

Stroke of Cardioembolic Origin: What We Have Learnt in the Past 10 Years?

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ABSTRACT

Cerebral infarctions of cardioembolic origin are usually large lesions and clinically severe conditions. Cardioembolic stroke is the most frequent ischemic infarction in very old subjects. The diagnosis has largely improved due to generalization of echocardiography in daily practice, the use of 24-h Holter monitoring, transcranial Doppler ultrasound and modern neuroimaging advances, as well as the development of specific biological markers. Vascular repermeabilization using thrombolytic treatment in selected patients has improved the prognosis, and new oral anticoagulants with a higher safety profile and a non-inferior or superior efficacy as compared to coumarin are important additions in the therapeutic armamentarium for preventing cardioembolic events in patients with non-valvular atrial fibrillation. Some clinical research lines remain open, such as genetic-related risk of atrial fibrillation.

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Key words: Cardioembolism; Lacunar syndromes; Lacunar stroke; Cerebrovascular diseases; Acute stroke

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INTRODUCTION

Cardioembolic cerebral infarction accounts for 18-25% of all cerebral infarctions and is the ischemic stroke subtype most commonly found in very old patients (>85 years of age). Cardioembolic stroke is a severe condition due to the large size of the infarction, with a high in-hospital mortality rate (6-27%) and significant neurological dysfunction; also, the risk of spontaneous infarct recurrence ranges between 1% and 10%^[1-3]. In the past 10 years, however, there has been substantial progress in the knowledge of the natural history of the disease as well as in the diagnosis and management of patients with cardioembolic stroke, a summary of which is here presented.

RECENT HISTORY AND NEW DISCOVERY

In the past decade, cardioembolic infarction continued to be the main presumptive diagnosis of ischemic stroke based on clinical and electrocardiographic data ("presumed cardioembolic cerebral infarction"). However, the introduction in routine daily practice of echocardiography, Holter monitoring of heart rhythm and sensitive neuroimaging techniques, such as diffusion-weighted (DW) magnetic resonance imaging (MRI) have represented a substantial advance in the clinical diagnosis of cardioembolic infarction. Echocardiography allows the non-invasive diagnosis of potentially emboligenous structural cardiopathies, 24-h Holter monitoring has been associated with the detection of clinically silent paroxysmal cardiac rhythm disturbances, and DW imaging may provide evidence of multiple acute and simultaneous cerebral infarctions, which is a characteristic feature of an emboligenic phenomenon. On the other hand, the development of biomarkers related to cardioembolism and the general use of thrombolytic therapy in the acute phase of stroke as well as the discovery and availability in the market of new oral anticoagulants for secondary stroke prevention have been crucial advances in the management of patients with cardioembolic stroke.

WHAT IS CARDIOEMBOLIC STROKE?

There are no absolute criteria for the diagnosis of cardioembolic infarction, although the following is required: (1) compatible neurovascular clinical picture; (2) recognition of an emboligenic

heart disease and (3) exclusion of carotid and/or cerebral atherosclerosis or other cause for the ischemic stroke. In the Sagrat Cor Hospital of Barcelona Stroke Registry, to classify a patient as having cardioembolic cerebral infarction, the following features are considered: presence of a medium-sized (maximal diameter of the lesion 1.5 to 3 cm) or large (>3 cm) cerebral infarction; cerebral cortex involvement on the brain computed tomography (CT) and/or MRI scans; sudden (minutes) or acute (hours) onset; stroke onset during ordinary daily activities; peak of deficit at onset; duration of focal neurological deficit >24 hours; absence of lacunar clinical syndrome; and identification of a commonly accepted cardiac source of embolus (the commonest high-risk cardioembolic conditions are atrial fibrillation, recent myocardial infarction, mechanical prosthetic valve, dilated cardiomyopathy and mitral rheumatic stenosis) in the absence of confirmatory investigative results (Doppler ultrasonography, carotid angiography or angio-MRI) of lesions (stenosis $\geq 50\%$) in the ipsilateral supra-aortic trunks.

In relation to clinical findings, symptoms caused by cardioembolic infarctions have been better defined^[1,4,5]. Patients typically present with a sudden onset of symptoms (< 5 minutes) and maximum focal neurological deficit at presentation (in 47-74% of cases). Between 19% and 31% of patients have altered consciousness at the onset of symptoms. Moreover, focal neurological deficits develop more frequently during daytime or after a Valsalva's manoeuvre, which suggest the possibility of a paradoxical embolism. On the other hand, some clinical syndromes are more common in patients with cardioembolic stroke, such as isolated Wernicke's aphasia or pure aphasia; in contrast, there is evidence of the low probability of cardioembolic origin for cerebral infarcts of the lacunar type due to the small size of the lesion and the topography of lacunes in distribution territory subcortical or brainstem penetrating arterioles (cardioembolism as a cause of lacunar stroke is found in only 2.6-5% of cases)^[1].

RISK FACTORS

The main cardiovascular risk factors in cardioembolic infarctions are atrial fibrillation and ischemic heart disease (Table 1). The presence of these risk factors may be of value to tentatively establish the subtype of stroke in patients with non-lacunar cerebral infarction. It is often difficult to early differentiate cardioembolic from atherothrombotic

Table 1 Cerebrovascular risk factors in 763 cardioembolic and 770 atherothrombotic patients with cerebral infarction collected from the Sagrat Cor Hospital of Barcelona Stroke Registry^[1,3].

Risk factors	Atherothrombotic (n=770)	Cardioembolic (n=763)
Hypertension	509 (66.1)	377 (49.4)
Atrial fibrillation	120 (15.6)	573 (75.1)
Diabetes mellitus	242 (31.4)	142 (18.6)
Hyperlipidemia	164 (21.3)	88 (11.5)
Previous cerebral infarction	164 (21.3)	146 (19.1)
Ischaemic heart disease	150 (19.5)	163 (21.4)
Transient ischaemic attack	116 (15.1)	73 (9.6)
Smoking (>20 cigarettes/day)	87 (11.3)	28 (3.7)
Chronic obstructive pulmonary disease	74 (9.6)	62 (8.1)
Peripheral arterial disease	100 (13)	50 (6.6)
Valve heart disease	11 (1.4)	130 (17)
Congestive heart failure	43 (5.6)	72 (9.4)
Obesity	36 (4.7)	17 (2.2)
Oral anticoagulants	18 (2.3)	63 (8.3)
Alcohol abuse (> 80 g/day)	26 (3.4)	5 (0.7)
Chronic liver disease	17 (2.2)	15 (2)
Previous cerebral hemorrhage	9 (1.2)	7 (0.9)

Percentages in parenthesis

infarction (the most frequent non-lacunar ischemic stroke subtypes) based solely on clinical criteria especially at the onset of neurologic deficit. A clinical study has shown that atrial fibrillation and sudden onset of symptoms were independently associated with cardioembolic stroke, whereas hypertension, chronic obstructive pulmonary disease (COPD), diabetes mellitus, hyperlipidemia and age were significantly associated with atherothrombotic infarction^[6].

DIAGNOSIS

Generalization of the use of non-invasive complementary cardiological studies in the routine clinical practice, such as echocardiography, which was initially restricted to young adults and patients with cerebral infarction of unknown cause and extended thereafter to all patients with a first-ever brain infarct allowed a better diagnosis of cardioembolism and a decrease in the frequency of cerebral ischemia of undetermined cause. Echocardiographic assessment is useful to visualize intracardiac thrombi and clinically silent and potentially emboligenous structural heart diseases, such as foramen ovale in association (or not) with atrial septal aneurysm^[6]. Ultrasound studies of the aortic arch have also contributed to optimize the diagnosis of complex atheromatosis of the aortic arch, which is an emergent etiology of primary or recurrent cerebral ischemia, mainly in the subgroup of patients with cerebral infarction of unknown cause^[7,8]. The main criterion of the emboligenous risk of aortic plaques is ≥ 4 mm in plaque thickness or presence of mobile components. The association of complex atheromatosis of the aortic arch with dense calcification of the mitral valve ring in another finding of interest. Calcification of the mitral valve ring has been traditionally considered a vascular risk factor despite the fact that calcium embolism is an exceptional cause of stroke. It may be argued that mitral valve ring calcification is an epiphenomenon and a marker of complex atheromatosis of the aortic arch, with its high emboligenous risk due precisely to this association.

The indication of a 24-hour (or longer) Holter monitoring and also, in selected cases, transtelephonic monitoring or subcutaneous implantation to obtain a prolonged duration of cardiac rhythm monitorization allowed to increase the diagnosis of rhythm disturbances with a high emboligenous risk, such as paroxysmal atrial fibrillation or sinus node disease^[6,9,10]. In a recent systematic review and meta-analysis of 32 prospective observational studies or randomized controlled trials of patients with ischemic stroke, transient ischemic attack, or both, who underwent any cardiac monitoring for a minimum of 12 hours, the overall detection rate of any atrial fibrillation was 11.5% [95% confidence interval (CI) 8.9-14.3%], although the timing, duration, method of monitoring, and reporting of diagnostic criteria used for paroxysmal atrial fibrillation varied. Also, detection rates were higher in selected (13.4%, 95% CI 9.0 to 18.4%) than in unselected patients (6.2%, 95% CI 4.4-8.3%)^[11]. At present, a person who spends 1% of time in atrial fibrillation is categorized the same as someone who spends 50% of time in atrial fibrillation and treated using the same risk schemes. This might not be optimal and a promising research field is to define 'a-total-time in atrial fibrillation' threshold above which stroke risk becomes significant.

The routine use of transcranial Doppler ultrasound has also contributed to improve the diagnosis of right-to-left shunt through a patent foramen ovale when 'bubble signs' are detected in the middle cerebral artery after injection of agitated saline via the antecubital vein. The most important limitation of transcranial Doppler ultrasound is the absence of a temporal bone window in 10% who suffer stroke, a fact which particularly affects the older population.

Moreover, this technique does not distinguish intracardiac from extracardiac shunts^[7].

On neuroimaging, cardioembolic infarctions predominate in the distribution territories of the carotid and the middle cerebral artery, and bihemispheric combined anterior and posterior circulation, or bilateral or multilevel posterior infarcts are suggestive of cardioembolism. Magnetic resonance imaging (MRI) studies can increase the suspicion of cardioembolism by demonstrating lesions not apparent on CT scans. Spontaneous hemorrhagic transformation occurs in up to 71% of cardioembolic strokes^[1,2].

The recent development of biological markers related to cerebral cardioembolism, such as high serum levels of brain natriuretic peptide or D-dimer are useful to increase the sensitivity of the diagnosis of embolic etiology of the brain infarction in those cases of cerebral ischemia of undetermined or mixed etiology^[12-14]. In a study that examined the diagnostic value of a panel of biochemical markers to differentiate stroke etiologies in 707 consecutive acute stroke patients, independent predictors of cardioembolic stroke were atrial fibrillation, other embolic cardiopathies, total anterior circulation infarction, brain natriuretic peptide (BNP) >76 pg/mL 2.3 and D-dimer >0.96 µg/mL. Even among patients with transient symptoms ($n=155$), a high BNP level identified cardioembolic etiology. A model combining clinical and biochemical data had a sensitivity of 66.5% and a specificity of 91.3% for predicting cardioembolism^[12].

TREATMENT AND PREVENTION

Vascular repermeabilization with the use of intravenous thrombolysis during the first 4½ window hours in the acute phase of cerebral ischemia has been shown to improve neurological recovery and reduce sequelae, independently of the subtype of stroke and its prognosis. The extensive use of this therapeutic option in the majority of stroke units has been a crucial advance in the management of stroke patients^[4,15-17]. Thrombolytic or mechanical intraarterial treatment within the first 6 hours of stroke onset in the territory of the middle cerebral artery or within the first 12 hours in the territory of the basilar trunk, which is currently performed in highly specialized reference centers or in the framework of clinical trials seems to become another relevant advance in the care of patients during the acute phase of stroke.

At the present time, three new oral anticoagulants have consistently shown a higher safety profile (dabigatran, rivaroxaban and apixaban) and a non-inferior (rivaroxaban) or superior (dabigatran 150 mg and apixaban) efficacy as compared to coumarin for preventing cardioembolic events in patients with non-valvular atrial fibrillation^[18,19]. As an additional advantage, these drugs do not need anticoagulant monitorization avoiding periodic haematological controls, which are indispensable in patients currently treated with anti-vitamin K anticoagulants. It has been suggested that rapid institution as soon as possible of therapeutic anticoagulation possible in cardioembolic infarction is safe and useful in the prevention of cerebral or systemic embolic recurrence^[20].

The evidence that neurogenesis and angiogenesis play a role at cerebral level favouring brain neuroplasticity^[21] and that are stimulated by movements and exercise of the affected hemibody supports the necessity to maintain an active and persistent attitude regarding physiotherapy and motor rehabilitation as an indispensable therapeutic approach to improve neurological sequelae in cardioembolic stroke patients.

Some clinical research lines remain open, such as genetic-related risk of atrial fibrillation^[22]. The understanding of genetic variation implicated in atrial fibrillation will undoubtedly have an important

impact on cardioembolism and recurrence, particularly because one third all strokes in patients above the age of 65 are associated with this common arrhythmia. Looking forward, diagnosis of embolism based on biomarkers for cases of cerebral infarctions of undetermined or unknown etiology and consolidation in daily practice of new oral anticoagulants as a more effective, safe and comfortable therapy are encouraging areas of scientific interest. At some point in the near future, evidence for answering these questions will be available, improving the standard for the best care of patients with cardioembolic infarction.

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CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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