Canadian Journal of Cardiology ■ (2016) 1–7

Clinical Research

Detecting Underlying Cardiovascular Disease in Young Competitive Athletes

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ABSTRACT

Background: Sudden cardiac death (SCD) is frequently the first manifestation of underlying cardiovascular disease in young competitive athletes (YCAs), yet there are no Canadian guidelines for preparticipation screening in this population. The goal of this study was to determine the prevalence of potentially lethal cardiovascular disease in a sample of Canadian YCAs by comparing 2 screening strategies.

Methods: We prospectively screened 1419 YCAs in British Columbia, Canada (age 12-35 years). We initially screened 714 YCAs using the American Heart Association 12-element recommendations, physical examination, and electrocardiogram (ECG) examination (phase 1). This strategy yielded a high number of false positive results; 705 YCAs were subsequently screened using a novel SportsCardiologyBC (SCBC) questionnaire and ECG examination in the absence of a physical examination (phase 2).

Results: Overall, 7 YCAs (0.52%) were found to have clinically significant diagnoses associated with SCD (4 pre-excitation, 1 long QT syndrome, 1 mitral valve prolapse, 1 hypertrophic cardiomyopathy). Six of

RÉSUMÉ

Introduction : La mort cardiaque subite (MCS) est souvent la première manifestation d'une maladie cardiovasculaire (MCV) sous-jacente chez les jeunes athlètes de compétition. Pourtant, il n'existe pas de lignes directrices canadiennes prônant un dépistage dans le cadre d'un examen de pré-participation chez cette population. Cette étude avait pour objectif de déterminer la prévalence d'une MCV potentiellement mortelle chez un échantillon de jeunes athlètes canadiens de compétition, en fonction de deux stratégies de dépistage.

Méthodes : Un dépistage prospectif a été effectué chez 1419 jeunes athlètes de compétition (de 12 à 35 ans) de Colombie-Britannique (Canada). De ce nombre, 714 se sont soumis à un premier dépistage fondé sur une anamnèse en 12 points recommandée par l'American Heart Association, un examen physique et un électrocardiogramme (ECG) (phase 1). Cette stratégie a donné lieu à un nombre élevé de faux positifs. Le dépistage chez les 705 autres athlètes a ensuite été réalisé au moyen d'un nouveau questionnaire proposé par SportsCardiologyBC (SCBC) et d'un ECG, sans examen

Sudden cardiac death (SCD) is the leading medical cause of death in athletes.[1] Sporting activity might predispose athletes with underlying cardiovascular conditions to develop life-threatening ventricular arrhythmias during physical exercise.[2] The American Heart Association (AHA) estimates the prevalence of an underlying cardiovascular disorder in young athletes that predisposes to SCD as 0.3%.[3]

SCD is often the first clinical manifestation of an underlying cardiovascular condition; up to 80% of athletes are previously asymptomatic.[2,4] Preparticipation screening (PPS) is the systematic practice of medically evaluating athletes for the purpose of identifying (or raising suspicion of) abnormalities that could provoke disease progression or sudden death.[3]

There is agreement among most international medical and sporting bodies that athletes should undergo some form of PPS. Presently, there are no formal Canadian PPS guidelines for young competitive athletes (YCAs).[5] The purpose of this prospective study was to: (1) ascertain the prevalence of conditions that can lead to SCD in a sample of Canadian YCAs; (2) assess the effectiveness of a revised questionnaire and screening approach on the positive predictive value (PPV)

Received for publication March 18, 2016. Accepted June 3, 2016.

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See page 6 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2016.06.007

the 7 athletes (85.7%) with disease possessed an abnormal ECG. Conversely, only 2 had a positive personal or family history (1 athlete had an abnormal ECG and family history). The SCBC questionnaire and protocol (phase 2) was associated with fewer false positive screens; 3.7% (25 of 679) compared with 8.1% (55 of 680) in phase 1 ($P = 0.0012$).

Conclusions: The prevalence of conditions associated with SCD in a cohort of Canadian YCAs was comparable with American and European populations. The SCBC questionnaire and protocol were associated with fewer false positive screens. The ECG identified most of the positive cases irrespective of screening strategy used.

Résultats : Un diagnostic d'importance clinique associé à la MCS a été posé chez 7 (0,52 %) jeunes athlètes de compétition (syndrome de préexcitation [4]; syndrome du QT long [1]; prolapsus de la valve mitrale [1]; et cardiomyopathie hypertrophique [1]). De ces 7 athlètes, 6 (85,7 %) ont obtenu un résultat anormal à l'électrocardiographie. Inversement, seulement 2 athlètes avaient des antécédents personnels ou familiaux (1 athlète cumulait un ECG anormal et des antécédents familiaux). Le pourcentage de faux positifs associé au protocole de la phase 2, qui misait notamment sur le questionnaire de SCBC, a été moins élevé : 3,7 % (25 sur 679) comparativement à 8,1 % (55 sur 680) dans le cadre de la phase 1 ($P = 0,0012$).

Conclusions : La prévalence des troubles associés à la MCS au sein d'une cohorte de jeunes athlètes canadiens de compétition était comparable à celle observée au sein de populations américaines et européennes. Les faux positifs associés au questionnaire de SCBC et au protocole de la phase 2 ont été moins nombreux. L'électrocardiographie a permis de repérer la plupart des cas positifs, peu importe la stratégie de dépistage employée.

of finding true disease; and (3) to assess the role of the electrocardiogram (ECG) in PPS in this population.

Methods

Design

This prospective observational cohort screening study was performed in the province of British Columbia, Canada from November 18, 2013 to October 15, 2015. The University of British Columbia Research Ethics Board approved this study (H13-01698). Participants aged 12 to 35 years who fulfilled a previously established definition of an 'athlete' were eligible for the study.[3] Athletes with previously diagnosed cardiovascular disease, missing documentation, or those who were lost to follow-up were excluded from analysis.

Protocols

There were 2 phases in this study (Fig. 1), representing 2 specific strategies for YCA screening.

Phase 1: modified 12-element AHA protocol with ECG. In phase 1, 714 participants were screened using modified AHA 12-element recommendations, a physical examination, and a resting 12-lead ECG. In addition to the 12-element 2007 AHA recommendations, 2 questions regarding the presence of palpitations and previous cardiac investigations were added.[3] These questions were subsequently introduced in the revised 14-element AHA recommendations released in 2014 during the course of the study, and are recommended in the 2015 guidelines.[6,7] Physicians who performed the physical examination included cardiologists, cardiology fellows, and internal medicine residents. Patients with abnormal physical examination findings as per AHA 12-item recommendations were referred for subsequent evaluation.[3] After screening the initial 714 athletes in 'phase 1,' investigators reviewed the proportion of patients who were found to have no evidence of disease during follow-up assessments with a cardiologist (8.1%). A second phase of screening was implemented with a goal to reduce false positive results (phase 2).

Phase 2: development of a novel screening questionnaire and protocol. To improve the PPV of the screening process, a second strategy that included a revised questionnaire and elimination of the physical examination and on-site physician was created. A literature search was conducted to find evidence-based questions that differentiated neurally-mediated syncope from cardiogenic syncope, and benign from pathological causes of chest pain and dyspnea[8-13] (Supplemental Table S1). The SportsCardiologyBC (SCBC) questionnaire and its development are described in Supplemental Table S2. To better delineate an athlete's symptoms as either concerning or benign more specific evidence-based follow-up questions were added. The SCBC questionnaire was designed with the intent of being administered by nonphysicians, and was piloted on 97 YCAs (Supplemental Fig. S1). On the basis of athlete responses and expert review, slight modifications were made to the questionnaire to further improve specificity and increase user readability. Rationale for final revisions, pilot cohort characteristics, and results are summarized in Supplemental Tables S3-S5. Because of minor differences in the questionnaires, the pilot cohort was not included in the primary analysis.

The SCBC protocol. The physical examination was eliminated from phase 2 of the study because abnormalities on physical examination were found to only result in false positive results. The novel SCBC questionnaire in combination with the resting 12-lead ECG comprised the SCBC protocol (phase 2), and was implemented in 705 YCAs.

Athlete evaluation

All ECG results were interpreted using the Seattle Criteria by cardiologists with expertise in athlete ECG interpretation (S.I., B.H.).[14] ECG results were read off-site using Cardioserver software and portable Mortara Instrument ECG machines (version 4.1.1; Milwaukee, WI).[15] The interpreting

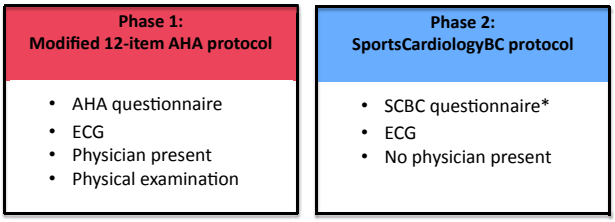

Figure 1. Protocols used to screen young Canadian young competitive athletes. *The SportsCardiologyBC (SCBC) questionnaire (Supplemental Table S2) was developed with evidence-based questions to improve the specificity of the screening questionnaire. The follow-up questions were added to better delineate athlete's symptoms as either concerning or benign. Additionally, the questionnaire was designed so that it could be administered independent of a physician's review of the athlete's responses. AHA, American Heart Association; ECG, electrocardiogram.

cardiologist was not aware of the findings on the history or physical examination. Only the age and sex of the athlete were made available at the time of ECG interpretation. Positive findings from the questionnaire, physical examination, or ECG led to further cardiologist evaluation. A handheld echocardiogram with colour Doppler (GE V-Scan[16]) was performed by a level 2 trained cardiologist on all athletes who required follow-up; borderline results were referred for formal echocardiography. Additional investigations ordered were at the discretion of the cardiologist. Screening was conducted at no cost to the athlete.

Cost analysis

A limited cost analysis was performed on the basis of the 2016 British Columbia Medical Services Plan fee schedule.[17] All costs were considered direct medical costs and expressed in 2016 Canadian dollars. Screening and follow-up costs were calculated. A breakdown of the costs is shown in Supplemental Tables S6 and S7.

Statistical analysis

The authors had full access to the data and take full responsibility for its integrity. Statistical analysis was conducted using SPSS Statistics version 20 (IBM Corp, Armonk, NY). Descriptive results were presented as absolute numbers and percentages. A Fisher exact test was used to assess the significance of differences between groups. PPV, defined as (true positive results/[true positive + false positive results]).

Results

A total of 1419 consecutive YCAs were screened. Ninety-six percent (n = 1359) of the athletes screened were eligible for the study (Fig. 2). Study participants were predominantly young men (Supplemental Table S8). In phase 1, 714 athletes were screened with 34 YCAs excluded. Fifty-seven (8.4%) of the 680 YCAs required follow-up with a cardiologist: 37 (64.9%) because of a positive personal history, 8 (14.0%) because of a concerning family history, 9 (15.8%) because of an abnormal physical examination, and 14 (24.6%) had an abnormal ECG result (Table 1). In phase 1, 30 of 57 (52.6%) athletes had multiple indications for follow-up.

In phase 2 of the study, after implementation of the revised screening questionnaire and elimination of the physical examination (SCBC protocol), 705 YCAs were tested with 26 athletes excluded. Of the 679 YCAs that were included in analysis, 30 (4.4%) required follow-up with a cardiologist. Twenty-four of the 30 athletes (80.0%) were referred for consultation and further evaluation because of abnormal results on the SCBC questionnaire. Seven of the athletes (23.3%) referred for further cardiovascular evaluation had an abnormal ECG as the reason for consultation. Only a single athlete had an abnormal ECG and abnormal results on the SCBC questionnaire. The indications for follow-up for the 2 protocols are summarized in Table 1. Phase 1 of the screening (AHA recommendations, physical examination, and ECG) resulted in follow-up in 8.4% of the athletes, whereas phase 2 of the screening (SCBC questionnaire and ECG with no physical examination) resulted in follow-ups in 4.4% of the athletes ($P = 0.0037$).

The prevalence of clinically significant cardiovascular disease in this sample of Canadian YCAs was 0.52% (see Table 2 for specific diagnoses). The ECG was the single most effective screening tool, with a PPV of 28.6% (7.1% in phase 1, 71.4% in phase 2) compared with the AHA questionnaire (4.1%) and physical examination (0%) in phase 1, and the SCBC questionnaire (0%) in phase 2 (Supplemental Table S9). The SCBC protocol, with a revised questionnaire and elimination of the physical examination, was more effective with a PPV of 16.7% vs a PPV of 3.5% in phase 1. The SCBC protocol reduced the proportion of false positive results from 8.1% to 3.7% ($P = 0.0012$).

The cost to screen a single athlete (not including follow-up costs) in phase 1 (AHA questionnaire, physical examination, and ECG) would be $14.42 if physician services were not reimbursed. If physician fees were accounted for, the cost to screen a single athlete would be $97.50 (Supplemental Table S7). In phase 2 (SCBC questionnaire and ECG with no physical examination and no physician) the cost to screen 1 athlete would be $14.42. In phase 1, the cost per diagnosis (screening plus follow-up costs) was $41,320.49 and $13,073.29 with and without physician reimbursement, respectively. Conversely, the cost per diagnosis for the SCBC protocol (phase 2) was $3,822.70.

Discussion

We sought to ascertain the prevalence of cardiac conditions associated with SCD in a sample of Canadian YCAs, and compare 2 protocols that used the resting 12-lead ECG as a part of PPS. The prevalence of clinically significant cardiac conditions in this sample of Canadian YCAs is in accordance with previous studies.[2] A reduction in false positive results occurred in phase 2 (SCBC protocol) compared with phase 1, resulting in a higher PPV for the SCBC protocol (phase 2). It must be noted that this improved PPV was influenced by the detection of ventricular pre-excitation (4 cases) and long QT (1 case) in phase 2 that were not seen in phase 1. The modified AHA questionnaire used in phase 1 produced twice as many false positive results compared with the SCBC questionnaire (47 vs 24). The physical examination component contributed to the higher number of false positive results in phase 1, but to a much lesser degree than the number of

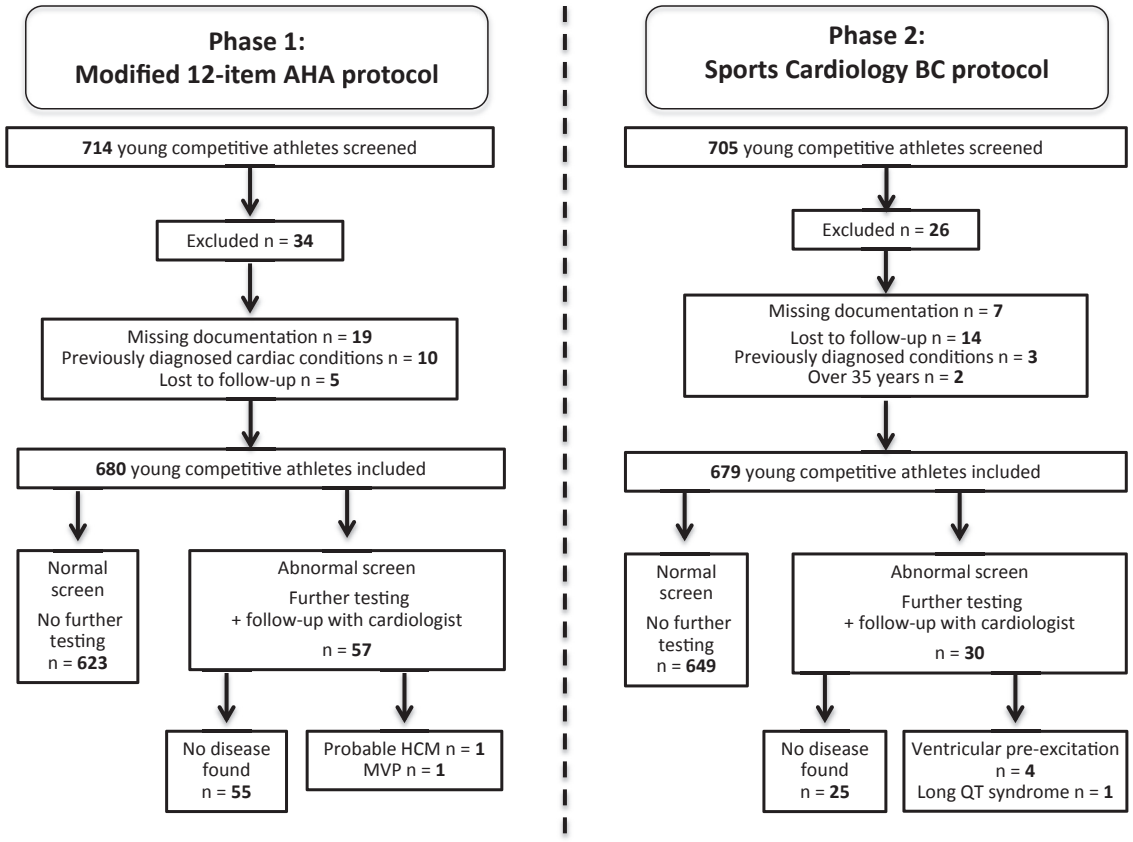

Figure 2. Young competitive athlete flow diagram. AHA, American Heart Association; HCM, hypertrophic cardiomyopathy; MVP, mitral valve prolapse.

false positive results generated by the history section of the modified AHA recommendations.

The reduction in false positive results observed is most likely attributable to the SCBC questionnaire. In isolation, the AHA and SCBC questionnaires identified 1 and 0 cases, respectively. It must be noted that the positive cases identified using the AHA questionnaire in isolation (mitral valve prolapse) and with ECG (probable hypertrophic cardiomyopathy [HCM]) would likely have been detected using the SCBC questionnaire because the participants reported multiple symptoms (syncope, palpitations, chest pain) and family history, respectively. The ECG for the entire cohort (in isolation) exhibited a superior PPV (28.6%) compared with either phase 1 (3.5%) or the SCBC protocol (16.7%).

Most YCAs who experience SCD are asymptomatic; therefore any questionnaire will have a limited sensitivity. Nonetheless, we believe athletes should be able to detail their personal and family history to raise suspicion of a potential underlying problem. Conditions associated with SCD in the YCA such as catecholaminergic polymorphic ventricular tachycardia, concealed long QT syndrome, coronary artery anomalies, coronary artery disease, and myocarditis might not be identified on a resting ECG examination but might manifest as vitally important symptoms warranting further evaluation. The value of the SCBC questionnaire is not in its power to identify cases with a greater ability than that of the AHA questionnaire but rather to decrease the number of false positive results. A reasonable degree of sensitivity to detect underlying disease is facilitated by the inclusion of the ECG.

The physical examination has limited power to detect causes of SCD such as coronary artery disease, coronary artery anomalies, ion channelopathies, accessory pathways, myocarditis, arrhythmogenic right ventricular cardiomyopathy, and dilated cardiomyopathy. Moreover, the physical examination exhibits modest sensitivity at detecting HCM; a pathologic systolic murmur can only be heard in approximately 25% of athletes with HCM.[18] However, the ECG is a more sensitive tool at identifying HCM with $>$ 90% of athletes with HCM who have an abnormal ECG examination.[18] The sensitivity of the ECG to raise suspicion of conditions associated with SCD in athletes is 10-fold greater than physical examination.[19]

The ECG (interpreted using the Seattle Criteria[14]), was effective at identifying clinically relevant subclinical conditions that were not detected in the history or physical examination. In our study, the ECG identified 85.7% (6 of 7) of our disease cases, whereas only 28.6% (2 of 7) would have been detected using history and physical examination (1 athlete had an abnormal ECG examination and family history). A meta-analysis of 15 screening studies showed that the combined average sensitivity to identify athletes with pathological conditions using history and physical examination was 20% and 9%, respectively. The ECG however, exhibited a sensitivity of 94%. Moreover, the positive likelihood ratio of the ECG was 14.8 compared with 3.2 and 2.9 for history and physical examination, respectively.[19] This improved sensitivity is because of the

Table 1. Indications for follow-up cardiovascular evaluation

Indicator	n	Finding resulting in diagnosis of true disease, PPV, %
Phase 1 (n = 680): modified AHA questionnaire	49*	4.1
Exertional chest pain	19	5.3
Palpitations with exercise	18	5.6
Exertional syncope/presyncope	16	6.3
Exertional dyspnea	15	0
Family history of heart conditions	7	14.3
Family history of sudden death	1	0
Phase 1: physical examination	9	0
Systolic murmur (≥ 3/6)	3	0
Features of Marfan syndrome	3	0
Diastolic murmur	1	0
Systolic click	1	0
Abnormal second heart sound	1	0
Phase 1: resting 12-lead ECG	14	7.1
T-wave inversion	4	25
Prolonged QT interval	2	0
Premature ventricular contractions	2	0
RVH and RAD	2	0
Biatrial abnormality	1	0
Left atrial enlargement, LAFB, RBBB	1	0
Left bundle branch block	1	0
Intraventricular conduction delay	1	0
Phase 2 (n = 679): SCBC questionnaire	24	0
Cardiovascular risk score ≥ 7	22	0
Family history of specified condition	1	0
Family history of sudden death	1	0
Phase 2: resting 12-lead ECG	7	71.4
Ventricular pre-excitation, WPW	4	100
Prolonged QT interval	3	33.3
Full cohort (n = 1359): resting 12-lead ECG	21	28.6

AHA, American Heart Association; ECG, electrocardiogram; LAFB, left anterior fascicular block; PPV, positive predictive value; RAD, right axis deviation; RBBB, right bundle branch block; RVH, right ventricular hypertrophy; SCBC, SportsCardiologyBC; WPW, Wolff-Parkinson-White.

*Multiple athletes had >1 indications for follow-up.

ability of the ECG to detect primary cardiomyopathies (HCM, arrhythmogenic right ventricular cardiomyopathy, and dilated cardiomyopathy) and potentially life-threatening electrical disorders such as Wolff-Parkinson-White syndrome, long QT syndrome, and Brugada syndrome.[20] The specificity for the interpretation of the athlete's ECG continues to improve with maintained sensitivity because of continual refinement of ECG interpretation criteria.[21] The current study provides further evidence to support the use of the ECG as an important tool in the screening of YCAs.

How to best screen YCAs has been extensively debated.[20,22] Nonetheless, some form of PPS (with or without an ECG) is recommended in the United States and mandated systematically in Italy, Japan, and Israel.[6] An Achilles' heel of PPS has long been the unacceptably high false positive rate and the costs associated with screening large numbers of athletes.[6] We sought to decrease the number of false positive screens by constructing a more specific questionnaire, and removing the physical examination component from the screening process. In phase 1 of the study, none of the 680 YCAs were found to have cardiac conditions associated with SCD on the basis of abnormal physical examination findings alone. The low yield of the physical examination to identify true pathology was in concordance with previous studies.[19]

Canada's universal health care plan covers physician costs, and as such, if screening in this population were to be implemented at a societal level, the presence of a physician would certainly be accompanied by concerns of cost-effectiveness and stewardship. The research team wanted to investigate a screening protocol that would be feasible in a publicly funded health care system. Investing more time in the history via a more specific questionnaire and abandoning the physical examination and on-site physician while keeping the ECG as a central part of the PPS process would potentially allow us to achieve this. Using this strategy, the SCBC protocol cost (CAD$14.42, not including follow-up costs) to screen a single athlete is lower than that reported in Italy and the United Kingdom (approximately CAD$72; €50 and £39, respectively).[23,24] To adequately ascertain if screening in this population would potentially reduce publicly funded health care costs, a cost-effectiveness analysis should be conducted.

If widespread PPS is to be adopted within Canada, the SCBC protocol is a potentially viable option. In our population of Canadian YCAs the 12-element AHA recommendations produced a significant number of false positive results from the personal history questionnaire and physical examination. Compared with history and physical examination, the ECG provided a superior ability to detect conditions associated with SCD in YCAs. We recognize that the PPS of YCAs is an area that is evolving. The findings herein might help create dialogue and serve as a basis for discussions and position statements or guidelines within Canada. Strengths of our

Table 2. Cardiovascular diagnoses associated with sudden cardiac death in our population

Age, years	Sex	Ethnicity	Indication(s) for screening	Further investigations	Cardiovascular condition
Phase 1: modified AHA questionnaire, resting 12-lead ECG, physical examination (n = 714)					
16	F	Caucasian	Reported syncope, chest pain, palpitations	ETT, Holter, ECHO	Mitral valve prolapse
16	M	Caucasian	Abnormal ECG, family history of bicuspid aortic valve (father)	ETT, Holter, ECHO, MRI, genetic testing	Probable hypertrophic cardiomyopathy
Phase 2: SCBC protocol; SCBC questionnaire, resting 12-lead ECG (n = 705)					
19	F	Caucasian	Abnormal ECG	ETT	WPW
20	F	Caucasian	Abnormal ECG	ETT	WPW
13	F	Caucasian	Abnormal ECG	ETT	WPW
13	F	Caucasian	Abnormal ECG	ETT, Holter	WPW
29	F	Caucasian	Abnormal ECG	ETT, Holter, genetic testing	Long QT syndrome

AHA, American Heart Association; ECG, electrocardiogram; ECHO, echocardiogram; ETT, exercise treadmill test; F, female; M, male; MRI, magnetic resonance imaging; SCBC, SportsCardiologyBC; WPW, Wolff-Parkinson-White.

protocol include: (1) a novel questionnaire that produces fewer false positive screens; (2) a protocol that can detect conditions associated with SCD in YCAs (primarily via ECG) while reducing false positive results; and (3) a protocol that does not rely on an on-site physician, thereby having the potential to improve applicability, accessibility, and potentially reduce health care costs.

Limitations

Similar to previous contemporary PPS studies, all participants did not undergo secondary testing such as echocardiography or exercise stress testing to further define athletes with true negative results. In a meta-analysis of 15 PPS studies, only 4 studies used some form of echocardiography (full or limited study) in all athletes during the screening process.[19] Our justification for not performing echocardiography on all of our volunteer athletes is on the basis of: (1) previous studies showing no incremental value in the addition of echocardiography to the PPS process;[25,26] and (2) the costs and participant burden to undergo secondary testing. However, we do recognize our SCBC questionnaire and ECG in isolation (removal of the physical examination and physician review) might have potentially eliminated athletes from subsequent follow-up who had unrecognized disease. Although the physical examination has limited ability to detect disease, we might have potentially missed rare causes of SCD such as Marfan syndrome, coarctation of the aorta, and severe valvular heart disease.[19]

Our intention was to screen athletes in an unselected manner. Although the 2 cohorts were intended to be similar, small unmeasurable differences (including temporal) might have contributed to the difference in diagnosed conditions associated with SCD between the 2 cohorts beyond chance alone. Additionally, despite a reasonable number of athletes screened, our study might still be underpowered to identify some conditions that are associated with SCD in the athlete, thus limiting our ability to generalize the applicability of our protocol. The SCBC questionnaire and protocol holds promise but warrants validation and further study.

Conclusions

The prevalence of potentially lethal cardiac conditions among our sample of Canadian YCAs was consistent with previous studies. Our novel, evidence-based questionnaire, in conjunction with elimination of the physical examination reduced the absolute number of false positive screens and increased the feasibility of expanding this strategy across a larger population. The incorporation of the ECG to the screening process increased the ability to detect subclinical disease that would have not otherwise been detected with history and physical examination, providing further support for the incorporation of the ECG into systematic PPS. The SCBC questionnaire in combination with an ECG is a promising, efficient, and feasible means of screening YCAs.

Acknowledgements

The authors thank Drs Anthony Della Siega, Kevin Pistawka, Shubhayan Sanatani, and the BC Inherited Arrhythmia Clinic for their help in athlete evaluation.

Funding Sources

This research was funded by the Vancouver General Hospital and University of British Columbia Hospital Foundation.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2016.06.007.