

# NT-proBNP as a biomarker of cardioembolic stroke

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In about 30-40 % of ischemic strokes, even after an extensive clinical investigation, it is not possible to determine any one etiology. It is possible that a fraction of these strokes, named cryptogenic, happen after an episode of paroxystic atrial fibrillation (AF) that was not registered. Strokes due to atrial fibrillation are usually severe, have a high recurrence rate and result in significant morbidity and costs.

The correct identification of a stroke etiology as cardioembolic is important as it has been shown that these patients benefit from anticoagulation. Studies show that the currently available methods to detect paroxystic atrial fibrillation have a low sensibility. This has led to the search for a biomarker of atrial fibrillation. Several studies have shown that NT-proBNP is increased during acute stroke. NT-proBNP is a peptide, which is produced in two major sites: the brain and the heart.

Four hypotheses have been put forward to try to explain this increase: release from the brain tissue, concomitant heart disease, atrial fibrillation, neurohumoral response.

Recent studies suggest that NT-proBNP may be used as a marker of cardioembolic stroke.

## Introduction

Stroke is the third largest cause of death in developed countries and the main cause of long-term morbidity. It has a great economic impact, accounting in some countries for 3-4 % of the annual health budget.

From an anatomopathological and physiopathological point of view strokes are divided in two groups: ischemic and hemorrhagic. About 80 % of strokes are ischemic and 20 % are hemorrhagic. Ischemic stroke is a heterogeneous pathology where extremely different causes can be found. Currently, ischemic strokes are preferentially divided according to their etiology into five groups using the mechanism-based TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification [1, 2]:

- Cardioembolic stroke, when there is a heart disease with embolic potential

- Large-artery disease where there is an atheromatous stenosis of a large intra- or extracranial vessel
- Small-vessel disease, when stroke results from occlusion of a small perforating artery
- Other determined disease, which includes causes such as dissection, vasculitis, hyperviscosity syndrome, antiphospholipids syndrome, among others
- Undetermined cause, when even after an extensive clinical investigation it is not possible to establish any one diagnosis or when more than one etiology is possible

After the diagnosis of stroke, an extensive etiological investigation should be undertaken. This should be as complete as possible so as to establish a specific etiology.

In about 30-40 % of ischemic strokes, even after an extensive clinical investigation, it is not possible to determine any one etiology. It is possible that a fraction of these strokes, named as cryptogenic, happen after an episode of paroxystic atrial fibrillation that was not registered [3]. Strokes due to atrial fibrillation are usually severe, with an estimated mortality at the first year of 50 %, have a high recurrence rate and result in significant morbidity and costs.

Most patients with ischemic stroke, including patients with an undetermined etiology, receive antiplatelets as secondary prevention therapy. However, it has been shown that oral anticoagulation (with an INR target range of 2.0-3.0) reduces the risk of recurrent stroke in patients with non-valvular atrial fibrillation, when compared with antiplatelets. It may also be associated with less severe stroke in case of recurrence. Oral anticoagulation is therefore recommended with Class I, Level A of evidence by the European Stroke Organization in patients with atrial fibrillation [4, 5].

Previous studies have shown that the available tests have a low sensibility to detect paroxystic atrial fibrillation. Although Holter monitoring is superior to routine ECG, in a systematic review the ability of a 24-72 hours Holter monitoring to detect paroxystic atrial fibrillation was 4.6 %. It has been shown that longer monitoring (4-7 days) detects AF in additionally 6-8 % of patients after a non-diagnostic Holter.

The use of event-loop recorders with a duration of 7 days, on day 0, 3 months and 7 months after a stroke detected AF in 14 % of patients after an initially negative Holter. Mobile Cardiac Outpatient Telemetry detected during a 21-day period AF in 23 % of patients with stroke or transient ischemic attack.

Therefore it is necessary to consider alternative ways to detect a possible cardioembolic etiology in patients with cryptogenic strokes. The relevance of a correct identification of the etiology of a stroke as cardioembolic has led to the hypothesis of using biomarkers for its diagnosis.

## Biomarkers

Biomarkers were defined in 2008 as molecular, biological or physical characteristics that indicate a specific physiological state. They are objectively measurable and can be used in clinical practice to identify the risk for a disease, diagnose a disease and its severity, to guide interventional strategies or to monitor patients' response to therapeutics.

Biomarkers that are currently used in cerebrovascular pathology happen to be either specific to the central nervous system or markers of systemic inflammation, fibrinolysis or hemostasis. Biomarkers from the blood, cerebrospinal fluid and brain tissue have been investigated. It would be ideal to be able to use a serum or plasma biomarker as it would be easily accessible, using a non-invasive procedure, and serial measures could be done over time.

Until now over 58 possible serum biomarkers and seven possible combinations have been studied in clinical practice.

## NT-proBNP

Previous studies have shown an increase of the serum concentrations of B-type or Brain Natriuretic Peptide (BNP) during acute stroke. BNP is a neurohormone, which has been studied and reported as a cardiac natriuretic hormone [6]. However, recent studies suggest that it may have an important role in acute stroke. It was

for the first time detected in porcine brain tissue in 1988 [7]. Later studies showed that it was also produced in the heart. Chemically BNP is a peptide, initially produced as a 108 aminoacid pro-hormone called proBNP.

After being secreted proBNP is cleaved into two fractions - the biologically active BNP (aa 77-108) and the N-terminal-proBNP (NT-proBNP) (aa 1-76) without biological activity. In healthy individuals BNP and NT-proBNP are present in almost equal concentrations in the plasma. However, NT-proBNP has got a half-life that is longer than the half-life of BNP. It is due to this fact that most trials use NT-proBNP instead of BNP.

Two main sources have been pointed out as responsible for BNP production: the brain, mainly the hypothalamus, and the heart. The heart is considered to be the main production site. In the heart the major stimulus for BNP synthesis and secretion is the stretching of the myocytes. In a normal physiological state, the ventricles are the major cardiac production site. Catecholamines, angiotensin II and endothelin may stimulate BNP production by paracrine or endocrine mechanisms.

It is presumed that NT-proBNP is cleared from the circulation by renal filtration and excretion. Biological effects of BNP include natriuresis, diuresis, vasodilation, inhibition of the renin-angiotensin-aldosterone axis and of the sympathetic nervous system. This peptide is currently used as a biomarker of left ventricular dysfunction and as a prognostic factor in patients with acute ischemic heart disease and heart failure.

It has been shown that NT-proBNP levels increase in patients with permanent or paroxysmic atrial fibrillation who have a preserved left ventricular systolic function. Levels of NT-proBNP significantly decrease after the restoration of sinus rhythm, by electric cardioversion. Although it is presumed that the increase in NT-proBNP has an atrial origin, there is no established explanation for this increase during AF.

## Nt-proBNP in cerebrovascular disease

Although NT-proBNP was first described in brain tissue, there is still little information concerning the role of this peptide in cerebrovascular disease. In recent years several studies have analyzed NT-proBNP or BNP during acute stroke [8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19]. Most of these single studies include less than 100 patients.

As the sampling regimes differed among the studies it is not possible to make a meta-analysis of when a peak is seen. However, increased levels for NT-proBNP or BNP were detected in all the studies. The majority of authors find that the increase is most likely due to heart dysfunction.

Montaner [20] studied the diagnostic value of a panel of potential biomarkers for the diagnosis of different ischemic stroke etiologies in a series of 707 patients with stroke or with a transient ischemic attack. Blood samples were drawn in the first 24 hours after stroke symptoms onset, when patients arrived at the emergency room. BNP was one of the biomarkers studied. Increased BNP levels were observed in patients with cardioembolic stroke. With  $> 76$  pg/mL as the cut-off point BNP indicated a cardioembolic etiology with a sensitivity of 72 %, a specificity of 69 %, a positive predictive value of 55 % and a negative predictive value of 82 %.

## Conclusion

Several studies have shown that NT-proBNP is increased during acute stroke. Four hypotheses have been put forward to try to explain this increase: release from the brain tissue, concomitant heart disease, atrial fibrillation, neurohumoral response. Recent studies suggest that NT-proBNP may be used as a surrogate marker of cardioembolic stroke. However, studies including a larger number of patients should be undertaken in order to verify this. The finding of a biomarker for cardioembolic stroke would undoubtedly improve the management of stroke patients.

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