The Real Thing

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Fifteen minutes into Tom Stoppard’s *The Real Thing*, the audience realizes it is seeing a play within a play, the reality of which will be expressed in a dimension yet to unfold. Dramatic license? Of course; and yet it is not far from what we experience in science. Whether because of or despite the fact that the molecular age is upon us, at times we succumb to the temptation to read universal reality (rather than the play within a play imposed by our experimental design) into our results. And there is nothing wrong with this if exercising our imaginations identifies the next set of questions that will reject or substantiate our hypotheses and bring us closer to the truth.

Translational Research (formerly Physiology) provides a potent vehicle for associating experimental reality with *The Real Thing*. Yet all the models we use, whether computers, cells, tissues, or animals, can spew forth data that muddy the distinction between what is real and unreal. One example this statement applies to is mouse physiology. Since the advent of transgenic technology, we have learned a great deal about the mouse, all of it relevant to the mouse, and some of it relevant to other forms of animal life. But what is relevant, where is it relevant, and when?

The study by Guo et al1 in this issue of Circulation Research is a case in point. The authors integrate molecular determinism, cellular manifestation, and in vivo expression. The result is an interesting counterpoint, incorporating that which seems absolute and that to which it might relate. The major conclusions, that Kv1.4 upregulation is an I to, f and I to, s components of the transient outward current, and slow (I to) components of the transient outward current, and slow (I to) -/– mouse? Second-degree atrio - and ventricular tachycardia but may alternatively represent an ion channels involved that would lead us to intuit this outcome. In fact, repolarization per se or postrepolarization refractoriness in AV junctional tissues is unlikely to be sufficiently prolonged to account for the magnitude of heart block shown in Figure 7C.1 As suggested by the authors, these findings warrant a detailed follow-up study of the AV specialized conducting system.

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The data raise a number of issues about comparative biology and the roles of specific ion currents within the species studied. It is clear that progressing from the wild-type mouse to the Kv4.2W362F model to the Kv4.2W362F × Kv1.4+ model (starting with normal and successively subtracting the repolarizing effects of Ito alone and Ito + Iin), there is a progression from prolongation of the ventricular myocardial action potential to the occurrence of early afterdepolarizations (EADs) that is revealed when cycle length is longest and at low temperature (which itself prolongs action potential duration). The electrocardiographic manifestations of this sequence of changes are only partially consistent with what the molecular and cellular electrophysiological data might predict. In light of the action potential changes, the expectation on ECG is a long QT interval and pause-dependent ventricular tachyarrhythmias, especially torsades de pointes.2,3 Yet only the first of these clearly occurs.

Why is this? There likely are a number of contributors. First, the wild-type mouse has a T wave that only another mouse could appreciate; in fact, it resembles the J point and ST segment more than the T wave of the human or canine ECG. Such resemblance is not surprising given the important contribution of I to the J point and early ST segment of the canine and, most likely the human, ECG.4,5 However, in the Kv4.2W362F × Kv1.4+ model, the murine T wave assumes an appearance that is almost respectable for a dog or human. This information expands our understanding of the determinants of the T wave in the mouse and the extent to which what is measured in mouse is applicable to human physiology. Part of the problem contributing to the T wave difference among species is that Ito, the major repolarizing current in the mouse, is a minor component of repolarization in human and canine ventricles, contributing to the notch of their epicardial and midmyocardial action potentials and having no major expression in endocardium.5 Intervening to abolish or markedly reduce Ito in the dog heart alters the transmural gradient for repolarization and alters T wave configuration,6,8 but does so in a way that would not significantly prolong the QT interval or be anticipated to induce EADs or torsades de pointes.

Does torsades de pointes, or indeed any arrhythmia, occur in the Kv4.2W362F × Kv1.4+ mouse? Second-degree atrioventricular (AV) block is present (see Figures 7A and 7B in Guo et al1), although there is nothing about the function of the ion channels involved that would lead us to intuit this outcome. In fact, repolarization per se or postrepolarization refractoriness in AV junctional tissues is unlikely to be sufficiently prolonged to account for the magnitude of heart block shown in Figure 7C.1 As suggested by the authors, these findings warrant a detailed follow-up study of the AV specialized conducting system.

In Figure 7C,1 a period of isorhythmic dissociation accompanies a rhythm arising in the ventricle that is possibly ventricular tachycardia but may alternatively represent an
accelerated idioventricular rhythm or the mouse equivalent thereof. Its initiating beat is slightly premature, after which its rate approximates that of the sinus rhythm. During this ventricular rhythm, the sinus maintains a constant rate until after the final ventricular beat, when a brief sinus pause precedes resumption of the normally propagated sinus rhythm. The ventricular arrhythmia does not appear derivative of EADs (nor do the authors claim any such derivation) for two reasons. First, it occurs at the time of a rapid atrial rate. This is hardly what one would expect of an EAD-induced arrhythmia, which would more likely follow a long pause or be interposed during a sinus or other bradycardia. Second, although the periods of AV block and long pauses are likely settings for EAD-induced ectopy, no ventricular tachyarrhythmias are seen here. Rather, the one escape beat displayed has a QRS vector and configuration identical to that of the sinus-originated QRS complexes and is equally narrow. It is far more in keeping with initiation in the AV junction or high in the ventricular conducting system as opposed to the myocardium. This observation does not completely rule out the possibility that the escape beat is triggered by an EAD, but it is far more likely that automaticity in the specialized conducting system is the mechanism.

Where does this discussion of the Guo et al study lead us? There are well-defined molecular lesions whose reflection at the level of cellular electrophysiology is clear. Expression at the level of the intact animal is less clear, and it is here that additional questions arise, as follows:

1. Should we look more diligently in the human for mechanisms whereby lesions in $I_{\text{to}}$ are expressed as arrhythmias, as opposed to simply considering $I_{\text{to}}$ as a modulator of repolarization in the human ventricle? Precisely this question about $I_{\text{to}}$ has been asked with respect to the generation of the ST-T wave anomaly of Brugada syndrome. Nonetheless, most cases of Brugada syndrome analyzed to date have shown abnormalities in the sodium channel SCN5A. Moreover, although decreasing $I_{\text{to}}$ can elevate the action potential plateau, which might lead to action potential prolongation, in elevating the plateau it might also turn on the delayed rectifier currents and thereby accelerate repolarization.

2. How far can we carry the results of experiments in mice, or indeed other nonhuman or noncardiac cells, to find results meaningful for the human heart? The answer to this question is entirely open-ended. We need only consider recent research on the congenital long-QT syndrome to understand how much can be accomplished and its wide-ranging impact on our understanding of human disease. First, we extend the autonomic nervous system? There are tantalizing indications that this might occur, because the unexplained Wenckebach periodicity of AV conduction in Figure 7A and the AV dissociation and accelerated idioventricular rhythm in Figure 7C are consistent with parasympathetic and sympathetic anomalies, respectively.

(4) How do we relate the T wave in the wild-type mouse to its human or canine counterpart, and to what extent can we accurately interpret the meaning of the wild-type or genetically altered murine T wave? A variation on this question was posed in articulate and thoughtful fashion in the middle of the last century, and it must be resolved if we are to maximize the information provided by murine models. We need to understand definitively whether the murine T wave is a model for that of the human or dog, or (as likely appears) is a model for the J point and early ST segment, or is something else.

(5) How do we diagnose arrhythmias in the mouse, and to what extent is any murine arrhythmia analogous to some human counterpart? Here we have problems. A ventricular arrhythmia with a rate of 700 bpm is not supportable in a human heart. Calling this arrhythmia ventricular tachycardia certainly is consistent with the normal range of murine heart rates and the rate and chamber of origin of the arrhythmia. Yet this same arrhythmia may not have the connotation of ventricular tachycardias in human subjects. The latter arrhythmias are usually associated with hemodynamic decompensation and, if not rapidly terminated or self-terminating, may be premorbid. Alternatively, does the murine ventricular tachyarrhythmia have the same function and meaning as an accelerated idioventricular rhythm in humans? Whereas most ventricular tachycardias are reentrant and often lethal, most accelerated idioventricular rhythms are automatic and can sustain pacemaker function and an organized heartbeat; clearly, the two have different mechanisms and different implications.

In summary, the study by Guo et al does precisely what one would hope of research of quality: it demonstrates a particular lesion, explores its expression at a variety of levels, and ultimately raises a new series of questions. Whether it represents The Real Thing, we do not yet know, but it does represent a provocative milestone.

References


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