

## Exercise: A Risky Subject in Arrhythmogenic Cardiomyopathy

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Numerous studies have shown that exercise benefits health in the general population, that it slows the aging process, and that it helps prevent heart disease and heart failure. However, in the case of inherited arrhythmias syndromes, exercise is also one of the main triggers for life-threatening arrhythmias and sudden cardiac death in several conditions that are vulnerable to adrenergic stress. After the 2005 36th Bethesda Conference recommendations<sup>1</sup> provided an overall restriction to eligibility and participation to competitive sport to basically all inherited arrhythmogenic conditions, several investigators proposed an alternative case-by-case approach, aimed at targeting specific diseases that associate specifically with adrenergic triggers. Recently, there has been an ongoing debate questioning if a more lenient approach could be applied also to adrenergic-mediated arrhythmias, such as in the case of the Long QT syndrome. The latter was supported by preliminary evidence from a single center, showing that participation in sport did not affect mortality in a group of 103 patients with Long QT syndrome protected by medical therapy.<sup>2</sup> Although further multicenter data, such as the ongoing international registry looking at the safety of sports in patients with Long QT syndrome or hypertrophic cardiomyopathy (URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT02549664), are needed to modify current recommendations in the context of long-QT syndrome and other channelopathies, the past few years have been providing robust evidence of the deleterious effects that exercise plays in the context of arrhythmogenic cardiomyopathy (ACM).

The link between ACM diagnosis and increased risk of sudden cardiac death in the athletic population has been recognized since the early description of the disease, in both patients and animal models.<sup>3,4</sup> In recent years, the work of James et al<sup>5</sup> and Sawant et al<sup>6</sup> provided a strong quantitative set of data, further corroborated by additional studies,<sup>7,8</sup> showing that exercise is a major contributor to disease progression in ACM. This group had the novel approach of collecting systematic retrospective and longitudinal exercise history from their patient population, with the goal of assessing, in a dose-dependent manner, the role of “nature versus nurture” in the disease progression.<sup>9</sup> Although retrospective interviews carry known limitations, because they are subjective and may have recall bias, they also have the advantage of reflecting real-life data that can be reasonably quantified, independently from the individual’s perception of being more or less active.

The initial study in 87 desmosomal mutation carriers<sup>5</sup> showed how survival from first arrhythmia and onset of severe heart failure were worse among athletes and how lifestyle changes with exercise reduction could alter and improve clinical course. A follow-up study from the same group<sup>6</sup> then demonstrated how exercise has an even more severe contribution to disease progression in “gene-elusive” patients, diagnosed by Task Force criteria in the absence of a positive genetic hit. In the current issue of this journal, Wang and colleagues<sup>10</sup> moved a step further in unraveling the relations between sport and ACM and focused their analysis on the impact of lifestyle changes and exercise reduction in patients with ACM with an implantable cardioverter defibrillator (ICD) implanted in primary or secondary prevention. The 129 patients studied reflect somehow a higher-risk group, who has already shown clinical features of the disease to the point of having an indication to an ICD. In this issue of the *Journal of the American Heart Association (JAHA)*, Wang et al<sup>10</sup> addressed the important question of whether exercise reduction could alter the incidence of appropriate shocks in this specific group and whether there was a quantitative relation between the extent of exercise reduction and the probability of having ventricular arrhythmias. Their results add to the body of data supporting restriction from endurance and strenuous exercise in the context of ACM, by showing that those patients who followed the advice of limiting physical

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activity had a significantly better survival from appropriate ICD therapy. Interestingly, in this population, ≈74% of patients did decrease exercise activities, a remarkable compliance with the physicians' advice. Considering that most patients reported at least 936 MET-h/y, consistent with the definition of "athlete," this finding is noteworthy.

Although the results of the study are somehow expected, by being in line with the existing data, one message coming from this work is of particular relevance: reducing the exercise "dose," which takes into account the intensity of the activity, has higher effect in decreasing arrhythmic risk than just maintaining the same intensity for a shorter duration. The results offer new data aimed to address a common question that clinicians face from patients after they are told to refrain from exercising: "Doctor, which physical activity would I still be able to do?" Exercise is often an integral part of the quality of life in these individuals, and a reaction, possibly linked to the stress generated by the new diagnosis, is frequently expressed as fear of increasing one's cardiovascular risk for acquired conditions by transitioning to a sedentary lifestyle. By showing that the higher risk of experiencing ICD shocks is tied to high-impact/high-intensity activities, and that only shortening exercise of high intensity is not sufficiently beneficial, the authors offer quantitative information that may facilitate compliance. Although previous studies claimed that leisure activities may not increase dramatically the risk of arrhythmias in ACM,<sup>8</sup> the current results identify a subgroup of high-risk patients with ACM with higher arrhythmic burden, in whom more aggressive restrictions should be enforced to avoid recurrent arrhythmias.

Patients diagnosed with ACM and negative genotype had the most beneficial effect from exercise reduction, in line with the observation that they are the subgroup affected the most by exercise in terms of disease progression.<sup>6</sup> Exercise is known to structurally affect the right ventricle, which is intrinsically more vulnerable and may develop maladaptive fibrosis.<sup>11</sup> However, it is possible that exercise may be proarrhythmic not only because of its link with adrenergic surge, but also via electrophysiologic remodeling. Countries that implemented preparticipation screening had shown dramatic reduction of ACM-related deaths in athletes.<sup>12</sup> The current study of Wang and colleagues<sup>10</sup> offers data suggesting that the electrophysiologic changes that strenuous exercise determine could be at least partially reversed by removing the "stressor" (ie, intense physical activity).

Still, this beneficial effect had only moderate impact on arrhythmia-free survival. Indeed, 66% of patients still experienced ventricular arrhythmias in the first 5 years after ICD implantation; and notwithstanding greater exercise reduction, there was still a 22%/year absolute risk of events. Hence, even a substantial lifestyle change was not sufficient alone to grant sufficient protection from arrhythmias. Indeed, the

study failed to show results compelling enough to modify the indication to implant an ICD after exercise reduction. Once again, this finding is not unexpected, considering that ACM is known to be one of the most lethal cardiomyopathies when left untreated, to the point that data on lethality from groups with lower rates of ICD implants are significantly higher than data coming from US cohorts in which the ICD is used more frequently.<sup>13</sup> Inasmuch as there is concrete value in attempting to control and correct environmental triggers in the setting of ACM, the quest for novel therapeutic venues that can help reduce the incidence of arrhythmic events in these patients remains an open challenge and is one of the most important tasks to address to improve patients' survival.

## Disclosures

None.

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