

VIEWPOINTS

We Have Plenty of Reasons to Propose New, Updated Policies for Preventing Sudden Cardiac Death in Young Athletes

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“The world as we have created it is a process of our thinking. It cannot be changed without changing our thinking.” (Albert Einstein)

See Article by Dorian et al.

We read with interest the recent article by Williams et al¹ and the accompanying editorial comment by Maron et al² on the current status of the discussion on preventing sudden cardiac death (SCD) in young athletes. SCD in the young is devastating to all involved—families, healthcare providers, the community—and attracts considerable attention from the public and media.³ As our esteemed teacher (Dr. Barry Maron) stated in foundational 2007 guidelines, preventing SCD in athletes is a basic constitutional duty in sports cardiology.⁴ Nonetheless, >10 years later, reports of SCD episodes in athletes continue unabated. These are often promptly followed by announcements of forthcoming autopsy, which offends the sensitivity of many families and exposes a failure to recognize conditions that we regularly detect in daily clinical experience. These observations belie the view put forth by Maron et al² that there is no reason to adopt electrocardiography or any other diagnostic method in place of the medical history and physical examination (H&P) initially recommended by the American

Heart Association/American College of Cardiology for detecting cardiovascular diseases in the young. This assumes that we should be satisfied with the supposed preventive achievements of H&P, but this notion has never been proven valid for diagnosing high-risk cardiovascular conditions (hr-CVCs) or saving lives—not in adequately sized populations, and not in well-designed, controlled studies.

Athletes and military personnel are at essentially the same risk for SCD during strenuous activities, yet only trivial advances have been made toward reducing the regular occurrence of SCD in these populations. This is particularly disappointing, because most cardiologists agree with Maron et al's claim that SCD during strenuous exertion is primarily caused by preexisting structural heart disease,⁴ such as cardiomyopathy and coronary artery anomalies (CAAs)—conditions that today's technological advances have rendered clinically and confidently identifiable. Even so, the true incidence and causes of SCD are unclear: In athletes, estimates vary from almost 1:1 million to 1:23 000 annually, and as high as 1:3000 in some subpopulations (basketball players).⁵ As for the US military, Eckart et al's⁶ 2004 study of 6.3 million candidates suggests an annualized short-term medical mortality rate of ≈13:100 000 recruits/year during 2-month boot camp training; interestingly, 87% of fatalities were exertion-related, and 33% of cardiac causes were CAA-related.

Our aim in this Viewpoints article is to reopen the discussion on what is easily within our capacity to do

Key Words: cardiomyopathy ■ congenital heart disease ■ coronary artery anomaly ■ risk ■ sudden cardiac death

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to prevent SCD in young athletes (at least, in the estimation of a group of involved and progressive investigators), rather than simply accepting unnecessary, presumably inescapable limitations. Developing more effective solutions will require: (1) prospective, preliminary screening protocols; (2) accurate definition of high-risk factors and their prevalence in candidates; (3) precise, consistent definitions of “strenuous exercise”; and (4) autopsy-based diagnoses from cardiovascular pathologists in fatality cases.

In 2010, we hypothesized that a more sensitive, accurate pre-participation testing modality for evaluating young athletes was needed, especially because identifying CAAs (among the top causes of SCD in adolescents⁷) by alternative methods (H&P, electrocardiography, echocardiography) is difficult and unreliable in adult-sized people. We studied the value of cardiac magnetic resonance imaging (CMR, or magnetic resonance imaging of the heart), jointly with a focused questionnaire and resting ECG (neither of which required administration by a specialized physician), in a general population of adolescent (aged 11–18 years) candidates for sports participation in Houston public schools ($n=5169$).⁷ Magnetic resonance imaging of the living body (popularly called “virtual autopsy”) is considered as accurate as traditional autopsy for diagnosing relevant cardiac structural defects.⁷ Unlike echocardiography, CMR enhances quantitative evaluation of the left ventricle, thereby allowing the precise description of as-yet-unspecified normal, abnormal, and high-risk ranges for various sex, age, body mass index, and race cohorts. CMR image acquisition is completed in a single 10-to-15-minute outpatient session that does not require intravenous contrast or medication.⁷

Final results from our CMR-based study are shown in Table S1.⁷ CMR was successfully completed and was diagnostic for structural hr-CVCs (with highly accurate positive and negative results) in >98% of those screened. H&P alone failed to identify any of the hr-CVCs eventually found with ECG or CMR, although H&P is essential for qualifying the clinical severity of some hr-CVCs and for suggesting the likelihood of familial and genetic influences (to be investigated further at a secondary evaluation). The overall prevalence of hr-CVCs was 1.47% (76/5169 cases, 5 times higher than usually assumed⁴). Of these, 18.4% (14/76 cases) were cardiomyopathies (3.9% [3 cases] were non-obstructive hypertrophic cardiomyopathy, and 14.5% [11 cases] were dilated cardiomyopathy [DCM]), and 30.3% (23/76 cases) were CAAs with intramural ectopic arteries. Only mild DCM was found in the few candidates with cardiomyopathy, having left ventricular ejection fraction between 40% and 50%. ECG hr-CVCs comprised 51.3% of overall hr-CVCs (of which 44.7% [34 cases] were related to

prolonged QTc when a QTc ≥ 470 ms was assumed to indicate hr-CVC, versus only 14.3% [7 cases] when a QTc ≥ 490 ms was assumed to indicate hr-CVC). Although established elite athletes are substantially absent at these ages, our population was active in exerting: 60% ran for >6 hours/week.

Most likely, adolescence is the optimal time to ascertain the presence of high-risk factors that could affect sports participation, either to discourage competitive exertion or to promote effective preventive intervention. Because we did not collect longitudinal follow-up data, we could not evaluate improved screening's effects on mortality, but we plan to evaluate this in a future clinical study (described below). Ultimately, an educated population should be entrusted to make definitive decisions about available alternatives.

In Williams et al,¹ 3620 high-school athletes (median age, 16 years) were screened with routine H&P and additional ECG; echocardiography was ordered only when initial screening abnormalities appeared. With this approach, 55% initially had positive findings (45% had positive history, 10% abnormal physical exam, 3% abnormal ECG); only 30% were studied by echocardiography. Hr-CVCs were detected in 0.4% of the sample (27% of the 1.47% found by our CMR-based screening in a similar cohort⁷), along with a low prevalence of cardiomyopathy (2 cases of hypertrophic cardiomyopathy, no DCM) and 1 CAA case (0.03%, 9% of the CAA rate identified by CMR in our study). ECG detected 9 cases of Wolff-Parkinson-White pre-excitation and 3 cases of prolonged QTc. Schwartz et al⁸ have shown that exertion is an important contributor to severe ventricular arrhythmias in long QT syndrome type 1 and that most sudden-death episodes occur during exercise. Whether this holds true for other prolonged QTc subtypes is unknown.^{8,9}

Although lacking data from a comparable gold-standard screening approach (as CMR would be), Williams et al¹ reveal the poor diagnostic performance of both H&P and ECG-based screening for cardiomyopathies and CAAs, suggesting that electrocardiography is best used to identify high-risk electrophysiological conditions predisposing to lethal arrhythmia, such as prolonged QTc and Wolff-Parkinson-White syndrome. Maron et al² correctly point out that hypertrophic cardiomyopathy is probably underrepresented in this evaluation; our recent work suggests that CAAs also were grossly underrepresented.⁷ In particular, symptoms were not associated with CAAs (our results indicate that 1 452 000 people in the United States carry potentially high-risk CAAs with intramural proximal course, but that only a few are symptomatic, and even fewer suffer SCD [mainly when young and during sports participation,

but not in adults and more sedentary military personnel¹⁰). We estimate that in the population studied by Williams et al,¹ as many as 15 additional expected cases of high-risk CAAs were not identified by either H&P, electrocardiography, or secondary echocardiographic screening.

A similar screening methodology (H&P, electrocardiography, and secondary echocardiography) was applied by Malhotra et al¹¹ in 11 168 British adolescent soccer players (95% male, mean age 16.4 years). In this cohort, 0.07% (8 cases) had cardiomyopathies (5 hypertrophic cardiomyopathy, 2 arrhythmogenic right ventricle cardiomyopathy, 1 DCM), 0.24% of the CMR-identified rate in our study,⁷ and 0.02% (2 cases) had CAAs (4.5% of the CMR-identified rate in our study⁷). Additionally, at a mean 10.6-year follow-up, SCD accounted for 8 deaths, all during exercise; of these, 7 were attributed to cardiomyopathy (3 cases were hypertrophic cardiomyopathy), and 6 had a negative initial echocardiogram that was not repeated during follow-up.

Results (in terms of hr-CVC diagnostic performance) from these 3 screening studies are compared in the Table. Our study aimed primarily to help validate the theory that CMR is a better method for diagnosing structural hr-CVC and for proceeding to future mortality studies. Consider that 1.47% was the prevalence of hr-CVC in our CMR-screened study population: If we apply that same prevalence to the 6 300 000 military recruits (over 25 years) reported by Eckart et al⁶ we would have identified 92 610 positive findings for hr-CVC (92 610:6 300 000 implies a prevalence rate of 1/68 recruits as carriers of hr-CVCs). Similarly, the rate of SCD was 1/100 000 carriers of hr-CVCs; the incidence of carriers who died within 2 months

would therefore be 64/92 610=7/10 000 (annualized to 42/10 000/year). We had the great advantage of disposing with a gold standard for diagnosing most of the structural hr-CVCs at hand, and essentially no false-negative error was allowed (unprecedented with alternative protocols). A potential limitation of our protocol (and most other similar screening protocols) is related to the search for arrhythmogenic right ventricular cardiomyopathy (ARVC). We depended on a family history of sudden cardiac arrest and ECG criteria for ARVC at primary screening, which seemed usual and appropriate, if not perfect. It is only at secondary screening that a workup in a case suggestive of ARVC would include: (1) H&P by a specialized physician, including detailed family history focused on ARVC; (2) a Holter monitor; (3) a treadmill test; (4) a late gadolinium-enhanced magnetic resonance imaging study and other testing as advised by electrophysiologists. The special Veneto (Italy) population called for special attention to ARVC, in view of the well-known increase in autopsy or genetic prevalence of ARVC. We are not aware of any area in North America in which a similar phenomenon was reported.

We still need to validate the theory that mortality can be reduced by knowing the causes and acting effectively on them, through effective treatment or withdrawal/disqualification from strenuous activities. We hope to accomplish this in a major project now being developed.

Cost is an important consideration for any population-based screening study. In our study, and assuming a dedicated screening facility that processes 20 cases/day, we found the cost of CMR to dedicated centers or providers is ≈\$250/patient.⁷ A CMR-based protocol can establish a reliable

Table. Comparison of Results From Cited Screening Reports

	Malhotra et al ¹¹ (H&P, Electrocardiography, Echocardiography) n (%)	Angelini et al ⁷ (H&P, Electrocardiography, CMR) n (%)	Williams et al ¹ (H&P, Electrocardiography, +/- Echocardiography) n (%)
Total	11 168	5169	3620
hr-CVC	42 (0.38)	76 (1.47)	15 (0.41)
hr-CMP	6 (0.05)	14 (0.27)	2 (0.06)
HCM	5 (0.04)	3 (0.06)	2 (0.06)
DCM	1 (0.01)	11 (0.21)	0 (0.00)
ARVC (by autopsy)	2 (0.02)	0 (0.00)	0 (0.00)
hr-ACAOS-IM	2 (0.02)	23 (0.44)	1 (0.03)
R-ACAOS-IM	1 (0.01)	17 (0.33)	1 (0.03)
L-ACAOS-IM	1 (0.01)	6 (0.12)	0 (0.00)
WPW	26 (0.23)	4 (0.08)	9 (0.25)

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance imaging; DCM, dilated cardiomyopathy; H&P, history and physical examination; HCM, hypertrophic cardiomyopathy; hr-ACAOS-IM, high-risk anomalous origin of coronary artery from the opposite sinus of Valsalva with intramural course; hr-CVC, high-risk cardiovascular condition; hr-CMP, high-risk cardiomyopathy; L-ACAOS-IM, left ACAOS from the right sinus with intramural course; R-ACAOS-IM, right ACAOS from the left sinus with intermural course; and WPW, Wolff-Parkinson-White syndrome.

diagnosis of 1 hr-CVC for every \$16 500 expended (CMR screening cost plus overhead cost, divided by prevalence). Importantly, the CMR screening protocol used in our study was based on methodology that is now a decade old; recent advances in rapid CMR could substantially reduce scan times and hence lower costs.¹²

We believe that an ideal screening plan in the young needs to be accurate and acceptable to the candidates (ie, expeditious, simple, and without side effects³). Our study showed that 98.5% of the candidates were able to receive a final diagnosis (negative) shortly after a single initial encounter, whereas positive primary diagnosis will require focused secondary testing in only 1.5% of cases.⁷ Current H&P-based protocols frequently require expensive and lengthy secondary testing, especially in high-risk athletes (elite, military recruits, professionals).¹

An alternative experience recently reported by McKinney et al¹³ involved a socialized comprehensive health system (Canadian, which is universal and financed by the fiscal system) in which preventive services include screening ahead of sport activities. There, H&P and ECG are done routinely for everyone, with echocardiography done on medical secondary order when needed. Hand-held echocardiography is generally used by technicians in the field. The global accuracy of screening results could be judged by the total prevalence of hr-CVC: 0.41% in McKinney et al¹³ versus the 1.47% found in our CMR-based study,⁷ ie, 29% of the gold-standard method. Although access to medical services is much improved in health systems like Canada's, the true cost, efficiency, and accuracy of structural screening of the heart are limited by unreliable and inconsistent methods (eg, hand-held echocardiography that misses most coronary anomalies). The time required to complete a screening program also is an important limitation: In initial primary H&P-based screening, the incidence of false-negative results must be high, and in positive cases, the follow-up can be quite long and expensive, with a probable high rate of candidates lost to follow-up (as suggested by our experience in public schools).

ISSUES FOR FURTHER CONSIDERATION

We believe that ongoing debate and future research into SCD in young athletes should further address the following foundational points.

1. **The severity of individual hr-CVCs that could lead to SCD during sports should be better established.** The 2007 guidelines⁴ included in their slate

of SCD causes several frequent but not usually lethal conditions, such as uncomplicated myocardial bridges, mitral valve prolapse, bicuspid aortic valve, and hypoplastic or abnormal-but-benign CAAs (if not featuring intramural course). This overly broad presentation obfuscates the identification of more important, truly high-risk conditions in SCD by demonstrable and credible evidence. SCD cases with normal autopsy (5%–40% of cases, in various reports¹⁴) are expected, but they should be investigated by cardiovascular pathologists and correlated with clinical information (even more relevant than genetic studies, which are subject to variable phenotypic penetration of potentially important genetic influences).

2. **The risk for SCD for each hr-CVC should be quantified.** We recently proposed¹⁵ that such quantification is most efficiently obtained by using a risk ratio related to strenuously exercising candidates and calculated as a fraction in which the numerator is the prevalence of a given condition in the cohort of victims of SCD, and the denominator is the prevalence of the same condition in coetaneous sedentary people carrying the same condition.⁷ Similar risk quantification may also critically improve decision making about continuing with sports participation for those with anomalies and may indicate the need for medical intervention (of any kind), while establishing a workable and objective standard policy.¹⁶ Importantly, in relationship to strenuous exercise, high-risk populations and hr-CVCs have additional relevance.

3. **Autopsy-based evaluation of SCD should be refined, particularly for cardiomyopathies and CAAs.** Autopsy reports of left ventricle hypertrophy may sometimes be inaccurate because of a "postmortem pseudo-systolic state" in which fluid is absorbed by the moribund myocardium in the first hours after death, falsely creating a hypertrophied appearance (by pseudo-systolic thickness measurements that simulate systolic, and not diastolic, thickness).¹⁷ Additionally, whole-heart weight cannot be taken as a fair or reliable measure of left ventricle hypertrophy; wall thickness and myocardial biopsy for disarray or scarring are much better parameters of high-risk hypertrophic cardiomyopathy. Left ventricle dilatation is better established by using circumferential length rather than diameter (especially in preserved specimens subject to variable degrees of compression artifact). Traditional autopsy approaches may lead to overestimation of hypertrophic cardiomyopathy incidence and underestimation of DCM incidence. Finally, autopsy evaluation of CAAs should include acquisition of intramural coronary artery cross-sections at proximal stenosis, orthogonally to the aortic wall lumen. The intramural histological cross-sectional area should then be compared with a distal reference vessel's

area for quantitative evaluation of stenosis (recognizing that the most important systolic compression is related to systolic aortic-wall expansion and cannot be seen on autopsy, but only with intravascular ultrasound imaging, *in vivo*).

4. **The notion of “acceptable cost” of any preventive screening platform should be clarified.** The acceptable cost of a preventive screening platform is a matter too delicate to be decided by the small community of sports cardiologists. It is better determined broadly by society at large, especially health providers, organizers of athletic activities in schools, and family representatives. Overall screening cost should include the cost and time for completing a secondary evaluation, especially in military recruits. Business entities involved in sports activities (see Table S2, North American Sports Market¹⁸), along with private and public schools, universities, professional teams, and insurance companies, have an interest in and a potential responsibility for preventing complications during sports activities.
5. **Effective diagnosis and prevention ahead of SCD should generally be pursued, jointly with optimization of in-the-field reanimation.** We believe that obtaining correct diagnosis and prevention ahead of sudden cardiac arrest or death is generally preferable to in-the-field reanimation, in terms of preventive-medicine concerns or residual brain impairment. Even so, the feasibility of preventing SCD in the young was vividly supported by the recent report by Kinoshi et al,¹⁹ who aggressively monitored marathon runners and ensured primary professional intervention within a couple of minutes of a collapse by positioning bicycle-mounted resuscitation teams every 200 meters along the trail. Notably, none of the 28 athletes attended to within 2 minutes of sudden cardiac arrest died or had irreversible brain damage (never previously reported in such a context). Although such an innovative approach might be expensive and difficult to implement generically or at large, this preliminary study succeeded both in greatly reducing mortality and brain damage in a unique scenario that highlighted the critical importance of early and effective intervention.

For dealing with SCD, we naturally would welcome any improvement in resuscitation efforts—but even more, we favor creating an optimal balance among alternative treatments (resuscitation and preventive treatment of known defects, privileging optimal-quality screening). Decreasing the number of these dramatic events (potentially exacerbated by inadequate screening) and curtailing SCD or brain damage in athletes should be favored

or at least tested. Until recently, we have not had the tools we need to test the theory that we know the reasons for SCD in athletes and that we can indeed prevent it by enacting a prospective, accurate screening plan.

Unfortunately, our initial study⁷ was limited by its design and budget in this regard and was therefore unable to verify this theory. Therefore, we are planning a prospective, controlled study with appropriate statistical power that can identify the main components of the mortality risk: (1) prevalence of potential hr-CVCs in the population being studied; and (2) screening methods, severity of exercising, details about individual resuscitation attempts, and diagnosis based on CMR or, in fatality cases, autopsy. Most likely, only a study of US military recruits can generate this level of fundamental evidence. Indeed, the unique scenario in the military includes: a large population at risk (during 2 months of boot camp); a consistent screening protocol (H&P followed by required testing, for comparison with a CMR-based primary protocol); a clear definition of the amount of exertion; definitive answers on causes of death based on obligatory cardiovascular autopsy; and disciplined follow-up surveillance of mental status following successful resuscitation after cardiac arrest.

Additionally, we would underscore that establishing the role of heat stroke in SCD also requires prospective attention and a scientific approach.²⁰

CONCLUSIONS

We welcome the work of Williams et al¹ as an important contribution to a body of literature describing the performance of an H&P-based approach to screening for hr-CVCs among young athletes. Our current assessment is that the 14-point version promoted by the American Heart Association/American College of Cardiology continues to underperform, with the result that many athletes have undiagnosed hr-CVCs and may therefore have significantly higher residual risk during sports competition and exercise than candidates screened with optimal techniques and follow-up treatment.

This Viewpoints article does not pretend to establish new guidelines; rather, it is a call to collegially consider a promising, modern alternative to existing suboptimal screening routines for pre-certifying young athletes. We do not suggest eliminating H&P from screening protocols, but only to reduce its standalone importance (ie, a negative H&P alone is inadequate for clearance; it must be supported with a gold-standard diagnostic workup, preferably with CMR). Continued research is essential to better ascertain the pathogenesis of, screen for, and treat hr-CVCs in confirmed high-risk populations. Ultimately,

sports cardiologists should certainly weigh in on the following questions:

1. What can we not ignore (ie, the minimal risk ratio)?
2. What can we afford (ie, the maximum screening budget)?
3. How much should sports-related institutions and business entities contribute financially toward preparticipation screening (given a market that should exceed \$75 billion in 2020¹⁸)?

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1 and S2

References 7 and 18

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SUPPLEMENTAL MATERIAL

Table S1. Prevalence of Potentially High-Risk Cardiovascular Conditions: Results from a Study of Middle-School and High-School Adolescents.

	Study Population (N=5,169)		11–14 Years (N=4310) n (%)	15–18 Years (N=859) n (%)
	n	% (95% CI)		
Total hr-CVCs	76	1.47 (1.16–1.84)	62 (1.44)	14 (1.63)
hr-ACAOS-IM	23	0.44 (0.28–0.67)	20 (0.46)	3 (0.35)
L-ACAOS-IM	6	0.12 (0.04–0.25)	6 (0.14)	0 (0.00)
RSV	2	0.04 (0.01–0.10)	–	–
NCS	2	0.04 (0.01–0.10)	–	–
High origin	2	0.04 (0.01–0.10)	–	–
R-ACAOS-IM	17	0.33 (0.19–0.53)	14 (0.32)	3 (0.35)
hr-CMP	14	0.27 (0.15–0.45)	6 (0.14)	8 (0.93)
DCM	11	0.21 (0.11–0.38)	5 (0.12)	6 (0.70)
HCM	3	0.06 (0.01–0.17)	1 (0.02)	2 (0.23)
ECG hr-CVC	39	0.75 (0.54–1.03)	36 (0.84)	3 (0.35)
Brugada	1	0.02 (0.00–0.11)	0 (0.00)	1 (0.12)
WPW	4	0.08 (0.02–0.20)	4 (0.09)	0 (0.00)
QTc ≥470 ms	34	0.66 (0.46–0.92)	32 (0.74)	2 (0.23)
NCLV*	959	18.55 (17.5–19.64)	810 (18.79)	149 (17.35)

* Not likely to be a high-risk condition.

ACAOS-IM indicates anomalous origin of coronary artery from the opposite sinus of Valsava with intramural course; CMP, cardiomyopathy; CVC, cardiovascular condition; DCM, dilated cardiomyopathy; ECG, electrocardiographic; HCM, hypertrophic cardiomyopathy; hr, high-risk; L-ACAOS-IM, left ACAOS from the right sinus with intramural course; NCLV, noncompaction left ventricle; NCS, noncoronary sinus; R-ACAOS, right ACAOS; RSV, right sinus of Valsava; WPW, Wolff-Parkinson-White anomaly.

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Table S2. North American Sports Market by Segment.

US\$ millions	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	CAGR
Media rights	14,595	16,305	18,372	19,073	20,138	20,910	21,708	22,597	23,862	25,267	4.6%
Gate revenues	17,448	17,963	18,649	19,015	19,189	19,551	20,203	20,763	21,255	21,763	2.5%
Sponsorship	14,689	15,481	16,301	16,658	17,169	17,865	18,892	19,439	20,129	20,648	3.8%
Merchandising	13,493	13,806	13,966	14,390	14,565	14,714	14,906	15,080	15,258	15,426	1.2%
Total	60,225	63,555	67,288	69,136	71,061	73,040	75,709	77,879	80,504	83,104	3.2%

CAGR indicates compound annual growth rate.

Used with permission from PricewaterhouseCoopers International Limited. At the gate and beyond: PwC outlook for the sports market in North America through 2023. 2019. Available at:

<https://www.pwc.com/us/en/industries/tmt/assets/pwc-sports-outlook-2019.pdf>.¹⁸