Evidence for efficacy of the Italian national pre-participation screening programme for identification of hypertrophic cardiomyopathy in competitive athletes

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Aims Hypertrophic cardiomyopathy (HCM) is a leading cause of sudden death in young athletes, and substantial interest persists in strategies for timely identification. We assessed the diagnostic efficacy of Italian pre-participation screening programme with 12-lead ECG (in addition to history and physical examination) for identification of HCM.

Methods and results Four thousand four hundred and fifty members of the Italian national teams, initially judged eligible for competition as a result of systematic pre-participation screening across Italy, subsequently underwent clinical and echocardiographic examination at the Institute of Sports Medicine and Science (Rome) to assess the presence of previously undetected HCM. None of the 4450 athletes showed clinical evidence of HCM. Other cardiac abnormalities were detected in only 12 athletes, including myocarditis (n = 4), mitral valve prolapse (n = 3), Marfan’s syndrome (n = 2), aortic regurgitation with bicuspid valve (n = 2), and arrhythmogenic right ventricular cardiomyopathy (n = 1). In addition, echocardiography identified four athletes with borderline left ventricular wall thickness (i.e. 13 mm) in the ‘grey zone’ of overlap between HCM and athlete’s heart. In two of these athletes, subsequent genetic analysis or clinical changes over an average 8-year follow-up resulted, respectively, in a definitive or possible diagnosis of HCM.

Conclusion The Italian national pre-participation screening programme including 12-lead ECG appears to be efficient in identifying young athletes with HCM, leading to their timely disqualification from competitive sports. These data also suggest that routine echocardiography is not an obligatory component of broad-based screening programmes designed to identify young athletes with HCM.

Introduction

Sudden and unexpected deaths in young competitive athletes are uncommon but highly visible events, which consistently raise concern and ethical issues in both the lay public and medical community.1,2 Hypertrophic cardiomyopathy (HCM) has been repeatedly reported as a leading cause of the athletic field deaths and is responsible for more than one-third of all such sudden deaths in the USA.3–5 However, the frequency of sudden death in young athletes due to HCM appears to be much lower in Italy.6,7

It has been hypothesized that this paradox is the consequence of the timely identification of young individuals with HCM by national pre-participation screening, a unique programme implemented by law in Italy over the last 25 years, which routinely includes the 12-lead ECG, in addition to history and physical examination.8 Therefore, we undertook the present analysis to determine whether the Italian pre-participation screening programme is responsible for the timely identification and disqualification of young athletes with HCM and, consequently, the low prevalence of athletic field deaths due to this disease.

Methods

Italian pre-participation screening programme

Systematic pre-participation screening of competitive athletes constitutes an Italian medical programme established by legislation in 1982 and implemented for the last 25 years.8 All citizens participating in organized and competitive sports are required to undergo preventive general medical and cardiovascular evaluation, which routinely includes 12-lead ECG, in addition to personal and family...
Study population
During the 9-year period (1990–1998), 4485 elite athletes had been referred consecutively to the Institute of Sport Medicine and Science. Each was regarded as an elite athlete and considered a candidate for national and international competition as a member of the Italian teams on the basis of their past athletic performance. These 4485 athletes had been previously examined within the national pre-participation screening programme in satellite centres throughout Italy, cleared medically, and judged eligible for sport competition. In each, the diagnosis of HCM (or other cardiac disease) had been considered to be excluded, based on history, physical examination, and 12-lead ECG. It was our objective at our institution in Rome to confirm the absence (or verify the presence) of the entire coding region of the genes more commonly implicated as disease-causing (i.e. MYH7, MYBPC3, TNNI3, TNNC1). Analysis was performed by PCR amplification of gene segments; both strands of the segments were then sequenced to identify specific DNA variants. This process analysed the entire coding region of each of the genes examined, including the exon–intron splice junctions encompassing 106 exons.

Follow-up
Athletes with structural cardiac abnormalities were managed according to the Italian guidelines for competitive sports eligibility, closely resembling Bethesda Conference No. 36 and recommendations of the European Society of Cardiology. Analysis was performed by direct DNA sequencing of the entire coding sequences of the genes more commonly implicated as disease-causing (i.e. MYH7, MYBPC3, TNNI3, TNNC1). The protocol of CMR study was previously reported. Genetic testing for HCM was performed by direct DNA sequencing of the entire coding sequences of the genes more commonly implicated as disease-causing (i.e. MYH7, MYBPC3, TNNI3, TNNC1). Analysis was performed by PCR amplification of gene segments; both strands of the segments were then sequenced to identify specific DNA variants. This process analysed the entire coding region of each of the genes examined, including the exon–intron splice junctions encompassing 106 exons.

Results
Hypertrophic cardiomyopathy
In 4397 of the 4450 athletes (98.8%), the clinical diagnosis of HCM was excluded by echocardiography, based on normal LV wall thicknesses (7–12 mm, mean 9.4 ± 1.2), in the absence of systolic anterior motion (SAM) of the mitral valve and LV outflow obstruction (Figure 1).

Athletes with physiological LV hypertrophy
A subset of 41 athletes showed LV hypertrophy, including 37 (0.8%, all males) with increased LV wall thicknesses (13–15 mm), associated with distinct cavity enlargement (end-diastolic transverse dimension, 55–65 mm); each had also normal LV systolic function (ejection fraction >50%) and diastolic filling pattern, without SAM and LV outflow obstruction.
and increased interstitial fibrosis. A molecular diagnosis of L V myocardial biopsy showed cardiac muscle cell disarray were present in the anterior septum, consistent with fibrosis. Small areas of post-gadolinium delayed hyperenhancement metric thickening of anterior ventricular septum (18 mm). Cardiac magnetic resonance imaging showed asym-
sions (represented by increase in maximum L V wall thickness from 13 to 15 mm, with reduction of cavity size from 50 to 30 mm), seven with T-wave inversion, two with abnormal R-wave progression in precordial leads, and in one with left atrial enlargement.

These athletes were engaged predominantly in rowing/ canoeing (n = 21) and road cycling (n = 9) and had achieved an international level of competition. Each was judged to have an expression of physiological LV hypertrophy and cardiac remodelling consistent with athlete’s heart.9,11,18 (Figure 1).

Athletes with LV hypertrophy in the grey zone
At initial evaluation, the remaining four athletes (0.1%; three males) had ventricular septal thickness of 13 mm, associated with non-dilated LV cavity (end-diastolic dimension 49–52 mm); each also had normal LV systolic function and diastolic filling pattern, in the absence of SAM or LV outflow obstruction (Table 1). ECGs were abnormal in three of these four athletes, showing increased R and/or S-wave precordial lead voltages (Sokoloff–Lyon index ≥30 mm), seven with deep narrow Q-waves (≥2 mm), six with T-wave inversion, two with abnormal R-wave progression in precordial leads, and in one with left atrial enlargement.

These athletes were engaged predominantly in rowing/canoeing (n = 21) and road cycling (n = 9) and had achieved an international level of competition. Each was judged to have an expression of physiological LV hypertrophy and cardiac remodelling consistent with athlete’s heart.9,11,18 (Figure 1).

Other cardiac abnormalities
Other structural abnormalities were identified by echocar-
diography (or additional diagnostic testing) in 12 of the 4450 athletes, most commonly myocarditis (n = 4) and mitral valve prolapse (n = 3) (Figure 2). Athletes with the Marfan syndrome and arrhythmogenic right ventricular cardiomyopathy (ARVC) were permanently disqualified from competitive sports.16,17 Athletes with myocarditis were temporarily withdrawn from regular training and compet-

Discussion
Sudden death in young athletes is a highly visible event, which continues to generate substantial interest and debate in the lay and medical communities,1,2 particularly with regard to the feasibility and efficacy of large population pre-participation screening,20–23 and criteria for selective withdrawal from competition of individuals at risk.16,17 Several investigations have clarified the spectrum of pathological conditions responsible for athletic field deaths, with HCM the most common in the USA and responsible for about one-third of all such events occurring during sport participation.2,3 In contrast, the number of athletic field deaths due to HCM in Italy is negligible,6,7 despite a prevalence of the disease in the general population apparently similar to that in other countries.24–28 This apparent paradox is believed to be consequence of the national pre-participation screening programme, introduced by law and implemented in Italy for more than 25 years.8 To establish evidence for this hypothesis, the present investigation was designed, in which a large cohort of about 4500 young competitive athletes who received medical clearance for sports participation at national pre-participation screening were
subsequently re-evaluated with echocardiography at the Institute of Sport Medicine and Science in Rome. On the basis of the known prevalence of the HCM phenotype identified by echocardiographic surveys in large diverse population studies (i.e. 0.1–0.2%),24–27 we assumed that five to 10 athletes would have been identified with HCM in our large cohort, if previous national pre-participation screening had been ineffective in detecting this disease. However, our study showed that despite careful and expert clinical and echocardiographic investigation, no unequivocal cases of HCM were recognized among the substantial number of athletes cleared at national pre-participation screening. Therefore, we conclude that the 12-lead ECG, as a routine element in the Italian national screening programme (in addition to history and physical examination), is effective in leading to the diagnosis of HCM, which may ultimately result in the prudent disqualification of athletes according to the current consensus guidelines.15–17

Therefore, our findings also infer that echocardiography did identify in this cohort a variety of cardiovascular diseases, which were not reliably predicted by ECG alone, including most commonly mitral valve prolapse and myocarditis, Marfan’s syndrome, and ARVC.

Of particular note are the four athletes initially considered to represent the overlapping grey zone between HCM and physiological LV hypertrophy of the athlete’s heart.11 These athletes were cleared at pre-participation screening, with ECG abnormalities that were judged to be innocent expressions of the athlete’s heart,12 consistent with their level of athletic training and not an indicator, per se, for disqualification based on European consensus guidelines.16,17 However, after serial echocardiographic testing and long-term observation over an average 8-year period, we were eventually able to make an unequivocal diagnosis of HCM in one of these athletes, by genetic testing, a methodology not available when this individual was initially evaluated. Another athlete had only equivocal findings supporting the diagnosis of HCM most recently,5 whereas two others did not develop morphological and clinical features of this disease over the long follow-up period. Clinical diagnosis of HCM may be difficult in young people, given that LV remodelling typically evolves over time and hypertrophy may be delayed even into adulthood.29,30 Indeed, this could explain the diagnostic scenario in our young athletes, in whom the clinical and phenotypic expressions of HCM were preceded over long periods of time by only ECG alterations.29–31 Although genetic testing could have resolved diagnosis earlier in such athletes, substantial obstacles nevertheless persist for translating DNA-based laboratory methods into routine clinical practice.30 Therefore, diagnosis of HCM was possible only after prolonged periods of observation. For these reasons, athletes in the borderline grey zone between athlete’s heart and HCM,11 although not necessarily disqualified from competition, nevertheless deserve continued clinical surveillance.

It is important to emphasize that the present study design was confined to those athletes who were previously judged to be free of cardiovascular disease at the national pre-participation screening assessment. We do not have access to data describing those athletes suspected to have (or documented with) cardiac abnormalities as a result of the screening programme (i.e. the positive test results). Therefore, in

<table>
<thead>
<tr>
<th>Athlete</th>
<th>Sex</th>
<th>Sport</th>
<th>Evaluation</th>
<th>Age (years)</th>
<th>Max. LV thickness (mm)</th>
<th>LVDD (mm)</th>
<th>LA (mm)</th>
<th>SAM</th>
<th>Other findings</th>
<th>HCM diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>Swimming</td>
<td>Initial</td>
<td>20</td>
<td>13</td>
<td>50</td>
<td>37</td>
<td>0</td>
<td>Cardiac myosin-binding protein C mutation (E542Q)</td>
<td>Definite</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Last</td>
<td>28</td>
<td>15</td>
<td>47</td>
<td>39</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>Rowing</td>
<td>Initial</td>
<td>20</td>
<td>13</td>
<td>52</td>
<td>34</td>
<td>0</td>
<td>Myocardial bridge on distal LAD; NVST</td>
<td>Possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Last</td>
<td>29</td>
<td>13</td>
<td>51</td>
<td>40</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>Swimming</td>
<td>Initial</td>
<td>21</td>
<td>13</td>
<td>53</td>
<td>40</td>
<td>0</td>
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<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Last</td>
<td>27</td>
<td>12</td>
<td>50</td>
<td>38</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
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<td>Initial</td>
<td>30</td>
<td>13</td>
<td>52</td>
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<td></td>
<td>Last</td>
<td>42</td>
<td>13</td>
<td>50</td>
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<td></td>
</tr>
</tbody>
</table>

F, female; LA, left atrium; LAD, left anterior descending coronary artery; LVDD, LV diastolic cavity dimension; max, maximum; M, male; NSVT, non-sustained ventricular tachycardia.

Table 1  Demographic, morphological, and clinical findings in four grey zone athletes at initial and most recent evaluation

Figure 2  Cardiovascular diseases unsuspected by national pre-participation screening, but identified for the first time by echocardiography (and other testing) at the Institute of Sports Medicine and Science. MVP, mitral valve prolapse.

Marfan’s syndrome (n = 2)
Aortic valve disease (n = 2)
MVP (n = 3)
ARVC (n = 1)
Myocarditis (n = 4)
this study, we are not able to resolve issues related to true-
positive and false-positive screening for HCM.
In conclusion, the present cohort study provides a
measure of clarity to several issues surrounding the
complex strategy of screening large populations of young
competitive athletes for HCM. From our data, based on a
large population of about 4500 trained athletes, it appears
that the national pre-participation screening programme
implemented in Italy with 12-lead ECG (in addition to
history and physical examination) is effective in identifying
HCM, thereby leading to the disqualification of these ath-
letes from competitive sports. Our findings also suggest
that routine echocardiography is not an absolutely necessary
component of such large-scale screening programmes
designed to recognize HCM in young athletes.

Conflict of interest: none declared.

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