NOVEL CARDIONEUROLOGICAL CORRELATIONS IN ATRIAL FIBRILLATION

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ABSTRACT

The relationship between atrial fibrillation and stroke is both a classical and a complicated one. In the current review we aimed at defining and refining of this relationship through the view of new clinical and pathogenic data, the issue of subclinical atrial fibrillation being a major issue.

Keywords: atrial fibrillation, subclinical, ischaemic stroke, novel technologies, tachyarrhytmias

Atrial fibrillation (AF) is the most common supraventricular tachyarrhythmia and is the most important cause of cardioembolic stroke. Its prevalence is between 1 and 2% and is increasing by age. Recent data from the US reveal that AF as a primary admission diagnosis has increased by 23% in 10 years (between 2000 and 2010) (1). The risks associated with non-valvular AF (NVAF), the most common type of AF, are related mainly with thromboembolic events (cerebral, systemic), but also to the possible progression of the disease to heart failure, death or cognitive disorders – dementia. Over 90% of thromboembolic events are cerebral and only 7% are systemic. Besides cardioembolic stroke in AF, well defined neurologically, “silent” ischaemic cerebral lesions on MRI scanning can be seen in 15 to 86% of patients. Their relation to cognitive disorders or dementia is more and more obvious. (2)

AF is a heterogeneous arrhythmia, with diverse etiologies and mechanisms, with varied pathological substrates, different clinical presentations, evolution and complex treatment. Besides the classical types of AF (paroxysmal, persistent, permanent), that share a similar cardioembolic risk, subclinical AF, silent or occult has become a current subject of interest. It is defined as a paroxysmal AF of variable duration (seconds, minutes or hours), frequently repetitive, asymptomatic or associated with imprecise symptoms and is revealed by electrocardiographic monitoring or dedicated cardiac monitoring devices. (3)

Subclinical AF (silent) is diagnosed in multiple clinical conditions, if adequate monitoring techniques are used:

1. In patients with acute ischaemic stroke and a history of AF or new AF after the index stroke;
2. In patients with cryptogenic stroke, without an obvious cause on full diagnostic workup;
3. In patients with implantable cardiac devices for other arrhythmias (ICD, PM);
4. After AF ablation;
5. In patients with a high risk for developing AF.

Recorded atrial tachyarrhythmias (especially AF) and their characteristics are of equal interest to the cardiologist and the neurologist regarding the long term arrhythmia implications, thromboembolic risk – especially stroke, the indication and type of the required antithrombotic medication.

This paper is intended to analyse some of the cardioneurological interrelations from the cerebral cardioembolic risk point of view, in light of the silent and symptomatic AF trials.

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Novel technologies and methods for the evaluation of symptomatic or asymptomatic tachyarrhytmias in stroke patients

In the last decade, arrhythmology has become a field of high interest among cardiologists, and new arrhythmia evaluation techniques have been developed, especially regarding transient asymptomatic atrial tachyarrhythmias, including AF. The currently available evaluation techniques allow ambulatory or in-hospital arrhythmia monitoring for different amounts of time (hours, weeks, months). (4) AF screening can be accomplished by ECG recording, single or repeated in the Emergency Department or by continuous ECG monitoring, in parallel with other cardiorespiratory variables, especially in admitted critical patients. The use of short term Holter ECG monitoring (24-48 hours) is widespread; this method is less sensitive in diagnosing atrial tachyarrythmias. ECG monitoring can be long-term (ex. 7 days), increasing the sensitivity of a AF diagnosis by lengthening the monitoring period. Continuous cardiac telemetry is an excellent method for identifying tachyarrhythmias in inhospital patients. (5) Recently, ambulatory mobile cardiac telemetry systems are beginning to be used (mobile cardiac outpatient telemetry – MCOT), which are able to store and transmit cardiac rhythm data up to 30 days. Such systems detect paroxysmal AF episodes in about 23% of patient with a cryptogenic stroke. (6)

"Loop recorder" systems can be used for long term arrhythmia monitoring– external or implantable (ILR). Currently, ILRs can autodetect AF episodes with a sensitivity of 96% and a specificity of 85%, even if lasting seconds to minutes, the majority being asymptomatic. (7)

Implantable cardiac devices – pacemakers (PM) and defibrillators (ICD) in patients with an indication for such devices, can provide information regarding asymptomatic arrhythmias. Continuous cardiac monitoring can accurately record short periods of AF, especially if the atrial electrogram is available. The risk for cerebral thromboembolism is related to the duration of the AF episodes (> 5-6 minutes), their frequency and the arrhythmic burden. (8)

The new methods and techniques for monitoring asymptomatic or symptomatic arrhythmias are especially used in stroke patients with an unknown source for deciding whether anticoagulation is indicated. The sequence of using arrhythmia diagnostic tools (particularly AF) in patients with a recent stroke was summarised in 4 steps: 1) ECG recording in the Emergency Department; 2) During the hospital admission: repeated ECG recordings, continuous cardiac telemetry, Holter monitoring; 3) The outpatient period, right after discharge: Holter monitoring 4) Prolonged outpatient period: mobile cardiac telemetry, external/implantable loop recorder. The number of patients diagnosed with AF after a stroke is related to the moment of monitoring after stroke, the monitoring length and the stroke subtype.

Atrial fibrillation in acute stroke

Nonvalvular AF is one of the strongest associated risk factors for ischaemic stroke: AF increases stroke rate by a factor of 5-6. AF prevalence in the Swedish adult population (> 20 years old) is 3.2% greater than in other European countries, where the number stands at 1-2%. In acute stroke patients, the AF prevalence is estimated to be between 15 and 35%, the data from trials being greatly heterogeneous. (9)

In patients with an acute stroke and AF, the arrhythmia is, in most cases, previously diagnosed, treated and precedes the stroke (~22.5% in a recent Swedish registry). (9) Rarely, stroke is a first manifestation of preexistent AF that remained asymptomatic (silent). A special situation is considered paroxysmal or persistent AF (PAF) that appears in the acute stroke period and is identified by 24-48h ECG continous monitoring or repeated ECG recordings, in an asymptomatic or slightly symptomatic patient. The presence of FAP in the acute stroke phase (in the first 1 to 7 days) in patients without pre-existent documented tachyarrhythmias (AF, atrial flutter, atrial tachycardia) has 3 main diagnostic and therapeutic consequences:

1) the current stroke is, most likely, cardioembolic;

2) the presence of a tachyarrhythmia can cause an embolic recurrence;

3) Anticoagulation becomes mandatory, except for contraindications, based on the CHA2DS2-VASc and HAS-BLED scores. From a pathogenic point of view, the tachyarrhythmia significance is different: sympathetic neurogenic mechanism, a cerebral lesions in specific territories, general factors that favoured arrhythmia development.

Trials regarding atrial tachyarrhythmias (paroxysmal) in the acute ischaemic stroke phase have increased in recent years, since cardiac rhythm monitoring has become widespread and is done for at least 24 hours in dedicated stroke units. The ESC (European Stroke Organisation) and the AHA/ASA (American Heart Association/American Stroke Association) recommend 24h ECG monitoring for de-

tecting occult/silent tachyarrhythmias when no other stroke causes are identified.

An older trial identified at least one episode of AF in 1-5% of ischaemic stroke patients with no history of AF that underwent 24-48h cardiac rhythm monitoring after admission. (10). Another study, which included data from 5 prospective trials, detected newly diagnosed AF in 4.6% of 588 TIA or stroke patients.(4) If a "loop recorder" had been used, the incidence of newly diagnosed AF was 5.7 to 7.1%. Data from the National Swedish Registry (RISK – Stroke and Patients Registry) reveal that in 94.083 patients, 33.4% had AF, of which 8.1% was newly diagnosed and in the rest the AF had been previously diagnosed. (9)

A recent meta-analysis that included data from 32 trials and 5038 stroke or TIA patients investigated: the rate of new AF detection by monitorisation, the time interval between the cerebral event and arrhythmia debut, the relationship between ECG monitoring duration and AF detection rate. The results are worthy of being mentioned. (11)

– The detection rate of new paroxysmal AF after an acute ischaemic stroke was 11.5%, with a wide range variation between studies. Newly diagnosed AF, symptomatic or silent was found more often in patients with an ischaemic stroke deemed cryptogenic (15.9%) than in unselected stroke patients.

– The median time for detecting AF after a stroke varied widely, between 12.5 hours – 36 hours – 11.4 days.

– Prolonged monitorisation, for over 72 hours, can increase the AF detection rate by 2-4% per every extra 24 hours of monitoring.

New AF and paroxysmal AF episodes after an acute ischaemic stroke, most being asymptomatic, raise other issues regarding the diagnostic significance and stroke outcome.

A first issue that is worth discusing is the length of the AF episode and the arrhythmic burden. Some trials ignore AF episodes shorter than 30 seconds, considering that these episodes are transitory and do not pose an embolic risk. Another opinion states that short and asymptomatic AF episodes can predict future arrhythmic events, evolving towards persistent AF. (12)

Acute stroke patients with previously diagnosed AF, but also patients with newly diagnosed AF in the acute stroke phase are associated with an increased risk of cardioembolic reccurence, that is more frequent in the first week after stroke. In the IST trial (International Stroke Trial), that included stroke patients with permanent AF, the stroke recurrence rate was 5% at 14 days. (13) Other trials found a stroke recurrence rate of 1% at 6 hours, 2% at 12 hours, 5% at 7 days and 10% at 14 days. (14) Risk factors associated with stroke recurrence in stroke patients with permanent or newly diagnosed AF were found to be the absence or inefficient anticoagulation, the presence of cardiac thrombi (recent or mobile), valvular prosthesis and infectious endocarditis.

Cryptogenic stroke in patients with atrial tachyarrhythmic episodes after the index cerebral event represents another important issue that is discussed elsewhere in this paper. AF episodes detected on short or long term monitoring are more frequent in patients with stroke deemed cryptogenic. In fact, it is presumed that the majority of cryptogenic strokes are cardioembolic. (15)

As it was mentioned in mutiple trials, about 10 to 20% of ischaemic stroke patients with a preexistent AF do not have a cardioembolic mechanism; other cardiovascular risk factors associated with AF can cause ischaemic stroke, such as large vessel disease, intracerebral atherosclerosis or other conditions. In these cases, AF is an associated comorbidity of relative little significance regarding the acute neurologic event, but its presence is important for preventing a future stroke by anticoagulation.

The relationship between cryptogenic stroke and subclinical AF

Cryptogenic stroke is a subtype of stroke of undefined cause, after the extensive cardiac, vascular and biological assessments could not establish the precise etiology. In acute stroke registries, about 30% of ischaemic strokes are considered cryptogenic, but in the last few years, the majority are considered to be secondary to subclinical AF (16). Cerebral angiography in cryptogenic stroke showed that the ischaemic cerebral events are rarely caused by large vessel thrombosis and arterio-arterial embolism.

Documenting subclinical AF episodes in cryptogenic stroke is dependent on the type of monitoring, the length and the arrhythmic burden in a given time interval and on other data related to the neurological event. 24 to 72-hour ECG monitoring detected new AF episodes in 2.4 to 6% of studied patients (17). Two trials in which a "loop recorder" had been used in patients with cryptogenic stroke revealed that intermittent AF was present in 17 and 25% of patients. (7,18).

Two trials with a large number of cryptogenic stroke patients, evaluated by rigorous monitoring techniques for detecting AF episodes and cardio-

embolism were recently published. The CRYSTAL-AF trial included 441 patients with cryptogenic stroke and monitored the occurrence of intermittent AF episodes at 6 and 12 months by ICM (implantable cardiac monitor) or by conventional methods (varied intervals of continuous ECG monitoring). The AF detection rate at 6 and 12 months was 8.9% and 12.4% in the ICM group and 1.4% and 2%, respectively, in the control group. About 2/3 of the AF episodes were asymptomatic and almost 60% were longer than 6 hours. Ischaemic stroke rates at 6 and 12 months where 5.2% and 7.1% in the ICM group and 8.6% and 9.1% in the control group. The investigators concluded that implantable monitoring devices are superior to conventional methods for the detection of AF after a cryptogenic stroke.(6)

The EMBRACE trial, published at the same time with the CRISTAL-AF trial, investigated the same AF issues in patients with a history of cryptogenic stroke (19). 572 patients with cryptogenic stroke or TIA, without a history of AF, were monitoring noninvasively for 30 days (record event trigger) or conventional 24-hour ECG monitoring. Intermittent AF with a duration longer that 30 seconds was found in 16.1% of patients in the interventional group compared to 3.1% in the control group ($p<0.001$). Patients with intermittent AF were older and had more frequent ectopic atrial activity compared to those without AF ($p<0.001$). These results suggest that short subclinical AF episodes could be predictive for subsequent episodes and seem to increase the risk of recurrent stroke, a finding also underlined in other studies (8,19). The length of paroxysmal AF episodes over 5-6 minutes was found to be a predictor for clinical AF and systemic embolism in the ASSERT and MOST trials (3,20).

In summary, the available trials underline that about 25% of cryptogenic stroke patients develop AF episodes, demonstrated by sensitive monitoing techniques, the rate of AF detection increasing with monitoring duration.

Implantable electronic cardiac devices and subclinical AF

Implantable cardiac devices (PM, ICD, CRT-D) used in several conditions simultaneously allow the study of atrial tachyarrhythmias that took place between the periodic device interrogations. The devices store information regarding the development of atrial tachyarrhythmias (including subclinical AF), the duration of each episode, the arrhythmic burden or the total effective e arrhythmia time, the relation between atrial tachyarrhythmias and AF. Based on these data, correlations can be made between the AF episodes (asymptomatic), the thromboembolic events and orienting the anti thrombotic treatment. (21)

PMs and ICDs have provided in research groups, information regarding subclinical episodes of AF in two situations: patients with a history of AF and patients with cryptogenic AF.

Most atrial tachyarrhythmias recorded by the implantable cardiac devices are of short duration, have a variable incidence and are asymptomatic. The detection of atrial tachyarrhythmias is made with a high sensitivity (98.1%) and specificity (100%); the duration of the AF episodes is also accurately established. (22). Atrial tachyarrhythmias with a duration of over 5 minutes have a probability of 97% of being AF. In observational studies it has been noted that AF delevoped, at 17 months, in 23% of patient having high cardiac rate atrial tachyarrhythmias (between 180 and 220 BPM) and a duration of at least 5 to 6 minutes. (23)

The detection of atrial tachyarrhythmias and new AF episodes in patients with a PM and ICD raises the issue regarding their clinical significance and the risk of cardioembolic stroke. Several clinical trials tried answering these questions (MOST, TRENDS, ASSERT).

The initial MOST trial (Mode Selection Trial) evaluated the clinical consequences of AF episodes detected by the PM. Evaluating the data from 312 patients showed that at least one episode of atrial tachyarrhythmia, with a duration of at least 5 consecutive minutes and a heart rate of 220 BPM was associated with an increased stroke risk (6.7x), an increased risk of developing permanent AF (5.93x) and non-fatal stroke (2.9x). The absolute stroke rate in the entire patient group was 3.2%: 5% in the tachyarrhythmia subgroup in(including AF) and 1.3% in the non-arrhythmia group. Detecting an AF episode by the PM of at least 5 minutes was a major result for subsequent studies (20).

The TRENDS trial, which included 2486 patients followed for 1.4 years, evaluated the link between the burden of atrial fibrillation/flutter, detected by PM or ICD, the thromboembolic risk and the cutoff value of the arrhythmic burden that increases the risk (24). The thromboembolic events were recorded in 1.6% of cases; their occurrence was associated with an AF burden of 5.5 hours. The thromboembolic risk was 2.5 times higher if patientspatients had >5.5 hours of AF in one day, compared to the group of patients who did not develop atrial fibrillation or flutter. (24).

The cardioembolic risk of atrial tachyarrhythmias detected by implanted cardiasc devices was also evaluated by investigating the deletion between the length of the AF and the CHADS2 score. In 568 patients with a PM and history of AF the total thromboembolic rate was 2.5%. In the CHADS2 0 group, the risk was low (0.8%), even if the patients had longer episodes of AF; for the CHADS2 over or equal to 3 group, the risk was high (5%), even if longer periods of AF were not detected. (25)

One of the reference trials is ASSERT (3). 2850 patients with an age of over or equal to 65 years, with hypertension, no history of AF, which had a PM or ICD implanted for various indications, where prospectively followed up for a median of 2.5 years. The main outcome was the detection of atrial tachyarrhythmias, episodes of AF and their correlation to stroke. At 3 months follow-up, at least one tachyarrhythmias that lasted for over 6 minutes was identified in 10.5% of patients, and at 2.5 hears in another 24.5 % (34.6% of patients). AF developed in 16% of patients. The mean detection time of the first episode was 35 days, which suggest that short term ECG monitoring can detect only a small number of AF episodes. At 2.5 years follow-up, 4.2% of patients with atrial tachyarrhythmias suffered an ischaemic stroke or systemic thromboembolism (twice as many when compared to the no-atrial arrhythmia group).

In summary, the trials that evaluated subclinical AF and the stroke risk in patients that had an implantable cardiac device lead to some new ideas, with very likely therapeutic consequences: 1. Atrial tachyarrhythmias with a high ventricular rate and a duration >5 minutes are more likely to develop into paroxysmal or persistent AF and carry a two-fold increase in stroke risk; 2. patients with episodic AF. The cumulated duration of AF of >5.5 hours is associated with an increased stroke risk (2.2-3.1x). At the same time, the CHADS2 score helps establish the stroke risk in patients with sublicinal atrial tachyarrhythmias.

Anticoagulation in silent AF?

The current guidelines for AF management recommend antihrombotic treatment, with some variations, for all types of AF (paroxysmal, persistent and permanent). Should asymptomatic AF episodes identified by different types of monitoring and carrying a thromboembolic risk receive the same anti thrombotic (anticoagulant) treatment?

Until now, based on published data, no specific recommendations have been made. Defining therapeutic indications is difficult because of the extremely diverse clinical settings in which AF episodes are identified, but also because of the individual characteristics of the tachyarrhythmia. The opportunity and decision in favour of anti thrombotic treatment should take into account:

1. History of ischaemic stroke or TIA of unknown etiology;

2. The characteristics of the asymptomatic AF episodes: length, frequency of occurrence and arrhythmia burden in a given time interval;

3. The CHADS2, or optimally the CHA2DS2-VASc score. In relation to these parameters, several treatment options have been established for patients with asymptomatic atrial tachyarrhythmias (especially AF) (23).

– Patients with cryptogenic stroke (or TIA) and subclinical AF episodes should receive long term anticoagulation therapy; these patients have a CHADS2 score of at least 2 and are at high risk of a thromboembolic recurrence. At the same time, patients require follow-up for identifying other stroke causes.

– Patients with atrial tachyarrhythmias and episodes of silent AF, of short duration (minutes) and a CHADS2 score of 0 need long term heart rhythm monitoring („loop recorder") for the diagnosis of atrial arrhythmias; anti platelet therapy (aspirin) is probably not necessary.

– Patients with episodic AF and a CHADS2 score of 1 can receive either aspirin, either anticoagulants, taking into account the hemorrhagic risk.

In recent years, the new oral anticoagulants (NOACs) have been validated in large RCTs that included patients with nonvalvular AF, to be superior or non inferior o VKA in embolic protection, and also safer. Several trials are ongoing using NOACs and VKA which should answer the question whether a certain type of treatment can improve the outcomes of patients with atrial tachyarrhythmias detected by continuous ECG monitoring. The TACTIC-AF (Tailored Anticoagulation for noncontinous AF), REVEAL-AF and ASSERT II trials can provide important data regarding the issue of subclinical AF. It is important that the time relation between the silent AF identified by an electronic monitoring device and the thromboembolic event is clearly defined. If the temporal relationship is positive, then the tachyarrhythmia is the cause of the event. When this relation is doubtful, the AF episodes can be a risk marker, and when a decision has to be made regarding anticoagulation concomitant risk factors for AF can play a role (26).

Primary prevention in subclinical AF?

The detection of subclinical AF (asymptomatic) in various patient groups (mentioned above) and the favourable results of antithrombotic therapy in preventing embolic events in these patients, has widened the clinical research field looking into the primary stroke prevention and timely AF detection.

Firstly, the screening of elderly population at risk for developing subclinical AF and the eventuality of a preventive therapy should be discussed. The prospective Scandinavian STROKESTOP trial (Population Screening of 75 and 76 year old Men and Women post silent AF) that followed up patients for 5 years, investigated if screening for subclinical AF can reduce stroke incidence in the studied population and if the screening is cost effective (27). The multicentric prospective REVEAL-AF trial (The Reveal XT Implantable Cardiac Monitor) that includes patients with a high risk for stroke and AF investigates the incidence of AF episodes with a duration over 6 minutes and the subsequent therapeutic modifications if AF is detected.

Other trials investigate the timely identification of AF by PM or CRT-D: COMPAS (Comparative follow-up Schedule with home monitoring), IMPACT (Impact of Biontronic Home Monitoring guided Anticoagulation on Stroke Risk in Patients with ICD and CRT-D). (28) The objectives of these trials are: a. Evaluating the efficiency of timely AF detection; b. if the initiation or discontinuation of anticoagulation in continously monitored patients improves clinical outcomes by reducing stroke rate, systemic embolism and bleeding.

In summary, current research involving the complex issue of subclinical AFv (asymptomatic) are generally oriented in two main directions: a. Optimal methods and techniques (external or implantable) for the screening of asymptomatic AF; b. Identifying population or patient groups at risk of developing asymptomatic AF and the therapeutic modalities of preventing cardioembolism.

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