

Biomarkers for prognosis in atrial fibrillation: unfulfilled hopes

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The most common tachyarrhythmia in clinical practice is atrial fibrillation (AF), which may be associated with serious consequences such as an increased risk of stroke, systemic embolism, congestive heart failure, and death. The management of almost all patients with AF involves prevention of thromboembolic complications. Moreover, treatment strategies for AF vary widely among clinicians. Two basic strategies for AF are available, namely, control of the ventricular rate or restoration and maintenance of sinus rhythm. The restoration of sinus rhythm has been shown to diminish subjective symptoms and to improve cardiac output and functional capacity. However, adverse effects of antiarrhythmic drugs and repeated cardioversions lead to decreased quality of life, and the treatment has not been shown to decrease mortality. Thus, optimal management of patients with AF requires an individualized approach, taking into account the underlying pathology. Appropriate management decisions might be aided by the identification of a subgroup of patients with AF who could benefit most from the rhythm control strategy.

New prognostic markers, including biochemical parameters, are currently being investigated. Persistent AF leads to electrical, structural, and neurohormonal remodeling of the atria; therefore, heart endocrine studies concerning patients with this arrhythmia have become increasingly important. Hemodynamic changes due to the loss of atrial systolic function also result in endocardial endothelium dysfunction and damage.

Lewicka et al.¹ investigated selected biomarkers as predictors of AF recurrence after successful electrical cardioversion. Aldosterone seems to play a specific role in the response of the heart to hemodynamic and neuroendocrine imbalances during persistent AF. Increased cardiac synthesis of aldosterone during AF in the absence of ventricular dysfunction has been reported by Goette et al.² Atrial overload and stretch also result in

increased production of natriuretic peptide type A (ANP), the first discovered neurohormone secreted by the heart. B-type natriuretic peptide (BNP) is released by cardiac ventricles in response to volume and pressure overload. Increased pressure in fibrillating atria results in increased wall tension and induces *BNP* gene expression in both ventricles and atria. Endothelin 1 (ET-1) is synthesized by the endothelium and is a sensitive biochemical marker of its dysfunction. Evaluation of changes in neurohormonal markers during persistent AF and following sinus rhythm restoration may lead to a better understanding of the pathophysiology of arrhythmia and help in predicting its clinical course. The main objective of the study by Lewicka et al.¹ was to investigate whether the plasma levels of selected biomarkers and their changes after electrical cardioversion can be useful in predicting sinus rhythm maintenance. Another objective of the study was to determine the impact of cardioversion in patients with persistent AF on the plasma concentrations of different biomarkers.

The study group consisted of 60 patients with dual-chamber pacemaker implanted in the past, persistent AF and preserved left ventricular systolic function, who underwent successful electrical cardioversion. The authors assessed the clinical value of plasma BNP, ANP, aldosterone, and ET-1 concentrations measured before and after cardioversion. They showed that only baseline plasma BNP concentrations, but not ANP, ET-1 or aldosterone levels, were useful for predicting AF recurrence. The authors assessed AF recurrence due to diagnostic functions and intracardiac recording obtained from dual-chamber pacemakers. It was a very accurate and consistent diagnostic method of AF episodes in the study group.¹

Previously published studies showed increased BNP levels in patients with AF and its decrease to normal values following sinus rhythm restoration.³ Studies, in which BNP levels were

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determined in patients without heart failure symptoms and with no left ventricular systolic dysfunction, suggests an independent effect of arrhythmia on this peptide secretion.⁴

BNP is an established marker of heart failure. Increased BNP levels in persistent AF has important practical implications for the diagnosis of heart failure. Increased BNP levels may result from the arrhythmia itself and should not necessarily be interpreted as indicating significant left ventricular dysfunction. The assessment of the prognostic significance of BNP in AF is even more difficult than defining its diagnostic utility. The authors, contrary to other investigators, showed that elevated baseline BNP levels were predictors of AF recurrence, but they were not an independent predictor in the multivariate analysis. Data available in the literature show that ANP levels in patients with AF are significantly higher compared with patients with similar clinical characteristics who were in sinus rhythm. Plasma ANP levels also decrease after successful cardioversion.⁵ Unfortunately, baseline plasma ANP levels do not predict long-term sinus rhythm maintenance after cardioversion. The results obtained by Lewicka et al.¹ were similar to other studies, in which authors were unable to show a relationship between baseline ANP levels and sinus rhythm maintenance.^{6,7}

The search for predictors of successful cardioversion and sinus rhythm maintenance has continued for years but has been largely inconclusive. According to the guidelines, apart from the duration of arrhythmia, no other clinical, echocardiographic, hemodynamic, or hormonal variable has an established prognostic role. In addition, the decision of whether to proceed with cardioversion or give up further attempts to restore the sinus rhythm cannot be definitely based on the assessment of the neurohormonal profile in patients with AF and preserved left ventricular systolic function.

Evidence from both experimental and clinical studies has shown an important role for the renin-angiotensin-aldosterone (RAA) system in patients with AF. Several studies have provided evidence that activation of the RAA system induces myocyte injury, proarrhythmic electrical remodeling, and fibrosis through aldosterone. Suppression of the RAA system either by angiotensin-converting enzyme inhibition or AT₁-receptor antagonist decreases the incidence of AF by reversing structural and electrical cardiac changes, known as cardiac remodeling, which leads to the development of arrhythmia.^{8,9}

Aldosterone has been shown to exert several deleterious effects provoking cardiac damage due to the stimulation of cardiac collagen synthesis, fibroblast proliferation, and myocardial fibrosis by the activation of local mineralocorticoid receptors, increasing AT₁-receptors, and enhancing local angiotensin-converting enzyme expression. In the study by Lewicka et al.,¹ baseline plasma aldosterone levels and the changes in

its levels after electrical cardioversion were not useful for predicting sinus rhythm maintenance. However, in another study, conversion of AF to sinus rhythm was associated with a significant decrease in serum aldosterone levels. Moreover, a notable decrease in plasma aldosterone concentrations after cardioversion was correlated with the maintenance of sinus rhythm during 30 days of follow-up.¹⁰

The effect of ET-1 on hypertrophy, pathological remodeling, and fibrosis of the atrial muscle may be significant in the pathophysiology of AF.¹¹ Unfortunately, Lewicka et al.¹ and other investigators confirmed that persistent AF does not affect plasma ET-1 concentrations in patients with preserved left ventricular systolic function. There were also no significant changes in plasma ET-1 levels after cardioversion.¹² However, a short duration of the arrhythmia and early-stage atrial disease in the examined group of AF patients may also have affected the results.

The atria that are structurally and functionally able to sustain sinus rhythm after cardioversion, differ from those in which AF recurs or becomes permanent. The selected neurohormones are sensitive biomarkers of these changes and provide an insight into the severity of atrial disease. However, the predictive role of these parameters in the clinical evaluation of patients with persistent AF still does not meet our expectations.

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