Newly Detected Atrial Fibrillation after Acute Stroke: A Narrative Review of Causes and Implications

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Keywords

Acute stroke · Atrial fibrillation · Cardiac autonomic nervous system · Poststroke inflammation

Abstract

Cardiac arrhythmias occur frequently in patients with acute stroke, with atrial fibrillation (AF) being the most common. Newly detected AF may lead to increased risk of ischemic stroke, which in turn generates stroke recurrence and adverse outcomes. Currently, most studies are focusing on the role of AF in ischemic stroke and attributing cryptogenic ischemic stroke to previously undetected AF. However, in these studies, subjects used to have neither symptoms of palpitation nor evidence of AF. A better understanding of this association will contribute to the management and therapy for patients after clinical decisions regarding stroke patients. Currently, the definition of newly detected AF has not come to an agreement, and the pathophysiology remains incompletely understood, possibly involving complex alterations in both the autonomic network and humoral regulation. Therefore, this review aims to introduce the definition and epidemiology of newly detected AF after stroke with up-

dated information and elucidate the potential pathophysiology, such as autonomic imbalance, catecholamine surge, poststroke systematic inflammation, and microvesicles and microRNAs.

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Introduction

Various types of electrocardiographic (ECG) abnormalities and cardiac arrhythmias are commonly observed after an acute cerebrovascular event, including ischemic and hemorrhagic stroke. These patterns of abnormalities vary from abnormal T waves and QT prolongation to some serious cardiac arrhythmias, such as atrial tachycardia, atrial fibrillation (AF), and even ventricular arrhythmias [1, 2]. Previous studies have reported a significantly higher frequency of newly detected arrhythmias, primarily AF, in patients with stroke than those without stroke [2, 3].

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Table 1. Summary of the literature describing the prevalence of poststroke AF

Author	Brain lesion	<i>n</i>	Recording method	Duration time	New AF, %
Liao et al. [6], 2007	Acute ischemic stroke	588	Holter monitoring	24–72 h	4.6
Lazzaro et al. [7], 2012	Acute ischemic stroke or TIA	133	Holter monitoring	29.8 h	6.0
Thakkar et al. [9], 2014	Acute ischemic stroke or TIA	52	Holter monitoring	24 h	5.8
Grond et al. [8], 2013	Acute ischemic stroke	1,135	Holter monitoring	72 h	4.3
Sanna et al. [11], 2014	Cryptogenic ischemic stroke or TIA	221	ICM	12 months	12.4
		220	Conventional follow-up		2.0
Tayal et al. [17], 2008	Cryptogenic ischemic stroke or TIA	56	MCOT	21 days	23.0
Bhatt et al. [13], 2011	Ischemic stroke or TIA	62	MCOT	28 days	24.0
Favilla et al. [12], 2015	Cryptogenic ischemic stroke or TIA	227	MCOT	28 days	14.0
Maramattom et al. [21], 2006	ICH	110	Continuous ECG monitoring		12.0
van Bree et al. [20], 2010	ICH	31	Admission ECG		10.0
Frontera et al. [22], 2008	SAH	580	Continuous ECG monitoring		3.2

ECG, electrocardiographic; AF, atrial fibrillation; SAH, subarachnoid hemorrhage; ICH, intracerebral hemorrhage; TIA, transient ischemic attack.

It is well-recognized that AF is the most common sustained cardiac arrhythmia and known as a key risk factor for ischemic stroke, increasing its risk by 5- to 6-fold independent of other risk factors [4]. Nevertheless, new AF can also be detected in patients after acute stroke without previous evidence of cardiac arrhythmias. A better understanding of this association will contribute to the management and therapy for patients after clinical decisions regarding stroke patients, such as how to choose an appropriate cardiac recording strategy, and whether to use oral anticoagulant therapy for stroke recurrence prevention.

Prevalence of Newly Detected AF after Stroke

AF detected after stroke is so complex that no currently used term fits adequately. We propose the term newly detected AF for AF detected by any ECG monitoring technology in patients (no previous past or recent history of AF) after stroke onset, which may consist of both pre-existing undetected AF prior to stroke and poststroke AF. Over 70% of cases have been diagnosed within the first 3 days after admission [5].

The incidence of new AF reported in studies varies from choices of cardiac monitoring device, interval between the start of monitoring and stroke onset, duration of cardiac monitoring, and different types of stroke, which is the most appropriate monitoring method is still up for debate. The literature describing the prevalence of poststroke AF is summarized in Table 1. It is observed that continuous monitoring methods could identify more AF than a routine Holter monitoring after acute stroke [6–14].

Given the paroxysmal characteristic of new AF, current guidelines recommend an ECG monitoring for 24 or more hours to exclude AF in patients with an acute ischemic stroke. However, the most effective and appropriate period of monitoring has not come to an agreement. It has been confirmed that a longer duration of monitoring substantially leads to increased detection of AF after ischemic events [15, 16]. In an analysis including a total of 8,715 patients from 31 studies, new AF was detected in 5.1% of patients with monitoring lasting <72 h, whereas the detection increased to 15% in studies with monitoring lasting more than 7 days [15].

Time between stroke onset and the start of monitoring should also be taken into consideration. For example, it

has been reported that initiation of MCOT 21 days after acute stroke yielded a 23% prevalence of new AF [17]. When intervals extended up to 33 and 77 days after the index event, a 17 and 16% prevalence of new AF was yielded, respectively [10, 14], demonstrating increased detection with earlier monitoring.

However, most of the above mentioned studies emphasized the role of previously undetected AF in acute ischemic stroke and failed to recognize that AF can also be the outcome of acute stroke, which is termed post-stroke AF. It has been reported that most cases of post-stroke AF could be detected within the first 3 days after admission and disappeared after a few days. The duration and potential recurrence of poststroke AF ranged from 3 to 77 days, 23 days on average [18]. Therefore, we believe that the earlier the episode of AF occurs after stroke, the more evident that AF will be a consequence of the stroke and not the cause of it.

Additionally, this hypothesis may be partly supported by new AF in patients with hemorrhagic stroke. The prevalence of new AF is less common in patients with hemorrhagic stroke, including intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), than with ischemic stroke [19–21]. In a cohort of 110 patients with no history of heart disease or ECG abnormalities, ECG abnormalities were identified in 64% after ICH, in which AF or flutter was 12% [21]. There are more literature reporting on ECG abnormalities in patients with SAH compared to ICH, and SAH seems to produce a more pronounced arrhythmogenic risk and clinical outcome [22]. But few studies specifically describe the prevalence of AF in patients after hemorrhagic stroke.

Pathophysiology

Autonomic Nervous System

ANS and AF

A number of animal and clinical studies have demonstrated that imbalance of the cardiac autonomic nervous system (ANS) plays a key role in AF occurrence and maintenance, and parasympathetic and sympathetic overactivity can both increase the vulnerability of AF. Early research found that vagal nerve stimulation may induce AF in dogs [23]. The effect of the vagal nerve on the atrium is mainly caused by the release of acetylcholine in the peripheral nerve, which activates acetylcholine potassium channel current on the myocardial membrane, resulting in shorter action potential duration (APD) and atrial effective refractory period (AERP), and a larger dis-

persion of AERP [24]. Later, however, a series of studies showed that low-level vagal nerve stimulation can prevent atrial structural remodeling (atrial enlargement and atrial fibrosis) and electrical remodeling (AERP shortening and dispersion of AERP increasing), which is considered as one of the most important mechanisms of genesis and progression of AF, thereby inhibiting AF occurrence [25, 26].

In addition to parasympathetic nerve, the role of sympathetic nerve seems to be more significant in the development of AF. It has been demonstrated that the increased distribution of sympathetic nerve in atrium is closely associated with AF inducibility and duration. Therefore, methods trying to attenuate sympathetic activity, such as stellate ganglion ablation and renal sympathetic denervation, can obviously inhibit AF inducibility [27, 28].

The principle sympathetic neurotransmitter norepinephrine interacts with β -adrenergic receptors on cardiomyocytes to execute adrenergic action, which provides a positive effect to Ca^{2+} -dependent cardiac function. However, the enhanced Ca^{2+} handling produced by β -adrenergic activation also promotes an ectopic activity via several mechanisms, such as enhanced automaticity, early afterdepolarizations, and delayed afterdepolarizations.

Imbalance of ANS after Acute Stroke

Clinical and experimental research has shown that autonomic dysfunction is commonly observed after acute stroke, which is generally evidenced by the loss of physiological regulation on heart rate and blood pressure. This abnormality further leads to reduced heart rate variability (HRV) and impaired baroreceptor reflex sensitivity (BRS) and increased catecholamine and cortisol levels [29]. The high-frequency (HF) component of HRV is generally representative of parasympathetic activity, and the low-frequency (LF) component is thought to be the combined sympathetic and vagal response to arterial baroreceptors. Roughly, a relatively greater parasympathetic activity is reflected by a low LF/HF ratio, while a higher sympathetic activity is reflected by a high ratio [30]. In a recent clinical study, HRV abnormalities were found in almost all patients with acute stroke, of whom 60% had an increased LF/HF ratio, suggesting a higher sympathetic activity [31].

The baroreceptor reflex can stabilize the heart rate and blood pressure when our body position changes. Impaired BRS was reported in patients with acute and subacute stroke [32]. Both reduced HRV and impaired BRS seem to

Fig. 1. Neural mechanism of poststroke AF. An acute stroke leads to autonomic imbalance, either parasympathetic overactivity or sympathetic overactivity. The excessive parasympathetic discharge results in a shorter APD and AERP, and a larger dAERP, by activating $I_{K_{ACh}}$, producing the spatial heterogeneity and reentry in atrium. Sympathetic hyperactivity after stroke leads to excessive release of catecholamines, which activates β -adrenergic receptors

on myocardial cells. Overactivation of β -adrenergic receptors can lead to abnormal cardiomyocytes Ca^{2+} handling, promoting an ectopic activity. Additionally, adrenergic activation can also lead to structural remodeling such as cell necrosis, myofibrillar degeneration, and fibrosis. AF, atrial fibrillation; APD, action potential duration; AERP, atrial effective refractory period; dAERP, dispersion of AERP; $I_{K_{ACh}}$, acetylcholine ACh potassium channel current.

be associated with poorer prognoses and long-term mortality in patients with acute ischemic stroke [32, 33].

Taken together, an imbalance of ANS after acute stroke, mainly sympathetic overactivation, may underlie the pathophysiology of AF occurrence. Autonomic imbalance may lead to atrial structural and electrical remodeling, increasing AF inducibility directly or indirectly. The neural mechanism of poststroke AF is described as Figure 1. Notably, poststroke autonomic imbalance might contribute not only to AF but also to other fatal and non-fatal arrhythmias and even myocardial injury [34].

Lesion Location on Cardiac Arrhythmia

There possibly exists a link between lesion location in the brain and the occurrence of severe cardiac arrhythmias, with the most important area being the insular cortex. The insular cortex and the subinsular white matter, which has blood supplied by the middle cerebral artery, serve as a crucial role in the central regulation of the autonomic network [29]. Damage of the insular cortex was independently associated with poststroke AF, with patients with insular cortex damage showing a 7-fold higher risk of AF than patients without insular involvement [35].

Interestingly, the role of the left and right hemisphere in regulation of autonomic nerve function may not be symmetrical. An early study reported that the heart rate decreased in patients with right-hemispheric inactivation by right intracarotid amobarbital injection, whereas the increased heart rate was observed after left-hemispheric inactivation by left intracarotid amobarbital injection [36], suggesting the right hemisphere primarily controls sympathetic activity, whereas parasympathetic activity is mainly controlled by the left. In a clinical research, including 103 patients with acute ischemic stroke, decreased HRV and frequent complex arrhythmias were more pronounced in subjects with right insular cortex infarction [37], which further suggested an ischemic lesion in the right insular cortex could reduce sympathetic tone and result in parasympathetic overactivity.

However, not all data support this hypothesis. Several clinical studies have suggested that ischemic stroke involving the right insular cortex might produce a much more excessive pathological discharge of the sympathetic nervous system than other regions of brain [38, 39]. The conflicting evidence indicates that the understanding of location for autonomic control centers may be oversimplified.

Besides the insular cortex, other parts of the cerebrum such as the anterior cingulate cortex, amygdala, parabrachial nucleus, hypothalamus, and periaqueductal gray matter are also involved in the central control of ANS and modulation of cardiac function [40]. Nevertheless, the connection between lesion location in the cerebrum and arrhythmia occurrence, especially AF, has been not clarified.

Catecholamine Surge and Myocardial Damage after Acute Stroke

Accumulated evidence has suggested both ischemic and hemorrhagic stroke can lead to myocardial damage, even in the absence of coronary heart disease. Elevated levels of TnI in plasma have been reported in up to 34% of patients with acute ischemic stroke and shown to be dependent on new-onset AF after ischemic stroke, which might serve as a predictor for the risk of new AF in post-stroke patients [41, 42].

The catecholamine surge hypothesis is possibly the most widely accepted mechanism linking myocardial damage to acute stroke. Released from the adrenal medulla and the sympathetic nerve endings, the secretion of catecholamines is mainly regulated by the activity of ANS. Several early studies have reported an elevated cat-

echolamine concentration in plasma after acute cerebrovascular events, accompanied by an increased incidence of arrhythmias. Sympathetic hyperactivity after stroke leads to excessive release of catecholamines. Catecholamines can enhance the activity of L-type Ca^{2+} channel and elevate the concentrations of Ca^{2+} in cytoplasm by activating β -adrenergic receptors on myocardial cells, thereby strengthening myocardial contractility. However, overactivation of β -adrenergic receptors can lead to intracellular Ca^{2+} overload and the muscle's failure to relax, resulting in metabolic imbalance and cell death [43]. In addition to myocardial necrosis, cardiac hypertrophy, myofibrillar degeneration, and fibrosis have also been reported in patients after stroke [44]. All of these may contribute to structural remodeling and abnormal conduction in the heart, which possibly serves as the substrate for AF occurrence and maintenance (Fig. 1).

Inflammation

Inflammation after Acute Stroke

Poststroke inflammation is an essential factor in stroke progression and other secondary complications such as brain edema, pathogen infections, and cardiovascular events. In the acute phase of stroke, cerebral injury leads to local inflammatory responses including microgliosis and astrogliosis, resulting in massive secretion of cytokines and chemokines [45], which occurs together with endothelial cell damage [46]. Increased blood – brain barrier (BBB) permeability, as a consequence of damaged endothelial cells, facilitates the infiltration of peripheral leukocytes and macrophages into cerebral tissue [47]. Necrotic cells from the ischemic lesion area release damage-associated molecular pattern molecules (DAMPs), such as high mobility group box 1 (HMGB1), heat shock proteins, and Peroxiredoxin (Prx) family proteins, for initial induction of the inflammatory response [48, 49].

HMGB1 can not only act the role of cytokine but also enhance the binding of other cytokines to Toll-like receptors (TLRs), especially TLR2 and TLR4, thus mediating inflammatory reaction. In addition to TLRs, HMGB1-RAGE-mediated pathway is also responsible for the activation of poststroke inflammation [49]. Prx family proteins are another key DAMP. When released extracellularly from necrotic cerebral cells, Prx proteins act as a neurotoxic danger signal initiating systematic inflammation by binding to TLR2 and TLR4 [48]. A recent study indicated that Prx proteins released extracellularly 12 h after stroke onset, delayed but existing longer than HMGB1 [48].

These DAMPs can primarily stimulate the migration and activation of macrophages via TLR2 and TLR4, which are originally responsible for sweeping away cell debris and helping restore neuronal functions. Nevertheless, once excessively activated, they can produce an adverse effect on neurons and endothelial cells and disrupt neurogenesis [47]. Activated microglia and macrophages polarize into the proinflammatory phenotype M1 and release proinflammatory cytokines [50]. As previously mentioned, increased BBB permeability, which may be further exacerbated by increased inflammatory cytokines, also facilitates these proinflammatory molecules to pass through the damaged BBB into the peripheral circulation, thereby inducing systematic inflammation.

Except for DAMPs, brain-derived antigens released from injured brain cell are also involved in the poststroke inflammatory response, such as glial fibrillary acidic protein, S100, and myelin basic protein [51]. After stroke, lymphocytes infiltrate the ischemic area for contact with brain-derived antigens from the peripheral immune system [52]. Meanwhile, the serum levels of brain-derived antigens markedly increased in patients after stroke, which might allow lymphocytes to encounter these antigens in peripheral lymphoid organs, inducing systematic inflammation [53].

A recent study has documented that the infiltration of neutrophils, lymphocytes, and macrophages was much higher in the myocardium of patients who died after SAH, suggesting a link between stroke and cardiac local inflammation [54]. However, the relationship between ischemic stroke and cardiac local inflammation has not been clearly reported.

AF Induced by Inflammation

AF may be one of the major secondary complications of systematic inflammation after stroke. It has been demonstrated that the presence of inflammation either in the myocardium or peripheral circulation is associated with AF occurrence and recurrence in postoperative AF [55]. A series of studies that examined interference with intrinsic and extrinsic cardiac autonomic nerves further support the intimate relationship between the levels of inflammatory factors and AF induction [28, 56–58].

Inflammatory mediators gradually lead to the alteration of atrial electrophysiology and structural substrates via different signal pathways, thereby resulting in the increased AF vulnerability. The detailed molecular pathophysiological mechanisms of electrical and structural remodeling in AF [59] and the association between inflammation and AF [55] have been previously reviewed respectively.

Different inflammatory cytokines have distinct influences on the function of ion channels and the change of structural substrates. For example, mice overexpressing tumor necrosis factor (TNF)- α in the heart had prolonged APD, decreased contractile function, and abnormal systolic and diastolic Ca^{2+} handling compared with a control group [60]. In addition to electrical remodeling, TNF- α can also activate myofibroblasts and increases the secretion of matrix metalloproteinase 2 in mice through the transforming growth factor- β signal pathway, which may contribute to atrial fibrosis and AF development [61].

Interleukin (IL)-6 is a pleiotropic cytokine acting as a mediator for both proinflammatory responses and cytoprotective functions. It physiologically promotes the synthesis of multiple inflammatory factors, such as TNF- α , C-reactive protein, fibrinogen, and IL-1 β [62]. Additionally, IL-6 promotes the expression of ICAM-1 and the activation of matrix metalloproteinases in cardiocytes, thereby inducing cardiomyocyte apoptosis and fibrosis.

Platelet-derived growth factor (PDGF), mainly produced by myofibroblasts and mast cells, is another inflammatory cytokine that has influence on both electrical and structural alterations in cardiomyocytes. It has been reported that PDGF-A promoted cell proliferation and collagen expression in cardiac fibroblasts in mice, contributing to atrial fibrosis and increased AF susceptibility [63]. Administration of PDGF has also been demonstrated to result in a significant reduction in peak L-type Ca^{2+} current density and Ca^{2+} transients in atrial myocytes, as well as APD shortening, which might contribute to atrial electrical remodeling [64].

In summary, after stroke, increased BBB permeability facilitates multiple DAMPs and inflammatory factors to infiltrate into the peripheral circulation, thereby inducing systemic inflammation. Meanwhile, these DAMPs can not only interact with immune cells but also directly activate the TLRs on the myocardial membrane, inducing the synthesis and release of inflammatory factors. Under the different effects of inflammatory factors, irreversible electrophysiological changes and structural remodeling gradually occur in atrium, promoting the occurrence and maintenance of AF. The inflammatory mechanism of poststroke AF is described as in Figure 2.

Microvesicles and MicroRNAs in Poststroke AF

Microvesicles are small membrane-enclosed vesicles produced by the outward budding and exocytosis of the plasma membrane into the extracellular space by several cell types. They mediate the interconnections among cells

Fig. 2. Inflammatory mechanism of poststroke AF. DAMPs and antigens release from lesion areas after acute stroke, which promotes the filtration of macrophages and lymphocytes and the releasing of proinflammatory cytokines. Increased BBB permeability, which may be further exacerbated by increased inflammatory cytokines, facilitates these proinflammatory molecules to pass through the damaged BBB into the peripheral circulation, thereby inducing systematic inflammation. The above pathological pro-

cesses ultimately contribute to the atrial electrical and structural remodeling, which possibly serves as the substrate for the occurrence and maintenance of AF. TNF- α , tumor necrosis factor- α ; IL-6, interleukin-6; IL-1 β , interleukin-1 β ; TGF- β , transforming growth factor- β ; PDGF, platelet-derived growth factor; AERP, atrial effective refractory period; dAERP, dispersion of AERP; DAMPs, damaged associated molecular patterns; BBB, blood – brain barrier.

to participate in different physiological or pathological processes such as inflammation, coagulation, and tumor progression [65]. A number of studies indicate that microvesicles may play a crucial role in secondary complications after ischemic and hemorrhagic stroke. It has been shown that the circulating levels of microvesicles are markedly elevated in patients with ischemic stroke, ICH, and SAH, and are consistent with a poorer clinical outcome [66–68]. A recent study has shown that the serum levels of microvesicles significantly increased in patients with persistent AF, which might mediate inflammation and platelet activation [69]. Therefore, we hypothesize that microvesicles may also serve as a mediator in poststroke AF.

MicroRNAs (miRNAs) are highly conserved noncoding RNAs that are abundantly contained in microvesicles and regulate gene expression at either the transcriptional or posttranscriptional level. Recent studies have revealed a pivotal role of miRNAs in the initiation and progress of cardiovascular disease, including AF. The role of miRNAs in the pathophysiology, diagnosis, and prognosis for AF has been exclusively reviewed [70]. Up until now, several miRNAs in atrial tissue, such as miR-1, miR-21, miR-26, miR-29, miR-30a/b, miR-31, miR-328, and miR-208a/b, have been reported to participate in atrial electrical and structural remodeling [70]. Interestingly, some of them like miR-21, miR-29, and miR-30a are also found to be upregulated in plasma samples of patients with acute

Fig. 3. The possible role of microvesicles and miRNAs in post-stroke AF. The levels of circulation microvesicles, mainly produced by endothelial cells and platelets, markedly increased after an acute stroke. Microvesicles may serve as a mediator in inflammation and poststroke AF by releasing miRNAs or other mole-

cules. Some miRNAs may participate in atrial electrical and structural remodeling in AF and their concentrations in plasma change after an acute stroke. The specific association needs to be further clarified. AF, atrial fibrillation.

stroke [71]. miR-126 plays a pivotal role in vasculogenesis and is considered a prognostic marker for vascular injury and endothelial dysfunction. In patients with acute ischemic stroke, the level of circulating miR-126 has been reported to be markedly downregulated [72]. The decreased serum level of miR-126 is thought to be highly associated with cardiovascular diseases such as AF, heart failure, and myocardial infarction [73], which supports the hypothesis that miR-126 may serve as a key mediator in poststroke cardiac complications. The role of microvesicles and miRNAs in the development of poststroke AF remains to be further studied. The possible role of microvesicles and miRNAs in poststroke AF is summarized in Figure 3.

Conclusion and Future Perspective

New AF after a cerebrovascular event is a frequent finding, and its clinical impact is so high that new therapeutic strategies have been proposed in patients who may have a paroxysmal nondetected arrhythmia. For this reason, the understanding of the pathophysiological mechanisms of AF after stroke is crucial and could provide new targets for future therapies in patients with stroke.

Poststroke pathophysiology is complex and possibly involves alterations in both the autonomic network and humoral regulation. Autonomic imbalance, catecholamine surge, neurogenic cardiac damage, and systematic inflammation after acute stroke can lead to atrial electrical remodeling and structural remodeling via different pathways, thereby facilitating the occurrence and maintenance of AF. Interestingly, according to a recent clinical study, the risk of ischemic recurrence in patients with poststroke AF seems to be lower compared to patients with AF diagnosed prior to stroke, suggesting different pathophysiology and cardiac features from general AF [74].

In addition, future researches are needed to clarify the association between the lesion area and arrhythmia occurrence, which may contribute to the treatment and management of patients with acute stroke.

Microvesicles and miRNAs are thought to play a pivotal role in the initiation and maintenance of AF and other cardiac complications after acute stroke. However, their underlying mechanisms remain unclear. We hypothesize that microvesicles and miRNAs may serve as a new predictive biomarker or therapeutic target for poststroke AF and other cardiac complications.

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Disclosure Statement

The authors have no conflicts of interest.

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