Familial hypertrophic cardiomyopathy: cornering the rat

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See article by Frey et al. [8] (pages 254–264) in this issue.

Hypertrophic cardiomyopathy is a terrible disease [1]. It is associated with negative hemodynamic changes leading to pulmonary congestion and low output, and with severe ventricular arrhythmias that in many cases are lethal. We have learned a good deal about the electrophysiology of this disease [2]. Unlike ischemic heart disease that predisposes to conduction block and reentrant arrhythmias on that basis, the lesion of hypertrophy involves repolarization [3]. Hypertrophied cells have long and non-uniform repolarization times. This dispersion of action potential duration is a milieu in which early afterdepolarizations can generate sustained and highly disorganized ventricular arrhythmias, manifest on the surface ECG as polymorphous ventricular tachycardia that quickly degenerates into ventricular fibrillation. As hypertrophy progresses, the situation is further complicated by fibrosis and irregular cell connection that increases the potential for transmyocardial reentry and arrhythmogenesis. Hypertrophied cells, already manifesting marked potassium channel abnormalities, are highly sensitive to metabolic conditions such as hypokalemia, or QT prolonging drugs that further prolong refractoriness, compounding the potential for polymorphic ventricular tachycardia [3,4]. Thus, in patients with hypertrophic disease, in particular the familial form, sudden and unexpected death is a heavy liability.

Unfortunately, we have not yet developed efficient methods to predict which patients are uniquely susceptible to this problem, nor have we available highly effective or safe drug therapy. In fact, many of the drugs that we ordinarily use for the suppression of ventricular arrhythmias are not applicable and may exacerbate the problem by further prolonging refractoriness [5]. Programmed stimulation, useful for studying conventional reentry in patients with prior infarction, is not of great utility. The implantable cardioverter-defibrillator (ICD) has been used for some time to treat arrhythmias in patients with hypertrophic myopathy. A recent analysis suggested its overall utility for patients who present with a malignant arrhythmia or are considered to be at risk by virtue of a symptom such as syncope or because of some other risk variable such as a very positive family history of sudden death [6]. As in other diseases, the ICD is a partial answer since it does not prevent the arrhythmia and the disorganized arrhythmias that many of these patients have cannot be pace-terminated necessitating painful shocks. Thus in many patients, especially those with frequent and disabling arrhythmias, adjuvant drug therapy is mandatory.

What is clearly needed is an optimal experimental model in which to study arrhythmia mechanism and then the effects of various therapies including antiarrhythmic drugs. Much work has already been done to increase understanding of the linkage between mutations and functional defects [7]. Frey et al. have taken these observations one step further and are beginning to unearth the link between gene mutations and arrhythmogenesis [8]. The availability of an animal model which replicates the electrophysiology of the human disease would represent a quantum leap forward in our ability to study hypertrophic disease and interventions to prevent the lethal arrhythmias which regularly accompany it. Aside from the most obvious implication of a possible genetically engineered ‘cure’ of the lesion (which we believe is a long way off), we may have the ability to bridge the species gap which has always, and appropriately, limited extrapolation of the results obtained in the basic laboratory to the human condition, especially with regard to arrhythmogenesis.

Before we get too carried away with the results of the fine paper of Frey et al., however, let us be careful to list the limitations of this relatively small study. First, it remains to be seen if the disease spawned by this transgenic experiment has the same electrophysiological charac-

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teristics as those which have been observed in homo sapiens. The rat has never been a particularly reliable animal model in this regard. The heart is small, and not able to sustain the multiple circuits that we think are the explanation for the disorganized nature of ventricular arrhythmias in hypertrophied hearts. Also, there is a very fine line between pathological and physiological hypertrophy in the working heart model, as the authors correctly point out. Where on that continuum one must be in order to exhibit myocardial electrical instability is not known and given the complexity of the disease, it may never be. Most importantly, we learned very little about arrhythmogenesis in these experiments. The authors relied on the observation of spontaneous arrhythmias or ‘sudden death’ as an indicator of electrical instability. Although these experiments were more frequent in the mutated animals, the number of observations was small and the observation methods crude so that the findings must be suspect. In addition, there were no attempts to systematically study the phenomenon using standard stimulation and recording techniques. It would be very useful to know if the action potentials of the cells of the transgenic hearts had characteristics that have been observed in the human disease, especially with regard to prolongation of repolarization and inhomogeneity. Are these cells susceptible to early afterdepolarizations and phase 2 reentry? Do relative bradycardia and drugs that increase refractoriness increase the potential for intramyocardial reentry and polymorphous ventricular tachycardia as in the human condition? How much does the interruption of normal cell-to-cell connection, a regular feature of the scarred, fibrotic heart in patients with familial hypertrophic cardiomyopathy, contribute to whatever electrical instability exists? These are all questions which may be answerable using this model but are yet to be explored. A particularly interesting feature of the research in this regard is a unique opportunity to understand whether there is a proportionality between the degree and extent of expression of the wild-type versus the mutated gene and the severity of the electrophysiologic alterations. This is particularly important given our published data that indicate that the regression of left ventricular hypertrophy using pharmacologic agents or mechanical means restores normal electrophysiology [9]. This proportionality between disease severity and arrhythmogenesis might help us to better understand the marked variability in arrhythmia density in affected individuals. It could also make it possible to better risk stratify based on genetic rather than phenotypic markers.

Obviously, much work is needed just to begin to answer these critical questions. What Frey et al. have done is let us peep into the future to see how we may be able to study complex diseases in animal models that more closely replicate the human condition. They have also set the stage for several important experiments to come. Because of our laboratory’s heavy emphasis on the electrophysiologic aspects of hypertrophic disease, we have focused on that aspect in this editorial, but there are numerous other avenues of investigation which will be explored based on data such as these [10]. We have a tremendous opportunity to unlock many biologic mysteries for the benefit of people afflicted with complex and lethal diseases such as familial hypertrophic cardiomyopathy. Let us not let the rat get away.

References