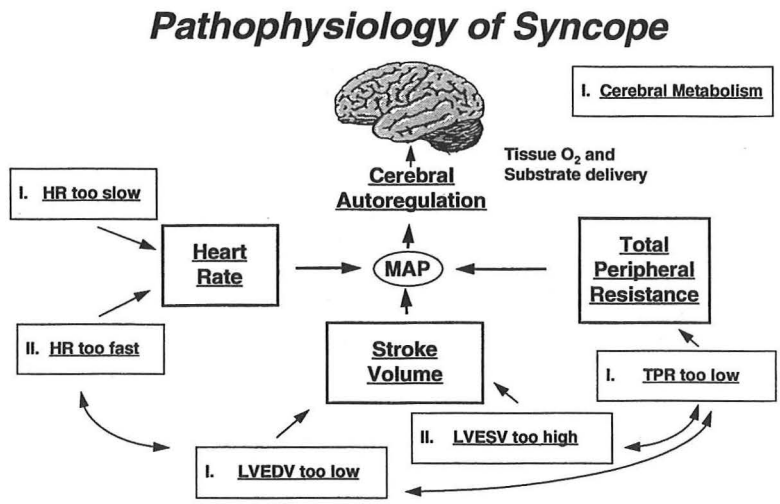
EXERTIONAL SYNCOPE: "FAINTNESS OF HEART" OR HARBINGER OF SUDDEN DEATH



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CASE HISTORIES

Case 1: A 17 year old female track star was competing in the district championships in the 5,000 meters. She was having an excellent race and was part of the final pack that was in contention for a medal. Just after crossing the finish line (in 17:55), she collapsed to the ground and according to bystanders, remained "unconscious" for about an hour.

Case 2: A 21 year old male college basketball star playing for a major college team led a 12 point run, mostly by a series of impressive fast breaks, in the middle of the first half of an early round of the NCAA tournament. After the last jam, he was fouled and walked to the foul line. While standing waiting to shoot, he slumped to the ground. Witnesses observed a generalized seizure.

Case 3: A 19 year old male wide receiver for a junior college football team was running a crossing pattern during practice when witnesses observed him to weave, stumble, then fall to the ground. The trainer arrived at the scene to find him alert and oriented. His BP was 135/80, pulse 110 and regular.

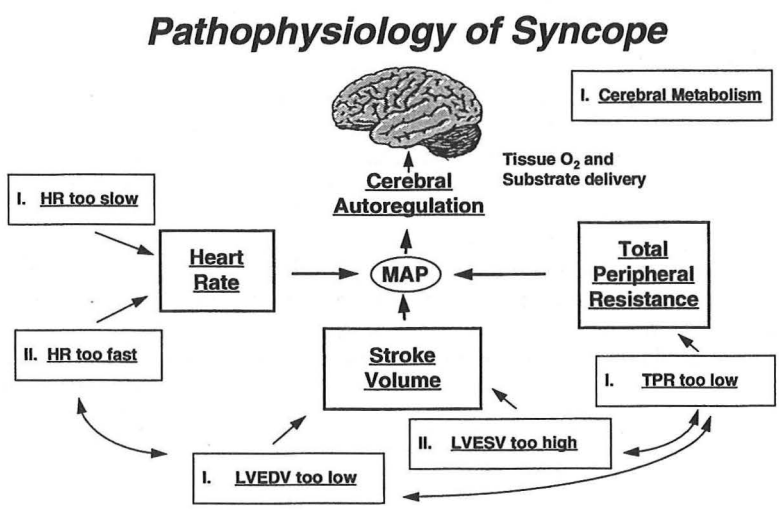
These case reports highlight a number of important issues in the evaluation of the athlete with syncope and we will return to them at the end of the presentation.

Syncope during exercise, particularly if it occurs in a competitive athlete, is an anxiety provoking event both for the patient and the evaluating physician, raising the specter of catastrophic injury or sudden death. Recent media coverage devoted to the collapse of high profile athletes such as Reggie Lewis and Hank Gathers has focused national attention on the process of evaluating such individuals, and the decision making strategy for determining their continued eligibility for sports participation (1). The purpose of this grand rounds is to present a pathophysiological framework for syncope during exercise, and to use this framework to derive a cost effective and appropriate work up for such patients. *Indeed it is a comprehensive understanding of the relevant pathophysiology that will allow the primary care physician to individualize the workup of any unique patient to obtain the most clinically relevant information.*

Pathophysiology of Syncope

Figure 1 represents a simplified strategy for evaluating the pathophysiological mechanisms of syncope with a focus on the factors that may be relevant to athletes or athletic competition.

Fig. 1



Cerebral Metabolism

Ultimately, syncope will occur when cerebral metabolism and thereby neuronal activity decreases below some critical level that is necessary to sustain consciousness (table 1).

Table 1

Cerebral Metabolism

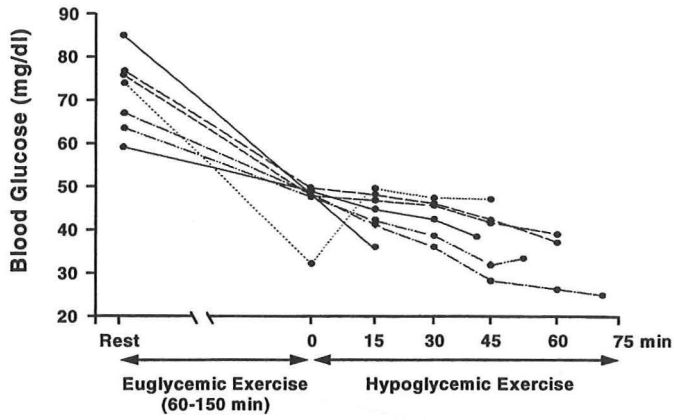
A. Abnormal electrical activity (seizure)

B. Abnormal substrate availability/utilization
   1. Hypoglycemia
   2. Hypoxia
   3. Hypocapnia (Hyperventialtion)
   4. Hyperthermia

This disruption of function may occur because of a primary disturbance in the brain, such as a seizure or hyperthermic insult (2), or inadequate availability of substrate for oxidative metabolism. It is possible for substrate availability to be compromised, even in the presence of normal systemic hemodynamics, under conditions of hypoglycemia, severe hypoxia such as during exercise at high altitude, or cerebral vasoconstriction induced by hyperventilation and hypocapnia. Most of these situations will be self-evident. For example, hyperthermia usually occurs during exercise in excessive heat and will be associated with elevated body temperature (>40.5^{o}C)(3,4).

Hypoglycemia should be considered of course in diabetic patients on insulin. However even in non-diabetics, hypoglycemia may occur after prolonged endurance exercise leading to depletion of hepatic and muscle glycogen stores (5). In one study (fig 2), > 35% (7/19) of individuals exercising at a moderate intensity (60% VO2max) for more than 150 minutes developed blood glucose concentrations < 45 mg/dl (5).

Fig. 2

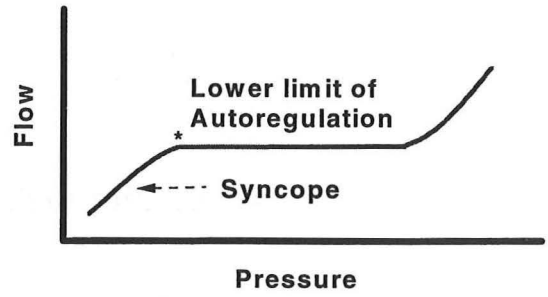


(from Felig et al, New Engl J Med 1982)

Most interestingly, the athletes who experienced hypoglycemia did not have more fatigue or less endurance than those who maintained blood glucose concentrations, and were able to sustain exercise for more than an hour under hypoglycemic conditions. Moreover, infusion of glucose to prevent the hypoglycemia had no effect on fatigue or endurance, though catecholamine levels were substantially reduced. Most of these individuals will have a recovery of blood glucose quickly after the cessation of exercise, though extreme cases requiring IV dextrose have been reported in some patients who engage in prolonged exercise while taking beta blockers (6), which may prevent normal neurohormonal compensation. Individuals with eating disorders, a condition which is common among female athletes (7), may have compromised carbohydrate stores and be at risk for similarly prolonged and clinically significant hypoglycemia (8). Such athletes are also at risk for other metabolic abnormalities which may prolong the QT interval leading to arrhythmias and even sudden death (9). However except for such specific situations, hypoglycemia during exercise does not usually cause symptoms and is rarely a cause for syncope.

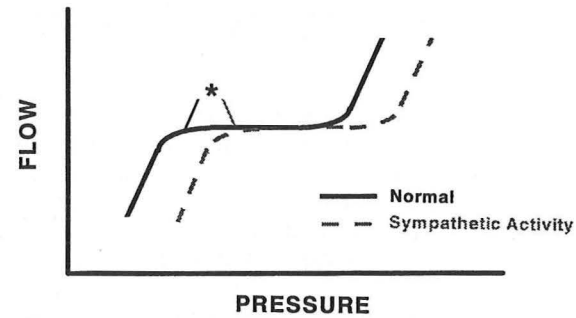
In the absence of these specific conditions directly affecting brain function, cerebral metabolism is primarily dependent on cerebral blood flow. The process of autoregulation (fig 3) serves to maintain cerebral blood flow constant over a relatively wide range of perfusion pressures (10). When the lower limit of autoregulation is reached, cerebral blood flow becomes dependent on arterial blood pressure and will decrease below a critical level if blood pressure falls, leading to syncope.

Fig. 3a



Endurance athletes, and individuals prone to orthostatic hypotension and syncope may have a rightward shift of the autoregulatory curve during orthostatic stress and thereby be particularly prone to syncope when blood pressure falls 11). We have previously hypothesized that this shift may be due to sympathetic activation, which is protective against cerebral edema during acute hypertension (12), but may be detrimental during relative hypotension (11).

Fig. 3b

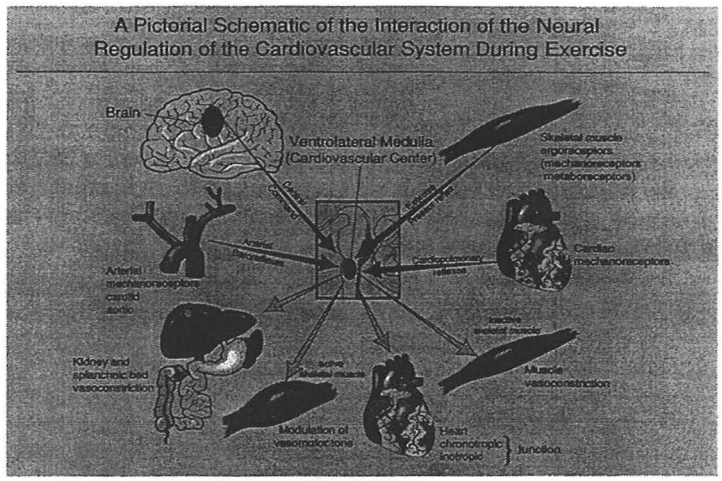


As Adapted from
Circulation 94
Levine, et al

Despite these relatively modest changes in cerebral autoregulation, under the majority of circumstances causing syncope, it is a fall in arterial pressure due to hemodynamic compromise that leads to reduced cerebral perfusion. Arterial pressure is a function of the **"triple product"** of heart rate x stroke volume (cardiac output) x total peripheral resistance (13). Therefore if blood pressure falls, it must fall as a consequence of a decrease in one or all of these critical variables, without adequate compensation by baroreflex mechanisms (tachycardia and vasoconstriction). In order to understand how exercise may affect blood pressure control acutely, it is critical to understand the normal changes in cardiovascular hemodynamics and autonomic function which occur during exercise (fig 4).

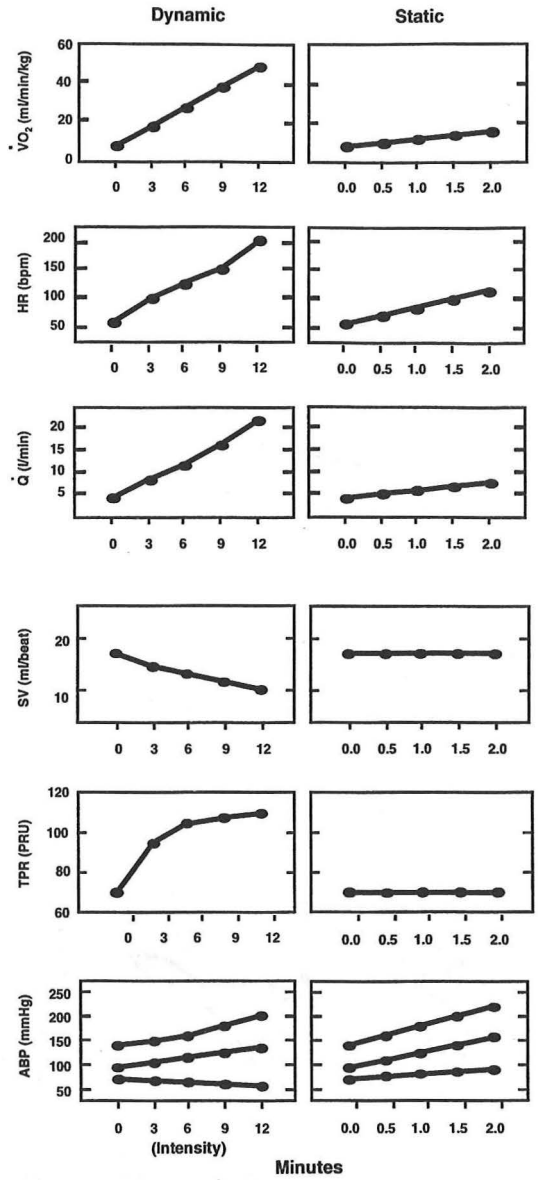
Cardiovascular Regulation During Exercise

Fig. 4



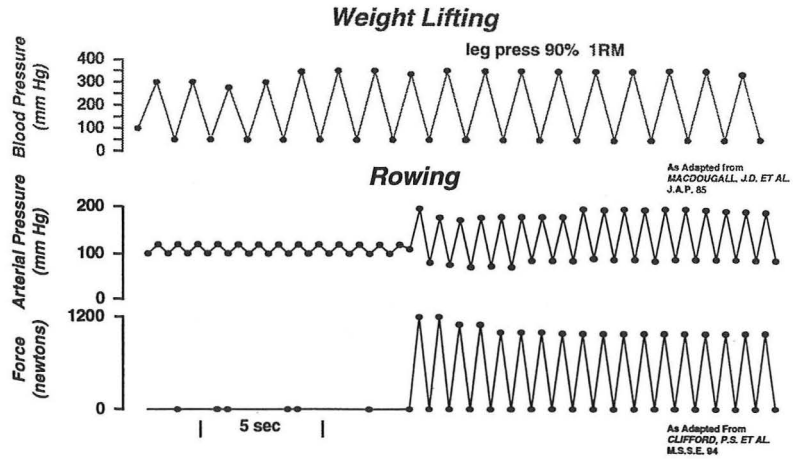
During dynamic exercise, the cardiovascular response to exercise is initiated by higher order centers in the brain, termed "central command" (14). As exercise continues, both mechanical and metabolic signals from active skeletal muscle provide feedback to cardiovascular centers in the brain to precisely match systemic oxygen delivery with metabolic demand (15). Vascular resistance decreases to facilitate increases in muscle perfusion, and cardiac output increases proportionate with oxygen uptake (in a 6/1 ratio) allowing the maintenance or even an increase mean arterial pressure. The cardiovascular responses to dynamic exercise and static exercise are significantly different: static exercise is associated with smaller increases in oxygen uptake, cardiac output, and stroke volume, but equivalent increases in blood pressure (16): (fig 5).

Fig. 5


Dynamic
Static
$\dot{V}O_2$ (ml/min/kg)
60
40
20
0
0 3 6 9 12
0.0 0.5 1.0 1.5 2.0
HR (bpm)
200
150
100
50
$\dot{Q}$ (l/min)
20
15
10
5
SV (ml/beat)
TPR (PRU)
120
100
80
60
ABP (mmHg)
250
200
150
100
50
(Intensity)
Minutes

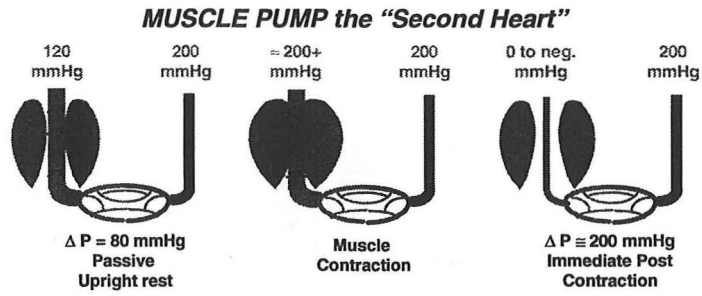
Many sports include a combination of both static and dynamic exercise. Under such circumstances, such as rowing, cycling, or jumping sports, increases in blood pressure may be particularly dramatic (16a-16c) (fig 6).

Fig. 6



Increases in heart rate and stroke volume contribute to the increase in cardiac output, with an active muscle pump (fig 7) being required to support venous return in the face of very high muscle blood flows (17,18).

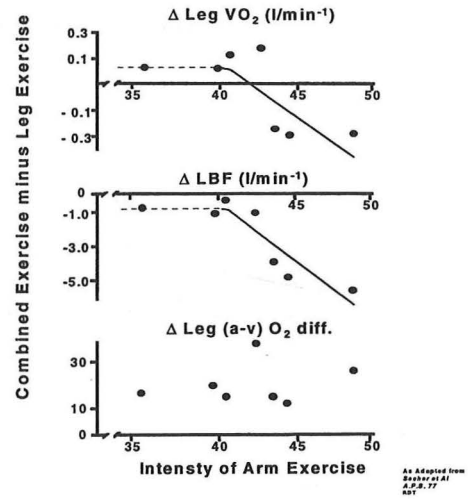
Fig. 7



During passive upright rest which distends the venous valves, hydrostatic pressure is distributed on both sides of the circulation and there is a net 80 mmHg driving pressure into the veins. During muscle contraction, the veins are emptied and the driving pressure back to the heart is substantially increased. Immediately after contraction, the now competent valves prevent back flow and the pressure in the emptied veins approaches zero, acutely increasing the driving pressure to venous return by 2-3 fold (from Rowell, Human Circulation, 1986)

In endurance athletes, at very high workrates with a large amount of active muscle mass, the capacity for muscle vasodilatation may exceed the cardiac pump capacity and blood pressure may decrease unless sympathetically mediated vasoconstriction occurs in active muscle (fig 8) as well as other vascular beds (19,20).

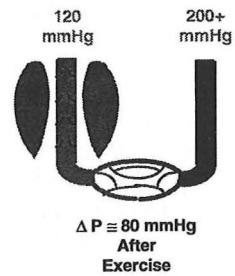
Fig. 8



In this landmark study by Secher et al (19), the addition of arm exercise to near maximal leg exercise, (here expressed as a percentage of the total of arm and leg oxygen uptake), caused a reduction in leg blood flow and oxygen uptake, without a change in oxygen extraction.

If exercise and muscle contraction cease abruptly, the pumping action of skeletal muscle is lost despite a persistent vasodilatation (fig 9).

Fig. 9



During exercise there is a marked redistribution of the cardiac output to skeletal muscle due to metabolic vasodilation. After exercise, without the muscle pump to increase venous return, cardiac filling may fall dramatically due to a reduction in LVEDV and SV, leading to hypotension and syncope.

The importance of this redistribution of the cardiac output into the venous capacitance was recognized more than 300 years ago by Lower (21) who wrote *in De Corde* in 1669:

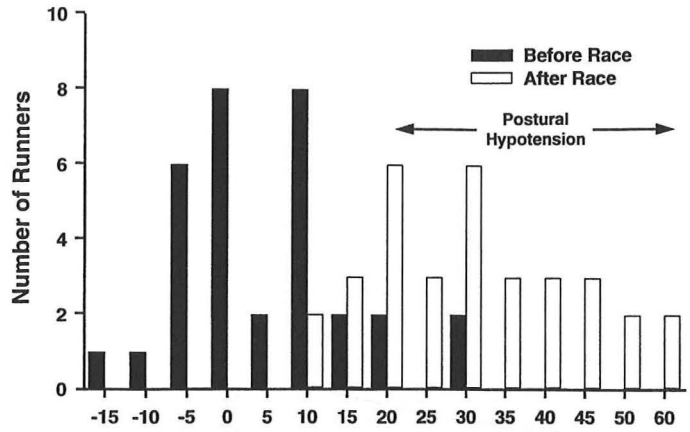
"...A defective pulse and langour of the spirit are thus the sequel to over-dilation of these veins--venous dilation anywhere diminishes the movement of the heart very appreciably by diverting the due supply and inflow of blood."

It should be no surprise therefore that blood pressure may fall acutely under such circumstances and syncope is relatively common in athletes who stand still immediately following a bout of intensive exercise, such as occurs after a road or track race, or at the foul line on a basketball court. Originally described by Gordon in 1907 (22), this process of post exercise hypotension was first systematically investigated in the 1940s by Ludwig Eichna at the Armored Medical Research Laboratory in Fort Knox, Kentucky (23).

In these "exhaustive" studies, the authors performed tilt table tests on 33 military recruits during and after a variety of different tests designed to elicit exhaustion including an uphill run on a treadmill wearing a full pack equivalent to 1/3 - 1/2 of body weight, and a 32 mile hike with a 20 lb pack in the shortest time possible (usually 7-9 hours). The key observations included: a) slightly more than 50% of the soldiers experienced post-exertional orthostatic hypotension, defined as a decrease in systolic blood pressure to below 100 mmHg , and more than 10 mmHg below the pre-exercise upright blood pressure; b) of these, an additional 50% (27% of the total) developed true syncope and were unable to remain in the tilt position for a full 5 minutes; c) repeat testing in susceptible individuals revealed continued syncope and orthostatic hypotension for an average of one and 2 hours respectively -- in one subject after the 32 mile hike, orthostatic hypotension was still present 12 hours after completion of the exercise, though there was no documentation of plasma volume or hydration status; d) simple maneuvers such as moving the legs were sufficient to restore blood pressure to normal during acute hypotension, emphasizing the importance of both peripheral redistribution of blood volume and the muscle pump.

More recently, studies by Noakes and colleagues (24) before and after an ultramarathon of 80 km (50 miles) revealed that 68% of runners experienced orthostatic hypotension during quiet standing, defined as a decrease in upright systolic blood pressure of more than 20 mmHg below pre-race upright values (fig 10). Although none of their subjects actually became syncopal, 23% had blood pressures below 90 mmHg and all of these had symptoms of dizziness and nausea and were encouraged to sit.

Fig. 10

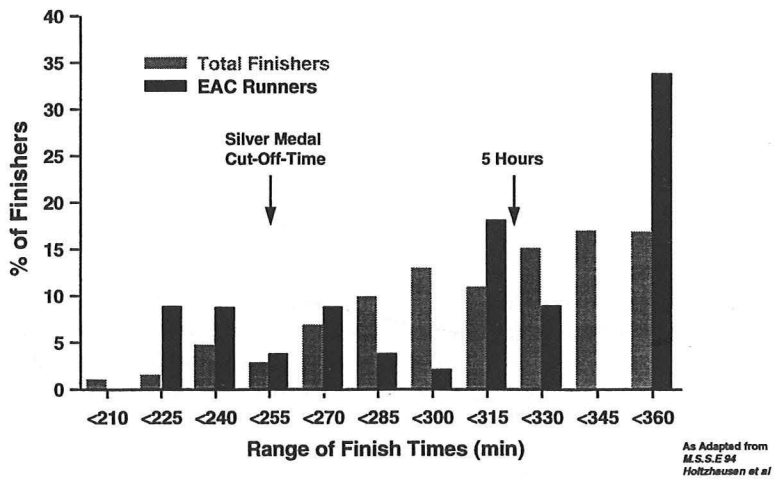


One interesting finding in this study was that the magnitude of the post-race orthostatic hypotension could not be related to the degree of plasma volume lost during the race, despite the fact that on average the runners had lost nearly 5% of body weight. Thus although dehydration probably contributed to reducing left ventricular filling and orthostatic hypotension, it appears likely that other factors regulating distribution of cardiac output such as thermoregulation may be more important. During severe heat stress, nearly a third of the cardiac output may be redirected to the skin to facilitate cooling (25).

In a previous study by the same investigators (26) a fortuitous circumstance allowed the authors to make some important observations regarding collapse of runners after a race. In this study, 75% of the field of nearly 5,000 runners finished in the last hour of the race, resulting in considerable crowding at the finish and forcing the athletes to stand in a slowly moving line for a number of minutes before their finishing times and positions could be recorded (26). This circumstance resulted in 46 runners who collapsed during or after the race. A number of key observations were made: a) the vast majority of these cases of "exercise associated collapse" occurred after the finish line and were associated with normal hemodynamics in the supine position, but orthostatic hypotension when standing; b) the occurrence of collapse appeared to be associated with an extraordinary effort on the part of the participant (fig 11), as evidenced by the increased frequency of collapse in runners who finished near cut off times for medals, or "race closure" (where times are no longer officially recorded; c) 100%

of runners who collapsed during the race had readily identifiable medical conditions such as angina, asthma, gastroenteritis, etc.

Fig. 11



In summary, syncope that occurs immediately following exercise can usually be explained by predictable hemodynamic responses that may be exacerbated in individual circumstances by heat stress, extraordinary effort, and most importantly by standing quietly in the upright position. Table 2 summarizes the potential mechanisms for a reduction in stroke volume leading to syncope.

Table 2a

LVEDV too low

A. ↓ Plasma Volume
   1. dehydration
   2. hemorrhage
B. Volume redistribution
   1. excessive peripheral pooling
   2. heat stress
      - - skin blood flow
C. RVOT obstruction
   1. Pulmonary hypertension
   2. PS

Table 2b

LVESV too high

A. LVOT obstruction
   1. Aortic stenosis
   2. HOCM
B. Contractile dysfunction
   1. Ischemia

In addition to changes in stroke volume, syncope may also be precipitated during or after exercise by an excessive reduction in total peripheral resistance. Table 3 summarizes these mechanisms.

Table 3

TPR too low

A. Excessive metabolic vasodilation
   - failure of sympathetic vasoconstriction (functional sympatholysis)

B. Vasodepressor reflex (sympathetic withdrawal)

C. Inappropriate release of vasodilatory substrates (anaphylaxis)

Although it is possible for vascular resistance to fall during exercise even in the face of an active muscle pump, such as the overwhelming vasodilatation of exercise induced anaphylaxis(27,28) or a vasodepressor reflex causing inappropriate sympathetic withdrawal (29-31), as a general rule, hypotension and true syncope during exercise suggest a potentially life threatening condition that must be carefully sought (32).

Life Threatening Causes of Syncope During Exercise

Most of the life threatening mechanisms of syncope affect cardiac rate (too slow or too fast), rhythm (dyscoordinated cardiac contraction), and/or ventricular filling. Table 4 summarizes these mechanisms. A heart rate that is too slow occurs rarely during exercise, though stimulation of ventricular afferents may induce a reflex bradycardia when these receptors are stimulated chemically (the Bezold-Jarisch reflex), as in myocardial ischemia, or mechanically by very high ventricular pressures such as in aortic stenosis (33), the obstructive form of hypertrophic cardiomyopathy (34), or paradoxically during hypovolemia (the "empty heart syndrome") (35). In the latter situation, a hypercontractile but hypovolemic heart, as is often observed immediately following exercise may dynamically stimulate ventricular mechanoreceptors in a fashion similar to obstructive lesions.

Table 4a

HR too Slow

A. Normal neural input
  1. Bradyarrhythmia or conduction abnormality

B. Abnormal neural input
  1. Cardioinhibitory reflex
    a. "empty heart syndrome"
    b. ↑↑ LV pressure
      - Aortic Stenosis
      - HOCM
    c. Ischemia
      - Coronary Artery Disease
      - Coronary anomaly

Table 4b

HR too fast

A. Tachyarrhythmia
  1. Supraventricular
    a. pre-excitation/afib
    b. other SVT
  2. Ventricular tachycardia/vfib

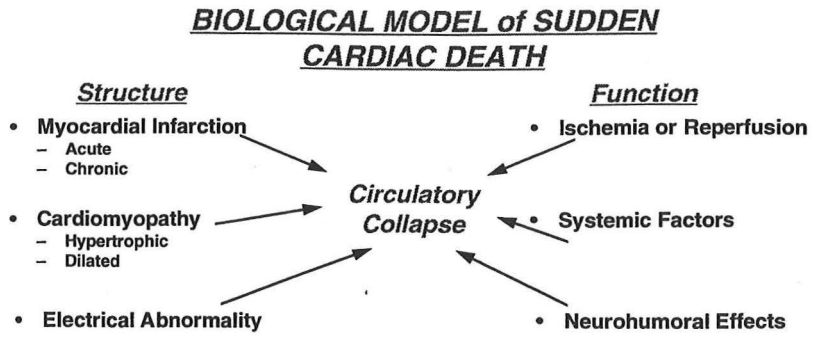
a. "abnormal" substrate	b. "normal" substrate
- myocardial scar (MI, CM)	- catecholamine induced VT
- HOCM	- drugs
- ARVD	
- Long QT	
- Ischemia	

Numerous reports exist in the literature documenting the at times profound bradycardia that can be observed under such circumstances (36-45). In general, simple behavioral modifications are all that are required to prevent recurrence, and medical intervention is rarely necessary. However in certain high risk sports were syncope may cause substantial risk to the life of the athlete (mountain climbing) or spectators (motor sports), more aggressive treatment could conceivably be required if behavioral modifications were unsuccessful (38,46).

More worrisome is a ventricular tachyarrhythmia which may impair left ventricular filling or lead to a failure of contraction and forward stroke volume. It is important to divide arrhythmias into those that are the result of abnormal underlying myocardial substrate, and those which occur in hearts that are otherwise normal. Conditions that lead to *abnormal substrate* include hypertrophic cardiomyopathy, the most common cause of sudden death in young athletes, and coronary artery disease, the most common cause of sudden death in older athletes (47).

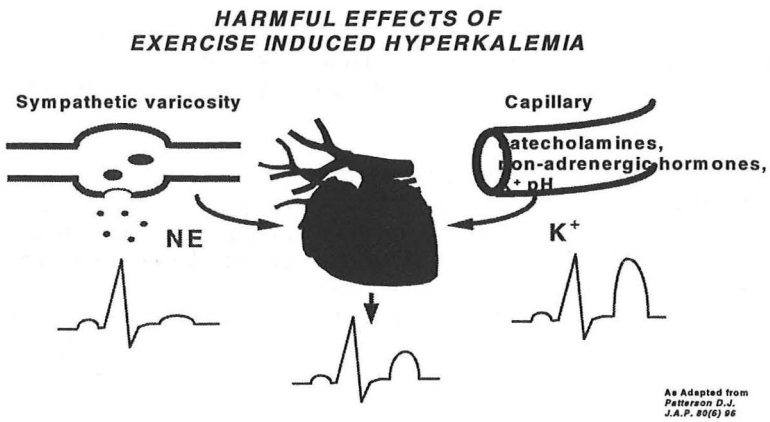
In considering the mechanisms underlying the causes of sudden cardiac death during exercise, it is useful to review the biological model of sudden death originally described by Myerburg (48).

Fig. 12



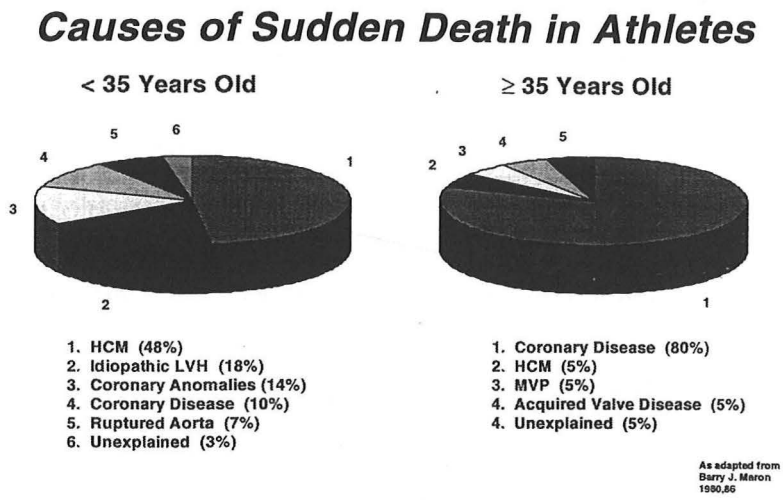
In this model, underlying structural abnormalities are influenced by alterations in functional state to alter contractile function and electrical conduction leading to arrhythmias and ultimately circulatory collapse (48). In addition to the hemodynamic effects of exercise discussed above, there are significant alterations in acid-base balance, electrolyte concentrations, and adrenergic stimulation that have important affects on electrical conduction. In particular, K^+ concentrations may increase to > 7-8 mmol/l, pH may decrease to below 7.10, and norepinephrine and epinephrine concentrations may increase 10 fold during maximal exercise (49). In the normal situation, the effects of catecholamines, and the metabolic effects appear to balance each other out allowing relatively normal conduction patterns, as described in a recent review by Paterson (fig 13).

Fig. 13



When the underlying myocardial substrate is abnormal however, high intensity exercise may lead to severe alterations in conduction patterns and life threatening arrhythmias. The validity of this model has been well documented in the literature in a number of publications investigating the causes of sudden death in athletes on the playing field. The most widely cited study was published by Maron et al (50), who identified the etiology of sudden death in athletes.

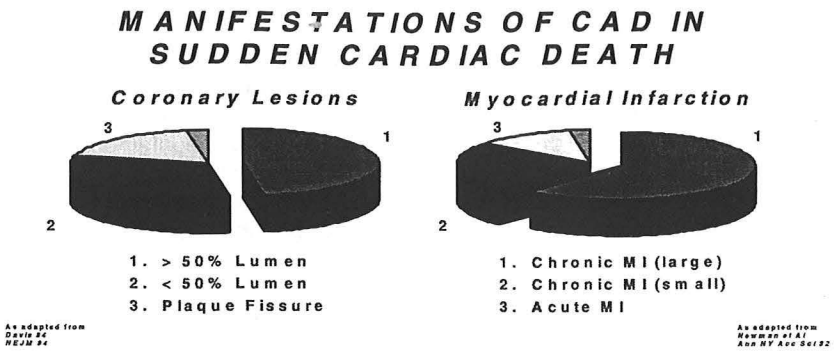
Fig. 14



In this landmark study, all cases of sudden death in athletes from 1950-1979 were systematically identified and the cause of death documented. 29 such deaths were identified with 28/29 having a clear structural abnormality. In young athletes, < 35 yrs, by far the most common abnormality identified was hypertrophic cardiomyopathy (HCM) followed by concentric LVH and coronary artery anomalies (left pie graph).

For older athletes, > 35 yrs, data were pulled from a variety of sources by Maron et al to construct the right pie graph, demonstrating that the vast majority of deaths in this age group are due to coronary artery disease (47). In such individuals, acute myocardial infarction is actually rare. However most patients who die suddenly from coronary artery disease have either an old MI (51) or an acute change in coronary plaque morphology that may or may not obstruct the lumen of the coronary artery (fig 15) (52).

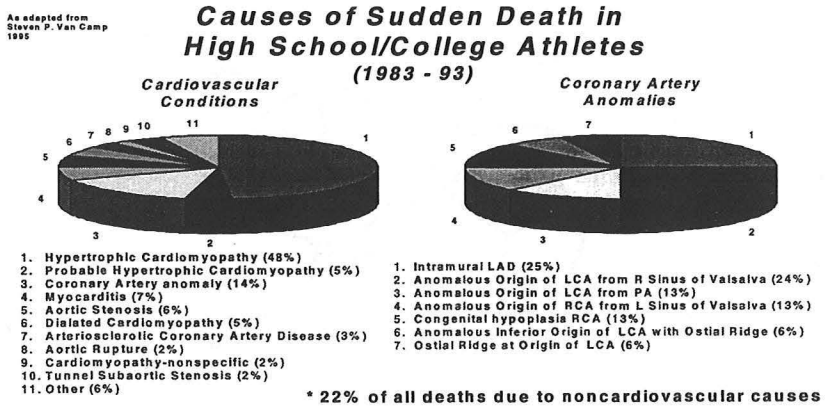
Fig. 15



Thompson has estimated that the rate of death during recreational, non-competitive sports such as jogging in a large population is 1 death/7,620 joggers/year, virtually all due to coronary artery disease (53). The acute risk of exercise in precipitating myocardial infarction has recently been identified (54,55). In all these studies, the risk of death or myocardial infarction during exercise is dramatically lower in regular exercisers as compared to habitually sedentary individuals (53,54,56).

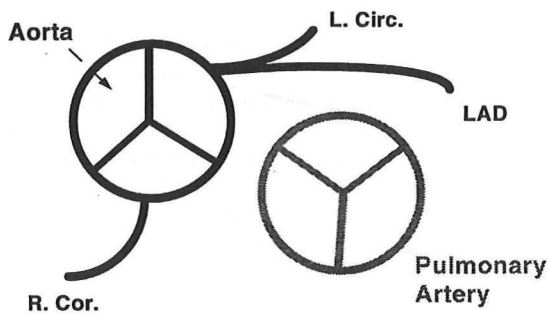
More recently, Van Camp et al (57) used the data base for the National Center for Catastrophic Sports Injury Research to identify 160 deaths in high school and college athletes due to non-traumatic causes between 1983-1993, and were able to ascertain the cause of death in 136 with a high level of confidence (fig 16). Of note, males outnumbered females by approximately 10:1, more than would be expected based on relative rates of participation (2:1).

Fig. 16



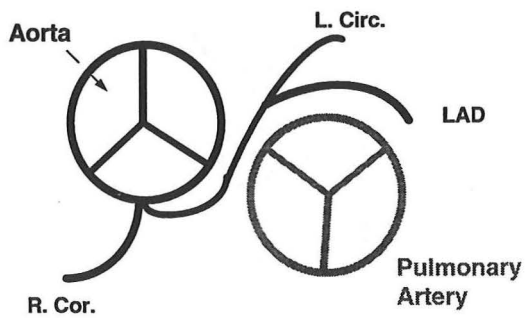
Three important points should be made regarding their data. First of all, in a much larger series, it confirms Maron's original observation that approximately 50% of all athletic deaths from cardiovascular causes are due to hypertrophic cardiomyopathy, with coronary artery anomalies being the second most common cause. Secondly, the most common congenital coronary artery anomaly identified was the anomalous take off of the left main coronary artery from the right sinus of Valsalva. In this condition, the left coronary artery passes between the aorta and pulmonary artery before it reaches the anterior of the left ventricle and presumably becomes compressed during high cardiac output states causing ischemia (58) (fig 17).

Fig. 17a



The normal origin and paths of the coronary arteries with each main branch originating from the appropriate sinus of Valsalva.

Fig. 17b

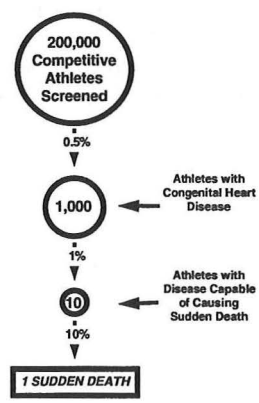


The most common congenital coronary artery anomaly with the left coronary originating from the right sinus of Valsalva and passing between the aorta and pulmonary artery .

Finally, a surprisingly large number of deaths (22%) were from non-cardiovascular causes, with hyperthermia (10%) and rhabdomyolysis in patients with sickle cell trait (5%) being the most common etiologies.

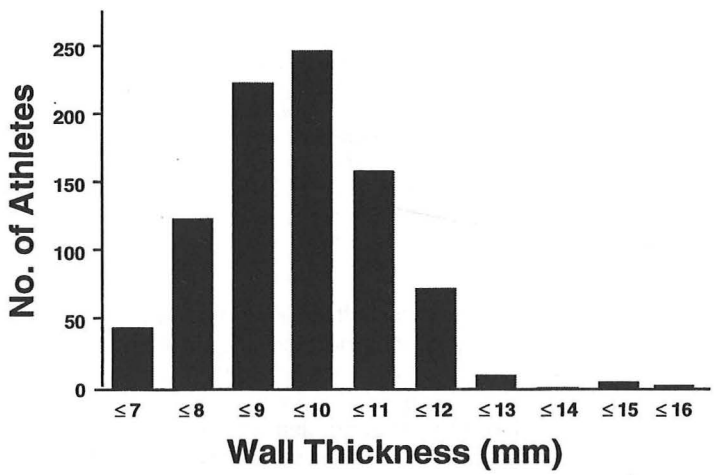
A recent publication by Maron et al (59) now including 158 athletes who died in the United States from 1985-1995 almost certainly duplicates a substantial number of the same patients reported by Van Camp (57). However this update makes 3 important points that were not emphasized in previous reports: a) in contrast to the experience of most tertiary referral centers specializing in hypertrophic cardiomyopathy, a substantial percentage of the sudden deaths during exercise due to cardiomyopathy occurred in blacks (n=59, 44%); b) there continues to be a subset of athletes who only have concentric LVH as the cardiovascular abnormality identified at autopsy as possibly contributing to death. This observation, which was noted in their original series (50) raises the possibility that there may be some gray area between the physiological hypertrophy of the "athletes heart" and the pathologic hypertrophy seen in conditions of increased pressure load (hypertension, AS) or volume load (MR, AI) on the heart; c) only 3/158 (4%) were suspected of having cardiovascular disease on a pre-participation physical exam with only 1 athlete having the correct diagnosis made antemortem (a basketball player with Marfan's syndrome who subsequently died of an aortic dissection). This statistic emphasizes the relative ineffectiveness of current screening procedures in preventing sudden death during sports. Large prospective studies have demonstrated that the yield of such screening is limited (60,61). For example figure 18 demonstrates that roughly 200,000 athletes would have to be screened (out of approximately 30,000,000 participants in high school and collegiate sports/yr) (57) in order to detect 1 athlete with sudden death, assuming a perfectly sensitive and specific test for detecting such an athlete (62).

Fig. 18



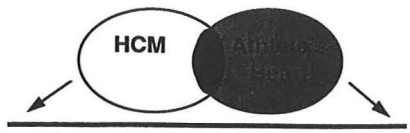
These statistics are compounded by the fact that hypertrophic cardiomyopathy may be particular difficult to diagnose in young competitive athletes in whom ventricular hypertrophy is a common finding (63). Some insight can be gained by a study of >1,000 elite Italian Olympic athletes, all of whom had echocardiography (64). Figure 19 shows the distribution of wall thickness in these athletes from all sports.

Fig. 19



This distribution demonstrates that the majority of even Olympic caliber athletes have a LV wall thickness that is less than 12 mm. The upper limit for wall thickness in these athletes was 15-16 mm, which occurred in some rowers and cyclists. These data suggest that if the LV wall thickness is greater than 16mm, then a pathologic, rather than a physiologic process should be suspected. There are a number of other differences between the athlete's heart and hypertrophic cardiomyopathy that may help to distinguish them (fig 20) (63).

Fig. 20



+	Unusual Patterns of LVH	-
+	LV Cavity < 45 mm	-
-	LV Cavity > 55 mm	+
+	LA Enlargement	-
+	Bizarre ECG Patterns	-
+	Abnormal LV Filling	-
-	¯ Thickness with Deconditioning	+
+	Family History	-
+	Genetic	-

Chromosome
14 - b myosin
1 - troponin T
15 - a tropomyosin
11 - ?

It is important to remember however that particularly in young athletes, full expression of the hypertrophic cardiomyopathy phenotype may not be complete until later in life, thus complicating the diagnosis. Even without the hypertrophy however, myofibrillar disarray makes such patients susceptible to life threatening arrhythmias, particularly if high risk features are present such as: a) family history of sudden death; b) documented presence of non-sustained ventricular arrhythmias; c) severe hemodynamic abnormalities such as a resting gradient > 50 mmHg or exertional hypotension (65).

Other Myopathic Processes

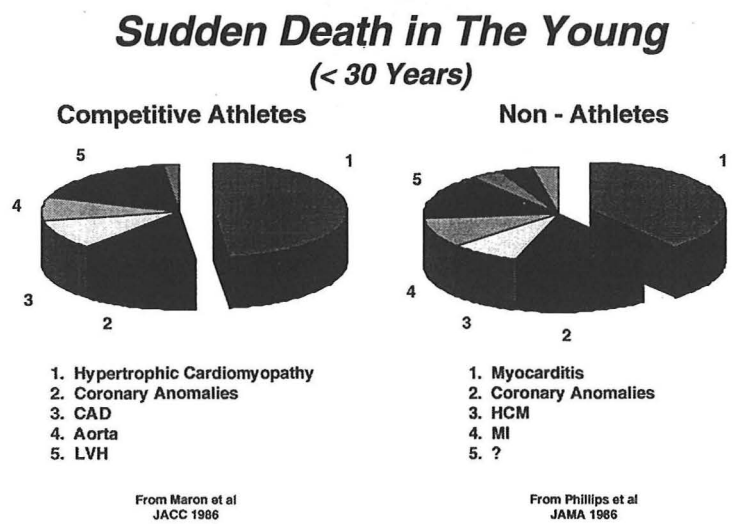
Although the most common cause of death during sports, at least in young American athletes, is clearly left ventricular hypertrophic cardiomyopathy, in some countries right ventricular cardiomyopathy, also termed arrhythmogenic right ventricular dysplasia, is relatively common. Particularly in the Veneto region of northern Italy, 20% of cases of sudden death in young people, <35 yrs of age are due to RVCM (66). This disease is characterized by patchy infiltration of the right ventricular free wall and is associated with hemodynamic and electrophysiological consequences which place the patient at substantial risk for sudden death during exercise. Specific criteria for the diagnosis of this condition have recently been published (67).

In addition to the inherited cardiomyopathies that are important risk factors for syncope and sudden death during exercise, there are also acquired

cardiomyopathies that must be recognized. The one that has received the greatest attention in recent years, particularly in the media has been that caused by cocaine use (65). Many of the recent high profile cases of sudden death in athletes likely had cocaine use as at least a contributing factor. Based in part on work done in the Parkland cath lab, it is now recognized that cocaine causes coronary vasoconstriction, increased myocardial oxygen demand, and may lead over time to a myopathic process that is both ischemic and non-ischemic in origin (68). Unfortunately, the use of cocaine by star athletes appears to be widespread (65).

Another acquired cardiomyopathy that may be more important than previously recognized, particularly in non-athletic populations, is viral myocarditis. In a study of military recruits who died suddenly during basic training, Phillips found pathologic evidence of myocarditis in nearly 40%, substantially more than had undiagnosed hypertrophic cardiomyopathy (69).

Fig. 21

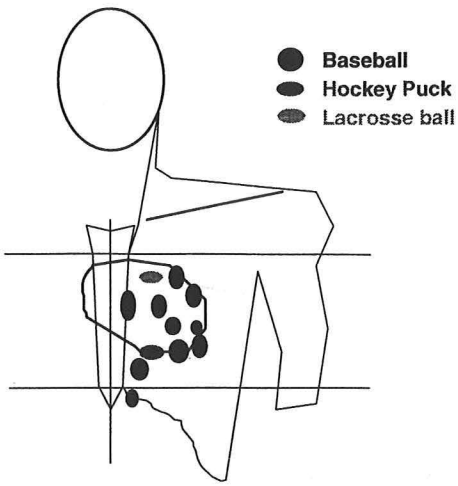


Similar data have also been published from the Israeli Defense Forces in whom a third of sudden deaths during heavy exertion appeared due to myocarditis (70). Most importantly, syncope during exercise occurred before the terminal event in a sizable fraction (23%) highlighting the importance of this phenomenon as a serious warning sign.

Finally, even apparently "normal" substrate may in some cases sustain an arrhythmia, particularly under the influence of drugs, trauma, or medications

(including non sedating antihistamines such as terfenadine, particularly when combined with erythromycin) (71-75). Recently, an article by Maron (76) emphasized the ability of direct trauma to the heart during sports as a potential mechanism for inducing a potentially lethal arrhythmia (fig 22).

Fig. 22



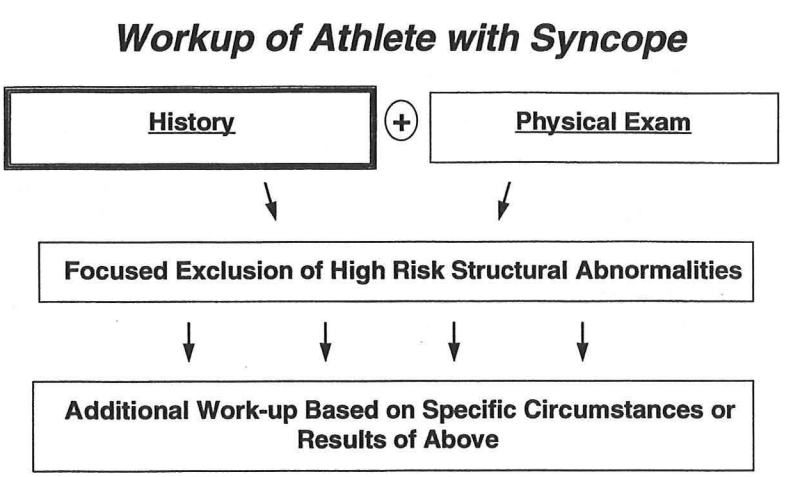
As adapted from
Barry J. Maron
1995

This figure demonstrates the point of contact in 12 cases of sudden death induced by direct trauma with a projectile during sports. Small children with relatively soft and compressible chests may be particularly vulnerable.

A Rational Approach to the Workup of the Athlete with Syncope

With the above pathophysiology in mind, the goal of the workup of an athlete with syncope is to exclude as best as possible, conditions that may be life threatening or result in catastrophic injury (fig 23).

Fig. 23



As outlined in figure 24 and summarized in table 5, the most important component of the workup is the medical history, which may come both from the athlete, as well as from knowledgeable observers.

Table 5

History

- True Syncope vs "collapse"
- Post event state: postictal, incontinence, rapid recovery vs prolonged unconsciousness
- Vital signs at scene
- During vs after exercise
- Prodromal events: palpitations, nausea, pruritis, wheezing, chest pain
- Body position and precipitating events
- Occurrence at other times vs only exercise
- Family history of sudden death

The evaluating physician must first of all distinguish between *true syncope* involving a loss of consciousness and presumably hemodynamic compromise, and the *"exercise associated collapse"* associated with an exhaustive effort. In true syncope from hemodynamic causes, the athlete usually recovers quickly with restoration of arterial pressure, unless resuscitation is required. After collapse associated with an exhaustive effort, athletes usually will have prolonged periods of "being out of it", even in the supine position with normal heart rate and blood pressure. This picture is in contrast to patients with syncope due to heat shock who are universally hypotensive and tachycardic (3,4). Athletes who are "unconscious," but able to assist in their own evacuation are unlikely to be in the immediate throes of a life-threatening arrhythmia, though other metabolic derangements are possible. It is in this *post-event state* that important clues to the etiology, such as seizure activity, incontinence, and *immediate vital signs* (including body temperature) should be sought. It must be emphasized however that seizures not uncommonly occur as a result of hypotension and reduced cerebral perfusion and therefore do not necessarily always imply epilepsy as the underlying cause of the syncope

The second critical distinction that must be made is whether the syncopal event occurred *during* or *immediately following exercise*. Orthostatic hypotension occurring after exercise, usually associated with sudden cessation of the muscle pump is much less ominous than the sudden loss of consciousness that occurs during exercise, which suggests an arrhythmic etiology. Prodromal symptoms such as palpitations (suggesting arrhythmia), chest pain (ischemia, aortic dissection), nausea (ischemia or high levels of vagal activity), wheezing and pruritus (anaphylaxis) are also significant, as is whether it occurs only during exercise, or with other precipitating events. As in the evaluation of syncope in non-athletes, it is also important to identify whether syncope or dizziness occur only in the upright position (orthostatic hypotension) or also sitting or supine (arrhythmia or non-hemodynamic cause). The practice of high risk behaviors such as recreational drug use, or eating disorders (particularly in female athletes) should be carefully investigated, though athletes may not always acknowledge such activity. A comprehensive medication list, including over the counter drugs is necessary. Finally, a family history of sudden death is critical to obtain, and if present, may identify very high risk subgroups with hypertrophic cardiomyopathy, long QT syndrome, or arrhythmogenic right ventricular dysplasia (65,67,77). The physical exam may help to refine a differential diagnosis established during the medical history and tailor further evaluation (table 6).

Table 6

Physical Exam

- **Vital signs supine and upright (at least 5 minutes standing)**
- **BP in arms/legs**
- **Body habits (pectus, Marfanoid features)**
- **Cardiac murmurs at rest and during Valsalva or rise from squatting position**

For all patients with true syncope, and some patients with exercise associated collapse, a focused set of tests designed to exclude high risk structural abnormalities that are known to be associated with sudden death is prudent (table 7).

Table 7

Focused Exclusion of High Risk Structural Abnormalities

ECG	**(QTc, pre-excitation, ST-T wave abnormalities, ischemic complications)**
ECHO	**(LV & RV size and function, valve structure, aortic annulus size, estimation of pulmonary systolic or mean pressure, Left main coronary ostial position)**
Exercise Test	**(Designed to reproduce conditions which provoked event)**

An electrocardiogram should be scrutinized for the presence of repolarization abnormalities, specifically the long QT syndrome, pre-excitation, left or right ventricular hypertrophy, and the complications of ischemic heart disease. An echocardiogram should be evaluated for valve structure, LV size, wall thickness, and contractile function, recognizing that a diagnosis of hypertrophic cardiomyopathy may be complicated in an athlete with physiological hypertrophy. The presence or absence of tricuspid regurgitation along with an estimation of peak right ventricular systolic pressure also should be reported specifically to exclude the diagnosis of pulmonary hypertension. In addition, a careful search for the ostium of the left main coronary artery should be made at the left sinus of Valsalva. If present and clearly identified, the most common life threatening coronary anomaly (take-off of the left coronary artery from the right sinus of Valsalva) can be excluded. Finally, an exercise test should be performed, designed to reproduce the conditions which provoked the syncopal event. Traditional clinical protocols such as the Bruce protocol are usually inadequate for

this purpose, and treadmills with a wide, long belt, rapid start and stop capabilities, and high speeds and grades may be necessary, along with some creativity on the part of the physician and technical staff.

Further diagnostic testing should be guided by the results of the history, physical exam, and focused testing described above (table 8).

Table 8

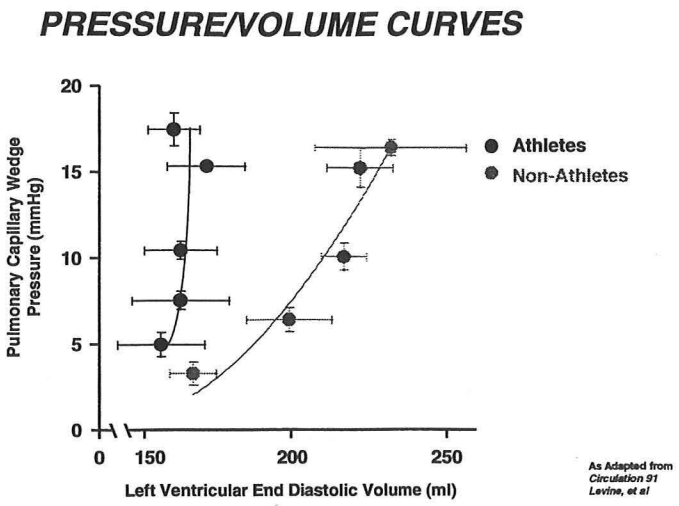
Additional Work-up Based on Specific Circumstances or Results of Above

SZ activity, Post ictal state, Incontinence	Palpitations, Family History, Suspicion of Arrhythmia	Older age, dyslipidemia symptoms of ischemia
↓	↓	↓
EEG, MRI of Brain	Holter, Looping event recorder, Electrophysiological Study	Adjunctive perfusion or contractile imaging following exercise, MRI for coronary anomalies

For example, patients with clear evidence of seizure activity, incontinence, and post-ictal confusion should undergo electroencephalography and magnetic resonance imaging of the brain to exclude a structural lesion in the brain. The presence of palpitations, abnormal ECG, family history of sudden death, or structural cardiac abnormalities should precipitate a more in depth search for an arrhythmia, including a looping event recorder and electrophysiological study for selected high risk patients. Athletes over the age of 35-40, particularly with dyslipidemia, or other risk factors for coronary artery disease may need adjunctive perfusion or contractile imaging after exercise to exclude myocardial ischemia more definitively. Young athletes who have symptoms strongly suggestive of ischemia, particularly if buttressed by objective abnormalities on ECG, echo or exercise testing have traditionally undergone coronary angiography for the exclusion of premature coronary artery disease or coronary anomalies. Magnetic resonance imaging has recently been shown to be an important non-invasive adjunct for this evaluation (78).

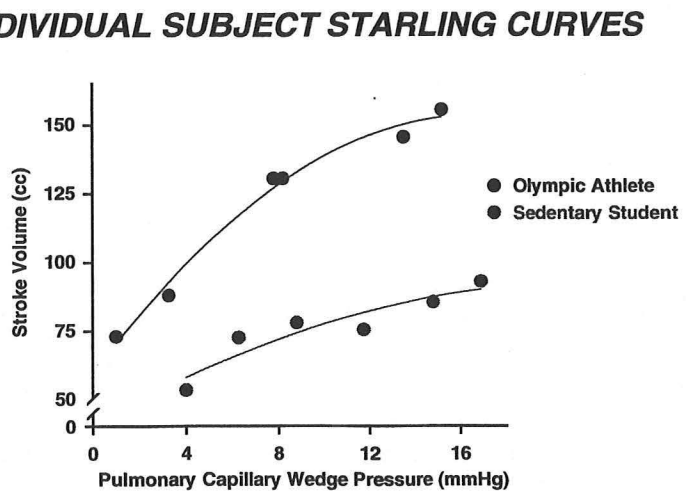
Conspicuously absent from this list is the use of tilt table testing for the diagnosis of neurocardiogenic syncope in endurance trained athletes (79). Well trained athletes develop cardiovascular adaptations that make them uniquely capable of sustaining high levels of aerobic power, including extraordinary vasodilating capacity in skeletal muscle (80) and large, compliant, distensible hearts that operate on the steep portion of the Starling curve (fig 24 a,b)(81).

Fig. 24a



Pressure-Volume curves in endurance athletes demonstrate the remarkable compliance and diastolic reserve (the ability to substantially increase LVEDV with an increase in filling pressure) of the endurance athlete.

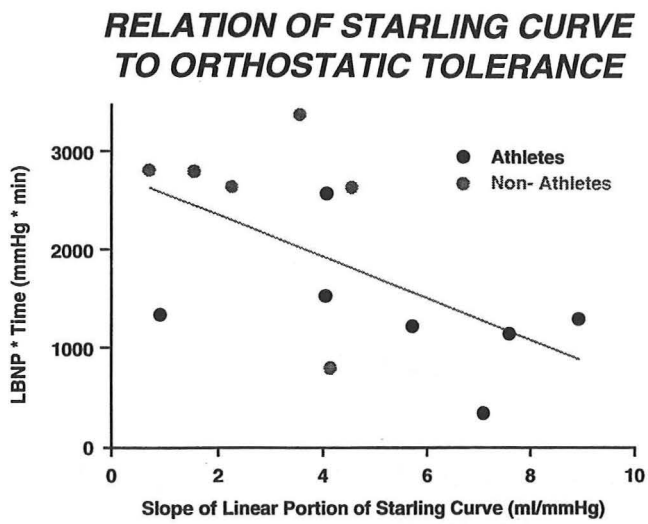
Fig 24b



This increase in LV chamber compliance allows large increases in stroke volume during exercise, but also results in large falls in stroke volume during orthostasis.

These adaptations are beneficial during exercise but place the athlete at a distinct disadvantage during orthostatic stress (fig 25) (13,81).

Fig. 25



The slope of the linear portion of the Starling curve is significantly related to orthostatic tolerance using lower body negative pressure (LBNP).

The unique susceptibility of endurance trained athletes to orthostatic intolerance has been well recognized and carefully investigated over the past 25 years, usually in athletes who do not have a clinical history of syncope (82). A recent symposium organized by the American College of Sports Medicine was recently devoted to this issue from a scientific perspective because of the unique insights it offers into the effect of exercise training on blood pressure regulation (83). Moreover, it is because of this association between exercise training and susceptibility to provocable orthostatic hypotension, that military and NASA pilots are discouraged from engaging in high volume and intensity exercise training. In our experience, nearly all well trained athletes will have premature near or true syncope during orthostatic tests involving lower body negative pressure or upright tilt. Tall athletes (basketball, volleyball, or football players for example), with large heart-to-eye distances and therefore large hydrostatic gradients may be particularly susceptible. Finally, it is important to recognize that tolerance to orthostatic stress is not a discrete variable that is present or absent, as is currently employed in tilt table tests. Rather it is a continuous variable that is an expression of a normal rather than abnormal reflex. Any individual will ultimately develop syncope given an adequate degree of orthostatic stress (84). Thus the presence

of provocable orthostatic hypotension and syncope are so common in endurance athletes without a clinical history of syncope, that routine tilt table testing appears unwarranted (79). The diagnosis of exercise or post-exercise neurocardiogenic syncope in these patients must be made based on the appropriate history, and after exclusion of other life threatening causes.

Footnote:

The fascination that our society has for athletes and exercise is remarkable. Former Chief Justice of the Supreme Court, Earl Warren probably summarized this phenomenon best when he wrote:

"The sports page records people's accomplishments - the front page nothing but their failures."

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