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

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a cardiomyopathy that primarily involves the right ventricle (RV). It is characterized by a gradual loss of myocytes and replacement by adipose and fibrous tissue. Until recently, the disease was not well recognized as a disease entity, and indeed had several names, including partial Uhl anomaly and RV dysplasia, and until 1996, it was classified as a dysplasia rather than a cardiomyopathy.

The phenotype of ARVC/D is highly variable, including ventricular tachycardia, supraventricular arrhythmias, right-heart failure, or asymptomatic presentations, but all too often the first and only symptom is sudden death. Because of the subtlety of the clinical phenotype, consensus criteria were developed on the basis of structural, functional, and electrocardiographic manifestations. ARVC/D prevalence has been estimated to be 1 in 5000. Family-related cases account for 30% to nearly 50% of all cases. In a particular instance, ARVC/D was demonstrated as being autosomal recessive and associated with noncardiac signs. In this ARVC/D form, the mutated gene coded for an essential component of desmosomes. Eight chromosomal loci have been mapped, but only 2 genes have been identified to date (for a review, see Paul et al). Despite this recent progress, there are many unanswered questions. Is the high prevalence of ARVC/D in young athletes true for the general population? What is the relationship between fibrofatty replacement of the RV free wall and His bundle and left ventricular (LV) anomalies? Here, we report on a 20-year retrospective study of 200 sudden death cases related to ARVC/D by autopsy findings. In fact, the circumstances of death were diverse, and death usually occurred during everyday life events. Autopsy findings showed that specific RV wall abnormalities.
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 3630 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, 1700 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.12,13 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 analyzed 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.1,6,14–16 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 χ² 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, 1930 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 20.5±12.5 years). The age and gender breakdown are shown in Table 1.
Circumstances of Death in Results.

ARVC/D. For explanation of circumstances of death in 98 female and 102 male cases of ARVC/D. Percentage of 5 types of circumstances of death in 198 cases. 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 versus 34.3±12.2 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 males, 9 females; average age 35.4±16.5 years). In all cases, surgery was performed for minor lesions (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 (Figure 1A) and macroscopic study (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% of cases); (2) mild forms extended from the anterior interventricular groove to the RV edge (35% of cases); and (3) major forms with cavity dilatation, which spared only 3 to 4 cm of the RV posterior juxtaseptal area (23% 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 (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 thickness17 (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.

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F indicates female; M, male.

Figure 4. Heart weight for females (A) and males (B). Bar for each weight category shows number of cases.

Figure 5. LV wall thickness for females (A) and males (B). Bar for each LV wall thickness shows number of cases.
His and Bundle-Branch Observations
Histological examination of the His bundle and its 2 branches enabled us to obtain results from 197 cases. In 63 cases (32%), no alteration was evidenced. In the remaining 134 cases (68%), conductive tissue was infiltrated by fibrosis only (107 cases, 54.3%; Figure 1D), adipose tissue only (16 cases, 8.1%), or adipose tissue and fibrosis (11 cases, 5.6%; Figure 1E). These 2 latter groups were pooled to compare distribution between males and females. There was no difference ($\chi^2=0.45, P=0.798$). Whereas in the right myocardium, the largest group had adipose tissue with fibrosis (74.5%), in the His bundle, the largest group had isolated fibrosis (54.3%). However, the group of isolated adipose tissue in the myocardium did not match the group of adipose tissue only in the His bundle. By comparison to these cases with ARVC/D, His and bundle branches of a group of 184 subjects with pulmonary causes of death (inhalation or acute and massive pulmonary infection) who were analyzed systematically showed an infiltration with adipose tissue, fibrosis, or both in fewer than 5% of the cases.

Left Ventricle
The LV was microscopically normal in 137 cases (68.5%). The most frequent anomaly was fibrosis (68 cases [34%]: interstitial [29 cases], perivascular [30], endocardial [9], or combined). Adipose tissue in the LV was rare, and its extent was limited to either the subepicardial area (8 cases) or the perivascular region associated with fibrosis (30 cases). Only 2 cases had lesions of myocarditis. LV histological involvement was not associated with age but was strongly associated with a greater heart weight (369.2 ± 98.9 versus 312 ± 64.6 g, $P<0.001$), a greater LV posterior wall thickness (12.4 ± 2.3 versus 10.5 ± 1.7 mm, $P<0.001$), and gender (36.1% males and 24.3% females with LV histological involvement, $P<0.01$). Only LV posterior wall thickness persisted as an independent factor of LV involvement.

Discussion
There have been several reports on estimation of the prevalence of ARVC/D in sudden death. These studies have reached different conclusions. On the basis of an infiltration of at least 75% of the RV free wall by adipose tissue, Shen et al.\textsuperscript{18} reported a percentage of 17% ARVC/D in a series of 54 sudden deaths in individuals aged 20 to 40 years. Recently, a 14% prevalence of death secondary to ARVC/D was shown in a series of 273 sudden cardiac deaths among people aged 1 to 35 years.\textsuperscript{11} By contrast, a much higher prevalence (32%) was reported in young competitive athletes.\textsuperscript{19} This discrepancy could be accounted for by the young age of individuals who participate in competitive sports activity and possibly by a role of sports activity in triggering cardiac arrhythmia in latent ARVC/D. In another study that examined 80 cases of SCD during sports activity, ARVC/D was the second-leading cause of death after hypertrophic cardiomyopathy in patients younger than 30 years of age but the fifth most prevalent cause in patients older than 30 years.\textsuperscript{13} By contrast, in the present series of 1930 cases of USCD, we report an overall prevalence of ARVC/D of 10.4%. This lower prevalence is probably a consequence of several inclusion criteria that differ from those of previous studies: the age range was much wider (1 to 65 years), circumstances of death were not selected, and cases with a known history of cardiac symptoms or disease were systematically discarded. In particular, this last criterion may have lowered the prevalence of ARVC/D, because we selected these particular cases of ARVC/D that commenced with a fatal event. By contrast, age range and criteria concerning circumstances of death, which may have influenced minimally the prevalence rate, provide a very innovative representation of ARVC/D. Sudden cardiac death secondary to ARVC/D was contemporaneous with sedentary activity in 75.8% of cases and with sports activity in only 3.5% of cases. Moreover, both genders were equally affected, and despite a broad peak in the 30s, ARVC/D may trigger death in every period of life. Altogether, these data change the image of ARVC/D as a disease that primarily kills young male athletes during sports exercise to that of a disease that causes death to males and females in their 30s engaged in daily life activities. Besides age, we failed to find any parameter that could potentially indicate a higher risk for USCD. Notably, the histological types of myocyte replacement (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 $\approx$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 anomalies also extend to other structures of the heart; in particular, the LV might be involved, as reported previously.\textsuperscript{20,21} LV hypertrophy is strongly associated with LV fibrosis infiltration 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 parameters were not recorded. The His bundle and its branches (but neither the sinus nor the AV node) were examined systematically, 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 bundle anomalies suggests that conduction anomalies and/or arrhythmias 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, I had a complete auriculoventricular block.

The histological criteria to ascertain ARVC/D are controversial. There is agreement on the fibrofatty variant, but the adipose variant is considered by some authors as normal and by others as pathological.\textsuperscript{22} 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 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

This work was supported in part by grants from the Hospices Civils de Lyon and the Université Claude Bernard Lyon 1 (to Drs Bouvagnet and Tabib) and the Fondation de la Recherche Médicale and the SEERAC and the Région Rhône-Alpes (to Dr Bouvagnet). The authors also acknowledge the Hospices Civils de Lyon, Université Claude Bernard Lyon 1, FRM, SEERAC and Région Rhône-Alpes.

References

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Circulation. 2003;108:3000-3005; originally published online December 8, 2003; doi: 10.1161/01.CIR.0000108396.65446.21

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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