Circumstances of Death and Gross and Microscopic Observations in a Series of 200 Cases of Sudden Death Associated With Arrhythmogenic Right Ventricular Cardiomyopathy and/or Dysplasia

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**Background**—Sudden death is a possible consequence of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D). Prevalence of ARVC/D in unexpected sudden cardiac death (USCD), however, remains imprecise, as do circumstances of death and ARVC/D-associated gross and microscopic findings, especially His bundle anomalies.

**Methods and Results**—We reviewed 14,000 forensic autopsies required by judicial authorities from January 1980 to January 1999 in a 2,000,000-resident area. Age, gender, and circumstances of death were recorded. Hearts were examined macroscopically and microscopically. In this series, the ARVC/D group accounted for 200 consecutive cases (10.4%) of USCD, including 108 males and 92 females (average age 32.5 and 34.5 years, respectively). Nearly one third of deaths occurred during the fourth decade of life. Circumstances of death were various, but 75.6% occurred during everyday life events (at home, 63.1%; in the street, 6.6%; or at work, 6.1%); only 7 cases (3.5%) occurred during sports activity. Nineteen cases (9.5%) happened during the perioperative period. Adipose infiltration of the right ventricle was either isolated (20%) or associated with fibrosis (74.5%) and lymphocytes (5.5%). A total of 14.5% of cases had cardiac hypertrophy, assessed by an increase in heart weight and/or left ventricular wall thickness. In most cases, the His bundle and its branches were abnormal either because of infiltration of adipose tissue (8.1%), fibrosis (54.3%), or both (5.6%).

**Conclusions**—In ARVC/D, both sexes are equally affected, and there is a peak of risk during the fourth decade. Death most frequently occurs during sedentary activity. His abnormalities and left ventricular hypertrophy may be associated with ARVC/D. (Circulation. 2003;108:3000-3005.)

Key Words: cardiomyopathy ■ death, sudden ■ tissue
were associated primarily with His bundle and LV abnormalities.

Methods

Study Population

Autopsies were performed when requested by judicial authorities for unexpected sudden deaths. From January 1980 to January 1999, the Forensic Institutes of Lyon and Saint-Etienne (France) performed 14,000 autopsies for a population of approximately 2 million inhabitants. Age, gender, and circumstances of death were obtained from police, forensic records, and relatives of the deceased person. A complete pathological examination of the heart-lung block was performed by 2 of us (A.T. and R.L.) according to a standardized protocol in 3,630 cases of natural death presumably due to cardiovascular or pulmonary lesions because no encephalic or visceral autopsy lesions could explain death, nor did toxicological examination disclose alcohol or drug abuse. In this group, 1,700 cases were classified as unexpected sudden cardiac death (USCD) because death could not be related to a noncardiac cause by autopsy and there was no history of cardiac disease.

Gross and Microscopic Examination of Heart-Lung Blocks

Heart-lung block gross (non–formalin-fixed) and microscopic examinations were performed as described previously. The heart weight and wall thickness of the LV and RV were recorded. A gross examination of coronary arteries, valves, walls, and cardiac chambers was performed that included transillumination with a source of light introduced inside the RV chamber (Figure 1A). The heart was then sectioned in slices of ~1 cm from the apex to the base, the plane of the section being perpendicular to the long axis of the heart. LV free wall thickness was measured away from the papillary muscle. Ventricular and septal walls were examined carefully, and blocks of the anterior and posterior free wall of the LV, RV, and interventricular septum were removed systematically for histopathologic study. Specimens were also taken from any gross abnormality. In this way, the sites of the so-called triangle of dysplasia were scrutinized for myocardial replacement. Finally, the upper portion of the ventricular septum was excised and sectioned to analyze the His bundle and its branches. Altogether, 15 to 20 samples were examined in each heart.

Tissue samples were stained with hematein-phloxine-safran, a method that stains fibrous tissue in golden yellow, cardiomyocytes in red, and nuclei in dark blue (method available on request to A.T.). ARVC/D diagnosis was made according to several morphological criteria. Diagnosis was based on myocardium absence between epicardial and endocardial layers in areas of the RV wall assessed by transillumination with a source of light introduced inside the RV chamber (Figure 1A) and by microscopic examination (Figure 1C). Epicardium and endocardium either joined up side by side or were separated by adult fatty tissue that sometimes contained sparse isolated myocardial cells or strongly disorganized clusters of myocardial cells trapped in fibrous tissue, including degenerating myocytes. Residual myocardium could be seen forming a subendocardial layer and in the trabeculae of the RV. Other microscopic anomalies could be noted, such as abnormal nuclei or a few lymphocytes in focal inflammation infiltrates. Partial wall replacement by fatty tissue alone was not included in this series if myocardial cells were not disorganized or isolated, because we considered these cases not to be ARVC/D but rather adipose infiltration.

Statistical Analysis

Continuous data are expressed as mean±SD. The Student t test was used to assess the significance of differences between 2 percentages. The chi-square test was used to assess the significance of differences between subgroups. The general linear model of SPSS statistical software (SPSS, Inc) was used for univariate ANOVA. A probability value of less than 0.05 was considered statistically significant.

Results

Prevalence of USCD Associated With ARVC/D

Of a series of 14,000 autopsies, 1,930 cases were classified as USCD because no noncardiac abnormalities were discovered by pathologist’s examination and no history of cardiac symptoms was disclosed. In this group of USCD and within the age range of 1 to 65 years, there were 200 cases of ARVC/D (10.4%).

Age and Gender

The group of 200 patients in whom ARVC/D was the only evidenced cause of death consisted of 108 males (5 to 57 years old, average 32.5±12.4 years) and 92 females (10 to 65 years old, average 32.5±12.4 years).
years old, average 35.5±12.0 years; \( P<0.08 \)). Both sexes were equally exposed to sudden death, and there was no age difference at death. As shown in Figure 2, there was a gradual increase of death until the late 30s, followed by a progressive decrease, so that 30% of the cases died during the fourth decade of life. Among the 4 children younger than 11 years of age, only 1 was a girl, and the youngest child was a 5-year-old boy.

**Circumstances of Death**

Circumstances of death were classified as follows: (1) at home (with or without witness), (2) during work, (3) during sports exercise, (4) in a street or another public location, or (5) under a particular circumstance. In 2 instances (1 female and 1 male), the circumstances of death could not be retrieved. The distribution of circumstances of death is presented in Figure 3. In most cases, death occurred during daily activity either at home, at work, or in the street, because 150 (75.8%) of 198 died in such circumstances. Overall, death at home accounted for 125 cases (63.1%). By contrast, only 4 females and 3 males died during physical exercise (3.5%). One male and 1 female were swimming and drowned. Other sports involved were jogging \( (n=3) \), tennis \( (n=1) \), boxing \( (n=1) \), and soccer \( (n=1) \). The age of subjects who died during exercise was less than the age of the rest of the group \( (23.0±11.2 \text{ versus } 34.3±12.2 \text{ years, respectively: } P<0.017) \). Only 6 cases had arrhythmic disorders recorded before death: 3 ventricular fibrillation, 1 ventricular tachycardia, and 1 auriculoventricular block.

In 19 patients, death was related to surgery, which occurred during the perioperative period \( (10 \text{ males, } 9 \text{ females; average age } 35.4±16.5 \text{ years}) \). In all cases, surgery was performed for minor lesions \( \text{eg, appendectomy, epistaxis, and cesarean section} \) either emergently \( (n=8) \) or scheduled \( (n=11) \) in patients with no cardiac history. Death occurred during anesthesia induction \( (n=4) \), during surgery \( (n=12) \), and up to 2 hours after surgery \( (n=3) \). Twenty-two patients died after a stressful or a specific event: minor car accident without visible injury or trauma \( (n=6) \), a fall in the street without injury \( (n=3) \), police arrest after a fight between young adults \( (n=1) \) or car theft \( (n=1) \), medical visit in a primary care physician or radiologist’s office \( (n=4) \), childbirth \( (n=2) \), hospitalization for suicide attempt with drugs using nonlethal doses \( (n=3) \), and influenza convalescence \( (n=2) \).

**Macroscopic Observations**

Lesion localization and extent were analyzed by transillumination \( \text{Figure 1A} \) and macroscopic study \( \text{Figure 1B} \). In most cases, lesions were located in the RV anterior wall in the mid portion along the interventricular groove. After both ventricles were sectioned on the level of the mid portion of the interventricular groove in a plane perpendicular to the long axis of ventricles, 3 patterns were observed in the RV circumference: (1) minor forms restricted to the 2- to 4-cm juxtaseptal anterior wall \( (40\% \text{ of cases}) \); (2) mild forms extended from the anterior interventricular groove to the RV edge \( (35\% \text{ of cases}) \); and (3) major forms with cavity dilatation, which spared only 3 to 4 cm of the RV posterior juxtaseptal area \( (23\% \text{ of cases}) \). In just 2% of cases, lesions were limited to the RV external edge.

Females and males more than 19 years of age had a mean heart weight of 311.4±66.4 and 365.3±74.8 g, respectively \( (P<0.00007) \). Although mean heart weight was normal for both sexes, the distribution of weight was abnormally wide, as shown in Figure 4. In females, 11 hearts weighed <240 g and 6 hearts weighed ≥430 g. Similarly, the dispersion of heart weight in males was wide, with 13 hearts weighing <280 g and 8 hearts weighing ≥480 g. It can be seen from Figure 4 that heart weight distribution appears to depart from a gaussian distribution.

The mean LV wall thickness values in females and males above the age of 19 years were 10.3±1.7 and 11.8±2.2 mm, respectively \( (P<0.0001) \). Among adults, 3 and 12 had a LV wall thickness ≥14 mm (females) and ≥15 mm (males), respectively \( \text{Figure 5} \). Altogether, 6 (7.3%) of 82 adult females and 13 (14.1%) of 92 adult males had either an increased heart weight or an increased LV wall thickness or
both, fulfilling criteria for cardiac hypertrophy. In individuals aged between 1 and 19 years of age, 10 of 26 had the criteria for hypertrophy according to age-related normal values as assessed by heart weight and/or LV wall thickness (Table). In conclusion, in children as well as in adults, ARVC/D was associated with LV hypertrophy in 14.5% of the cases (29/200). There was no difference in gender or age at death between hypertrophied and nonhypertrophied ARVC.

**Microscopic Observations**

**Right Ventricle**
The main lesion consisted of myocardial disappearance, either complete or with some remaining small islets of myocardial cells. Various aspects were observed in the fatty tissue replacing the myocardium. Adipose infiltration was rarely seen alone (40 of 200 cases, 20%). More frequently (149 of 200 cases, 74.5%), adipose replacement was associated with fibrosis. This fibrosis, which could be observed in the remaining disorganized myocardial cells, was either finely interstitial (127 of 200, 63.5%) or, much more rarely, made prominent mutilating blocks (11 cases, 5.5%). Myocardial cells that were trapped in this fibrous tissue showed signs of degeneration (intracytoplasmic vacuoles and myofibrillar loss). In 11 additional cases (5.5%), fibrosis extended to the vessels and the pericardium. Finally, in a few cases (n=11, 5.5%), the abnormal area was infiltrated by rare isolated lymphocytes. No difference was found in age, gender, circumstances of death, heart weight, LV posterior wall thickness, or LV histological involvement between these groups of RV histological abnormalities (adipose alone, adipose with fibrosis, and adipose with lymphocyte infiltration). The endocardium layer was often thickened by fibrosis, but papillary muscles always remained normal.

**Children With Evidence of LV Hypertrophy**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Gender</th>
<th>Heart Weight, g</th>
<th>LV Wall Thickness, mm</th>
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<td>12</td>
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<tr>
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<td>13</td>
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</tbody>
</table>

F indicates female; M, male.
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was reported in young competitive athletes. 19 This discrep-
ence of ARVC/D in sudden death. These studies have
There have been several reports on estimation of the preva-
ance could be accounted for by the young age of individuals
in adults in the present study, but we could not relate LV
dimensions to body weight and height because these parama-
ters that could potentially indicate a higher risk for USCD.
Notably, the histological types of myocyte replace-
ment (adipose alone, adipose with fibrosis, or adipose with
lymphocyte infiltration) may lead to USCD and have no
detectable effect on the circumstances of death.
By contrast, it was a surprise to note that =10% of USCDs
associated with ARVC/D occurred during the perioperative
period. This suggests that patients with ARVC/D might be
difficult to resuscitate after a cardiac arrest, because patients
were within a medical environment when they had cardiac
arrhythmias, a situation that is relatively more favorable than
the other circumstances noted. It could also suggest that some
anesthetic drugs might trigger arrhythmias in untreated
ARVC/D patients.

Despite a predominant impact on the RV, ARVC/D anom-
malies also extend to other structures of the heart; in particular,
the LV might be involved, as reported previously.20,21 LV hypertrophy is strongly associated with LV fibrosis infil-
tration but not with fibrofatty replacement of the RV. LV
involvement appeared to be more prevalent in children than
in adults in the present study, but we could not relate LV
dimensions to body weight and height because these param-
eters were not recorded. The His bundle and its branches (but
neither the sinus nor the AV node) were examined systema-
tically, and it was observed that the disease very often
extended to conduction bundles (68%) with fibrous (54.3%),
adipose (8.1%), or fibrofatty (5.6%) infiltration. His bundle
anomalies have thus far been overlooked because it was
presumed that ARVC/D individuals were dying of lethal
arrhythmias that arose from the RV free wall. The fact that
two thirds of USCDs associated with ARVC/D have His
anomalies suggests that conduction anomalies and/or arrhyth-
mias arising from the conductive tissue might be responsible
for some deaths. Among the rare cases in which cardiac
activity could be recorded in the present study, 1 had a
complete auriculoventricular block.

The histological criteria to ascertain ARVC/D are contro-
versial. There is agreement on the fibrofatty variant, but the
adipose variant is considered by some authors as normal22
and by others as pathological.23 We consider that isolated
adiposis infiltration is pathological if it is associated with disorganized strands of myocytes that might be isolated. We did not find any association between a particular parameter and the adipose type alone or the adipose and fibrous subsets, which suggests that if there are 2 different entities, both lead to sudden cardiac death in similar conditions. The prevalence of inflammation varies widely in different studies from 2% to 79% compared with 5.5% in the present report and 19% in another. Inflammation is not a cause of ARVC/D but rather an aggravating factor.

Acknowledgments
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References
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