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EDITORIAL COMMENT

The Female Side of the Heart

Sex Differences in Athlete's Heart*

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Most of the previous knowledge on the athlete's heart was derived from data collected in males and (improperly) assumed to represent the "normal" physiologic response induced by the athletic lifestyle. Only a few reports in past years have extensively described the characteristics of the athlete's heart in women (1).

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In this issue of *iJACC*, the investigation by Finocchiaro et al. (2) extends the understanding of the female athlete's heart by introducing the concept of left ventricular (LV) geometry, as classified by normal, eccentric remodeling (increased LV mass with normal relative wall thickness [RWT]), concentric remodeling (increased RWT with normal LV mass), and concentric hypertrophy (increased RWT and LV mass) (2). Finocchiaro et al. (2) observe that most athletes, irrespective of sex (69% of males and 71% of females), maintain a normal LV geometry. This finding is not totally unexpected, in consideration that exercise-induced hemodynamic overload (increased pre-load) induces, according to Laplace's law, a proportionate increase in LV cavity size and wall thickening (3).

However, when the overload is more substantial, by including also an increased after-load (such as occurs in endurance sport), the extent of LV wall thickening becomes more relevant. The combined increase in pre- and after-load for prolonged periods of time induces a greater LV wall thickening, leading to concentric remodeling/hypertrophy. In the Finocchiaro et al. (2) study, a subset of athletes (15%) showed concentric LV hypertrophy/remodeling, mostly comprised of males, with only a tiny proportion of females (4%; $p = 0.001$). The most common physiologic response in females was, instead, an eccentric LV hypertrophy, which was observed in 22% of females (compared with 16% of males; $p < 0.001$) (2).

In power sports, a prevalent pressure overload (increased after-load) operates for a short duration but several repetitions. This stimulus is associated with concentric LV remodeling, which is responsible for a mild increase in LV wall thickness with unchanged cavity size, and increased RWT. In the Finocchiaro athlete's cohort, this pattern was found in about 15% of the females (with similar proportion of males). However, and of relevance, the extent of LV wall thickening in female power athletes did not exceed the upper normal limits (i.e., 11 mm) (4), substantiating the results of previous reports (5).

This observation is of clinical relevance by confirming that absolute LV wall thickness in white female athletes (i.e., 11 mm) never extends into the gray area of wall thickness (i.e., 13 to 15 mm) compatible with diagnosis of hypertrophic cardiomyopathy, because it occurs in an important minority (3%) of males (6). However, it should also be noted that a small, but not negligible, proportion of female black athletes (3%) may present larger absolute LV wall thickness, up to 13 mm (4), falling in the cited gray area (6). In conclusion, physiologic remodeling in white females does not usually raise doubts of differential diagnosis with hypertrophic cardiomyopathy, but it may do so in a small subset of Afro-Caribbean female athletes (4).

It is worth noting that cardiac remodeling affects, even substantially, the other cardiac chambers in female and male athletes. Right ventricular (RV) remodeling deserves particular attention in consideration of the potential adverse clinical consequences attributed to long-term endurance conditioning. Available data suggest that female endurance athletes show increased RV cavity size compared

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with control subjects, characterized by an enlarged RV inflow (by about 10%), with only mild changes of the outflow tract. In association, RV thickness is also increased (by an average 13%) (7). As shown for LV, the absolute RV dimensions are smaller in female compared with male athletes: RV diastolic area (by 23%) and RV outflow tract (by 8%) (8). When normalized to body size, differences reduce greatly for RV chamber area and reverse for RV outflow tract (5% larger in females).

The extent of RV remodeling largely depends on the type of sport; RV dimensions show increasing values from skill, power, mixed, to endurance sports. A similar trend is observed for RA size (8). Rarely, the RV chamber shape is altered, with a rounded apex and prominent trabecular pattern (8).

Practical clinical consequence of RV remodeling is the dimensional overlap of RV outflow tract with the RV cutoff for diagnosis of arrhythmogenic RV cardiomyopathy (9). Zaidi et al. (10) observed that a large subset of female athletes (14%) showed absolute RV outflow dimensions meeting the major criteria advised by the Task Force. To avoid misinterpretation, it seems convenient to refer uniquely to the normalized RV outflow dimensions, which have shown to drastically reduce the overlap (to 4%) with major Task Force criteria (8). Indeed, regardless of the extent of morphologic remodeling, indexes of RV function (tricuspid annular plane systolic excursion, percent fractional shortening) remain normal in female athletes, such as previously reported in male athletes (8).

In the clinical evaluation of the female athlete's heart, the electrocardiogram plays a relevant and reassuring role, because of the usual lack in female athletes of the alterations, often marked and bizarre, observed in male athletes (11). Specifically, changes in expression of cardiac remodeling distinctive to an electrocardiogram, such as increased R/S-wave voltages suggestive for LV hypertrophy, early repolarization pattern, or marked sinus bradycardia, are far less common in female than male athletes (12).

Moreover, the electrocardiogram abnormality expression of underlying disease, such as inverted T waves, also appears different; specifically, female athletes commonly present an inverted T-wave in anterior precordial leads, whereas male athletes present inferior and lateral leads (11). This concept is confirmed in the present study, where Finocchiaro et al. (2) report the presence of T-wave inversion in anterior precordial leads in 9% of females (vs. 4% of males; $p < 0.05$), and in inferior leads in 5% of males (vs. 2% in females; $p < 0.02$). This behavior is also observed in athletes of black ethnicity: black females usually present inverted T waves in anterior precordial leads (and in a greater proportion than white ones; 14% vs. 2%; $p < 0.001$) (4). Furthermore, the authors of the present study (2) were intrigued to search for a relationship between these electrocardiographic abnormalities and the LV geometry patterns, but no differences in distribution of abnormal electrocardiogram patterns were observed in athletes with normal versus abnormal LV geometry (2).

Finally, it is worth noting that the published studies suggest a significantly lower prevalence of cardiac diseases associated with risk of sudden cardiac death in females, particularly arrhythmogenic cardiomyopathies (e.g., hypertrophic cardiomyopathy, arrhythmogenic RV cardiomyopathy). Females represent a tiny minority of the athletes dying suddenly (13,14), with the ratio of male to female averaging to 10:1 (14). At pathologic examination, most of the females show a structurally normal heart, suggesting that electrical diseases (e.g., long LQ syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia) were likely responsible for death, more than cardiomyopathies or coronary artery disease (15). If female athletes are less prone to die suddenly from structural disease, it is likely that their genetic and hormonal makeup protects them from developing an arrhythmogenic substrate. Increasing evidence also exists for the role of sympathetic tone as a trigger for life-threatening ventricular arrhythmias in athletes, and evidence suggests that female athletes show, in response to a challenging test, a lower sympathetic activation compared with males (16).

The disproportionate lower risk for sudden cardiac death observed in females cannot be simply the consequence of smaller participation in sport, neither lower intensity nor duration of exercise conditioning. Understanding the genetic and/or hormonal mechanisms that females possess to neutralize the risk of acute cardiac events is an intriguing issue, which may open the door to a novel approach to reduce the occurrence of such devastating events in young athletes.

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