Clinical and prognostic value of selected markers of myocardial fibrosis in arrhythmogenic right ventricular cardiomyopathy

Background

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a heart muscle disease characterized by progressive fibrofatty replacement of the myocardium, leading to electrical instability and ventricular arrhythmias, as well as heart failure in the later stages of the disease. In most cases, ARVC is caused by mutations in genes encoding desmosomal proteins, resulting in cardiac myocyte detachment and death. The disease predominantly affects the right ventricle, but biventricular and left-dominant forms are also observed. Therapeutic decisions on cardioverter-defibrillator (ICD) implantation or heart transplantation are challenging because the course of ARVC is hard to predict.

Recently, numerous novel biomarkers have been studied in cardiology and the results suggest that some of them will be introduced into routine clinical practice. Among these novel biomarkers are markers of myocardial fibrosis, such as the soluble form of the ST2 protein (sST2), galectin-3 (Gal-3) and extracellular matrix metalloproteinases (MMPs). According to current knowledge, it seems that markers of myocardial fibrosis could be potentially promising factors in the clinical and prognostic evaluation of ARVC patients.

Aims

The study aimed to establish the role of serum levels of selected markers of myocardial fibrosis (sST2, Gal-3, MMP-2, MMP-9) in the clinical assessment of ARVC patients in terms of myocardial dysfunction, heart failure symptoms and arrhythmias. Another goal was to evaluate the prognostic value of these biomarkers in predicting cardiac death or heart transplantation and life-threatening ventricular arrhythmias during follow-up. Moreover, a comparison of the clinical and prognostic value of markers of myocardial fibrosis with biomarkers routinely used in clinical practice such as natriuretic peptides (NT-proBNP) and highly sensitive troponin T (hsTnT) has been planned.

Methods

Ninety-one patients with a definite diagnosis of ARVC according to the current 2010 International Task Force Criteria were included (59 male, mean age 47 ± 16 years). Serum levels of selected markers of myocardial fibrosis (sST2, Gal-3, MMP-2, MMP-9), as well as NT-proBNP and hsTnT, were measured. Patients were evaluated for their medical history, and electrocardiograms and imaging results were analyzed. Furthermore, subjects were followed for the primary endpoint (cardiac death or heart transplantation) and secondary endpoints (hospitalizations due to heart failure, ventricular arrhythmia defined as sudden cardiac death, ventricular fibrillation, sustained ventricular tachycardia or appropriate ICD intervention, and atrial arrhythmias).

Results

In ARVC patients, a correlation was found between higher serum levels of sST2, MMP-2, NT-proBNP and hsTnT (but not Gal-3 and MMP-9) and right ventricular dilatation, systolic dysfunction of both ventricles, presence of moderate/severe tricuspid regurgitation and greater dimensions of both atria. Subjects with a history of life-threatening ventricular arrhythmia (ventricular fibrillation or haemodynamically unstable ventricular tachycardia), as well as those with a history of supraventricular arrhythmia (atrial fibrillation, atrial flutter or atrial tachycardia), had higher concentrations of MMP-2, NT-proBNP and hsTnT. Regarding atrial arrhythmias, a stronger correlation was observed for MMP-2 compared to NT-proBNP and hsTnT.

During follow-up (median 36.4 [29.8-41.2] months), a combined endpoint of death or heart transplantation was reached by 13 patients (14%). These subjects had higher levels of sST2, MMP-2, NT-proBNP and hsTnT (no such correlation was found for Gal-3 and MMP-9). The same four biomarkers predicted unscheduled hospitalizations due to heart failure during observation. Independent risk factors for death or heart transplantation in ARVC patients were a history of atrial tachycardia, right ventricular end-diastolic area ≥ 39.0 cm2 and NT-proBNP concentration ≥ 890.3 pg/ml. No correlation was found between the concentration of any of the studied biomarkers and episodes of ventricular arrhythmia during follow-up. MMP-2 was the only one among the studied biomarkers to predict atrial arrhythmia. Higher levels of MMP-2 and a greater area of the right atrium appeared to be risk factors for the first episode of atrial fibrillation.

Conclusions

Higher serum levels of sST2, MMP-2, NT-proBNP and hsTnT correlate with disease severity and are risk factors for poor prognosis in ARVC. History of atrial tachycardia, right ventricular end-diastolic area $\geq$ 39.0 cm^2 and NT-proBNP concentration $\geq$ 890.3 pg/ml are independent predictors of death or heart transplantation. Biomarkers have no value in predicting ventricular arrhythmia in ARVC. MMP-2 concentration is a potentially valuable predictor of atrial arrhythmia, including the first episode of atrial fibrillation.

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