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RIGHT VENTRICULAR FATTY REPLACEMENT AS THE POSSIBLE MISSING LINK BETWEEN FATTY LIVER AND SUDDEN DEATH

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ABSTRACT. THE ASSOCIATION BETWEEN FATTY LIVER and sudden death has long been suspected, particularly in forensic pathology, but its pathogenic mechanisms remain elusive. This report describes several cases of fatty liver-associated sudden death in connection with extensive right ventricular fatty replacement. On the basis of the findings described in this study, it is hypothesized that extensive fatty replacement of the right ventricle is the missing link between fatty liver and sudden death, particularly in alcoholics and possibly also in obese and diabetic patients. In support of this proposed link, relevant literature on arrhythmogenic right ventricular cardiomyopathy, alcoholic and nonalcoholic steatosis/steatohepatitis, and fatty liver-associated sudden death is also discussed. It is suggested that right ventricular fatty replacement associated with fatty liver may represent a unique subset of arrhythmogenic right ventricular cardiomyopathy caused by chronic lipid metabolic disturbances.

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1. INTRODUCTION

The association between fatty liver and sudden death, especially in alcoholics, has long been suspected in forensic pathology. In 1926, Le Count and Singer [1] described a group of patients with chronic alcoholism who suffered a sudden death, and the main significant postmortem findings included massive hepatic steatosis. The authors were able to exclude delirium tremens, acute alcohol poisoning, and hepatic cirrhosis as the causes of death in these patients. In a more recent study [2], Copeland analyzed 118 medical examiner's cases of death. Among the victims, most of them were "found dead" at home with a past history of heavy alcohol drinking. All the cases were carefully analyzed with regard to the cause of death, age, race, sex, blood alcohol content, drugs detected at autopsy, scene circumstances, geographic location of the terminal incident, history of drinking prior to the terminal incident, average weights of key target organs, and the histopathology of the liver. It was found that most of the cases involved older white males who died from "chronic alcoholism" but with a terminal negative blood alcohol. Histopathological examination of the liver often revealed extensive fatty metamorphosis rather than cirrhosis, with otherwise negative autopsy findings. Some of the epidemiological and pathological studies have also suggested a relationship between the presence of fatty liver and sudden death [3-5]. This report describes new clinical and pathological observations which point to an association between fatty liver, fatty replacement of the right ventricle of the heart, and sudden death, and it is hypothesized that severe fatty replacement of the right ventricle is the possible missing link between fatty liver and sudden death.

2. REPORT OF CASES

Six autopsy cases were included in this report. In all 6 cases, the deceased died suddenly either being observed in cardiopulmonary arrest or "found dead" at home by relatives. There was no evidence of foul play by scene investigations. Toxicology studies showed no evidence of drug toxicity, except for case #3. The history of each case and general postmortem findings are summarized TABLE 1.

In this study, all six cases showed unequivocal gross and microscopic evidence of transmural fatty replacement of the right ventricle. FIG.1 shows the typical gross finding of extensive fatty replacement of right ventricular myocardium. This change was more prominent at the anterioapical and anteriolateral walls, although the posteroinferior wall and the infundibulum were also involved. Right ventricular fatty replacement observed in these cases is different from a mere increase of subepicardial fat which is usually non-infiltrative and well demarcated from myocardium (see FIG. 1C for comparison). All of the cases also had some degrees of cardiomegaly with mild right ventricular dilatation. Microscopically, there was extensive transmural fatty infiltration of right ventricular wall. Myofibers were largely replaced by mature adipose tissue in a lacelike manner. Some of the cases also showed focal fibrosis and chronic inflammatory cell infiltrate (FIG. 2). There was no significant coronary artery disease (CAD) or coronary artery stenosis, except for case #5 which showed moderate CAD, but without evidence of coronary artery thrombosis or myocardial infarction. The cardiac findings in all 6 cases are summarized in TABLE 2. Cardiac valve lesions were not observed in any of the cases. In the left ventricle, adipose and fibrous tissues were mainly located on the epicardium particularly around the coronary vessels and were not transmural infiltrative. There were no significant gross and histopathological changes in the left ventricles, and left ventricular dilatation was not observed.

All cases were associated with various degrees of fatty liver with or without inflammation and fibrosis (TABLE 3). The fatty liver was predominantly macrovesicular steatosis with a centrilobular distribution. FIG. 4 shows histological changes of both right ventricular fatty replacement and fatty liver in all 6 cases.

3. DISCUSSION

The mysterious association between fatty liver and sudden death has long been suspected, particularly in forensic pathology. The literature mainly described this phenomenon in alcoholics. It is interesting to note that fatty liver is not only associated with alcoholics, but also with obesity, diabetes, medications and other conditions [6].

TABLE 1. HISTORY AND GENERAL FINDINGS AT AUTOPSY.

Case #	Gender	Age (year)	Weight (lb)	History	Blood alcohol	Cause of death
1	male	40's	300	non-alcoholic	–	presumed cardiac
2	male	30's	210	non-alcoholic	<0.01%	presumed cardiac
3	male	50's	225	unknown	0.011%	drug overdose
4	male	50's	175	alcoholic	<0.01%	presumed cardiac
5	male	60's	175	alcoholic	0.085%	presumed cardiac
6	female	60's	160	alcoholic	0.422%	pneumonia

TABLE 2. FINDINGS IN THE HEART.

Case #	Heart weight (g)	CAD	Right ventricular fatty infiltrate
1	620	minimal	transmural fatty, with focal chronic inflammatory cell infiltrate
2	420	minimal	transmural fibrofatty, with focal chronic inflammatory cell infiltrate
3	480	minimal	transmural fatty, with focal chronic inflammatory cell infiltrate
4	480	minimal	transmural fatty, with focal chronic inflammatory cell infiltrate
5	420	moderate	transmural fibrofatty
6	300	minimal	transmural fatty

TABLE 3. FINDINGS IN THE LIVER.

Case #	Liver weight (g)	Steatosis	Inflammation	Fibrosis
1	2800	moderate	minimal	minimal
2	1980	minimal	minimal	minimal
3	2900	mild to moderate	minimal	minimal
4	1900	marked	mild to moderate	marked
5	1800	marked	minimal	mild
6	1910	marked	minimal	mild

Morbid obesity and diabetes also pose a higher risk for unexplained sudden death [7,8]. The underlying pathogenic mechanisms remain elusive. Some of the proposed mechanisms in the literature include dilated cardiomyopathy, prolonged QT interval, and metabolic abnormalities sometimes seen in alcoholics and obesity [4,9-12]. Dilated cardiomyopathy was not observed in any of the cases included in this study. Instead, right ventricular fatty replacement was the common finding in all six cases.

It is recently known that fatty replacement of the right ventricle is associated with sudden cardiac death in arrhythmogenic right ventricular cardiomyopathy (ARVC). ARVC is characterized by transmural fatty or fibrofatty replacement of the ventricular myocardium. This process appears to be more evident in the right ventricle, and it usually

results in ventricular tachyarrhythmias along with a high risk of unexpected cardiac arrest and sudden death. The pathological process appears to originate at the subepicardium and then extends to the endocardium as a wave-front phenomenon [12]. At the boundary with the adipose front, the residual myocytes usually appear as thin interlacing strands. Also, small disperse islands of myocytes are often seen within the adipose tissue. The dispersion of residual electrically-conducting myocytes within the fibrofatty tissue accounts for the delay of the intraventricular impulse transmission and persistence of electrical depolarization during diastole (late potential) [13] as well as for the onset of re-entrant circuit with premature ventricular beats and ventricular tachycardia.

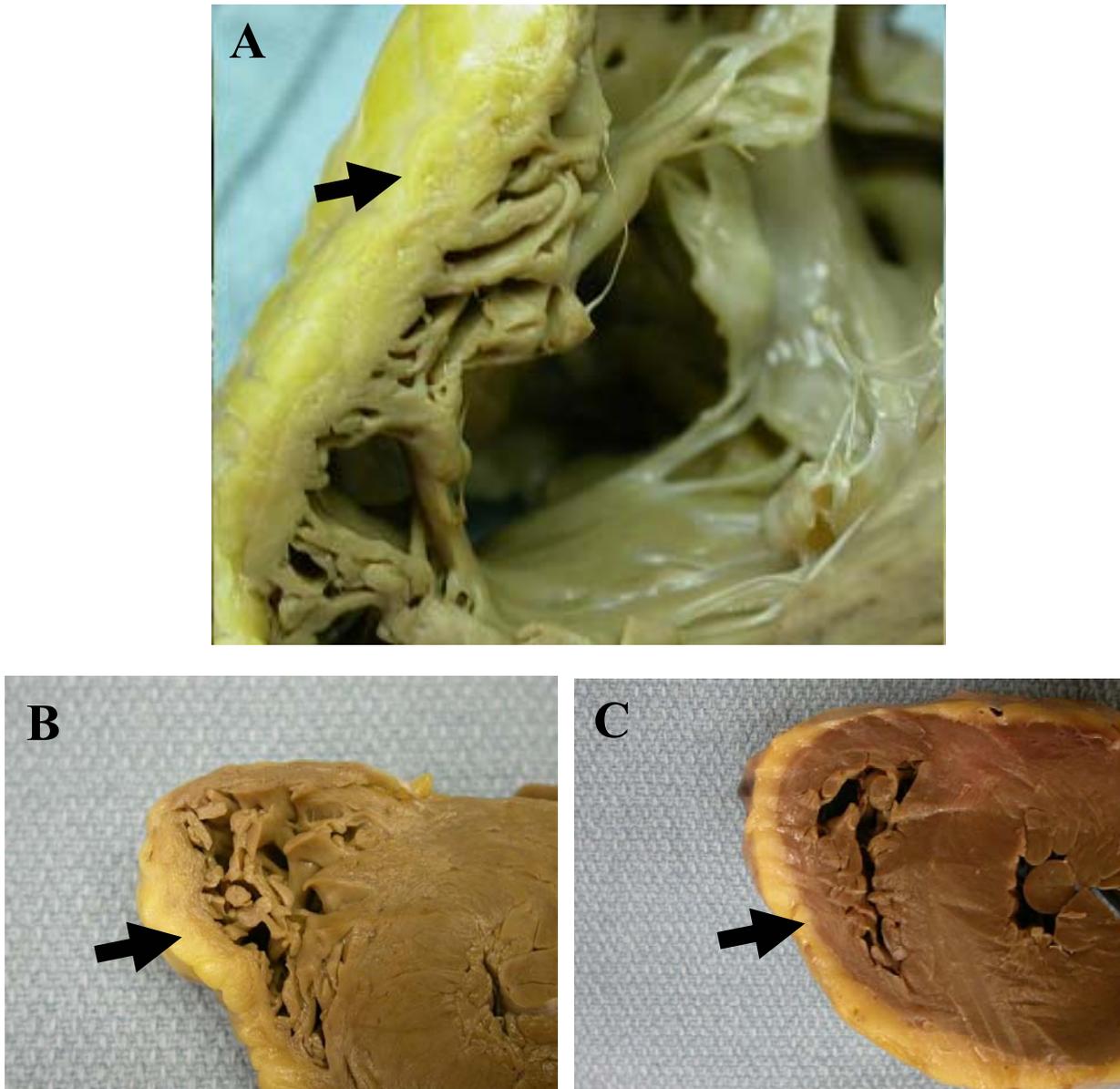


FIGURE 1. RIGHT VENTRICULAR FATTY REPLACEMENT IN COMPARISON WITH MERE INCREASE OF SUBEPICARDIAL FAT.
Panels A and B: Transmurular fatty replacement of right ventricular myocardium (arrow). Note that the right ventricle is slightly dilated. *Panel C:* Mere increase of subepicardial fat which is non-infiltrative and well demarcated from myocardium (arrow). The heart shown in *A* and *B* was the same heart from case #6, while the heart in *C* was from a different case that the victim did not have fatty liver whose data was not included in this study.

The etiology and pathogenesis of ARVC are still unknown. Congenital defect, genetics, and acquired factors have been suggested. According to the congenital/genetic theory, the progressive loss of myocardium is considered secondary to spontaneous

myocyte death due to certain types of genetic defects [14]. Acquired factors such as viral or autoimmune myocarditis have also been considered [15]. It was also suggested that the myocellular damage, regardless of the types of the triggers, could be apoptotic in nature [16]. It is thought that

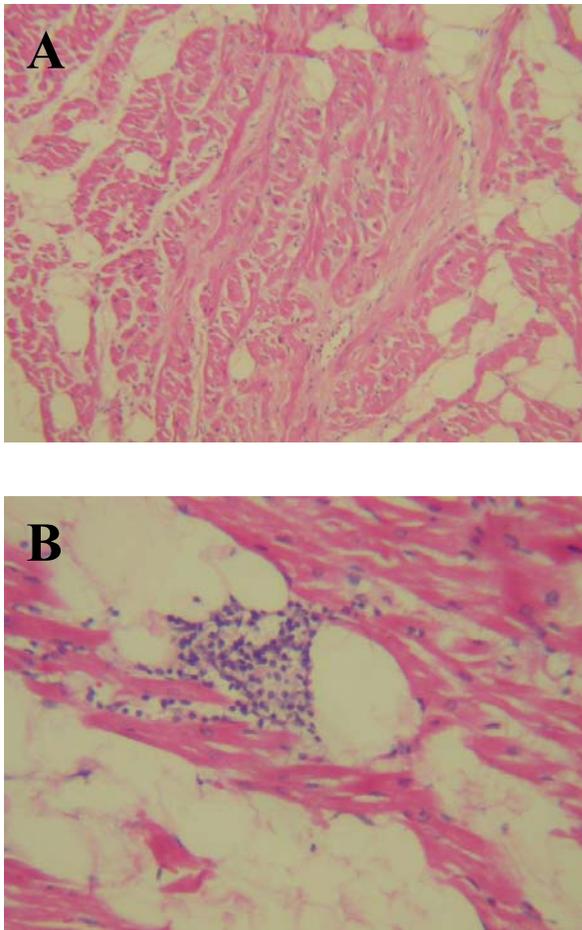


FIGURE 2. HISTOLOGY OF RIGHT VENTRICULAR FATTY REPLACEMENT WITH FOCAL FIBROSIS (A) AND CHRONIC INFLAMMATION (B) IN CASE #2.

adipose replacement follows myocyte loss. However, others have also suggested a progressive transdifferentiation from myocytes to adipocytes as an alternate pathogenetic mechanism for myocyte loss and adipose replacement [17].

Macrovesicular hepatic steatosis results from a complex combination of pathogenetic alterations that include increased delivery, inadequate oxidation, and decreased secretion of various forms of lipid, especially triglycerides, in the liver. This type of steatosis is commonly seen in obesity, alcoholic liver disease, insulin resistance and diabetes, cachexia, and a wide variety of drug-induced and inherited metabolic disorders [18]. Marked macrovesicular steatosis may be associated with or serve as a substrate for induction of

subsequent processes that result in necroinflammation and fibrosis [19]. Many processes are interrelated either in the initiation or the end results of fat accumulation, liver cell damage, and necrosis. These include oxidative stress, generation of free radicals and lipid peroxidation, aberrant cytokine release, increased expression of cytochrome P450 2E1 (CYP2E1) in hepatocytes [20], and mitochondrial dysfunction involving fatty acid oxidation and/or energy homeostasis [21]. It has been shown that the toxic effect of ethanol metabolite acetaldehyde in cardiomyocytes is probably through mechanisms related to CYP 2E1, xanthine oxidase and lipid peroxidase [22,23]. Free radical-mediated mechanisms have been implicated in ethanol-induced toxicity in various extrahepatic tissues including the heart [24].

On the basis of the observation of an association between fatty liver, right ventricular fatty replacement, and sudden death as described in this study, it is hypothesized that severe right ventricular fatty replacement is the missing link between fatty liver and sudden death. The common underlying metabolic disturbances whether due to alcohol, obesity, diabetes or other conditions that induce hepatic fatty change are also likely to be the culprit in the cause of right ventricular fatty replacement, resulting in an increased risk of cardiac arrhythmia and sudden death. In the report that suggested myocyte transdifferentiation as a possible pathogenetic mechanism for ARVC [17], the authors described the patient in their study had high blood levels of triglyceride (450 mg/dL), although it was not known whether or not the patient also had fatty liver.

Different morphologic features of ARVC have been described in the literature. Microscopically, two main patterns have been defined: one is the fatty or infiltrative type, and the other is the fibrofatty or cardiomyopathic type. The fatty/infiltrate pattern usually shows normal or slightly atrophic myocytes being replaced by mature adipocytes in a lacelike manner. The infiltrating adipocytes are contiguous to and indistinguishable from subepicardial adipose tissue. This pattern is predominantly associated with a right ventricular localization. In one of the studies, hearts from the fatty/infiltrative group were mostly obtained at autopsy of patients who died suddenly. Hearts from

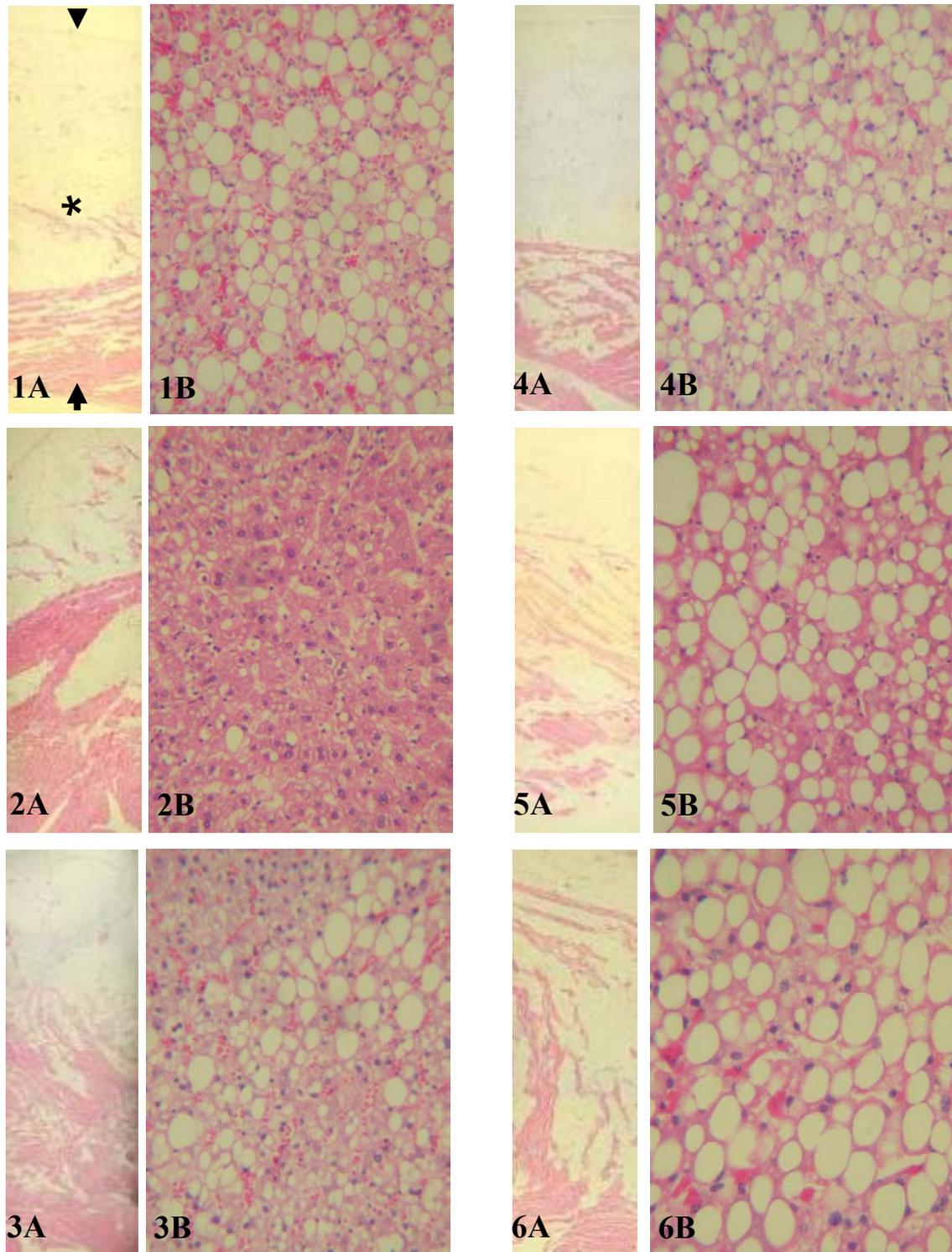


FIGURE 3. SIDE BY SIDE COMPARISON OF RIGHT VENTRICULAR FATTY REPLACEMENT (A) AND FATTY LIVER (B) IN EACH CASE (TOTAL 6 CASES). 1A-6A show right ventricular fatty replacement with fatty infiltration from epicardium (arrow) extending to the endocardium (arrow head). Residual myocytes (*) appear as thin interlacing strands or small dispersed islands within the adipose tissue. 1B-6B show various degrees of fatty liver.

the fibrofatty/cardiomyopathic group with myocardial replacement by fibrofatty tissue and chronic inflammation came mainly from heart transplants for congestive heart failure [25]. It is still unclear whether fatty/infiltrative and fibrofatty/cardiomyopathy groups correspond to distinct forms of the same disease. Nevertheless, both groups showed similar occurrence of threatening ventricular arrhythmia [25]. Right ventricular fatty replacement originally considered as a variant of normal is now considered as a pathologic condition. It appears to be an overlooked, yet frequently observed phenomenon of the human species [26]. Like hepatic steatosis versus steatohepatitis, whether right ventricular fatty replacement develops with or without fibrosis and inflammation may be determined by various local and systemic factors including the intensity and duration of the insults and host responses, rather than indicating a different pathogenic process as suggested by Burke et al [27]. Nevertheless, most of the cases reported here appear to represent a unique clinical and pathological subset of ARVC which is likely to be caused by lipid metabolic disturbances and associated with fatty liver. The only exception is case #2 which appears to fit the classic ARVC with fibrofatty right ventricular replacement and focal chronic inflammation and interestingly, only minimal hepatic steatosis

From my observations, the mere increase in the subepicardial fat is very different from fatty replacement of the right ventricle. Increase of non-infiltrative, well-demarcated subepicardial fat may not be a risk factor for sudden death. It is the infiltrative fatty or fibrofatty replacement of the right ventricle that makes the heart electrically vulnerable. In addition, it appears that the association between fatty liver and fatty replacement of the right ventricle is also likely to be a quantitative one (i.e., the more severe the hepatic steatosis, the more extensive the fatty replacement of right ventricle, and maybe the higher risk of sudden cardiac death). Although quantitative analysis was not made in this study, note that case #3 has relatively mild hepatic steatosis and less extensive fatty replacement of the right ventricle, comparing to cases #1, 4, 5, and 6 (FIG. 4). Although the victims in cases #3 and #6 were died of non-cardiac causes, they were likely carrying the

risk of sudden cardiac death as the others described in this report. Since case #1 had no history of alcoholic abuse and the patient was morbidly obese with fatty liver, it may represent a case of nonalcoholic steatosis/steatohepatitis-related right ventricular fatty replacement.

In summary, this report describes, for the first time, the observation of an association between fatty liver, fatty replacement of right ventricle, and the occurrence of sudden death. It is suggested that the disturbances of lipid metabolism likely contribute to the development of both fatty liver and fatty replacement of the right ventricle. The fatty replacement of the right ventricle is believed to be the missing link for the long-observed mystery between fatty liver and sudden death, particularly occurring in alcoholics and possibly also in obesity and diabetes.

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