Specific Characteristics of Sudden Death in a Mediterranean Spanish Population

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Most of the data reported on sudden cardiac death has been from studies of Anglo-Saxon patients. We conducted a study to ascertain the relation between sudden death (SD) and some epidemiologic, clinical, and biochemical parameters and to assess the coronary histopathologic aspects of subjects in a Spanish population who had died suddenly. A total of 204 subjects (86% men), aged 12 to 80 years (mean 54 ± 15), who had died from out-of-hospital natural SD were evaluated. Only 15% of subjects had been previously diagnosed with heart disease. Pathologic evidence of underlying cardiovascular disease was found in 90% of cases, with coronary heart disease (CHD) the most frequent (58%). The CHD was acute coronary thrombosis in 41% and a stable plaque with luminal narrowing of ≥75% in 59%. An old myocardial infarction was found in 31% of the SD victims. Cardiac hypertrophy was found in 48%, with no relation between the presence of cardiac hypertrophy and CHD. Patients with stable plaques had a greater heart weight than did those with acute coronary thrombosis (p = 0.02). Male gender, older age, smoking, and low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio of ≥3 were associated with CHD. A greater percentage of patients with an eroded and/or ruptured plaque than patients with a stable plaque were smokers. Only smoking and a low-density lipoprotein/high-density lipoprotein cholesterol ratio of ≥3 were associated with an eroded and/or ruptured plaque. In conclusion, compared with the findings from studies of Anglo-Saxon patients, a lower incidence of CHD and acute coronary thrombosis and a greater incidence of cardiac hypertrophy were found in SD victims of a Mediterranean Spanish population. © 2011 Elsevier Inc. All rights reserved. (Am J Cardiol 2011;107:622–627)

Sudden death (SD) represents 12% to 13% of overall natural mortality when the temporal definition is restricted to death occurring <2 hours after the onset of symptoms,1–4 with approximately 50% of deaths in patients with cardiovascular disease.5–7 Sudden cardiac death (SCD) represents about 80% to 90% of all SDs.2,3,8 Therefore, SCD constitutes one of the most important challenges of modern cardiology. Our understanding of the pathophysiologic mechanisms of SCD, as well as the correlation between SCD and associated diseases and risk factors, has mainly been based on data from studies of white Anglo-Saxon patients that showed coronary heart disease (CHD) to be a fundamental cause of SCD.9,10 The Seven Countries Study demonstrated in a 25-year follow-up period that Southern European cohorts had a lower risk of fatal CHD than other European or United States cohorts.11 However, only partial data on the incidence of SCD in Spain are available,8 and it is unknown whether its clinical and pathologic characteristics differ from those reported from Anglo-Saxon countries.12 The present study was designed to investigate the relation between SCD and different epidemiologic, clinical, and biochemical parameters in a Spanish population and to characterize the coronary histopathologic features of the subjects who died suddenly.

Methods

A total of 204 victims of out-of-hospital natural SD aged 12 to 80 years from 2 Spanish autonomous communities, Catalonia and Andalusia, were included. Those who had died long after an aborted SD were excluded. Autopsy was performed within 18 hours after death. A
forensic autopsy protocol\textsuperscript{13,14} was applied. Femoral blood and vesical or pelvic kidney urine samples were obtained by puncture. The coronary arteries and myocardium were specifically studied.

Information on the sociodemographic data, cardiovascular risk factors, and present and previous disorders suggesting cardiovascular disease in the victims and their relatives was obtained from the close family or friends by telephone questionnaire. The cardiovascular risk factors were collected as continuous (i.e., height, weight, body mass index), categorical (i.e., yes, no, exsmoker for smoking), and dichotomous (i.e., regular alcohol intake, physical activity, diabetes, hypertension, dyslipemia, and the use of psychoactive drugs) variables. In the case of previously recognized heart disease, an attempt was made to compare the data obtained from the relatives with the data retrieved from the hospital records.

SD was defined as a natural, nonviolent, unexpected death occurring within 1 hour of the onset of symptoms or within 24 hours of a previously stable medical condition, if the event had not been witnessed.

Death from CHD was diagnosed when cross-sectional luminal narrowing of a major coronary artery of $\geq 75\%$ or an acute thrombosis related to rupture or erosion of a coronary plaque was found. The culprit plaque was defined as that with an acute thrombus or, in its absence, that with the greatest degree of cross-sectional luminal narrowing relative to the internal elastic lamina at the narrowest segment. An acute ruptured plaque consisted of a continuous luminal thrombus with an underlying lipid-rich core. When the thrombus was in direct contact with the intimal layer, without rupture of a lipid pool, the plaque was defined as eroded. Vulnerable plaques were defined as having a fibrous cap $\leq 65\ \mu m$ with macrophage and T-lymphocyte infiltration. Stable plaques were defined as those causing luminal narrowing of $\geq 75\%$ in the absence of luminal thrombosis and were considered vulnerable or nonvulnerable.\textsuperscript{12}

A heart weight $>450\ g$ in men and $>400\ g$ in women was considered cardiac hypertrophy.\textsuperscript{15,16} We used the heart weight, instead of left ventricular thickness, because the heart rate might provide more information about the cardiac mass. In dilated hearts with an abnormal cardiac mass, the left ventricular thickness can sometimes be normal.

The smoking status of each patient was classified as current daily smoker,\textsuperscript{17} nonsmoker, or exsmoker.

Hypertension was defined according to the guidelines of the European Society of Hypertension/European Society of Cardiology.\textsuperscript{18}

The heart tissue was fixed in formaldehyde by retrograde perfusion at systemic pressure. The coronary arteries were dissected and embedded in paraffin, and 5-$\mu m$-thick sections were stained with hematoxylin-eosin. The coronary arteries were studied by serial sectioning at 3-mm intervals after decalcification. Any segment showing cross-sectional luminal narrowing of $>50\%$ was studied histologically.

Histologic images were studied in a Leica MZ-9.5 (Leica Microsistemas, Barcelona, Spain) stereomicroscope to quantify the stenotic area. Image capture and morphometric study were performed using a Sony 3CCD color video camera and processed using Visilog (Sony ESPAC, Barcelona, Spain), version 4.1.5 (Noesis, Saint Aubin, France), software.

Labeled blocks from a representative transverse slice of the anterior, lateral, and posterior free wall of the left ventricle, posterior free wall of the right ventricle, and anterior and posterior interventricular septum and 1 block from each atrium were taken for study of the myocardium. In addition, any area with a significant macroscopic abnormality was sampled and analyzed using hematoxylin-eosin, Masson’s trichrome, and Van Gieson stains.

Two investigators, using a double-headed light microscope, performed the analysis simultaneously.

From the blood samples, the total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very-LDL cholesterol, chylomicrons, apolipoproteins B and CIII, and lipoprotein (a) were measured. The cotinine and glucose levels were obtained from the urine samples (Roche Diagnostics, San Cugat del Vallès, Barcelona, Spain and DRG Diagnostics, Marburg, Germany).

Descriptive analyses were initially performed. The quantitative variables are reported using the mean and standard deviation. Relations between categorical variables were studied using the chi-square test. A comparison of the quantitative variables between the 2 groups was performed using the $t$ test and of ordinal variables using the Mann-Whitney nonparametric $U$ test.

The variables analyzed univariately by logistic regression analysis to predict coronary artery disease and type of atherosclerotic plaques included gender, age, body mass index ($<24.9\ vs\ 25\ to\ 29.9\ vs\ \geq 30\ kg/m^2$), presence or absence of smoking, hypertension, diabetes, alcohol intake, physical activity (yes vs no), diabetes (yes vs no) and LDL/HDL cholesterol ratio ($<3\ vs\ \geq 3$).

Variables showing statistical significance ($p<0.10$) were included in the multivariate regression model to determine which were independently related to the prognosis. In all analyses, contrasts were made bilaterally with an $\alpha$ of 5$\%$ (Statistical Package for Social Sciences, version 15.0, SPSS, Chicago, Illinois).
Results

A total of 204 subjects (86% males), who had died from out-of-hospital natural SD, were evaluated. Of the 204 subjects, 175 were males (86%) and 29 were females, with a mean age of 54 ± 15 years (males 53 ± 15 years; females 61 ± 13 years; p = 0.014). Only 21 subjects were <35 years (range 12 to 34).

The mean body mass index was 30 ± 8 kg/m² and was greater for the females than for the males (34 ± 10 vs 29 ± 8 kg/m²; p = 0.024). Of the 204 subjects, 58% (62% of males and 27% of females) were smokers, 52% had a history of regular alcohol intake, 39% had a history of hypertension, 35% a history of dyslipidaemia, and 18% had a history of diabetes mellitus. The smokers were younger than the nonsmokers (52 ± 13 vs 57 ± 18 years, respectively; p <0.001). Those with hypertension were older than those without (60 ± 13 vs 49 ± 16 years, respectively; p <0.0001). The mean age of those with an LDL/HDL cholesterol ratio of ≥3 was 54 ± 16 years and was 55 ± 13 years for those with an LDL/HDL cholesterol ratio <3 (p = 0.59). Of the subjects with diabetes mellitus, the mean age was 61 ± 12 years compared to 52 ± 16 years for those without diabetes mellitus (p <0.001).

The urine cotinine level was measured in 75% of the subjects. A high association (87%) was found between cotinine present in the urine and data on positive smoking status.

A history of cardiovascular symptoms was found in 33% of the subjects (60% females), including dyspnea, angina, and/or syncope, but only 15% had been previously diagnosed with heart disease (15% males and 13% females), with documented myocardial infarction in 10%.

Of the 204 subjects, 14% had a family history of SD and 24% had a first-degree relative who had had myocardial infarction.

Most deaths occurred while the subject was resting or doing mild exercise (71%), and, from the information provided by the family and relatives, 20% of those whose death was witnessed had complained of chest pain.

Table 2
Biologic risk factors for sudden death (SD) cases stratified by heart disease status and culprit plaque type

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHD and Non-CHD</th>
<th>Culp Plaque Type</th>
<th>p Value</th>
<th>Eroded and/or Ruptured</th>
<th>Stable (≥75%) and/or Vulnerable</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 119)</td>
<td>(n = 85)</td>
<td></td>
<td>(n = 49)</td>
<td>(n = 70)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>6.5 ± 2.1</td>
<td>5.2 ± 1.8</td>
<td>&lt;0.001</td>
<td>6.9 ± 2.2</td>
<td>6.1 ± 2.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.5 ± 1.5</td>
<td>2.0 ± 1.2</td>
<td>0.05</td>
<td>2.6 ± 1.5</td>
<td>2.3 ± 1.5</td>
<td>0.23</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mmol/L)</td>
<td>1.0 ± 0.4</td>
<td>1.2 ± 0.5</td>
<td>0.05</td>
<td>1.0 ± 0.4</td>
<td>1.1 ± 0.4</td>
<td>0.40</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol (mmol/L)</td>
<td>3.9 ± 1.4</td>
<td>3.2 ± 1.3</td>
<td>&lt;0.001</td>
<td>4.4 ± 1.4</td>
<td>3.6 ± 1.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Low-density lipoprotein/high-density lipoprotein cholesterol ratio</td>
<td>4.3 ± 2.2</td>
<td>3.1 ± 1.8</td>
<td>&lt;0.001</td>
<td>4.9 ± 2.3</td>
<td>3.9 ± 2.0</td>
<td>0.008</td>
</tr>
<tr>
<td>Very-low-density lipoprotein cholesterol (mmol/L)</td>
<td>0.9 ± 0.6</td>
<td>0.7 ± 0.6</td>
<td>0.01</td>
<td>1.0 ± 0.7</td>
<td>0.8 ± 0.6</td>
<td>0.08</td>
</tr>
<tr>
<td>Chylomicrons (mmol/L)</td>
<td>1.7 ± 1.1</td>
<td>1.1 ± 0.5</td>
<td>0.27</td>
<td>1.6 ± 1.3</td>
<td>1.8 ± 1.0</td>
<td>0.29</td>
</tr>
<tr>
<td>Lipoprotein (a) (g/L)</td>
<td>0.7 ± 0.6</td>
<td>0.6 ± 0.5</td>
<td>0.61</td>
<td>0.7 ± 0.6</td>
<td>0.7 ± 0.5</td>
<td>0.88</td>
</tr>
<tr>
<td>Apolipoprotein B (g/L)</td>
<td>1.2 ± 0.4</td>
<td>0.9 ± 0.4</td>
<td>&lt;0.001</td>
<td>1.3 ± 0.4</td>
<td>1.1 ± 0.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Apolipoprotein CIII (g/L)</td>
<td>0.2 ± 0.1</td>
<td>0.1 ± 0.1</td>
<td>&lt;0.001</td>
<td>0.2 ± 0.1</td>
<td>0.1 ± 0.1</td>
<td>0.33</td>
</tr>
<tr>
<td>Urine glucose (mmol/L)</td>
<td>24.1 ± 64.9</td>
<td>10.7 ± 44.5</td>
<td>0.90</td>
<td>30.0 ± 80.5</td>
<td>18.3 ± 45.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Urine cotinine (positive)</td>
<td>52%</td>
<td>45%</td>
<td>0.31</td>
<td>71%</td>
<td>37%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

All parameters were measured from blood samples, unless indicated otherwise.

Of the 204 cases, 183 (90%) could have been related to underlying cardiovascular disease. Heart disease was found in 161 subjects (79%), with CHD the most frequent (58%) and significantly different (p = 0.016) between the males (62%) and females (38%). Hypertensive cardiac hypertrophy was found in 20 subjects (9.9%), aortic dissection in 9 (4.4%), and pulmonary embolism in 8 (3.9%). In 14 subjects, the cause of death could not be ascertained (Table 1).

The mean heart weight was 498 ± 123 g (454 ± 115 g in females and 506 ± 123 g in males; p = 0.038). Cardiac hypertrophy was diagnosed in 41% of the females and 49% of the males (48% of those with SD). In the males, a significant relation (p <0.0001) was found between cardiac hypertrophy and a history of hypertension, with 75% of those with hypertension versus 34% of those without, having a hypertrophic heart. No relation was found between cardiac hypertrophy and CHD.

On histologic study of the myocardium, a scar from an old, healed, myocardial infarction was found in 64 subjects (31% of all those with SD) and was more frequent in male patients >60 years old (47% vs 29%; p = 0.015). No differences related to age were found in the female patients.
Finally, 46% of these cases did not meet the criteria (eroded or ruptured plaque/luminal cross-sectional narrowing ≥75%) to consider SD related to CHD. The coronary arteries were evaluated in all SD subjects. A single vessel (left anterior descending coronary artery, circumflex coronary artery, or right coronary artery) was affected in 43 subjects (36%); 2 vessels in 48 (40%), and 3 vessels in 28 (24%). No females had the main left coronary artery affected, and in only 15 cases (14% of males) was this vessel affected. In 74% of the subjects with CHD, the left anterior descending coronary artery was affected.

The biologic risk factors for SCD according to a diagnosis of CHD or non-CHD and the type of culprit plaque are listed in Table 2. Regarding coronary plaque morphology, an eroded (53%) and/or ruptured plaque (47%) was observed as the culprit plaque in 49 subjects (41%). In the remaining (59%), a stable plaque with cross-sectional luminal narrowing of ≥75% was considered the culprit plaque, with a vulnerable anatomy in 4 (Figure 1). An old myocardial infarction was present in 45% of those with an eroded or ruptured culprit plaque and in 60% of those with a stable culprit plaque.

A relation was found between the type of culprit plaque and heart weight, with patients with stable plaques having a greater cardiac weight (528 ± 119 g vs 479 ± 99 g; p = 0.025). The same relation was found when a healed myocardial infarction was present in either of these groups (564 ± 122 g vs 491 ± 107 g; p = 0.017). In hearts with acute thrombosis, the mean heart weight was 511 ± 90 g for those with a ruptured plaque and 451 ± 100 g for those with an eroded plaque (p = 0.023). An eroded or ruptured plaque was found in 33% of those with a history of hypertension versus 67% of those without hypertension (p = 0.04) and in only 13% of the group with cardiac hypertrophy and a history of hypertension.

The patients with CHD were significantly older than those without (57 ± 12 vs 50 ± 18 years; p < 0.01). The CHD prevalence was significantly greater in the males than in the females (91% vs 9%; p < 0.01).

Regarding biologic cardiovascular risk factors, no significant differences were found between SCD with CHD and SCD without CHD, except for apolipoprotein B, apolipoprotein CIII, and the lipid profile. HDL cholesterol,

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LDL cholesterol, and very-LDL cholesterol were significantly greater in those with CHD (Table 2).

From the multivariate regression analysis, only male gender, older age, smoking, and an LDL/HDL cholesterol ratio of $\geq 3$ were significantly associated with CHD (Table 3).

Those with an eroded and/or ruptured culprit plaque were younger ($54 \pm 12$ vs $59 \pm 12$ years; $p = 0.04$) and more likely to be smokers ($76\%$ vs $54\%; p = 0.03$) than those with a stable culprit plaque. Using univariate regression analysis, younger age, smoking history, and an LDL/HDL cholesterol ratio of $\geq 3$ were associated with an eroded and/or ruptured culprit plaque (acute thrombosis). However, on multivariate regression analysis, only smoking history (odds ratio $2.5$; $p = 0.04$) and an LDL/HDL cholesterol ratio of $\geq 3$ (odds ratio $4.2$; $p = 0.005$) were associated with these types of plaque (Table 4). Furthermore, using multivariate regression analysis, no significant difference between a ruptured or an eroded plaque and the cardiovascular risk factors studied was found.

Discussion

In Anglo-Saxon countries, CHD has been the underlying cause of SD in $80\%$ to $90\%$ of cases.\textsuperscript{19,20} The incidence of SCD in Spain has been estimated to be one of the lowest in the industrialized countries.\textsuperscript{8,21} However, the prevalence of cardiovascular risk factors in the Mediterranean area\textsuperscript{22,23} is not as low as one might expect. The results of the present study have provided epidemiologic and, in particular, anatomicopathologic information on SD in Spain that might explain the differences in SD between Anglo-Saxon and some Mediterranean countries; these differences are probably related to lifestyle and environment.\textsuperscript{24}

As reported in other studies,\textsuperscript{25,26} a significant observation was the high percentage of those who died from SD who had a history of SD ($14\%$) or myocardial infarction ($24\%$) in first-degree relatives. Logically, this would support the idea of a genetic factor involved in SD and, in particular, CHD, as recently reported.\textsuperscript{27} A case-control study by Friedlander et al\textsuperscript{25} revealed that a family history of acute myocardial infarction or SD was more common among those who had died from SD than in control subjects, with this association mostly independent of other common risk factors with familial aggregation.

According to the information provided by the family and relatives, only $20\%$ of those who had died from SD had complained of chest pain, lower than the $37\%$ reported in the Maastricht study.\textsuperscript{28} This is consistent with the lower incidence of underlying CHD in our study population. It might indicate that SD could be the first manifestation of cardiovascular disease, as has been reported by other studies,\textsuperscript{9,29} making it difficult to establish methods of preventing SD in the general population.

In the present study, $90\%$ of cases were associated with cardiovascular disease, with CHD the most frequent. Compared to the findings from studies of Anglo-Saxon patients, we found a clearly lower incidence of CHD ($58\%$ vs $80\%$ to $90\%$)\textsuperscript{9} and acute coronary thrombosis ($41\%$ vs $52\%$).\textsuperscript{12} These findings support the lower incidence of acute coronary syndrome reported in the Mediterranean area, long considered a consequence of diet\textsuperscript{30} and/or, in a broader aspect, the “Mediterranean culture.” However, the involvement of factors such as genetics should also be considered. It is well known that when examining the same levels of cholesterol, the incidence of myocardial infarction has been lower in Spain than in Anglo-Saxon countries.\textsuperscript{22,31}

In contrast to what has been reported in Anglo-Saxon populations, we found a greater percentage of cardiac hypertrophy without significant disarray ($48\%$ vs $13$ to $15\%$).\textsuperscript{22,33} In our male subjects, this was related to hypertension ($p < 0.001$). The Massa Ventricolare Sinistra Nell’ipertensione Arteriosa study\textsuperscript{24} showed the strong, continuous, and independent relation between the left ventricular mass and subsequent cardiovascular morbidity, including SD.

Pathologic signs of CHD were found predominantly in our male subjects ($62\%$ vs $38\%$); however, a low number of female subjects were included in the present study. In $59\%$ of those with CHD, a stable plaque was considered the culprit plaque responsible for SD and a healed myocardial infarction was found in $60\%$ of these cases. This might suggest that if acute myocardial ischemia is a cause of SD, arrhythmia in the setting of myocardial scars could also be a very important component.

A relation was found between stable plaque and cardiac hypertrophy, with patients with stable plaques having a greater cardiac mass ($528 \pm 19$ vs $479 \pm 99$ g; $p = 0.025$). As with the findings from Burke et al,\textsuperscript{12,35} our study showed a lower frequency of acute coronary thrombosis in patients with cardiac hypertrophy and a history of hypertension. An eroded or ruptured plaque was found in only $33\%$ of those with a history of hypertension compared to $67\%$ of those without hypertension.

Regarding the remaining coronary risk factors, a significant relation was found between CHD and male gender, older age, smoking, and LDL/HDL cholesterol ratio of $\geq 3$. When we attempted to analyze its influence on the plaque type, patients with eroded and/or ruptured plaques were found to be younger ($p = 0.04$), more likely to be smokers ($p = 0.03$), and to have a greater probability of an LDL/HDL cholesterol ratio of $\geq 3$ ($p = 0.004$). In contrast, gender, diabetes, regular alcohol intake, and hypertension could not be related to the type of plaque.

The possible limitations of the present study included that, although it was performed prospectively, it was not possible to perform autopsy studies every day, rendering it impossible to obtain exact information on the incidence and prevalence of SD in this population. Nevertheless, we believe our findings can provide important epidemiologic and anatomicopathologic information and offer us the possibility of establishing comparative data with the data from Anglo-Saxon countries. Also, in accordance with previous reports,\textsuperscript{36} we found a lower prevalence of CHD in females with SD (Table 3). Nevertheless, we must emphasize the low number of females subjects included in our study. Finally, although we have previously justified the use of heart weight instead of the left ventricular wall thickness as a variable, this could be considered a possible limitation. Therefore, we conducted a supplementary analysis to study the relation between the thickness of the left ventricle and the presence of coronary disease, without finding a relation between these 2 variables. Moreover, a significant linear
correlation ($r^2 = 0.144$) was seen between the heart weight and ventricular wall thickness.

In 14 cases, no abnormal pathologic findings were found. At least some of these cases might correspond to an undiagnosed channelopathy. Even though minor structural myocardial abnormalities had been reported in some asymptomatic or asymptomatic patients with a channelopathy, such as Brugada syndrome, usually no structural alterations will be demonstrated by routine invasive and noninvasive examinations. We believe that 1 of our patients might have presented with Brugada syndrome because in a pre-employment medical examination, an atypical right bundle branch block on the electrocardiogram was reported.

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