Sports participation in non-compaction cardiomyopathy: a systematic review

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ABSTRACT
Non-compaction cardiomyopathy (NCCM) is typified by deep invaginations of the myocardium and is caused by an arrest of normal myocardial morphogenesis. NCCM was once considered rare, but is now widely recognised owing to frequent use of advanced imaging techniques. NCCM can also be detected when competitive athletes undergo preparticipation screening for cardiac disease or when being evaluated for cardiac symptoms. It is not clear how athletes with NCCM should be managed. We searched PubMed and Google for articles addressing the issue of NCCM and athletic participation. We were able to identify only 18 cases of NCCM described in the context of sports, athletics or exercise. We conclude that there are insufficient data to develop firm recommendations on how to manage vigorous activity in patients with NCCM and future registries of sudden death in athletes should include a careful search for cases of NCCM among the victims so that clinicians can develop more definitive recommendations for athletes with this condition.

INTRODUCTION
Non-compaction cardiomyopathy (NCCM) was once considered to be rare, but widespread use of echocardiography has increased recognition of this cardiac disease. The true prevalence of NCCM is unknown but estimates range from 0.014% to 1.26%. Engberding first described ‘non-compaction’ as isolated persistent myocardial sinusoids in the left ventricle (LV) in a 33-year-old woman who presented with exertional dyspnoea and palpitations. The term ‘non-compaction’ was first used by Chin et al. The American Heart Association (AHA) has classified NCCM as a primary genetic cardiomyopathy and the WHO and the European Society of Cardiology place NCCM in the category of unclassified cardiomyopathies.

Cardiac trabeculae are formed during the early stages of cardiac development to increase surface area and facilitate diffusion of nutrients from blood to the myocardium. Development of the coronary vasculature allows myocardial nutrients to be supplied via blood vessels and leads to subsequent compaction of the trabeculae. This reduces the inner trabeculated myocardial layer and increases the thickness of the outer compacted myocardial layer. An arrest in this endomyocardial morphogenesis leads to non-compaction. The severity and the extent of myocardial non-compaction depend on when, in development, the arrest occurs. Trabeculations are most often seen at the apex, lateral wall and inferior walls of the LV (figures 1 and 2).

NCCM is inherited predominantly in an autosomal dominant pattern in adults whereas in paediatric cases, the mode of transmission is X linked. Genetic defects have been identified in up to 42% of NCCM patients (78% of children and 35% of adults). Common genetic mutations seen in NCCM patients involve genes encoding for α-dystrobrevin (DTNA), tafazzin (TAZ or G 4.5), sarcomere protein genes (α-cardiac actin (ACTC), β-miosin heavy chain (MYH7) and troponin T2), lim domain binding protein 3 (ZASP), lamin A/C (LMNA) and calsequestrin (CASQ2). Negative genetic testing does not rule out a genetic cause of NCCM indicating that other yet unidentified genetic abnormalities may exist. NCCM is associated with dilated cardiomyopathy and 55% of the families of NCCM patients have both NCCM and dilated cardiomyopathy.

The diagnosis of NCCM requires the use of cardiac imaging such as echocardiography or cardiac MRI (see table 1 for diagnostic criteria and figures 1–3), but many patients with NCCM are initially identified by an abnormal ECG. The increased use of the ECG to screen athletes has increased the use of echocardiography in asymptomatic individuals and led to identifying asymptomatic individuals with NCCM since 87% of individuals with NCCM have an abnormal ECG. Similarly the use of these modalities to evaluate athletes with non-specific, but possibly cardiac symptoms has also identified athletes with NCCM. Such athletes are now routinely prohibited from participating in vigorous sports, but the evidence for these recommendations is unclear. Guidelines regarding sports participation for patients with NCCM are limited. The 36th Bethesda Guidelines excludes patients with NCCM from most competitive sports owing to the paucity of data in this disease, whereas AHA guidelines do not address the issue. Consequently, we performed a systematic search of the medical literature to examine NCCM in general and the management of athletes with NCCM in particular.

METHODS
We searched PubMed, Ovid and Google Scholar using the terms—non-compaction, exercise, sports, running, football, athletics and competitive sports alone and in combination for English language articles reporting NCCM in the setting of exercise and/ or sports. We identified relatively few articles, so extended our search to all languages. We used Google Translate to translate one Spanish article to English. We reviewed abstracts through July 2012 and articles addressing non-compaction associated with exercise, sports and athletics were examined in detail.
Figure 1 Transthoracic echocardiography (4-chamber view) with an arrow indicating apical trabeculations in the left ventricle (Courtesy of Dr David I Silverman MD, Cardiology Department, Hartford Hospital, Hartford, Connecticut, USA).

Figure 2 An arrow showing trabeculations in the left ventricle (Courtesy of Dr David I Silverman MD, Cardiology Department, Hartford Hospital, Hartford, Connecticut, USA).
RESULTS
The search yielded 18 cases (table 2) that described NCCM in exercise, sports and athletics. Fifteen case reports were in English and one in Spanish. Two English reports included more than one case. There were 13 men and 5 women. The mean age of the patients was 29±17 years. There were 10 athletic or sports related NCCM cases and eight cases in participants doing regular exercise. The type of exercise was not described in these eight cases.

The most common presenting symptom during activity (exercise or sports or athletics) was brief syncope (50%, 9/18 cases) without prodromal signs. None of the 18 cases had syncope at rest. Two of the nine with syncope had LV dysfunction (25%) in one case and ‘low’ in the other. Ejection fraction was not mentioned in two of the nine with syncope. Two NCCM cases presented with seizures and syncope prior to their sudden deaths. Neither had a history of syncope and both first experienced syncope while running.

Four patients (22%) presented with systemic thromboembolic events including two transient ischaemic attacks and bilateral pulmonary embolism. Cardiac thrombi were identified in two of the three cases presenting with cerebrovascular accidents, demonstrating that athletes with this condition can present with cardiac thrombi. The case with bilateral pulmonary emboli presented with haemoptysis during scuba diving so that the relationship between thrombosis and LV NCCM is unclear. An additional case was that of a male athlete with bicuspid aortic valve whose NCCM was detected during routine echocardiographic follow-up.

A family history of sudden cardiac death (SCD) was present in 8 of 18 cases (44%). One had a brother who died suddenly at the age of 17 while cycling and a sister who died suddenly at the age of 21 while running. Another had a brother and sister who died suddenly during exercise. An additional case had four members of his family with unexplained sudden death at a young age.

None of the cases had a specific arrhythmia that was predictive of NCCM. Sustained ventricular tachycardia (VT) was observed in four cases. Premature ventricular complexes (PVCs) were also seen in one of these four cases. Two additional cases had PVCs. Left ventricular hypertrophy was the most consistent ECG finding. A 14-year-old boy presented with syncope while running and had an ECG evidence of accelerated atrioventricular conduction (Wolff-Parkinson-White syndrome).

Management of the survivors among these active participants with NCCM varied. Two were advised to avoid vigorous sports including one after the implantable cardioverter defibrillator (ICD) was implanted. Both of these patients, after informed discussion, continued light, low-impact activity which included golf. ICD implantation was recommended in seven patients, although one refused. Anticoagulation with warfarin was initiated in two cases with identified thrombus or a history suggestive of thrombus. Four additional cases were anticoagulated as a precaution to reduce the risk of stroke.

DISCUSSION
We performed this systematic review of exercise and NCCM because we have recently encountered several cases of this condition in athletes and found no clear guidelines on how such patients should be managed. Our review identified only 18 cases

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### Table 1: Investigational criteria proposed to identify NCCM

<table>
<thead>
<tr>
<th>Study</th>
<th>Investigation used</th>
<th>Diagnostic criteria</th>
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</thead>
<tbody>
<tr>
<td>Chin et al</td>
<td>Echocardiography</td>
<td>A. XY ratio ≤0.5 (when measured at end-diastole from parasternal short axis view or apical view)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X=distance between epicardial surface and trough of the trabecular recesses (compacted layer of LV)</td>
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<tr>
<td></td>
<td></td>
<td>Y=distance between epicardial surface and peak of trabeculation (total thickness of LV)</td>
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<tr>
<td></td>
<td></td>
<td>B. Two layered structure of myocardium comprising of compacted layer and non-compacted layer</td>
</tr>
<tr>
<td>Jenni et al</td>
<td>Echocardiography</td>
<td>A. Absence of coexisting cardiovascular abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B. Maximum end-systolic ratio of NC to C layers is &gt;2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C. Predominant localisation of abnormalities in mid-lateral, apical and mid-inferior areas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D. Colour Doppler evidence of deeply perfused intertrabecular recesses</td>
</tr>
<tr>
<td>Stollberger et al</td>
<td>Echocardiography</td>
<td>A. &gt;3 Trabeculations arising from LV wall, apically to papillary muscles and visible in one echocardiographic image plane at end-diastole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B. Trabeculations form the NC part of a two-layered myocardial structure, best visible at end-systole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C. Intertrabecular spaces perfused from the ventricular cavity, as visualised with the colour Doppler echocardiography</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D. Trabeculations move synchronously with C myocardium</td>
</tr>
<tr>
<td>Petersen et al</td>
<td>MRI</td>
<td>Ratio of NC/C layer &gt;2.3 (when measured in end-diastole)</td>
</tr>
<tr>
<td>Belanger et al</td>
<td>Echocardiography</td>
<td>Classified as none, mild, moderate and severe based on:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A. NC/C ratio</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B. LVNC area</td>
</tr>
<tr>
<td>Jacquier et al</td>
<td>MRI</td>
<td>LV trabeculated area &gt;20% of global LV mass (when measured in end-diastole)</td>
</tr>
<tr>
<td>Paterick et al</td>
<td>Echocardiography</td>
<td>A. Evaluation of the trabeculations’ sizes (NC myocardium) to C wall thicknesses in multiple imaging windows and at different ventricular levels throughout the cardiac cycle</td>
</tr>
<tr>
<td>Melendez-Ramirez et al</td>
<td>CT scan</td>
<td>NCC ratio ≥2.2 in ≥2 myocardial segments</td>
</tr>
</tbody>
</table>

* = criteria refined since 2002.
† = multidetector CT.
C, compacted; LV, left ventricle; NC, non-compacted; NC/C, ratio of the thickness of the non-compacted layer of myocardium to the compacted layer of myocardium in the LV; NCCM, non-compaction cardiomyopathy.
of NCCM in athletes or in participants presenting with exercise-related symptoms.

A compilation of five studies including 241 cases of NCCM suggest that NCCM usually presents in the fifth decade of life (mean age 41 years), that males predominate (65%) and that the most common presenting symptom observed in 60% of these cases is dyspnoea on exertion. In contrast, the mean age of presentation in our small series was only 29 years, but this may be because of the fact that younger individuals are more likely to be physically active and thus included in our review. We cannot exclude the possibility that physically active individuals with NCCM present at a younger age because exercise produces the symptoms. We did observe male predominance but the most frequent presenting symptom in our series was exercise-related syncope. We cannot generalise about symptoms in physically active participants, however, because of the small number of cases included in our collected series. Our results do suggest that NCCM needs to be considered in the differential for exertion-related syncope.

The mechanism of exercise-induced syncope in NCCM is unclear. NCCM patients have coronary microcirculatory dysfunction which can reduce contractility, produce ischaemia and result in subendocardial scar that could function as an arrhythmogenic substrate. Fibrosis is also commonly observed in these patients. Ischaemia-induced arrhythmias could arise from reduced perfusion of the trabeculations since they are more distant than normal from the epicardial coronary blood supply. In addition, NCCM can be associated with developmental arrest of the conduction system.

It is likely that syncope and SCD are produced by similar mechanisms in NCCM patients. SCD occurred in 7.6% of 241 NCCM cases who were followed for a mean duration of 39 months. In this study, reduced left ventricular ejection fraction (LVEF) was associated with increased mortality in NCCM suggesting that athletes with normal LV function are at reduced risk compared with athletes with reduced LV function. A smaller series of 34 NCCM cases followed for mean of 44 months observed that 18% died suddenly. No study included only asymptomatic individuals so it is unclear if this high risk of SCD applies to asymptomatic athletes.

Data on LVEF were available in 14 of 18 cases and 8 of these 14 (57%) cases had a LVEF less than 50% whereas another series found that 84% of the 105 NCCM cases had LVEF less than 50%. The difference is probably because of the fact that we collected only physically active individuals without evidence of heart failure whereas 68% of non-athletic NCCM cases presented with heart failure.

Four patients in our series presented with thrombotic events probably related to thrombus formation in myocardial trabeculae. One of these four presented with pulmonary embolic although the relationship of this condition to NCCM is unclear. There are sparse data on the use of anticoagulation in NCCM, which must be decided on an individual case-by-case basis.

Cases collected for the current review probably overestimate the cardiovascular problems associated with NCCM since cases with adverse outcomes are more likely to be reported than asymptomatic individuals with NCCM. We are unable to evaluate the type of exercise practiced by eight of the cases. Data on race was available only in three case reports. Ethnic variations may influence the differences in clinical symptoms, outcomes and prevalence in populations since our review includes case reports from nine different countries spread over three continents and since LV trabeculation varies with race.

Hypertrabeculation was noted in 7% of male athletes compared with 0.93% of female athletes (p<0.015), although none of these athletes fulfilled the criteria for NCCM. Specifically healthy athletes of African descent have a greater degree of LV trabeculation and this should be considered to avoid...
<table>
<thead>
<tr>
<th>Study/year</th>
<th>Country</th>
<th>Language</th>
<th>Age/gender</th>
<th>Activity (sports/exercise)</th>
<th>Clinical presentation</th>
<th>Family history of SCD</th>
<th>ECG findings</th>
<th>Diagnostic imaging</th>
<th>EF</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacob and Wang (2012)</td>
<td>USA</td>
<td>English</td>
<td>17/M</td>
<td>Wrestling</td>
<td>Bradycardia and recurrent exertional syncope, presyncope</td>
<td>Yes</td>
<td>Sinus bradycardia</td>
<td>2D-echo and cardiac MRI</td>
<td>60%</td>
<td>β-blocker, ICD, dual-chamber pacemaker, no intramural sports and low-impact activity regimen (golf)</td>
</tr>
<tr>
<td>Guvenc et al (2011)</td>
<td>Turkey</td>
<td>English</td>
<td>52/F</td>
<td>Exercise</td>
<td>Chest pain, palpitations and exercise-induced RVOT</td>
<td>No</td>
<td>RVOT on exercise ECG</td>
<td>2D-echo and cardiac MRI</td>
<td>45%</td>
<td>β-blocker and no indication for ICD</td>
</tr>
<tr>
<td>Aquieri et al (2011)</td>
<td>Spain</td>
<td>Spanish</td>
<td>33/M</td>
<td>Football</td>
<td>Unconscious after blow to chest in game</td>
<td>No</td>
<td>Ventricular flutter</td>
<td>2D-echo and cardiac MRI</td>
<td>67%</td>
<td>ICD, β-blocker and limited physical activity</td>
</tr>
<tr>
<td>Seethala et al (2011)</td>
<td>USA</td>
<td>English</td>
<td>63/F</td>
<td>Exercise, treadmill</td>
<td>Exercise intolerance</td>
<td>Yes</td>
<td>VT on exercise testing, LVH and PAC</td>
<td>2D-echo and cardiac MRI</td>
<td>55%</td>
<td>β-blocker and declined ICD</td>
</tr>
<tr>
<td>Kocharian et al (2010)</td>
<td>Iran</td>
<td>English</td>
<td>9/M</td>
<td>Running</td>
<td>Syncope, sudden death after running</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Expired</td>
</tr>
<tr>
<td>Kocharian et al (2010)</td>
<td>Iran</td>
<td>English</td>
<td>16/F</td>
<td>Exercise</td>
<td>Syncope, sudden death after running</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Expired</td>
</tr>
<tr>
<td>Ho et al (2010)</td>
<td>USA</td>
<td>English</td>
<td>14/M</td>
<td>Running</td>
<td>Palpitations, hemiparesis and cardiac arrest</td>
<td>N/A</td>
<td>Sinus rhythm with WPW syndrome</td>
<td>2D-echo and cardiac MRI</td>
<td>Normal</td>
<td>Successful ablation of accessory pathway, ICD and anticoagulation</td>
</tr>
<tr>
<td>Vathyan et al (2009)</td>
<td>USA</td>
<td>English</td>
<td>19/M</td>
<td>High school athlete*</td>
<td>Haemoptysis during scuba diving and chest pain</td>
<td>Yes</td>
<td>Sinus tachycardia and LVH</td>
<td>2D-echo and cardiac MRI</td>
<td>16%</td>
<td>ICD, anticoagulation, β-blocker and ACE inhibitor</td>
</tr>
<tr>
<td>Alqhtani (2009)</td>
<td>Canada</td>
<td>English</td>
<td>22/M</td>
<td>Scuba diving and hockey</td>
<td>Dyspnoea and syncpe</td>
<td>N/A</td>
<td>Left axis deviation and ST elevation in leads V1–V3</td>
<td>2D-echo and cardiac MRI</td>
<td>49%</td>
<td>Monitoring every 3 months with ECG, echo and CXR</td>
</tr>
<tr>
<td>Iwashima et al (2008)</td>
<td>Japan</td>
<td>English</td>
<td>12/M</td>
<td>Running</td>
<td>Exercise intolerance</td>
<td>No</td>
<td>Intraventricular conduction delay</td>
<td>2D-echo and TEE</td>
<td>63%</td>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>Cavusoglu (2008)</td>
<td>Turkey</td>
<td>English</td>
<td>19/M</td>
<td>Exercise</td>
<td>Palpitations, hemiparesis, and chest pain</td>
<td>N/A</td>
<td>Sinus rhythm with WPW syndrome</td>
<td>2D-echo and cardiac MRI</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Wozniak et al (2008)</td>
<td>N/A</td>
<td>English</td>
<td>50/M</td>
<td>Long distance runner</td>
<td>Chest discomfort at rest and exertion intolerance</td>
<td>Yes</td>
<td>Normal</td>
<td>N/A</td>
<td>N/A</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>Carejo et al (2004)</td>
<td>Italy</td>
<td>English</td>
<td>25/M</td>
<td>Football</td>
<td>Palpitations during exercise</td>
<td>N/A</td>
<td>Resting and effort ECG were normal</td>
<td>2D-echo</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Weiford et al (2004)</td>
<td>USA</td>
<td>English</td>
<td>42/F</td>
<td>Exercise</td>
<td>Chest discomfort, palpitations and exercise intolerance</td>
<td>No</td>
<td>Criteria for LVH and ECG event recorder showed episodes of atrial fibrillation</td>
<td>2D-echo</td>
<td>20%</td>
<td>Anticoagulation, ACE inhibitor, β-blocker and advised to avoid pregnancy</td>
</tr>
<tr>
<td>Antoniades (2003)</td>
<td>Cyprus</td>
<td>English</td>
<td>19/M</td>
<td>Exercise and climbing</td>
<td>TIA while doing exercise</td>
<td>Yes</td>
<td>Normal EG and no ECG changes on exercise test or ambulatory ECG recordings</td>
<td>2D-echo and MTE</td>
<td>45%</td>
<td>Anticoagulation, ACE inhibitor and β-blocker</td>
</tr>
<tr>
<td>Bax et al (2002)</td>
<td>Netherlands</td>
<td>English</td>
<td>37/M</td>
<td>Exercise</td>
<td>Syncope and acute occlusion of ciliary arteries</td>
<td>Yes</td>
<td>LVH, PVCs on Holter and NSVT</td>
<td>2D-echo and cardiac MRI</td>
<td>55%</td>
<td>Anticoagulation, ACE inhibitor, β-blockers and statins. ICD was pending. EP study was pending</td>
</tr>
</tbody>
</table>

*Symptoms not during athletic activity.

EF, ejection fraction; ICD, implantable cardioverter-defibrillator; LVH, left ventricular hypertrophy; MTE, multiplanar transesophageal echocardiography; NSVT, non-sustained ventricular tachycardia; PAC, premature atrial tachycardia; PVC, premature ventricular complexes; RVOT, right ventricular outflow tract tachycardia; SCD, sudden cardiac death; TEE, transesophageal echocardiogram; WPW, Wolff Parkinson White Syndrome; 2D-echo, two-dimensional echocardiogram.
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overdiagnosis of NCCM.\textsuperscript{41} This increase in trabeculations could also be further exaggerated by the cardiac adaptations produced by exercise training.

**CONCLUSIONS AND CLINICAL IMPLICATIONS**

The major limitation of this review is the small number (n=18) of reported cases. This means that our review and the available medical literature is insufficient to provide firm guidance on how active patients with NCCM should be managed. Consequently, advice regarding physical activity should be provided on an individual case basis considering such factors as whether or not the athlete is symptomatic especially with exercise, the importance of athletics to the athlete, the degree of myocardial dysfunction and the extent of myocardial trabeculations.

It is of concern, however, that 17% of the physically active NCCM cases we identified presented with SCD on exertion and that 50% presented with exercise syncope. We are always restrict with athletes in general when their condition is associated with symptoms during exercise. Five patients\textsuperscript{28}–\textsuperscript{30} in our series underwent exercise testing. PVCs and sustained VTs were seen in two patients\textsuperscript{29}–\textsuperscript{30} and one case\textsuperscript{20} had PVCs. It is prudent that all athletes or active individuals with NCCM should undergo exercise testing that mimics as closely as possible the cardiovascular demands of their sport activity. This testing should be performed prior to considering allowing them to exercise vigorously so that arrhythmias and exercise-induced hypotension can be excluded. Ambulatory ECG monitoring may also be useful to detect cardiac arrhythmias that would prohibit exercise participation families and the athlete should also clearly understand the risk attendant continued athletic competition. More conclusive recommendations on how to manage asymptomatic athletes with this condition must await more knowledge on NCCM in general. Nevertheless, the high rates of SCD reported in the literature to date do suggest that clinicians should provide conservative advice to athletes until more concrete advice is possible.

**What this study adds**

- There appears to be a high rate of sudden cardiac death in physically active individuals with non-compaction cardiomyopathy (NCCM).
- Physically active individuals diagnosed with NCCM should undergo exercise testing prior to participation in sports.
- Clinicians should provide conservative advice to physically active individuals with NCCM until more concrete evidence is available.

**Contributors**

HG and PT made contributions substantially to the concept and design of the study, analysis and interpretation of the data and drafting and revising the manuscript critically for intellectually important content. HG was involved in the acquisition of the data.

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**Competing interests**

None.

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**REFERENCES**


