CASE REPORT

Allen P. Burke,[1] *M.D.; Stephen Robinson,*[1] *M.D.; Stephen Radentz,*[2] *M.D.; John Smialek,*[3] *M.D.; and Renu Virmani,*[1] *M.D.*

Sudden Death in Right Ventricular Dysplasia with Minimal Gross Abnormalities*

REFERENCE: Burke AP, Robinson S, Radentz S, Smialek J, Virmani R. Sudden death in right ventricular dysplasia with minimal gross abnormalities. J Forensic Sci 1999;44(2):438–443.

ABSTRACT: Arrhythmogenic right ventricular cardiomyopathy is emerging as a relatively common cause of exercise-induced sudden death in the young. The diagnostic criteria at autopsy are, however, not fully established, leading to both over- and underdiagnosis. We report a young man and a young woman dying suddenly of right ventricular dysplasia during exercise, in whom the gross autopsy findings in the right ventricle were minimal or even absent. However, the histologic features in both right and left ventricles were typical of the disease, and consisted of fibrofatty infiltrates with typical myocyte degeneration of the right ventricle and subepicardial regions of the left ventricle. These cases illustrate that microscopic findings are diagnostic and may be present in the absence of gross findings. Marked fat replacement is not essential for the diagnosis of right ventricular dysplasia, and the right ventricle should be extensively sampled histologically in all cases of sudden unexpected death, especially those that are exercise related.

KEYWORDS: forensic science, forensic pathology, cardiomyopathy, sudden death, right ventricle

Arrhythmogenic right ventricular cardiomyopathy (ARVC) has recently been included in the World Health Organization's classification of cardiomyopathies (1). Most patients are young adults at the time of diagnosis. The presenting symptoms are often caused by ventricular tachyarrhythmias that may result in sudden cardiac death. The mean age for patients dying suddenly is usually in the third decade (2,3). In Northern Italy, ARVC is the leading cause of exercise-related sudden death (3). In the U.S., however, ARVC is a relatively uncommon cause of sudden unexpected death, for reasons that are unclear (4).

The pathologic features at autopsy have been described in relatively few series (3–7). In all of these series, fat replacement (or fat ''infiltration'') of the right ventricle has been considered essential for the diagnosis. However, it has long been appreciated by pathologists, and recently verified morphometrically, that fat is a normal constituent of the right ventricle, especially the anterior wall (7,8). Therefore, other criteria must be met before the diagnosis of ARVC can be established. Right ventricular aneurysms are characteristic of the disease, but are present in only 50% of cases (5). Pathologic changes, other that fat infiltrates, that are frequently seen in ARVC include fibrosis, inflammation, and subepicardial left ventricular scars (6,9,10). These features may be helpful in the pathologic diagnosis, but are not often appreciated grossly.

In this report we present two patients with exercise-related sudden death (a typical presentation for ARVC) that had histologic fibrofatty infiltrates, with focal inflammation, in the right and left ventricles, typical of ARVC. However, gross fat replacement of the right ventricle or ventricular thinning was lacking in both cases. We propose that, contrary to previous reports, grossly visible fat replacement is not a *sine qua non* for the diagnosis of ARVC; rather, the microscopic features are more typical and diagnostic. The two cases presented herein have significant implications for pathologists, especially forensic pathologists, who are faced with diagnosing ARVC in cases of sudden cardiac death.

Case Report #1

A 47-year-old black female (5 ft-6 in., 128 lb) (167 cm, 58 kg) collapsed during aerobics class. She had no history of previous cardiac symptoms and her medical history was unremarkable. Despite maximal resuscitative efforts, she was pronounced dead soon after arrival at a local hospital.

At autopsy, significant findings were limited to the heart, and a toxicological drug screen was negative. The heart weighed 345 g. The apex of the heart was formed by the left ventricle, and although there was mild dilatation of the base of the right ventricle, no right ventricular aneurysms were present. The minimum right ventricular thickness was 3 mm. The epicardial fat was unremarkable, as were the endocardium and valves. On gross examination, the only abnormality noted was a focal scar in the left ventricular posterior wall, which was located in the subepicardial region towards base, and was not clearly visible on cross-section (Fig. 1*a*). Specifically, there was no fat or fibrosis seen grossly in the right ventricle, which measured 4 mm thick. The left ventricular free wall was 10 mm thick, and the ventricular septum measured 13 mm thick. The coronary arteries demonstrated a right dominant

[1] Department of Cardiovascular Pathology, Armed Forces Institute of Pathology, Washington, DC.
[2] Assistant Medical Examiner, Office of Chief Medical Examiner, State of Maryland, Baltimore, MD.
[3] Professor, Department of Pathology, University of Maryland, Baltimore, MD.

* The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Army, the Department of the Air Force, or the Department of Defense.

Received 29 May 1998; and in revised form 6 July 1998; accepted 6 July 1998.

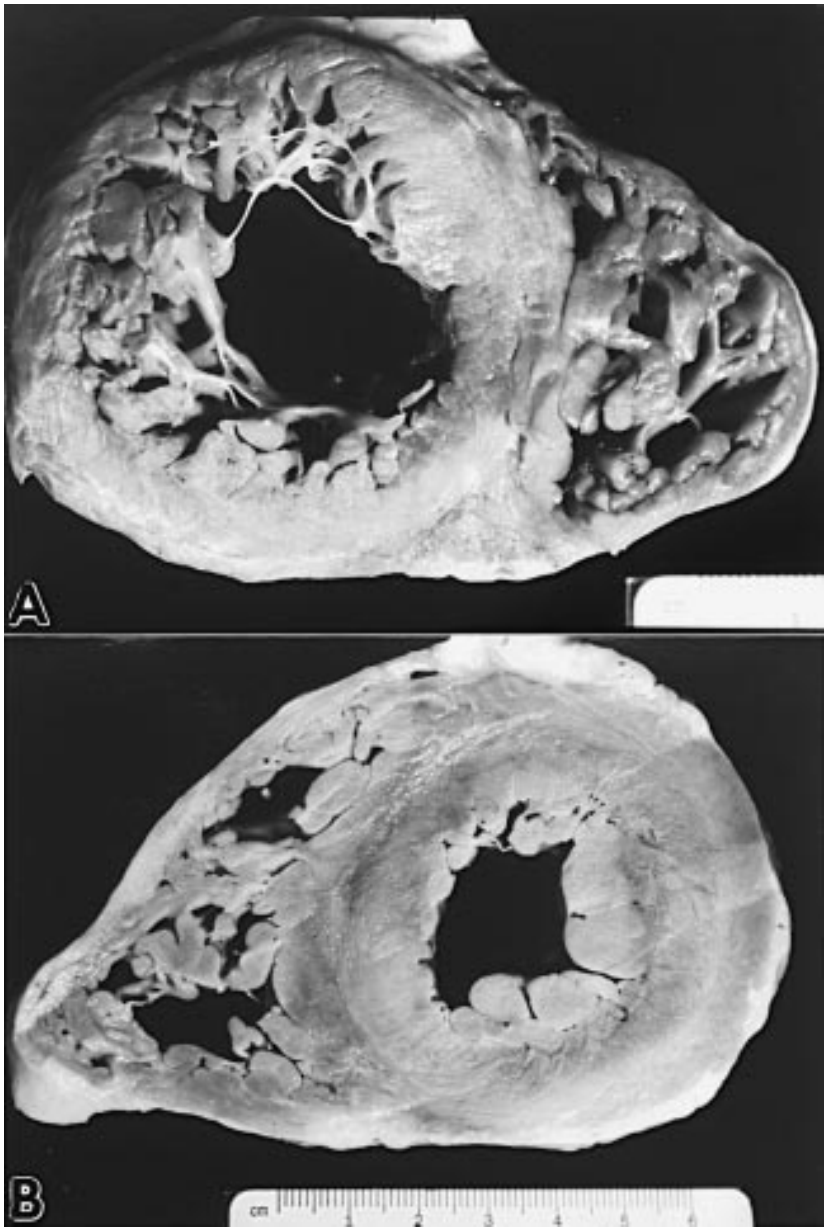

FIG. 1—*Gross heart findings. (*A*) The heart from case 1 demonstrates no obvious gross abnormality. No scarring is seen in this slice of the left ventricular posterior wall. (*B*) The heart from case 2 demonstrates mild left ventricular hypertrophy. There is focal fat infiltration in the anterior wall (arrow) of the right ventricle, which histologically only showed the presence of fat and no fibrosis.*

pattern and there were only fatty streaks present without atheroma formation.

Histologic sections demonstrated subepicardial fat replacement with fibrosis in the right ventricle (Fig. 2*a*). In areas of fibrosis, vacuolated bubbly myocytes were present (Fig. 2*b*). There was focal inflammation of the right ventricle. These changes were present only in the posterobasal area of the right ventricle and could be demonstrated only after sampling five areas of the right ventricle. Likewise there were scars in the left ventricular free wall with focal fat replacement (Figs. 2*c,d*). As in the right ventricle, in areas of fibrosis, vacuolated, bubbly myocytes were also present in the left ventricle (Fig. 2*e*).

Case Report #2

A 23-year-old black male collapsed while playing basketball. He had a previous history of syncopal episodes and had been seen in emergency room and advised to see a cardiologist. However, a cardiac evaluation had never been performed. He had a history of cocaine abuse; otherwise, his medical history was negative. Despite resuscitative efforts, he was pronounced dead in a local emergency room.

At autopsy the only significant findings were present in the heart. Toxicological analysis of the blood was negative for drugs. The urine demonstrated cocaine metabolites (2-benzoylecgonine and ecgonine methyl ester). The heart weighed 620 g, and demonstrated concentric left ventricular hypertrophy (Fig. 1*b*). The left ventricular free wall was 18 mm thick, and the ventricular septum 20 mm thick. The right ventricle was 4 mm thick and grossly unremarkable, without fat infiltrates or scars. The valves were essentially unremarkable with the exception of mild fenestrations of the aortic valve. The coronary circulation was right dominant without significant atherosclerosis.

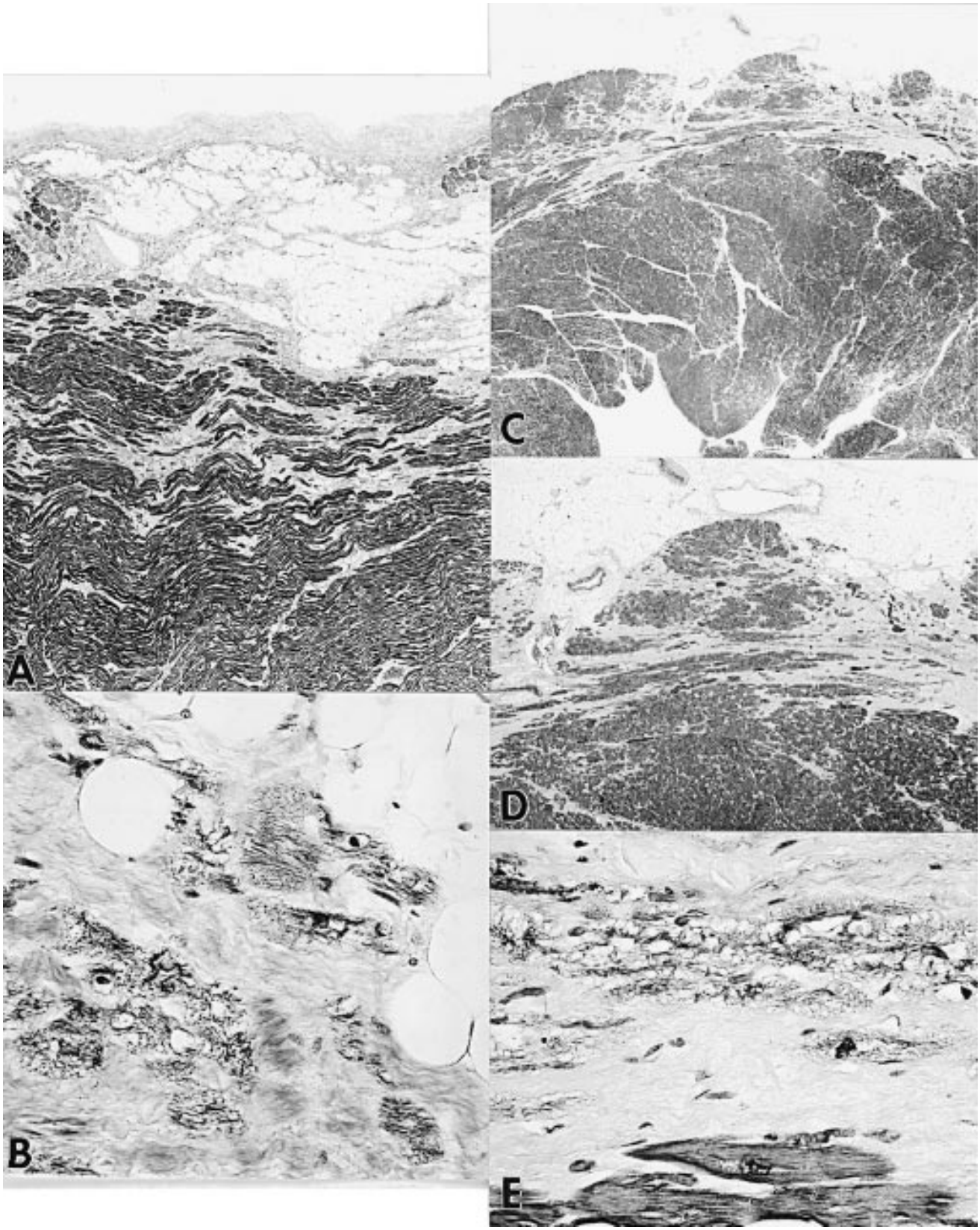

FIG. 2—*Histologic features, right ventricular cardiomyopathy, case 1.* (A) *There is mild subepicardial fat infiltration in the right ventricle, to an extent that is commonly seen in normal hearts. However, there is fibrosis associated with the fat, and islands of residual myocytes are present near the subepicardium, suggesting that the fat is not physiologic.* (B) *A higher magnification of the right ventricle demonstrates typical bubbly myocytes in areas of scarring.* (C) *The left ventricle demonstrates a subepicardial scar, in a pattern that is typical for ARVC.* (D) *A higher magnification demonstrates replacement fibrosis with areas of myocyte loss.* (E) *A high magnification demonstrates typical bubbly myocytes adjacent to collagen deposition in the left ventricle.*

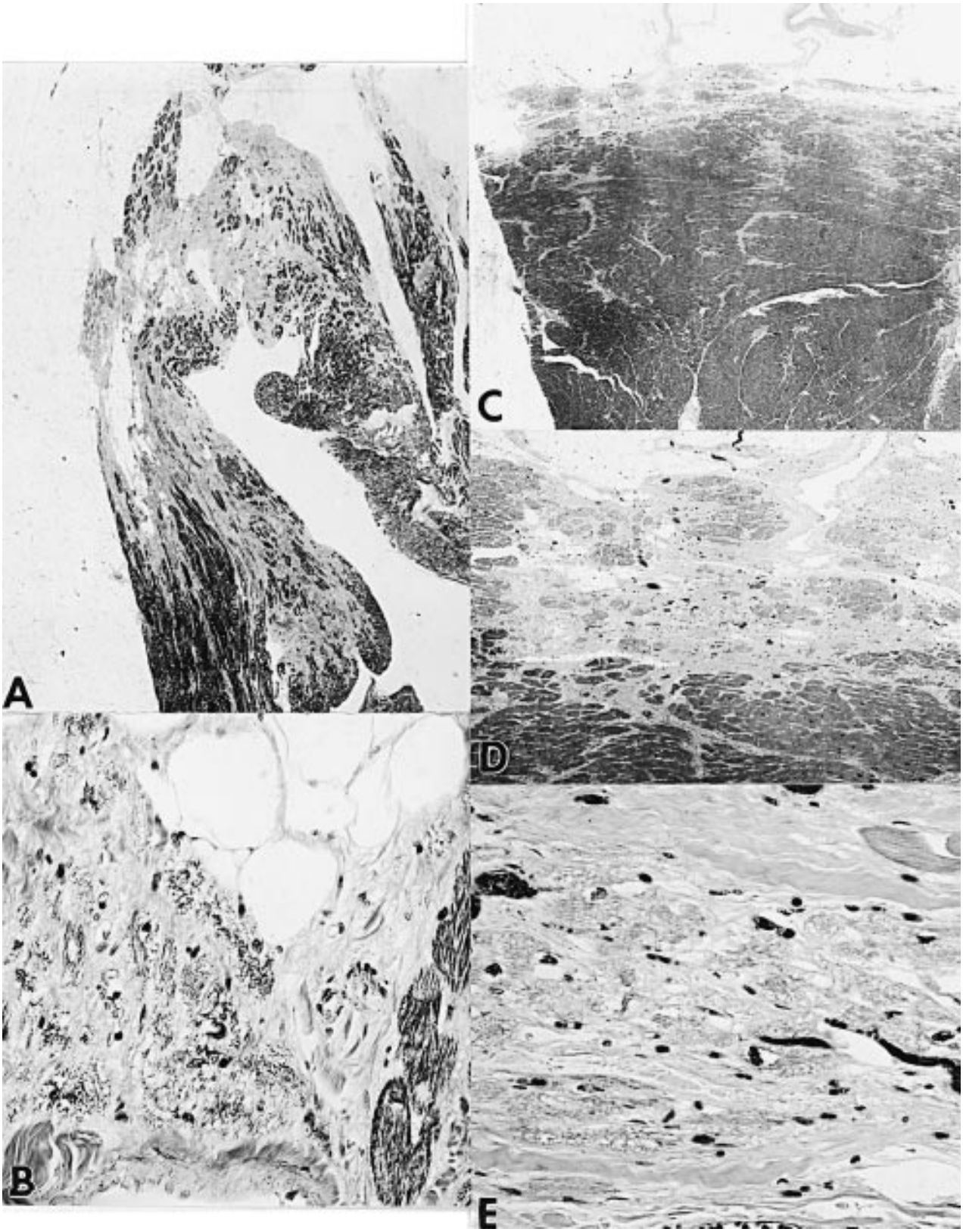

FIG. 3—*Histologic features, right ventricular cardiomyopathy, case 2.* (A) *The typical fibrofatty replacement of the right ventricular wall is present in a section taken from the posteroapical area. The amount of fat, however, is relatively minimal.* (B) *A high magnification demonstrates typical bubbly myocytes in areas of scar.* (C) *The left ventricle demonstrates subepicardial scarring nearly identical in appearance to case 1.* (D) *A higher magnification of Fig. 1C demonstrates scarring with minimal fat infiltrates.* (E) *The bubbly myocytes in areas of scar, typical of ARVC, are present in the left ventricle.*

Histologic sections showed focal fibrosis with fat infiltration in the right ventricle (Fig. 3*a*). In areas of fibrosis, there was myocyte vacuolization (Fig. 3*b*) with scattered lymphocytic infiltrates. These areas were located only in the posterior and mid-ventricle near the base; only two of eight sections of the right ventricle sampled demonstrated histologic changes of ARVC. The left ventricle demonstrated subepicardial scarring with focal fat infiltrates (Fig. 3*c*). Myofiber disarray was not present in areas of the ventricular septum. As in the right ventricle, areas of bubbly myocytes were present in the left.

Comment

The cause of death in case #1 was clearly related to the biventricular changes of ARVC. In case #2, there were several potential causes of death. Concentric left ventricular hypertrophy, which in this case was possibly related to cocaine abuse, may lead to ventricular arrhythmias and sudden death (11). Drug intoxication was considered an unlikely cause of death because of a lack of cocaine in the serum or blood. The changes of ARVC were considered a likely contributing cause of death, as ARVC predisposes to exercise-related arrhythmias (3), unlike concentric left ventricular hypertrophy (11). It is probable that ARVC and cocaine-related cardiac hypertrophy together participated in the cause of sudden death in this case.

The autopsy findings of ARVC have been tabulated in four series (3,4,6,7). The heart is generally normal in size or slightly enlarged. The right ventricle is dilated, often only focally, and there is usually an area of myocardial thinning up to 2 mm or less. Aneurysmal thinning may occur anywhere in the right ventricle, especially the right ventricular outflow tract, apex, and posterobasal segment. The epicardial fat is typically not significantly increased. The left ventricle is typically normal, although it has recently been appreciated that subepicardial scars are present in over 50% of cases (6,7).

The histologic features of ARVC are quite varied, and there is still disagreement on those features which are diagnostic. The three elements which may or may not be present in right ARVC include fibrosis, fat, and inflammation. Fat infiltration of the right ventricular myocardium is usually considered a *sine qua non* for the diagnosis of right ventricular cardiomyopathy. Fibrosis, on the other hand, is only sometimes considered a required feature (5). The disease has been pathologically subclassified based on the proportion of fat and fibrous tissue present. Italian investigators recognize a lipomatous and fibrolipomatous pattern (5,12) and Lobo et al. add a third type in which there is an absence of myocardium with apposition of endocardium and epicardial tissue (6). It has been more recently demonstrated that massive fat replacement of the right ventricle in the absence of fibrosis should be considered a separate entity that is not as frequent or arrhythmogenic as ARVC (7). The presence of myocarditis is variable, is not usually considered a diagnostic feature, and has led to arguments that ARVC may be a post-inflammatory cardiomyopathy, as opposed to a true dysplasia (5).

A review of the available information on ARVC reveals that most of the diagnostic features are nonspecific, that the relevance of the proportion of fat and fibrous tissue in the diagnosis is controversial, and that the diagnosis rests on the coexistence of several findings in the appropriate clinical setting. We propose that, on the basis of the cases presented in this report and recently published data (7), the primary diagnostic features of ARVC are histologic, and consist of three elements found in a typical distribution. These elements are fat replacement (which may be minimal or only microscopically appreciated), fibrosis, and degenerating, vacuolated myocytes trapped within areas of fibrosis. The distribution of these three elements is the right ventricle (either predominantly subendocardial, subepicardial, or transmural (7)), as well as the left ventricle, in a purely subepicardial position. If these criteria are met, then subtle cases of ARVC (such as seen in these cases) will not be missed. Conversely, if these criteria are strictly applied, cases of fat replacement of the right ventricle, which may be normal or a different process, will not be misdiagnosed as ARVC.

Because fat is a normal component of the right ventricle, especially the anterior wall near the apex (7), fat is likely the least reliable criterion for diagnosis, and must be seen in conjunction with the other two features. The vacuolated myocytes typical of ARVC may represent a form of lipid metaplasia (13), and a precursor to the presence of more abundant areas of fat replacement. It is not surprising, therefore, that in some instances of ARVC, the degree of mature fat replacement may be minimal, as seen in the cases in this report.

The emphasis on the histologic criteria for the diagnosis of ARVC should not detract from the importance and recognition of the familiar gross features, which are right ventricular thinning and fat replacement of the outflow, posterobasal and apical regions (7,9). In these cases, areas for sampling to detect microscopic features of ARVC are readily apparent. However, as the two cases reported here demonstrate, generous histologic sampling of grossly normal right ventricular myocardium should be performed in all cases of unexpected sudden death, especially in exercise-related deaths with left ventricular scarring. We recommend, in cases of exercise-related sudden death without obvious cause, that six sections of the right ventricle be processed for histologic evaluation: anterior, lateral, and posterior free walls, both at the base and apex.

It has been demonstrated that ARVC is familial in approximately 30% of patients (2,14,15). Therefore, a specific diagnosis of ARVC is important to make at forensic autopsy, in light of genetic counseling that may be rendered. For this reason, appreciation of the more subtle microscopic forms of ARVC, as presented in these reports, is vital. On the other hand, pure fat infiltration of the right ventricle, without fibrosis, is uncommonly a cause of lethal arrhythmias and does not appear to have a familial tendency (7). Although ARVC with minimal histologic findings, such as these cases, may be a lethal disease, it remains to be demonstrated if the genetic and familial basis for the disease is similar to that of more typical gross forms.

References

1. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathy. Circulation 1996;841–2.
2. Nava A, Thiene G, Canciani B, Scognamiglio R, Daliento L, Buja G, et al. Familial occurrence of right ventricular dysplasia: A study involving nine families. J Am Coll Cardiol 1988;12:1222–8.
3. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med 1988;318:129–33.
4. Goodin JC, Farb A, Smialek JE, Field F, Virmani R. Right ventricular dysplasia associated with sudden death in young adults. Mod Pathol 1991;4:702–6.
5. Basso C, Thiene G, Corrado D, Angelini A, Nava A, Valente M. Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis? Circulation 1996;94:983–91.
6. Lobo FV, Heggtveit HA, Butany J, Silver MD, Edwards JE. Right

ventricular dysplasia: morphological findings in 13 cases. Can J Cardiol 1992;8:261–8.
7. Burke AP, Farb A, Tashko G, Virmani R. Arrhythmogenic right ventricular cardiomyopathy and fatty replacement of the right ventricular myocardium: Are they different diseases? Circulation 1997; 97:1571–80.
8. Fontaliran F, Fontaine G, Fillette F, Aouate P, Chomette G, Grosgogeat Y. Nosologic frontiers of arrhythmogenic dysplasia. Quantitative variations of normal adipose tissue of the right heart ventricle. Arch Mal Coeur Vaiss 1991;84:33–8.
9. Marcus FI, Fontaine G. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: a review. Pacing Clin Electrophysiol 1995;18:1298–314.
10. Davies MJ. Arrhythmogenic right ventricular dysplasia: the phenotypic range defined. Br Heart J 1994;71:214.
11. Burke AP, Farb A, Virmani R, Goodin J, Smialek J. Sports- and non sports-related sudden cardiac death. Am Heart J 1991;121: 568–75.
12. Daliento L, Turrini P, Nava A, Rizzoli G, Angelini A, Buja G, et al. Arrhythmogenic right ventricular cardiomyopathy in young versus adult patients: similarities and differences. J Am Coll Cardiol 1995;25:655–64.
13. Masani F, Aizawa Y, Izumi T, Shibata A. An ultrastructural study on arrhythmogenic right ventricular dysplasia with special reference to lipid droplets. Heart Vessels Suppl 1990;5:55–8.
14. Pinamonti B, Miani D, Sinagra G, Bussani R, Silvestri F, Camerini F. Familial right ventricular dysplasia with biventricular involvement and inflammatory infiltration. Heart Muscle Disease Study Group. Heart 1996;76:66–9.
15. Anguera Ferrando N, Pujadas Capmany R, Abardia Oliva X, Casasus Ramon A. Familial association of arrhythmogenic dysplasia of the right ventricle and obstructive hypertrophic myocardiopathy. Med Clin (Barc) 1993;101:798.

Additional information and reprint requents:
Renu Virmani, M.D.
Department of Cardiovascular Pathology
Armed Forces Institute of Pathology
Washington, DC 20306-6000