

# Patients With Epilepsy Who Die Suddenly Have Cardiac Disease

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**Background:** Approximately 1 in 1000 patients with epilepsy dies suddenly and unexpectedly with no obvious medical cause. The purpose of this study was to determine if the hearts of such individuals harbor occult cardiac pathology.

**Design:** Following a comprehensive protocol, we performed careful pathologic evaluations of the hearts of 7 patients with epilepsy who died suddenly and 13 previously healthy people who died by hanging or a drug overdose. Hearts were studied only when there was no history or gross anatomical evidence of heart disease or the use of adrenergic drugs.

**Methods:** Multiple sections of each heart were evaluated independently by 2 cardiac pathologists who were blinded to patient group.

**Results:** Pathologic conditions were found in 5 hearts in the group with epilepsy and in none of the hearts in the comparison group. Four of the 7 hearts in the group with epilepsy had evidence of irreversible pathology in the form of perivascular and interstitial fibrosis. These 4 hearts plus a fifth had evidence of reversible pathology in the form of myocyte vacuolization. Lesions occurred predominantly in the subendocardium.

**Conclusion:** Our results support the hypothesis that patients with epilepsy who die suddenly and unexpectedly have cardiac pathologic conditions that may be responsible for their deaths.

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**I**N ADDITION to the problems of their disease, patients with epilepsy carry the risk of sudden and unexpected death, with an estimated prevalence of approximately 1 per 1000 patients with epilepsy.<sup>1,2</sup> The mechanism for sudden death in the patient with epilepsy remains a mystery. Because arrhythmias follow neural activation in both humans and experimental models,<sup>3-5</sup> one explanation is that the patient with epilepsy dies of a cardiogenic cause. Although some researchers have reported myocardial ischemia<sup>6</sup> and arrhythmias<sup>7</sup> in patients with temporal lobe epilepsy, others<sup>8</sup> have found normal electrocardiographic findings in large prospective surveys of patients with epilepsy. Thus, no data currently exist to support a neurocardiologic mechanism for sudden death in epilepsy.

Since sudden death is such a rare occurrence for any one patient with epilepsy, we reasoned that a better strategy for finding a link between cardiac dysfunction and sudden death in epilepsy would be to perform a careful pathologic evaluation of the hearts of patients with epilepsy who died suddenly and unex-

pectedly. We were encouraged to take this approach by the report of heavier hearts in such individuals.<sup>9</sup> We now report finding evidence of cardiac pathology in the hearts of 5 of 7 patients with epilepsy who died suddenly and in none of 13 hearts from a comparison group of individuals who died by suicide or a drug overdose.

## RESULTS

The 7 patients with epilepsy ranged in age from 12 to 44 years, with the average age at death being 25 years. There were 5 males and 2 females. Four patients were white and 3 were black. No patient was hospitalized at the time of death, and all were ambulatory. The comparison group ranged in age from 18 to 37 years, with the average age at death being 25 years. Seven subjects died by hanging and 6 of a drug overdose. There were 9 males and 4 females. Eight of these subjects were white and 5 were black.

Review of available records for the 7 patients with epilepsy revealed that 4 had a known illness duration ranging from 9 to 27 years (average, 17 years). None of the 7 patients had a seizure frequency

## SUBJECTS AND METHODS

The subjects were 7 consecutive patients with epilepsy who died suddenly and 13 individuals who died by hanging or a drug overdose. Subjects in both groups were all negative for 3 major exclusion factors: evidence of the use of adrenergic drugs, such as amphetamines or cocaine, by blood test; history of pre-existing heart disease; and any pathologic evidence of overt heart disease at autopsy, eg, coronary artery or valvular disease or heart failure. Hearts were removed, flushed with water, opened, and examined for gross pathologic conditions, after which they were fixed with 10% formalin for subsequent histological evaluation. Transmural blocks were taken from each heart in the following distribution: from the anterior, lateral, and inferior sections from apical, middle, and basal sites of the left ventricle (n = 9); from the lower half of each papillary muscle (n = 2); and from the anterior, lateral, and inferior sections from the middle site of each right ventricle (n = 3). Each block was embedded in paraffin and sections were cut for staining with hematoxylin-eosin.

Blocks were analyzed independently by 2 pathologists (R.V.S. and R.T.) blinded to diagnosis. Myocyte vacuolization<sup>10</sup> and interstitial edema were considered to be abnormalities indicative of reversible cell damage. Contraction band necrosis, hemorrhage, fibrosis, and progression of hyper eosinophilia of myocardial fibers with or without nuclear pyknosis were considered to be abnormalities indicative of irreversible changes.

Each pathologist rated each block for reversible and irreversible pathology using a 4-point severity scale (0, normal; 1, scanty or focal pathology; 2, patchy pathology; and 3, diffuse pathology). Points of discrepancy were reviewed in a consensus meeting of the 2 pathologists. If consensus could not be reached, the lower of the 2 scores was used.

greater than 1 seizure per month in the year prior to his/her death. No patient had a history of status epilepticus.

All patients with epilepsy had been prescribed anticonvulsants in the period prior to death, but only 2 patients had therapeutic levels of anticonvulsants as determined by a postmortem toxicologic examination. Four of the 7 patients were found dead in bed, 2 were found dead on the floor of the home, and 1 was found dead shortly after a witnessed tonic-clonic seizure. In none of the cases was the police investigation or findings at autopsy indicative of asphyxia. Only 1 patient had neuropathologic findings, ie, communicating hydrocephalus.

Seizure type was known in 6 of the 7 patients; in all, it was generalized seizure disorder. Electroencephalographic reports were available for 6 of the 7 patients. One patient had normal findings both awake and asleep. The remaining patients had different electroencephalographic findings: bilateral temporal lobe spikes; 3 per second spike and wave; abnormal, diffuse slowing, no spikes;

moderately abnormal bilateral central dysfunction; and abnormal with spike wave discharges, left parietal area.

There was no significant difference between the 2 groups in either heart weight or heart weight corrected for height. Histological examination of specimens from the control cases showed no pathologic abnormalities of any kind. Five of the 7 hearts of the patients with epilepsy had foci of myocyte vacuolization, a potentially reversible abnormality. In each of these cases, lesions were found in the left ventricle and septum, while right ventricular lesions were found only in 3 cases. Of the 67 lesions found, 63 were in the endocardium. Median lesion severity was 1 for 2 cases, 2 for 1 case, and 3 for 2 cases.

In contrast to these reversible lesions, irreversible lesions were found in only 4 hearts and were far fewer in number. Of the 22 lesions found, 12 consisted of perivascular fibrosis occurring preponderantly in the midzonal region. While the fibrosis was usually limited to the areas immediately surrounding the vessel, some sections showed the fibrosis extending away from the vessel and interdigitating between bundles of myocardial fibers. In other cases, although much less frequently, the fibrosis showed the same extension but was accompanied by loss of myocardial fibers. Of the remaining 10 irreversible ventricular lesions, half were in the subendocardial and half in the midzonal region. Median lesion severity was 1 for 2 cases, 2 for 1 case, and 3 for 1 case. These lesions consisted of interstitial fibrosis accompanied by loss of myocardial fibers. The 4 affected hearts each had both forms of pathologic conditions (**Figure**).

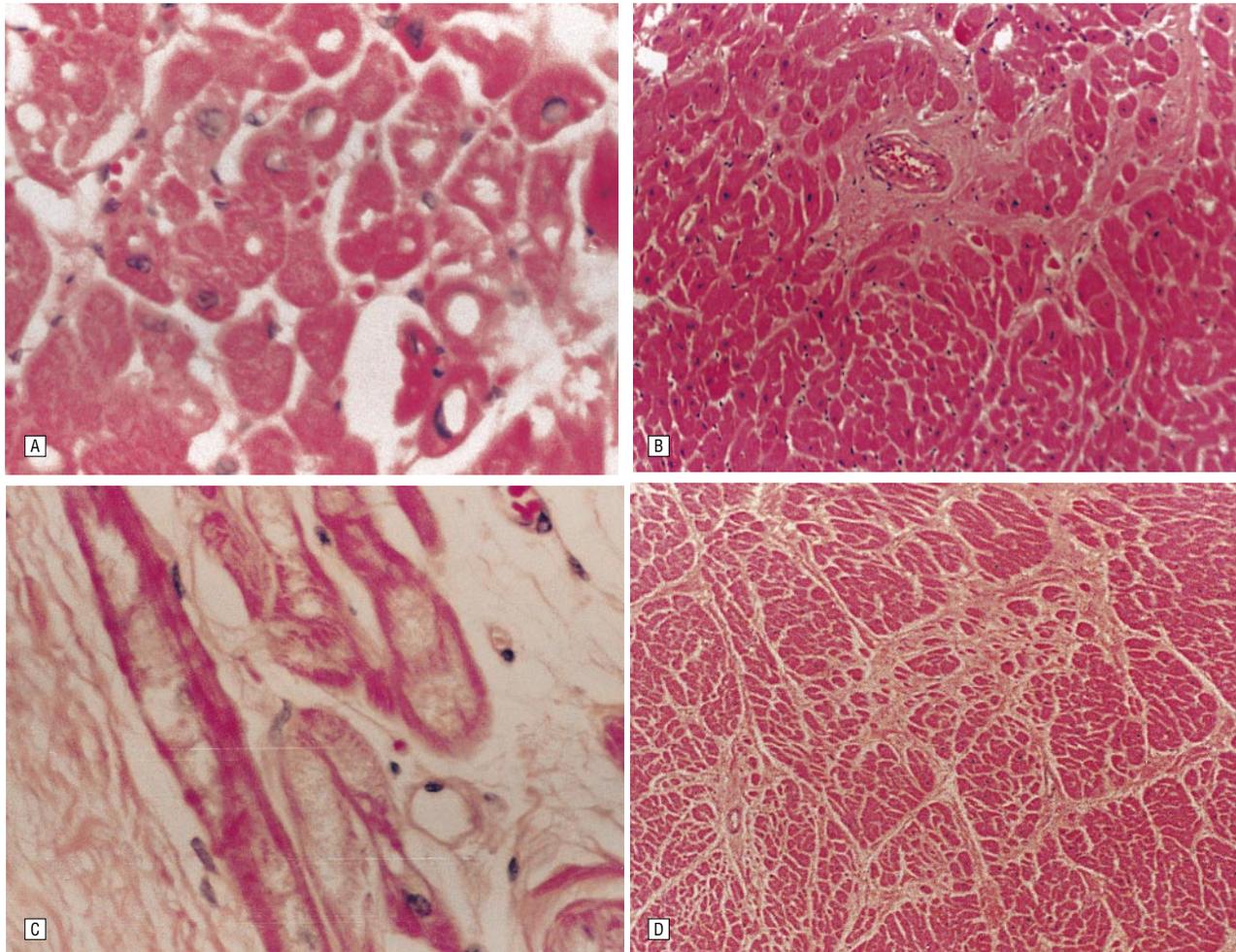
No obvious relationship existed between the duration of seizure disorder for the 4 patients for whom this information was available and the severity of reversible or irreversible cardiac lesions.

## COMMENT

Although earlier studies have surveyed electrocardiograms in patients with epilepsy in a search for cardiac abnormalities, we reasoned that evaluating the hearts of epileptic sudden death victims might provide more enlightening data. The results of this study support that view. We performed a blinded study of cardiac pathologic conditions in patients with epilepsy who died suddenly and a comparison group of otherwise healthy people dying suddenly by hanging or a drug overdose. To minimize chances of arriving at a false conclusion, we studied the hearts from subjects with no evidence of adrenergic drug use, no history of heart disease, and no pathologic evidence of heart disease on gross examination.

None of the 13 comparison group hearts harbored pathologic conditions, but 4 of the 7 epileptic sudden death victims had evidence of irreversible cardiac pathologic conditions, with half of these conditions being perivascular fibrosis and the other half, interstitial fibrosis. These same 4 patients plus a fifth patient had evidence of a reversible cardiac pathology in the form of what has been termed *myocyte vacuolization*,<sup>10</sup> or *colliquative myocytolysis*.<sup>11</sup>

The critical question concerns the cause of these lesions. Subendocardial myocardial vacuolization as noted



A, Myocytes with vacuolization; note in lower right the nucleus being displaced by vacuole. This is an example of a reversible pathologic condition (original magnification  $\times 400$ ). B, Several longitudinally cut myocytes showing areas of vacuolization (original magnification  $\times 400$ ). C, Diffuse interstitial fibrosis with multiple areas of myocyte replacement by connective tissue (original magnification  $\times 40$ ). This is an example of an irreversible pathologic condition. D, Perivascular fibrosis, another irreversible condition (original magnification  $\times 100$ ). All specimens were stained with hematoxylin-eosin.

herein is thought to occur in a setting of chronic subendocardial ischemia,<sup>10</sup> but from what source in the setting of normal coronary arteries? Some time ago, one of us (B.H.N.)<sup>12</sup> hypothesized that brain activation could produce coronary vasomotion in the absence of coronary pathologic conditions with resulting ischemic disease in the heart. A recent review supported that hypothesis.<sup>13</sup> To explain the pathology we found, we believe the same mechanism of significant coronary vasomotion occurred. Myocyte vacuolization is reversible, but if the process were recurring, one would expect it to proceed to scarring, which we found in the form of fibrosis. Spasm of small resistive vessels would explain the perivascular location of the fibrosis noted and that of larger vessels would explain the interstitial fibrosis with myocardial cell loss.

Whether this postulated vasomotion occurred subclinically or with frank convulsions is not known. However, the finding of irreversible pathologic conditions implicates an ongoing process in the hearts of these patients with epilepsy that by definition has to be independent of any terminal cardiac event producing ischemia. Subarachnoid hemorrhage is known to produce cardiac dam-

age with resultant ventricular wall motion abnormalities.<sup>14</sup> Although the changes following subarachnoid hemorrhage may reflect vasospasm, the mechanism is probably due to massive catecholamine discharge, because contraction band necrosis is ubiquitous following such acute massive insults to the brain. We did not find contraction band necrosis in any of the hearts evaluated in this study. The absence of this pathologic finding precludes invoking the mechanism of high levels of circulating catecholamines<sup>15</sup> as the cause of the findings in the hearts of patients with epilepsy who died suddenly.

Patients with epilepsy who die suddenly are young, ambulatory, tend to be black, have infrequent but a long history of a seizure disorder, preponderantly tonic-clonic in type, and frequently have subtherapeutic levels of anticonvulsants.<sup>1</sup> In addition to this characterization of patients prone to sudden death, we now have one more piece of information—evidence of cardiac damage in most patients. Interestingly, in a study of insula cortex stimulation in rats in which cardiac arrhythmias leading to asystole were produced, myocyte vacuolization was found in 58% of the animals (Stephen M. Oppenheimer, MBBS, oral communication,

November 1996). Although neither perivascular nor interstitial fibrosis was noted in the animal models, we expect that animal models of more chronic activation of neurocardiologic links might produce the same pathologic conditions we found. Nonetheless, as is the case with the finding of subtherapeutic anticonvulsant levels at the time of death,<sup>1</sup> we still do not know the exact roles these myocardial pathologic conditions seen in most cases play in the overall pathophysiologic mechanisms leading to death. However, the existence of ischemic foci, such as those we found, certainly predisposes to arrhythmogenesis, especially in the setting of sufficient adrenergic input.<sup>4</sup>

The finding of irreversible pathologic conditions argues strongly against a simple epiphenomenon. Our working hypothesis is that the irreversible pathologic conditions are indicative of previous cardiac damage due to seizure, which sensitizes the patient's heart to a subsequent seizure with its attendant autonomic storm. By studying the link between epilepsy and cardiac pathology, we may be able to arrive at strategies to reduce the number of patients with epilepsy who die suddenly with no apparent cause.

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