Comparison of Heart Mass in Seizure Patients Dying of Sudden Unexplained Death in Epilepsy to Sudden Death due to Some Other Cause

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Abstract: Proposed mechanisms by which sudden unexplained death syndrome in epilepsy (SUDEP) occurs include cardiac dysrhythmias. We hypothesized that individuals dying of SUDEP would have enlarged hearts compared with normal, increasing the risk of sudden cardiac death should the autonomic nervous system initiate a dysrhythmia. We performed a retrospective case-control study in a medical examiner population, comparing the mean heart mass in a group of individuals who died of SUDEP to a group of individuals with epilepsy who died suddenly due to some unrelated cause (non-SUDEP). We found no significant difference in the mean heart mass between the 2 groups when analyzing the unadjusted data. Upon stratifying the cases by age, however, we found a significant reduction in the frequency of SUDEP in individuals 40 or more years of age with an increased heart mass compared with those younger. This reduced frequency disappeared when cases where the cause of death was indeterminate between SUDEP and heart disease were reclassified from non-SUDEP to SUDEP. With increasing age, the likelihood of finding a cause of death that competes with the possibility of SUDEP increases, making SUDEP appear to be a phenomenon of the young. The inclusion of seizure deaths evaluated in a medical examiner office in studies of SUDEP would provide the benefit of a more certain diagnosis in each given case. Moreover, the inclusion of cases from the medical examiner population would stem attrition in a clinical study due to loss to follow-up.

Key Words: epilepsy, seizure, SUDEP, death, heart

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Epilepsy has the potential to cause sudden death, a condition sometimes identified as sudden unexplained death syndrome in epilepsy (SUDEP). SUDEP is identified by Earnest et al[1] as death due to epilepsy with no anatomic cause found at autopsy. Various mechanisms by which SUDEP may occur have been proposed, including asphyxiation,[1] cardiac arrhythmia precipitated by a seizure discharge acting via the autonomic nervous system, respiratory arrest,[2] and autonomically induced metabolic derangements.[3] Individuals with large hearts are at risk for developing a dysrhythmia, independent of the cause of enlargement.[4] We hypothesized, therefore, that individuals dying of SUDEP might have large hearts, making them more susceptible to sudden cardiac death should the autonomic nervous system initiate a dysrhythmia. This study compares the mean heart mass of individuals who died of SUDEP to the mean heart mass of individuals with epilepsy who died suddenly due to some cause other than SUDEP.

MATERIALS AND METHODS

We conducted a retrospective study of all cases investigated by the Jefferson County Coroner/Medical Examiner Office during the 15 years from 1986 to 2000. Cases were identified by a computer search for all individuals in which the cause of death was listed as a seizure and for all cases in which toxicological analysis revealed the presence of an antiepileptic medication (phenytoin, phenobarbital, carbamazepine, valproic acid, or felbamate). We found 261 cases by this search. We reviewed the investigative reports, autopsy findings, and, when available, hospital records for each of the 261 cases. Because this study was a comparison of measured heart mass, cases were excluded from further study if any 1 of the following criteria proved true:

1. The case was an external examination only or else, as in one case, an organ donor, so that heart mass was unavailable (N = 62). (External examinations tended to be done on cases such as motor vehicle accidents and suicidal gunshot wounds.)

2. The decedent was fewer than 14 years of age (5 decedents were 14 to 18 years of age, and all 5 had heart masses in keeping with the expectation for adults based on total body mass). (N = 15, 4 of which were counted above as cases without an autopsy.)

3. The decedent was decomposing to such a degree as to alter normal organ weights. (Eight decedents displayed some degree of decomposition, but the decomposition was relatively mild in each case, and in all 8 cases the observed heart mass was equal to or greater than the expected mass; N = 0.)

Exclusion of the net 73 cases above left 188 autopsies where an adult heart mass was available. In each autopsy, the heart was removed along with 1 to 2 cm of the aorta and pulmonary trunk. The observed heart mass was determined by weighing the fresh heart in a metric pan scale after blood and clots were removed from the heart. The epicardial fat was left intact for weighing.

The 188 cases were reviewed to determine whether the available history indicated that the decedent had a chronic seizure disorder. Cases were excluded from further study if any 1 of the following criteria proved true:

1. The decedent received antiepileptic medication in a hospital as a therapeutic precaution following an acute head injury that led to death in a matter of hours or days (N = 12).

2. The decedent took antiepileptic medication as a prophylactic measure following a remote head injury, but the decedent never had a seizure between the time of injury and death months to years after the injury (N = 1).

3. No definite history of seizures could be determined due to incomplete history or poor documentation (N = 17).

4. The anticonvulsant detected in blood was more likely present because of abuse or suicide or, in the case of carbamazepine, as a treatment of mood stabilization, than as a treatment of seizures (N = 25).

Exclusion of the 55 cases above left 133 cases where the decedent had evidence of a seizure disorder. The 133 cases were reviewed for circumstances surrounding death that fit the criteria for SUDEP. The criteria for SUDEP were established by an advisory committee convened in 1993[5] and are as follows:

1. The victim suffered from epilepsy, defined as recurrent unprovoked seizures.

2. The victim died unexpectedly while in a reasonable state of health.

3. The death occurred "suddenly" (in minutes), when known.

4. The death occurred during normal activities (eg, in or around bed, at home, at work) and benign circumstances.

5. An obvious medical cause was not found.

6. The death was not the direct result of the seizure or status epilepticus.

The above criteria exclude accidental deaths secondary to seizures but include deaths with or without evidence of a seizure near the time of death.[5]

We recorded the heart and combined lung masses in each case (lungs were removed and weighed separately). We also reviewed the microscopic sections of heart, when available, for contraction band necrosis. We next assigned each decedent to 1 of 4 categories based on the case history and the autopsy findings: (1) sudden, unexpected death due to the decedent's epilepsy; (2) death due to an accident or injury occurring as a result of a seizure (eg, drowning in a tub); (3) death unrelated to epilepsy (eg, gunshot wound); or (4) unable to determine degree to which epilepsy contributed to death. To be assigned to the category of death due to SUDEP, the decedent had to meet all the criteria listed above for SUDEP; thus, those individuals in categories 2 and 4 were classified as non-SUDEP deaths. The distribution into the 4 groups is shown in Table 1.

The goal of this study is to compare the heart mass of individuals who died of SUDEP to that of individuals with epilepsy who died suddenly due to some cause other than SUDEP. To accomplish this goal, we used a *t* test to compare the mean heart mass between these 2 groups of decedents. We also sought to determine any significant difference between the observed and expected heart masses. To calculate expected heart mass, we used the decedent's total body mass in kilograms and a conversion factor. The heart mass for humans is significantly correlated, albeit roughly, to total body mass.[6] Kitzman et al[6] derived formulae for estimating heart mass from body mass based on sex. Kitzman et al[6] found total body mass to be a better predictor of normal heart mass than either body surface area or body height. Figure 1 shows a graph of the heart masses plotted against the body masses. While a general trend is clear, the correlation is only moderate, as shown by a correlation coefficient (r) = 0.55.

TABLE 1. Classification of 133 cases in study

Group	Cases, No.	SUDEP category	Mean heart mass, g
Seizure disorder led to death	57	1	358
Seizure led to accident leading to death	8	0	399
Seizure disorder unrelated to cause of death	26	0	
Seizure disorder a possible cause of death*	42	0	

*Dilemma in cause of death between seizure disorder and alcoholism in 18 cases, seizure disorder and heart disease in 12 cases, seizure disorder and alcoholism and heart disease in 8 cases, and seizure disorder and some other cause not already listed in 4 cases.

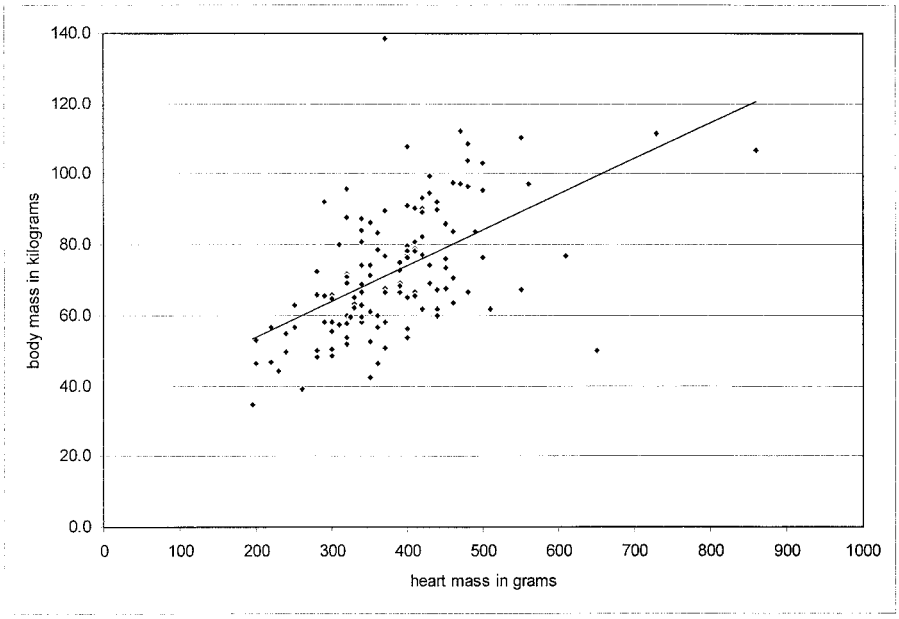

FIGURE 1. Plot of heart mass versus body mass ($r = 0.551$).

Removal of the 5 most prominent outliers (body mass >120 kg or heart mass >600 g) improves the correlation coefficient slightly to $r = 0.62$. The degree of correlation in our cases is in keeping with the findings of Kitzman et al,[6] who had a correlation coefficient of $r = 0.5$. Using this information, each decedent was assigned into a dichotomous category for having a heavy heart, based on whether the difference between the observed heart mass and the expected heart mass was greater than 100 g. One hundred grams was chosen because the overall standard deviation was 97 g, and thus roughly 85% of the cases would have a difference less than 100 g, given that the data were distributed normally. We then used logistic regression to calculate the relative risks (RRs) and 95% confidence intervals (CIs) for the association between SUDEP and greater than expected heart mass. The RR is the ratio of the incidence of having a particular characteristic, a heavy heart in this case, among those dying of SUDEP to the incidence of having that same characteristic among those who did not die of SUDEP. As a ratio, the RR can range from 0 to positive infinity, with 1 representing the null value (ie, no difference between groups). In the context of this study, RR values greater than 1 would indicate that SUDEP decedents were more likely to have a heavy heart, whereas values of less than 1 would indicate the converse. The 95% CI provides an indication of the precision of the RR estimate. Finally, because SUDEP and non-SUDEP decedents may differ with respect to characteristics such as age, hypertension, and alcoholism, the RRs were also calculated adjusting for these characteristics. The RRs were also stratified according to these characteristics to determine whether they modified any observed association between SUDEP and having a heavy heart. Age was determined at the time of identification of the body. Hypertension was determined by history or by inference based on findings of concentric left ventricular hypertrophy or arteriolar wall thickening in the kidneys. Alcoholism was determined by history.

RESULTS

The ages ranged from 14 to 77 years, with an average age of 44 years. The mean body mass was 72.2 kg, with a range of 34.5 to 72.2 kg and standard deviation of 17.9 kilograms. The overall mean heart mass was 380 g, with a range of 195 to 860 g and a standard deviation of 97.4 g. The combined lung masses ranged from 400 to 2320 g, and there was no statistically significant difference between the mean combined lung mass in the SUDEP group compared with the non-SUDEP group (means 1120 g and 1160 g, respectively; $P > 0.5$). Contraction band necrosis was detected in 5 of the 120 cases in which microscopic sections of myocardium were available for review. All 5 cases exhibiting foci of contraction band necrosis had heart disease sufficient to account for death, whether due to narrowing of coronary arteries by atherosclerotic plaque or by hypertensive heart disease, and thus the deaths in these 5 cases were not classified as SUDEP.

Like the lungs, the mean heart mass in the SUDEP group did not significantly differ from the mean heart mass in the non-SUDEP group (means 360 g and 400 g, respectively; $P > 0.5$). Decedents with SUDEP were 70% less likely to have a heart mass at least 100 g greater than expected based on body mass compared with non-SUDEP decedents (RR 0.30; 95% CI 0.12 to 0.75).

Figure 2 shows a graph of the difference between observed heart mass and expected heart mass plotted against the decedent's age. A trend toward an increase of observed heart mass over expected heart mass with increasing age distinguishes the plots of the SUDEP versus non-SUDEP groups. This trend is reflected in the ORs when the groups are stratified by age. Those decedents younger than 40 years of age who died of SUDEP were nearly 50% less likely to have a heart mass at least 100 g greater than expected based on body mass compared with non-SUDEP decedents (RR 0.54; 95% CI 0.16 to 1.78). The risk of having an enlarged heart was even less in decedents 40 years of age or older, who were nearly 80% less likely to have a heart mass at least 100 g greater than expected based on body mass compared with non-SUDEP decedents (RR 0.22; 95% CI 0.06–0.86).

Finally, a multivariable logistic regression analysis revealed that of the factors age, sex, race, body mass, heart mass, and evidence of hypertension or alcoholism, only age was a significant predictor of SUDEP.

DISCUSSION

Our analysis shows no significant difference in the mean heart mass in those individuals who die of SUDEP compared with patients with epilepsy who die of some cause other than SUDEP. This finding is in keeping with a report by Opeskin et al,[7] but it contradicts the findings reported by Leestma.[8]

It may be that there is no significant difference to detect, or it may be that a difference exists, but it is too slight to be detected by the design of this study. As Figure 1 makes clear, the computation of an expected heart mass from body mass yields a crude estimate, and thus any difference in mean heart mass must be great to be detected by this approach. Due to the variability in biologic systems, it is unlikely that the estimation of heart mass from body mass can be made more accurate. Systematic error may also play a role in our failure to find a significant difference in the mean heart mass of the 2 groups. Hangartner et al[9] report that total heart mass is a poor predictor of cardiac hypertrophy compared with the mass of the left ventricle alone, a figure determined by weighing the fixed tissue after removing the epicardial fat and detaching the left ventricle from the atria and right ventricular free wall. The Fulton technique described by Hangartner et al[9] for determining the mass of the left ventricle was used by Opeskin et al[7] in their study, but the technique is little used in routine forensic practice and certainly was not done in cases in our office. Nevertheless, our conclusion is the same as that of Opeskin et al,[7] namely, that there is no significant difference in the mean heart mass in those individuals who die of SUDEP compared with patients with epilepsy who die of some cause other than SUDEP.

Leestma[8] makes no mention of using a special technique for determining heart mass in the cases he presented in a chapter on the pathology of sudden death associated with seizures, and yet Leestma presented a striking difference of about 150 g between the observed heart mass and the expected heart mass in a group of 42 men with a history of seizures. Leestma[8] determined his estimated heart mass by using a regression equation based on body height reported by Zeek.[10] Kitzman et al[6] report that their findings for height were similar when compared with those of Zeek,[10] but they found total body mass to be a better predictor of heart mass than body height. Our own calculations also yielded a better correlation coefficient for estimated heart mass based on total body mass ($r = 0.55$) versus body height ($r = 0.46$). In any case, the use of Zeek's[10] formula to calculate the expected

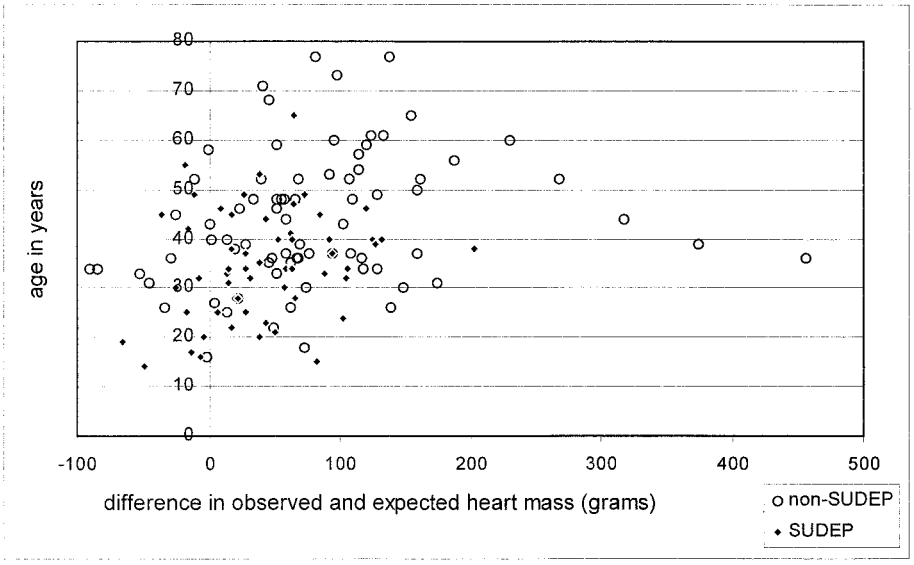

FIGURE 2. Plot of (observed heart mass − expected heart mass) by age.

heart mass in our own study led to the same results as calculations based on total body mass.

Although Leestma[8] found a striking difference between the observed heart mass and the expected heart mass in men, he was unable to draw any statistical inference from his data for women in his study. It is unclear why Leestma[8] found such a striking difference between the expected and observed heart masses in men only. Perhaps the relatively small number of women in his study did not afford a sample size sufficient to detect a difference.

In his studies on the effect of cocaine on heart mass, Karch et al[11] showed that men (but not women) with a history of cocaine use, when considered as a group, had a significantly greater observed mean heart mass compared with expected mean heart mass, as well as a significantly greater heart mass compared with the heart mass of controls matched for age, body mass, and sex. Karch et al[11] caution, however, that the variability inherent in biologic systems causes such overlap of the heart mass between the 2 groups in his study that no meaningful conclusion concerning past cocaine use can be made based on an increased heart mass. Likewise, the inherent variability of heart mass in decedents with and without epilepsy is so great that we could show no significant difference between the means of the 2 groups. A larger study with hundreds of cases in each category might have sufficient power to detect a statistical difference, but even then the inability to infer a conclusion in a given case would remain.

Conditions that we thought might modify our results, such as hypertension and alcoholism, did not do so. The only modifying factor was age, as demonstrated by stratified analysis and logistic regression. Criterion 5 for the diagnosis of SUDEP requires that no obvious medical cause for death be found upon review of the case. Annegers and Coan[5] distinguish between "definite SUDEP" and "probable SUDEP." In definite SUDEP, the case meets all 6 criteria established by the advisory committee and has sufficient descriptions of the circumstances surrounding death and a postmortem report. In probable SUDEP, the case meets all 6 criteria, but no postmortem data are available. Because the overall rate of postmortem examinations in the nation is around 14%,[12] Annegers and Coan[5] state that working definitions for SUDEP must include probable cases along with definite cases. All cases in this study did have details concerning the circumstances surrounding death and autopsy findings. Criterion 5 makes the diagnosis of SUDEP similar to the diagnosis of sudden infant death syndrome (SIDS), namely, it excludes from consideration any case where another factor, such as heart disease, is a competing cause of death. In classifying the deaths in this study, cases were marked where either SUDEP or heart disease (whether hypertensive or atherosclerotic) could have caused death. When the cases in this study were classified as SUDEP or non-SUDEP according to the 6 given criteria, the presence of a heart 100 g heavier than expected seemed to have a protective effect, lowering the risk of death by SUDEP by anywhere from 50% to 80%. This protective effect disappears when cases where death could be due to SUDEP or heart disease were reclassified from non-SUDEP to SUDEP. The crude RR prior to reclassification was 0.30 (CI 0.12 to 0.75), and following reclassification the crude RR odds ratio rose to 0.59 (CI 0.34 to 1.03). The decreased risk of dying of SUDEP that having a heavy heart seems to confer is an illusion. The presence of a heavy heart at autopsy leads to a diagnosis of heart disease as the cause of death rather than SUDEP; it is in this way that an enlarged heart seems to protect someone from dying of SUDEP.

With increasing age, the likelihood of finding a cause of death that competes with the possibility of SUDEP increases, and this dilemma is compounded when no autopsy is done. Annegers et al[13] are correct to point out that there may be an upper limit where the incidence of sudden unexplained death in individuals with epilepsy does not differ from that of the general population. The inclusion of seizure deaths evaluated in a medical examiner office would provide the benefit of a more certain diagnosis in a given case. In addition, the inclusion of cases from the medical examiner population would stem attrition in a study due to loss to follow-up.

CONCLUSIONS

We found no difference in the mean heart mass of individuals dying of SUDEP compared with a control group of individuals with epilepsy who died of some cause other than SUDEP. The diagnosis of SUDEP is a diagnosis of exclusion. Like SIDS, any anatomic, toxicological, or scene finding that accounts for death precludes a diagnosis of SUDEP, and thus older patients, who are more likely to have concurrent disease, are less likely to have their death ascribed to SUDEP. Studies of SUDEP that include medical examiner populations offer a ratio of definite SUDEP cases to probable SUDEP cases greater than is available from hospital-based series alone.

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