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Sudden Death in Young Adults

An Autopsy-Based Series of a Population Undergoing Active Surveillance

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Objectives The purpose of this study was to define the incidence and characterization of cardiovascular cause of sudden death in the young.

Background The epidemiology of sudden cardiac death (SCD) in young adults is based on small studies and uncontrolled observations. Identifying causes of sudden death in this population is important for guiding approaches to prevention.

Methods We performed a retrospective cohort study using demographic and autopsy data from the Department of Defense Cardiovascular Death Registry over a 10-year period comprising 15.2 million person-years of active surveillance.

Results We reviewed all nontraumatic sudden deaths in persons 18 years of age and over. We identified 902 subjects in whom the adjudicated cause of death was of potential cardiac etiology, with a mean age of 38 ± 11 years. The mortality rate for SCD per 100,000 person-years for the study period was 6.7 for males and 1.4 for females ($p < 0.0001$). Sudden death was attributed to a cardiac condition in 715 (79.3%) and was unexplained in 187 (20.7%). The incidence of sudden unexplained death (SUD) was 1.2 per 100,000 person-years for persons <35 years of age, and 2.0 per 100,000 person-years for those ≥35 years of age ($p < 0.001$). The incidence of fatal atherosclerotic coronary artery disease was 0.7 per 100,000 person-years for those <35 years of age, and 13.7 per 100,000 person-years for those ≥35 years of age ($p < 0.001$).

Conclusions Prevention of sudden death in the young adult should focus on evaluation for causes known to be associated with SUD (e.g., primary arrhythmia) among persons <35 years of age, with an emphasis on atherosclerotic coronary disease in those ≥35 years of age. (J Am Coll Cardiol 2011;58:1254–61) © 2011 by the American College of Cardiology Foundation

Sudden death of the healthy young adult is uncommon, but receives substantial attention from the media and raises issues of accountability for screening programs (1). The relative importance of different etiologies of sudden death varies among studies. Among cohorts collected using passive surveillance (e.g., newspaper accounts and Internet queries), hypertrophic cardiomyopathy was the most commonly identified abnormality in sudden death of young adults and young athletes (2–4). Passive surveillance methods are, however, subject to ascertainment and referral bias. Studies utilizing active surveillance to collect all deaths in a defined population, found by administrative diagnostic coding or death certificate review, have found either no identifiable structural abnormality or coronary artery disease (CAD) in the majority of cases of sudden death (5–11).

Despite advances in defining the causes of sudden death and dramatic developments in the ability to screen for genetic diseases and premature atherosclerosis (12–24), recommendations for screening the young, apparently healthy adult have not changed over the past 4 decades.

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Although guidelines critically consider the role of electrocardiographic and molecular screening in select cases at elevated risk (i.e., recurrent syncope, family history of premature unexplained sudden death), the widespread utility of these technologies is uncertain (12,14,25).

Military personnel provide a unique opportunity to examine the cause-specific nature of sudden death in an ethnically heterogenous population. Each applicant to the military undergoes a screening questionnaire with rejection for hypertension, known structural heart disease, symptomatic arrhythmia, and most congenital anomalies (8). However, disqualification for cardiac or vascular system abnormalities is very rare, with an annual rate of disqualification of 0.015% in the year 2000 (8). The military population is unique in that the exact number of persons under examination is clearly identifiable; all health care, whether in or outside of military health care systems is captured and documented; and there is established centralization of all autopsy reporting. Active surveillance in health and in death, with routine performance of an autopsy, allows for reduction of case referral bias, as might be seen in high-profile cases with disproportionate media attention. We describe the leading causes of death in this active surveillance population.

Methods

The patient population included all uniformed personnel from the Department of Defense. Anyone dying while on active duty was included, from initial entry (i.e., recruits) and those throughout active service, but excluding retired personnel. All uniformed personnel, whether in a combatant or support role, are required to maintain a level of both physical fitness and weight control throughout active service. The most recent demographics find that the population under surveillance has an average age of 28.2 years and is 84.0% male; and although not recorded before 2003, the most recent accession data identified an entry population that self-reported as 72.7% Caucasian, 15.0% African American, 1.2% Pacific Islander, and 2.6% Asian.

For each death, a detailed report to include autopsy is filed with the Armed Forces Institute of Pathology in accordance with established protocol (26). Although not all autopsies were performed at the Armed Forces Institute of Pathology, in Washington, DC, the Office of the Armed Forces Medical Examiner system appoints Regional Medical Examiners, board certified in forensic examination by the American Board of Pathology, to serve as worldwide consultants. Nontraumatic deaths were identified through the Department of Defense mortality registry. Cases were eligible for review if they were categorized as sudden unexplained deaths (SUD) or deaths due to the following causes: cardiac, exertional heat illness, vascular, asthma, and all exercise-related deaths not elsewhere classified. Demographic data and details surrounding the circumstances of the fatal incident were obtained from the pathology reports, reports from the criminal investigative division, and available antemortem medical records.

Abbreviations and Acronyms

ASCAD = atherosclerotic coronary artery disease

CAD = coronary artery disease

SCD = sudden cardiac death(s)

SUD = sudden unexplained death(s)

The records from each case which met the inclusion criteria were assembled and reviewed by the authors. Adjudication of each case by at least 3 authors was performed, and a final determination was made as to clinical cause of death. In no case was there exclusion of a case due to disagreement as to characteristics and etiology of death. Sudden death was defined as an event resulting in death or terminal life support within 1 h of collapse, or an unwitnessed but unexpected death in the absence of known or suspected condition that may predispose to terminal illness. Deaths were defined as cardiac in origin if there was autopsy confirmed heart disease with clinical circumstances consistent with a potential cardiac etiology of death (excluding, for example, incidental cardiac disease in a patient who experienced traumatic death). SUD was defined as any sudden death unexplained by pre-existing disease and without identifiable cause on post-mortem examination.

Specific cardiac causes of sudden death were defined as follows: atherosclerotic coronary artery disease (ASCAD) was considered the cause when gross pathologic and/or histopathologic findings indicated an acute or recent myocardial infarction or occlusive ASCAD. Hypertrophic cardiomyopathy was based on gross pathologic and histologic findings consistent with the diagnosis (27,28), to include nondilated left ventricular hypertrophy, in the absence of coexistent disease that could cause in magnitude of hypertrophy evident. Myocarditis was based on histopathologic diagnosis of inflammatory infiltrates in accordance with Dallas criteria (29). Dilated cardiomyopathy was based on left ventricular dilation in the absence of histologic changes consistent with an inflammatory cardiac condition and in the absence of CAD. Anomalous coronary arteries were considered causative when specific anomalies known to be associated with sudden death were noted on autopsy or a coronary anomaly was the only finding. Those anomalies felt to be associated with sudden death included any anomalous left main coronary artery with take-off from the right coronary cusp and a course between the pulmonary artery and aorta, anomalous right coronary artery with oblique take-off, and regional acute or chronic corresponding regional perfusion defect. Separate coronary ostia, cloacal left main coronary artery, and anomalous circumflex off the right coronary cusp were not considered to be causative of sudden death. Hypertensive cardiomyopathy was based on left ventricular hypertrophy or dilation in the setting of known clinical hypertension. Arrhythmogenic right ventricular dysplasia was based on gross pathologic and histologic findings focusing on structural and histologic manifestations (30). Ischemic heart disease was attributed as the cause of

death when evidence of remote myocardial infarction was present.

Crude mortality rates are presented as deaths per 100,000 person-years (calculated by multiplying numeric death rates [number of deaths per number of population] by period of observation). Population data were obtained from the Defense Manpower Data Center (31). The annual variability of the total population was <3.9% with a standard deviation of 1.4% (maximum observed population 1.42 million annually, minimum observed population 1.37 million annually, mean 1.39 ± 0.02 million persons annually). Confidence intervals for mortality rates were calculated by method of Poisson's distribution. Student *t* test was used for comparison of continuous variables and the chi-square test for categorical variables. All p values were considered significant when <0.05. Statistical analysis was performed using JMP Professional software (SAS Institute, Cary, North Carolina). The study was approved by the institutional review board, and sponsored by a grant from the Air Force Medical Research Program (AF/SGRS).

Results

For the period from 1998 to 2008, there were 14,771 deaths identified. Of this population, 5,681 deaths were due to accidents, 3,811 were due to enemy hostile action, 478 were the result of homicide, 1,997 were the result of suicide, and 75 were the result of terrorist attacks. Of the 2,729 remaining cases, there were 1,044 nontraumatic suspected cardiac deaths identified from 1998 to 2008. Of these, we excluded 51 (5.1%) subjects for lack of clinical record or autopsy, 130 (12.5%) subjects for unavailability of records, and 12 (1.2%) subjects for what was determined to be a clear noncardiac etiology. We identified 902 subjects with full records available for review for whom the adjudicated cause of death was of potential cardiac etiology, which serves as our cohort.

The mean age of the population was 38.4 ± 10.5 years (median 39.6 years, interquartile range [25th, 75th percentiles]: 30.4, 45.9 years), and 871 male (96.6%). The mortality rate for sudden cardiac death (SCD) per 100,000 person-years for the study period was 6.68 (95% confidence interval: 6.24 to 7.14) for males and 1.40 (95% confidence interval: 0.95 to 1.98) for females ($p < 0.0001$). As seen in Figure 1, mortality rates increased with age from 3.25 per 100,000 person-years for subjects <20 years of age, to 105.57 per 100,000 person-years for those >50 years of age. Mortality rates were not statistically different for males and females under 20 years of age ($p = 0.084$) or 20 to 24 years of age ($p = 0.067$), but point estimates were consistent with a trend for greater deaths among males. However, sudden death mortality rates were greater for males than for females for all other age groups ($p < 0.01$). Demographics of the population are in Table 1. The population was predominantly Caucasian, although African Americans were also well represented. Anthropometrics revealed that subjects ≥35 years of age weighed slightly more than those <35 years of age, but were no more likely to be considered either overweight or obese using standard definitions (32).

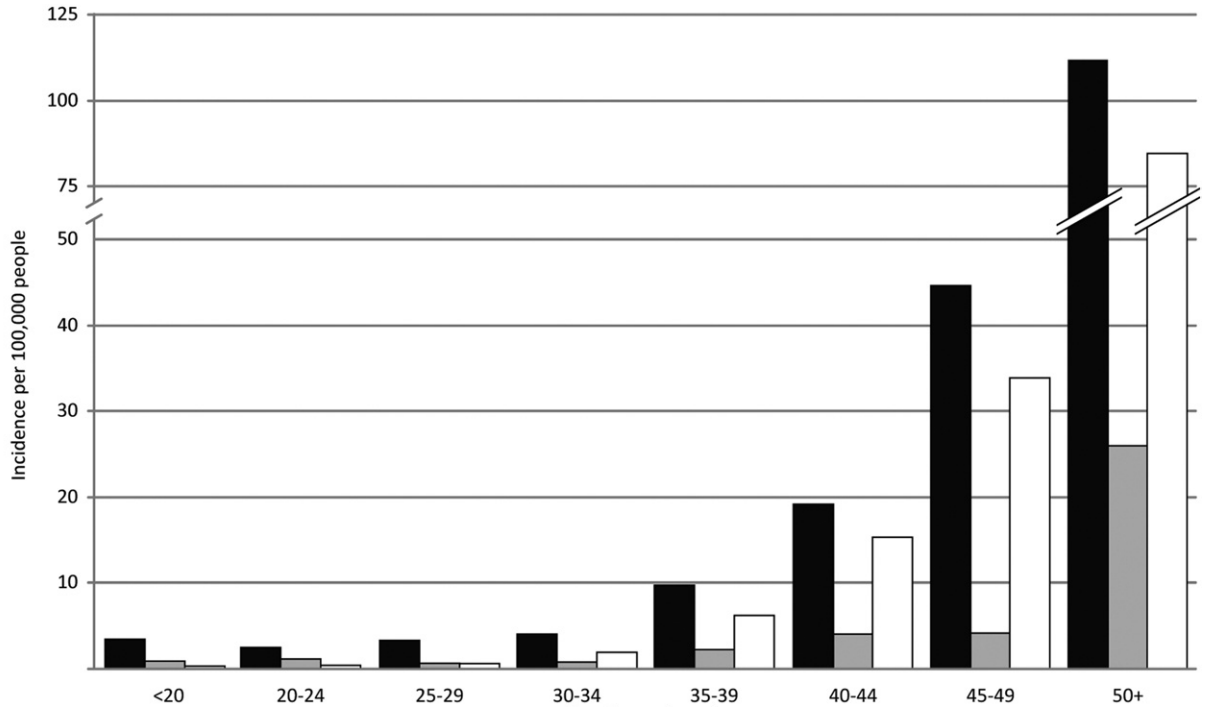
Circumstances of sudden death. Death was witnessed in 617 (68.4%) cases, and verified as temporally associated with exertion in 361 (40.0%) of witnessed cases, as seen in Table 2. Sudden death during exertion was more common among those <35 years of age compared with those ≥35 years of age (140 of 298 [47.0%] vs. 221 of 604 [36.6%]; $p < 0.001$). The majority of exertional deaths were during recreational sports. Sudden death during "military training" was almost exclusively during organized physical training (138 of 150 [92.0%]). While organized physical training includes a combination of calisthenics, strength-building exercises, and aerobic cardiovascular conditioning, in most cases, the specific activity at the time of death was not reported. The most commonly reported activity temporally related to death during organized physical training was running, which was reported in 114 (31.6%) of the exertional deaths.

Information was available on 528 (58.5%) subjects that allowed for the definitive determination of presence or absence of any prodrome within the week before the terminal event. A prodrome was documented in 278 (52.7%) of those who died. Symptoms reported included chest pain in 142 (51.8%), dyspnea in 61 (21.9%), and syncope in 20 (7.2%). Further results as to outcome of testing, if any, referable to identified prodrome was not available, and in many cases, the prodrome was immediately antecedent to death.

Death was reported as out of the hospital (205 [22.7%]), within the Emergency Department (462 [51.2%]) or after admission to the hospital (108 [12.0%]), and was otherwise not specified (107 [11.8%]). Of the 570 subjects transported to the hospital, the initial cardiac rhythm was reported in 122 (21.4%) subjects. The reported rhythms included ventricular fibrillation (62 [50.8%]), asystole (40 [32.8%]), electromechanical dissociation/pulseless electrical activity (11 [9.0%]), pathologic bradycardia (5 [4.1%]), and ventricular tachycardia (4 [3.3%]). On-scene treatment was reported to have occurred in 638 (70.7%), to include cardiopulmonary resuscitation in 605 (67.1%), attempted external shock in 267 (29.6%), and documented care by an advanced cardiac life support provider in 533 (59.1%).

Causes of sudden death. Sudden death was attributed to an identifiable structural cardiac finding in 715 (79.3%) and was without structural abnormality identified (SUD) in 187 (20.7%) (Tables 3 and 4). In subjects <35 years of age, the leading cause of death was SUD (n = 123 [41.3%]), whereas in those ≥35 years of age, the leading cause of death was ASCAD (n = 442 [73.2%]).

DEATH DUE TO ATHEROSCLEROTIC CORONARY DISEASE. There were 511 deaths due to ASCAD, with a mean age of 43 ± 8 years. The incidence of death due to ASCAD was 0.65 per 100,000 person-years for those <35 years of age, and 13.69 per 100,000 person-years for those ≥35 years of age ($p < 0.001$). There were 206 (40.3%) deaths during



	<20	20-24	25-29	30-34	35-39	40-44	45-49	50+
■ Males	3.37	2.44	3.32	3.99	9.69	19.22	44.65	111.45
■ Females	0.83	1.09	0.62	0.68	2.13	3.96	4.08	25.94
RR	3.72	1.96	4.53	5.90	4.30	4.80	10.18	6.11
95% CI	0.9-15.5	1.0-3.9	1.4-14.4	1.5-24.0	1.8-10.5	2.0-11.7	2.5-41.1	1.9-19.2
□ASCAD	0.26	0.33	0.52	1.77	5.82	14.40	31.90	83.54

Figure 1 **Mean Incidence of SCD as Function of Age, Stratified by Sex and Overall Incidence Due to ASCAD**

Data table demonstrates incidence per 100,000 people under active surveillance, relative rate (RR) and 95% confidence interval (CI) comparing incidence of sudden cardiac death (SCD) in males **(solid bars)** to females **(shaded bars)**. Additional information includes incidence of atherosclerotic coronary artery disease (ASCAD) **(open bars)** as a function of age.

exertion, most commonly physical fitness training (n = 103 [44.6%]) or recreational sports (n = 81 [35.1%]). A prodrome was reported in 166 (32.4%) subjects, with chest pain reported in 111 (21.7%), dyspnea in 27 (5.3%), palpitations in 2 (0.4%), and syncope in 2 (0.4%).

Comparing sequential age groups of males, mortality from atherosclerotic disease as a function of increasing age group demonstrated no significant increase in mortality due to atherosclerotic coronary disease until after age 30 years (Fig. 1). There was a statistically significant increase in mortality due to atherosclerotic coronary disease in each age group beyond age 30 years, with a relative risk from 2.27 to 3.33 for each 5-year period. Among females, mortality as a function of increasing age group demonstrated no significant change in mortality with each successive age group, but due to male predominance in the sample, the analysis was under-powered.

Risk factors and known serologic levels of lipids are as noted in Table 5. The mean total cholesterol at the time of death from atherosclerosis was 215 mg/dl, with a mean high-density lipoprotein cholesterol of 40 mg/dl. On autopsy of subjects who died of atherosclerotic coronary disease, the mean cardiac mass was 457 ± 77 g, with a mean maximal left ventricular wall thickness of 1.6 ± 0.4 cm. There was evidence of remote myocardial infarction or fibrosis in 156 (30.5%) cases, with suggestion of recent myocardial infarction with ongoing necrosis in 50 (9.8%). Among deaths due to ASCAD, the incidence of antemortem symptoms referable to cardiovascular disease was 56.1%.

DEATH DUE TO HYPERTROPHIC CARDIOMYOPATHY AND HYPERTENSIVE CARDIOMYOPATHY. There were 83 subjects who died of either hypertrophic cardiomyopathy (n = 57 [6.3%]) or hypertensive cardiomyopathy (n = 26 [2.9%]). The mortality rate from hypertrophic cardiomyopathy was 0.41 per 100,000 person-years, and from hypertensive cardiomyopathy, it was 0.19 per 100,000 person-years.

There was no difference in the cardiac mass of subjects with death due to hypertrophic cardiomyopathy compared to those with death due to hypertensive cardiomyopathy (501 ± 77 g vs. 505 ± 78 g, p = 0.867), nor in maximal left ventricular thickness (2.0 ± 0.4 cm vs. 1.9 ± 0.3 cm, p =

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Table 1 Demographic and Clinical Characteristics of 902 Cases of Adjudicated Unanticipated Sudden Cardiac Death in a Cohort Undergoing Active Surveillance, Stratified by Age <35 Years or ≥35 Years

Characteristics	Total (n = 902)	<35 Yrs of Age (n = 298)	≥35 Yrs of Age (n = 604)	p Value
Age, yrs	38 ± 11	26 ± 5	45 ± 6	<0.001
Race				<0.001
Caucasian	608 (67.4%)	176 (59.1%)	432 (71.5%)	
African American	217 (24.1%)	100 (33.6%)	117 (19.4%)	
Pacific Islander	19 (2.1%)	7 (2.4%)	12 (2.0%)	
Asian	17 (1.9%)	6 (2.0%)	11 (1.8%)	
Male	871 (96.6%)	282 (94.6%)	589 (97.5%)	0.032
Anthropometrics				
Height, inches [cm]	71 ± 3 [180 ± 8]	70 ± 3 [178 ± 8]	71 ± 4 [180 ± 10]	0.448
Weight, pounds [kg]	199 ± 32 [91 ± 15]	192 ± 33 [87 ± 15]	204 ± 30 [93 ± 14]	<0.001
Body surface area, m^2	2.12 ± 0.20	2.08 ± 0.20	2.14 ± 0.19	<0.001
BMI, kg/m^2	28.3 ± 4.2	27.4 ± 4.6	28.8 ± 0.19	<0.001
Medical history				
Overweight, BMI >25 kg/m^2	427 (47.3%)	143 (48.0%)	284 (47.0%)	0.839
Obese, BMI >30 kg/m^2	167 (18.5%)	52 (17.5%)	115 (19.0%)	0.626
Diabetes mellitus	10 (1.1%)	1 (0.3%)	9 (1.5%)	0.179
Hypertension	115 (12.8%)	19 (6.4%)	96 (15.9%)	<0.001
Hyperlipidemia	99 (11.0%)	14 (4.7%)	85 (14.1%)	<0.001

Values are mean ± SD or n (%).
BMI = body mass index.

0.466). Myofibrillary disarray was only positively identified in 12.3% of cases diagnosed with hypertrophic cardiomyopathy. Hypertrophic cardiomyopathy was described in reports most commonly as "asymmetric left ventricular hypertrophy," but also as "sigmoid septum in the setting of biventricular hypertrophy" and "massive enlargement of interventricular septum." It is uncertain if these cases of increased left ventricular mass represent a phenotypic variation of the more conventional hypertrophic cardiomyopathy, and further research in this regard is intended (28).

Table 2 Specific Activities at Time of Exertional Sudden Death in 361 Young Adults

Recreational sports	186 (51.5%)
Running	114 (31.6%)
Basketball	20 (5.5%)
Walking	14 (3.9%)
Swimming	11 (3.0%)
Weightlifting	5 (1.4%)
Baseball	4 (1.1%)
Biking	4 (1.1%)
Military training	150 (41.6%)
Organized physical training*	138 (38.2%)
Road march/land navigation	7 (2.0%)
Miscellaneous	5 (1.4%)
Miscellaneous	17 (4.8%)
Not specified	8 (2.2%)

*Organized physical training defined as group-level activity to include performance of physical fitness testing (sit-up, push-ups, and timed distance running). Additional recreational sports representing <1% included football (n = 3), racquetball (n = 3), soccer (n = 3), volleyball (n = 2), hiking (n = 1), paintball (n = 1), and tennis (n = 1). Miscellaneous causes included moving furniture and/or equipment (n = 8), mowing lawn (n = 4), dancing (n = 2), fighting (n = 2), and sexual intercourse (n = 1).

SUDDEN UNEXPLAINED DEATH. There were 187 sudden deaths without identifiable alternative cause, representing 41.3% of all deaths of persons <35 years of age, and 10.6% of all deaths of persons ≥35 years of age. There was no statistically significant difference in the identification of sudden unexplained death as a function of race (Caucasian 20.1%, African American 22.6%, Asian 23.5%, Pacific

Table 3 Cause-Specific Findings in 902 Cases of Adjudicated Unanticipated Sudden Cardiac Death Stratified by Age <35 Years and ≥35 Years in a Cohort Undergoing Active Surveillance

Findings	<35 Yrs of Age (n = 298)	≥35 Yrs of Age (n = 604)	p Value
Sudden unexplained death	123 (41.3%)	64 (10.6%)	<0.001
Atherosclerotic disease	69 (23.2%)	442 (73.2%)	<0.001
Hypertrophic cardiomyopathy	38 (12.8%)	19 (3.1%)	<0.001
Myocarditis	17 (5.7%)	13 (2.2%)	0.009
Idiopathic dilated cardiomyopathy	14 (4.7%)	21 (3.5%)	0.478
Anomalous coronary artery	12 (4.0%)	1 (0.2%)	<0.001
Hypertensive cardiomyopathy	11 (3.7%)	15 (2.5%)	0.419
Arrhythmogenic RV dysplasia	4 (1.3%)	6 (1.0%)	0.737
Ischemic cardiomyopathy	2 (0.7%)	14 (2.3%)	0.135
Other*	8 (2.7%)	9 (1.5%)	—

Data presented as raw (columnar percent [incidence]). *Other cases (n = cases <35 years of age, cases ≥35 years of age, respectively): additional causes of death associated with coronary artery disease included coronary artery bridge (n = 6, 1), spontaneous coronary thrombosis (n = 1, 2%) and spontaneous coronary dissection (n = 0, 1); causes of death associated with valvular heart disease included aortic valve disease (n = 0, 3), mitral valve disease (n = 1, 1), and endocarditis (n = 0, 1).
RV = right ventricle.

Table 4 Leading Cause-Specific Findings in Adjudicated Unanticipated Sudden Cardiac Death Stratified by Age <35 Years and ≥35 Years and Exertional Status in a Cohort Undergoing Active Surveillance

	<35 Yrs of Age		≥35 Yrs of Age	
Findings	Exertional (n = 140)	Nonexertional (n = 158)	Exertional (n = 221)	Nonexertional (n = 383)
Sudden unexplained death	54 (38.6%)	69 (43.7%)	19 (8.6%)	45 (11.8%)
Atherosclerotic disease	34 (24.3%)	35 (22.2%)	172 (77.8%)	270 (70.5%)
Hypertrophic cardiomyopathy	19 (13.6%)	19 (12.0%)	8 (3.6%)	11 (2.9%)
Myocarditis	5 (3.6%)	12 (7.6%)	1 (0.5%)	12 (3.1%)
Idiopathic dilated cardiomyopathy	2 (1.4%)	12 (7.6%)*	5 (2.3%)	16 (4.2%)
Anomalous coronary artery	11 (7.9%)	1 (0.6%)*	0 (0.0%)	1 (0.3%)

Data presented as raw (columnar percent [incidence]). Comparison of exertional versus nonexertional without statistical significance except as annotated (*$p < 0.001$).

Islander 21.1%; $p = 0.947$). There was no difference in the incidence of prodrome comparing subjects with death due to SUD (48.5%) and death due to ASCAD (56.1%, $p = 0.231$). Comparing subjects with sudden unexplained death to those with death due to ASCAD, the incidence of antemortem syncope or palpitations was 7.5% versus 2.2%, respectively ($p = 0.002$), and of chest pain or dyspnea, it was 4.3% versus 14.5% ($p < 0.001$).

Discussion

This autopsy-based series, using active surveillance of patients in a defined population, found that sudden unexplained cardiac death, presumably arrhythmic, is the most common cause among patients <35 years of age, and as expected, atherosclerotic heart disease increases in importance over the age of 30 years, becoming the dominant cause.

Active surveillance trials in studies using autopsy for definitive diagnosis have previously suggested similar results (6,8,9,33). In an Italian group studied from 1979 to 1999, within an ethnically homogenous population of nearly 4.4 million, researchers found 300 cases of sudden death among young adults (ages 12 to 35 years) who had undergone screening by history, physical examination, electrocardiogram, and limited exercise testing (33). In this group, SUD was the leading cause of death (25.6%), followed by atherosclerosis (20.9%) and arrhythmogenic right ventricular dysplasia (13.4%). Hypertrophic cardiomyopathy was found in only 8.3% of cases. Likewise, in a smaller cohort in Olmstead County, Minnesota, from 1960 to 1989, among those <35 years of age with SCD (n = 23), SUD (47.8%) and atherosclerosis (34.8%) were the most common causes of death (34). Previous work by our group using a cohort of recruits (e.g., limited to those within the first 10 weeks of initial entry to the military) found that in review of 6.3 million initial entry trainees from 1977 through 2001, there were 126 sudden, nontraumatic deaths during training, with no previously documented cardiovascular disease and no known family history. In that population, with a median age of 19 years, the leading causes of death were sudden unexplained cardiac death (34.9%), or death related to coronary pathology (30.9%) (8). In contrast to the present study, prior work was limited to sudden deaths that occurred specifically during initial entry training to the military, whereas current work is not only more comprehensive in period of observation, but is also more representative of differing socioeconomic status. Doolan et al. (9) reported a series of 10,199 autopsies in a region serving >2 million persons in Australia; of 193 SCD in young adults, sudden death occurred in the setting of a structurally normal heart in 60 (31.1%), with the combination of hypertrophic cardiomyopathy/unexplained left ventricular hypertrophy in 29 (15.0%). Similarly, utilizing a nationalized autopsy database in Sweden, Wisten et al. (6) identified SUD in the setting of a structurally normal heart in 38 (21.0%) and hypertrophic cardiomyopathy in 19 (10.5%). Thus, although sudden unexplained cardiac death is consistently the most common category of sudden death in young adults, work by Ackerman and Tester (23) have shown that more than one-third

Table 5 Demographic and Clinical Characteristics of the 2 Leading Causes of Sudden Cardiac Death in 902 Cases in a Cohort Undergoing Active Surveillance

Characteristics	ASCAD (n = 511)	SUD (n = 187)	p Value
Age, yrs	43 ± 8	32 ± 11	<0.001
Age <35 yrs	69 (13.5%)	123 (65.8%)	<0.001
Male	503 (98.4%)	174 (93.1%)	<0.001
Medical history			
Obese, BMI >30 kg/m^2	99 (19.4%)	25 (13.4%)	0.084
Diabetes mellitus	11 (2.2%)	3 (1.6%)	0.770
Hypertension	137 (26.8%)	23 (12.3%)	<0.001
Hyperlipidemia	156 (30.5%)	18 (9.6%)	<0.001
Cholesterol screening	126 (24.6%)	40 (21.4%)	
Total cholesterol	215 [184, 243]	182 [159, 216]	<0.001
HDL	40 [34, 51]	47 [39, 60]	0.004
LDL	137 [112, 164]	116 [97, 140]	0.003
Triglycerides	134 [94, 215]	92 [55, 139]	<0.001

Values are mean ± SD, n (%), or median [interquartile range at 25%, 75%], with comparisons done using Mann-Whitney U test for nonparametrics

ASCAD = atherosclerotic coronary artery disease; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SUD = sudden unexplained death.

of these unexplained cases are associated with a currently identifiable ion channel mutation.

There are several potential causes of SUD in our cohort. First, we cannot exclude that structural abnormalities escape detection in some cases, but given the intense search for a cause, until we can pursue ultrastructural or molecular disease as a course of clinical care, this will remain a limitation to autopsy-based studies. Under-identified focal myocarditis, mild right ventricle involvement with arrhythmogenic right ventricular cardiomyopathy/dysplasia and hypertrophic cardiomyopathy cannot be excluded, although the methods allowed for a comprehensive identification. Potential causes for death in an otherwise normal-appearing heart may include an accessory pathway (i.e., Wolff-Parkinson-White) with a rapid arrhythmia due to atrial fibrillation, ion channel abnormalities including the long-QT syndrome, short-QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and early repolarization syndromes. Investigators with the ORE-SUDS (Oregon Sudden Unexplained Death Study) database (16) identified 12 patients who experienced SUD, and potassium channel defects were identified in 17%. Genetic testing of kindred of those who experienced SUD report as many as 40% with a mutation responsible for catecholaminergic polymorphic ventricular tachycardia, long-QT syndrome, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy/dysplasia, hypertrophic cardiomyopathy, or familial dyslipidemias (12,23,35).

Study limitations. By virtue of a military population, there is risk of ascertainment bias. Although exclusion from military service due to cardiovascular causes is extremely rare, persons who pursue military training are not likely to be experiencing symptoms that may be referable to cardiovascular disease, no different from self-selection of subjects in athlete studies. Additionally, a person with a known pre-existing disease state that might preclude participation in strenuous athletic or military training may never join the military and would, therefore, never come to the attention of the investigators. That limits the generalizability of our findings to persons with no known childhood disease state. Mandated weight control and physical fitness standards may limit the generalizability to groups with a similar lifestyle. Additionally, there is the possibility that the adjudicated cause of death was not representative of the mechanism of death. Although autopsy reports and available records were available in all included cases, there was no reexamination of the originally submitted gross or histologic material beyond that previously performed, and may or may not have been originally performed by any of the authors.

Conclusions

Our findings suggest that prevention of sudden death among young adults under the age of 35 years should focus on evaluation for causes not associated with structural heart disease, classified as SUD. There should be a continued focus on the prevention of atherosclerotic heart disease starting at an age younger than that normally considered to be at risk. Because symptoms referable to cardiovascular disease were not commonly reported, lipid panels only demonstrated small variations from the mean, and the overall low risk profile of the patients experiencing events, consistent with that of prior studies (36,37); newer risk factors and advanced, safer imaging may be requisite before we can make an impact on identifying persons at risk for premature sudden death due to atherosclerosis.

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Key Words: hypertrophic cardiomyopathy ■ resuscitation ■ sudden death ■ unexplained death ■ young adult.