Commentary

Unraveling the genetics and mechanisms of cardiac arrhythmia

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In this issue of the PNAS, Papadatos *et al.* (1) analyze the mechanism of arrhythmia in the heart after targeted disruption of the cardiac sodium channel, Scn5a. They combine a wide variety of techniques (including genetic deletion, cellular electrophysiology, morphology, and electrocardiography) in an *integrated* approach to unravel the sequence of events all of the way from the genetic to the whole organism level. They are therefore able to show that the effect of the deletion is to reduce the ionic current carried by sodium channels, so that the propagation among cardiac cells is slowed. This slowing generates arrhythmia because it allows more time for a wavefront to encounter cells that are reexcitable before the wavefront dies out. A sustained rapid reentrant circuit can then be established. This is called a tachycardia and can be fatal.

The range of techniques used in this work is unusual. But such large-scale integrative work, involving several laboratories and therefore a substantial list of authors, is necessary if we are to connect genetics to cell, system, and whole-organ physiology. The reason is that there are many levels of organization among genes and their effects on organs and systems, including feedback on gene activation and expression from the higher levels. The mechanisms of a disease state may require detailed understanding at any one (and usually more than one) of these levels.

Cardiac arrhythmia is a good example. First, because there are known mechanisms at several different levels—subcellular, cellular, and multicellular. The arrhythmia analyzed by Papadatos *et al.* (1) depends on slowed conduction between cardiac cells and necessarily requires study at the level of the whole organ to complement that at the gene and cellular levels. Second, because the genetic bases of a substantial number of cardiac arrhythmias are beginning to be understood (2). Thus, Clancy and Rudy (3) incorporated the known disturbances to the sodium channel properties resulting from the ΔKPQ mutation, a three-amino acid deletion (lysine-proline-glutamine) that affects channel inactivation and is associated with a congenital form of the long-QT syndrome, in which the interval between depolarization (the Q wave of the electrocardiogram) and repolarization (the T wave) is prolonged. They showed that this deletion generates unusual forms of repolarization in a cardiac cell model. Similar behavior has been found for a missense sodium channel mutation (4, 5) underlying part (but only part) of the pathology of the Brugada syndrome—a genetic condition that predisposes to sudden ventricular fibrillation (see also ref. 6 for a more complete account of this pathology) and for the D1790G mutation (7). In both cases, the mutations strongly affect the voltage dependence of sodium channel gating. These are examples of arrhythmic mechanisms generated primarily at the cellular level. We have still to work out exactly how they trigger arrhythmias at the multicellular level, but the presumption is that delayed repolarization, including the additional waves known as early afterdepolarizations, increases the spatial voltage gradients sufficiently to trigger repetitive reexcitation of the ventricle.

Subcellular mechanisms include calcium oscillations occurring during ischemia or during treatment with cardiac glycosides, which can also now be successfully modeled (8, 9). These oscillations are generated by the feedback loops controlling calcium release from the sarcoplasmic reticulum (10). In turn, they generate depolarizing electric current by activating the sodium-calcium exchanger (11), thus initiating additional excitations, out of phase with the normal rhythm, which are known as ectopic beats. Our knowledge here is also still incomplete. Fortunately, ectopic beats do not always trigger fatal arrhythmias. We have yet to determine what other factors are involved. In the case of ischemia, changes in action potential duration are almost certainly involved in increasing spatial dispersion of repolarization, whereas potassium accumulation is involved in slowing conduction (12).

From a healthcare perspective, there is a very high degree of interest in this type of problem. The reason is that more than half the drug withdrawals required by the U.S. Food and Drug Administration in Washington (FDA) since 1998 have been attributable to cardiac side effects, most of them arrhythmias. The problem is that clinical trials often show a very small (often less than 1%) adverse reaction. It is possible that many of these patients are genetically prone to arrhythmia. If they could be identified (and excluded from the trials), the benefits for the other 99% could be very great indeed. The idea of selecting drugs for specific subgroups of patients is becoming increasingly important (13).

It is important to note that most of the drugs concerned were not intended to be cardiac drugs. These side effects turn up with nearly all classes of drugs, including anti-histaminics (14), anti-cancer compounds, anti-emetics, antibiotics, and antimigraine drugs (see http://georgetowncert.org/qtdrugs_torsades.asp). The problem is therefore serious and costly (a single failed drug may represent a $500 million investment). The widespread nature of the problem is attributable to the high degree of receptivity of one of the channel proteins, I_{Kr}, on which cardiac repolarization depends. A heart that is already prone to arrhythmia, because of slowed conduction/and or failure of repolarization as a consequence of genetic or disease disturbance of sodium or other channels and transporters, may therefore be tipped over into a fatal state by even a modest amount of I_{Kr} block.

We therefore need a better understanding of how the different lower-level mechanisms of arrhythmia interact at the organ level. Whole-organ models with detailed anatomy (15, 16), incorporating the relevant cellular biochemistry and physiology (ref. 17; see Fig. 1), have a clear role to play in unraveling these interactions. My own research group is collaborating with that of Peter Hunter in linking together cellular biochemistry, cellular electrophysiology, coronary flow (18), and whole-organ electrical activity in an attempt to reconstruct the steps in an acute ischemic heart attack all the way from coronary arterial block to the initiation of fatal arrhythmia (9).

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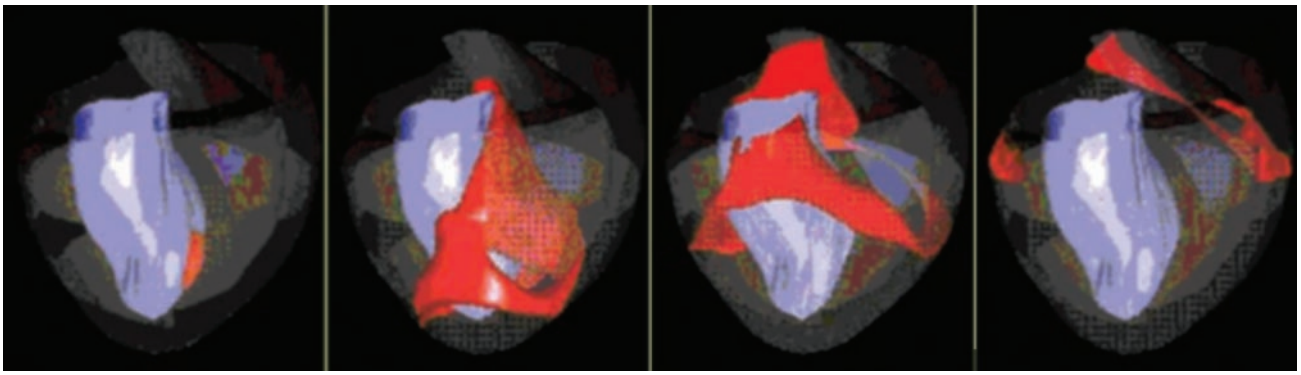

Fig. 1. Simulation of the spread of the electrical activation wavefront in an anatomically detailed cardiac model (17). The wavefront (shown here in red, with the endocardial surface of the ventricle in blue) is generated by ionic current flowing through sodium channels. As each cell becomes excited it passes current to neighboring cells. The speed of conduction depends on the intensity of the sodium current. Earliest activation occurs at the left ventricular endocardial surface near the apex (*Left*). Activation then spreads in an endocardial-to-epicardial direction (outward) and from apex toward the base of the heart (upward, *Center* frames). The activation sequence is strongly influenced by the fibrous-sheet architecture of the myocardium, as illustrated by the nonuniform transmission of excitation. In normal conduction, as in this simulation, the wavefront dies out as it reaches the top (base) of the ventricle, because the conduction is so rapid that the wavefront cannot encounter any more cells to excite. Computer modeling on this whole-organ level with equations based on channel protein properties could form the basis of reconstructing arrhythmias generated by mutations of the cardiac sodium channel. Future work should therefore explore how slowed conduction of the kind investigated by Papadatos *et al.* (1) allows reentrant circuits to be created.

With advances in understanding the genetics of cardiac arrhythmia and in how to predict ECG changes from disturbances of channel and transporter mechanisms (6, 19), it is conceivable that we will be able to identify which drugs may produce cardiac side effects at a much earlier stage in the development process. Even more ambitiously, we may discover how to fine-tune drug action to avoid the problem altogether. We also need better medication directed specifically against cardiac arrhythmia following a decade of largely disappointing clinical trials (20). Multitarget drugs have shown a possible way forward here (21). It is significant that the one drug, amiodarone, which has shown some promise in clinical trials as an anti-arrhythmic agent, is also a good example of a multiaction drug with a primary blocking action on potassium channels, weaker actions on sodium and calcium channels, and moderate actions on α and β adrenergic receptors. The reduced activity of calcium channels is almost certainly crucial to its success because, in cell model simulations, this can eliminate the tendency of potassium channel block to produce early after-depolarizations (5). I believe that this comparative success of a multiaction drug is significant. Nature's own "drugs"—hormones and transmitters—are also multiaction compounds. They play the "orchestra" of protein transporters and receptors in subtle ways. We should learn from how nature achieves this "harmony," which means that we should first unravel the complexity of physiological organization. In addition to the processes I have already mentioned, it is important also to include the interactions between biochemical and physiological events (22) and the feedback between mechanical and electrical events (23), both of which contribute greatly to arrhythmia generation.

In summary, we need detailed understanding of the mechanisms of cardiac arrhythmia at *all* the relevant levels. Papadatos *et al.* (1) have taken an important step forward in helping us to achieve this understanding in relation to slowed conduction. It is significant, therefore, that the first of the large-scale anti-arrhythmia trials, the Cardiac Arrhythmia Suppression Trial (CAST; see ref. 24), was based on testing drugs like encainide and flecainide that reduce sodium channel conductance. The hope was that by reducing excitability one might suppress arrhythmias. In fact, these drugs promoted arrhythmias, probably by slowing conduction, i.e., precisely the arrhythmic mechanism evoked by the genetic disruption studied by Papadatos *et al.* Unraveling the consequences of genetic changes is one way of arriving at the knowledge required to design better treatment.

Work in my laboratory is supported by the British Heart Foundation, Medical Research Council, the Wellcome Trust, and by Physiome Sciences.

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