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REVIEW ARTICLE

A review on the spectrum of atrial fibrillation detected after a stroke

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Abstract

This article reviews the concept of atrial fibrillation (AF) detected after a stroke (AFDAS) as a potentially different entity than known AF (KAF). For this, we describe the pathogenesis of neurogenic AF, the relevance of stroke induced heart injury, and other mechanisms in the development of AFDAS as opposed to a cardiogenic mechanism in KAF. Later, we will highlight the differences in characteristics and prognosis of KAF and AFDAS and provide existing evidence that supports the importance of this differentiation for clinical practice and future research.

Keywords: *Atrial fibrillation. Stroke. AFDAS. Pathophysiology.*

Una revisión del espectro de fibrilación auricular detectada después de un ataque cerebrovascular

Resumen

Este artículo revisa el concepto de Fibrilación auricular (FA) detectada después de un ACV (AFDPA) como una entidad potencialmente diferente a la AF conocida (AFC). Para esto describimos la fisiopatología de la AF neurogénica, la relevancia de la lesión cardiaca inducida por ACV (LCIA), y otros mecanismos del desarrollo de AFDPA en oposición al mecanismo cardiogénico de la AFC. Posteriormente, resaltamos las diferencias en características y pronóstico de la AFC y AFDPA y proveemos la evidencia existente que soporta la importancia de esta diferenciación en la práctica clínica y para la investigación a futuro.

Palabras clave: *Fibrilación auricular. Ictus. AFDPA. Fisiopatologia.*

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Introduction

Atrial fibrillation (AF) affects 2-4% of global population[1]. It is characterized by poor contractility, increased automaticity, decreased refractoriness, and re-entry activity[2]. The strong association between AF and ischemic stroke was stablished decades ago, with studies showing an increased risk of stroke in patients with AF (≅ 5 times higher), and a high prevalence of AF in patients with ischemic stroke (≅ 20 to 30%)[3]. Recent studies on sequential heart rhythm evaluation in post-stroke patients have shown that AF can be diagnosed *de novo* in up to 20% of post-stroke patients, half of the diagnosis are made during the hospitalization period, and an additional 11% is diagnosed in the early post-hospitalization months[4]. Previously, the association between AF and stroke was considered to be unidirectional (e.g., AF as the cause of cardioembolic stroke). More recently, the relationship between these two entities has been shown to be more complex than that, as AF and stroke can possibly coexist as bystander and can even be the consequence of a recent stroke through a pathophysiological pathway involving inflammation, autonomic dysfunction and the so-called stroke-Induced Heart Injury (SIHI), as one of the clinical expressions of the stroke-heart-syndrome (SHS)[5].

AF pathophysiology

Most AF cases occur in the context of abnormal atrial substrate (also called atrial cardiopathy) that encompasses chronic structural, electrical, and hemodynamical derangements of the left atrium. This type of AF has been called cardiogenic AF because it entirely depends on cardiac disease[6]. Age is the strongest risk factor for cardiogenic AF, with a yearly increase in prevalence of approximately 5% after the age of 65[7]. AF is more frequent in Caucasians compared with non-Caucasians[8]. Mutations and certain gene polymorphisms for ion channels, transporters, and structural components of myocytes, have been associated with the disease[9,10]. Other conditions associated with AF are cardiovascular risk factors such as hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, and sleep disordered breathing; acute illnesses such as surgery or sepsis; and cardiovascular comorbidities, including coronary artery disease, heart failure, valvular heart disease, and left ventricular systolic disfunction[11-13]. Finally behavioral or social factors such as smoking, alcohol use, obesity, unhealthy dietary habits, sedentary lifestyle, and intense physical activity, are also associated with increased AF risk[11,14]. The multiple atrial abnormalities established in this setting include structural remodeling, abnormalities in calcium handling, fibrosis and conduction slowing and blockade pathophysiological routes which all account for the development and maintenance of arrhythmogenesis[15].

AF can also be secondary to a stroke, as it is one of the manifestations of the SHS, in which case it is called neurogenic AF. Other manifestations of SHS include electrocardiography (ECG) changes (e.g., QT prolongation), heart failure, acute coronary syndrome, Takotsubo syndrome, and sudden death[6,16]. Mainly based on research in animals, three main mediators to SIHI has been described: the first one is an immunological cascade including systemic inflammatory response, pro-inflammatory cytokines, and macrophage infiltration[17]. The second is humoral changes, mainly on norepinephrine levels and catecholamine production systemically and in cardiac tissue respectively[18]. The third mediator is neuronal, where direct damage to the central autonomic network including the insular cortex, amygdala, anterior cingulate cortex, ventromedial prefrontal cortex, etc., is associated with autonomic dysfunction and altered cardiac autonomic control through Vagus nerve and paravertebral ganglia with subsequent arrhythmogenic effects on cardiomyocytes[19]. Stablished risk factors for SHS are stroke severity, stroke involvement of the central autonomic network (especially the insular cortex), age, and previous history of coronary or structural heart disease[16].

Atrial fibrillation detected after stroke (AFDAS)

Rhythm evaluation is a vital step in the study for stroke etiology. ECG, telemetry, Holter, and long-term monitoring are often used to detect AF in patients without a previous diagnosis of it; finding AF in a patient with a history of a stroke usually is considered an indication for oral anticoagulation (OAC)[1]. If AF is newly detected after a stroke, at least two possibilities must be considered: the patient had a previously undetected AF probably secondary to cardiac abnormalities and atrial cardiopathy, or the patient had never had AF before and developed AF as a consequence at least partially of the stroke[20].

Studies comparing AFDAS versus known AF (KAF) in stroke patients have shown that these populations have different baseline characteristics. Patients with AFDAS are healthier than KAF patients: a meta-analysis showed that they have fewer cardiovascular risk factors (hypertension, dyslipidemia, coronary artery disease, prior myocardial infarction, congestive heart failure, peripheral

artery disease and previous stroke or TIA), and fewer cardiac functional or structural abnormalities (left atrial (LA) diameter, left ventricular ejection fraction)[21].

On the other hand, there is evidence supporting that AFDAS patients have larger strokes, higher NIHSS, and higher proportion of insular involvement than both patients with KAF and patients in sinus rhythm[22,23]. AFDAS also seems to occur more frequently among ischemic stroke than in transient ischemic attack patients[24], which aligns with the concept that more severe strokes, which more extensive and definite involvement of the central autonomic network (CAN) would be more likely to be associated with more SIHI. Interestingly, AFDAS status compared to KAF and no-AF has been shown to be associated with additional ECG and echocardiographic markers of SIHI, such as troponin I levels, heart failure (acute or exacerbated), acute coronary syndrome and clinically relevant arrhythmias in post-stroke patients, even after the adjustment for confounders[25]. In the latter study, LA volume index was also associated with AFDAS.

Several markers have been described in association with atrial cardiopathy. These include LA strain, LA size, p-wave terminal force in V1, natriuretic peptides levels, and cardiac troponin levels among many others[6,26,27]. Atrial cardiopathy seems to play a role as facilitator of arrhythmogenesis in AFDAS, just as it does for AF development in patients without a stroke[28]. A "rise and fall" pattern of cardiac troponin typical of acute myocardial injury instead of chronically increased troponin more characteristic of chronic myocardial injury is a biomarker that may be used to differentiate patients with SIHI and probable neurogenic AFDAS from patients with chronic cardiac abnormalities with probable cardiogenic AFDAS[29]. This concept remains to be proven. It seems plausible that KAF and AFDAS patients with a more abnormal atrial substrate share a predominantly cardiogenic physiopathology, and AFDAS patients with a previously normal or close to normal atrial substrate and markers associated to SIHI have a predominant neurogenic physiopathology (neurogenic AFDAS). Atrial cardiopathy may be a facilitator for AF development after a stroke in patients without previous AF.

A recent meta-analysis found that increasing age, female sex, hypertension, NIHSS score, previous stroke, intravenous thrombolysis, brain natriuretic peptide, and high-density lipoprotein levels are associated with AF detection after stroke; and smoking, low-density lipoprotein, and triglyceride levels are associated with no AF detection after stroke[30]. Other studies have also considered ischemic heart disease, LA enlargement, heart failure, and troponin levels as risk factors for AFDAS. A summary of the different markers and predictors of AFDAS, SIHI, and atrial cardiopathy is shown in figure 1.

It must be noted that patients with AF detected on admission ECG do not behave the same as the rest of AFDAS patients[31]. Studies have shown that baseline characteristics and the risk of recurrent stroke are similar to that of patients with permanent AF, so the current recommendation is to consider these patients as not having AFDAS, but a higher burden AF, as they probably have a previously unrecognized AF[32].

AFDAS as an incidental finding

Prolonged cardiac monitoring in patients with subclinical AF and incident ischemic stroke during monitoring have shown that up to 70% of strokes do not have temporal relationship with arrhythmic episodes. In addition, long-term continuous cardiac monitoring in patients with ischemic stroke secondary to large- or small-vessel disease have an AF detection rate of up to 12% in a year[33,34], similar to that found in patients with cryptogenic stroke[35]. This highlights the fact that the detection of AFDAS does not necessarily mean that AF was the etiological determinant for the stroke, and it can be either a bystander or a consequence of the stroke.

Implications of differentiating AFDAS from KAF

There are differences in prognosis between KAF and AFDAS. AFDAS patients have lower AF burden, concept supported by the high proportion of AFDAS episodes lasting < 30 s, having lower rates of sustained AF, and higher rates of spontaneous conversion to sinus rhythm[23,36]. These findings are probably associated to the lower burden of atrial cardiopathy, which is known to have a role in maintaining and perpetuating AF[37]. Additionally, a more benign risk profile of AFDAS has been demonstrated with a lower risk of recurrent stroke than in KAF by around 26%, but with a risk of death not clearly lower. Conversely, the risk of recurrent stroke in AFDAS is twice as high as the risk of patients with no-AF and the risk of death in AFDAS is around 60% higher than that of patients with no-AF[21,29,38,39]. As a consequence, the risk profile of AFDAS as a whole seems to be located somewhere in the middle between KAF and no-AF. The relatively lower embolic risk of AFDAS is explained by the interplay between AF burden, but a lower severity of underlying atrial cardiopathy (e.g., lower prevalence of LA enlargement), and a lower prevalence of other cardiovascular risk factors[29].

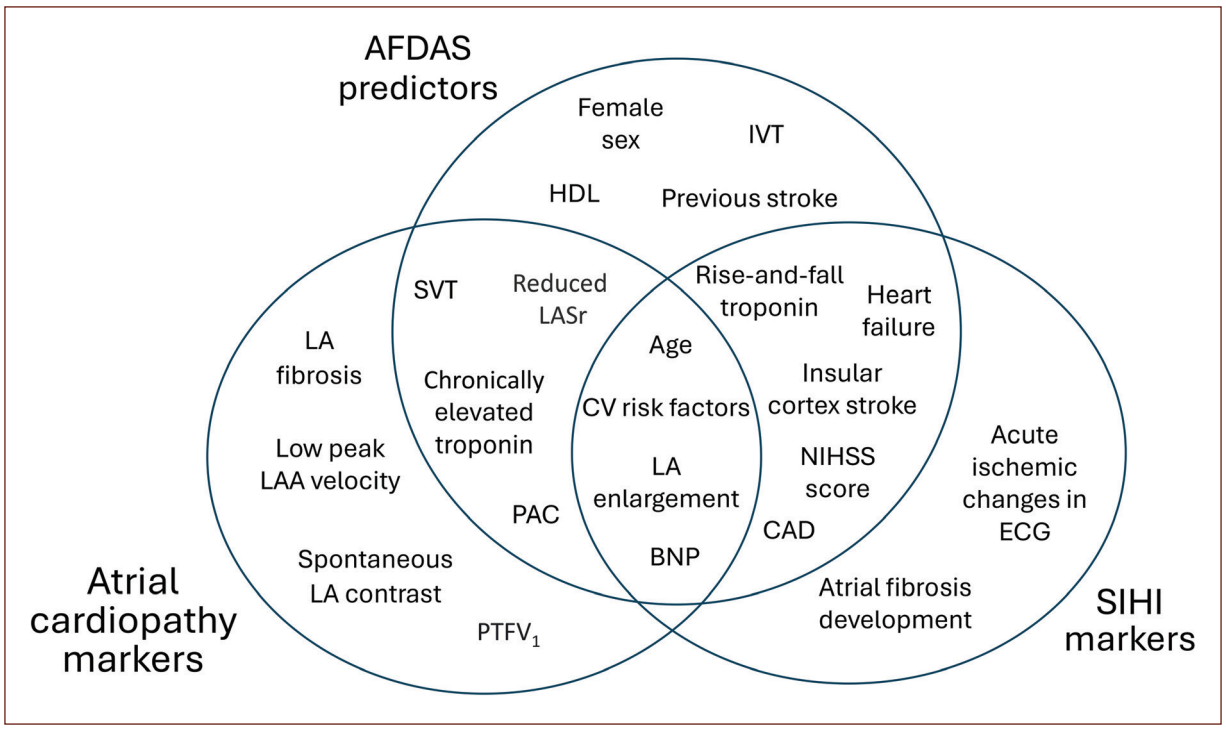

Figure 1. Atrial cardiopathy, stroke-induced heart injury, and atrial fibrillation detected after a stroke proposed markers and predictors. Many of these markers are shared between the three entities. BNP: brain natriuretic peptide; CAD: coronary artery disease; HDL: high density lipoprotein; IVT: intravenous thrombolysis; LASr: left atrial reservoir strain; PAC: premature atrial complexes; PTFV1: P-wave terminal force in lead V1; SVT: supraventricular tachycardia.

AF secondary to thyrotoxicosis has a similar behavior than AFDAS. Studies have shown lower risks of all-cause mortality and ischemic stroke (HR: 0.66, and 0.73 respectively, both with $p < 0.0001$) in patients with thyrotoxic AF compared with non-thyrotoxic AF patients[40]. This supports the idea of non-cardiogenic AF to have a lower thromboembolic risk than cardiogenic AF again probably because of a more normal atrial substrate and lower frequency of cardiovascular risk factors.

A retrospective study showed that OAC is effective in preventing recurrence of stroke in AFDAS patients compared to no-OAC without a significant increase in hemorrhage, but this study was likely based on patients with high burden AF based on a short duration of monitoring for its detection[41]. A recent meta-analysis on prolonged cardiac monitoring-detected AFDAS failed to demonstrate efficacy of this strategy for prevention of ischemic stroke recurrence[29]. To date non-differentiated AFDAS is treated the same way as KAF, and OAC is usually initiated. This approach is further supported by the recent results of the ARTESIA clinical trial, which showed that apixaban reduced the risk of stroke and systemic embolism in patients with device-detected subclinical AF compared to Aspirin[42].

In figure 2, there a schematic representation of the continuum of neurogenic AFDAS, cardiogenic AFDAS and KAF, its baseline characteristics, risk of stroke, and potential benefit from OAC.

Gaps in knowledge

It is challenging to differentiate whether AFDAS is more likely to have neurogenic origin rather than a cardiogenic origin. A *black-or-white* approach to this matter is also probably wrong, as true AFDAS most likely depends on the interplay of both neurogenic and cardiogenic factors[22]. A better understanding on atrial cardiopathy and SIHI markers is needed, as the accurate detection of these entities is a promising strategy to help us determine the pathophysiology underlying an individual's AFDAS and probably improve prognostic and therapeutic approaches.

Possibly, neurogenic AFDAS would require different therapeutic approaches from KAF. Indeed, patients with AFDAS may benefit from early rhythm control[43]. Steroids, statins, β-blockers, renal sympathetic innervation, aldosterone antagonist and renin inhibitors, has been proposed to potentially interfere with AF development in other scenarios and may be used in post stroke patients[20,44-46].

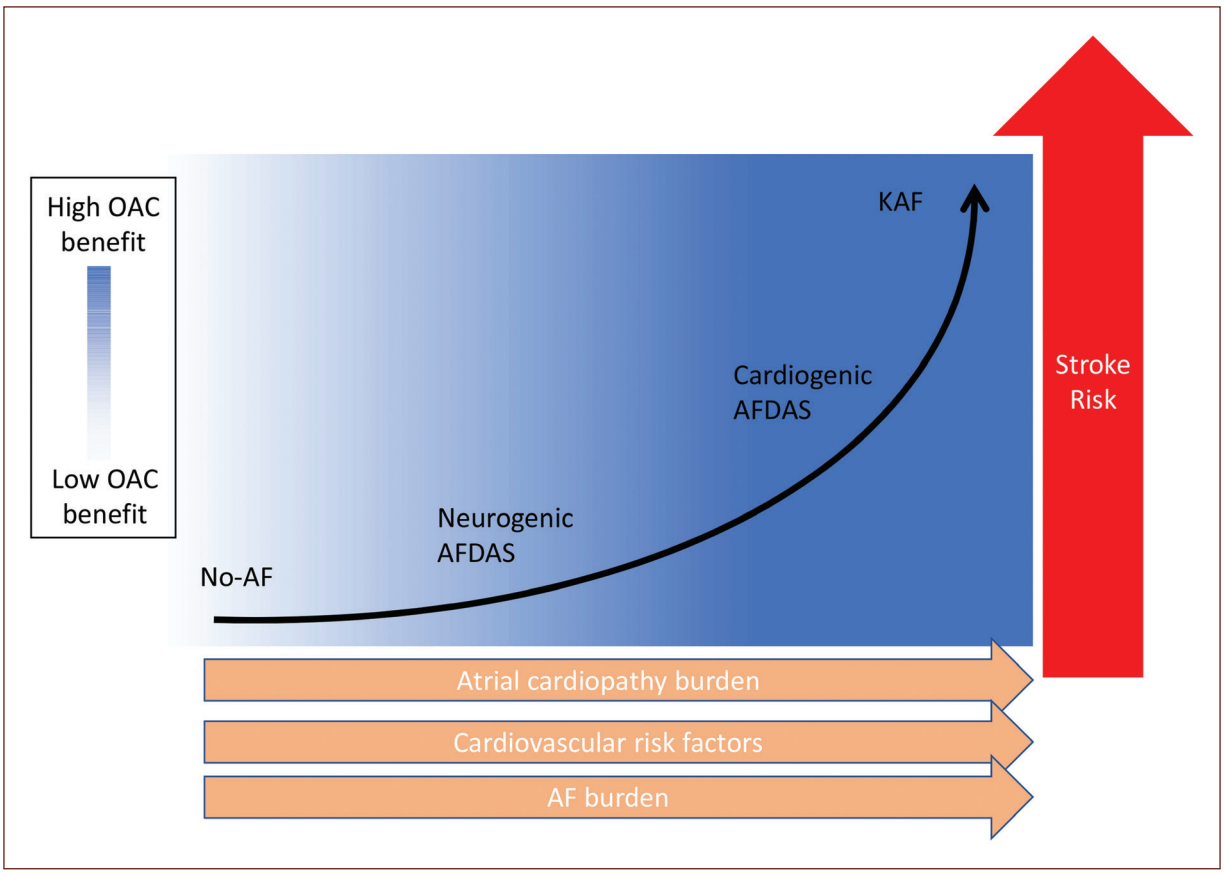

Figure 2. Representation of the spectrum of the disease in AFDAS, where cardiogenic AFDAS is most closely related to KAF in terms of baseline characteristics, burden of the arrhythmia and risk of stroke and neurogenic AFDAS represents a milder entity than both cardiogenic AFDAS and KAF. AF: atrial fibrillation; AFDAS: atrial fibrillation detected after stroke; KAF: known atrial fibrillation; OAC: oral anticoagulation.

Current practice is to use anticoagulation in most AFDAS patients, but data is lacking to determine if selected patients with AFDAS of low embolic risk (low AF burden, few cardiovascular risk factors) may not surpass the currently established threshold for the use direct oral anticoagulants of a ischemic stroke rate > 0.9%/year[47]. Furthermore, current American Heart Association AF management guidelines strongly recommend using anticoagulants in patients with AF and an estimated annual risk of stroke ≥ 2%. It is likely that the majority of cardiogenic AFDAS will benefit from OAC as it is more closely related to KAF, but it is not clear if the subgroup of neurogenic AFDAS has a low enough risk of stroke recurrence where OAC may not be needed. A "pill in the pocket" anticoagulation regime using continuous cardiac monitoring and intermittent periods of anticoagulation when AF is detected may be an alternative approach[48]. Another option would be to use stricter criteria for starting anticoagulation based on higher CHA_2DS_2-VASc score or higher burden of the arrhythmia.

Finally, if AFDAS is detected shortly after the stroke, does it mean that it represents a high-burden AF? or is it because the first few days after a stroke is the period where the manifestations of the SHS are on its peak? Close follow-up to better measure the burden of AF in probably neurogenic AFDAS patients is a possible option to determine if its burden is significant enough to require OAC.

Conclusions

AFDAS constitutes a spectrum of a frequently progressive disease. At the one end, there are patients with lower burden of cardiac abnormalities and cardiovascular risk factors at baseline, where stroke-mediated neurogenic mechanisms could have had more impact on AFDAS development. Some of these patients may

be incidentally diagnosed with AF by applying post-stroke prolonged cardiac monitoring at a very early stage of disease[49]. Others may experience short bursts of neurogenic AFDAS as a transient and self-limited phenomenon. At the other end, there are patients with higher burden of cardiac abnormalities and cardiovascular risk factors before the stroke, in whom cardiogenic mechanisms were probably the cause of asymptomatic AF some time before the stroke, but only recognized after the cerebrovascular event. Recognizing this disease spectrum opens the possibility of offering different therapeutic approaches for neurogenic AFDAS, using maybe more rigorous burden measurement strategies, or a higher threshold for OAC initiation than for cardiogenic AFDAS and KAF. Most importantly, the future research exploring the AFDAS concept may help understand the pathophysiology of AF, both in patients with and without stroke.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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