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Original article

MMP-9 in atrial remodeling in patients with atrial fibrillation

MMP-9 dans le remodelage des oreillettes chez les malades atteints de fibrillation atriale

J. Lewkowicz [a,*], M. Knapp [b], A. Tankiewicz-Kwedlo [c], R. Sawicki [b], M. Kamińska [b], E. Waszkiewicz [b], W.J. Musiał [b]

[a] *Department of Cardiosurgery, Medical University of Białystok, ul. M. Skłodowskiej-Cure 24a, 15-276, Białystok, Poland*
[b] *Department of Cardiology, Medical University of Białystok, Białystok, Poland*
[c] *Department of Monitored Pharmacotherapy, Medical University of Białystok, Białystok, Poland*

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Abstract

Introduction. – Atrial fibrillation (AF) is the most common arrhythmia and is associated with significant morbidity and mortality. The impact of matrix metalloproteinases (MMPs) on structural atrial remodeling and sustainment of AF in patients with persistent and permanent AF is unresolved.

Objectives. – The aim was to evaluate MMP-9 and its tissue inhibitor-1 (TIMP-1) as markers of atrial remodeling in patients with persistent AF (PAF) who underwent electrical cardioversion (ECV) and in patients with permanent AF (continuous AF, CAF).

Patients and methods. – Plasma levels of MMP-9 and TIMP-1, clinical findings, and echocardiographic parameters were evaluated in 39 patients with AF and in 14 controls with sinus rhythm.

Results. – The concentrations of MMP-9 were significantly higher in patients with PAF and CAF compared to controls. There was a significant increase of MMP-9 after ECV in the persistent AF group. The values of TIMP-1 were not significantly different between the groups. In patients with AF, MMP-9 levels were positively related to posterior wall thickness of the LV ($r = 0.356$, $P = 0.049$) and body mass index ($r = 0.367$, $P = 0.046$).

Conclusion. – Elevated levels of MMP-9 were related to the occurrence and maintenance of AF. This suggests that MMP-9 can be a marker of atrial remodeling in patients with AF. Regulation of the extracellular collagen matrix might be a potential therapeutic target in AF.

Keywords: Atrial fibrillation; Atrial remodeling; Matrix metalloproteinases; Tissue inhibitors of metalloproteinases

Résumé

Introduction. – La fibrillation atriale (FA) est un trouble du rythme du cœur très fréquent, augmentant considérablement la morbidité et la mortalité. L'influence des métalloprotéinases matricielles (MMP) sur le remodelage structurel des oreillettes et la présence de la fibrillation atriale (FA) chez les malades atteints de fibrillation atriale persistante et permanente reste toujours inexpliquée.

Objectif. – L'objectif a été d'évaluer la concentration de MMP-9 et de son inhibiteur tissulaire-1 (TIMP-1) comme marqueurs du remodelage des oreillettes chez les patients atteints de fibrillation atriale persistante (FA persistante) après la procédure de cardioversion électrique (CVE) et chez les patients atteints de fibrillation atriale permanente (FA permanente).

Patients et méthodes. – La concentration de MMP-9 et TIMP-1, les caractéristiques cliniques et les paramètres échocardiographiques ont été évalués chez 39 patients atteints de FA et chez 14 personnes en rythme sinusal (témoin).

Résultats. – La concentration de MMP-9 a été statistiquement plus élevée chez les patients atteints de FA persistante et de FA permanente que chez ceux du groupe témoin. Après la cardioversion électrique (CVE), une forte augmentation de la concentration de MMP-9 a été observée chez les patients du groupe FA persistante. Les différences de la concentration de TIMP-1 n'ont pas été observées entre les groupes. Chez les patients atteints de fibrillation auriculaire, la concentration de MMP-9 correspond positivement à l'épaisseur de la paroi postérieure gauche du ventricule ($r = 0{,}356$, $p = 0{,}049$) et à l'indice de masse corporelle ($r = 0{,}367$, $p = 0{,}046$).

* Corresponding author.
E-mail address: janka.lewkowicz@wp.pl (J. Lewkowicz).

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Conclusion. – L'augmentation de la concentration de MMP-9 a été associée à la survenue et la présence de FA. Il en résulte que MMP-9 peut être considéré comme marqueur du remodelage des oreillettes chez les patients souffrant d'arythmie. La régulation de l'activité des enzymes de la matrice extracellulaire peut avoir des objectifs thérapeutiques potentiels.

Mots clés : Fibrillation atriale ; Remodelage des oreillettes ; Métalloprotéinases matricielles ; Inhibiteurs tissulaires des métalloprotéinases

1. Introduction

It is now widely recognized that atrial fibrillation (AF), although considered as a benign arrhythmia, is associated with a significant increase in mortality and morbidity [1,2], as well as rising costs of treatment [3]. The currently available therapeutic approach has limited efficiency and many side effects. The mechanisms underlying AF have consequently received a great deal of attention due to these side effects. It has been proved that structural, contractile, and electrical changes in the atria create conditions which induce atrial remodeling and promote the occurrence and maintenance of AF. Many studies highlight an association between the imbalance of extracellular matrix (ECM) deposition and degradation with atrial remodeling and the presence of AF [4–7].

Recent studies show that matrix metalloproteinases (MMPs) — the family of enzymes that degrade ECM proteins and their tissue inhibitors (TIMPs) — are implicated in atrial fibrosis and enlargement [4,8]. It has been also reported that the imbalance between MMPs and TIMPs is playing a key role in the development and sustainment of the arrhythmia.

We hypothesized that the cardiac extracellular matrix remodeling, essential for atrial fibrosis and enlargement, occurs shortly after the development of persistent AF and that structural changes in the atrial extracellular matrix are reflected in altered levels of certain circulating matrix biomarkers. We accordingly investigated the correlation between serum levels of MMP-9 and TIMP-1 in patients with persistent and permanent AF and clinical findings as well as echocardiographic measurements.

2. Patients and methods

2.1. Study participants

Thirty-nine adults with atrial fibrillation admitted to the Cardiology Department of the Medical University in Bialystok, Poland were enrolled in the study. Twenty-six AF patients had a recognized persistent AF and 25 of them underwent an electrical cardioversion (ECV) after unsuccessful pharmacological cardioversion, according to the ESC guidelines [9]. Thirteen from the group with AF had a recognized permanent AF and were on oral anti-coagulants with a target range of 2.0–3.0 according to the international normalized ratio (INR). Patients with conditions associated with elevated serum concentrations of myocardial or tissue fibrosis markers such as acute or chronic inflammatory diseases, metabolic bone diseases, malignancies, connective tissue disorders, liver diseases, hyperthyroidism, recent surgery, pulmonary fibrosis, and chronic obstructive pulmonary disease, or myocardial infarction were excluded from the study. Hemodynamically unstable patients were also excluded.

The duration of AF was estimated on the basis of patient history. Successful cardioversion was defined as a stable sinus rhythm lasting for at least 24 hours after the procedure.

The control group consisted of 14 volunteers with sinus rhythm (SR) and no history of arrhythmia and was matched for age, sex and coexisting diseases.

This study was approved by The Local Ethics Committee and complies with the Declaration of Helsinki. Informed written consent was obtained from all the subjects before the initiation of any study procedures.

2.2. Laboratory methods

Blood samples were obtained from all patients via a peripheral vein. In patients with persistent AF who underwent an ECV blood samples were taken twice —— in the morning before the procedure and within 24 hours after the ECV. Within an hour after collection, blood samples were centrifuged at 4000 × *g* for 10 minutes. The serum was separated into aliquots and stored at –80 °C.

Serum levels of MMP-9 (total: pro- and active forms) and TIMP-1 were measured by a commercial standardized in vitro enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Research and Diagnostic Systems Ltd, Abington, UK). Hematological and biochemical parameters were determined by routine techniques using an automated analyzer in the local laboratory.

2.3. Echocardiographic procedures

Transthoracic two-dimensional and M-mode echocardiograms with Doppler measurements were performed according to local practice in all subjects using The EnVisor Ultrasound System and iE33, Philips Medical Systems Nederland B.V. Measurements collected were left atrial diameter (LAD), left atrial diameter indexed to body surface area (LADI), left ventricular end-diastolic diameter (LVEDD), left ventricular septal and posterior end-diastolic wall thickness (PWT of LV), left ventricular ejection fraction (LVEF) at the baseline and the presence of