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Sudden Unexpected Death in Young Athletes: Reconsidering "Hypertrophic Cardiomyopathy"

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REVIEW ARTICLE

Sudden Unexpected Death in Young Athletes: Reconsidering "Hypertrophic Cardiomyopathy"

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ABSTRACT

Hypertrophic cardiomyopathy is considered a principal cause of sudden unexpected cardiac death in young athletes. However, a number of demographic features observed in these deaths are not consistent with the diagnosis. All of these characteristics instead share in common a propensity for ventricular hypertrophy, implying that these deaths may reflect electrical stability in the extremely rare athlete with exaggerated myocardial hypertrophy in response to sports training. This review provides an evidence-based line of reasoning that supports this concept. *Pediatrics* 2009;123:1217–1222

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Key Words
sudden death, cardiomyopathy, exercise training, arrhythmias

Abbreviations
HCM— hypertrophic cardiomyopathy
BSA— body surface area

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HYPERTROPHIC CARDIOMYOPATHY (HCM) has traditionally been considered a major cause of sudden unexpected cardiac death in young athletes, the reported diagnosis at autopsy in approximately one half of cases in which an etiology is determined.[1,2] Such tragedies are consistent with the malignant ventricular arrhythmias, occult nature, and predisposition to sudden death with physical exertion observed in patients with this condition.[3] By the commonly accepted scenario, then, the youth with preexisting, unsuspected HCM suffers sudden death as a consequence of the cardiovascular stresses imposed by sports training and competition. Accordingly, preventive efforts have focused on means of identifying the at-risk athlete during the preparticipation assessment.[4] Given the difficulty detecting HCM on routine medical screening, it is fortunate that the risk of sports-related death from this condition is extremely low (~1 in 400 000 athletes; yearly frequency: 0.0002%).[5]

However, in a recent commentary I pointed out that a number of demographic findings among cases of sudden death in athletes are not at all consistent with the recognized features of the clinical entity HCM.[6] These findings, related to gender, race, sexual maturation, and athletic training, suggest instead that myocardial hypertrophy per se serves as the primary determinant defining risk for sudden death in young athletes. I proposed that electrophysiological instability related to exaggerated hypertrophy during sports training in the rare, particularly susceptible athlete might serve as the substrate for sudden death rather than previously unrecognized HCM. Moreover, I suggested that recurrent sympathoadrenal cardiac stimulation associated with athletic training might underlie this tragic chain of events.

It is the purpose of this review to expand on this point of view with a comprehensive examination of factors that might predispose young athletes to sudden death during sports play. These considerations will raise challenge to the traditional perception of the role of occult HCM as the etiologic factor in these tragic deaths.

DEMOGRAPHIC FEATURES

Several demographic and epidemiologic factors evident among cases of sudden unexpected cardiac death in young athletes are inconsistent with the clinical profile typically observed in patients with known HCM.[6] Moreover, each of these features permits inferences regarding a link between myocardial hypertrophy and these events.

The Frequency of HCM Among Cases of Sudden Death During Exercise Differs in Young Athletes Compared With Nonathletic Populations

Among sudden cardiac deaths in athletes, HCM typically accounts for ~50% of cases in which an etiology is determined.[1,2] Yet, HCM is a much less conspicuous diagnosis in large survey studies of sudden death during vigorous physical activity in young military personnel. Eckart et al[7] examined autopsy reports of 108 cases of sudden death during exercise among 6.3 million US military recruits. In 38 of them, no identifiable etiology was discovered. Among those with findings of previously unsuspected heart disease ($n = 64$), the majority (61%) were related to congenital coronary artery anomalies. Only 8 (13%) were considered to have HCM, but only a single case demonstrated a combination of myocyte hypertrophy and cellular disarray, the hallmark pathologic findings of this condition. Similarly, on a review of the postmortem findings of 19 US Air Force recruits who died during vigorous exercise, Phillips et al[8] reported only 2 cases of HCM. These observations suggest a specific association between sudden death with myocardial hypertrophy and sports participation.

Myocardial hypertrophy is, of course, a well-recognized concomitant of athletic training. The pattern of ventricular thickening, in general, reflects the type of sport involved.[9] Chamber enlargement with minor degrees of eccentric hypertrophy is typical of endurance athletes (ie, distance runners), and significant concentric hypertrophy without ventricular dilatation is observed in power athletes (ie, weight lifters), whereas a combination of these 2 responses is seen in most other sports activities. Overall, well-trained athletes demonstrate a ventricular thickness that is ~14% greater than that of nontrained subjects.[10,11]

Consistent with these findings, some athletes demonstrate a ventricular wall thickness that exceeds the upper limit of normal among untrained individuals (~12 mm), and a small percentage of them exhibit levels of ventricular hypertrophy that are observed in autopsy studies of athletes who died as a result of supposed HCM (20 ± 4 mm).[12] For instance, among the 947 elite athletes described by Pelliccia et al,[11] 16 (mostly rowers) had values between 13 and 16 mm. Roeske et al[13] reported that 14% of a group of professional basketball players had a ventricular septal thickness of ≥14 mm. Of the 42 players studied, 4 (10%) had a septal/posterior wall-thickness ratio of ≥1.3, which is a diagnostic criterion for HCM. In a study of 10 elite rowers, the average ventricular septal thickness was found to be 13 ± 1 mm.[14]

Sudden Death in Athletes as a Result of Reported HCM Has Occurred Almost Entirely in Males

In their 10-year report from the National Center for Catastrophic Sports Injury Research, Mueller et al[2] identified 56 cases of HCM or "probable" HCM in sudden deaths of young athletes. Of these deaths, all but 1 occurred in males. In their description of 48 cases of HCM among occurrences of sudden cardiac death in 134 young athletes, Maron et al[1] found it only in 2 females. These findings stand in sharp contrast to those in clinical patients with HCM, in which there is no gender predilection.[3,15]

When matched for training volume, female athletes have lower measures of ventricular wall thickness than their male counterparts.[16] However, compared with untrained subjects, female and male athletes demonstrate similarly increased values (~14%).

Prepubertal Athletes Are Not Evident in Reports of Sudden Death in Athletes Related to HCM

Survey reports such as those by Mueller et al[2] and Maron et al[1] did not include sudden deaths resulting from HCM in young athletes below the age of 13 years. Although clearly it cannot be assumed from this that such tragedies have not occurred in this age group, the published literature notably gives little such indication. This is surprising given (1) the millions of prepubertal participants in sports such as soccer, football, basketball, and swimming and (2) the fact that the diagnosis of HCM and associated occurrences of sudden death are well recognized in the general young childhood population.[17,18]

Research data exist to suggest that myocardial hypertrophic responses to exercise training might be less in prepubertal compared with mature subjects.[19–22] For instance, Nottin et al[21] compared echocardiographic findings in groups of highly trained adult and child cyclists. When adjusted for body size, no significant difference in ventricular septal wall thickness was observed between child cyclists and untrained controls (7 ± 1 vs 7 ± 1 mm·[BSA]$^{-0.5}$, respectively), whereas the cyclists had greater ventricular diastolic dimension (39 ± 3 and 36.0 ± 3 mm·BSA$^{-0.5}$, respectively). Among the adults, cyclists had the expected increase in both wall thickness (8 ± 1 vs 7 ± 1 mm·BSA$^{-0.5}$, respectively) and diastolic dimension (40 ± 5 vs 37 ± 2 mm·BSA$^{-0.5}$, respectively) compared with controls.

The marked predilection of postpubertal males for sports-related death with supposed HCM suggests a facilitating role of androgenic hormonal stimulation in these events. The anabolic effects of testosterone and its analogues on muscle tissue are well recognized, and animal studies have verified this influence on cardiac myocytes as well.[23] Pertinent to the present discussion, testosterone has been demonstrated to facilitate skeletal muscle hypertrophic responses to physical training in humans. Bhasin et al[24] described increases in skeletal muscle size and strength with resistance training in men that were substantially augmented by the concomitant administration of exogenous testosterone. The report by Koenig et al[23] of a study in rodents suggested similar training-induced effects of testosterone on the myocardium. In response to a period of chronic exercise, male animals demonstrated greater myocardial hypertrophy than females, an effect that was eliminated by orchidectomy and restored with administration of testosterone.

The Incidence of Sudden Cardiac Death Resulting From HCM Is Disproportionately High Among Black Athletes

Among 102 cases, Maron et al[25] reported that deaths resulting from HCM during sports play were more common in black than white athletes (55%% vs 41%). Of the 56 sudden cardiac deaths in athletes attributed to HCM compiled by Mueller et al,[2] 59% were white and 36% were black. The precise increased risk to black athletes cannot be determined, because data regarding racial participation according to sport are not available. Still, the racial bias indicated by these studies (1) cannot be explained by sport-participation rates and (2) is not reflective of patients with clinical HCM, in whom the incidence of this condition in black athletes (~8%) reflects the frequency of black people in the general population.[25,26]

Basavarajaiah et al[27] provided information indicating that elite black athletes exhibit greater myocardial hypertrophy (without other indicators of HCM), independent of blood pressure, than white athletes. Among 300 nationally ranked British athletes in 6 sports, black competitors demonstrated greater left ventricular wall thickness (11 ± 1 compared with 10 ± 1 mm in white athletes), and 18% had a wall thickness of >12 mm compared with 4% of the white athletes.

In a group of 265 predominantly black athletes (mostly football players), the mean ventricular septal

thickness was 11 mm (range: 7–18 mm), with 11% demonstrating a value of ≥13 mm.[28] Although studies in white athletes have not shown thickening of this extent,[11,29] these reports have sampled participants in different sports, which makes comparisons problematic.

In the study by Basavarajaiah et al[27] cited above, 68% of the black athletes exhibited criteria for left ventricular hypertrophy on resting electrocardiograms compared with 40% of the white athletes. This observation is consistent with the findings of Magalski et al,[30] who examined the influence of race on electrocardiographic findings in 1959 college football players. "Abnormal" tracings, including findings that satisfied criteria for ventricular hypertrophy, were found in 30% and 13% of black and white athletes, respectively.

Considerable amounts of data indicate that, in general, black people have greater responses to cardiovascular stress than do white people.[31] Compared with white people, black people demonstrate a higher blood pressure response to exercise,[32] heightened sympathetic response to cold pressor tests,[33] and greater evidence of left ventricular hypertrophy on electrocardiograms at a given level of hypertension.[34] Hammond et al[35] compared ventricular hypertrophy on echocardiograms in black and white adults at similar levels of sustained hypertension. A ventricular septal thickness of >13 mm was found in 24% of the black subjects and 18% of the white subjects, and a posterior wall thickness of >11 mm was seen in 25% and 15%, respectively.

ROLE OF VENTRICULAR HYPERTROPHY

As outlined above, factors that are closely linked to risk of sudden death from supposed HCM during sports play are not characteristic of this disorder seen in the general population. The observed data indicate that participation in sports training, gender, level of sexual maturation, and race all strongly influence these events, biases not characteristic among patients with HCM. Each of these variables do, however, have 1 aspect in common: they are all associated with a propensity for ventricular hypertrophy. Considering these data, then, it is reasonable to propose that the majority of sudden unexpected cardiac deaths in youth during sports play are related to fatal dysrhythmias in the very rare athlete with exaggerated hypertrophic response to sport training rather than occult HCM.

Considerations of the role of hypertrophy and associated dysrhythmias in the etiology of sudden death further support this concept. Myocyte hypertrophy is a recognized substrate for risk of sudden death from malignant ventricular arrhythmias associated with sudden death in patients with heart disease. Electrophysiologic alterations that underlie these rhythm abnormalities include prolonged action potential duration, regional repolarization delays (related to a reduction in the transient outward K^+ current), and a decrease in effective membrane capacity.[36]

Similar arrhythmogenic electrophysiologic changes may occur with the myocardial hypertrophic response to endurance training. Gwathmey et al[37] compared electrophysiologic properties of the myocardium in aged rats who underwent 8 weeks of exercise training and untrained controls. The exercised animals displayed an 18% smaller action potential amplitude that was 37% longer than that in the untrained (delay in phase 3 repolarization). Paralleling findings in the pathologic model, Natali et al[38] demonstrated that action potential duration affected by exercise in rats was region-specific within the heart.

In reviewing these data, Hart concluded that "the tissue and cellular electrical features of exercise-induced hypertrophy seem to parallel those of hypertrophy from other causes."[39] He proposed that "intensive athletic training is associated with a small but finite risk of sudden death, which may be a consequence of the cellular electrical changes of mild-moderate hypertrophy."

There is no question that sports training profoundly affects the electrophysiologic properties of the athlete's heart. Electrocardiographic changes commonly observed in highly trained athletes, including atrioventricular block, atrial and ventricular ectopy, ST-segment and T-wave abnormalities, and intraventricular conduction delays, may reflect intrinsic electrical alterations in response to hypertrophy or the influence of alterations in autonomic tone.[40]

Monitoring studies that compared the frequency of ventricular ectopy in athletes and nonathletes have provided conflicting information. Some indicated a propensity for ventricular dysrhythmias in athletes compared with nonathletes,[41,42] whereas others showed no group differences.[43,44] It is important to note, however, that a decrease in both myocardial hypertrophy and frequency of ventricular ectopy in athletes has been reported after a period of detraining.[45,46]

Biffi et al[47] found a high incidence (77%) of ventricular ectopy among 175 elite-level Italian athletes (mean age: 23 ± 6 years) studied with 24-hour electrocardiographic recordings. More than 1000 premature ventricular contractions per day were recorded in 12%, and in this group, one third demonstrated couplets (paired ectopic beats). In the entire study group, 8 (5%) athletes had nonsustained ventricular tachycardia. Among all these athletes, who did not have exaggerated ventricular hypertrophy (mean ventricular septal thickness: 9 ± 1 mm), no significant relationship was found between left ventricular mass and ventricular ectopy.

In the absence of symptoms or evidence of structural heart disease, ventricular ectopy in trained athletes has generally been considered physiologic and benign.[42] However, those otherwise healthy athletes with potentially life-threatening arrhythmias (ventricular tachycardia, multifocal ectopy) have created a dilemma regarding decisions surrounding the safety of continued sports play.[48]

SYMPATHOADRENERGIC STIMULATION

Sympathoadrenergic activity is arrhythmogenic, increases dramatically during exercise, and serves as a well-documented stimulus for ventricular hypertrophy. In addition, repetitive adrenergic stimulation can produce cardiac anatomic features that mimic those of HCM.[49–54] It is reasonable to consider, then, that repeated

increases in sympathetic drive or circulating catecholamines might play a role in the myocardial hypertrophy observed in athletes as well as occurrences of sudden death during sports play.

Witzke and Kaye[49] administered nerve growth factor (a stimulant of cardiac adrenergic innervation) to newborn puppies. Compared with untreated littermates, these animals demonstrated myocardial hypertrophy with a septal/free wall ratio of >1.5 and dramatic myofibrillar disarray on histologic examination, features that are typical of patients with HCM. In rats, Ostman et al[50] demonstrated a 16% rise in myocardial norepinephrine concentrations that paralleled cardiac hypertrophy after 15 weeks of exercise. Laks et al[51] infused dogs with subhypertensive doses of norepinephrine for periods ranging from 6 to 63 weeks. Ventricular wall thickness at the left apex averaged 14 ± 1 mm compared with 9 ± 1 mm in untreated animals, whereas left base thicknesses were 18 ± 1 and 11 ± 1 mm, respectively. Other investigators have reported similar hypertrophic responses in animals to adrenergic infusions.[52–54]

The repetitive exercise of physical training in human athletes simulates the catecholamine-infusion studies in animals noted above. During an acute bout of high-intensity exercise, plasma norepinephrine levels rise ~16-fold above resting values,[55] and after extended endurance competition such as marathon running, levels remain elevated for many hours.[56] The myocardium of the training athlete, thus, is exposed to regular repeated "doses" of sympathetic stimulation and circulating catecholamines in much the same way as the animals who demonstrate cardiac hypertrophy after chronic infusion of adrenergic drugs.

It is reasonable to conclude that such chronic sympathoadrenergic stimulation might play a role in the production of myocardial hypertrophy in the athlete. That individual variability in the magnitude of myocardial response to this repetitive stimulation might play a role in defining risk for sudden death in athletes is an intriguing, although entirely speculative, possibility.

IMPLICATIONS

The myocardial hypertrophy and electrophysiologic features of the athlete's heart have been considered physiologic, with a benign prognosis[57]; on the basis of the perceived uneventful natural course in almost all of these competitors, this would seem to be almost invariably true. However, the information reviewed here suggests that in the extremely rare athlete (1 in 400 000), exaggerated hypertrophy in response to training can serve as a substrate for fatal dysrhythmias. Although such cases of sudden death have traditionally been assigned to HCM, demographic feature of sudden cardiac death in young athletes are not consistent with this diagnosis. Instead, these features implicate a primary role of cardiac hypertrophy, triggered by sports training and facilitated by circulating testosterone and sympathoadrenergic stimulation, in these tragedies.

The anatomic cardiac features of trained athletes, in a small number of cases, can mimic both those of clinical HCM and autopsied cases of sudden death in athletes. As Pluim et al concluded in respect to the athlete's heart, "it is not possible to distinguish physiologic and pathologic hypertrophy on anatomic criteria only."[36]

Concerning prevention, in this model of causality one is confronted with the same difficult dilemma as in the traditional HCM-related construct: how do we detect that 1 exceedingly unique athlete out of almost half a million who is at risk for sudden death? The strategies between the two, however, would be different. In the latter, the focus centers on means of detecting through medical screening the athlete with preexisting disease, whereas in the former it would be important to identify the would-be athlete who is predisposed to an exaggerated myocardial hypertrophic response and/or electrical instability in response to training. To accomplish this, a great deal more needs to be understood regarding the mechanisms for ventricular hypertrophy, electrophysiologic changes, and myocardial response to sympathoadrenergic stimulation that occur with sports training.

Genetic factors are documented determinants of magnitude of ventricular hypertrophy with training,[58] and early studies have identified specific alleles that influence wall thickness in athletes.[59] A clearer understanding of the genetic mechanisms involved might provide a means of identifying athletes at particular propensity for ventricular hypertrophy with training.

CONCLUSIONS

The demographic characteristics of sudden death in youth athletes with myocardial hypertrophy at autopsy are not consistent with clinical HCM. These findings suggest, instead, that such deaths are related to the ventricular hypertrophy of sports training per se in the context of increased risk created by race (black), gender (male) and biological development, and/or length of training. The extreme rarity of these tragic events creates a major challenge for preventive efforts. Still, a greater understanding of the structural and electrophysiological features of the young athlete may provide insight into a means of identifying the extraordinarily rare athlete at risk.

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THE EPIDEMIC THAT WASN'T

"When the use of crack cocaine became a nationwide epidemic in the 1980s and '90s, there were widespread fears that prenatal exposure to the drug would produce a generation of severely damaged children. Newspapers carried headlines like 'Cocaine: A Vicious Assault on a Child,' 'Crack's Toll Among Babies: A Joyless View' and 'Studies: Future Bleak for Crack Babies.' But now researchers are systematically following children who were exposed to cocaine before birth, and their findings suggest that . . . encouraging stories . . . are anything but unusual. So far, these scientists say, the long-term effects of such exposure on children's brain development and behavior appear relatively small. 'Are there differences? Yes,' said Barry M. Lester, a professor of psychiatry at Brown University who directs the Maternal Lifestyle Study, a large federally financed study of children exposed to cocaine in the womb. 'Are they reliable and persistent? Yes. Are they big? No.' Cocaine is undoubtedly bad for the fetus. But experts say its effects are less severe than those of alcohol and are comparable to those of tobacco—2 legal substances that are used much more often by pregnant women, despite health warnings."

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