

Cardiac pathologic findings reveal a high rate of sudden cardiac death of undetermined etiology in younger women

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Background Between 1989 and 1998 there was a 21% increase in estimated sudden cardiac death among US women aged 35 to 44 years. In contrast, the sudden cardiac death rate in age-matched men showed a decreasing trend (−2.8%). Due to under-representation of younger adults in published autopsy series, etiologies of sudden cardiac death merit further investigation.

Methods We reviewed autopsy and detailed cardiac pathologic findings in younger women (age 35-44 years) from a 270-patient, 13-year (1984-1996) autopsy series of sudden cardiac death, and performed comparisons with findings in age-matched men.

Results Women aged 35 to 44 years constituted 32% of all women in the series compared to men, who constituted 24% of total men ($P = .004$ vs women). A presumptive cause of sudden cardiac death could not be determined in 13 women (50%). Among women, 6 cases (22%) had significant coronary artery disease. Findings in others included coronary artery anomalies ($n = 3$), myocarditis ($n = 2$), hypertrophic cardiomyopathy ($n = 1$), coronary artery dissection ($n = 1$) and accessory pathway ($n = 1$). In younger men, a presumptive cause of sudden cardiac death remained undetermined in only 24% ($P = .025$ vs younger women), and coronary artery disease accounted for 40% of cases.

Conclusions In younger women, despite autopsy and detailed cardiac pathologic examination, an attributable cause of sudden cardiac death was not determined in 50% of cases; a 2-fold increase compared to men of the same age. Given the dynamic and multifactorial nature of sudden cardiac death, comprehensive population-based investigations are likely to be necessary to further investigate this unexpected sex-based disparity. (*Am Heart J* 2003;146:635–9.)

Recent surveillance data (1989-1998) have revealed alarming trends for sudden cardiac death in younger US women.¹ Although sudden cardiac death rates declined in all other adults aged >35 years, there was a 21% increase in the rate for women aged 35 to 44 years over this 10-year period. In contrast, younger men were observed to have decreasing rates of sudden cardiac death. The cause/causes of the disproportionately increased sudden cardiac death rate in younger women remains unknown.

Because women are exposed to fewer traditional risk factors for sudden cardiac death than men, primary prevention and risk stratification may be most challenging in women.² This is especially true for younger women, who have the lowest incidence of coronary artery disease. Although sudden cardiac death is likely to be a dynamic, multifactorial process,^{3,4} autopsy and detailed cardiac pathologic evaluation can often identify an attributable etiology of sudden cardiac death.⁵ However, women aged 35 to 44 years are poorly represented in available autopsy series. We evaluated autopsy findings and detailed cardiac pathology after sudden cardiac death in this subgroup and compared them to age-matched men from a 13-year (1984-1996) autopsy series of sudden cardiac death.

Methods

Registry of archived hearts

The Jesse E Edwards Cardiovascular Registry (St Paul, Minn) has provided detailed cardiovascular pathology expertise for over 45 years. In the process, the Registry has archived >14,000 hearts. As described previously,⁶ a detailed

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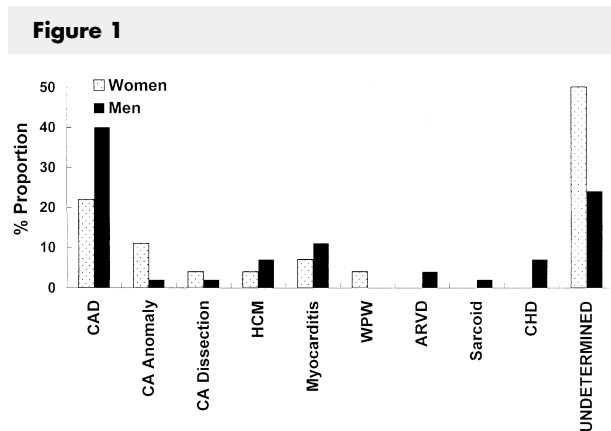
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Sex-based distribution of presumed etiologies of sudden cardiac death. These data represent comparisons between 27 women and 45 men. CAD, Coronary artery disease; CA, coronary artery; HCM, hypertrophic cardiomyopathy; WPW, Wolff-Parkinson-White syndrome; ARVD, arrhythmogenic right ventricular dysplasia; CHD, congenital heart disease.

cardiac pathologic examination is conducted for each archived heart. In addition, we collected and catalogued additional data for each patient, including autopsy findings, available clinical history, toxicological findings and the medical examiner's report.

Definition and inclusion criteria

Among witnessed deaths, sudden cardiac death was defined as death due to cardiac causes within 6 hours of symptom onset. Among unwitnessed deaths, patients were included if they were reported to have been observed symptom-free in the prior 24 hours. To conform with more recent standard definitions of sudden cardiac death, a separate analysis was also performed in subjects who had sudden cardiac death within 1 hour of symptoms (witnessed) or were observed alive and symptom free within the preceding 24 hours (if unwitnessed). Patients were excluded if post-mortem findings, including toxicological screen, suggested a noncardiac cause of sudden death. The Registry database was queried to identify all patients presenting with sudden cardiac death (age >20 years) during the period 1984 to 1996.

Referral sources

Only cases referred from within the state of Minnesota were included. As previously described,⁶ the major sources of referral were the medical examiners and pathologists from the local 3-county region (Hennepin, Ramsey, and Anoka counties; at least 87% of total cases in the series), which constitute the Minneapolis-St Paul greater metropolitan area. State regulations direct medical examiners to investigate virtually all cases of sudden death for persons aged <60 years.

Identification of presumed etiology

For all patients, pathologic examination of the archived heart was conducted at the Registry (whole heart as well as

tissue blocks), in addition to prior autopsy by the referring physician. Detailed methods of pathologic examination have been described previously.⁶ Briefly, after conducting a gross cardiac exam, cross-sectional diameter of coronary arteries was measured and $\geq 50\%$ stenosis was considered significant coronary artery disease. Subsequently, hematoxylin and eosin, trichrome and elastic-van Gieson stained slides were prepared and examined from 5 to 7 prespecified cardiac anatomical regions. In a total of 18 patients from the 35- to 44-years age group, a detailed examination of the conduction system was also performed. Findings of left ventricular hypertrophy (>16 mm thickness of compact myocardium of the left ventricle), mitral valve prolapse, or interstitial fibrosis were considered to be nonspecific for sudden cardiac death. Both gross and histologic changes were required to be present to make a diagnosis of mitral valve prolapse. An attributable etiology was identified in cases where clinical history and/or pathologic exam yielded findings strongly associated with sudden cardiac death. When the clinical history was noncontributory and detailed pathologic examination revealed a structurally normal heart or only nonspecific structural abnormalities, the etiology of sudden cardiac death was considered to be undetermined. As a general practice, a detailed systematic conduction system examination (serial, 5 mm sections) was conducted only in the absence of any other discernable cardiac structural abnormalities.

Statistical methods

The χ -square test was used to assess differences in proportion between subgroups of men and women. The Student *t* test was employed to assess age differences.

Results

Presumed etiologies of sudden cardiac death

During the period 1984 to 1996, a total of 270 cases of sudden cardiac death (age >20 years) were referred to the Registry. Thirty-one percent of all cases in the series were women. Women aged 35 to 44 years constituted 32% of all women in the series (27 of 84 cases, mean age 39 ± 3 years) in contrast to men, who constituted 24% of total male cases (45 of 176 cases, $P = .004$ vs women; mean age also 39 ± 3 years). After review of available clinical information, autopsy findings and detailed pathologic assessment of the heart, the distribution of presumed etiologies of sudden cardiac death based on sex are shown in Figure 1. Among women who underwent detailed cardiac conduction system examination ($n = 8$), abnormalities were detected in 3 cases. After completion of clinical-pathologic correlation, there were 13 women (50% of younger women) in whom a presumed cause of sudden cardiac death could not be determined.

There was a higher proportion of significant coronary artery disease in men compared with women (40% vs 22%). Of the younger men, a detailed evaluation of the conduction system was performed in 10 cases with detection of abnormalities in 3 cases. In 11

cases (24%), an attributable etiology of sudden cardiac death could not be determined ($P = .025$ vs younger women). For both women and men, comparisons of the average age of subgroups with coronary artery disease, presumed etiology identified, and presumed etiology undetermined, respectively, did not reveal significant differences ($P =$ not significant for all).

Cardiac pathologic findings in patients with unexplained sudden cardiac death

In the age group 35 to 44 years, the overall proportion of sudden cardiac death of undetermined etiology was 33%. Most patients had evidence of ≥ 1 nonspecific cardiac structural abnormality, including mitral valve prolapse, left ventricular hypertrophy, and nonspecific myocardial interstitial fibrosis (Table D). Except for a 44-year old male patient with findings of Marfan's syndrome, no patient had extra-cardiac findings suggestive of a noncardiac cause of sudden death.

Discussion

From a total of 270 cases of sudden cardiac death, 72 patients were identified in the age group 35 to 44 years, of which 27 were women (32% of total women) and 45 men (24% of total men). Detailed cardiac pathologic examinations revealed significant sex-related differences. As expected, the rate of associated significant coronary artery disease was lower in younger women versus men (22% vs 40%). However, the significantly high rate of unidentified cause of death in younger women was an unexpected finding. After detailed autopsy, cardiac pathologic examination and analysis of available clinical findings, 50% of women had sudden cardiac death of undetermined etiology compared to 24% of men.

Younger women in the age group of interest are poorly represented in existing autopsy series of sudden cardiac death, particularly during the time period of the present study. Shen et al examined the population-based incidence of sudden cardiac death in adults aged 20 to 40 years from an autopsy series of 54 patients during 1960 to 1989.⁷ It is of interest that the sex distribution of cases, as well as the incidence of coronary artery disease, were similar to the present study. The lack of an attributable etiology of sudden cardiac death in 50% of younger women, despite detailed cardiac pathologic evaluation, is a striking observation and must be addressed. In recent years, there is increasing recognition of syndromes of sudden cardiac death that may escape diagnosis despite clinical and pathological evaluation, especially if prior 12-lead electrocardiograms are not available.^{6,8,9} Community medical records were reviewed in detail for patients with structurally normal hearts, but not for all patients. Due to the retrospective nature of the study, it is difficult

Table I. Detailed pathologic findings in patients with sudden cardiac death of undetermined etiology

Sex	Age (y)	Autopsy findings
F	36	Left ventricular hypertrophy
F	41	Left ventricular hypertrophy
F	36	Left ventricular hypertrophy, nonspecific fibrosis
F	38	Mild coronary artery disease (<40%), morbid obesity
F	42	Mitral valve prolapse
F	39	Mitral valve prolapse
F	43	Mitral valve prolapse
F	37	Mitral valve prolapse, AV nodal artery (60% lesion)
F	36	Mitral valve prolapse, left ventricular hypertrophy
F	42	Mitral valve prolapse, left ventricular hypertrophy, nonspecific fibrosis
F	40	Mitral valve prolapse, non-specific fibrosis, mild coronary artery disease (<50%)
F	43	No abnormalities detected
F	44	Nonspecific fibrosis
M	39	Left ventricular hypertrophy
M	36	Left ventricular hypertrophy
M	39	Left ventricular hypertrophy
M	36	Left ventricular hypertrophy, nonspecific fibrosis
M	39	Left ventricular hypertrophy, quadriplegia
M	38	Mitral valve prolapse, left ventricular hypertrophy
M	36	Mitral valve prolapse, left ventricular hypertrophy
M	40	Mitral valve prolapse, left ventricular hypertrophy
M	43	Mitral valve prolapse, mild coronary artery disease (<50%)
M	37	No abnormalities detected
M	37	No abnormalities detected

to ascertain whether collection of electrocardiograms by the Edwards Registry was complete. In addition, patients were relatively young, and several may have had sudden death as the first manifestation of cardiac disease. Consequently, we were unable to exclude a diagnosis of the long QT or Brugada syndromes in all patients. Findings from the International LQTS Registry indicate that women constitute a higher proportion (70%) of people affected with congenital long QT syndrome.¹⁰ In addition, female patients with the long QT syndrome have an increased risk of cardiac events during adulthood, compared to males.¹⁰ Interestingly enough, patients with the acquired long QT syndrome also manifest identical sex-specific trends (ie, approximately 70% cases of ventricular proarrhythmia occur in women).^{11,12} More recently, results from the SWORD trial showed women were at significantly higher risk of torsades de pointes after treatment with d-sotalol.¹³

Although the list of genetic variants likely associated with the acquired long QT syndrome continues to increase,¹⁴⁻¹⁶ the exact incidence in the general population remains unknown.

The majority of patients with sudden cardiac death of undetermined etiology had left ventricular hypertrophy or mitral valve prolapse or both (Table D). Left ventricular hypertrophy has been associated with increased mortality¹⁷ and mitral valve prolapse with increased risk of sudden death.¹⁸⁻²² However, due to their high frequency in the general population, these cardiac structural abnormalities are not likely to represent specific etiologic conditions for sudden cardiac death.^{23,24} However, mechanisms of fatal arrhythmia are likely to be multifactorial^{3,4} and the possible contribution of the above conditions in combination with other substrates/triggers cannot be ruled out.²⁵ Although our results do not provide specific explanations for the increasing sudden death rates in younger women, they do suggest that preventive measures based on traditional risk factors are unlikely to arrest this unexpected tendency. With the observed general female predilection for torsade de pointes arrhythmia, the trends for use of other potential cardiac repolarization-prolonging agents, including recreational drugs, should also merit further evaluation. Finally, the continued discoveries of newer genetic defects predisposing to sudden cardiac death suggest the existence of other new and hitherto undiscovered genetic etiologies.²⁶

Limitations

For the purpose of this investigation, sudden cardiac death was defined as sudden death of presumed cardiac etiology, occurring within 6 hours of onset of symptoms (if witnessed) or within 24 hours of the patient being observed in good health (if unwitnessed). In view of the prevailing definition of sudden cardiac death, we also performed an analysis of 63 of the 75 younger patients (22 women) who had sudden cardiac death within 1 hour of onset of symptoms or within 24 hours of being observed alive (unwitnessed deaths). Trends were similar. Among female patients, a presumed cause of sudden cardiac death could not be determined in 50%. Of the male patients, the presumed etiology was undetermined in 27% ($P = .07$ vs females).

Although there was a consistent referral pattern, the possibility of a sex bias exists. However, the sex distribution in our series (approximately one third were women) is consistent with previous autopsy series,⁷ cohort studies,²⁷ as well as investigations of survivors of sudden cardiac death,²⁸ which would argue against sex bias. In addition, a potentially useful attribute of our autopsy series is the relatively young age of subjects compared to other autopsy series (average age 42

years). This was likely a reflection of a referral pattern affected by state regulations (see Methods, Referral sources). With respect to the cardiac pathological examination, although an overall detailed gross and histologic examination of the heart was conducted in all cases, the conduction system was examined in detail only for 18 cases (8 women, 10 men). It is possible that a small abnormality of the conduction system or AV nodal artery may have been missed in some cases.

Conclusions

In the age group 35 to 44 years, younger women had an unexpectedly high proportion of sudden cardiac death of undetermined etiology (50%); a 2-fold increase compared to age-matched men. A prospective, population-based evaluation, with special emphasis on nontraditional risk factors/triggers for sudden death and genetic evaluation, is warranted.

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