Mechanisms of Cardioembolic Stroke

Marco R. Di Tullio, MD, and Shunichi Homma, MD

Address
Cardiology Division, Columbia-Presbyterian Medical Center, 630 West 168th Street, New York, NY 10032, USA.
E-mail: md42@columbia.edu

Current Cardiology Reports 2002, **4:**141–148
Current Science Inc. ISSN 1523-3782

Cardiac embolism is often involved as a mechanism for embolic stroke, and may be implicated in many strokes that have traditionally been considered of unknown origin (cryptogenic strokes). In recent years, significant advancements have been made in understanding and reducing the risk of stroke from long-known cardioembolic sources (atrial fibrillation, intracardiac thrombus or tumor, infective endocarditis). Also, improved cardiac imaging, especially transesophageal echocardiography, has allowed the identification of newer embolic sources of stroke (aortic atheromas, patent foramen ovale, atrial septal aneurysm). This article reviews the current understanding of cardiac embolism as a mechanism for stroke, and the preventive options that are currently adopted to decrease the stroke risk.

Introduction

Stroke is the third leading cause of death in the United States. Approximately 700,000 strokes occur every year, and an estimated 3 million stroke survivors currently live in the United States. Cardioembolic stroke accounts for an estimated 15% to 20% of all ischemic strokes. Moreover, many strokes labeled as *cryptogenic*, or strokes of unknown origin, have clinical features and brain imaging findings compatible with embolism, in the absence of a clearly identifiable source. In recent years, considerable effort has been devoted to the identification of new potential cardioembolic sources of stroke, especially after the introduction of transesophageal echocardiography (TEE) has allowed a more accurate examination of the cardiac structures. Considerable progress has been made in the prevention of stroke associated with such known risk factors as atrial fibrillation and myocardial infarction. Transthoracic echocardiography (TTE) and TEE are by far the most commonly used diagnostic techniques to search for cardiac embolic sources, and it is calculated that approximately 25% of all TEEs are performed for this indication. In this review, we discuss cardiac abnormalities certainly or potentially associated with increased risk for ischemic stroke, the use of echocardiography to detect them, and therapeutic and preventive options that are either generally accepted or under investigation.

Traditional Cardioembolic Sources

Atrial fibrillation

Atrial fibrillation is associated with a 5% risk of stroke per year, approximately two to seven times greater than that of subjects without atrial fibrillation [1–3]. The stroke risk is much higher (17 times) in patients with atrial fibrillation from rheumatic heart disease [4]. Overall, one out of six strokes occurs in patients with atrial fibrillation [5]. The severity of stroke also tends to be greater in patients with atrial fibrillation than in patients in normal sinus rhythm. The prevalence of atrial fibrillation in the population increases with age (from less than 1% below age 60 to over 6% in those over 80 years of age) [1], and so does the associated proportion of strokes. Conditions such as congestive heart failure, coronary artery disease, diabetes mellitus, arterial hypertension, and history of prior thromboembolism increase the risk of stroke associated with atrial fibrillation to 10% to 12% per year [6,7]. The stroke risk associated with recurrent atrial fibrillation has been considered to be lower than that of chronic atrial fibrillation, but recent studies suggest that chronic and recurrent atrial fibrillation appear to carry very similar stroke risk [7]. Atrial fibrillation in the absence of organic heart disease or risk factors (*lone* atrial fibrillation) appears to carry significantly lower risk, especially in younger patients (approximately 1.3% per year).

Atrial fibrillation is associated with blood stagnation in the left atrium, which in turn predisposes to thrombus formation, especially in the left atrial appendage, with consequent increased rate of cerebral embolization. Large clinical trials have shown a benefit of treatment with warfarin and, to a lesser extent, aspirin for the primary and secondary prevention of thromboembolic complications. Adjusted-dose warfarin has been proven superior to low-dose warfarin plus aspirin in patients at high risk of thromboembolic complications (identified by at least one of four criteria: systolic blood pressure > 160 mm Hg, previous embolic events, congestive heart failure or fractional shortening < 25% on echocardiogram, female sex over age 75).

In the Study on Prevention in Atrial Fibrillation (SPAF) III [8], the stroke incidence was 1.9% per year for adjusted-dose warfarin, compared with 7.9% per year for the combination therapy. For patients with lower risk, treatment with aspirin 325 mg/d was associated with a relatively low stroke incidence (2.0% per year).

Based on patients' risk profile, adjusted-dose oral anticoagulation with warfarin has been recommended in patients whose stroke risk on aspirin is deemed to be over 6% per year, whereas aspirin has been proposed in those with a risk of 2% per year or less. Patients with intermediate stroke risk represent a group in which opinions on oral anticoagulation are divided. Recently, risk-based guidelines for stroke prevention have been jointly issued by the American Heart Association, the American College of Cardiology, and the European Society of Cardiology [9••]. According to these guidelines, adjusted-dose anticoagulation is recommended in high-risk patients (patients over 75 years of age, especially women; patients over the age of 60 with diabetes mellitus or coronary artery disease; all patients with risk factors for thromboembolism such as heart failure, left ventricular ejection fraction less than 35%, history of hypertension, prior thromboembolism, rheumatic heart disease, prosthetic heart valves, thrombus detected by echocardiography). In these patients, the International Normalized Ratio (INR) should be kept between 2.0 and 3.0 (except in patients with rheumatic heart disease or prosthetic valves, who may require an INR between 2.5 and 3.5, or higher). Patients at lower risk (age 60–75 years and no risk factors with thromboembolism) can be treated with aspirin 325 mg/day.

Left ventricular thrombus

Myocardial infarction (MI) and dilated cardiomyopathy are most frequently associated with left ventricular thrombus formation. TTE is the most commonly used diagnostic test for the detection of left ventricular thrombus (Fig. 1). The use of TEE in the setting should be reserved to cases with suboptimal transthoracic views, as the sensitivity of TEE for the diagnosis of apical thrombus is not significantly higher than that of a diagnostically adequate TTE.

Myocardial infarction

Approximately 1% to 2.5% of patients with acute MI will suffer a stroke during the first 4 weeks following the acute event, with approximately 50% of all strokes occurring in the first 5 days [10]. The risk of stroke remains high in the first 3 months, and progressively decreases thereafter. Factors affecting the risk of stroke are the infarction location (anterior MI has a fourfold greater incidence of thrombus formation, and therefore a stronger embolic risk, than inferior MI), the coexistence of left ventricular dysfunction or atrial fibrillation, and a history of systemic or pulmonary embolism. History of arterial hypertension and prior stroke also increase the stroke risk [10]. The rate of thrombus formation following anterior infarction is estimated at 25% to 30%, compared with approximately 5% after inferior infarction. Without anticoagulation, about 25% of these thrombi would embolize, and anticoagulation is thought to reduce this number in half. Thrombus can form within 1 day of infarction, and the highest incidence of thrombus is observed during the first week. In the case of anterior wall infarction, anticoagulation with heparin is recommended upon presentation, and until the presence of thrombus is ruled out using TTE. In patients with inferior infarction, anticoagulation is usually delayed until TTE is performed, and started only if a thrombus is identified. However, at least one large post-MI study failed to confirm an association between infarction location and stroke risk [11], suggesting that mechanisms other than thrombus formation may also contribute to the increased risk of stroke post-MI.

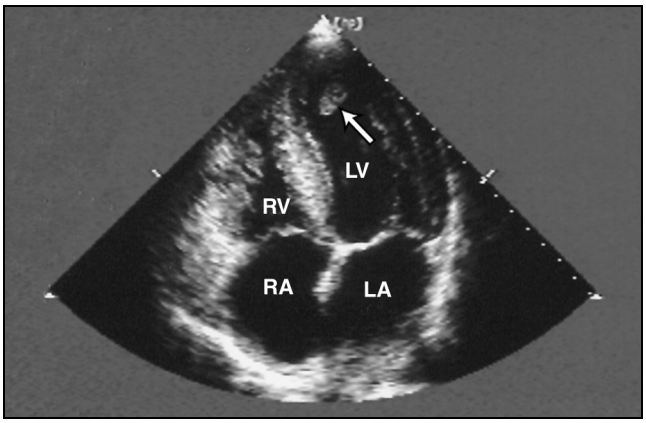

Figure 1. Protruding apical thrombus (*arrow*) by transthoracic echocardiography. LA—left atrium; LV—left ventricle; RA—right atrium; RV—right ventricle.

Thrombus characteristics such as size, protrusion, and mobility, which can be accurately evaluated by TTE, also affect the embolic risk. For high-risk patients, prophylaxis with warfarin aiming for an INR of 2.0 to 3.0 is recommended [12•]. The duration of anticoagulation is generally limited to the first 6 months, after which the thrombus is thought to stabilize, and its embolic potential to decrease. Aspirin is generally administered thereafter. However, anticoagulation has also been shown to decrease the risk of stroke by 40% over a 3-year follow-up period in the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial, although at the cost of an increased frequency of major bleeding complications [13]. Long-term anticoagulation appears to be especially beneficial in patients who have decreased left ventricular ejection fraction. In the Survival and Ventricular Enlargement (SAVE) trial [14], every decrease of five percentage points in ejection fraction was associated with an 18% increase in stroke risk. In that study, patients with an ejection fraction equal to or lower than 28% had an almost twofold increase in the risk of stroke compared with patients with ejection fraction over 35%.

Dilated cardiomyopathy

Data on the prevalence of left ventricular thrombi in dilated cardiomyopathy are sparse, with reported figures ranging from 0% to over 30%. Traditionally, the risk of embolization has been considered to be 2% to 4% per year, and to parallel the worsening of left ventricular dysfunction. However, in the Study of Left Ventricular Dysfunction (SOLVD) [15], the relation between worsening ventricular dysfunction and increased thromboembolic risk was observed only in women, who also had a greater absolute risk than men (2.4 events per 100 patient-years, vs 1.8 events per 100 patient-years in men).

In the absence of controlled studies on the efficacy of anticoagulation in patients with left ventricular dysfunction, prophylactic anticoagulation is generally recommended in patients with previous episodes of thromboembolism, documented left ventricular thrombus, or atrial fibrillation [16•]. In patients without any of these conditions, aspirin may represent an effective alternative, while also reducing the risk of bleeding complications. In the previously mentioned SAVE trial [14], aspirin alone appeared to decrease the relative risk of stroke by 56%, an effect only slightly inferior to that of warfarin.

Infective endocarditis

The presence of vegetations on the aortic and mitral valves, most commonly due to infective endocarditis, is associated with an increased risk of stroke. Almost 25% of patients presenting with acute endocarditis, and having one or more TEE-detected valvular vegetations, suffer a stroke early in the course of the disease [17]. The involvement of the mitral valve is associated with a greater stroke risk than when only the aortic valve is affected [17]. TEE has much greater sensitivity than TTE for the diagnosis of endocarditis, and provides information on vegetation characteristics that affect the embolic risk (Fig. 2). Vegetation size over 10 mm, mobility, consistency, and involvement of more than one valve leaflet are all associated with increased embolic risk [17,18,19•]. There appears to be no significant difference among various microorganisms as far as potential for embolization [18], with the possible exception of an increased risk from *Staphylococcus aureus* infection.

The risk of cerebral embolization during infective endocarditis is highest in the first 7 to 10 days after presentation, and decreases thereafter [18], provided effective antibiotic treatment is instituted under the guidance of blood cultures results. Surgery is usually reserved for complications such as intractable congestive heart failure, cardiac abscess, recurrent embolization, or persistently positive blood cultures despite antibiotic treatment. Early surgery is also warranted in the case of fungal endocarditis.

Infective endocarditis is a severe complication in patients with prosthetic heart valves, and warrants early surgical consideration. However, surgery for acute prosthetic endocarditis is a high-risk procedure with considerable morbidity and mortality, especially in the case of mitral involvement.

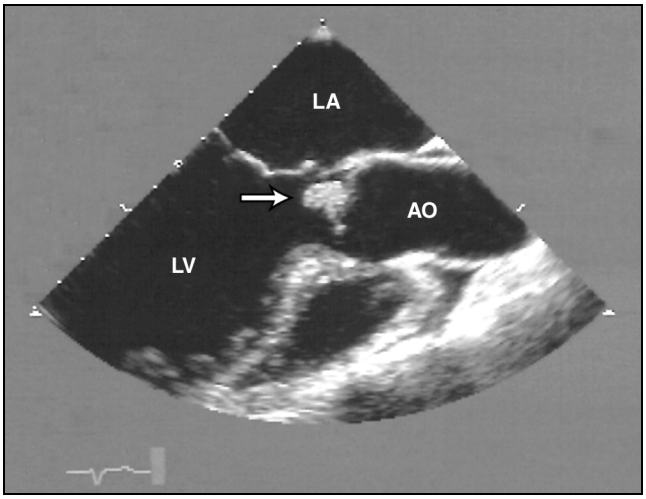

Figure 2. Large vegetation (*arrow*) on the aortic valve by transesophageal echocardiography in the setting of infective endocarditis. Ao—ascending aorta; LA—left atrium; LV—left ventricle.

Cardiac tumors

Primary cardiac tumors are rare, occurring in less than 0.2% of subjects in an unselected autopsy series [20]. However, cardiac tumors, and especially myxomas and papillary fibroelastoma, are associated with high frequency of embolic events. Approximately 75% of all cardiac tumors are benign, 50% of which are myxomas. Myxomas can occur anywhere in the heart, but the left atrium is by far the most common location (about 75% of all myxomas), with the tumor often originating from the fossa ovalis area of the interatrial septum [20]. Due to this preferential location, myxomas tend to embolize to the systemic circulation, with the brain being the most frequent target. Overall, it is estimated that 30% to 40% of myxomas will embolize [20], to the cerebral circulation in over 50% of cases. Embolization may be caused by tumor fragmentation, or secondary to superimposed thrombus formation. Large, mobile myxomas are more likely to embolize, as are myxomas whose surface consists of many fine, villous excrescences, than myxomas with polypoid aspect [20]. TEE is invaluable in defining such tumor characteristics, and therefore guiding the therapy. Occasionally, myxomas may become infected, in which case the risk of embolization greatly increases. Surgical resection of the tumor to prevent embolization is recommended in all cases of myxomas, and especially when one of the aforementioned characteristics is present.

Papillary fibroelastomas are another group of benign tumors frequently associated with cerebral embolism. Fibroelastomas tend to originate on cardiac valves, and may be isolated or multiple. Embolic events are often their first clinical manifestation, due to the tumor location on highly mobile valve leaflets. As for myxomas, the embolic mechanism is often tumor fragmentation, but embolization of superimposed thrombus is also possible. Surgical resection is indicated for fibroelastomas,

with oral anticoagulation usually reserved in cases in which surgery is contraindicated [21].

Malignant primary tumors of the heart (angiosarcoma, rhabdomyosarcoma) are rare. Metastatic tumors to the heart are 20 to 40 times more frequent than primary tumors [21], and may be the result of lymphatic or hematogenous dissemination, or of direct extension. Cerebral embolization may occur as a part of the clinical picture. Treatment may involve surgical resection, but depends largely on the nature and extension of the neoplastic process.

Left atrial thrombus and spontaneous echocontrast

The introduction of TEE has allowed a much better visualization of the left atrium, which, because of its posterosuperior location within the heart, is difficult to image accurately using a transthoracic approach. In particular, TEE allows for the visualization of the left atrial appendage, the most common location for thrombus formation in patients with atrial fibrillation (Fig. 3), and of the atrial side of prosthetic mitral valves, where thrombus or vegetation are more likely to form.

A thrombus in the left atrial appendage is present in 10% to 20% of patients with atrial fibrillation undergoing TEE [22]. Although the prevalence of thrombus is higher with chronic atrial fibrillation (27%), a substantial proportion of patients with atrial fibrillation of less than 3 days duration (14%) may also have it [22]. The frequency of thrombus becomes much higher (up to 40%) in patients with atrial fibrillation and a recent embolic event [23]. In these patients, there does not appear to be any significant difference in thrombus frequency between chronic and paroxysmal atrial fibrillation [22]. Aside from atrial fibrillation, several clinical conditions have been identified that constitute risk factors for left atrial thrombus formation. Among them, those most frequently involved are mitral stenosis, severe left ventricular dysfunction, left atrial dilatation, or the presence of a prosthetic mitral valve.

Cerebral embolization appears to be frequent in patients with left atrial thrombus. The presence of a thrombus in the left atrial appendage on TEE has been shown to be associated with a threefold increase in the risk of stroke [24••]. Oral anticoagulation with warfarin is generally used to promote thrombus resolution, and therefore decrease the associated stroke risk. In a series of 174 patients with left atrial thrombus [25], thrombus resolution was documented in 80% of cases following 47 ± 18 days of therapeutic oral anticoagulation. Therefore, prophylactic anticoagulation for at least 3 weeks has become the norm for patients undergoing electrical cardioversion for atrial fibrillation, a procedure that carries an increased risk of stroke due to the sudden restoration of a coordinated electrical, and therefore functional, left atrial activity. In these cases, anticoagulation should also be continued for several weeks after successful cardioversion, because the occurrence of a period of functional "stunning" of the atrium after cardioversion, and the consequent blood stagnation, may result in thrombus formation. This may later lead to thrombus dislodgment and embolization once the normal atrial function resumes. Recently, however, the use of TEE to guide cardioversion in patients with atrial fibrillation, searching for left atrial thrombus, has been shown to be a viable alternative to prolonged prophylactic anticoagulation, allowing to shorten the duration of anticoagulation in patients without documented thrombus. This strategy does not appear to result in a significant increase in the rate of subsequent cerebral embolization, while also reducing the incidence of bleeding complications [26••]. The indication for anticoagulation following cardioversion remains unchanged even in the case the TEE-guided strategy is adopted.

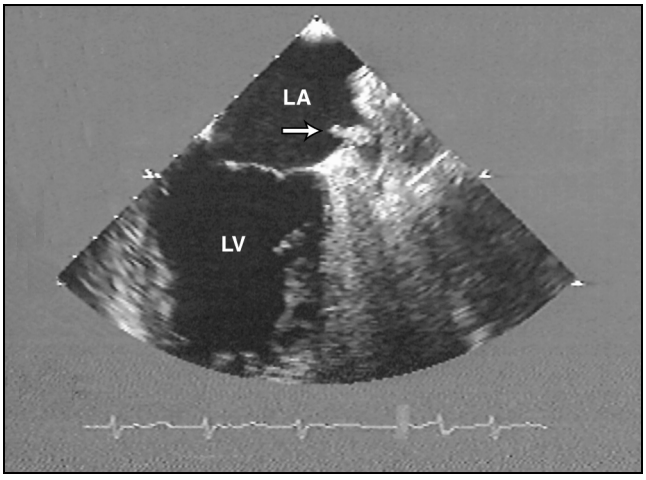

Figure 3. Thrombus (*arrow*) at the entrance of the left atrial appendage by transesophageal echocardiography in a patient with atrial fibrillation. LA—left atrium; LV—left ventricle.

Spontaneous echocontrast (SEC) is defined as swirling, smoke-like echodensities seen within a cardiac chamber, usually the left atrium, in the presence of stagnant blood flow. Because of the proximity of the esophagus to the left atrium, SEC in the left atrium can be easily visualized by TEE. SEC is present in over 50% of patients undergoing TEE for atrial fibrillation [27]. Occasionally, SEC may be present in subjects in normal sinus rhythm (approximately 2% of patients undergoing TEE), but almost exclusively in the presence of a significantly dilated left atrium with depressed function [28]. The presence of SEC is a strong predisposing factor to thrombus formation [24••]. Not surprisingly, therefore, SEC has been shown to increase the risk of ischemic stroke by three to four times [24••,27].

Oral anticoagulation decreases the risk of stroke associated with SEC [24••,27]. In the Stroke Prevention in Atrial Fibrillation (SPAF) III trial [24••], adjusted-dose warfarin treatment was associated with a stroke incidence of 4.5% per year, compared with 18.2% per year for treatment with low-dose warfarin plus aspirin. Adjusted-dose warfarin was also associated with reduced rate of thrombus formation in patients with SEC (4% vs 15%).

Recently Discovered Cardioembolic Sources

In recent years, considerable efforts have been made in trying to decrease the fraction of ischemic strokes labeled as cryptogenic, searching for newer cardioembolic sources that may elucidate the stroke mechanism in individual patients. TEE has been instrumental to this pursuit, allowing for the identification of previously unsuspected embolic sources (such as proximal aortic atheromas), or to a better visualization of embolic sources already suspected on the basis of TTE findings (patent foramen ovale, atrial septal aneurysm).

Proximal aortic atheromas

The presence of large atheromas in the ascending aorta and the aortic arch has been shown to be associated with an increased risk of cerebral embolic events in patients over the age of 60 years. The initial evidence was provided by a large necropsy study [29], in which patients who had died from ischemic stroke had a significantly higher frequency of ulcerated plaques in the proximal portion of the aorta than patients who had died from other neurologic diseases (26% vs 5%). These data have subsequently been confirmed in vivo by several TEE-based studies, both using a case-control design [30,31], or a prospective cohort design [32]. The increase in stroke risk imparted by large or complicated atheromas in these studies has ranged from 2.6-fold to ninefold. Protruding arch atheromas have also been shown to carry significantly increased risk of cerebral embolic events after cardiopulmonary bypass, or following invasive procedures on the ascending aorta, such as cardiac catheterization, and especially intra-aortic balloon pump placement.

The increase in stroke risk from aortic atheromas has mainly been associated in the literature with the thickness of the atheroma, with 4 mm or 5 mm chosen as threshold of increased risk in different studies [30,31]. TEE has been extensively used to assess aortic atheromas, and provides information on atheroma thickness and morphologic features (Fig. 4). It is not entirely clear whether atheroma thickness is directly related to the stroke mechanism, or may represent a marker for other conditions (such as severe, generalized atherosclerosis, including intracranial atherosclerosis), which might be the actual culprit for the stroke. The presence of complex morphologic characteristics of the atheroma (ulcerations or mobile components, the latter indicative of superimposed thrombus) appears more likely to be directly involved in the stroke mechanism, and has indeed been shown to increase the stroke risk by up to 17 times [33]. Conversely, the presence of calcifications within the atheroma has been noted to decrease the risk of stroke in comparison with noncalcified lesions, possibly signaling a more stable atheroma less likely to embolize. Studies are in progress to assess the role of possible cofactors on the risk of stroke. Among them, coagulation abnormalities and lipid disorders might be associated with an increased atheroma-related stroke risk, probably acting through enhanced thrombus formation and plaque destabilization, respectively.

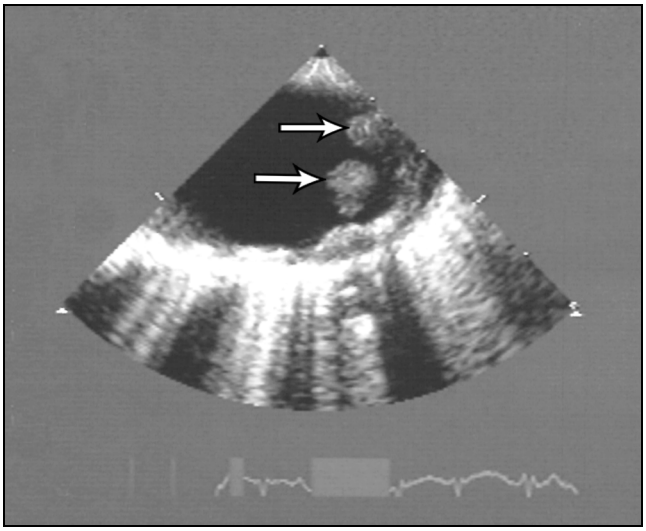

Figure 4. Complex atheroma of the aortic arch by transesophageal echocardiography. Superimposed thrombi (*arrows*) are visible.

The optimal therapeutic approach to stroke patients with proximal aortic atheromas is still controversial. Systemic anticoagulation with warfarin, aimed at achieving an INR between 2 and 3, has been shown to reduce the stroke risk in patients with ulcerated or mobile atheromas [24••]. The indication for anticoagulation in the case of large (> 4 mm thick) but noncomplex atheromas is more controversial, although some data have been published in its support [34•]. Surgical endarterectomy has been proposed to remove atheromas with large mobile components, which are at very high risk for embolization. However, morbidity and mortality for this type of operation have been reported to be very high [35•], suggesting that its use should be reserved to carefully selected cases. To date, there are no controlled studies that have assessed the possible role of antiplatelet agents and lipid lowering drugs to decrease the stroke risk associated with protruding atheromas of the proximal aorta.

Patent foramen ovale

Patent foramen ovale (PFO) is remnant of the fetal circulation that, supposed to close after birth, instead remains pervious in 20% to 25% of normal adults. Although most people will not experience any problem from it, a PFO may occasionally act as a conduit for paradoxic embolization, which is the embolization to the systemic arterial circulation of fragments of a thrombus originating in the systemic venous circulation.

Patent foramen ovale has been shown to be associated with an increased risk of ischemic stroke, and especially cryptogenic stroke [36,37]. This appears to be especially true for younger cryptogenic stroke patients [36]. Paradoxic embolization is advocated as the stroke mechanism for PFO-related stroke, and occasionally cases of thrombus lodged within the PFO have indeed been reported. However, and despite the strong epidemiologic association, a PFO-related stroke in individual patients is usually

a presumptive diagnosis, given the practical impossibility to document paradoxic embolization as the actual culprit for the stroke. Circumstantial evidence may therefore become important in establishing the diagnosis of paradoxic embolization. The presence of a large PFO with significant right to left shunt detected by TEE may lend support to the hypothesis of paradoxic embolization, as larger PFO size (> 2 mm) has been shown to be associated with cryptogenic stroke [38]. Larger PFO size has also been shown to be associated with a greater frequency of superficial infarcts, suggestive of embolic mechanism, on brain imaging [39]. The detection of a coexistent deep venous thrombosis, which has been documented in a substantial proportion of patients with cryptogenic stroke and a PFO, may further corroborate the hypothesis of paradoxic embolization as the stroke mechanism. Blood testing for hypercoagulable states may also be of value in this setting.

Transthoracic echocardiography with contrast injection is usually adopted as a screening test for PFO presence. However, TEE is far more sensitive than TTE for PFO detection, and provides direct visualization of the PFO (Fig. 5), thus allowing measurement of the PFO opening size, and quantification of the associated shunt.

The therapeutic approach to stroke patients with PFO remains controversial. Warfarin or aspirin has empirically been used for secondary prevention, with stroke or TIA recurrence rates ranging from 4.7% to 6.7% per year [40,41]. However, treatment assignment was not randomized in these studies. The relative efficacy of warfarin and aspirin has only recently been tested in a rigorous fashion in the The National Institute of Neurologic Disorders and Stroke-sponsored PFO in Cryptogenic Stroke Study (PICSS), a randomized multicenter study on 630 stroke patients undergoing TEE, the results of which will soon be published. Surgical closure of the PFO has been performed in patients unwilling or unable to be anticoagulated, with stroke or TIA recurrence rates ranging between 4.4% and 9.5% per year in recent series [42,43]. Recently, percutaneous transcatheter closure has also been performed, with recurrent neurological events rate ranging from 2.4% to 6.3% per year in the most recent series [44•,45]. However, the long-term safety of these closing devices is unknown.

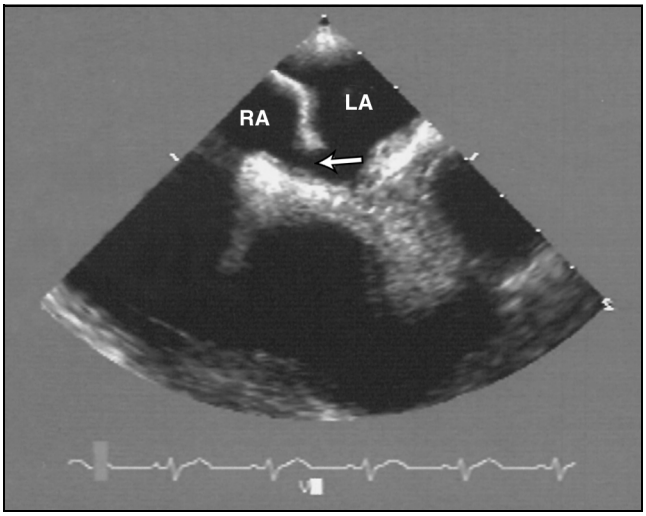

Figure 5. Visualization of patent foramen ovale (PFO) by transesophageal echocardiography. The PFO opening is visible (*arrow*).

Atrial septal aneurysm

Atrial septal aneurysm (ASA) is a discrete protrusion (at least 10 mm) of a portion of the atrial septum into either atrial chamber. This condition, easily to diagnose by TEE and occasionally by TTE, is relatively uncommon in the general population, having been detected in 2.2% of 363 normal subjects undergoing TEE [46•]. Its frequency, however, is three to four times higher in stroke patients than in age-matched controls [46•]. When an ASA is detected, an associated PFO is present in 55% to 70% of cases; therefore, the stroke mechanism associated with the presence of an ASA is thought to be mediated through the PFO in most cases [46•]. An alternative stroke mechanism, in situ thrombus formation and subsequent embolization, appears less often involved. In a series of 195 patients with TEE detected ASA, thrombus was visualized in only two cases [47]. However, the association of ASA and PFO appears to carry a greater stroke risk than PFO alone [40], and it is not entirely clear whether this is due to PFO characteristics (*ie*, larger size of PFOs that are associated with ASA), or intrinsic characteristics of the ASA (thickness, mobility). The therapeutic approach to patients with PFO and ASA is similar to that of patients with PFO alone, with the notable exception that transcatheter closure may be contraindicated, due to the excessive mobility of some ASA.

Valve strands

Valve strands (filamentous material attached to the valve leaflet in the absence of clinical evidence of infective endocarditis) are frequently discovered by TEE, especially on the mitral and aortic valves. Their frequency has been described as high as 40% to 45% in male and female subjects of all ages undergoing TEE [48]. Left-sided valve strands have been linked to an increased risk of stroke in several case-control studies [49,50], but this increased risk has not been confirmed in prospective studies. When valve strands are an incidental TEE finding, the subsequent incidence of cerebrovascular events appears to be as low as 1% to 2% on an average follow-up of 4 years [48]. In elderly patients with a recent prior stroke, mitral valve strands were not found to carry an increased risk for recurrent cerebrovascular events [50]. Because of these findings, it is not clear whether valve strands represent a risk factor for stroke per se, or are rather a marker of other conditions that may predispose to stroke in subsets of patients. Likewise, it is unclear whether any prophylactic treatment for valve strands in stroke patients is necessary, and of which kind (anticoagulation, antiplatelet agents).

Conclusions

Cardiac embolic sources are often implicated in the etiology of ischemic stroke. Recent research, and the introduction of TEE, has led to the identification of newer potential cardioembolic sources for ischemic stroke. This has decreased the proportion of strokes considered cryptogenic, and will conceivably continue to do so in the future. At the same time, a better understanding of traditional embolic sources has resulted in great advancements in the strategies aimed at reducing the associated embolic risk. Further research should be aimed at clarifying the relative importance of newer cardioembolic sources and devising therapeutic options, with the aim to improve preventive strategies for reducing the stroke risk in individual patients.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Flegel KM, Shipley MJ, Rose G: **Risk of stroke in non-rheumatic atrial fibrillation.** *Lancet* 1987, **1:**526–529.
2. Wolf PA, Abbott RD, Kannel WB: **Atrial fibrillation as an independent risk factor for stroke: the Framingham Study.** *Stroke* 1991, **22:**983–988.
3. Krahn AD, Manfreda J, Tate RB, *et al.*: **The natural history of atrial fibrillation: incidence, risk factors and prognosis in the Manitoba Follow-Up Study.** *Am J Med* 1995, **98:**476–484.
4. Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB: **Epidemiologic assessment of atrial fibrillation and risk of stroke: the Framingham Study.** *Neurology* 1978, **28:**973–977.
5. Hart RG, Halperin JL. **Atrial fibrillation and thromboembolism: a decade of progress in stroke prevention**. *Ann Intern Med* 1999, **131:**688–695.
6. Laupacis A, Boysen G, Connolly S, et al.: **Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials.** *Arch Intern Med* 1994, **154:**1449–1457.
7. Hart RG, Pearce LA, Rothbart RM, *et al.*, for the Stroke Prevention in Atrial Fibrillation Investigators: **Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy.** *J Am Coll Cardiol* 2000, **35:**183–187.
8. Stroke Prevention in Atrial Fibrillation Investigators: **Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial.** *Lancet* 1996, **348:**633–638.
9. •• **ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation.** *J Am Coll Cardiol* 2001, **38:**1231–1265.

Extensive review of the state of the art in the management of atrial fibrillation, and guidelines for the treatment of atrial fibrillation and its sequelae.

10. Mooe T, Eriksson P, Stegmayr B: **Ischemic stroke after acute myocardial infarction. A population-based study.** *Stroke* 1997, **28:**762–767.
11. Bodenheimer MM, Sauer D, Shareef B, *et al.*: **Relation between myocardial infarct location and stroke.** *J Am Coll Cardiol* 1994, **24:**61–66.
12. • Fifth ACCP Consensus Conference on Antithrombotic Therapy (1998): **Summary Recommendations.** *Chest* 1998, **114(suppl):**439S–769S.

Recommendations for antithrombotic therapy in a variety of diseases, both from therapeutic and preventive standpoints.

13. Azar AJ, Koudstaal PJ, Wintzen AR, *et al.*: **Risk of stroke during long-term anticoagulant therapy in patients after myocardial infarction.** *Ann Neurol* 1996, **39:**301–307.
14. Loh E, Sutton MS, Wun CC, *et al.*: **Ventricular dysfunction and the risk of stroke after myocardial infarction.** *N Engl J Med* 1997, **336:**1916–1917.
15. Dries DL, Rosenberg Y, Waclawiw M, Domanski M: **Ejection fraction and risk of thromboembolic events in patients with systolic dysfunction and sinus rhythm: evidence for gender differences in the studies of left ventricular dysfunction trials.** *J Am Coll Cardiol* 1997, **29:**1074–1080.
16. • Koniaris LS, Goldhaber SZ: **Anticoagulation in dilated cardiomyopathy.** *J Am Coll Cardiol* 1998, **31:**745–748.

Review of published data on dilated cardiomyopathy and embolic risk, and efficacy of oral anticoagulation and antiplatelet treatment to decrease the risk.

17. Cabell CH, Pond KK, Peterson GE, *et al.*: **The risk of stroke and death in patients with aortic and mitral valve endocarditis.** *Am Heart J* 2001, **142:**75–80.
18. Sanfilippo AJ, Picard MH, Newell JB, *et al.*: **Echocardiographic assessment of patients with infectious endocarditis: prediction of risk for complications.** *J Am Coll Cardiol* 1991, **18:**1191–1199.
19. • Di Salvo G, Habib G, Pergola V, *et al.*: **Echocardiography predicts embolic events in infective endocarditis.** *J Am Coll Cardiol* 2001, **15:**1069–1076.

In 178 patients undergoing TEE for endocarditis, there was a 37% overall incidence of embolic events. Predictors of embolic events were vegetation size (> 10 mm, 60% embolic rate) and mobility (62% embolic rate). Embolic events rate for large (> 15 mm) mobile vegetations was 83%.

20. Reynan K: **Cardiac myxomas.** *N Engl J Med* 1995, **333:**1610–1617.
21. Sastre-Garriga J, Molina C, Montaner J, *et al.*: **Mitral papillary fibroelastoma as a cause of cardiogenic embolic stroke: report of two cases and review of the literature.** *Eur J Neurol* 2000, **7:**449–453.
22. Stoddard MF, Dawkins PR, Prince CR, Ammash NM; **Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study.** *J Am Coll Cardiol* 1995, **25:**452–459.
23. Manning WJ, Silverman DI, Waksmonski CA, *et al.*: **Prevalence of residual left atrial thrombi among patients with acute thromboembolism and newly recognized atrial fibrillation.** *Arch Intern Med* 1995, **155:**2193–2198.
24. •• The Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography: **Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation.** *Ann Intern Med* 1998, **128:**639–647.

Aortic plaques, left atrial appendage thrombus, and spontaneous echo-contrast are all associated with increased risk of thromboembolism in patients with atrial fibrillation. Warfarin treatment decreases the incidence of events associated with spontaneous echo-contrast and complex aortic plaques.

25. Jaber WA, Prior DL, Thamilarasan M, *et al.*: **Efficacy of anticoagulation in resolving left atrial and left atrial appendage thrombi: a transesophageal echocardiographic study.** *Am Heart J* 2000, **140:**150–156.
26. •• Klein AL, Grimm RA, Murray RD, *et al.*, for the 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:**1411–1420.

After transesophageal echocardiography excludes the presence of left atrial appendage thrombus, cardioversion for atrial fibrillation can be safely performed without prior 3 weeks of anticoagulation. Embolic events rate is similar (0.8% vs 0.5%), hemorrhagic events are less frequent (2.9% vs 5.5%, $P = 0.03$).

27. Leung DY, Black IW, Cranney GB, *et al.*: **Prognostic implications of left atrial spontaneous contrast in nonvalvular atrial fibrillation.** *J Am Coll Cardiol* 1994, **24:**755–762.

28. Sadanandan S, Sherrid MV: **Clinical and echocardiographic characteristics of left atrial spontaneous echo contrast in sinus rhythm.** *J Am Coll Cardiol* 2000, **35:**1932–1938.
29. Amarenco P, Duyckaerts C, Tzourio C, *et al.*: **The frequency of ulcerated plaques in the aortic arch in patients with stroke.** *N Engl J Med* 1992, **326:**221–225.
30. Amarenco P, Cohen A, Tzourio C, *et al.*: **Atherosclerotic disease of the aortic arch and the risk of ischemic stroke.** *N Eng J Med* 1994, **331:**1474–1479.
31. Di Tullio MR, Sacco RL, Gersony D, *et al.*: **Aortic atheromas and acute ischemic stroke: a transesophageal echocardiographic study in an ethnically mixed population.** *Neurology* 1996, **46:**1560–1566.
32. Tunick PA, Rosenzweig BP, Katz ES, *et al.*: **High risk for vascular events in patients with protruding aortic atheromas: a prospective study.** *J Am Coll Cardiol* 1994, **23:**1085–1090.
33. Di Tullio MR, Sacco RL, Savoia MT, *et al.*: **Aortic atheroma morphology and the risk of ischemic stroke in a multiethnic population.** *Am Heart J* 2000, **139:**329–336.
34.• Ferrari E, Vidal R, Chevalier T, Baudouy M: **Atherosclerosis of the thoracic aorta and aortic debris as a marker of poor prognosis: benefit of oral anticoagulants.** *J Am Coll Cardiol* 1999, **33:**1317–1322.

Oral anticoagulation with warfarin, besides reducing mortality and embolic events rate in patients with mobile aortic plaques, also reduces the risk of thromboembolic events in patients with large (> 4 mm) but noncomplex plaques (antiplatelet agents vs warfarin: 5.9, 95% CI 1.4–15).

35.• Stern A, Tunick PA, Culliford AT, *et al.*: **Protruding aortic arch atheromas: risk of stroke during heart surgery with and without aortic arch endarterectomy.** *Am Heart J* 1999, **138:**746–752.

In 268 patients with large or mobile plaques in the aortic arch undergoing heart surgery, the incidence of intraoperative stroke was high (15.3%). Age (OR 3.9, $P = 0.01$) and arch endarterectomy (OR 3.6, $P = 0.001$) were independent predictors of intraoperative stroke.

36. Lechat P, Mas JL, Lascault G, *et al.*: **Prevalence of patent foramen ovale in patients with stroke.** *N Engl J Med* 1988, **318:**1148–1152.
37. Di Tullio M, Sacco RL, Gopal A, *et al.*: **Patent foramen ovale as a risk factor for ischemic stroke.** *Ann Intern Med* 1992, **117:**461–465.
38. Homma S, Di Tullio MR, Sacco RL, *et al.*: **Characteristics of patent foramen ovale associated with cryptogenic stroke: a biplane transesophageal echocardiographic study.** *Stroke* 1994, **25:**582–586.
39. Steiner MM, Di Tullio MR, Rundek T, *et al.*: **Patent foramen ovale size and embolic brain imaging findings among patients with ischemic stroke.** *Stroke* 1998, **29:**944–948.
40. Mas JL, Zuber M, for the French study group on patent foramen ovale and atrial septal aneurysm: **Recurrent cerebral events in patients with patent foramen ovale or atrial septal aneurysm, or both, and cryptogenic stroke.** *Am Heart J* 1995, **140:**1083–1088.
41. Cujec B, Mainra R, Johnson DH: **Prevention of recurrent cerebral ischemic events in patients with patent foramen ovale and cryptogenic strokes or transient ischemic attacks.** *Can J Cardiol* 1999, **15:**57–64.
42. Homma S, Di Tullio MR, Sacco RL, *et al.*: **Surgical closure of patent foramen ovale in cryptogenic stroke patients.** *Stroke* 1997, **28:**2376–2381.
43. Dearani JA, Ugurlu BS, Danielson JK, *et al.*: **Surgical patent foramen ovale closure for prevention of paradoxical embolism-related cerebrovascular ischemic events.** *Circulation* 1999, **100:**II 171–175.
44.• Windecker S, Wahl A, Chatterjee T, *et al.*: **Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long-term risk of recurrent thromboembolic events.** *Circulation* 2000, **101:**893–898.

In 80 patients undergoing transcatheter PFO closure after at least one paradoxical embolic episode, the combined incidence of stroke, TIA, and peripheral embolism was 3.4% per year over a mean follow-up of 1.6 ± 1.4 years.

45. Hung J, Landzberg MJ, Jenkins KJ, *et al.*: **Closure of patent foramen ovale for paradoxical emboli: intermediate-term risk of recurrent neurological events following transcatheter device placement.** *J Am Coll Cardiol* 2000, **35:**1311–1316.
46.• Agmon Y, Khandheria BK, Meissner I, *et al.*: **Frequency of atrial septal aneurysms in patients with cerebral ischemic events.** *Circulation* 1999, **99:**1942–1944.

In 363 normal subjects and 355 age- and sex-matched patients with cerebral ischemic events undergoing TEE as part of the Stroke Prevention: Assessment of Risk in a Community (SPARC), prevalence of atrial septal aneurysm was 2.2 % and 7.9%, respectively ($P = 0.002$)

47. Mugge A, Daniel WG, Angermann C, *et al.*: **Atrial septal aneurysm in adult patients. A multicenter study using transthoracic and transesophageal echocardiography.** *Circulation* 1995, **91:**2785–2792.
48. Roldan CA, Shively BK, Crawford MH: **Valve excrescences: prevalence, evolution and risk for cardioembolism.** *J Am Coll Cardiol* 1997, **30:**1308–1314.
49. Roberts JK, Omarali I, Di Tullio MR, *et al.*: **Valvular strands and cerebral ischemia. Effect of demographics and strands characteristics.** *Stroke* 1997, **28:**2185–2188.
50. 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:**1574–1578.