Predicting Heart Failure in Arrhythmogenic Right Ventricular Cardiomyopathy

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Don Fabrizio had always known that sensation. For a dozen years or so he had been feeling as if the vital fluid, the faculty of existing, life itself in fact and perhaps even the will to go on living were ebbing out of him slowly but steadily, as grains of sand cluster and then up one by one, unhurried, unceasing, before the narrow neck of an hourglass.

Now it was not a river erupting over him but an ocean, tempestuous, all foam and raging white-flecked waves . . .

—The Death of a Prince; Giuseppe di Lampedusa, The Leopard

In his classic novel, The Leopard, Giuseppe di Lampedusa chronicles the life of Don Fabrizio Corbera, Prince of Salina, and his family, set against the beauty and aristocratic splendor of 1860s Sicily. At its core, however, The Leopard is a story about change, social, political, personal, and ultimately physical, as Don Fabrizio finally faces his own, inevitable mortality. In the penultimate chapter, Lampedusa poetically described Don Fabrizio’s last hours, although he had felt his life slowly ebbing away over many years, initially as grains of sand falling through an hourglass, increasing in intensity to a roaring waterfall and finally a tempestuous ocean of white-flecked waves as he nears death. Close to death, he is aware of a young woman among his weeping relatives, a woman he had previously seen searching for him at a train station, indicative that the signs of our mortality are present before the unavoidable finality. For Don Fabrizio, she represents the embodiment of Venus, and ultimately that which cannot change, the inevitable transition from this life to the next. As he finally succumbs, . . . the crashing of the sea subsided altogether.

Predicting the functional decline associated with cardiovascular disease secondary to ventricular dysfunction allows adoption of management strategies to alleviate the morbidity, recurrent hospitalization, and mortality associated with heart failure. Cardiopulmonary exercise testing (CPET) has become a central component in the investigation, management, and prognostication of patients with heart failure secondary to varying causes. Noninvasive and reproducible, it allows determination of specific patterns of oxygen uptake, carbon dioxide excretion, and ventilation, which reflect the functional reserve and overall performance of the cardiopulmonary system.

In this issue of the Journal of the American Heart Association (JAHA), Scheel and colleagues describe the safety and utility of CPET in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC), a diagnosis for which this specific investigative modality has not previously been described. The article raises several important issues.

First, the study brings increasing awareness that heart failure is an important component within the overarching disease spectrum of arrhythmogenic cardiomyopathies, which have traditionally been perceived as predominantly arrhythmic disorders, falling between inherited arrhythmia syndromes and the more traditional dilated and hypertrophic cardiomyopathies. Recognition of a broader phenotype beyond just classic, right-sided variants has led to adoption of the term arrhythmogenic cardiomyopathies, defined as an arrhythmogenic disorder of the myocardium not secondary to ischemic, hypertensive, or valvular heart disease, and incorporates a broad spectrum of genetic, systemic, infectious, and inflammatory disorders. Classic right-sided disease, ARVC, is the best known of the arrhythmogenic cardiomyopathies, and is the focus of this study. ARVC is most commonly associated with genetic variants in the desmosomal genes (predominantly plakophilin-2) with a phenotype ranging from exertional ventricular tachycardia more characteristic of catecholaminergic polymorphic ventricular tachycardia to an increasingly appreciated end-stage cardiomyopathy requiring

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mechanical ventricular support and cardiac transplantation. Although the progression from an arrhythmic to an overt cardiomyopathic phenotype is typically seen in the latter stages of the disease, biventricular disease with severe heart failure may be an early and presenting manifestation. Recognition that heart failure is an important feature of both desmosomal and nondesmosomal arrhythmogenic cardiomyopathies has important implications not only for the specific patient, but also in appropriate cascade screening and management of potentially affected family members.

Second, and reassuringly, CPET appears to be safe in patients with ARVC and does not appear to induce sustained ventricular tachycardia. As the authors note, the ability of exercise to induce ventricular tachycardia in ARVC is well recognized, and may in fact be a helpful diagnostic tool in early phases of the disease. Conversely, this may limit patients with an established diagnosis of ARVC and history of ventricular tachycardia being offered CPET because of perceived arrhythmic risk, thereby denying them an important clinical investigation. The data presented herein, albeit in a relatively small number of patients, the vast majority of whom had a history of ventricular tachycardia, are therefore encouraging. Although exercise has been linked to disease progression in ARVC, this largely relates to endurance activities performed over many years, so it seems unlikely CPET, even when performed repeatedly, would lead to a significant increase in arrhythmic burden or deterioration of contractile ventricular function.

Third, standard metrics for identifying patients with ARVC who progressed to transplantation appeared unhelpful in heart failure driven predominantly by right ventricular remodeling; echocardiographic indexes of evolving left ventricular contractile dysfunction (namely, end diastolic dimension and ejection fraction) were neither suggestive of end-stage heart failure nor different in the 10 patients who ultimately underwent transplantation compared with the 26 who did not. Similarly, moderate to severe right ventricular dysfunction was no different in the transplant group, although a trend to right ventricular dilatation was present. This suggests different parameters are needed to identify those with ARVC at highest risk. Right ventricular failure typically relates to secondary pulmonary hypertension and excessive pressure loading, resulting from left ventricular systolic or diastolic dysfunction, so primary right ventricular disease, as seen in ARVC, represents a new and unique challenge in the investigation and management of heart failure.

In this study, ventilation/carbon dioxide excretion was statistically associated with transplant-free survival as opposed to oxygen uptake, and correlated inversely with invasive measures of cardiac output, still considered the gold standard. Prior studies have demonstrated ventilation/carbon dioxide excretion may be a useful prognostic metric in adult patients with noncyanotic congenital heart disease. Given the high prevalence of right-sided heart disease after congenital cardiac surgery, this population potentially represents a closer correlate to ARVC than other forms of heart failure dominated by left ventricular dysfunction, albeit one with a fundamentally different cause driven by chronic abnormalities in ventricular loading as opposed to genetically determined loss of intercellular coupling and communication. Ventilation/carbon dioxide excretion reflects ventilation-perfusion mismatch, and because of the linear relationship between ventilation and carbon dioxide production, and unlike oxygen uptake, is independent of effort. As such, the relationship has been proposed as a more robust assessment of cardiovascular performance in situations of submaximal exercise, an issue in ~20% of the tests performed in this study. Submaximal exertion may be more prevalent in ARVC compared with other diagnoses, given the potential patient perceived risk of arrhythmia and implantable cardioverter-defibrillator therapy. Unlike the findings presented herein, however, in one analysis of 1375 adults with congenital heart disease, oxygen uptake and heart rate response provided the greatest value in predicting subsequent mortality. ARVC may be different, or future studies incorporating larger numbers may yield different findings.

Although the results of this study are of great interest, questions remain that pose exciting possibilities. One of the inherent limitations of clinical research in rare genetic disorders is the relatively small number of patients with heterogeneous phenotypes. Although all patients enrolled in this study fulfilled diagnostic criteria, as set out by the 2010 International Task Force, a proportion of patients had genetic variants in desmoplakin (DSP), TMEM43, and phospholamban (PLN), all of which have a higher prevalence of left ventricular dysfunction, although interestingly none of these patients was in the transplant group. It is therefore important we compare like with like to maximize the interpretability and implementation of the results in clinical management.

The small number of patients included, the varied use of CPET method, and the lack of serial testing in most patients again limit interpretation of the results. Well-designed prospective studies incorporating larger numbers of phenotypically homogeneous patients will hopefully begin to answer these questions, and also further elucidate the fundamental mechanisms whereby abnormalities of right ventricular functional reserve and ventricular-pulmonary vascular coupling combined with deleterious effects on left ventricular mechanics lead to an overall decline in cardiovascular performance in ARVC. The beneficial downstream effect of disease recognition, cascade screening, risk stratification, and detailed arrhythmia management in ARVC has been evolution of an older population exposed to the longer-term risks of cardiomyopathy and heart failure, and this is therefore an important step to better define the natural history and maximize patient care in the longer-term.
Members of the medical community involved in the investigation of ARVC from its initial description to the current era have a long-established track record of collaborative research through multicenter studies and registries. The serial use of CPET in a prospective and structured manner across multiple centers, enrolling sufficient patients at a relatively early stage in their clinical course, will hopefully allow presymptomatic identification of those at risk of subsequent heart failure, with the timely employment of appropriate management. Such a study would be a welcome and valuable addition to our understanding of this fascinating disease.

In clinical research, the key to obtaining a meaningful assessment of human physiological features and their association with different diseases is measuring the right things in the right people at the right time. Therefore, like Don Fabrizio, we need to be cognizant that life starts to ebb away long before the onset of clinical symptoms, such that we need mechanisms by which we can identify and intervene on the physiological changes that precede clinical heart failure in ARVC, in the hope we can slow the grains of sand turning to a tumultuous ocean.

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