O ur understanding of the function of the Kv1.4 K$^+$ channel in cardiac physiology has changed over time. The Kv1.4 gene was the first mammalian gene identified that encoded a rapidly inactivating or transient K$^+$ channel.1,2 Previous attempts at cloning mammalian K$^+$ channels based on homology to the Drosophila Shaker gene, which encodes a rapidly inactivating channel, had unexpect-
dedly turned up several delayed rectifier channels. There were high expectations, therefore, when the Kv1.4 gene was shown to encode a transient channel, and it was quite reasonably suggested that the Kv1.4 channel could underlie the transient outward K$^+$ current ($I_{\text{o}}$) in cardiac muscle.3 A rival for the affections of $I_{\text{o}}$ aficionados soon appeared, however, with the identification of a second family of transient channels, which contained two members known as Kv4.1 and Kv4.2.3,4 On the basis of the observation that the Kv4.2 gene was expressed in heart, it was suggested that these channels also might underlie the $I_{\text{o}}$.5

Initial interest in the molecular basis of the $I_{\text{o}}$ focused almost exclusively on Kv1.4,6–8 however, and the Kv4.2 channel languished largely unnoticed. There were several reasons for this. The Kv4.2 channel, when expressed in Xenopus oocytes, was something of an ugly duckling. It activated more slowly than $I_{\text{o}}$, and its inactivation phase was complex and incomplete, with multiple inactivation rates and a nonactivating sustained component.4 This unfavorable aesthetic appearance was largely due to the limitations of the Xenopus oocyte expression system used in the initial studies, which appears to lack a factor that can modify the kinetic properties of the channel.9 The molecular identity of this factor remains a mystery, but it is apparently ubiquitous, because the Kv4.2 channel, when expressed in most mammalian cell lines, has fast kinetics, more closely resembling the kinetic properties of $I_{\text{o}}$.10 The sensitivity of the Kv4.2 channel to blockade by 4-aminopyridine (4-AP) was lower than expected,5 although this also appears to be due at least in part to the oocyte expression system, with generally higher sensitivity found when the channel is expressed in cell lines.10 Another important factor reckoning against the Kv4.2 channel was the difficulty in finding Kv4.2 transcripts in human heart mRNA or cDNA libraries.

The Kv1.4 channel also had some flaws. In particular, it recovered from inactivation very slowly, significantly more slowly than did the native $I_{\text{o}}$ found in most cardiac tissues.1,2,6 This failing could be partly accounted for by use of a complex scheme of heteromultimer formation between Kv1.4 and Kv1.2 channel subunits.7 The resultant heteromultimers recovered from inactivation more rapidly than did Kv1.4 homomultimers, although still not as rapidly as did the native $I_{\text{o}}$.7

Perceptions of the relative importance of the Kv1.4 and Kv4.2 channels began to shift with the observation that Kv4.2 gene expression paralleled the gradient of $I_{\text{o}}$ expression in rat ventricular free wall whereas Kv1.4 gene expression did not.11 This result suggested that the Kv4.2 channel made a major contribution to the $I_{\text{o}}$ in rat heart.11 Once attention became focused on the Kv4.2 channel, the fortunes of the Kv1.4 channel plunged rapidly. It was found that the Kv1.4 channel protein was expressed very poorly, if at all in rat ventricle or atria, suggesting that posttranscriptional mechanisms inhibited expression of the Kv1.4 protein in the bulk of rat myocytes.12 The pattern of Kv1.4 expression during postnatal development was found to be the opposite of the pattern of $I_{\text{o}}$ expression, with Kv1.4 expression decreasing during development whereas the $I_{\text{o}}$ increases.13 The nature of the state-dependent blockade by 4-AP of the $I_{\text{o}}$ channel was found to be similar to Kv4.2 and quite different from Kv1.4.10,14

The problem posed by the absence of Kv4.2 expression in human heart was solved by the cloning of the Kv4.3 gene, and the Kv4.3 channel was shown to underlie the bulk of the $I_{\text{o}}$ in canine and human ventricle.15 Studies using the antiarrhythmic agent flecainide proved particularly informative, because this drug blocked $I_{\text{o}}$ and Kv4 channels at concentrations that were largely without effect on the Kv1.4 channel.10,15 Complementary results were obtained with two other pharmacological agents, H$_2$O$_2$ and spider toxins known as heteropodatoxins.15,16 Dominant negative or antisense approaches directed against Kv4 channels reduced $I_{\text{o}}$ in cultured rat myocytes,17,18 and expression of a dominant negative Kv4 channel subunit eliminated $I_{\text{o}}$ in ventricular myocytes of transgenic mice,19 again suggesting that Kv4 channels underlie the bulk of the $I_{\text{o}}$ in these tissues. Finally, the apparent coup de grâce was delivered using knockout of the Kv1.4 gene in mice. Absence of the Kv1.4 gene had no obvious effect on $I_{\text{o}}$ expression in mouse heart.20

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Department of Neurobiology and Behavior, State University of New York at Stony Brook, Stony Brook, NY.

Correspondence to Dr David McKinnon, Department of Neurobiology and Behavior, State University of New York at Stony Brook, Stony Brook, NY 11794-5230. E-mail dmckinnon@epo.som.sunysb.edu

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Editorial

Molecular Identity of $I_{\text{o}}$

Kv1.4 Redux

David McKinnon
The relevancy of the Kv1.4 channel to cardiac physiology was thus called into question. Now, in a study published in this issue of Circulation Research, some steps have been taken toward the rehabilitation of the Kv1.4 channel. In this study, it is suggested that in rabbit, but not human, atrial myocytes, the Kv1.4 channel may make a significant contribution to $I_{\text{to}}$. The $I_{\text{to}}$ in rabbit heart has an unusually slow rate of recovery from inactivation, similar to the slow time course seen for the Kv1.4 channel. That the $I_{\text{to}}$ can have different kinetic properties in different cardiac tissues has been known for some time, and it has been noted previously that there are two potential explanations for this phenomenon: (1) the $I_{\text{to}}$ in different tissues is produced by more than one gene product, or (2) the kinetic properties of Kv4 channels can be modified, either enzymatically or by association with another subunit to reduce the rate of recovery from inactivation. The study by Wang et al does not definitively exclude either possibility. The pharmacological properties of the rabbit atrial $I_{\text{to}}$ (sensitivity to 4-AP and $\text{H}_2\text{O}_2$) raise the possibility that the Kv1.4 channel contributes to the rabbit atrial $I_{\text{to}}$. Direct comparison of the use-dependent unblocking of rabbit atrial $I_{\text{to}}$ by 4-AP with either human $I_{\text{to}}$ or the Kv4.3 channel is difficult, however, because rabbit $I_{\text{to}}$ channels do not recover significantly during the interpulse intervals used in this protocol. The finding that the Kv1.4 protein is expressed in rabbit atria is also suggestive, and important, because of the previous difficulties in detecting this protein in cardiac tissue. The results obtained with antisense oligonucleotides directed against the Kv1.4, Kv4.2, and Kv4.3 transcripts are confusing, however, because treatment of cultured rabbit atrial myocytes with any of the three antisense oligonucleotides reduces the $I_{\text{to}}$, with Kv4.3 oligonucleotides having the largest effect. It is difficult, at present, to reconcile the electrophysiological results, which suggest that the native current has relatively uniform properties, with the antisense results, which suggest that at least two distinct channels should be present. The results are intriguing, however, and it will be interesting to see if similar results are found in other cardiac tissues that express $I_{\text{to}}$ with slow recovery kinetics, such as canine and human Purkinje cells and endocardial myocytes. Some preliminary studies suggest that this may prove to be the case. The different properties of human and rabbit atrial $I_{\text{to}}$ highlight once again the surprisingly large differences in the cellular and molecular physiology of cardiac myocytes found in different species. It is humbling to recognize that a rat neuron generally has more in common with its human equivalent than does a rodent cardiac myocyte with a human one.

The study by Wang et al artfully integrates both molecular and cellular electrophysiological techniques to support their arguments. It is part of a very positive trend in ion channel studies, in which both electrophysiological and molecular studies are being regularly combined to study important physiological systems. Although molecular techniques have great definitive power, they often lack the subtlety necessary to form the fine-grained picture of reality that cellular physiology studies can produce. The interplay between these two approaches to ion channel studies is in many ways unique, because most other disciplines lack an equivalent to the highly quantitative results produced by cellular electrophysiology.

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David McKinnon

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