JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 65, NO. 14, 2015

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jacc.2015.01.046

EDITORIAL COMMENT

Further Evidence of Harm From Exercise in ARVD/C*

Daniel P. Judge, MD, Stephen P. Chelko, PhD

Exercise is loathsome. And it cannot be any benefit when you are tired, and I was always tired.

—Mark Twain (1)

The evidence implicating exercise as a pathogenic factor in arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) continues to grow. Early reports of this condition recognized its occurrence with athletic activity, and later studies strengthened this association (2,3). Retrospective quantification of exercise for 87 people with desmosome mutations demonstrated that those with the highest levels of exercise developed earlier and more severe manifestations of this inherited cardiomyopathy (3). In a complementary analysis of 82 patients with ARVD/C, those without desmosomal mutations or family history of ARVD/C had performed more intense exercise (4). These findings support an emerging paradigm in which both genetic predisposition and environmental factors interact around a threshold for phenotypic expression of ARVD/C (5).

SEE PAGE 1438

Many questions remain regarding the pathogenesis of ARVD/C, and in this issue of the *Journal*, Cruz et al. (6) highlight an alternative approach to its investigation. Using an adeno-associated virus (AAV)-mediated gene transfer protocol, they overexpressed a common human *PKP2* mutation in mice. A single intravenous injection of an AAV vector, harboring the *PKP2* p.Arg735Ter mutation, led to cardiac production of truncated plakophilin-2 for 10 months. Unfortunately, this was insufficient for recapitulating ARVD/C. However, on the basis of prior human, murine, and cellular studies implicating exercise as harmful in the context of desmosome mutation (3,7,8), Cruz et al. (6) subjected these AAV-treated mice to forced swim exercise. Indeed, exercised *PKP2* mutant mice demonstrated reduced global right ventricular (RV) ejection fraction compared with exercised mice with wild-type *PKP2* transgene or sedentary mutant mice.

This work is notable for some important findings. The authors demonstrate that AAV achieves robust cardiac expression, with recapitulation of RV dysfunction induced by the addition of mutant human *PKP2*. We can explain more than 50% of this disease on the basis of a desmosome mutation, yet rare or novel variation in these genes commonly occurs among asymptomatic control subjects (9,10). The use of this technology would allow uncertain desmosome variants to be assessed similarly, which is certainly easier than generating mice with knock-in mutations. Somewhat surprisingly, the investigators were able to induce cardiac dysfunction despite a normal content of murine plakophilin-2 by overexpressing the truncated human protein. The majority of *PKP2* mutations led to premature transcript termination, which suggests it is caused by insufficient protein. Furthermore, *Pkp2* haploinsufficiency led to sodium current deficits in murine hearts, and *PKP2* knockdown in HL-1 myocytes produced features of ARVD/C (11,12). However, the initial report of *PKP2* mutations causing ARVD/C demonstrated that some truncating mutations have normal mutant *PKP2* messenger ribonucleic acid content, without degradation by nonsense-mediated messenger ribonucleic acid decay (13). The findings by Cruz et al. (6) add further support for a dominant-negative

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Department of Medicine/Cardiology, Johns Hopkins University School of Medicine, Baltimore, Maryland. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose. Hugh Calkins, MD, served as Guest Editor for this article.

pathogenesis imparted by *PKP2* mutations, in addition to prior evidence regarding haploinsufficiency. This work also contributes to the growing body of evidence that indicates that hearts with desmosome mutations are more susceptible to exercise-induced dysfunction than those without a desmosome mutation.

Although this AAV model is efficient and relatively inexpensive compared with other methods of investigation, it falls short in a few ways. First, the pathological hallmarks of disease are largely absent, including a lack of fibrofatty scar, plakoglobin redistribution, or even ultrastructural changes in the cardiac desmosome by transmission electron microscopy. Still, Cruz et al. (6) demonstrated punctate junctional distribution of the principal gap junction protein connexin-43 (Cx43) in exercised mutant mice compared with continuous distribution of Cx43 at myocyte junctions in sedentary mutant mice. Abnormal Cx43 distribution is an important, yet nonspecific, histological feature of ARVD/C (14). Although the authors reported a small increase in the QRS duration in mutant mice compared with controls, they did not show significant arrhythmias or decreased survival as a consequence of mutant *PKP2* overexpression.

Aerobic exercise has remarkable cardiovascular benefits, decreasing the risk of atherosclerosis, reducing death from heart failure, lowering blood pressure, decreasing abdominal fat, lowering glycosylated hemoglobin in diabetes mellitus, and improving sarcopenia (15–18); however, endurance athletics is not without some risk. La Gerche et al. (19) investigated 40 subjects who participated in endurance races (3 to 11 h in duration) and showed that this level of exercise causes acute RV, but not left ventricular, dysfunction. The mechanism of RV dysfunction in response to exercise is not known. One simple explanation is that the thin-walled RV is stretched by the larger volumes and cardiac output required by aerobic activity, and desmosome mutations cause a loss of myocyte cell adhesion, which worsens the response to exercise. Although this explanation is appealing, it does not adequately account for some of the other mechanistic data published for ARVD/C. Several investigations have highlighted an important role for diminished Wnt/β-catenin signaling in ARVD/C, although exercise appears to stimulate the canonical Wnt pathway (20,21). Peroxisome proliferator-activated receptor (PPAR)-γ and PPAR-α stimulation of induced pluripotent stem cell-derived cardiomyocytes from patients with ARVD/C leads to exaggerated lipogenesis and apoptosis, which implicates this pathway in ARVD/C pathogenesis (22). Because exercise upregulates the PPAR-γ pathway, this may contribute to the harmful effects of exercise for patients with ARVD/C (23).

As several groups continue to address these tantalizing questions regarding the pathogenic effects of exercise, improved understanding of the interaction of desmosome mutations, aerobic activity, and cardiac metabolism should lead to better estimation of risk and more effective therapies to prevent ARVD/C and sudden cardiac death.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Daniel P. Judge, Johns Hopkins School of Medicine, Department of Medicine/Cardiology, 720 Rutland Avenue, Suite 1049, Baltimore, Maryland 21205. E-mail: djudge@jhmi.edu.

REFERENCES

1. Twain M. "Mark Twain Himself: A Pictorial Biography." Columbia, MO: University of Missouri; 2002:266.

2. Marcus FI, Fontaine G. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: a review. Pacing Clin Electrophysiol 1995;18:1298–314.

3. James CA, Bhonsale A, Tichnell C, et al. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. J Am Coll Cardiol 2013;62:1290–7.

4. Sawant AC, Bhonsale A, te Riele ASJM, et al. Exercise has a disproportionate role in the pathogenesis of arrhythmogenic right ventricular dysplasia/cardiomyopathy in patients without desmosomal mutations. J Am Heart Assoc 2014;3:e001471.

5. La Gerche A. Defining the interaction between exercise and arrhythmogenic right ventricular cardiomyopathy. Eur J Heart Fail 2015;17:128–31.

6. Cruz FM, Sanz-Rosa D, Roche-Molina M, et al. Exercise triggers ARVC phenotype in mice expressing a disease-causing mutated version of human plakophilin-2. J Am Coll Cardiol 2015;65:1438–50.

7. Kirchhof P, Fabritz L, Zwiener M, et al. Age- and training-dependent development of arrhythmogenic right ventricular cardiomyopathy in heterozygous plakoglobin-deficient mice. Circulation 2006;114:1799–806.

8. Hariharan V, Asimaki A, Michaelson JE, et al. Arrhythmogenic right ventricular cardiomyopathy mutations alter shear response without changes in cell-cell adhesion. Cardiovasc Res 2014;104:280–9.

9. den Haan AD, Tan BY, Zikusoka MN, et al. Comprehensive desmosome mutation analysis in North Americans with arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circ Cardiovasc Genet 2009;2:428–35.

10. Kapplinger JD, Landstrom AP, Salisbury BA, et al. Distinguishing arrhythmogenic right ventricular cardiomyopathy/dysplasia-associated mutations from background genetic noise. J Am Coll Cardiol 2011;57:2317–27.

11. Cerrone M, Noorman M, Lin X, et al. Sodium current deficit and arrhythmogenesis in a murine model of plakophilin-2 haploinsufficiency. Cardiovasc Res 2012;95:460–8.

12. Chen SN, Gurha P, Lombardi R, Ruggiero A, Willerson JT, Marian AJ. The hippo pathway is activated and is a causal mechanism for adipogenesis in arrhythmogenic cardiomyopathy. Circ Res 2014;114:454–68.

13. Gerull B, Heuser A, Wichter T, et al. Mutations in the desmosomal protein plakophilin-2 are

common in arrhythmogenic right ventricular cardiomyopathy [published correction appears in Nat Genet 2005;37:106]. Nat Genet 2004;36:1162–4.

14. Asimaki A, Tandri H, Huang H, et al. A new diagnostic test for arrhythmogenic right ventricular cardiomyopathy. N Engl J Med 2009;360:1075–84.

15. Palmefors H, DuttaRoy S, Rundqvist B, Börjesson M. The effect of physical activity or exercise on key biomarkers in atherosclerosis: a systematic review. Atherosclerosis 2014;235:150–61.

16. O'Connor CM, Whellan DJ, Lee KL, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009;301:1439–50.

17. Landi F, Marzetti E, Martone AM, Bernabei R, Onder G. Exercise as a remedy for sarcopenia. Curr Opin Clin Nutr Metab Care 2014;17:25–31.

18. Stewart KJ. Exercise training and the cardiovascular consequences of type 2 diabetes and hypertension: plausible mechanisms for improving cardiovascular health. JAMA 2002;288:1622–31.

19. La Gerche A, Burns AT, Mooney DJ, et al. Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. Eur Heart J 2012;33:998–1006.

20. Garcia-Gras E, Lombardi R, Giocondo MJ, et al. Suppression of canonical Wnt/beta-catenin signaling by nuclear plakoglobin recapitulates phenotype of arrhythmogenic right ventricular cardiomyopathy. J Clin Invest 2006;116:2012–21.

21. Fujimaki S, Hidaka R, Asashima M, Takemasa T, Kuwabara T. Wnt protein-mediated satellite cell conversion in adult and aged mice following voluntary wheel running. J Biol Chem 2014;289:7399–412.

22. Kim C, Wong J, Wen J, et al. Studying arrhythmogenic right ventricular dysplasia with patient-specific iPSCs. Nature 2013;494:105–10.

23. Thomas AW, Davies NA, Moir H, et al. Exercise-associated generation of PPARγ ligands activates PPARγ signaling events and upregulates genes related to lipid metabolism. J Appl Physiol 2012;112:806–15.

KEY WORDS arrhythmia, cardiomyopathy, exercise, sudden cardiac death