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PRE-CLINICAL RESEARCH

Direct Thrombin Inhibitors Prevent Left Atrial Remodeling Associated With Heart Failure in Rats

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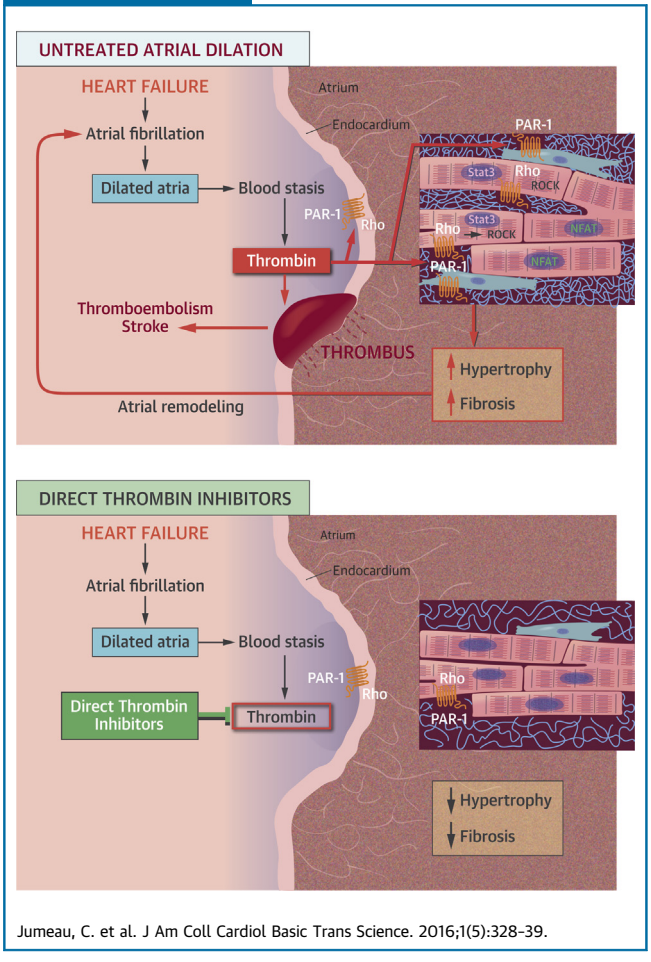
VISUAL ABSTRACT



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HIGHLIGHTS

- **Oral direct anticoagulants such as DTIs, but not vitamin K antagonist, diminish the progression of atrial dilation associated with heart failure in a rat model.**
- **Prevention of atrial dilation by DTI is associated with decreased duration of atrial arrhythmia induced by burst pacing.**
- **DTI inhibits interstitial fibrosis, extracellular matrix remodeling, and hypertrophy of atrial myocardium.**
- **Plasma DTI concentrations inhibiting atrial remodeling are lower than those required for therapeutic anticoagulant activity.**
- **DTIs may be of interest to prevent the progression of atrial fibrillation substrate in addition to their anticoagulant activity.**

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SUMMARY

The present study tested the hypothesis that thrombin participates in formation of left atrial remodeling and that direct oral anticoagulants, such as direct thrombin inhibitors (DTIs), can prevent its progression. In a rat model of heart failure associated with left atrial dilation, we found that chronic treatment with DTIs reduces the atrial remodeling and the duration of atrial fibrillation (AF) episodes induced by burst pacing by inhibiting myocardial hypertrophy and fibrosis. In addition to the prevention of thromboembolism complicating AF, DTIs may be of interest to slow down the progression of the arrhythmogenic substrate. (J Am Coll Cardiol Basic Trans Science 2016;1:328–39)

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ANP = atrial natriuretic peptide

BNP = brain natriuretic peptide

CTGF = connective tissue growth factor

DTI = direct thrombin inhibitor

MHC = myosin heavy chain

MI = myocardial infarction

NFATc3 = nuclear factor of activated T cells 3

PAI = plasminogen activator inhibitor

PAR = protease-activated receptor

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice (1). It is associated with a 5-fold risk of stroke and systemic thromboembolisms. During AF, thrombus formation is promoted by blood stasis in poorly contractile atria together with a hypercoagulable state, as indicated by high circulating levels of fibrinolytic degradation products, plasminogen activator inhibitor (PAI)-1, and thrombin-antithrombin complex (2). For all of these reasons, anticoagulation is a central therapeutic target for most AF patients. Anticoagulation can be achieved via vitamin K antagonists or, more recently, with direct thrombin inhibitors (DTIs) or direct factor Xa inhibitors, referred to as non-vitamin K antagonist oral anticoagulants (3).

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Thrombin is the central protease of the coagulation cascade. It converts soluble plasma fibrinogen into insoluble clot-forming fibrin polymers, and activates several positive feedback steps to amplify its own generation (4). In addition, thrombin has pleiotropic cellular effects through the cleavage of protease-activated receptor (PAR)-1, including hemostasis, inflammation, cellular growth, and proliferation (4–6). For instance, PAR-1 promotes hypertrophy of neonatal rat cardiomyocytes and deoxyribonucleic acid synthesis in fibroblasts (5,7). In mice, PAR-1 overexpression induces eccentric hypertrophy and dilated cardiomyopathy, whereas PAR-1 deficiency is associated with reduced left ventricle dilation after myocardial infarction (MI) (8).

Several hormones, peptides, or pathways are recognized to be involved in atrial remodeling, including the renin angiotensin system (9), but little is known about the role of thrombin. In vitro, this protein induces alterations of the electric and mechanical properties of rabbit left atrial strips, which are prevented by the DTI dabigatran and a PAR-1 antagonist (10). The present in vivo study was undertaken to test the hypothesis that thrombin participates in left atrial remodeling and AF substrate formation, known to be promoted by heart failure (11–13), and that DTI can slow their progression. It was conducted using a rat model of heart failure secondary to an extensive MI, which is associated with left atrial remodeling and AF susceptibility (14,15). We found that DTIs and PAR-1 antagonists prevent atrial remodeling and reduce AF susceptibility.

METHODS

MODEL OF ATRIAL REMODELING FOLLOWING INFARCTION-INDUCED HEART FAILURE. This study had the approval of the local animal research ethics committee and the French Ministry of Education and Research (authorization N°00429.03). Male OFA Sprague-Dawley rats weighting 200 to 220 g were obtained from Charles River Laboratories (L'arbresle, France) and housed for 10 days before the surgery. Animals were anesthetized with intraperitoneal injection of 30 mg/kg sodium pentobarbital and received a subcutaneous injection of 1.5 mg/kg meloxicam for pain. MI was achieved by thoracotomy and transient occlusion of the left anterior

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