Daily Peaks in the Incidence of Sudden Cardiac Death and Fatal Stroke in Niigata Prefecture

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To clarify the circadian variation in sudden death (SD) in Japan, where the causes of sudden death differ from those in the USA, we examined all of the death certificates from 1984 to 1986 in Niigata Prefecture, Japan. We defined SD as death which occurred within 1 h from the onset of the underlying cause. A significant circadian variation, with a high incidence between 6 and 8 am and a secondary peak between 6 and 8 pm, was found in the occurrence of sudden cardiac death (SCD, n=2953). Although the proportion of SCD due to acute myocardial infarction (AMI) was as low as 28% of SCD cases, the circadian variation of SCD was similar to that previously reported in the USA. In SCD due to AMI in males (n=487), a significant circadian variation with 3 peaks, including a primary peak between 4 and 6 am, was evident. There was also a marked increase in the incidence of fatal stroke between 6 and 8 pm (n=529). We concluded that 1) a circadian variation with two peak incidences, one between 6 and 8 am, and one between 6 and 8 pm, was characteristic of SCD in general, 2) there was a primary peak between 4 and 6 am for SCD due to AMI in males, and 3) there was a peak between 6 and 8 pm in the incidence of fatal stroke for both men and women. (*Jpn Circ J* 1996; **60**: 193–200)

RECENT epidemiological studies in the USA^{1,2} and Europe³ have found circadian variation in the occurrence of sudden cardiac death (SCD). According to these reports, the incidence of SCD began to increase at 6 am, reached a peak between 8 am and noon, began to rise again at 4 pm after a decrease in the early afternoon, and reached an evening peak between 6 and 8 pm. The circadian rhythm of the onset of non-fatal acute myocardial infarction (AMI)^{4–6} in these studies was similar. Mull-

er and co-workers^{7–9} suggested that an increase in the activity of the sympathetic nervous system which occurred in the morning might have contributed to the peak levels in these studies.

Forty-five to 60 percent of the cases of sudden death (SD) are due to cardiovascular diseases, 2/3 of which involve ischemic heart disease (IHD), according to American and European studies^{10–12}. Therefore, the circadian variation of SCD might be the same as that of AMI, since IHD is the major cause of SCD. In Japan, IHD accounts for about 50% of the cases of SD due to cardiovascular diseases^{10,13–17}. In addition, the ratio of death due to IHD to all deaths in Japan is only about 1/5 of that in the USA. For

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TABLE I FREQUENCY OF OCCURRENCE OF SUDDEN DEATH AND THE SUBJECT NUMBERS FOR ANALYZING CIRCADIAN VARIATION

underlying cause of death	AMI	OCD	Stroke	NCD	SCD	the total of SD
ICD-9 Code	410	390–398, 420–429, 441, 745–747	430–434	Other codes		
frequency of occurrence	776	2232	547	230	3008	3785
unknown gender	4	9	3	2	13	18
unknown time of death	6	36	15	2	44	39
numbers for analysis	766	2187	529	226	2953	3763
males	487	1251	313	157	1738	2243
females	279	936	216	69	1215	1520

AMI, indicates acute myocardial infarction; OCD, other cardiovascular diseases; NCD, non-circulatory diseases; SCD, sudden cardiac death; SD, sudden death. SCD was defined as SD due to AMI or OCD. SD was defined as the death occurring within 1 h from the onset of the underlying cause.

example, while there were 301.8 cardiac deaths per 100,000 population in the USA in 1988, there were only 129.3 in Japan in 1989!⁸ There were 207.3 deaths due to IHD per 100,000 population in the USA, as opposed to only 41.5 in Japan in the same year, and the percentage of deaths due to cardiac diseases excluding IHD was 30% in the USA and 67% in Japan. This study was designed to identify the similarities and differences in the circadian variation of the onset time among SCD, SD due to AMI, and SD due to fatal stroke.

METHODS

Sampling

This study was based on all of the death certificates for natural deaths that occurred in Niigata Prefecture, Japan, which has a population of approximately 2.5 million, from January 1984 to December 1986. There are no reports that the causes of death or the daily living conditions in Niigata are markedly different from those in other areas in Japan. We examined all of the death certificates and identified all of the cases in which death occurred within 24 h from the onset of a direct cause for subjects who were at least 15 years old at the time of death; a total of 10471 cases were selected. We determined the underlying cause of death for each case by classifying all of the information on the death certificate as either a direct or indirect cause of death, and also reviewed other physical conditions on the death certificate. Only diseases which occurred within 30 days before death were considered as candidates for the underlying cause of death.

The common cold was not considered a candidate for the underlying cause of death.

If one of the qualifying diseases was AMI, rupture of the aortic aneurysm or stroke, we determined that the underlying cause was that disease; otherwise we determined that the underlying cause was the qualifying disease with the earliest onset. All of the cases that were described as neoplasm or senile decay on the death certificate, except cases in which the underlying cause was AMI, rupture of the aortic aneurysm or stroke, were not considered sudden death. Finally, all of the selected cases who died within 1 h from the onset of the underlying cause of death were considered SD. Cases in which the exact length of time that had elapsed from the onset to death was unclear (for example, within 1 day, within half a day, and so forth) were not considered SD. We classified SD into 4 groups based on the underlying cause: SCD due to AMI, fatal stroke, SCD due to cardiovascular diseases other than AMI (other cardiovascular diseases, OCD), and SD due to non-circulatory diseases. We defined SCD as SD due to AMI or OCD.

Overall, 3785 SD's, 3008 SCD's, and 547 fatal strokes occurred during the 3 years of the study period. Of these, only 2953 SCD cases and 529 fatal stroke cases were analyzed because in 13 SCD cases (4 cases of AMI and 9 cases of OCD) and 3 cases of fatal stroke, the gender of the deceased was unknown, and in 42 SCD cases (6 cases of AMI and 36 cases of OCD) and 15 cases of fatal stroke, the time of death was unclear. The frequency of the occurrence of SD and the number of subjects for analysis in each group are shown in Table I.

Fig 1. The frequency of sudden cardiac death by time of day for both sexes combined. A significant circadian variation was found ($p < 0.001$). A superscript **** shows that the incidence was significantly ($p < 0.0001$) higher than the minimum incidence between 0 and 2 am. The peak incidence in the morning was not significantly different from that in the evening.

Data Analysis

We obtained the time of the onset by subtracting the time which elapsed until death from the time of death. To observe the circadian variation of SCD, the number of SCDs in each 2 h interval from 0:00 am to 12:00 pm was counted. The statistical significance of the circadian variation, ie, the distribution of the number of deaths in the twelve 2 h intervals, was tested using the chi-square method for differences from a hypothetical uniform distribution for SD due to each cause. To test the statistical significance of the differences between the circadian variations for 2 groups (males vs females and in-hospital vs out-of-hospital), the chi-square method was used with a 2×12 table.

The chi-square test was also used to compare the incidence in a given period with the minimum incidence, and to compare the peak incidence in the morning with that in the evening. Since 12 tests (11 tests comparing the incidence in each period with the minimum incidence, and one test comparing the peak incidence in the morning with that

Fig 2. The frequency of sudden cardiac death due to acute myocardial infarction by time of day for males, females, and both sexes combined. A significant circadian variation was found ($p < 0.01$) for each group, and the circadian variation in males was significantly different from that in females ($p < 0.05$). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ and **** $p < 0.0001$; significantly different from the minimum incidence between 2 and 4 am.

in the evening) were performed for the circadian rhythm in each group, the level of significance was corrected using the Bonferroni inequality method. Thus, when the probability was less than the significance level $\alpha/12$, we expressed it as $p < \alpha$.

RESULTS

Sudden Cardiac Death

Fig 1 shows the distribution of SCD by time of day for both sexes combined. A significant circadian variation was found, but the circadian variation in males was not significantly different from that in females. The difference between SCD for in-hospital deaths and that for out-of-hospital deaths was also not significant. The minimum incidence occurred between midnight and 2 am. A morning peak was found between 6 and 8 am and the incidence remained high until noon. After the incidence decreased in the early afternoon, it began to rise again from 4 pm and reached a secondary peak between 6 and 8 pm. The difference between the two peaks was not significant.

Fig 3. The frequency of fatal stroke by time of day for both sexes combined. A significant circadian variation was found ($p < 0.01$), but the circadian variation in males was not significantly from that in females. ** $p < 0.01$, *** $p < 0.001$ and **** $p < 0.0001$; significantly different from the minimum incidence between 0 and 2 am. The peak incidence in the morning was significantly different from that in the evening (## $p < 0.01$).

Sudden Cardiac Death Due to Acute Myocardial Infarction

Fig 2 shows the distribution of SCD due to AMI in males and females, and in both sexes combined. A statistically significant circadian variation was found for each group, and the difference between the circadian variation in males and that in females was significant ($p < 0.05$). In males, the incidences between 4 and 8 am, 10 and 12 am, and 4 and 8 pm were significantly higher than the minimum incidence between 2 and 4 am. There were three peaks: between 4 and 6 am; between 10 and 12 am; and between 6 and 8 pm. The difference between the incidence at the first peak and that at the third peak was not significant. In females, the incidences between 6 and 8 am and between 8 and 10 am as well as those in each period except that between noon and 2 pm were significantly higher than the minimum incidence between 2 and 4 am. There was one peak in the morning and a slight increase between 8 and 12 pm. The morning increase in SCD due to AMI in males began between 4 and 6 am, which was earlier than that in females.

Fatal Stroke

Fig 3 shows the distribution of fatal stroke by time of day for both sexes combined. Although a statistically significant circadian variation was found, the difference between the circadian variation in males and that in females was not significant. The incidences between 6 am and noon and between 4 pm and midnight were significantly higher than the minimum incidence between midnight and 2 am. There were two peaks; one between 8 and 10 am and another between 6 and 8 pm. The peak incidence in the evening was higher than that in the morning ($p < 0.01$). The percentage of the incidence between 6 and 8 pm for both sexes combined was 14.4%, which was significantly higher than that in SCD (11.2%, $p < 0.05$) by the chi-square test.

DISCUSSION

The Accuracy of the Death Certificate

1) Diagnosis on the Death Certificate

One possible problem when considering the cause of SD is that the diagnosis made by the attending physician is a probable diagnosis that in many cases is not very accurate because of the very short time course to death. Patients who have died of unknown etiology are often diagnosed as acute heart failure^{13,14}. Hence, there could be several patients who died of AMI or fatal stroke among those diagnosed to have died of acute heart failure on the death certificate. No autopsy sub-samples could be obtained in this study, since 1 to 3 years had passed since the subjects had died.

Therefore, we examined the similarity between the clinical diagnosis given before autopsy and the autopsy diagnosis for all of the autopsy cases examined from 1984 to 1986 in Niigata Prefecture¹⁹⁻²¹. Among 60 cases whose clinical diagnosis was death due to AMI, 90% were diagnosed by autopsy as AMI. Among 181 cases whose clinical diagnosis was death due to stroke, 94% were diagnosed by autopsy as stroke. In all of the 54 cases who were diagnosed by autopsy as subarachnoid hemorrhage, death was diagnosed as stroke in the clinical diagnosis.

Onodera and colleagues²² reviewed the charts and interviewed the attending physicians for 153 cases who were diagnosed as

AMI or heart failure on the death certificate to assess the accuracy of the death certificate in Japan. Out of 28 cases who had been diagnosed as AMI on the death certificate, 92.9% were definite AMI with increased enzymes and/or ST elevation on ECG. On the other hand, only 7.2% of the 125 cases diagnosed to have died from heart failure had definite AMI.

Based on these reports, a diagnosis of AMI or stroke on the death certificate should be sufficiently accurate for our investigation.

2) Time on the Death Certificate

Unfortunately, there have been no reports on the accuracy of the time of death on death certificates in Japan. As the first step in this study, we selected cases who died within 24 h from the onset of the direct cause of death. There were several cases in which the time from the onset to the time of death on the death certificate was indefinite, such as within 1 day, within 12 h, within 2 h and so on. Although these may have included some SD cases who actually died very soon after the onset of the underlying cause, there could have just as likely been more cases in which the time of death was not estimated accurately. Therefore, these cases were excluded from this study. The time from the onset to death was described in minutes or as instantaneous death for almost all of the cases we selected.

There are very few homeless people in this prefecture, and most of these cases would have attracted the immediate attention of family or neighbors. Therefore, we considered that the time of the onset in SD cases in this study was also sufficiently accurate to support a circadian variation in the occurrence of SD.

Circadian Variation of Sudden Cardiac Death

Our study showed a prominent circadian variation in SCD, with a primary peak between 6 and 8 am, a high incidence from 8 am to noon and a secondary peak between 6 and 8 pm. The circadian variations in SCD for in-hospital deaths were similar to those for out-of-hospital deaths. The morning peak in incidence in this study was 2 h earlier than that in previous reports, while a high incidence from 6 am to noon is a com-

mon characteristic. Although the proportion of SCD due to AMI was lower than that in previous reports,¹⁰⁻¹² the circadian variation reported here was similar to that previously reported in the USA^{1,2} and Europe.³ AMI accounted for 28% of the SCD in this study. It must be noted that SCD in which IHD played a minor role showed a circadian variation similar to that of SCD in which IHD played a major role. Therefore, we suggest that this circadian variation is a feature not only of SCD due to AMI or non-fatal AMI, but also of SCD in general.

Circadian Variation of Sudden Cardiac Death Due to Acute Myocardial Infarction

In male SCD due to AMI, a significant circadian variation was evident, with a primary peak between 4 and 6 am, a secondary peak between 10 am and noon, and a tertiary peak between 6 and 8 pm. The morning increase in this group began between 4 and 6 am, which was earlier than that in females. The first peak was as high as the evening peak. In females, a significant circadian variation was also evident, but a peak was observed only between 6 and 8 am, and this was significantly different from the circadian variation in males.

The peak between 4 and 6 am was found only in SCD due to AMI in males, and has not been reported previously in the circadian variation of SCD and non-fatal AMI in the USA and Europe.¹⁻⁹ Muller and co-workers⁷⁻⁹ suggested that the increase in SCD between 8 am and noon was precipitated by an increase in the activity of the sympathetic nervous system, blood pressure,^{23,24} heart rate,²³⁻²⁶ platelet aggregability,²⁷ serum cortisol^{28,29} and other factors.²⁹⁻³³ The peak in SCD due to AMI between 6 and 8 am in females and that between 10 am and noon in males could be related to an increase in the activity of the sympathetic nervous system. However, it is questionable whether the peak between 4 and 6 am in males had a similar relationship because this period is generally during sleeping hours.⁶

In a survey of the life style of about 90000 Japanese people in 1990³⁴ 95.7% of males and 97.7% of females were sleeping at 4:30 am and 88.4% of males and 88.6% of females were sleeping at 5:30 am. The percentage of people who woke up between

4 and 6 am was higher among females (21.4%) than males (16.5%). Therefore, it is unlikely that the high incidence of SCD due to AMI during this period for males was related to increased activity of the sympathetic nervous system with awakening.

Japanese are subjected to frequent spastic angina, and the incidence in males is higher than that in females³⁵. In patients with chronic stable angina,³⁶⁻⁴¹ the frequency of myocardial ischemic episodes is relatively low between 4 and 6 am. In patients with Prinzmetal angina, however, there is a lack of distinct circadian periodicity, and the frequency of myocardial ischemic episodes is higher during this period.^{36,38} In addition, the incidence of non-fatal AMI in this period is relatively decreased.⁶ Therefore, we presumed that the peak in SCD due to AMI in males between 4 and 6 am in this study was related to coronary artery spasms.

For females, the period between 6 and 8 am is the busiest time in the morning for housework. However, this is not an active time for males;³⁴ since males usually become busy after 9 am. It was considered that the period between 6 and 8 am and the period between 10 am and noon were similar in that females and males both began working hard during these periods, respectively. This working status might be related to the onset of SCD due to AMI and the peak in the morning. There was a slight increase between 8 and 12 pm in females, but not in males. In addition, more females (30%) than males (12%) are busy due to housework or business at 10 pm.³⁴ This may be related to the slight increase between 8 and 12 pm in females.

There was a peak incidence between 6 and 8 pm in SCD and in SCD due to AMI. Myers and Dewar³ also examined the incidence of SCD in this period. They suggested that this increase was related to eating and drinking, which were concentrated in this period. Blood pressure and heart rate decreased during the afternoon and then began to increase between 6 and 8 pm.^{20,21} Eating and drinking are also concentrated in this period in Japan.³⁴ According to a study that analyzed the circadian rhythm of blood pressure using frequency analysis in Japan, the maximum blood pressure was most frequently observed between 4 and 8 pm.⁴²

Therefore, this peak in the incidence of SCD could be related to an increase in blood pressure and heart rate caused by eating and drinking. In addition, there have been reports of cases in which alcohol produced a vasospasm.^{43,44} This could be related to an increase in endothelin by ethanol, especially in males.

Circadian Variation of Fatal Stroke

We also observed a remarkable increase in the incidence of fatal stroke between 6 and 8 pm and this increase was significantly higher than that in SCD. Autopsy reports of death within 24 h from the onset of the underlying cause in Tokyo¹⁶ revealed that hemorrhagic diseases accounted for 97% of deaths due to stroke. Therefore, most of the cases of fatal stroke in this study may have been caused by hemorrhagic diseases in which there was massive bleeding, considering that the course of the disease was less than 1 h. This suggests that other factors related to bleeding may have also been present during this period.

In a report on the circadian variation of the onset of subarachnoid hemorrhage, there were two peaks, one between 10 and 12 am and another between 6 and 8 pm, and these two peaks had a similar incidence.⁴⁵ According to Andreotti and co-workers,⁴⁶ the activity of tissue plasminogen activator is the highest, and that of plasminogen activator inhibitor is the lowest, between 4 and 6 pm. Therefore, it seems likely that blood fibrinolytic activity increases⁴⁷ remarkably in this period and continues until 8 pm. Blood pressure and heart rate would have been increased by eating and drinking during this period as described above. Therefore, a combination of these factors may have caused bleeding, and resulted in an increase in the incidence of fatal stroke in this period.

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