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EDITORIAL COMMENT

Use of Mouse Models to Evaluate Novel Therapeutic Approaches to Treatment of Arrhythmogenic Right Ventricular Cardiomyopathy

The Future Is Now*

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Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited cardiomyopathy that is characterized by ventricular arrhythmias, an increased risk of sudden death, and abnormalities of right ventricular (RV) structure and function. The pathological hallmark of ARVD is myocyte loss with fibro-fatty replacement. Since the first detailed clinical description of the disorder in 1982, significant advances have been made in our understanding of all aspects of this disease (1–3). Particular focus has been placed on optimizing the approach to diagnosis of ARVD (4).Over the last decade, mutations in several desmosomal proteins have been identified as the genetic basis of ARVD (5–7). On the basis

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of these findings it is now recognized that ARVD is a disease of desmosomal dysfunction (8). According to this conceptual framework of ARVD, defective desmosomal proteins lead to impaired mechanical coupling between individual cells, resulting in myocyte detachment and degeneration, especially under conditions that increase myocardial strain. This leads to myocyte loss, replacement fibrosis, and adiposis, with or without inflammation, which might be nonspecific responses to myocyte injury. In addition to this mechanical mechanism of ARVD is a second mechanism that results from the fact that some desmosomal proteins are also nuclear signaling molecules. Mutations of desmosomal proteins might therefore also lead to dysregulated gene expression. This conceptual framework of the pathogenic basis of ARVD is welcomed, because it explains many of the clinical observations that have been made in patients with ARVD. These observations include a delayed age of onset with subsequent progression as well as the association between vigorous exercise and development of ARVD. It also explains why the RV, which is more distensible than the left ventricle due to its thinner wall and asymmetric shape, is more often involved in ARVD. Furthermore, defects in mechanical coupling of myocytes have also been shown to lead to impairment in electrical coupling. Ultrastructural evaluation of the myocardium of patients with ARVD has shown reduced expression of several intercalated disc proteins, including Connexin-43, a key component of gap junctions (8,9). This finding might account for the development of conduction delay and arrhythmias, even in the absence of significant structural defects in the early "concealed" phase of the disease.

Although there has been remarkable progress made concerning the diagnosis of ARVD, the genetic basis of ARVD, and the pathophysiologic basis of this disease, there has been remarkably little research on 3 critical areas: 1) prevention of disease development in susceptible individuals; 2) prevention of progression and development of clinically manifest disease; and 3) approaches to reverse ARVD in affected individuals. The cornerstone of therapy for patients with ARVD at present is placement of an implantable defibrillator for prevention of sudden death and administration of antiarrhythmic agents and/or catheter ablation to decrease the frequency of sustained ventricular arrhythmias (3,10).

In this issue of the *Journal*, Fabritz et al. (11) use a mouse model of ARVD to test, for the first time, a novel load-reducing therapeutic strategy for prevention of the development of ARVD. The authors test their hypothesis in heterozygous plakoglobin-deficient mice and wild-type littermates who were subjected to 7 weeks of endurance training (swimming). In a randomized and blinded study design, mice were treated with load-reducing therapy (furosemide and nitrates) versus water. The mice were evaluated with echocardiography and electrophysiology testing with an isolated heart apparatus. In addition, the myocardial tissue was evaluated with a number of basic techniques including Western blots, immunohistology, and quantitative polymerase chain reaction. The results of this study revealed that load-reducing therapy prevented exercise-induced RV enlargement. Furthermore, the rate of inducibility of ventricular tachycardia was lower in heterozygous mice who received load-reducing therapy as compared with control subjects. In addition, the authors demonstrated that RV longitudinal conduction velocity was reduced in untreated mice as compared with mice who received load-reducing therapy.

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This study represents a very important step forward in our efforts to develop pharmacological, nonpharmacological, and lifestyle strategies focused on prevention of disease development in susceptible individuals, prevention of progression and development of clinically manifest disease, and the development of approaches to reverse ARVD in affected individuals. In writing this editorial, I am charged with helping to interpret the results of this study in the context of both my experience with ARVD as well as the considerable body of previously published data on ARVD. It is important to consider for a moment that there has never been a prospective randomized clinical trial of any therapeutic modality for treatment of patients at risk of or affected by ARVD. This likely reflects both the rarity of this disease, the heterogeneous nature of the patient population, the often slow rate of disease progression, challenges with obtaining funding for clinical trials in patients with ARVD, as well as the reluctance of physicians and patients to participate in prospective randomized clinical trials. Because of these many obstacles, all forms of treatment of ARVD are based mainly on empiric information, clinical experience, and expert opinion. Now we advise patients to dramatically reduce their degree of exercise, and we prohibit patients with ARVD from participating in competitive sports. We also attempt to initiate beta-blocker therapy and therapy with angiotensin-converting enzyme inhibitors. Finally, we advise implantable cardioverter-defibrillator insertion in probands who meet diagnostic criteria for ARVD. Pharmacological therapy and catheter ablation are used to decrease the frequency of appropriate implantable cardioverter-defibrillator therapies for ventricular tachycardia. The results of this study are striking, because to the best of my knowledge, this is the first study that has tested a treatment strategy for ARVD in a prospective and blinded trial. The authors are to be congratulated for breaking this enormous barrier and initiating what I hope will be a long series of studies investigating potential treatment strategies for ARVD. Our enthusiasm for this report needs to be tempered somewhat, because it is clear that many questions remain unanswered. Perhaps the most immediate question is "Can the results of this study be applied to patients at risk of development of ARVD or those with established ARVD?" In my mind the answer is probably no. The concept of treating patients who are susceptible to ARVD or have established ARVD with a diuretic feels uncomfortable. These patients for the most part are not fluid-overloaded, and I am concerned about the potential risks associated with electrolyte depletion that might result from diuretic use. Similarly, I would also find it uncomfortable to start prescribing nitrates to patients with potential or established ARVD. We are all well aware of the problems of nitrate intolerance as well as the well-recognized side effects of nitrate therapy. So for me, the implications of this study are merely that I will now advise patients with ARVD to decrease their salt intake. It is unfortunate that the authors did not select what I consider to be a clinically more viable treatment strategy, especially beta-blockers and angiotensin-converting enzyme inhibitors. These treatment strategies make sense to me, as a clinician caring for patients with ARVD. Other limitations include the small size of the study, the short duration of follow-up, and the use of only 1 mouse and genetic model of ARVD. It is also notable that this particular mouse model of ARVD does not manifest the hallmark clinical ARVD finding of fibro-fatty myocardial replacement. Furthermore, this study did not address the question of whether load-reducing therapy can reverse the development of ARVD in mice with established disease.

Those involved in this field are grateful to Fabritz et al. (11) for their considerable effort in performing and presenting the result of their novel study. I am sure that all of those involved with the field of ARVD share my excitement that this study has ushered in a new era of using mouse and other animal models of ARVD to evaluate potential therapeutic strategies for treatment of patients and families who suffer from this condition.

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