Potassium Channel Remodeling in Heart Disease

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KEYWORDS

• Cardiac repolarization • Heart disease • Potassium • Potassium channel • Arrhythmia
• Atrial Fibrillation

KEY POINTS

- Cardiac repolarization and underlying ionic mechanisms are substantially altered by heart disease.
- In hypertrophy, myocardial infarction, and heart failure, potassium channels and currents are downregulated and repolarization is delayed, creating a substrate for ventricular tachyarrhythmia.
- Mechanisms leading to arrhythmia with potassium channel downregulation include early afterdepolarizations, reduced cardiomyocyte resting membrane resistance, and increased repolarization heterogeneity.
- A variety of extracardiac conditions (eg, hypokalemia, class III antiarrhythmic drugs) further reduce repolarization reserve and increase the arrhythmic risk in patients with heart disease.
- In atrial fibrillation, the combined effects of reduced calcium current and increased potassium current reduce action potential duration and refractory period and promote reentry, while hyperpolarizing the resting membrane potential, stabilizing reentrant rotors.

INTRODUCTION

Potassium channels are substantially altered in cardiovascular diseases (for an overview, see **Table1**). Teleologically, the types of potassium channel remodeling could be classified into 2 general secondary categories. The first type of remodeling, occurring in the ventricles with heart failure (HF), aims to prolong the action potential (AP) to increase calcium entry into the cytoplasm and compensate cardiomyocyte contraction. The second type of remodeling process, typically occurring in atria during atrial fibrillation (AF), aims to shorten the cardiomyocyte refractory period to allow cardiomyocytes to sustain very high activation rates. These pathophysiologic processes are complex and include redundancy and negative feedback. Although apparently designed to maintain cardiac homeostasis, they also induce electrophysiologic alterations that lead to potentially serious arrhythmias. Therefore, understanding them is of value for cardiologists in daily practice. In addition, K^+ channel remodeling can be induced by a host of other cardiac and extracardiac conditions.

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Table 1
Main disease-related modifications in K^+ currents in pathologic situations

	Ventricular Hypertrophy		Heart Failure		Myocardial Infarction		Atrial Fibrillation	
Current Density	Exercise	Overload	Atria	Ventricle	Border Zone	Normal Zone	Atria	PV[a]
APD	↔	↑	—	↑	↑	↑	↓	↓
I_{to}	↔	↓	↓	↓	↓/↔[b]	↓	↓	↓
I_{Kur}[c]	—	—	—	—	—	—	↓(?)[d]	—
I_{K1}	↑	↓	↔	↓	↓	↓	↑	↓
I_{Kr}	↔	↓	↔	↔	↓	↓	↔	↑
I_{Ks}	↔	—	↓	↓	↓[e]	↓	↔	↑
I_{Kss}	↑	↓	—	↔	—	—	—	—
I_f[f]	—	—	↓	—	—	—	—	—
$I_{K(Ach,c)}$[c]	—	—	—	—	—	—	↑	—
$I_{K(ATP)}$	—	—	—	—	—	↑	?[d]	—
I_{SK}	—	—	—	↑	—	↑	↔[d]	↑
I_{K2P}[c]	—	—	—	—	—	—	↑	—

When discrepancies were noted across models, results documented on human samples are reported.

Abbreviations: ↑, current is increased; ↓, current is decreased; ↔, current is unchanged; APD, action potential duration; I_{to}, transient outward K^+ current; I_{K1}, inward rectifier K^+ current; I_{K2P}, 2-pore-domain K^+ current; I_{Kur}, ultrarapid rectifier K^+ current; I_{Kr}, delayed rectifier K^+ current; I_{Ks}, slow rectifier K^+ current; I_{Kss}, steady-state outward K^+ current; $I_{K(ACh)}$, acetylcholine-dependent K^+ current; I_{SK}, small calcium-activated K^+ current; PV, pulmonary veins.

[a] Compared with the left atrium.

[b] I_{to} is reduced initially then return to normal within 2 months.

[c] Atrial-specific currents.

[d] Conflicting results.

[e] ERG, KvLQT1 and minK are down regulated at day 2 after MI then ERG and KvLQT1 normalized at day 5 after MI, whereas minK remains downregulated.

[f] In sinoatrial node.

Data from Refs.[7,12,30,73,74]

Cardiac repolarization is in itself a complex process. Current state of the art recognizes more than 10 different types of cardiac K^+ currents, and more than 20 types of K^+ channels are known to be expressed in the heart.[1,2] Herein, we aim to present the K^+ channel remodeling processes in 4 common pathologic situations: cardiac hypertrophy, HF, myocardial infarction (MI), and AF. Specific regional remodeling profiles such as the border zone of the MI scar and the pulmonary veins (PVs) are also detailed.

OVERVIEW OF THE REMODELING PROCESSES OF POTASSIUM CHANNELS IN PATHOLOGIC SITUATIONS

Remodeling of K^+ Currents Associated with Hypertrophy

Hypertrophy

Cardiac hypertrophy is an adaptive response to volume or pressure overload that occurs in various pathologic situations (hypertension, valvular ischemic or congenital heart diseases). In hypertensive patients, there is a weak but significant correlation between QTc interval and blood pressure and hypertrophic indices like the Cornell voltage indices.[3] It is also known that hypertensive patients with prolonged QTc intervals are at increased risk of cardiovascular morbidity and mortality.[4] In patients with successful antihypertensive therapy, left ventricular mass reduction is correlated with a decrease in the QTc interval[5]; for a review, see Ref.[6] In experimental models of cardiac hypertrophy, prolongation of repolarization has been documented by longer QTc intervals and AP durations (APDs). In patch clamp analysis, total K^+ current amplitudes are similar in cardiac hypertrophy subjects and controls, but because the membrane capacitance is larger in hypertrophy, the resulting K^+ current densities are reduced in cardiac hypertrophy.[7] This phenomenon has been documented for transient outward K^+ current (I_{to}), I_{K1} and slow rectifier K^+ current (I_{Ks}): compared with control, proteins and transcripts