Stepping Closer, But Not Stepping Too Much, Toward Exercise Recommendations for Lamin A/C Genotype–Positive Patients

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Landmark work from nearly 2 decades ago has had a major influence on our understanding of the benefit of increasing aerobic fitness for mitigating death in the apparent healthy and in those with established cardiovascular disease.[1] Indeed, since the work of Myers et al,[1] the research and clinical community has come to better appreciate the beneficial effects of long-term exercise, whereby increasingly greater exercise dosing confers a concomitant increase in exercise capacity.[2] The past 2 decades have also generated intriguing data that high-intensity interval exercise, seemingly intended for only well-trained healthy individuals (as it facilitates high-volume exercise training in a reduced time window), is possible for, and may confer antiremodeling benefit in, patients with reduced ejection fraction after short-[3] and long-term[4] training. Exercise for patients with impaired systolic function is generally considered to be safe and improve patient symptoms and quality of life.[5,6] But are there limits to exercise volume recommendations in patients with, or at risk for, left ventricular systolic dysfunction? Indeed, not all left ventricular dysfunction is the same, nor are the physiological benefits or exercise recommendations,[7–10] and recent data further highlight the importance of appreciating exercise volume when considering exercise recommendations for some of these patients.[11]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Skjølsvik et al[11] present provocative data from their cross-sectional study that suggest greater exercise volume may potentiate cardiac remodeling in patients who are A/C lamin genotype positive. Specifically, the authors studied 69 well-characterized (see Table 1 in reference 11) diagnosed A/C lamin genotype patients, aged 42±14 years (46% women), recruited from a single center. Of study patients, 41% (n=28) were probands and 59% (n=41) were family members. Exercise volume history was obtained via (structured) telephone interview or questionnaire (by mail) and quantified by allocating reported activities and sports participation >3 metabolic equivalents using the updated and highly referenced 2011 Compendium of Physical Activities.[12] This cumulative lifetime exercise metric was computed from the age of 7 years to diagnosis/echocardiographic study, and the number of years over the lifetime exercise hours was standardized to account for age as a confounding variable. Those with a value above the group median of 4160 hours (interquartile range, 1041–6924 hours) were considered active (n=34 patients; cumulative lifetime exercise=4.5 h/wk) versus those at or below the median, who were considered sedate (n=35 patients; cumulative lifetime exercise=0.8 h/wk). Cardiac assessment was performed by echocardiography in all patients, and cardiac magnetic resonance imaging was performed in a subset of patients. Conduction abnormalities, ventricular arrhythmias, and skeletal muscle function were also assessed.

Active A/C lamin genotype–positive patients tended to be probands (53% of patients), displayed greater cardiac remodeling (ejection fraction, 43±13%; end-systolic volume, 79±39 mL; end-diastolic volume, 133±49 mL) compared with sedate patients (ejection fraction, 51±11%; end-systolic volume, 55±22 mL; end-diastolic volume, 111±25 mL), and subsequently were more frequently diagnosed with dilated cardiomyopathy (65% of patients); higher NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels corroborated the echocardiographic remodeling evidence in active patients. Reduced left ventricular ejection fraction persisted in active patients with the standardized lifetime exercise analysis and when adjusted for age; higher frequency of dilated cardiomyopathy diagnosis also persisted in active patients when adjusted for age and sex. When the study group (n=69) was analyzed in tertiles of lifetime exercise, left ventricular ejection fraction decreased an absolute 4% per increasing cumulative lifetime exercise tertile, and this effect held true with standardized lifetime exercise analysis. Analysis of age-

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related survival free from a reduction in left ventricular ejection fraction (n=69) revealed that active patients were younger when diagnosed with low ejection fraction (defined as <45%), and this was also the case specifically for active family members but not probands. Conduction abnormalities and ventricular arrhythmias did not differ between active and sedate patients, potentially because of statistical power and/or the small number of related observations in the study.

The investigators have previously reported that lamin A/C genotype–positive patients display high cardiac penetrance (85%) at a young age that approaches ≈100% by the age of 60 years, with ≈20% of these patients requiring cardiac tranplantation.[13] Notably, arrhythmogenic right ventricular dysplasia/cardiomyopathy–associated desmosomal mutation carriers may also be at increased risk for greater age-related cardiac penetrance with elevated levels of exercise,[14] and this likely accelerates ventricular remodeling.[15] In their current study, Skjølsvik et al[11] extend prior work by gaining insight into the possible role exercise volume may have on the progression of cardiac remodeling in lamin A/C genotype–positive patients. A major strength of the current study[11] is that the investigators demonstrate that the impaired cardiac function in active compared with sedate lamin A/C genotype–positive patients is independent of age and sex, and these findings are generally compelling given the quantification of cumulative lifetime exercise, cardiac function, and genetic analyses. On balance with the intriguing finding of the study by Skjølsvik et al,[11] readers need to frame their appreciation of the presented data with the study's unavoidable methodologic constraints. Specifically, physical activity reporting by patients in the study is clearly subject to recall bias, and this is noted by the authors. Given the nature of lamin A/C genotype detection in the population, it would be difficult to obtain prospective and more objective assessments of exercise habits. Nevertheless, long-term observational studies that determine physical activity more objectively, such as with physical activity monitors, should be pursued to guide more definitive conclusions about the amount of physical activity that is safe to better inform exercise guidelines for such patients.

Does the study by Skjølsvik et al[11] provide definitive evidence for an exercise safety risk in patients with A/C lamin genotype? The findings by the authors certainly compel readers to appreciate the likelihood for an association between exercise volume and cardiac remodeling in lamin A/C genotype–positive patients. Notably, and by well-accepted physical activity recommendation standards,[16] the active patient group in the study by Skjølsvik et al[11] would not be considered to be engaging in an overabundance of physical activity, which truly speaks to the relatively low (yet undefined) threshold for what is considered a safe physical activity volume in lamin A/C genotype–positive patients.

Disclosures

None.

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