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Chapter

Atrial Cardiopathy and Cryptogenic Stroke

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Abstract

Cryptogenic stroke (CS) is defined as the presence of cerebral infarcts, the cause of which has not been identified despite an appropriate diagnostic evaluation, and it accounts for approximately 30–40% of all ischemic strokes. There is a certain subgroup of CS with embolic characteristics on neuroimaging studies and no evidence of atrial fibrillation alternative or any alternative cause. Recent data suggest that disorders of the atrium, even without atrial fibrillation, could increase thromboembolic risk. The pathological atrial substrate, or atrial cardiopathy (AC), may be an important and underrecognized cause of cryptogenic strokes. This chapter will review the information on the rationale and data behind the concept of atrial cardiopathy, its pathophysiology, proposed biomarkers of atrial cardiopathy, and therapeutic implications.

Keywords: cryptogenic stroke, atrial fibrillation, atrial cardiopathy, atrial disease, atrial dysfunction

1. Introduction

Cryptogenic stroke (CS) can be defined as the presence of cerebral infarcts, the cause of which has not been identified after an appropriate diagnostic evaluation is performed, and it accounts for approximately 30–40% of all ischemic strokes.

To define an ischemic event as cryptogenic, four conditions must be excluded: (1) small deep infarcts in the distribution of penetrating cerebral vessels (<15 mm on CT, <20 mm on MRI diffusion images); (2) intracranial or extracranial stenosis (>50% luminal stenosis of the artery supplying the ischemic area); (3) a defined cardioembolic source identified by transthoracic echocardiography or electrocardiography (ECG); or (4) certain defined entities such as vasculitis, hypercoagulability, migraine, vasospasm, and dissection [1].

There is a subgroup of CS with imaging features suggestive of a distant embolic source. Such characteristics are the presence of multiple, cortical infarcts affecting the territory of major branches of the cerebral arterial tree, with non-lacunar appearance. This subtype has been referred to as Embolic Stroke of Undetermined Source (ESUS) to describe an embolic-appearing CS [2].

Some proposed mechanisms for CS include paroxysmal atrial fibrillation (AF), patent foramen ovale, aortic arch atheroma, atherosclerosis of intracranial and extracranial vessels, hypercoagulability, and cerebral vasculitis.
Identifying the main cause of ischemic stroke is more than an academic issue since each specific stroke subtype often guides secondary stroke prevention strategies.

A novel potential cause of CS is atrial cardiopathy (AC), which involves atrial structural or functional abnormalities that may occur with AF, but also in the absence of AF. There are many CS patients with evidence suggestive of AC indicated by the presence of one of its serum, imaging, or ECG biomarkers, which could potentially explain some of these “unexplained” strokes [3].

Actually, the clinical value of identifying patients with AC is that it not only reduces diagnostic uncertainty, avoiding the need to search for other causes of stroke, but it may also have specific implications for treatment.

2. Atrial cardiopathy: rationale and biological mechanisms

AC is an emerging potential etiology of CS and refers to left atrial structural or functional disorders that may occur with AF but also in its absence. However, if an AF is diagnosed in the context of an ischemic stroke, definite cardioembolic origin is usually established unless a concurrent source is present.

The disorders of the left atrium (LA) can be congenital or acquired. Among the latter, left atrial enlargement (LAE) provides a ground for thrombus formation through stasis, inflammation, and endothelial dysfunction. The consequence may be visible with echocardiography as spontaneous echogenicity, sludge, or directly as a thrombus, all different stages of a thrombotic substrate. In addition, myocardial fibrosis may provide another mechanism for cardiac embolism. It involves the progressive accumulation of fibrotic tissue within the LA myocardium, basically related with the senescence of the heart, but also associated with acute or chronic systemic inflammation. This leads to fibrotic replacement, structural remodeling, and electrical changes, predisposing to AF [4, 5].

Among congenital disorders, certain LA morphologies as well as the size of LAA orifice are thought to increase the thromboembolic risk. A retrospective study of 932 patients with AF who were evaluated with cardiac images (CCT or CMR) categorized the left atrial appendage (LAA) into four distinct morphologies: chicken wing (48%), cactus (30%), windsock (19%), and cauliflower (3%). The prevalence of ischemic stroke among different LAA morphologies was: 4% in chicken wing, 10% in windsock, 12% in cactus, and 18% in cauliflower. Moreover, the number of trabeculations was an independent predictor of stroke risk, and in this regard, the cauliflower morphology seems to have the highest risk. In the same way, LAA flow velocity is a known inverse marker of stroke risk. This flow velocity was highest among patients with chicken wing as opposed to non-chicken-wing morphology, which may also explain why the chicken wing morphology has the lowest risk of ischemic stroke. Also, a larger LAA orifice area has been associated with ischemic stroke. Perhaps, LAA morphology can still be a predictor of thrombus generation and embolic risk even in the absence of AF [6].

Accordingly, these data compilations suggest that electrical AF does not provide the unique explanation for embolic events in patients with evidence of atrial dysfunction and that AC is an innovative factor to keep in mind.

Although the specific criteria for AC are being refined, it may be diagnosed by the presence of one of the biomarkers of left atrial dysfunction that will be detailed below.
3. Biomarkers of atrial cardiopathy

The diagnostic algorithm for AC should follow a step-by-step strategy, in which the risk factors for atrial heart disease, electrical and mechanical atrial dysfunction, and increased thrombotic risk must be identified. The markers of left atrial dysfunction can be divided into three groups:

1. Echocardiographic (enlargement, volume and/or function of the left atrium, anatomy of the left atrial appendage, and spontaneous echocardiographic contrast).
2. Electrocardiographic (increased terminal force of the P wave in V1, episodes of subclinical atrial tachyarrhythmia, atrial extrasystoles, and interatrial block).
3. Serum biomarkers (N-Terminal pro-Brain Natriuretic Peptide and highly sensitive cardiac troponin assay).

3.1 Echocardiographic biomarkers

a. Left atrial enlargement: In population-based studies, LAE has been shown to be associated with incident AF and incident ischemic stroke risk. An analysis from the Framingham study showed that LA diameter was associated with stroke risk in men and women. An analysis from the Northern Manhattan Stroke Study (NOMASS) showed an association between left atrial index and ischemic stroke. Also, this study demonstrated that moderate to severe LAE is an independent predictor of recurrent stroke risk.

b. Spontaneous echogenicity: Spontaneous echogenicity (SE) can be detected by transesophageal echocardiography, less commonly through a transthoracic view. It is an echocardiographic feature characterized by a dynamic smoke-like appearance in the left atrium or left atrial appendage and is a demonstration of blood stasis and hypercoagulability, particularly in an enlarged LA.

c. Echocardiographic markers of left atrial appendage: In sinus rhythm, the LAA is a contractile structure that empties all its contents with each beat. In atrial fibrillation, there is a loss of its contractile property with dilatation, which leads to slowed blood flow, with the consequent increase in the risk of thrombosis. Approximately 90% of the thrombi located in the left atrium are found within the appendage. In fact, recent trials of left atrial appendage closure showed that successful LAA closure was non-inferior to warfarin in reducing the risk of ischemic stroke, suggesting a functional and structural role of the LAA, greater than AF itself, in ischemic stroke risk.

As mentioned above, different LAA morphologies may also be associated with different flow velocities in the LAA, leading to different thrombosis risk levels.

Reduced LAA flow velocity on echocardiography can promote stasis and thrombus formation. In a post-hoc analysis from the Stroke Prevention in Atrial Fibrillation (SPAF)-III trial that included 721 patients who underwent TEE, a peak anterograde flow velocity of less than 20 cm/s was independently associated with thrombus formation and risk of cardio embolism.
3.2 Electrocardiogram markers

a. Paroxysmal supraventricular tachycardia: Although paroxysmal supraventricular tachycardia (PSVT) has been considered a conduction disorder arising mostly in young and healthy individuals, there is evidence that proposes that it occurs in two different populations: young patients with lone PSVT and older patients with cardiovascular disease. Furthermore, there are studies reporting that nearly 12% of patients with PSVT develop incident AF during a 1-year follow-up. It seems that in certain individuals, PSTV may be a prelude of atrial cardiopathy.

b. Increased P-wave terminal force in V1: The P-wave terminal force in lead V1 (PTFV1) on ECG measures the electrical conduction through the atria. Any disorder in atrial functioning may cause prolongation in the P-wave terminal force. Evidence from observational cohorts suggests that elevated PTFV1 is associated with the risk of ischemic stroke, particularly those related to embolism (cryptogenic or cardioembolic) and independent of AF.

c. Others: Prolongation of the PR interval on ECG is another biomarker of atrial disease. There is a reported association between PR interval prolongation and incident AF after cryptogenic stroke. Furthermore, a recent multicentric study showed that a prolonged PR interval (PR ≥ 200 ms) was more prevalent in cryptogenic stroke. Bayes syndrome, an arrhythmological syndrome characterized by advanced interatrial block, is another potential biomarker of atrial cardiopathy. This syndrome is a predictor of AF, ischemic stroke risk particularly of the cardioembolic subtype, silent cerebrovascular disease, and vascular cognitive impairment.

3.3 Cardiac magnetic resonance imaging markers

3.3.1 Atrial fibrosis and delayed gadolinium enhancement

Cardiac MRI (CMR) has been used for cardiac disorders, but its use in cryptogenic stroke is not well established. There is a potential role for CMR in the diagnostic evaluation of patients with cryptogenic stroke to identify potential etiologies such as cardiac thrombi, cardiac tumors, aortic arch disease, and other rare cardiac anomalies. It can also provide data on certain functional and structural parameters of the LA and the LAA associated with ischemic stroke risk. Cardiac fibrosis can be detected on MRI as a delay in uptake of gadolinium. The relationship between cardiac fibrosis on cardiac MRI and stroke risk remains unclear. Therefore, studies investigating this association are needed to determine whether and to what extent gadolinium enhancement is delayed and is associated with thromboembolic risk in the absence of AF.

3.4 Serum biomarkers

a. NT-proBNP: N-Terminal pro-Brain Natriuretic Peptide (NT-pro-BNP) is a serum biomarker of cardiac disease that partly reflects atrial myocyte dysfunction. An elevated NT-pro-BNP level is a marker of cardiac dysfunction and stretch, volume overload, and a predictor of cardiovascular events including incident AF. Studies have shown an association between elevated NT-proBNP and ischemic
stroke, particularly of the embolic subtype. In fact, a post-hoc analysis of the WARSS trial showed a reduction in the risk of stroke or death at 2 years among those patients with the highest NT-proBNP values (> 750 pg./ml) assigned to warfarin rather than aspirin.

b. HS cTnT: Cardiac troponin (cTnT) is another serum biomarker of cardiac injury, often used to determine the presence of cardiac ischemia. A highly sensitive (hs) cTnT assay can detect concentrations more than 10 times lower than conventional assays used for the detection of acute cardiac ischemia. HS cTnT is associated with the risk of cardiovascular events in observational studies. In the ARIC study (n = 10,902, mean follow up 11.3 years), the highest quintile showed an association between hs cTnT and ischemic stroke risk but not between HS cTnT and non-lacunar strokes. Therefore, HS cTnT is another serum biomarker of cardiac injury that is associated with embolic stroke subtypes [7–9].

4. Therapeutic implications

Patients with atrial cardiopathy and cryptogenic stroke may benefit from anticoagulation therapy for secondary stroke prevention. Anticoagulation therapy has been shown to reduce stroke risk in certain cardiac disorders. In patients with AF, anticoagulation with warfarin or a novel oral anticoagulant is associated with at least 50% reduction in risk of stroke or systemic embolism.

Warfarin also reduces the risk of ischemic stroke in patients with mechanical heart valves and in those with left ventricular thrombus after anterior myocardial infarction.

Given that most cardiac thrombi in patients with AF arise in the left atrium/ left atrial appendage, and since anticoagulation is effective in reducing the risk of cardiac thrombi, it is possible that patients with AC and CS constitute another group of patients who may benefit from anticoagulation therapy.

To date, AF is the only marker of left atrial dysfunction for which anticoagulation has been shown to provide a greater reduction of stroke risk than antiplatelet therapy.

Additional trials testing the efficacy of anticoagulant therapy in individuals with markers of AC are required.

The ongoing ATTICUS and ARCADIA trials are trying to validate this hypothesis, and the results may have implications for secondary stroke prevention as well as primary prevention. If anticoagulant therapy demonstrates a reduction in recurrent stroke in the AC high-risk population, it may be beneficial for patients with AC and no history of stroke [3, 10, 11].

5. Conclusions

The key to prevention of stroke is understanding its cause. AC, as determined by the presence of biomarkers of left atrial dysfunction, may constitute one of the mechanisms beyond CS, and validation of this concept would allow a therapeutic strategy to be implemented not only in secondary but also in primary prevention. Awaiting the occurrence or detection of AF in CS patients with AC may expose them to another event, so clinical trials testing anticoagulation versus antiplatelet therapy to reduce stroke risk are needed and welcome.
6. Key points

• AC may be defined as a functional or structural disorder of the left atrium.

• Biomarkers of atrial dysfunction or cardiopathy have been associated with a risk of first and recurrent ischemic stroke, particularly those related to embolism.

• Up to one-third of ischemic strokes are currently cryptogenic. Approximately 65% of CS patients have AC, as evidenced by at least one of its biomarkers.

• 70% of CS patients do not have AF, even after 3 years of cardiac monitoring. This indicates that AF may not be the only necessary substrate for cardioembolism.

• Patients with AC and CS may benefit from anticoagulation therapy for secondary stroke prevention, and ongoing trials are underway.
References


