Atrial cardiopathy: a mechanism of cryptogenic stroke

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Abstract

Introduction—Cryptogenic stroke accounts for approximately 30% of all ischemic strokes. Recently, atrial cardiopathy diagnosed by the presence of one of its serum, imaging, or electrocardiogram biomarkers has been shown to be associated with ischemic stroke, particularly of embolic subtypes.

Areas covered—This paper aims to summarize data on occult atrial fibrillation and stroke, provide an overview on mechanisms, such as inflammation and fibrosis, of stroke in atrial cardiopathy, critically review data on biomarkers of atrial cardiopathy and their association with stroke, and suggest therapeutic implications, including directions for future research.

Expert commentary—Atrial cardiopathy may constitute one of the mechanisms in cryptogenic stroke, and patients with evidence of atrial cardiopathy constitute a group of patients in whom clinical trials are warranted to test anticoagulation versus antiplatelet therapy to reduce stroke recurrence risk. In addition, more studies are needed to determine the degree of overlap between these atrial cardiopathy biomarkers and which one is more useful in predicting the risk of stroke and response to anticoagulation therapy.

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1. Cryptogenic stroke

Several mechanisms can lead to ischemic stroke and, among these, cardioembolic stroke subtype carries the highest risk of mortality and poor functional outcome.[1] Nearly 30% of ischemic strokes, however, are suspected to be related to a proximal cardio-aortic source and are referred to as stroke of unknown cause, or "cryptogenic" stroke.[2] A characteristic imaging finding in cryptogenic stroke is the presence of one or more superficial infarcts on neuroimaging, a finding present in up to 60% of patients with cryptogenic stroke.[3] The appearance of these infarcts, affecting the territory of major branches or distal end vessels of the cerebral arterial tree, suggests a distant embolic source. The recognition of this feature was a driving force for investigators to introduce the term Embolic Stroke of Undetermined Source (ESUS) to describe an embolic-appearing non-lacunar infarct in the absence of intracranial or extracranial stenosis of 50% or more, major cardioembolic source such as atrial fibrillation (AF), or other determined stroke mechanism.[4]

There are several proposed mechanisms for cryptogenic stroke, including occult paroxysmal AF, patent foramen ovale, substenotic atherosclerosis, hypercoagulability, and infectious or inflammatory cerebral vasculitis.[5, 6] Since stroke prevention strategies differ among these mechanisms, determining the root cause of ischemic stroke, where possible, is more than just an academic issue.

2. Subclinical AF and ischemic stroke risk

With the increasing use of cardiac pacemakers, there has been an increased frequency of detection of asymptomatic brief runs of paroxysmal occult AF.[7] Studies investigating the association between these brief asymptomatic episodes of AF and stroke risk yielded mixed results. Studies have shown an increased risk of stroke with runs of AF less than the six minutes typically considered to establish a diagnosis of AF. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study included 4060 patients with AF randomized to rate vs. rhythm control strategies. In this study, 481 patients (12%) had asymptomatic AF and the risk of stroke at 5 years was similar between patients with symptomatic vs. asymptomatic AF (3.8% vs. 4.4%, p = 0.52).[7] In this study, however, nearly 60% of asymptomatic AF episodes were over 30 days in duration and only 4% were of less than 6 hour duration. Therefore, while this study showed an increased risk of stroke in patients with asymptomatic AF, it did not establish an increased stroke risk in patients with brief episodes of AF. The Asymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing Trial (ASSERT) trial enrolled 2580 patients 65 years or older with hypertension and no history of AF in whom pacemakers were implanted. During the first 3 months, 261 (10.1%) patients developed subclinical atrial tachyarrhythmias, and these were associated with increased ischemic stroke risk (HR 2.49 95% CI 1.28-4.85; mean follow up 2.5 years). Moreover, an analysis of the Stroke prevention Strategies based on

Atrial Fibrillation information from implanted devices (SOS AF) project (n = 10,106 patients with cardiac devices and at least 3 months follow up) showed an association between episodes of AF lasting 5 minutes or longer and stroke risk (HR 1.76 95% CI 1.02-3.02).[8] This study, like others, showed an association between AF burden and ischemic stroke risk (adjusted hazard ratio = 1.03 per hour of AF duration; 95% CI 1.00–1.05, P = 0.040).[8] On the other hand, the Registry of Atrial Tachycardia and Atrial Fibrillation Episodes (RATE) enrolled 5379 patients with pacemakers (mean follow up 22.9 months). Compared to patients with no AF, patients with episodes of AF 20 seconds duration (n=12.2%) had a similar risk of stroke or TIA (HR 0.87 95% CI 0.58 – 1.31), whereas patients with episodes of AF 20 seconds or longer were more likely to have incident stroke or TIA (HR 1.51 95% CI 1.03-2.21).[9] A major limitation of this study is the relatively short duration of follow-up and the small number of patients with only short runs of AF. Therefore, it remains unclear whether brief runs of subclinical AF are associated with a high enough stroke risk to warrant anticoagulation.

While anticoagulation therapy has been associated with reduced stroke risk in patients with AF[10], it remains unclear whether anticoagulation therapy reduces the risk of stroke in patients with very brief or infrequent runs of subclinical AF. Ongoing clinical trials will help address this question. The Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA; NCT01938248) trial aims to enroll 4000 patients with device-detected AF of duration between 6 minutes to 24 hours and randomize them to apixaban and aspirin. The primary outcome of this study is ischemic stroke and systemic embolism at 3 years follow up.

3. AF detection after cryptogenic stroke

Prior studies have shown a strong association between AF and ischemic stroke[11], particularly of embolic appearance.[12] Therefore, cardiac monitoring for AF detection after a cryptogenic stroke has been an area of interest. Retrospective studies showed an AF detection rate of up to 7% on serial electrocardiograms (ECGs) or 24-48 hour Holter monitors[13], up to 25% with 28-day cardiac monitors[2, 14], and up to 30% at 3 years using implantable monitors.[15] This research culminated in two randomized controlled trials showing that outpatient cardiac monitoring after cryptogenic stroke can increase detection of AF beyond standard monitoring approaches.

The 30-Day cardiac event monitor belt for recording paroxysmal atrial fibrillation after a cerebral ischemic event (EMBRACE) trial randomized 572 patients 55 years or older with a cryptogenic stroke or transient ischemic attack (TIA) to non-invasive ambulatory 30 day continuous ECG monitoring vs. 24-hour Holter monitor. This study showed an increased detection rate of AF episodes 30 seconds or longer using the 30 day monitor as opposed to the 24-hour Holter monitor (16.1%, vs. 3.2%, p<0.001).[16] The cryptogenic stroke and underlying atrial fibrillation (CRYSTAL-AF) study randomized 441 patients 40 years or older with a cryptogenic stroke or TIA to implantable cardiac monitor (ICM) for 3 years vs. conventional follow-up. This study showed an increased detection of AF lasting 30 seconds or longer in the ICM group as compared to the conventional follow-up group at 6 months (8.9% vs. 1.4%, p<0.001) and 3 years (30.0% vs. 3.0%, p<0.001).[17]

In these studies, over 95% of patients with AF detected were placed on oral anticoagulation therapy for secondary stroke prevention. Although the stroke rate at 1 year was lower in patients randomized to ICM in CRYSTAL-AF as compared to conventional monitoring (7.1% vs. 9.1%, p > 0.05), CRYSTAL-AF was underpowered to determine a secondary stroke prevention benefit[17] and therefore studies are needed to determine whether anticoagulation of patients with brief runs of paroxysmal occult AF detected on outpatient cardiac monitoring after a cryptogenic stroke leads to a reduction in the risk of recurrent stoke.

4. AF and Stroke: association or causality

While AF has been shown to be associated with ischemic stroke, the causal association between the two remains circumstantial.[18] Most importantly, while ASSERT and The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke (TRENDS) both show an association between subclinical AF and ischemic stroke, there was no consistent temporal association between AF and stroke. In both studies, only 25% of patients were in AF in the 30 days prior to their embolic event[19, 20]; this lack of temporality suggests that AF may not be the direct cause of stroke in most patients with this dysrhythmia. Instead, AF may be a marker of an underlying risk of embolic stroke associated with atrial dysfunction.

5. Atrial Cardiopathy: Rationale and Biological Mechanisms

There are many compelling reasons to argue that AF is a marker of atrial disease and that atrial dysfunction or cardiopathy may be the underlying cause of stroke in most patients with this dysrhythmia. The relationship between AF and ischemic stroke does not clearly satisfy the Bradford-Hill criteria for causality.[18] Most importantly, the lack of direct evidence of a causal association, including a temporal relationship, between AF and thromboembolic events in most patients with this arrhythmia provides evidence that atrial cardiopathy may underlie most strokes in patients with AF and that AF is itself another biomarker of atrial disease.[18] In addition, there is data to suggest that relying on a surface ECG to detect AF may underestimate atrial disease or dysfunction and perhaps the attributed embolic risk. There is data, for example, to suggest an electromechanical dissociation between surface ECG and echocardiographic left atrial function. A study of 41 patients with AF after elective cardioversion showed that nearly one-third of patients had non-sinus contraction of the left atrial appendage (LAA) while in normal sinus rhythm on the surface ECG.[21] In fact, another study showed that 6 out of 24 patients with a history of AF and recent stroke undergoing a transesophageal echocardiogram (TEE) had a LAA flow pattern characteristic of AF despite being in sinus rhythm at the time of the TEE. These data suggest the possibility of electromechanical dissociation between the surface ECG and echocardiographic LAA function during episodes of sinus rhythm.[22] Furthermore, certain genetic mutations that are associated with AF can be associated with ischemic stroke even before subjects have evidence of AF. For instance, Icelandic investigators have reported an association between two single nucleotide polymorphisms (rs2200733 and rs10033464) associated with increased risk of AF[23] and ischemic stroke, especially those thought to be cardioembolic, even in those not detected to have active AF.[24]

Another congenital predisposition to embolic risk may be related to the morphology of the left atrial appendage. The LAA varies significantly in shape, size, and orientation to adjacent cardiac structures.[25] A study of 500 postmortem hearts demonstrated that the LAA most commonly has 2 lobes (54%), followed by 3 lobes (23%), 1 lobe (20%), and 4 lobes (3%).[26] In patients with AF, the number of lobes has been shown to be an independent risk factor for the presence of thrombus.[27]

Traditionally, TEE has been used to characterize LAA morphology beyond the number of lobes, too.[28] More recently, cardiac computed tomography (CCT) and cardiac magnetic resonance (CMR) have been used to further describe LAA morphology. A retrospective study of 932 patients with AF who underwent CCT or CMR categorized the LAA into four distinct morphologies: chicken wing (48%), cactus (30%), windsock (19%), and cauliflower (3%) (Figure).[29] In this study, the prevalence of ischemic stroke among different LAA morphologies was: 4% in chicken wing, 10% in windsock, 12% in cactus, and 18% in cauliflower. Compared with chicken wing morphology, there was a higher adjusted odds of stroke or TIA with the other morphologies: cactus (odds ratio [OR] 4.1, p = 0.046), windsock (OR 4.5, p = 0.038), and cauliflower (adjusted OR 8.0, p = 0.056). Other studies of patients with AF have also shown an inverse association between chicken-wing morphology and risk of ischemic stroke[29, 30] and covert brain infarcts.[31] Furthermore, cauliflower LAA morphology was an independent predictor of stroke risk, presumably related to extensive LAA trabeculations.[32] LAA flow velocity, another inverse marker of stroke risk, was highest among patients with chicken-wing as opposed to non-chicken wing morphology,[28, 33, 34] which may also explain why chicken wing morphology has the lowest risk of ischemic stroke. In addition, larger LAA orifice area has also been shown to be associated with ischemic stroke.[30, 35]

It is also possible that LAA morphology is a predictor of thrombus formation and thromboembolic risk even in the absence of AF. More studies are needed to determine the risk of thromboembolic events in patients with non-chicken wing compared to chicken wing LAA morphology in patients without AF.

Other acquired disorders of the left atrium may also provide a milieu for thrombus formation. Left atrial enlargement (LAE), for instance, can promote stasis, endothelial dysfunction, and thrombus formation. LAE has been associated with spontaneous echocardiographic contrast and thrombus formation.[36] In addition, cardiac fibrosis may provide another mechanism for cardiac embolism. Cardiac fibrosis represents the progressive accumulation of fibrotic tissue within the myocardium, a process that occurs with aging of the heart[37–39] and may be particularly more common in patients with systemic inflammatory states (systemic infections and inflammatory disorders) and low-grade subclinical inflammatory states such as coronary artery disease.[40] These result in myocardial infiltration by inflammatory cells such as macrophages and activation of the renin-angiotensin pathway which in turn leads to fibrotic changes and electrical and structural remodeling of the myocardium which is a milieu in which AF occurs.[41] In fact, studies have shown up-regulation of various inflammatory cytokines such as interleukin-1 and 6 in AF, and these cytokines are linked to progression of AF burden and re-occurrence of AF after cardioversion.[18] Therefore, while cardiac fibrosis may occur in the setting of AF-related

atrial remodeling, it can occur with other factors resulting in atrial dysfunction such as advanced age[37–39], valvular heart disease, hypertension, congestive heart failure, and ischemic coronary heart disease.[42] Thus atrial fibrosis may precede AF, or indeed be present even in the absence of development of AF. In fact, recent literature supports the idea that AF likely occurs in the setting of cardiac scar tissue or fibrosis as evident on cardiac magnetic resonance imaging with delayed gadolinium enhancement studies.[43, 44]

Therefore these data combined suggest that electrical AF does not provide the sole mechanism of embolic events in patients with evidence of atrial dysfunction and that other mechanisms such as genetic factors, atrial enlargement, fibrosis, or inflammation may provide an explanation of embolic stroke even in the absence of AF.

6. Biomarkers of Atrial Cardiopathy

6.1 Echocardiographic biomarkers

a. Left Atrial Enlargement—In population-based studies, LAE has been shown to be associated with incident AF[45] and incident ischemic stroke risk after adjusting for several confounders including AF.[46, 47] An analysis from the Framingham study showed that LA diameter was associated with stroke risk in men (adjusted HR per 10 mm increase 2.4, 95% CI 1.6-3.7) and women (adjusted HR per 10 mm increase 1.4, 95% CI 0.9-2.1).[46] An analysis from the Northern Manhattan Stroke Study (NOMASS) showed an association between left atrial index and ischemic stroke (adjusted OR 1.47 per 10 mm/1.7 m^2, 95% CI 1.03-2.11).[47] More recently, another analysis of NOMASS (n = 655 patients, median follow up 4 years) showed that moderate to severe LAE is an independent predictor of recurrent stroke risk, particularly related to embolism (adjusted HR 2.83 95% CI 1.03-7.81).[48] Furthermore, a recent analysis from the Cardiovascular Health Study showed that LAE is associated with prevalent ischemic infarcts (adjusted RR 1.20 95% CI 1.08-1.34) and more so with non-lacunar infarcts (HR 1.28 95% CI 1.06-1.55) but not with white matter disease grade, independent of several confounders such as AF and congestive heart failure (unpublished data). These studies suggest a mechanistic relationship between LAE and ischemic stroke.

b. Spontaneous echocardiographic contrast—Spontaneous echocardiographic contrast (SEC) is rarely detected on transthoracic echocardiography but not uncommonly detected on transesophageal echocardiography. It is characterized by a dynamic smoke-like appearance on echocardiography in the left atrium or left atrial appendage and is probably a manifestation of red blood cell aggregation and hypercoagulability, particularly in an enlarged left atrium.[49] This accounts for at least two of the three factors of Virchow's triad (stasis and hypercoagulability), providing an explanation for the association between SEC and thrombus formation, embolism, and death in patients with non-valvular AF in prior studies. In patients with AF, several studies have shown the association between SEC and thrombus formation. In a post hoc-analysis of the Stroke Prevention in Atrial Fibrillation (SPAF) trials (n = 382 AF patients undergoing TEE), for example, SEC was present in nearly 63% of patients, was associated with LAA thrombus (14% vs. 3%, p< 0.001), and was the only independent predictor of future embolic events.[50]

c. Left atrial appendage echocardiographic markers

c. Left atrial appendage echocardiographic markers—The left atrial appendage is thought to be the main location of left atrial thrombi in patients with AF. In a TEE study that included 317 patients with AF and a recent embolic event, about 20% had evidence of thrombus, all of which were in the left atrial appendage.[51] In fact, recent trials of left atrial appendage closure showed that successful left atrial appendage closure was non-inferior to warfarin in reducing the risk of ischemic stroke, suggesting a functional and structural role of the left atrial appendage, more than the fibrillating left atrium itself, in ischemic stroke risk.[52]

Reduced left atrial appendage flow velocity on echocardiography can promote stasis and thrombus formation. In a cross-sectional study of patients with AF with and without stroke, patients with stroke had a lower left atrial appendage flow velocity (36 ± 19 vs 55 ± 20 cm/s, p <0.001).[35] In a post-hoc analysis from the 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 (relative risk 2.6, p = 0.02) and risk of cardioembolism. [53] A more recent cross-sectional study of 360 patients with atrial fibrillation (160 with stroke, 200 without stroke) also showed that lower left atrial appendage flow velocity was associated with ischemic stroke risk.[30]

While there is evidence that the LAA is the site of the majority of cardiac thrombi in patients with AF, there is limited data to suggest it is also the site of the majority of thrombi in patients with cryptogenic stroke. First, up to 20% of patients with cryptogenic stroke are found to have AF within 30 days of diagnosis.[16] Second, a recent study showed an increased prevalence (65%) of biomarkers of atrial dysfunction (defined by severe left atrial enlargement on 2-D echocardiogram, p-wave terminal force in V1 $\geq$ 5000 μV*ms, or NT-proBNP $\geq$ 250 pg/mL) in patients with cryptogenic stroke.[54] Third, analysis of clot histology showed that clots extracted from patients with cryptogenic stroke were similar to those with cardioembolic stroke subtype suggesting that patients with cryptogenic and cardioembolic subtypes may share the same origin and milieu of thrombus formation.[55] Therefore, the LAA may also be an important site of thrombus formation in patients with cryptogenic stroke, and echocardiographic biomarkers of LAA dysfunction may provide a better estimate of the stroke recurrence risk in this patient population.

6.2 Electrocardiogram markers

a. Paroxysmal supraventricular tachycardia—While paroxysmal supraventricular tachycardia (PSVT) has been considered to be a conduction disorder arising mostly in young and healthy individuals[56], recent evidence suggests that as with paroxysmal AF, there are two subsets of patients with PSVT: young patients with lone PSVT and older patients with cardiovascular disease.[57] Moreover, studies have shown that nearly 12% of patients with PSVT develop incident AF during a 1 year follow up.[58] Therefore, while PSVT may in many patients represent a congential atrial dysrhythmia, it may also be a manifestation of atrial cardiopathy and associated increased stroke risk. In fact, an analysis of a large administrative dataset showed an association between PSVT and stroke risk that was independent of several confounding factors, including AF (adjusted HR 2.10, 95% CI 1.69-2.62).[59]

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.[60] Therefore, disorders causing atrial dysfunction such as hypertrophy, fibrosis, and elevated filling pressures may cause prolongation in the P-wave terminal force.[60, 61] While studies have shown an association between PTFV1 and incident AF[36, 62], recent data also show an association between PTFV1 and ischemic stroke risk independent of AF. An analysis of the Multi-Ethnic Study of Atherosclerosis (n = 6741, median follow up 8.5 years) showed that PTFV1 was associated with incident stroke (HR per SD 1.21, 95% CI 1.02-1.44).[63] Another analysis from the Atherosclerosis Risk in Communities study (n = 14,542 participants, median follow up 22 years) showed an association between PTFV1 and incident ischemic stroke (HR 1.33, 95% CI 1.11-1.59) and incident non-lacunar stroke (HR 1.49, 95% CI 1.07-2.07) but not lacunar stroke (HR 0.89, 95% CI 0.57-1.40).[64] An analysis of the Northern Manhattan Study (n = 1039 participants) showed an association between PTFV1 and incident ischemic stroke (adjusted HR 1.20, 95% CI 1.03-1.39) and particularly of embolic subtypes (adjusted HR 1.31, 95% CI 1.08-1.58).[65] PTFV1 has also been associated with vascular brain injury. Another analysis of the Cardiovascular Health Study (n = 3129 participants) showed an association between PTFV1 and prevalent infarcts (RR per SD 1.09, 95% CI 1.04-1.16) and more so with prevalent non-lacunar infarcts (RR per SD 1.22, 95% CI 1.08-1.38) on follow-up brain MRI.[66] This data suggests a mechanistic relationship between atrial cardiopathy and thromboembolic risk.

c. Others—Bayes syndrome, an arrhythmological syndrome characterized by advanced interatrial block, is another potential biomarker of atrial cardiopathy. Studies have shown that Bayes syndrome is a predictor of AF, ischemic stroke risk particularly of cardioembolic subtype, silent cerebrovascular disease, and vascular cognitive impairment.[67, 68]

Prolongation of the PR interval on ECG is another possible biomarker of atrial disease. Studies have shown an association between PR interval prolongation and incident AF[69] and AF detection after cryptogenic stroke.[70] Furthermore, a recent multicenter study showed that a prolonged PR interval (PR 200 ms) was more prevalent in cryptogenic stroke as opposed to stroke of known non-cardioembolic mechanism.[71]

6.3 Cardiac magnetic resonance imaging markers

a. Atrial fibrosis and delayed gadolinium enhancement—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, independent of AF, remains unclear, however, and therefore studies investigating this association are needed to determine whether and to what degree is delayed gadolinium enhancement associated with thromboembolic risk in the absence of AF.[72]

6.4 Serum biomarkers

a. NT-proBNP—N-Terminal pro-Brain Natriuretic Peptide (NTpro-BNP) is a serum biomarker of cardiac disease. It is released by the myocardium in response to stretch and is increased in heart failure, structural heart disease, AF, and other situations of ventricular strain.[73] NT-proBNP is an independent predictor of cardiovascular events including incident

AF in epidemiological and clinical populations,[74–77] and NT-proBNP has been associated with subclinical cerebrovascular disease[78] and risk of cardioembolic stroke.[79, 80] NT-proBNP is also associated with increased likelihood of detection of paroxysmal AF in patients with ischemic stroke.[81, 82]

An analysis from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort (n = 1502, mean follow up 5.4 years) showed an association between serum NT pro-BNP (highest vs. lowest quartile) and stroke risk (adjusted HR 2.9, 95% CI 1.9-4.5) and this association was strongest with cardioembolic subtypes (adjusted HR 9.1, 95% CI 2.9-29.2).[76] In another study from Sweden (n = 4862 participants, mean follow up 14.9 years), elevated NT-proBNP was associated with ischemic stroke, an association driven by its association with cardioembolic stroke subtype (adjusted HR for 4th vs. 1st quartile 5.64, 95% CI 1.66-19.20).[79] Another analysis from the ARIC study cohort (n = 10,902 participants, mean follow up 11.3 years) showed an association between NT-proBNP level (highest vs. lowest quintile) and ischemic stroke (adjusted HR 2.61, 95% CI 1.83-3.74) and non-lacunar infarcts (adjusted HR 2.29, 95% CI 1.42-3.67), but not lacunar infarcts (adjusted HR 1.22, 95% 0.56-2.66) (23471272)

Therefore, as with other biomarkers of atrial cardiopathy, there is an association of NT pro-BNP and ischemic stroke driven by embolic stroke subtypes, arguing for a mechanistic relationship between the two.

b. HS cTnT—Cardiac troponin (cTnT) is another serum biomarker of cardiac disease. Cardiac TnT is used as a measure of cardiac injury and may be elevated in clinical and subclinical myocardial injury and structural heart disease.[83] 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.[83] HS cTnT has been shown to be associated with the risk of cardiovascular events in epidemiological and clinical populations.[74–77] An analysis of the ARIC study (n = 10,902 participants, mean follow up 11.3 years) showed an association between hs cTnT (highest vs. lowest quintile) and ischemic stroke risk (adjusted HR 2.04, 95% CI 1.42-2.95) and non-lacunar strokes (adjusted HR 2.02, 95% CI 1.22-3.35) but not lacunar strokes (adjusted HR 1.49, 95% CI 0.65-3.39).[84]

Therefore HS cTnT is another serum biomarker of cardiac injury that is associated with embolic stroke subtypes. A better understanding of stroke mechanisms in patients with elevated hs cTnT may help improve stroke prevention strategies.

6.5 Serum mRNA and clot histology

Serum gene expression signatures may differ between stroke subtypes. Investigators have previously identified a set of 40 genes that help distinguish between cardioembolic and atherosclerotic subtypes.[85] In a study analyzing serum mRNA on 76 patients with ischemic stroke, serum mRNA accurately predicted each of cardioembolic and large vessel disease stroke subtypes with very high accuracy (> 90%). In addition, this study found that 41% of patients with cryptogenic stroke had a serum mRNA profile similar to that of cardioembolic stroke and only 17% had a serum profile similar to that of large vessel disease, suggesting that the majority of patients with cryptogenic stroke have a cardiac source.[85]

In addition, histological clot analysis may help identify stroke subtype. An analysis of clot histology in patients with ischemic stroke undergoing mechanical thrombectomy showed that clots extracted from patients with cryptogenic stroke were similar to those with cardioembolic stroke subtype (high proportions of fibrin/platelets, low erythrocytes, and high leukocytes) and different from those with atherosclerotic subtypes, suggesting that patients with cryptogenic and cardioembolic subtypes may share the same origin and milieu of thrombus formation.[55]

7. Atrial cardiopathy and cryptogenic stroke

Atrial cardiopathy may be defined in general terms as a functional or structural disorder of the left atrium. Practically speaking, the value of the term atrial cardiopathy rests in its role as a marker of increased risk of thromboembolism, and particularly stroke. While specific criteria for atrial cardiopathy, or thresholds indicative of increased risk, are evolving, it may be provisionally diagnosed by the presence of one of the biomarkers of left atrial dysfunction discussed above, including left atrial size, P wave dispersion on the EKG, PSVT, atrial fibrosis, or elevation in serum biomarkers associated with atrial dysfunction. Some of these biomarkers may not be specific to atrial dysfunction, and the relative importance of different biomarkers has yet to be established. Thrombus formation in atrial cardiopathy is likely related to the interaction between global cardiac and atrial dysfunction described previously, along with a generalized and local pro-thrombotic and inflammatory state.

In an analysis of the Columbia University Specialized Programs of Translational Research in Acute Stroke (SPOTRIAS) dataset, nearly 65% of patients with cryptogenic stroke have atrial cardiopathy as evidenced at least one of the biomarkers described above. Allowing a 30% detection of AF, this implies that nearly 35% of patients have evidence of atrial cardiopathy without AF.[86] Moreover, another study showed that biomarkers of atrial cardiopathy such as PTFV1 and LAE are weakly associated with AF detection on 30 days monitor after cryptogenic stroke suggesting that previously reported associations between these markers and stroke may not be entirely mediated by concomitant AF.[87] This study, however, had several limitations including a small sample size and no outpatient cardiac monitoring was performed.

Since the concept of atrial cardiopathy is fairly novel, cut off values for its biomarkers remain unclear. In addition, the relationship between these biomarkers is uncertain. For instance, the value of each biomarker when compared to the others and degree of overlap needs to be better established. These biomarkers and their association with cerebrovascular disease are summarized in the Table.

8. Therapeutic implications

Patients with atrial cardiopathy and cryptogenic stroke constitute a group of patients who may benefit from anticoagulation therapy for secondary stroke prevention. Anticoagulation therapy has been shown to reduce the stroke risk in a few 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 embolic.[88–90] In addition, warfarin reduces the risk of ischemic stroke in patients with low ejection fraction when compared to aspirin (HR 0.52, 95% CI 0.33-0.88, p = 0.0055)[91] This benefit, however, was outweighed by an increased risk of intracerebral hemorrhage. Warfarin also reduces the risk of ischemic stroke in patients with mechanical heart valves,[92] and in those with left ventricular thrombus after anterior myocardial infarction.[93]

Since 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 plausible that patients with atrial cardiopathy and cryptogenic stroke constitute another group of patients who may benefit from anticoagulation therapy. In fact, a post-hoc analysis of the Warfarin Aspirin Recurrent Stroke Study (WARSS) provided evidence that in patients with the most elevated NT-proBNP (> 750 pg/ml) treatment with warfarin was associated with a reduced risk of stroke or death at 2 years when compared to treatment with aspirin (HR 0.30, 95% CI 0.12-0.84; P=0.021).[94]

This provides compelling evidence for conducting clinical trials testing anticoagulation therapy vs. antiplatelet therapy in patients with atrial cardiopathy and cryptogenic stroke aiming to improve secondary stroke prevention strategies. To this end, a randomized controlled trial will test the hypothesis that the anticoagulant apixaban is superior to aspirin for patients with unexplained stroke who also have one of several biomarkers indicative of left atrial cardiopathy. This trial, the National Institute of Neurological Disorders and Stroke–funded Atrial Cardiopathy and Antithrombotic Drugs in Prevention after Cryptogenic Stroke Trial (ARCADIA) will enroll 1100 patients with cryptogenic stroke at 120 US sites.

9. Conclusion

Atrial cardiopathy may constitute one of the mechanisms in cryptogenic stroke, and patients with evidence of atrial cardiopathy constitute a group of patients in whom clinical trials are warranted to test anticoagulation versus antiplatelet therapy to reduce stroke recurrence risk. In addition, more studies are needed to determine the degree of overlap between these atrial cardiopathy biomarkers and which one is more useful in predicting the risk of stroke and response to anticoagulation therapy.

10. Expert Commentary

Biomarkers of atrial dysfunction or cardiopathy have been shown to be associated with ischemic stroke risk, and particularly those related to embolism. These biomarkers may help provide a better understanding of stroke mechanisms in patients with cryptogenic stroke and therefore may constitute a therapeutic target to improve stroke prevention strategies in this patient population. It is also important to determine if the stroke risk attributed to these biomarkers is independent of co-existing atrial fibrillation.

11. Five-year view

Clinical trials are needed to study the effect of anticoagulation on reducing the risk of stroke in patients with atrial cardiopathy. In addition, more studies are needed to determine the degree of overlap between these atrial cardiopathy biomarkers, and to establish which biomarkers are most useful in predicting the risk of stroke and response to anticoagulation therapy.

12. Key issues

- Atrial cardiopathy may be defined in general terms as a functional or structural disorder of the left atrium.

- Biomarkers of atrial dysfunction or cardiopathy have been associated with ischemic stroke risk, and particularly those related to embolism

- Nearly 65% of patients with cryptogenic stroke have atrial cardiopathy as evidenced by at least one of the biomarkers

- Patients with atrial cardiopathy and cryptogenic stroke constitute a group of patients who may benefit from anticoagulation therapy for secondary stroke prevention, and ongoing trials are underway.

Acknowledgments

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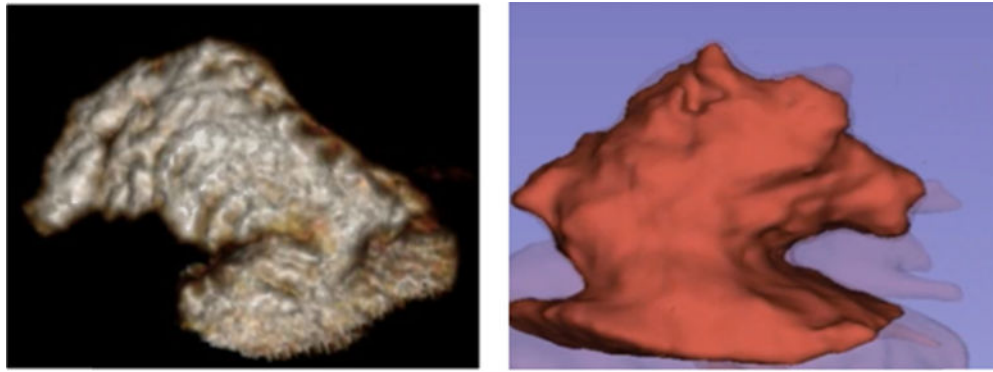
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Figure.
Left side showing a chicken wing left atrial appendage morphology in a 55 year old man with symptomatic carotid stenosis and right side showing the a cauliflower left atrial appendage morphology in a 61 year old man with recurrent cryptogenic strokes.

Table

Atrial biomarkers and stroke

Cardiac biomarker	Association
Atrial Fibrillation	Associated with ischemic stroke and embolic infarcts
Atrial Cardiopathy Biomarkers	
Paroxysmal Supraventricular Tachycardia	Associated with ischemic stroke
Increase P-wave Terminal Force in V1	Associated with ischemic stroke, embolic stroke subtypes, and brain infarcts
Left Atrial Enlargement	Associated with ischemic stroke, embolic stroke subtypes, and brain infarcts
N-terminal pro b-type natriuretic peptide	Associated with ischemic stroke, cardioembolic stroke subtypes, and brain infarcts
High sensitivity cardiac troponin T	Associated with ischemic stroke and cardioembolic stroke subtypes
Left atrial appendage biomarkers in atrial fibrillation	
Left appendage morphology	Non-chicken wing morphology associated with ischemic stroke
Spontaneous echocardiographic contrast	Associated with ischemic stroke risk and embolic events
Reduced left atrial appendage flow velocity	Associated with ischemic stroke