Molecular Basis of Functional Myocardial Potassium Channel Diversity

Jeanne M. Nerbonne, PhD[a,b,*]

KEYWORDS

• Action potentials • Propagation • Repolarization • Dispersion • K^+ channels
• Pore-forming subunits • Accessory subunits • Macromolecular protein complexes

KEY POINTS

- Cellular electrophysiological studies have distinguished multiple types of voltage-gated inward and outward currents that contribute to action potential repolarization in mammalian cardiac cells.
  - Considerable progress has been made in identifying the pore-forming Kv and Kir α subunits contributing to the formation of most of the K^+ channels expressed in mammalian cardiac myocytes.
  - Biochemical studies have provided some insights into the molecular mechanisms underlying the observed heterogeneities in the expression of myocardial Kv and Kir currents.
- Considerable evidence suggests that native myocardial K^+ channels, like other ion channels, likely function in macromolecular protein complexes, comprising pore-forming α subunits and multiple cytosolic and transmembrane accessory/regulatory subunits.
- An important focus of future work will likely be on defining the physiologic roles of the many K^+ channel accessory subunits in the generation of native myocardial K^+ channels and on defining the molecular mechanisms controlling the properties and the cell surface expression of native cardiac K^+ channels.

INTRODUCTION

The normal mechanical functioning of the mammalian heart depends on proper electrical function, evident in the sequential generation of action potentials in cells in the "pacemaker" regions and the propagation of activity through the ventricles.[1–3] The waveforms of action potentials in individual cardiac cells (**Fig. 1**) reflect the coordinated activation and inactivation of inward (Na^+ and Ca^{2+}) and outward (K^+) current-carrying ion channels.[1] The propagation of electrical activity and the coordinated electromechanical functioning of the heart also depend on electrical coupling between cells, mediated by gap junctions.[4] The rapid upstroke of action potentials in atrial and ventricular myocytes, attributed to inward currents through voltage-gated Na^+ (Nav) channels, is followed by slower repolarization and plateau phases (see **Fig. 1**), reflecting increased outward currents through multiple types of K^+ channels and inward currents through voltage-gated Ca^{2+} (Cav) channels. Cell-type–specific and regional differences in the waveforms of action potentials, which impact the normal spread of excitation in the myocardium and the

[a] Department of Internal Medicine, Washington University Medical School, 660 South Euclid Avenue, Box 8086, St Louis, MO 63110, USA; [b] Department of Developmental Biology, Washington University Medical School, St Louis, MO 63110, USA
* Corresponding address.
E-mail address: jnerbonne@wustl.edu

Card Electrophysiol Clin 8 (2016) 257–273
http://dx.doi.org/10.1016/j.ccep.2016.01.001

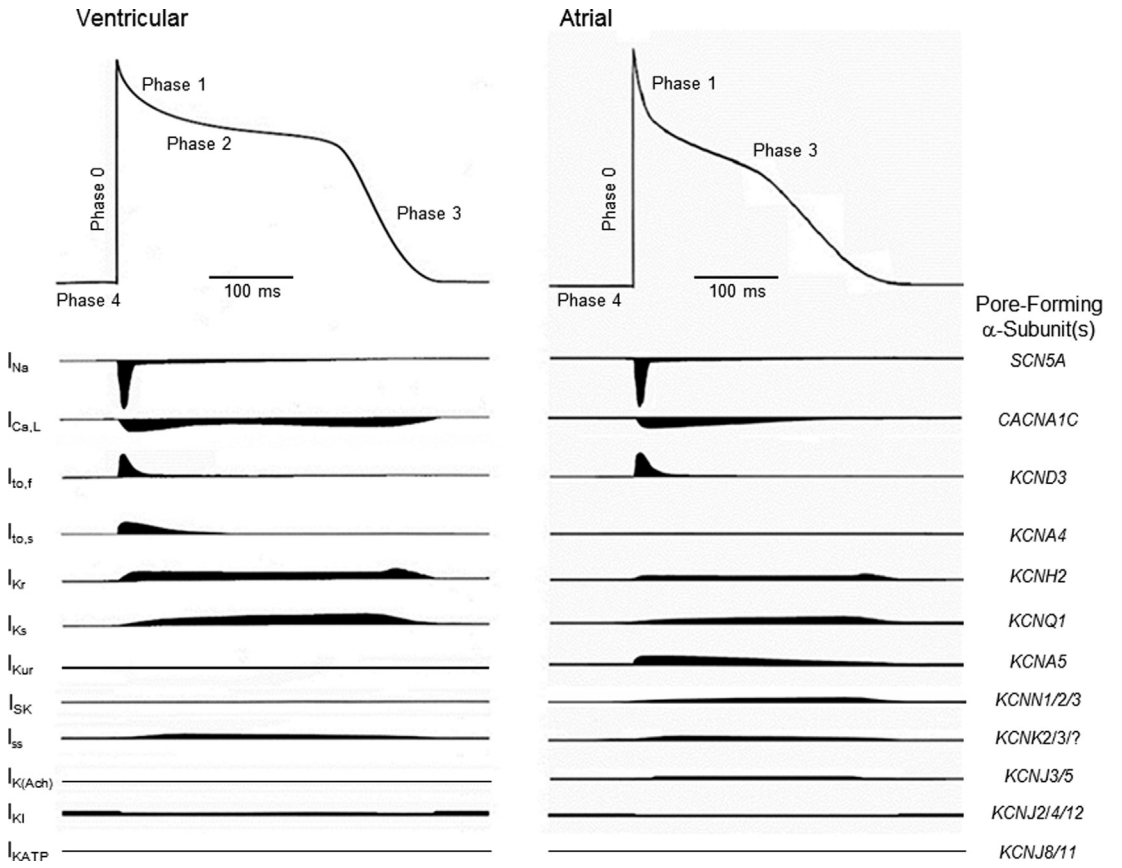

Fig. 1. Action potentials and underlying ionic currents in adult human ventricular and atrial myocytes. The major ionic currents shaping action potential waveforms in human atrial and ventricular myocytes are schematized. The names of the individual ionic currents are indicated to the left of the records, and the main pore-forming (α) subunits encoding the K^+ channel underlying these currents are indicated to the right of the records. There are differences in the relative expression levels of several of the repolarizing K^+ currents and/or in the relative contributions the various K^+ currents make to shaping action potential waveforms and controlling repolarization in ventricular and atrial myocytes.

dispersion of repolarization in the ventricles, reflect differences in the expression and/or the properties of inward Nav and Cav, as well as several outward K^+, channels.[1–3]

In contrast to the Nav and Cav channels, there are multiple types of cardiac K^+ channels, both voltage-gated K^+ (Kv) and non–voltage-gated, inwardly rectifying, K^+ (Kir) channels (**Table 1**)[5–7] encoded by Kv and Kir subunits (**Fig. 2**). As in other tissues and cell types, there are additional (non–voltage-gated) "leak" K^+ channels thought to be encoded by a novel class of K^+ channel (K2P) subunits with 2 pore domains (see **Fig. 2**), several of which are also expressed in the heart.[1] It is well-documented that changes in the densities, distributions, and properties of Kv and Kir channels are evident in a variety of myocardial diseases, and these changes alter repolarization, influence propagation, and decrease rhythmicity, effects that can produce substrates for the generation of life-threatening arrhythmias.[1] Although less well studied, changes in K2P channel expression and/or function in inherited/acquired cardiac disease would also be expected to impact myocardial excitability and arrhythmia susceptibility.[1]

Considerable progress has been made in defining the biophysical properties, the functional roles, and the cell-type–specific differences in expression of the various myocardial K^+ currents (see **Table 1**). In addition, a large number of Kv, Kir, and K2P channel pore-forming (α) subunits[8] that encode the underlying K^+ current-carrying ion channels have been identified (see **Fig. 2**), and many of these are expressed in the heart.[1] Considerable progress also has been made in defining the relationships between expressed Kv and Kir α subunits and functional myocardial Kv and Kir channels, and studies completed to date