Remodeling of Ion Channel Expression in Patients with Chronic Atrial Fibrillation and Mitral Valvular Heart Disease

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Background/Aims: Underlying cardiac pathology and atrial fibrillation (AF) affect the molecular remodeling of ion channels in the atria. Changes in the expression of these molecules have not been demonstrated in Korean patients with mitral valvular heart disease. Thus, the purpose of this study was to analyze ion channel expression in patients with chronic AF and mitral valvular heart disease.

Methods: A total of 17 patients (eight males and nine females; mean age, 57 ± 14 years [range, 19 to 77]) undergoing open-heart surgery were included in the study. Twelve patients (seven with coronary artery disease and five with aortic valvular disease) had sinus rhythm, and five patients (all with mitral valvular disease) had chronic, permanent AF. A piece of right atrial appendage tissue (0.5 g) was obtained during surgery. RT-PCR was used to evaluate the expression of L-type Ca2+ channels, ryanodine receptor (RyR2), sarcoplasmic reticular Ca2+-ATPase (SERCA2), gene encoding the rapid component of the delayed rectifier I kr (HERG), gene encoding calcium-independent transient outward current Ito1 (Kv4.3), gene encoding the ultrarapid component of the delayed rectifier I ku (Kv1.5), K+ channel-interacting protein 2 (KChIP2), hyperpolarization-activated cation channel 2 associated with the pacemaker current Ir (HCN2), and gene encoding Na+ channel (SCN5A).

Results: Reduced L-type Ca2+ channel, RyR2, SERCA2, Kv1.5, and KChIP2 expression and borderline increased HCN2 expression were observed in the patients with AF and mitral valvular heart disease. Left atrial diameter was negatively correlated with RyR2 and KChIP2 expression. Fractional area shortening of the left atrium was positively correlated with RyR2 and KChIP2 expression.

Conclusions: Alterations in ion channel expression and the anatomical substrate may favor the initiation and maintenance of AF in patients with mitral valvular heart disease. (Korean J Intern Med 2010;25:377-385)

Keywords: Atrial fibrillation; Electrical remodeling; Ion channels

INTRODUCTION

Atrial fibrillation (AF) begets AF; that is, AF itself alters atrial electrophysiological properties in a manner that favors the induction and maintenance of AF (i.e., electrical remodeling) [1]. The major mechanisms of electrical remodeling are initiated by an increased atrial rate. The roughly 10-fold atrial rate increase caused by AF substantially increases cellular Ca2+ loading by Ca2+ intake through Ica [2]. Progressive Ca2+ loading threatens cell viability, and cells respond to minimize the impact of the increased rate on the intracellular Ca2+ load. Thus, defense mechanisms include voltage-dependent and intracellular Ca2+ concentration-dependent Ica inactivation. Decreases in Ica reduce Ca2+ entry and help to prevent Ca2+ overload; however, because Ica is a key contributor to the action potential plateau, reductions in Ica decrease the action potential duration (APD), reduce the refractory...
period, and promote the induction and maintenance of AF by multiple-circuit reentry [3]. Changes in a number of ionic currents have been detected in persistent and permanent human AF. An increased IK1 [4], lack of change in INa [5], decreased Ito [4], and decreased ICa [5,6] have been reported. Corresponding changes in IKur (no change [5], decreased [4]), IKr, IKs, and If are not well established [7].

Changes in the gene or protein expression of the channels responsible for action potential generation have been reported in AF. Changes in the expression of molecules such as gene encoding calcium-independent transient outward current Ito1 (Kv4.3) [8], α1c (ICa) [9], gene encoding the ultrarapid component of the delayed rectifier IKu (Kv1.5) [4], gene encoding the rapid component of the delayed rectifier Ikr (HERG) [8], and hyperpolarization-activated cation channel 2 associated with the pacemaker current I (HCN) [10] have also been reported. Molecules related to Ca²⁺ homeostasis in cardiomyocytes include ryanodine receptor (RyR2), sarcoplasmic reticular Ca²⁺-ATPase (SERCA2), phospholamban, calsequestrin, and L-type Ca²⁺ channels.

Decreased SERCA2 and L-type Ca²⁺ channel expression has been reported in AF, and the expression of other molecules may be unaltered [9].

The assembly of four voltage-gated K⁺ channel Kv α-subunits into a tetrameric structure creates a functional Ito channel. Reduced Ito levels have been reported in various conditions, including heart failure [11] and myocardial infarction [12] as well as AF, and the magnitude of Ito may affect APD [13]. Kv4.3 is responsible for most of the Ito current in the human atrium. Assembly of the β-subunits into pore-forming tetramers is sufficient to generate functional K⁺ channels. Kv expression is modulated by cytoplasmic proteins such as β-subunits, K⁺ channel-interacting protein (KChIP) 2, frequenin, and K⁺ channel-associated protein (KChAP). KChIP was recently shown to associate with Kv4 [14]. Of the three KChIP types known (KChIP1, KChIP2, and KChIP3), KChIP2 is expressed in the human heart. KChIP2 may be a regulatory subunit of Kv4.3 [15].

Expression changes in these molecules have not been demonstrated in Korean patients with mitral valvular heart disease. Therefore, the purpose of this study was to analyze the expression status of these molecules in patients with chronic AF and mitral valvular heart disease.

**METHODS**

**Patients and atrial tissue collection**

A total of 17 patients (eight males and nine females; mean age, 57 ± 14 years [range, 19 to 77]) undergoing open heart surgery for coronary artery bypass, valve repair, or replacement were included in the study. Twelve patients had sinus rhythm (SR): coronary artery disease (n = 7, CAD-SR) and aortic stenosis/stenoininsufficiency (n = 5, AVD-SR). Five patients had permanent AF (longer than 6 months) and mitral stenosis (MVD-AF). Written informed consent was obtained from each patient before all procedures. Echocardiography was performed within 1 week, and cardiac catheterization was performed within 1 month prior to surgery. The clinical characteristics of each group are listed in Table 1. A piece of right atrial appendage tissue (0.5 g) was obtained during surgery. The excised samples were immediately frozen in liquid nitrogen and stored at -80°C until use.

**Transthoracic echocardiography**

A 2.5-MHz phased array transducer and standard echocardiographic system (Acuson Sequoia C256, Siemens, Washington, DC, USA) were used to measure cardiac structural and functional parameters. Three diameters within the left atrium (LA) were measured: height in the parasternal long-axis view (LA1), width in the tilted parasternal short-axis view (LA2), and height in the apical four-chamber view (LA3). The left atrial volume was calculated as \( \frac{\pi \times LA1 \times LA2 \times LA3}{8} \). The apical four-chamber view was obtained and recorded on videotape for subsequent off-line measurements. For the LA and right atrium (RA), the largest atrial area (AAmax) during ventricular systole and smallest area (AAmin) during ventricular diastole were measured. Atrial fractional area shortening (FAS) was calculated as \( \frac{AA_{max} - AA_{min}}{AA_{max}} \times 100 \). In the AF group, the average of three consecutive cardiac cycles was used for echocardiographic measurement. Pulmonary artery systolic pressure (PASP) was estimated from the trans-tricuspid pressure gradient by Doppler examination.

**Cardiac catheterization**

All cardiac catheterization procedures were performed as a preoperative evaluation. In cases of rheumatic valvular heart disease, right and left heart catheterization was performed to obtain hemodynamic profiles of each chamber and cardiac function. In cases of coronary artery...