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BRAIN - HEART AN ETARNAL UNION, BUT SOMETİMES DANGEROUS

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Introduction

Cardiac arrhythmias, by disrupting blood flow, specially to the brain, may induce neurological manifestations. They tend to occur in an unpredictable manner leading to sudden stroke events.

In the relationship "brain-heart", cardiac arrhythmias interfere on two main levels. At first, heart rate changes may result in thromboembolic events with cerebral insults. But cerebral focal lesions may induce not only elecrocardiographic changes, but also cardiac arrhythmias or disturbances of cardiovascular reflexes.

The purpose of this article is to review the mechanisms of cardiac arrhythmias induced by cerebral lesions and develop the current management of atrial fibrillation that frequently results in stroke events.

Cardiac consequences of cerebral lesions

Over the past half century, the possibility that acute strokes may result in cardiac rhythm disturbances, as well as myocardial structural damages has become the subject of several studies (1-5). In humans, it was demonstrated that central nervous system (CNS) lesions may induce heart rate and electrocardiographic abnormalities (6). They affect mainly repolarisation and may lead to severe cardiac arrhythmias (7). Such changes are more frequent consequence of hemisphere than brainstem infarction (8).

The role of CNS on the heart rate was firstly demonstrated by Beattie & al. (9). In their experiment, the cats were protected from cardiac arrhythmias if submitted to Sherringtonian decerebration. Since many animal and human studies have confirmed the importance of autonomic mechanisms in the onset of neurogenic cardiac arrhythmias. Indeed the peripheral autonomic nervous system is influenced by specific structures in the brainstem and cerebral hemispheres, more specifically the brainstem reticular formation, various thalamic and hypothalamic nuclei, the limbic lobe and the prefrontal neocortex. Various ascending and descending pathways interconnect these regions (10).

The sympathetic neurones that influence cardiac activity, both chonotropic and ionotropic, are limited to the upper thoracic segments of the cord. (T1-T4). The descending pathways which innervate and regularize these sympathetic preganglionic neurones, arise from hypothalamic, midbrain, pontine, and medullary cells groups, containing about 20 different amines and peptides. The discharges of these neurones are dependent and independent of baroreceptors inputs and indicate mainly a sympatoexcitatory function. On the contrary, the vagal preganglionic cardiomotor neurones are located in the nucleus ambiguous and less in the dorsal vagal nucleus. They also share inputs from numerous regions of the forebrain hypothalamus, amygdala, and lower brainstem.

At the hemispheric level, cardiac arrhythmias are frequent during the acute phase of stroke. For example, Dimant and Grob found ECG abnormalities seven times more frequent in stroke patients (4). It is Usually admitted that new ECG changes may occur in 15% to 30 % of ischemic or haemorrhagic events and different ECG patterns are reported (Table 1) Indeed, since the first investigation of cortical cardiac control sites, different animal and human studies have partially elucidated the cortical site of cardiac representation (11). It resides in the insular cortex, beneath the frontoparietal and temporal opercula. The middle cerebral artery divides its surface in two parts. In the rat, cardiopulmonary activities are represented in the posterior part of the insular cortex. Pressor responses are mainly located in the rostral posterior part, meanwhile depressor responses are situated in the caudal posterior insula (12,13). Moreover from studies with microstimulation of the insular cortex, a cardiac chronotropic map was derived. Location of pure tachycardia is within the rostral part and bradycardia is produced by stimulation of the insula induce modifications of blood pressure and heart rate. Right insular activities lead to elevation of blood pressure and heart rate (pressor responses), where as the opposite effect is obtanied by stimulation of the left side (14,15,16). Lane & al. evaluated patients with right hemisphere strokes and demonstrated a differential influence of stroke localisation on the type and severity of arrhythmias. They speculated that parasympathetic activity was diminished

ipsilateral to the affected hemisphere with an increase in sympathetic tone on that side (17). From the Lausanne Stroke Registry, Vingerhoets & al. confirmed this lateralization of cardiac responses (18). They demonstrated that atrial fibrillation is more common following insular infarction than after other types of stroke and involvement of the left parietoinsular region was predominant. Moreover it seems that intracerebral haemorrhage induced atrial fibrillation more often than embolic infarction.

Table 1: Main electrocardiographic changes and cardiac arrhythmias related with stroke

Prolongation of the QT interval	atrial fibrillation
T waves of increased amplitude and duration	multifocal ventricular premature beats
abnormal U waves	couplets
Q waves with ST segment depression	unsustained ventricular tachcycardia
	bradycardia
	torsades de pointes
	asystole

Table 2: Annual rates of stroke on pooled data of 5 main trials

	rate of stroke per year (%)	
	placebo	warfarin
Independent risk factors		
HTA	5.6	1.9
diabetes	8.6	2.8
prior stroke or TIA	11.7	5.1
age < 65 yr		
no risk factor	1	1
≥1 risk factor	4	1.7
age 65-75 yr		
no risk factor	4.3	1.1
≥1 risk factor	5.7	1.7
age > 75 yr		
no risk factor	3.5	1.7
≥1 risk factor	8.1	1.2
risk factors in any of 5 trials		
congestive heart failure	6.8	1.6
angina pectoris	6.7	0.9
myocardial infarction	8.2	3.3
current smoker	2.5	1.3
peripheral vascular disease	6	1.8
female	5.8	0.9
intermittent AF	5.7	1.7
AF duration > 1 yr	4.4	1.5

A second pathway mediates the cardiac effects of stroke. It includes the medial frontal cortex and passes through the hypothalamus and amygdala (19).

The cardiac effect of lateralization may be explained by functional asymmetry in autonomic cardiac innervation and because the central autonomic pathways descend uncrossed. On the right side, the parasympathetic and sympathetic nerves influence the sinus node, whereas they regulate the atrioventricular node and the ventricules. Stimulation of the left side will modify the atrioventricular conduction, the ventricular fibrillation threshold, the Q-T time, and the S-T segment of the ECG.

The ECG changes are mainly represented by disturbances of ventricular depolarisation and therefore they explain a propensity to the development of cardiac arrhythmias. The ECG modifications are generally QT interval prolongation, septal U vawe, T vawe anomalies, and ST segment elevation or depression. They occurred in 15% to 30% of events (5). They can predict the onset of cardiac arrhythmias. The most frequent abnormality is atrial fibrillation. But multifocal ventricular premature beats, couplets, ventricular tachycardia, torsades de pointes, and asystole may happen. In a study, in which the ECG was taken within 3 days of admission, atrial fibrillation occurred in 21% of cases, followed by ventricular arrhythmias (13%) (4). In two other studies using Holter data from patients with cerebral infarction, intracerebral haemorrhage, or transient ischemic attacks, ventricular arrhytmias were more frequent, about %60 (20,21). Their incidence is various in studies because of the different methods of arrhythmia assessment (5). When prolonged monitoring is conducted, arrhytmias may occur in 10% to 20% of stroke events.

The possibility of associated cardiac disease as a cause of the ECG changes following acute stroke was ruled out by different clinical and autoptic studies (22,23). Indeed, to exclude the effects of concomitant coronary artery disease, Goldstein compared the ECGs taken during the acute phase of stroke and those taken an average 4 months earlier. Prolongation of QT interval was noticed in 32% of stroke patients and in 2% of the controls. T wave inversion appeared in 15% of the stroke group and abnormal U wave in 13.8% patients of this study were autopsied and no evidence of an acute ischemic cardiac event was demonstrated (24). Another study with autoptic confirmation of acute cerebral infarctions revealed no coronary occlusion (25). Lavy & al. followed 25 patients without evidence of previous cardiac disease of 52 patients with an acute ischemic stroke or intracerebral haemorrhage (26). 44% showed ECG changes or cardiac arrhythmias. Usually these ECG effects are evanescent and resolve over a period of days to months (25).

There is also evidence that stroke is associated with myocardial damage, but not ischemic lesions.

In this situation, the CPK level rises progressively and reach a maximum after 4 days, which is unusual in the ischemic processus associated with cardiac injury. In spite of the absence of coronary disease, autopsy demonstrates scattered subendocardial haemorrhages with myocytolysis, that may involve the conducting system (22,23). The lesions are centred around intracardiac nerves. Therefore the catecholamines probably play a role in the cause of these pathological changes.

Thence it becomes more and more and more evident that acute stroke may modify heart function, even without coronary disease. This is likely to contribute also to sudden mortality following ischemic or haemorrhagic events. Therefore we suggest that cardiac monitoring for at least 24 hours is necessary after acute stroke. Special attention will be addressed to patients with ventricular repolarisation changes, as well as those with insular lesion.

Cerebral consequences of cardiac arrythmias

Non rheumatic atrial fibrillation (AF) is the most frequent cardiac arrhytmia and certainly the most diffucult to treat. Its prevelance increases with age (2-4% before years and more than 17% after 80 years) (27). It is present in about 15% of patients with ischemic stroke. In the great majority of cases, it is associated with cardiopathy (valvulopathy, cardiomyopathy, coronary disease, HTA, etc...).

In presence of AF, it is always important to distinguish between paroxysmal or chronicle AF and if a cardiopathy is associated or not. Moreover risk factors for the occurrence of AF include age, diabetes, HTA, congestive heart failure, valvulopathy and myocardial infarction (28). Transient AF in elderly patients is usually related with transient hyperadrenergic states: infection, anaemia, pulmonary diseasei hyperthyroidism, etc... Echocardiographic risk factors include increased left atrial size, left ventricular wall thickness, and decreased left ventricular fractional shortening (29).

The most important consequence of AF is thromboembolic events. According to epidemiological data, the presence of AF increases the risk of stroke threefold to fivefold, specially with advancing age, and the risk of mortality threefold. This risk varies between 1% and 5% per year (30,31). The stroke recurrence rate is situated between 2% and 15% per year following the first stroke event, and is 5% yearly thereafter, with a mortality rate of 5% per year (32,33). Strokes are usually due to embolism from left atrial thrombi. Indeed, transesophageal echocardiographic examination allows to detect left atrial thrombi in about 15-30% of cases (34,35).

Since the beginning of 1990s, the treatment of patients with AF was precisely evaluated by six large clinical trials. Five of them have focused on stroke prevention, while a more recent trial has studied the secondary prevention of recurrent vascular events after recent TIA or minor stroke (32,36-49).

Primary prevention

5 major trials have compared the efficacy of anticoagulants, aspirin or placebo in the primary prevention of stroke (32,36-39). All these studies demonstrated a real benefit of anticoagulants for the prevention of stroke, with a weak haemorrhagic risk between 0.8% and 2.5%

The Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) evaluated 420 AF patients who received either low-dose of warfarin or placebo (37). The incidence of major embolic events in patients receiving warfarin was 0.41% per year versus 2.98% per year in the placebo group. The relative risk reduction was 86% with warfarin. The Stroke Prevention Atrial Fibrillation (SPAF) trial enrolled 1330 AF patients to receive 325 mg aspirin per day, low-dose warfarin, or placebo (32). The incidence of major embolic events was 6.3% per year in the placebo group, 3.6% in the aspirin group, and 2.3% in the warfarin group. The risk reduction was 42% with aspirin and 67% with warfarin. The secondary analysis of SPAF data revealed that patients can be divided into a low risk group (<3%/year) and a high risk (>7%/year) of embolic events according to the presence or not of a history of HTA, previous embolism, and recent heart failure (41). In the Copenhagen AFASAK study, 1007 patients received either full-dose warfarin, or 75 mg per day of aspirin, or placebo (36). Once more the warfarin group had a significantly reduced incidence of embolic events (Risk reduction: 59)%. The Canadian Atrial Fibrillation Anticoagulation (CAFA) study randomised 187 patients receiving full-dose warfarin or placebo (38). The warfarin group had an incidence of major embolic events of 3.5% per year versus 5.2% per year in the placebo group, with a risk reduction of %37. Finally, the SPINAF study enrolled 571 patients receiving warfarin versus placebo and demonstrated a risk reduction of 79% in warfarin-treated patients (39). To identify criterias predictive of a high or low risk of stroke, and assess the efficacy of antithrombotic therapy, the data of these five trials have been

recently joined (42). According to these pooled data, the rate of stroke per year in non-treated patients with AF is %4.5. If independent risk factors for stroke were considered, this rate varied from %1 in patients younger than 65 years and with no other risk factors to %8.1 in patients older than 75 years who had one or more of the other risk factors.

The independent risk factors for stroke pointed out by pooled data are advancing age, HTA, diabetes. or prior stroke or TIA. In patients with lone AF younger than 60 years, no stroke occurred and the type of AF (paroxysmal or constant) had no effect on the stroke incidence. Other independent risk factors among the five trials, which were not independent in the collaborative analysis, have also an effect on the rate of stroke per year (Table). Only in the SPAF study, the echocardiographic findings were analysed and increased left atrial size and decreased left ventricular function have been retained as independent risk factors of stroke (43). However, an analysis of pooled echocardiographic data is ongoing.

Thus the major risk factor of stroke in patients with AF is a history of prior stroke or TIA. In this case, the annual rate of stroke is as high as %12. Also this result has been confirmed by the European Atrial Fibrillation Trial (EAFT) collaborative study (40). Moreover, the collaborative analysis of five main trials has confirmed that anticoagulants reduce the risk of embolic events by about two-thirds and mortality by one-third. The annual risk of intracerebral bleeding is lower than %1. Anticoagulants decreased by %48 the rate of the combined events of stroke, systemic embolism, or death. Meanwhile, the annual of stroke in anticoagulated patients was %1.4.

The efficacy for aspirin therapy from AFASAK and SPAF-1 studies were very different (36,32). The first study with aspirin 325 mg/day found to decrease the risk of stroke only by %44, meanwhile therapy with aspirin 75 mg/day revealed a non significant reduction of %16. When data are combined with the results of the EAFT study, aspirin reduced the risk of stroke by %36 (40). This modest is seen mainly among patients with HTA. A more recent study, the SPAF-II study suggests that aspirin is almost half as effective as warfarin (44). But according to the recent data of SPAF study, this therapy is unuseful in patients with congestive heart failure, left ventricular dysfunction, uncontrolled hypertension, a history of prior embolic event or in women older than 75 years (45).

Secondary prevention

Secondary prevention is more important for neurologists, since patients with a recent stroke are referred to them. The results of the European Atrial Fibrillation Trial offered recently essential responses for the management of patients with recent TIA or minor stroke (<3 months) were randomised to open treatment with anticoagulants (INR range: 2.5-4.0) or double-blind treatment with 300 mg aspirin or placebo, and followed during 2.27 years.

The rate of primary events per year was %8 in patients on anticoagulants versus %17 in placebo-treated patients. The risk of stroke alone was decreased from %12 to %4 per year. These results are similar to those of primary prevention studies, except for the much higher risk of subsequent stroke. On the other hand, in all aspirin-treated patients, the annual rate of primary outcome events was %15 against %19 in those on placebo. Thus this study has clearly demonstrated that anticoagulants are significantly more effective than aspirin and thus it determines the optimal therapy in patients with a recent TIA or minor stroke.

Risk of major bleedings

In the collaborative analysis of five main trials, the rate of intracerebral haemorrhage in warfarin-treated group was %0.3 per year versus %0 in the EAFT study and the incidence of combined bleeding events was %2.8 per year on anticoagulation (40,42). On the other hand, in the SPAF-II trial, the rate intracranial haemorrhage was %1.8 in the subgroup of elderly patients with a mean age of 80 years and who received warfarin (44). But the selection of patients was less restrictive than in the five trials, which explains this difference. Likewise thesurprising result of the EAFT study is explained by the small group of elderly patients. Only 79 patients of 80 years do not allow statistical analysis about the effect of age.

Current recommendations for therapy with anticoagulants

Before anticoagulation therapy, it is necessary to assess thromboembolic risk due to AF alone, haemorrhagic risk and risk of falls or other trauma. If this therapy is judged safe, it is recommended to introduce warfarin therapy at a dose that prolongs the prothrombin time and INR of 2.0 to 3.0 patients with small to moderate-sized stroke (46). Anticoagulation ought to be postponed 5 to 10 days in patients with large embolic stroke

to avoid an haemorrhagic transformation. Anticoagulation treatment should be given for as possible. In patients, specially than 65 years, without clinical or echocardiographic risk factors, use of aspirin (325 mg/day) seems reasonable, but the treatment should be changed if risk factors emerge.

In very elderly patients (>80 years), increasing age is an independent risk factor for embolic events. But there is no consensus of an increased risk of bleeding during anticoagulation therapy. Hart&al. estimated that anticoagulation at conventional doses increases the risk of intracranial haemorrhage by 7-10 times, specially if there is less restrictive selection of patients and uncertain anticoagulation monitoring (47). In fact, it seems logical that elderly patients has an higher risk of haemorrhage in reason of increased comorbidity. Unfortunately, the small number of patients with intracranial bleeding in the different trials do not allow a good evaluation of the related with the effect of age. Moreover, the SPAF-III study evaluated the benefit of adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients (48). This study demonstrated that adjusted-dose warfarin is more efficacious for stroke prevention than low-intensity, fixed-dose warfarin plus aspirin. Thus very elderly patients seem to have also much to win from anticoagulation. We recommend anticoagulation therapy for such patients with recent stroke who have no contraindication for anticoagulants.

Conclusion

During the acute phase of stroke, the possibility of heart rate disturbances or unpredictable cardiac arrhythmias must not be neglected. Special attention would be addressed to patients with insular infarction. Because of the relatively high frequency of heart rate modifications, cardiac monitoring is recommended at least during the first 24 hours in order to prevent dramatic consequences.

Moreover, with the pooled data of collaborative studies and the EAFT study, the optimal therapy in AF patients with a recent TIA or stroke is now more clearly defined.

Anticoagulation is the most effective treatment in reducing the risk of thromboembolic events, These results indicate that patients who are less than 60 years old and have no other risk factors do not have a higher risk of stroke than normal patients. Instead, for subjects older than 75 years of age, the real benefit of anticoagulants remain unclear because of higher risk for haemorrhagic consequences. However, if there is no contraindication, anticoagulants would be proposed for this group of elderly patients with other risk factors. Maintenance of international normalised ratio between 2.0 and 3.0 may make age a less important factor.

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