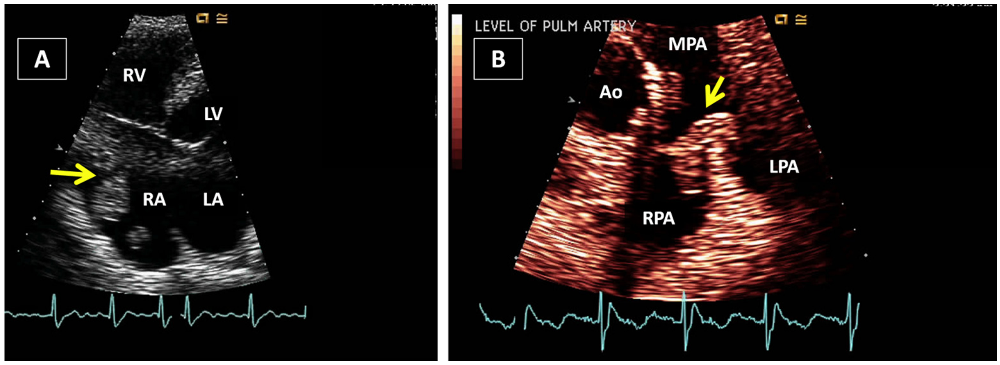

Figure 36 Clot in transit: right atrial and pulmonary artery (PA) level. **(A)** Two-dimensional transthoracic echocardiographic image in an off-axis four-chamber view demonstrates a venous clot in transit (*arrow*) in the right atrium. Video 38 corresponds to **(A)**. **(B)** Two-dimensional TTE at the level of pulmonary artery shows a saddle embolus (*arrow*) at the bifurcation of the main PA (MPA) into the right PA (RPA) and left PA (LPA). *Ao*, Ascending aorta. Video 39 corresponds to **(B)**.

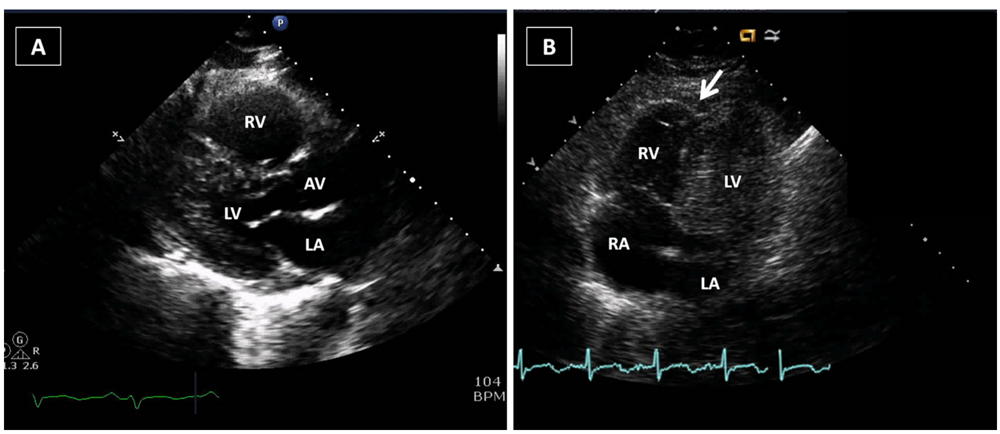

Figure 37 PE: TTE. **(A)** TTE in the parasternal long-axis view demonstrates a markedly dilated right ventricle (RV) in a patient with acute PE. Video 40 corresponds to **(A)**. **(B)** TTE in the apical four-chamber view demonstrates the McConnell sign (*arrow*). Video 41 corresponds to **(B)**.

- Elevated RV systolic pressure
- Increased tricuspid regurgitation jet severity
- Elevated right atrial pressure as evidenced by plethora of inferior vena cava with no inspiratory collapse
- McConnell sign (hypokinesis of the basal and mid RV free wall, with preserved contractility of apex)
- Rarely, visualization of thrombi in transit from systemic veins to pulmonary arteries

RV dilatation is defined by an RV/LV ratio > 1:1 as well as other criteria discussed in the guidelines on chamber quantification.[50] The presence of RV strain in patients with PE is prognostically important and associated with significantly higher in-hospital mortality, as well as being one of the best predictors of poor early outcome.[197-199]

TTE is not sufficiently sensitive to rule out PE.[5] Imaging modalities other than echocardiography, such as computed tomographic angiography (Figure 38), should be used to diagnose PE.[200] A PE presenting with hypotension is called massive PE. In patients with nonmassive PEs, either focused or comprehensive TTE can be used to risk-stratify patients into two groups: submassive PE (patients with no hypotension but with RV strain or myocardial necrosis) and low risk (patients with no hypotension nor RV strain).[201-204]

There is certainly a role for focused cardiac ultrasound in the emergency department in patients with suspected PE to prioritize further testing, alter differential diagnosis assessments, and assist with treatment decisions in the severely compromised patient.[205] However, it should be noted that an increased RV/LV ratio is not specific for PE and that acute and chronic RV abnormalities may exist in patients with chronic obstructive pulmonary disease, obstructive sleep apnea, pulmonary hypertension, right-heart failure, and right-sided myocardial infarction, among others.[206]

Recommendations for Echocardiography in Patients with Suspected PE

Echocardiography Recommended

- TTE is recommended for risk stratification in patients with PE (primarily for assessment of RV size and function).
- TEE may be considered in acutely ill, unstable patients in whom hemodynamically significant PE is suspected.

Echocardiography Not Recommended

- Echocardiography is not recommended as a primary means of diagnosing PE.

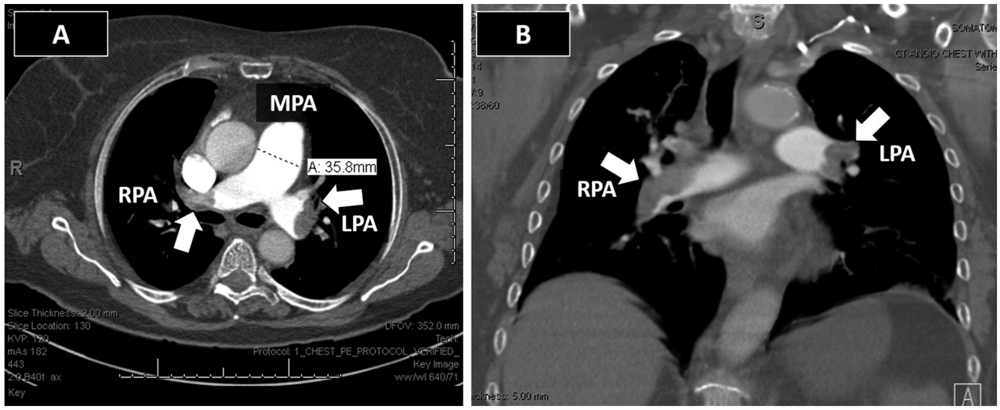

Figure 38 PE: CT. Contrast-enhanced CT of the chest demonstrates multiple bilateral pulmonary emboli (*arrows*) in axial **(A)** and coronal view **(B)**.

CARDIAC AND AORTIC EMBOLISM DURING CARDIAC SURGERY AND PERCUTANEOUS INTERVENTIONS

Embolism from the heart and blood vessels is a rare complication of cardiac surgery and percutaneous interventions. Before the widespread use of arterial cannulation for angiographic imaging and intervention, the reported incidence of spontaneous embolism from the aorta, on the basis of autopsy studies, ranged from <1% to 3.4%.[207-209]

Cardiac Catheterization

Embolism is a rare complication of cardiac catheterization, although debris was isolated from >50% of guiding catheters in one series.[210] The reported incidence of clinically apparent embolism during cardiac catheterization is in the range of 1.4% to 1.9%. Because there is no significant difference in embolic risk between femoral and radial access, the ascending aorta is likely the main source of emboli.[211] CES is a rare complication of cardiac catheterization.

Cardiac Surgery

The risk for embolism from the aorta during cardiac surgery is strongly correlated with the degree of atherosclerosis in the ascending aorta. The brain is the most common destination of such emboli, although emboli to multiple peripheral organs have also been reported. Surgical coronary revascularization may have a higher risk for embolism from the aorta compared with surgical valve repair or replacement.[212] In an autopsy study of 221 patients with a mean age of 66 years (58.8% men) who had undergone myocardial revascularization or valve operations between 1982 and 1989, cholesterol embolization was seen in 48 patients (21.7% of the autopsy series), while thromboemboli were noted in 14 of them (6.3%). Cholesterol embolization was three times more common in patients undergoing coronary revascularization surgery (43 of 165 patients [26.1%]) compared with those undergoing valve surgery (five of 56 patients [8.9%]). The risk for cholesterol embolization after cardiac surgery was strongly related to the degree of atherosclerosis in the ascending aorta and the patients' age. In another study, the brain was the most common destination site of cholesterol emboli (eight of 48 patients), followed by the spleen (five patients), kidneys (five patients), and pancreas (three patients). Thirty of the 48 autopsied patients had multiple atheroembolic sites.[212]

The 2007 guidelines for the performance of a comprehensive intraoperative epiaortic ultrasonographic examination by the ASE and allied societies details the role of ultrasound imaging in embolism detection and prevention during cardiac surgery. In surgical patients, transesophageal echocardiographic evidence of atheroma burden warrants an epiaortic examination to confirm level of atherosclerosis in the ascending aorta before surgical manipulation.[213]

Percutaneous Interventions

Percutaneous wires, catheters, and other devices may dislodge preexisting intracardiac and intra-aortic masses to cause systemic embolism. Because TEE is typically used to guide many percutaneous procedures, the presence of a mass that has a potential for embolization should be excluded. For instance, intracardiac thrombus, especially LAA thrombus, should be excluded during any intracardiac percutaneous intervention, such as percutaneous mitral balloon valvuloplasty, paravalvular leak closure, or percutaneous closure of the LAA.

Periprocedural stroke and systemic embolism may also be observed during TAVR. In a randomized trial, strokes were reported in 1.5% to 6% of patients treated with TAVR. There was an increased risk for 30-day strokes (minor and major strokes and TIAs) with TAVR compared with surgical aortic valve replacement (5.5% vs 2.4%, $P = .04$).[214] Further discussion on the use of echocardiography in transcatheter intervention for valvular heart disease can be found in a separate guidelines document.[215]

Recommendations for Echocardiography in Patients Referred for Cardiac Surgery or Percutaneous Intervention

Echocardiography Recommended

- TEE or intracardiac echocardiography is recommended in all patients before intracardiac percutaneous intervention to exclude potential cardiac sources of emboli that might be dislodged during intervention.
- The routine preoperative use of TEE to identify and manage aortic atheromatous disease is recommended in patients with increased risk for embolic stroke, including those with histories of cerebrovascular or peripheral vascular disease and those with evidence of aortic atherosclerosis or calcification by other imaging modalities, including preoperative or intraoperative MRI, CT, or chest radiography. TEE may allow the surgeon to individualize the surgical technique and potentially reduce the incidence of embolic stroke.

STROKE IN THE PEDIATRIC POPULATION

Stroke is rare in young adults (<50 years of age) and even less common in the pediatric population. Studies have shown that the annual incidence of stroke in young adults ranges from 10 to 23 cases per 100,000 persons per year.[216,217] In children, after excluding stroke due to perinatal trauma, the incidence is lower at about two or three cases per 100,000 persons per year.[218] Of these cases, 24% to 57% are thought to have embolic causes.[219] Embolic stroke in children can be due to hypercoagulable conditions or paradoxical embolus due to intracardiac or intravascular shunt. As in adults, strokes in pediatric patients may also be due to left-heart lesions with embolic potential, such as vegetations, tumors, and thrombi.

Many diseases predispose to hypercoagulability in children. Among the most common is sickle-cell disease, which has a 220 times higher annual incidence of stroke than the normal population.[220] Others include protein C deficiency, homocysteinuria, thrombotic thrombocytopenia purpura, and hyperlipidemia.

Certain congenital heart defects with intracardiac or intravascular shunt lesions predispose children to embolic stroke. Paradoxical embolism is discussed elsewhere in these guidelines, so the focus here is on the anatomic factors predisposing to embolic stroke in children. Among these, ASD and PFO receive the most attention.

PFO is generally accepted to be present in about 25% of the adult population and is typically more common in the pediatric population. ASD is one of the most common congenital heart defects (Figure 39 and Video 42). Myriad studies have evaluated the role of PFO closure for secondary prevention of stroke after a previous ischemic cerebral event. However, there is no consensus on whether to close a PFO if one is found or to use medical therapy.[162,221,222] Although device closure of PFOs is typically safe and feasible in children,[223] one study showed increased risk for complications from ASD device closure in small children (<15 kg).[224]

Many other congenital heart or vascular defects predispose patients to a pulmonary-to-systemic, or right-to-left, shunt. Additionally, the presence of pulmonary hypertension in unrepaired congenital heart defects such as ASD and ventricular septal defect increase the likelihood of right-to-left shunt.

Patients with cyanotic heart disease often have erythrocytosis and in severe cases have hypercoagulability. Surgically repaired single-ventricle patients with Fontan circulation often have creation of a fenestration between the systemic venous conduit to the pulmonary arteries (the Fontan conduit) and the atrium, serving as a pressure-release “pop-off” to promote forward flow in the conduit, but also allowing right-to-left shunting of blood. These patients have increased incidence of stroke.[225]

Pulmonary AVM is a connection between the pulmonary artery and pulmonary vein, which allows bypass of circulation through the lung. This not only causes cyanosis but also can serve as a pathway for paradoxical embolus, and case reports exist of pulmonary AVM being cited as a probable cause of embolic stroke.[226,227] Another rare congenital vascular abnormality known in case reports to cause embolic stroke is persistent left superior vena cava draining to the left atrium.[228]

Role of Echocardiography in Evaluation of Systemic Embolism in Pediatric Patients

Echocardiographic imaging of pediatric patients is typically accomplished by 2D transthoracic study. Fortunately, children often have excellent transthoracic imaging windows, and TEE is rarely needed for diagnostic purposes. Three-dimensional imaging, while gaining popularity, has not found mainstream use in pediatric echocardiography laboratories for the diagnosis of congenital heart defects. Rather, 3D imaging has become helpful in providing alternative views of pathology for surgical or interventional planning.

It is often difficult for echocardiographers not accustomed to performing echocardiography on children to fully diagnose congenital heart defects, and therefore it is usually preferable when a defect is suspected for the patient to undergo TTE at a pediatric-specific laboratory.

Saline contrast bubble studies have an important role in diagnosing potential pathways of paradoxical emboli in cases in which standard imaging with color Doppler is inadequate (Figure 40 and Video 43). Although the technique for bubble study is described elsewhere in these guidelines, a few considerations for the pediatric population must be made:

1. Often young children cannot follow instructions for the Valsalva maneuver, so an alternative is to press on the liver while injecting agitated saline.
2. To detect pulmonary AVM by bubble study, one must be able to distinguish the atrial septum from the entrance of the pulmonary veins, which is where the entrance of bubbles would be seen in a positive study for AVM. In children this can often be accomplished by imaging from the subcostal long-axis view, focusing on the left atrium, or in the suprasternal notch “crab view,” which shows the origins of each of the pulmonary veins. Note that the suprasternal notch view should be used after ruling out atrial-level shunt from other views.
3. Persistent left superior vena cava draining to the left atrium would only be detected by bubble study where agitated saline is injected into the left arm.

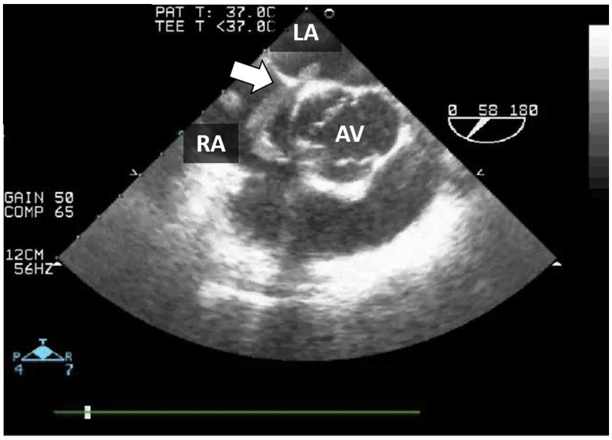

Figure 39 Pediatric TEE: paradoxical thromboembolism. A pediatric midesophageal 2D transesophageal echocardiographic short-axis aortic valve view demonstrates paradoxical thromboembolism (*arrow*) through a PFO. Video 42 corresponds to Figure 39.

Recommendations for Echocardiography in Pediatric Patients with Suspected Systemic Embolism

Echocardiography Recommended

- TTE is recommended in all children in whom embolic stroke is suspected.
- Agitated saline contrast bubble study may be necessary to determine right-to-left shunt pathway.
- Echocardiographic imaging in children with suspected cardiac source of embolism should be performed at a pediatric laboratory.

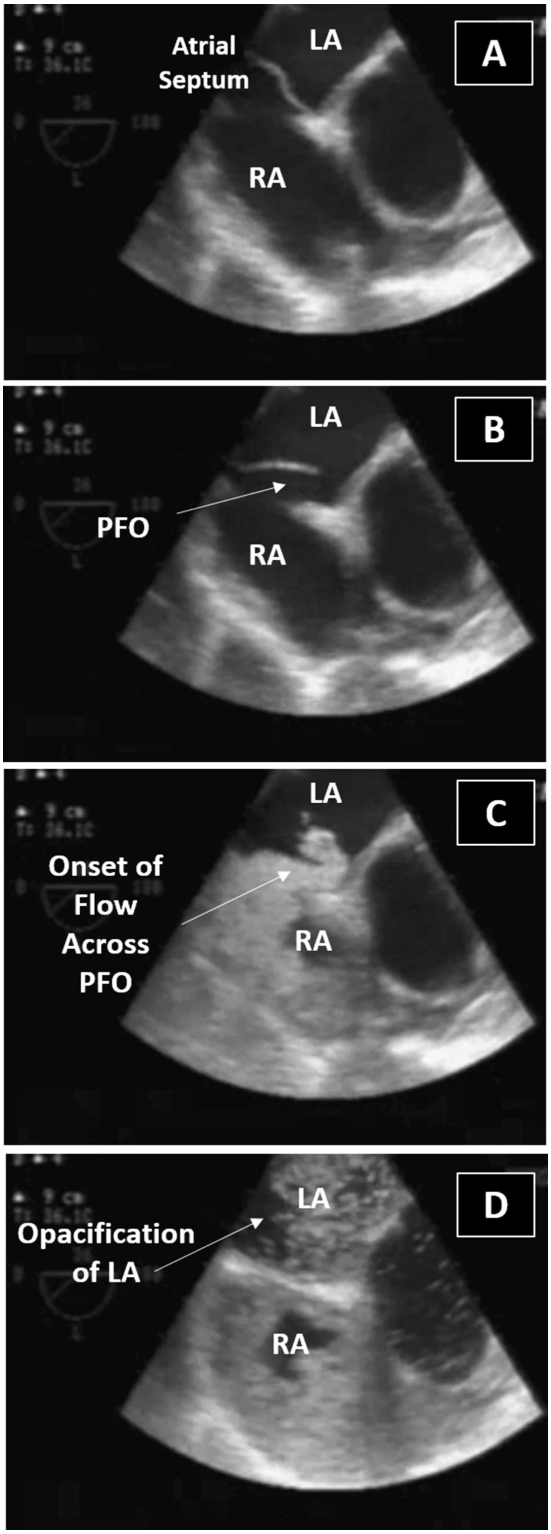

Figure 40 Pediatric TEE: PFO on saline contrast imaging. A pediatric midesophageal 2D TEE demonstrates the temporal progression **(A–D)** of agitated saline contrast passage from the right atrium into the left atrium in a pediatric patient with a PFO and a large left-to-right shunt. Video 43 corresponds to Figure 40.

Echocardiography Potentially Useful

- TEE for evaluation of embolic stroke should be rare in children and is recommended only when TTE windows are poor.

NOTICE AND DISCLAIMER

REVIEWERS

This document was reviewed by members of the 2014-2015 ASE Guidelines & Standards Committee and the 2014-2015 ASE Board of Directors. Guidelines Committee reviewers included Federico Asch, MD, FASE, Piers C. A. Barker, MD, FASE, Merri L. Bremer, EdD, RN, RDCS, ACS, FASE, Patrick Collier, MD, PhD, FASE, Mary Corretti, MD, FASE, Adam Dorfman, MD, FASE, Fadia Makarem Ezzeddine, RT, RCS, FASE, Carrie Ferguson, RDCS, FASE, John W. Fornace, DO, FASE, Lanqi Hua, RDCS, FASE, Thomas Johnson, MD, FASE, Allan L. Klein, MD, FASE, Tasneem Naqvi, MD, FASE, Patricia M. Restrepo, Vandana Sachdev, MD, FASE, Anita Sadeghpour, MD, FASE, Elaine A. Shea, APS, RCCS, FASE, Roman M. Sniecinski, MD, FASE, Steven Walling, RCS, RDCS, FASE.

Board of Directors reviewers included Benjamin F. Byrd III, MD, FASE, Hollie D. Carron, RDCS, FASE, Meryl S. Cohen, MD, FASE, Benjamin W. Eidem, MD, FASE, David H. Forst, MD, FASE, Kathryn E. Glas, MD, FASE, Aasha S. Gopal, MD, FASE, Kenneth D. Horton, RCS, FASE, Allan L. Klein, MD, FASE, Joe R. Kreeger, ACS, RCCS, RDCS, FASE, Leo Lopez, MD, FASE, Sunil Mankad, MD, FASE, Elizabeth F. McIlwain, MHS, RCS, FASE, Sherif F. Nagueh, MD, FASE, Tasneem Z. Naqvi, MD, FASE, Richard A. Palma, RDCS, RCS, APS, FASE, Andy Pellett, PhD, RCS, RDCS, FASE, Sue D. Phillip, RCS, FASE, Juan Carlos Plana, MD, FASE, Madhav Swaminathan, MD, FASE, Matt M. Umland, RDCS, FASE, Neil J. Weissman, MD, FASE, Susan E. Wiegers, MD, FASE.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.echo.2015.09.011.

REFERENCES

1. Centers for Disease Control and Prevention. Stroke facts. Available at: http://www.cdc.gov/stroke/facts.htm. Accessed October 28, 2015.
2. Adams HP Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.

3. Strandberg M, Marttila RJ, Helenius H, Hartiala J. Transoesophageal echocardiography in selecting patients for anticoagulation after ischaemic stroke or transient ischaemic attack. J Neurol Neurosurg Psychiatry 2002;73:29-33.
4. American Heart Association & American Stroke Association. Cryptogenic stroke initiative. Available at: http://www.strokeassociation.org/STROKEORG/AboutStroke/TypesofStroke/CryptogenicStrokesofUnknownCause/Cryptogenic-Stroke-Initiative_UCM_471631_Article.jsp#.VjD9L7erR9M. Accessed October 28, 2015.
5. Douglas PS, Garcia MJ, Haines DE, Lai WW, Manning WJ, Patel AR, et al. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 Appropriate Use Criteria for Echocardiography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance American College of Chest Physicians. J Am Soc Echocardiogr 2011;24:229-67.
6. Pepi M, Evangelista A, Nihoyannopoulos P, Flachskampf FA, Athanassopoulos G, Colonna P, et al. Recommendations for Echocardiography in the Diagnosis and Management of Cardiac Sources of Embolism. Eur J Echocardiogr 2010;11:461-76.
7. Ustrell X, Pellisé A. Cardiac Workup of Ischemic Stroke. Current Cardiology Reviews 2010;6:175-83.
8. Lang RM, Badano LP, Tsang W, Adams DH, Agricola E, Buck T, et al. EAE/ASE Recommendations for Image Acquisition and Display Using Three-Dimensional Echocardiography. J Am Soc Echocardiography 2012;25:3-46.
9. Porter TR, Abdelmoneim S, Belcik JT, McCulloch ML, Mulvagh SL, Olson JJ, et al. Guidelines for the Cardiac Sonographer in the Performance of Contrast Echocardiography: A focused update from the American Society of Echocardiography. J Am Soc Echocardiogr 2014;27:797-810.
10. Bavalia N, Anis A, Benz M, Maldjian P, Bolanowski PJ, Saric M. Esophageal perforation, the most feared complication of TEE: Early recognition by multimodality imaging. Echocardiography 2011;28:E56-9.
11. Hahn RT, Abraham T, Adams MS, Bruce CJ, Glas KE, Lang RM, et al. Guidelines for performing a comprehensive transesophageal echocardiographic examination: recommendations from the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. J Am Soc Echocardiogr 2013;26:921-64.
12. McNamara RL, Lima JA, Whelton PK, Powe NR. Echocardiographic identification of cardiovascular sources of emboli to guide clinical management of stroke: A cost-effectiveness analysis. Ann Intern Med 1997;127:775-87.
13. Meenan RT, Saha S, Chou R, Swarztrauber K, Pyle Krages K, O'Keeffe-Rosetti MC, et al. Cost-effectiveness of echocardiography to identify intracardiac thrombus among patients with fi rst stroke or transient ischemic attack. Med Decis Making 2007;27:161-77.
14. de Bruijn SF, Agema WR, Lammers GJ, van der Wall EE, Wolterbeek R, Holman ER, et al. Transesophageal echocardiography is superior to transthoracic echocardiography in management of patients of any age with transient ischemic attack or stroke. Stroke 2006;37:2531-4.
15. Ulrich JN, Hesse B, Schuele S, Vlassak I, Sila CA, Jaber WA. Single-vessel versus multivessel territory acute ischemic stroke: Value of transesophageal echocardiography in the differentiation of embolic stroke. J Am Soc Echocardiogr 2006;19:1165-9.
16. De Abreu TT, Mateus S, Correia J. Therapy implications of transthoracic echocar-diography in acute ischemic stroke patients. Stroke 2005;36:1565-6.
17. 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.
18. Warner MF, Momah KI. Routine transesophageal echocardiography for cerebral ischemia. Is it really necessary? Arch Intern Med 1996;156:1719-23.
19. Wolber T, Maeder M, Atefy R, Bluzaite I, Blank R, Rickli H, et al. Should routine echocardiography be performed in all patients with stroke? J Stroke Cerebrovasc Dis 2007;16:1-7.
20. Reynolds HR, Jagen MA, Tunick PA, Kronzon I. Sensitivity of transthoracic versus transesophageal echocardiography for the detection of native valve vegetations in the modern era. J Am Soc Echocardiogr 2003;16:67-70.
21. Ha JW, Shin MS, Kang S, Pyun WB, Jang KJ, Byun KH, et al. Enhanced detection of right-to-left shunt through patent foramen ovale by transthoracic contrast echocardiography using harmonic imaging. Am J Cardiol 2001;87:669-71.
22. Schwammenthal E, Schwammenthal Y, Tanne D, Tenenbaum A, Garniek A, Motro M, et al. Transcutaneous detec-tion of aortic arch atheromas by suprasternal harmonic imaging. J Am Coll Cardiol 2002;39:1127-32.
23. Arboix A, Alió J. Acute cardioembolic stroke: an update. Expert Rev Cardiovasc Ther 2011;9:367-9.
24. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 1982;57:769-74.
25. Komar M, Olszowska M, Przewłocki T, Podolec J, Stępniewski J, Sobień B, et al. Transcranial Doppler ultrasonography should it be the first choice for persistent foramen ovale screening? Cardiovasc Ultrasound 2014;12:16.
26. Serena J, Jiménez-Nieto M, Silva Y, Castellanos M. Patent foramen ovale in cerebral infarction. Current Cardiol Rev 2010;6:162-74.
27. Mojadidi MK, Roberts SC, Winoker JS, Romero J, Goodman-Meza D, Gevorgyan R, et al. Accuracy of transcranial Doppler for the diagnosis of intracardiac right-to-left shunt: a bivariate meta-analysis of prospective studies. JACC Cardiovasc Imaging 2014;7:236-50.
28. Jin KN, Chun EJ, Choi SI, Ko SM, Han MK, Bae HJ, et al. Cardioembolic origin in patients with embolic stroke: spectrum of imaging findings on cardiac MDCT. AJR Am J Roentgenol 2010;195:W38-44.
29. Veinot JP, Harrity PJ, Gentile F, Khandheria BK, Bailey KR, Eickholt JT, et al. Anatomy of the normal left atrial appendage: a quantitative study of age-related changes in 500 autopsy hearts: implications for echocardiographic examination. Circulation 1997;96:3112-5.
30. Di Biase L, Santangeli P, Anselmino M, Mohanty P, Salvetti I, Gili S, et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. J Am Coll Cardiol 2012;60(6):531-8.
31. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285:2370-5.
32. Lowe BS, Kusunose K, Motoki H, Varr B, Shrestha K, Whitman C, et al. Prognostic significance of left atrial appendage "sludge" in patients with atrial fibrillation: a new transesophageal echocardiographic thromboembolic risk factor. J Am Soc Echocardiogr 2014;27:1176-83.
33. Hajjiri M, Bernstein S, Saric M, Benenstein R, Aizer A, Dym G, et al. Atrial fibrillation ablation in patients with known sludge in the left atrial appendage. J Interv Card Electrophysiol 2014;40:147-51.
34. Masawa N, Yoshida Y, Yamada T, Joshita T, Ooneda G. Diagnosis of cardiac thrombosis in patients with atrial fibrillation in the absence of macroscopically visible thrombi. Virchows Arch A Pathol Anat Histopathol 1993;422:67-71.
35. Tziakas DN, Chalikias GK, Papanas N, Stakos DA, Chatzikyriakou SV, Maltezos E. Circulating levels of collagen type I degradation marker depend on the type of atrial fibrillation. Europace 2007;9:589-96.
36. Pollock C, Taylor D. Assessment of left atrial appendage function by transesophageal echocardiography. Implications for the development of thrombus. Circulation 1991;84:223-31.

37. Grimm RA, Stewart WJ, Maloney JD, Cohen GI, Pearce GL, Salcedo EE, et al. Impact of electrical cardioversion for atrial fibrillation on left atrial appendage function and spontaneous echo contrast: characterization by simultaneous transesophageal echocardiography. J Am Coll Cardiol 1993;22:1359-66.
38. Fatkin D, Kuchar DL, Thorburn CW, Feneley MP. Transesophageal echocardiography before and during direct current cardioversion of atrial fibrillation: evidence for "atrial stunning" as a mechanism of thromboembolic complications. J Am Coll Cardiol 1994;23:307-16.
39. Lown B, Perlroth MG, Kaidbey S, Abe T, Harken DE. Cardioversion of atrial fibrillation. A report on the treatment of 65 episodes in 50 patients. N Eng J Med 1963;269:325-31.
40. Lown B. Electrical reversion of cardiac arrhythmias. Br Heart J 1967;29: 469-89.
41. Grimm RA, Stewart WJ, Black IW, Thomas JD, Klein AL. Should all patients undergo transesophageal echocardiography before electrical cardioversion of atrial fibrillation? J Am Coll Cardiol 1994;23:533-41.
42. Black IW, Fatkin D, Sagar KB, Khandheria BK, Leung DY, Galloway JM, et al. Exclusion of atrial thrombus by transesophageal echocardiography does not preclude embolism after cardioversion of atrial fibrillation: A multicenter study. Circulation 1994;89:2509-13.
43. Kahn SR, Solymoss S, Flegel KM. Nonvalvular atrial fibrillation evidence for a prothrombotic state. CMAJ 1997;157:673-81.
44. Roldán V, Marín F, Marco P, Martínez JG, Calatayud R, Sogorb F. Hypofibrinolysis in atrial fibrillation. A Heart J 1998;136:956-60.
45. Tsai LM, Chen JH, Tsao CJ. Relation of left atrial spontaneous echo contrast with prethrombotic state in atrial fibrillation associated with systemic hypertension, idiopathic dilated cardiomyopathy, or no identifiable cause (lone). Am J Cardiol 1998;81:1249-52.
46. Nozawa T, Inoue H, Hirai T, Iwasa A, Okumura K, Lee JD, et al. D-dimer levels influences thrombotic events in patients with atrial fibrillation. Int J Cardiol 2006;109:59-65.
47. Heppel RM, B. K, McLenachan JM, Davies JA. Hemostatic and hemodynamic abnormalities associated with left atrial thrombosis in nonrheumatic atrial fibrillation. Heart 1997;77:407-11.
48. Choudhury A, C., Blann AD, Lip GY. Elevated platelet microparticle levels in nonvalvular atrial fibrillation; relationship to p-celecton and anti thrombotic therapy. Chest 2007;131:809-15.
49. Tsang TS, Abhayaratna WP, Barnes ME, Miyasaka Y, Gersh BJ, Bailey KR, et al. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? J Am Coll Cardiol 2006;47:1018-23.
50. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39.
51. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol 2011;57:e101-98.
52. Zabalgoitia M, Halperin JL, Pearce LA, Blackshear JL, Asinger RW, Hart RG, et al. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. Stroke Prevention in Atrial Fibrillation III Investigators. J Am Coll Cadriol 1998;31: 1622-6.
53. Klein AL, Grimm RA, Murray RD, et al., Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. N Engl J Med 2001;344:1411-20.
54. Munir S, Chang JH, Salahudeen SR, Baranchuk A, Morris C, O'Reilly M, et al. Atrial thrombi detection prior to pulmonary vein isolation: cardiac computed tomography versus transesophageal echocardiography. Cardiol J 2015; http://dx.doi.org/10.5603/CJ.a2015.0017 [Epub ahead of print].
55. Schmidt M, Daccarett M, Marschang H, Ritscher G, Turschner O, Brachmann J, et al. Intracardiac echocardiography improves procedural efficiency during cryoballoon ablation for atrial fibrillation: a pilot study. J Cardiovasc Electrophysiol 2010;21:1202-7.
56. Thomas L, Boyd A, Thomas SP, Schiller NB, Ross DL. Atrial structural remodeling and restoration of atrial contraction after linear ablation for atrial fibrillation. Eur Heart J 2003;24:1942-51.
57. Jongbloed MR, Bax JJ, Lamb HJ, Dirksen MS, Zeppenfeld K, van der Wall EE, et al. Multislice computed tomography versus intracardiac echocardiography to evaluate the pulmonary veins before radiofrequency catheter ablation of atrial fibrillation: A head-to-head comparison. J Am Coll Cardiol 2005;45:343-50.
58. To AC, Gabriel RS, Park M, Lowe BS, Curtin RJ, Sigurdsson G, et al. Role of Transesophageal Echocardiography Compared to Computed Tomography in Evaluation of Pulmonary Vein Ablation for Atrial Fibrillation (ROTEA study). J Am Soc Echocardiogr 2011;24:1046-55.
59. Asinger RW, Mikell FL, Elsperger J, Hodges M. Incidence of left –ventricular thrombosis after acute transmural infarction. Serial evaluation by two-dimensional echocardiography. N Engl J Med 1981;305:297-302.
60. Visser CA, Kan G, Lie KI, Durrer D. Left ventricular thrombus following acute myocardial infarction: A prospective echocardiographic study of 96 patients. Eur Heart J 1983;4:333-7.
61. Jugdutt BI, Sivaram CA. Prospective two-dimensional echocardiographic evaluation of left ventricular thromboembolism after acute myocardial infarction. J Am Coll Cardiol 1989;13:554-64.
62. Kalra A, Jang IK. Prevalence of early left ventricular thrombus after primary coronary intervention for acute myocardial infarction. J Thromb Thrombolysis 2000;10:133-6.
63. Nihoyannopoulos P, Smith GC, Maseri A, Foale RA. The natural history of left ventricular thrombus in myocardial infarction: a rationale support of masterly inactivity. J Am Coll Cardiol 1989;14:903-11.
64. Chiarella F, Santoro E, Domenicucci S, Maggioni A, Vecchio C. Predischarge two-dimensional echocardiographic evaluation of thrombosis after acute myocardial infarction in the GISSI-3 study. Am J Cardiol 1998; 81:822-7.
65. Solheim S, Seljeflot I, Lunde K, Bjørnerheim R, Aakhus S, Forfang K, et al. Frequency of left ventricular thrombus in patients with anterior wall acute myocardial infarction treated with percutaneous coronary intervention and dual antiplatelet therapy. Am J Cardiol 2010;106:1197-200.
66. Weinsaft JW, Kim HW, Shah DJ, Klem I, Crowley AL, Brosnan R, et al. Detection of left ventricular thrombus by delayed-enhancement cardiovascular magnetic resonance. J Am Coll Cardiol 2008;52:148-57.
67. Koniaris LS, Goldhaber SZ. Anticoagulation in dilated cardiomyopathy. J Am Coll Cardiol 1998;31:745-8.
68. Meltzer RS, Visser CA, Fuster V. Intracardiac thrombi and systemic embolization. Ann Intern Med 1986;104:689-98.
69. Johannessen KA, Nordrehaug JE, von der Lippe G, Vollset SE. Risk factors for embolization in patients with left ventricular acute myocardial infarction. Br Heart J 1988;60:104-10.
70. Haugland JM, Asinger RW, Mikell FL, Elsperger J, Hodges M. Embolic potential of left ventricular thrombi detected by two-dimensional echocardiography. Circulation 1984;70:588-98.
71. Domenicucci S, Bellotti P, Chiarella F, Lupi G, Vecchio C. Spontaneous morphologic changes in left ventricular thrombi two-dimensional echocardiographic study. Circulation 1987;75:737-43.
72. Srichai MB, Junor C, Rodriguez LL, Stillman AE, Grimm RA, Lieber ML, et al. Clinical, imaging, and pathological characteristics of left Ventricular Thrombus: A comparison of contrast-enhanced magnetic resonance imaging, transthoracic echocardiography, and transesophageal echocardiography with surgical or pathological validation. Am Heart J 2006;152: 75-84.
73. van Dantzig JM, Delemarre BJ, Bot H, Visser CA. Left ventricular thrombus in acute myocardial infarction. Eur Heart J 1996;17:1640-5.
74. Senior R, Becher H, Monaghan M, Agati L, Zamorano J, Vanoverschelde JL, et al. Contrast Echocardiography: Evidence-Based

Recommendations by European Association of Echocardiography. Eur J Echocardiogr 2009;10:194-212.

75. Kurt M, Shaikh KA, Peterson L, Kurrelmeyer KM, Shah G, Nagueh SF, et al. Impact of contrast echocardiography on evaluation of ventricular function and clinical management in a large prospective cohort. J Am Coll Cardiol 2009;53:802-10.
76. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr., Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633-8.
77. Bonow RO, Carabello BA, Kanu C, de Leon AC Jr., Faxon DP, Freed MD, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. Circulation 2006;114: e84-231.
78. Oh J, Seward J, Tajik A. The Echo Manual. 3rd ed. Rochester, MN: Lippincott Williams & Wilkins; 2006.
79. Kaymaz C, Ozkan M, Ozdemir N, Kirma C, Deligönül U. Spontaneous echocardiographic microbubbles associated with prosthetic mitral valves: mechanistic insights from thrombolytic treatment results. J Am Soc Echocardiogr 2002;15:323-7.
80. Jacob S, Tong AT. Role of echocardiography in the diagnosis and management of infective endocarditis. Curr Opin Cardiol 2002;17:478-85.
81. O'Brien JT, Geiser EA. Infective endocarditis and echocardiography. Am Heart J 1984;108:386-94.
82. Gilbert BW, Haney RS, Crawford F, McClellan J, Gallis HA, Johnson ML, et al. Two-dimensional echocardiographic assessment of vegetative endocarditis. Circulation 1977;55:346-53.
83. Shively BK, Gurule FT, Roldan CA, Leggett JH, Schiller NB. Diagnostic value of transesophageal compared with transthoracic echocardiography in infective endocarditis. J Am Coll Cardiol 1991;18:391-7.
84. Erbel R, Rohmann S, Drexler M, Mohr-Kahaly S, Gerharz CD, Iversen S, et al. Improved diagnostic value of echocardiography in patients with infective endocarditis by transoesophageal approach. A prospective study. Eur Heart J 1988;9:43-53.
85. Daniel WG, Mügge A, Grote J, Hausmann D, Nikutta P, Laas J, et al. Comparison of transthoracic and transesophageal echocardiography for detection of abnormalities of prosthetic and bioprosthetic valves in the mitral and aortic positions. Am J Cardiol 1993;71:210-5.
86. Daniel WG, Mügge A, Martin RP, Lindert O, Hausmann D, Nonnast-Daniel B, et al. Improvement in the diagnosis of abscesses associated with endocarditis by transesophageal echocardiography. N Engl J Med 1991;324:795-800.
87. De Castro S, Cartoni D, d'Amati G, Beni S, Yao J, Fiorell M, et al. Diagnostic accuracy of transthoracic and multiplane transesophageal echocardiography for valvular perforation in acute infective endocarditis: Correlation with anatomic findings. Clin Infect Dis 2000;30:825-6.
88. Habib G. Embolic risk in subacute bacterial endocarditis: determinants and role of transesophageal echocardiography. Curr Cardiol Rep 2003;5:129-36.
89. Grabowski M, Hryniewiecki T, Janas J, Stępińska J. Clinically overt and silent cerebral embolism in the course of infective endocarditis. J Neurol 2011;258:1133-9.
90. Snygg-Martin U, Gustafsson L, Rosengren L, Alsiö A, Ackerholm P, Andersson R, et al. Cerebrovascular complications in patients with left-sided infective endocarditis are common: a prospective study using magnetic resonance imaging and neurochemical brain damage markers. Clin Infect Dis 2008;47:23-30.
91. Thuny F, Di Salvo G, Belliard O, Avierinos JF, Pergola V, Rosenberg V, et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. Circulation 2005;112:69-75.
92. Vilacosta I, Graupner C, San Román JA, Sarriá C, Ronderos R, Fernández C, et al. Risk of embolization after institution of antibiotic therapy for infective endocarditis. J Am Coll Cardiol 2002;39:1489-95.
93. Di Salvo G, Habib G, Pergola V, Avierinos JF, Philip E, Casalta JP, et al. Echocardiography predicts embolic events in infective endocarditis. J Am Coll Cardiol 2001;37:1069-76.
94. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:e521-643.
95. Moder KG, Miller TD, Tazelaar HD. Cardiac involvement in systemic lupus erythematosus. Mayo Clin Proc 1999;74:275-84.
96. Roldan CA, Shively BK, Crawford MH. An echocardiographic study of valvular heart disease associated with systemic lupus erythematosus. N Engl J Med 1996;335:1424-30.
97. Zuily S, Regnault V, Selton-Suty C, Eschwège V, Bruntz JF, Bode-Dotto E, et al. Increased risk for heart valve disease associated with antiphospholipid antibodies in patients with systemic lupus erythematosus: meta-analysis of echocardiographic studies. Circulation 2011;124:215-24.
98. Reisner SA, Brenner B, Haim N, Edoute Y, Markiewicz W. Echocardiography in nonbacterial thrombotic endocarditis: from autopsy to clinical entity. J Am Soc Echocardiogr 2000;13:876-81.
99. Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. Medicine (Baltimore 1985;64:16-35.
100. el-Shami K, Griffiths E, Streiff M. Nonbacterial thrombotic endocarditis in cancer patients: pathogenesis, diagnosis, and treatment. Oncologist 2007;12:518-23.
101. Lee RJ, Bartzokis T, Yeoh TK, Grogin HR, Choi D, Schnittger I. Enhanced detection of intracardiac sources of cerebral emboli by transesophageal echocardiography. Stroke 1991;22:734-9.
102. Dutta T, Karas MG, Segal AZ, Kizer JR. Yield of transesophageal echocardiography for nonbacterial thrombotic endocarditis and other cardiac sources of embolism in cancer patients with cerebral ischemia. Am J Cardiol 2006;97:894-8.
103. Roldan CA, Shively BK, Crawford MH. Valve excrescences: prevalence, evolution and risk for cardioembolism. J Am Coll Cardiol 1997;30: 1308-14.
104. Freedberg RS, Goodkin GM, Perez JL, Tunick PA, Kronzon I. Valve strands are strongly associated with systemic embolization: a transesophageal echocardiographic study. J Am Coll Cardiol 1995;26:1709-12.
105. Tice FD, Slivka AP, Walz ET, Orsinelli DA, Pearson AC. Mitral valve strands in patients with focal cerebral ischemia. Stroke 1996;27:1183-6.
106. Cohen A, Tzourio C, Chauvel C, et al. Mitral valve strands and the risk of ischemic stroke in elderly patients. The French Study of Aortic Plaques in Stroke (FAPS) Investigators. Stroke 1997;28:1574-8.
107. Isada LR, Torelli JN, Stewart WJ, Klein AL. Detection of fibrous strands on prosthetic mitral valves with transesophageal echocardiography: another potential embolic source. J Am Soc Echocardiogr 1994;7:641-5.
108. Orsinelli DA, Pearson AC. Detection of prosthetic valve strands by transesophageal echocardiography: Clinical significance in patients with suspected cardiac source of embolism. J Am Coll Cardiol 1995;26:1713-8.
109. Lin CS, Schwartz IS, Chapman I. Calcification of the mitral annulus fibrosus with systemic embolization. A clinicopathologic study of 16 cases. Arch Pathol Lab Med 1987;111:411-4.
110. Hill EE, Herijgers P, Claus P, Vanderschueren S, Peetermans WE, Herregods MC. Abscess in infective endocarditis: the value of transesophageal echocardiography and outcome: a 5-year study. Am Heart J 2007;154:923-8.
111. Eicher JC, De Nadai L, Soto FX, Falcon-Eicher S, Dobsák P, Zanetta G, et al. Bacterial endocarditis complicating mitral annular calcification: a clinical and echocardiographic study. J Heart Valve Dis 2004;13:217-27.
112. Antonini-Canterin F, Capanna M, Manfroni A, Brieda M, Grandis U, Sbaraglia F, et al. Association between mitral annular calcium and carotid artery stenosis and role of age and gender. Am J Cardiol 2001;88:581-3.
113. Adler Y, Vaturi M, Fink N, Tanne D, Shapira Y, Weisenberg D, et al. Association between mitral annulus calcification and aortic atheroma: a

prospective transesophageal echocardiographic study. Atherosclerosis 2000;152:451-6.
114. Benjamin EJ, Plehn JF, D'Agostino RB, Belanger AJ, Comai K, Fuller DL, et al. Mitral annular calcification and the risk of stroke in an elderly cohort. N Engl J Med 1992;327:374-9.
115. Kizer JR, Wiebers DO, Whisnant JP, Galloway JM, Welty TK, Lee ET, et al. Mitral annular calcification, aortic valve sclerosis, and incident stroke in adults free of clinical cardiovascular disease: the Strong Heart Study. Stroke 2005;36:2533-7.
116. Shohat-Zabarski R, Paz R, Adler Y, Vaturi M, Jortner R, Sagie A. Mitral annulus calcification with a mobile component as a possible source of embolism. Am J Geriatr Cardiol 2001;10:196-8.
117. Gueret P, Vignon P, Fournier P, Chabernaud JM, Gomez M, LaCroix P, et al. Transesophageal echocardiography for the diagnosis and management of nonobstructive thrombosis of mechanical mitral valve prosthesis. Circulation 1995;91:103-10.
118. Barbetseas J, Nagueh SF, Pitsavos C, Toutouzas PK, Quiñones MA, Zoghbi WA. Differentiating thrombus from pannus formation in obstructed mechanical prosthetic valves: an evaluation of clinical, transthoracic and transesophageal echocardiographic parameters. J Am Coll Cardiol 1998;32:1410-7.
119. Girard SE, Miller FA Jr., Orszulak TA, Mullany CJ, Montgomery S, Edwards WD, et al. Reoperation for prosthetic aortic valve obstruction in the era of echocardiography: trends in diagnostic testing and comparison with surgical findings. J Am Coll Cardiol 2001;37:579-84.
120. Lin SS, Tiong IY, Asher CR, Murphy MT, Thomas JD, Griffin BP. Prediction of thrombus-related mechanical prosthetic valve dysfunction using transesophageal echocardiography. Am J Cardiol 2000;86:1097-101.
121. Michelena HI, Enriquez-Sarano M, Sundt TM 3rd. A torn 15-year-old aortic bioprosthesis in the setting of percutaneous coronary intervention: echocardiographic diagnosis and pathologic correlation. A case report. J Heart Valve Dis 2009;18:228-31.
122. Tong AT, Roudaut R, Ozkan M, Sagie A, Shahid MS, Pontes Júnior SC, et al. Transesophageal echocardiography improves risk assessment of thrombolysis of prosthetic valve thrombosis: results of the international PRO-TEE registry. J Am Coll Cardiol 2004;43:77-84.
123. Pislaru SV, Michelena HI, Mankad SV. Interventional echocardiography. Prog Cardiovasc Dis 2014;57:32-46.
124. Ragland MM, Tak T. The role of echocardiography in diagnosing space-occupying lesions of the heart. Clin Med Res 2006;4:22-32.
125. Peters PJ, Reinhardt S. The echocardiographic evaluation of intracardiac masses: a review. J Am Soc Echocardiogr 2006;19:230-40.
126. Sharma S, Tsyvine D, Maldjian PD, Sambol JT, Lovoulos CJ, Levy G, et al. An intriguing association: atrial myxoma and cerebral cavernous hemangioma: Case report and review of literature. J Am Soc Echocardiogr 2011;24:110.e1-4.
127. Lepper W, Shivalkar B, Rinkevich D, Belcik T, Wei K. Assessment of the vascularity of a left ventricular mass using myocardial contrast echocardiography. J Am Soc Echocardiogr 2002;15:1419-22.
128. Dujardin KS, Click RL, Oh JK. The role of intraoperative transesophageal echocardiography in patients undergoing cardiac mass removal. J Am Soc Echocardiogr 2000;13:1080-3.
129. Pucci A, Gagliardotto P, Zanini C, Pansini S, di Summa M, Mollo F. Histopathologic and clinical characterization of cardiac myxoma: review of 53 cases from a single institution. Am Heart J 2000;140:134-8.
130. Shapiro LM. Cardiac tumours: diagnosis and management. Heart 2001;85:218-22.
131. Tolstrup K, Shiota T, Gurudevan S, Luthringer D, Luo H, Siegel RJ. Left atrial myxomas: correlation of two-dimensional and live three-dimensional transesophageal echocardiography with the clinical and pathologic findings. J Am Soc Echocardiogr 2011;24:618-24.
132. 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;103:2687-93.
133. Klarich KW, Enriquez-Sarano M, Gura GM, Edwards WD, Tajik AJ, Seward JB. Papillary fibroelastoma: echocardiographic characteristics for diagnosis and pathologic correlation. J Am Coll Cardiol 1997;30:784-90.
134. Gowda RM, Khan IA, Nair CK, Mehta NJ, Vasavada BC, Sacchi TJ. Cardiac papillary fibroelastoma: a comprehensive analysis of 725 cases. Am Heart J 2003;146:404-10.
135. Goldstein SA, Evangelista A, Abbara S, Arai A, Asch FM, Badano LP, et al. Multimodality imaging of diseases of the thoracic aorta in adults: From the American Society of Echocardiography and the European Association of Cardiovascular Imaging: Endorsed by the Society of Cardiovascular Computed Tomography and Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2015;28:119-82.
136. Mecklai A, Rosenzweig B, Applebaum R, Axel L, Grossi E, Chan A, et al. Intimal sarcoma in the aortic arch partially obstructing the aorta with metastasis to the brain. Tex Heart Inst J 2014;41:433-6.
137. Tunick PA, Kronzon I. Atheromas of the thoracic aorta: clinical and therapeutic update. J Am Coll Cardiol 2000;35:545-54.
138. Saric M, Kronzon I. Embolism from aortic plaque: atheroembolism (cholesterol crystal embolism). In: Basow DS, editor. UpTo- Date. Waltham: UpToDate; 2011.
139. Kronzon I, Saric M. Cholesterol embolization syndrome. Circulation 2010;122:631-41.
140. Saric M, Kronzon I. Aortic atherosclerosis and embolic events. Curr Cardiol Rep 2012;14:342-9.
141. Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull W Jr, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Circulation 1995;92:1355-74.
142. Applebaum RM, Kronzon I. Evaluation and management of cholesterol embolization and the blue toe syndrome. Curr Opin Cardiol 1996;11:533-42.
143. Tunick PA, Krinsky GA, Lee VS, Kronzon I. Diagnostic imaging of thoracic aortic atherosclerosis. AJR Am J Roentgenol 2000;174:1119-25.
144. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2873-926.
145. Hahn RT, Abraham T, Adams MS, Bruce CJ, Glas KE, Lang RM, et al. Guidelines for performing a comprehensive transesophageal echocardiographic examination: Recommendations from the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. J Am Soc Echocardiogr 2013;26:921-64.
146. Tunick PA, Kronzon I. Protruding atherosclerotic plaque in the aortic arch of patients with systemic embolization: a new finding seen by transesophageal echocardiography. Am Heart J 1990;120:658-60.
147. Jones EF, Kalman JM, Calafiore P, Tonkin AM, Donnan GA. Proximal aortic atheroma: an independent risk factor for cerebral ischemia. Stroke 1995;26:218-24.
148. Amarenco P, Cohen A, Tzourio C, Bertrand B, Hommel M, Besson G, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. N Engl J Med 1994;331:1474-9.
149. Koppang JR, Nanda NC, Coghlan C, Sanyal R. Histologically confirmed cholesterol atheroemboli with identification of the source by transesophageal echocardiography. Echocardiography 1992;9:379-83.
150. Coy KM, Maurer G, Goodman D, Siegel RJ. Transesophageal echocardiographic detection of aortic atheromatosis may provide clues to occult renal dysfunction in the elderly. Am Heart J 1992;123:1684-6.
151. Ko Y, Park JH, Yang MH, Ko SB, Choi SI, Chun EJ, et al. Significance of aortic atherosclerotic disease in possibly embolic stroke: 64-multidetector row computed tomography study. J Neurol 2010;257:699-705.

152. Zahuranec DB, Mueller GC, Bach DS, Stojanovska J, Brown DL, Lisabeth LD, et al. Pilot study of cardiac magnetic resonance imaging for detection of embolic source after ischemic stroke. J Stroke Cerebrovasc Dis 2012;21:794-800.
153. Khatri IA, Mian N, Alkawi A, Janjua N, Kirmani JF, Saric M, et al. Catheter-based aortography fails to identify aortic atherosclerotic lesions detected on transesophageal echocardiography. J Neuroimaging 2005; 15:261-5.
154. Silvestry FE, Cohen MS, Armsby LB, Burkule NJ, Fleishman CE, Hijazi ZM, et al. Guidelines for the echocardiographic assessment of atrial septal defect and patent foramen ovale: from the American Society of Echocardiography and Society for Cardiac Angiography and Interventions. J Am Soc Echocardiography 2015;28:910-58.
155. Kiserud T. Physiology of the fetal circulation. Semin Fetal Neonatal Med 2005;10:493-503.
156. Mielke G, Brenda N. Cardiac output and central distribution of blood flow in the human fetus. Circulation 2001;103:1662-8.
157. Blackburn ST. Maternal, Fetal and Neonatal Physiology: A Clinical Perspective. Philadelphia: Saunders; 2003.
158. Friedman AH, Fahey JT. The transition from fetal to neonatal circulation: normal responses and implications for infants with heart disease. Semin Perinatol 1993;17:106-221.
159. Mann D, Mehta V. Cardiovascular embryology. Int Anesthesiol Clin 2004;42:15-28.
160. 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.
161. Cabanes L, Mas JL, Cohen A, Amarenco P, Cabanes PA, Oubary P, et al. Atrial septal aneurysm and patent foramen ovale as risk factors for cryptogenic stroke in patients less than 55 years of age. A study using transesophageal echocardiography. Stroke 1993;24:1865-73.
162. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: A meta analysis of case-control studies. Neurology 2000;55:1172-9.
163. Hanley PC, Tajik AJ, Hynes JK, Edwards WD, Reeder GS, Hagler DJ, et al. Diagnosis and classification of atrial septal aneurysm by two-dimensional echocardiography: Report of 80 consecutive cases. J Am Coll Cardiol 1985;6:1370-82.
164. Pearson AC, Nagelhout D, Castello R, Gomez CR, Labovitz AJ. Atrial septal aneurysm and stroke: a transesophageal echocardiographic study. J Am Coll Cardiol 1991;18:1223-9.
165. Lechat P, Mas JL, Lascault G, et al. Prevalence of patent foramen ovale in patients with stroke. N Engl J Med 1988;318:1148-52.
166. Webster MW, Chancellor AM, Smith HJ, Swift DL, Sharpe DN, Bass NM, et al. Patent foramen ovale in young stroke patients. Lancet 1988;2:11-2.
167. Job FP, Ringelstein EB, Grafen Y, Flachskampf FA, Doherty C, Stockmanns A, et al. Comparison of transcranial contrast Doppler sonography and transesophageal contrast echocardiography for the detection of patent foramen ovale in young stroke patients. Am J Cardiol 1994; 74:381-4.
168. 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.
169. Yeung M, Khan KA, Shuaib A. Transcranial Doppler ultrasonography in the detection of venous to arterial shunting in acute stroke and transient ischaemic attacks. J Neurol Neurosurg Psychiatry 1996;61:445-9.
170. Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. N Engl J Med 2007;357: 2262-8.
171. Kent DM, Trikalinos TA, Thaler DE. Patent foramen ovale and cryptogenic stroke. N Engl J Med 2008;358:1519-20.
172. Rigatelli G, Aggio S, Cardaioli P, Braggion G, Giordan M, Dell'avvocata F, et al. Left atrial dysfunction in patients with patent foramen ovale and atrial septal aneurysm: An alternative concurrent mechanism for arterial embolism? JACC Cardiovasc Interv 2009;2:655-62.
173. Goch A, Banach M, Piotrowski G, Szadkowska I, Goch JH. Echocardiographic evaluation of the left atrium and left atrial appendage function in patients with atrial septum aneurysm: implications for thromboembolic complications. Thorac Cardiovasc Surg 2007;55: 365-70.
174. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP, PFO in Cryptogenic Stroke Study (PICSS) Investigators. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in cryptogenic stroke study. Circulation 2002;105:2625-31.
175. Messé SR, Silverman IE, Kizer JR, Homma S, Zahn C, Gronseth G, et al. Practice parameter: Recurrent stroke with patent foramen ovale and atrial septal aneurysm: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2004;62:1042-50.
176. Bridges ND, Hellenbrand W, Latson L, Filiano J, Newburger JW, Lock JE. Transcatheter closure of patent foramen ovale after presumed paradoxical embolism. Circulation 1992;86:1902-8.
177. Serena J, Marti-Fàbregas J, Santamarina E, Rodríguez JJ, Perez-Ayuso MJ, Masjuan J, et al. Recurrent stroke and massive right-to-left shunt: Results from the prospective Spanish multicenter (CODICIA) study. Stroke 2008;39:3131-6.
178. Van Camp G, Schulze D, Cosyns B, Vandenbossche JL. Relation between patent foramen ovale and unexplained stroke. Am J Cardiol 1993;71: 596-8.
179. Stewart MJ. Contrast echocardiography. Heart 2003;89:342-8.
180. Goldhaber SZ. Pulmonary embolism. N Engl J Med 1998;339:93-104.
181. Tapson VF. Acute pulmonary embolism. N Engl J Med 2008;358: 1037-52.
182. Carson JL, Kelley MA, Duff A, Weg JG, Fulkerson WJ, Palevsky HI, et al. The clinical course of pulmonary embolism. N Engl J Med 1992;326: 1240-5.
183. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999;353:1386-9.
184. Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979–1998: an analysis using multiple-cause mortality data. Arch Intern Med 2003;163:1711-7.
185. Nijkeuter M, Söhne M, Tick LW, Kamphuisen PW, Kramer MH, Laterveer L, et al. The natural course of hemodynamically stable pulmonary embolism: clinical outcome and risk factors in a large prospective cohort study. Chest 2007;131:517-23.
186. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011;123:1788-830.
187. Beer JH, Burger M, Gretener S, Bernard-Bagattini S, Bounameaux H. Outpatient treatment of pulmonary embolism is feasible and safe in a substantial proportion of patients. J Thromb Haemost 2003;1:186-7.
188. Kovacs MJ, Anderson D, Morrow B, Gray L, Touchie D, Wells PS. Outpatient treatment of pulmonary embolism with dalteparin. Thromb Haemost 2000;83:209-11.
189. Wells PS, Kovacs MJ, Bormanis J, Forgie MA, Goudie D, Morrow B, et al. Expanding eligibility for outpatient treatment of deep venous thrombosis and pulmonary embolism with low-molecular-weight heparin: a comparison of patient self-injection with homecare injection. Arch Intern Med 1998;158:1809-12.
190. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W, Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 2002;347:1143-50.
191. Vanni S, Polidori G, Vergara R, Pepe G, Nazerian P, Moroni F, et al. Prognostic value of ECG among patients with acute pulmonary embolism and normal blood pressure. Am J Med 2009;122:257-64.
192. Konstantinides S, Geibel A, Olschewski M, Kasper W, Hruska N, Jäckle S, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation 2002;106:1263-8.
193. Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. Circulation 2003;107:2545-7.

194. Sanchez O, Trinquart L, Caille V, Couturaud F, Pacouret G, Meneveau N, et al. Prognostic factors for pulmonary embolism: the prep study, a prospective multicenter cohort study. Am J Respir Crit Care 2010;181:168-73.
195. Jiménez D, Aujesky D, Moores L, Gómez V, Martí D, Briongos S, et al. Combinations of prognostic tools for identification of high-risk normotensive patients with acute symptomatic pulmonary embolism. Thorax 2011;66:75-81.
196. Ribeiro A, Lindmarker P, Juhlin-Dannfelt A, Johnsson H, Jorfeldt L. Echocardiography Doppler in pulmonary embolism: right ventricular dysfunction as a predictor of mortality rate. Am Heart J 1997;134:479-87.
197. Goldhaber S. Pulmonary embolism thrombolysis: broadening the paradigm for its administration. Circulation 1997;96:716-8.
198. Ten Wolde M, Söhne M, Quak E, Mac Gillavry MR, Büller HR. Prognostic value of echocardiographically assessed right ventricular dysfunction in patients with pulmonary embolism. Arch Int Med 2004;164:1685-9.
199. Bova C, Greco F, Misuraca G, Serafini O, Crocco F, Greco A, et al. Diagnostic utility of echocardiography in patients with suspected pulmonaryembolism. Am J Emerg Med 2003;21:180-3.
200. Miniati M, Monti S, Pratali L, Di Ricco G, Marini C, Formichi B, et al. Diagnosis of pulmonary embolism: results of a prospective study in unselected patients. Am J Med 2001;110:528-35.
201. Kasper W, Konstantinides S, Geibel A, Olschewski M, Heinrich F, Grosser KD, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. J Am Coll Cardiol 1997;30:1165-71.
202. Mansencal N, Vieillard-Baron A, Beauchet A, Farcot JC, El Hajjam M, Dufaitre G, et al. Triage patients with suspected pulmonary embolism in the emergency department using a portable ultrasound device. Echocardiography 2008;25:451-6.
203. Grifoni S, Olivotto I, Cecchini P, Pieralli F, Camaiti A, Santoro G, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation 2000;101:2817-22.
204. Taylor RA, Davis J, Liu R, Gupta V, Dziura J, Moore CL. Point-of-care focused cardiac ultrasound for prediction of pulmonary embolism adverse outcomes. J Emerg Med 2013;45:392-9.
205. Labovitz AJ, Noble VE, Bierig M, Goldstein SA, Jones R, Kort S, et al. Focused cardiac ultrasound in the emergent setting: a consensus statement of the American Society of Echocardiography and American College of Emergency Physicians. J Am Soc Echocardiogr 2010;23:1225-30.
206. Madan A, Schwartz C. Echocardiographic visualization of acute pulmonary embolus and thrombolysis in the ED. Am J Emerg Med 2004;22:294-300.
207. Flory CM. Arterial occlusions produced by emboli from eroded atheromatous plaques. Am J Pathol 1945;21:549-65.
208. Kealy WF. Atheroembolism. J Clin Pathol 1978;31:984-9.
209. Cross SS. How common is cholesterol embolism? J Clin Pathol 1991;44:859-61.
210. Keeley EC, Grines CL. Scraping of aortic debris by coronary guiding catheters: a prospective evaluation of 1,000 cases. J Am Coll Cardiol 1998;32:1861-5.
211. Johnson LW, Esente P, Giambartolomei A, Grant WD, Loin M, Reger MJ, et al. Peripheral vascular complications of coronary angioplasty by the femoral and brachial techniques. Cathet Cardiovasc Diagn 1994;31:165-72.
212. Blauth CI, Cosgrove DM, Webb BW, Ratliff NB, Boylan M, Piedmonte MR, et al. Atheroembolism from the ascending aorta: an emerging problem in cardiac surgery. J Thorac Cardiovasc Surg 1992;103:1104-11. discussion 1111–1112.
213. Glas KE, Swaminathan M, Reeves ST, Shanewise JS, Rubenson D, Smith PK, et al. Guidelines for the performance of a comprehensive intraoperative epiaortic ultrasonographic examination: recommendations of the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists; endorsed by the Society of Thoracic Surgeons. J Am Soc Echocardiogr 2007;20:1227-35.
214. Daneault B, Kirtane AJ, Kodali SK, Williams MR, Genereux P, Reiss GR, et al. Stroke associated with surgical and transcatheter treatment of aortic stenosis: a comprehensive review. J Am Coll Cardiol 2011;58:2143-50.
215. Zamorano JL, Badano LP, Bruce C, Chan KL, Gonçalves A, Hahn RT, et al. EAE/ASE recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease. J Am Soc Echocardiogr 2011;24:937-65.
216. Jacobs BS, Boden-Albala B, Lin IF, Sacco RL. Stroke in the young in the northern Manhattan stroke study. Stroke 2002;33:2789-93.
217. Marini C, Totaro R, De Santis F, Ciancarelli I, Baldassarre M, Carolei A. Stroke in young adults in the community-based L'Aquila registry: incidence and prognosis. Stroke 2001;32:52-6.
218. Roach ES, Golomb MR, Adams R, Biller J, Daniels S, Deveber G, et al. Management of stroke in infants and children: A scientific statement from a special writing group of the American heart association stroke council and the council on cardiovascular disease in the young. Stroke 2008;39:2644-91.
219. 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.
220. Dowling MM, Lee N, Quinn CT, Rogers ZR, Boger D, Ahmad N, et al. Prevalence of intracardiac shunting in children with sickle cell disease and stroke. J Pediatr 2010;156:645-50.
221. Bartz PJ, Cetta F, Cabalka AK, Reeder GS, Squarcia U, Agnetti A, et al. Paradoxical emboli in children and young adults: Role of atrial septal defect and patent foramen ovale device closure. Mayo Clin Proc 2006;81:615-8.
222. Carroll JD, Saver JL, Thaler DE, Smalling RW, Berry S, MacDonald LA, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med 2013;368:1092-100.
223. Kutty S, Sengupta P, Khandheria B. Patent foramen ovale: The known and the to be known. J Am Coll Cardiol 2012;59:1665-71.
224. Bartakian S, Fagan TE, Schaffer MS, Darst JR. Device closure of secundum atrial septal defects in children <15 kg: Complication rates and indications for referral. JACC Cardiolasc Interv 2012;5:1178-84.
225. Barker PC, Nowak C, King K, Mosca RS, Bove EL, Goldberg CS. Risk factors for cerebrovascular events following Fontan palliation in patients with a functional single ventricle. Am J Cardiol 2005;96:587-91.
226. Ahn KT, Choi J-H, Park SW. Pulmonary arteriovenous fistula in a patient with cryptogenic stroke. Heart 2011;97:2093.
227. Doering F, Eicken A, Hess J. Ischaemic stroke with intact atrial septum – exclude arteriovenous malformations. Cardiol Young 2014;24:145-7.
228. Butera G, Salvia J, Carminati M. When side matters: Contrast echocardiography with injection from the left antecubital vein to detect a persistent left superior vena cava draining to the left atrium in a patient with cerebral stroke. Circulation 2012;125:e1.
229. Calvert PA, Rana BS, Kydd AC, Shapiro LM. Patent foramen ovale: anatomy, outcomes, and closure. Nat Rev Cardiol 2011;8:148-60.