CLINICAL AND STATISTICAL EVALUATION OF THE OCCURRENCE OF ACUTE MYOCARDIAL INFARCTION IN THE COLD INLAND AREA OF HOKKAIDO

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We made a clinical and statistical evaluation of the occurrence of acute myocardial infarction with respect to the relation between its occurrence and the meteorology of the cold inland area of Hokkaido (the Kamikawa Basin) over a period of 10 years (1976–1985).

A total of 581 cases were studied. Monthly fluctuation of incidence was not found to be statistically significant. A cold period in the Kamikawa Basin was defined in this study as the period when ordinary mean atmospheric temperatures were below 0°C (from 7 Nov. to 16 Apr.). Canonical discriminant analysis was applied to 10 meteorological factors between the days with occurrences and those without occurrences (245 days vs 245 days) in the cold periods of the investigated 10 years, and between the days with outdoor occurrences and those without occurrences (37 days vs 37 days). In order to compare the regional difference, this analysis was done on the same 10 factors for the cold periods over 3 years in Yamagata (46 days vs 46 days). The F values of 0.0003, 0.0155 and 0.0098 respectively in the above 3 analyses were small ($\leq F_9^1(0.25) = 1.51$).

A circadian rhythm of 2 cycles/day was recognized concerning the time of occurrence by power spectral analysis of the data of 562 patients for whom the time of the onset of myocardial infarction was known. Subdividing the patients into 2 groups according to physical activity just before the occurrence, the group who experienced an occurrence at rest showed a rhythm of 1 cycle/day, and the group who experienced an occurrence on effort showed a rhythm of 2 cycles/day.

Therefore, the 10 meteorological factors could not discriminate the probabilities between the days with occurrences and the days without occurrences of myocardial infarction in the cold periods. On the other hand, it was suggested that biological intrinsic rhythm participates in triggering the occurrence of myocardial infarction.

Key words:

Myocardial infarction
Circadian rhythm
Multivariate analysis
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ACCORDING to the 1985 statistics on the cause of death in Japan, high mortality was caused by malignant neoplasm (25.0%), heart disease (18.8%), and cerebrovascular disease (17.9%).¹ Among heart diseases, these classified

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Fig.1. Monthly incidence of acute myocardial infarction from 1976 to 1985 (n = 581). Every month is corrected to have 30.44 days. The value of chi square is 12.96 ($p > 0.25$).

as ischemic heart disease, that is acute myocardial infarction and other ischemic heart diseases (classification number 51, 52) gave a high mortality of 41.2 per 100,000 of the population in 1984. Thus there were about 49,500 deaths from heart disease in the estimated population of 120,235,000 in Japan of that year.¹

The direct provocative mechanism of acute coronary obstruction is still controversial. However, since thrombus formation is observed in most acute coronary obstructive lesions in post-mortem examination,² several factors related to thrombus formation such as an enhancement in platelet aggregation can be considered to trigger the occurrence of acute myocardial infarction.

Exposure to cold releases catecholamine, provokes a rise in blood pressure and induces vasoconstriction. It might indirectly cause coronary occlusion as an extrinsic environmental factor. Asahikawa experienced the coldest recorded temperature in Japan of -41.0°C . 76% of patients with acute myocardial infarction in Asahikawa are hospitalized in the Asahikawa Municipal Hospital.³

In this study, patients with myocardial infarction who were admitted to this hospital were reviewed, and a multivariate analysis of meteorological

factors was made in order to assess the influence of the weather in cold periods in the Kamikawa Basin, including Asahikawa, on the occurrence of myocardial infarction. Furthermore, similar referential analysis was made regarding the occurrence of myocardial infarction in Yamagata of Tohoku District.

Hematological factors such as platelet aggregation, platelet count, PTT and antithrombin activity might be related to the thrombus formation. Furthermore, blood pressure, catecholamine, and coronary vasospasticity are regarded as the factors that could contribute to acute coronary obstruction. These factors mentioned above have circadian rhythm in a living human body.⁴⁻⁷

In the present study, power spectral analysis was attempted in order to find out whether there was some cycle in the occurrence of acute myocardial infarction in which the above mentioned factors could have an impact.

1. Assessment of Influence of Meteorological Factors in the Kamikawa Basin on the Occurrence of Acute Myocardial Infarction

1-1 Subjects and Methods

(1) Subjects

According to the data for the past 30 years reported by the Asahikawa Local Meteorological Observatory,⁸ the period when the average temperature is 0°C or less is usually between 7 November and 16 April in Asahikawa. In this study, we termed this a cold period. From the meteorological data relating to the cold periods in the 10 years from 1976 to 1985, the following 10 factors were extracted; X_1 : the mean atmospheric pressure, X_2 : the mean temperature, X_3 : the difference in the mean temperature between the day with occurrence and the previous day, X_4 : the maximum temperature, X_5 : the minimum temperature, X_6 : the daily range of temperature, X_7 : the difference in the maximum temperature between the day with occurrence and the previous day, X_8 : the difference in the minimum temperature between the day with occurrence and the previous day, X_9 : the difference in daily range of temperature between the day with occurrence and the previous day, X_{10} : the mean humidity.

Six hundred and eighty six patients with acute myocardial infarction were admitted to the Asahikawa Municipal Hospital in the 10 years from 1976 in compliance with the diagnostic standard described below.

TABLE 1 CORRELATION MATRIX OF 10 METEOROLOGICAL FACTORS OF THE 245 DAYS WITH OCCURRENCES IN THE COLD PERIODS IN THE KAMIKAWA BASIN

	mean atmosph.	mean temp.	Δ mean temp.	max. temp.	min. temp.	temp. differ.	Δ max. temp.	Δ min. temp.	Δ temp. differ.	mean moist.
mean atmosph.	1.000	0.063	0.154	0.111	-0.012	0.205	0.190	0.022	0.153	-0.236
mean temp.	0.063	1.000	0.279	0.961	0.941	-0.161	0.265	0.270	-0.045	-0.324
Δ mean temp.	0.154	0.279	1.000	0.283	0.176	0.141	0.879	0.811	-0.066	-0.038
max. temp.	0.111	0.961	0.283	1.000	0.841	0.088	0.331	0.231	0.064	-0.351
min. temp.	-0.012	0.941	0.176	0.841	1.000	-0.465	0.127	0.303	-0.219	-0.259
temp. differ.	0.205	-0.161	0.141	0.088	-0.465	1.000	0.307	-0.180	0.509	-0.098
Δ max. temp.	0.190	0.265	0.879	0.331	0.127	0.307	1.000	0.575	0.325	-0.005
Δ min. temp.	0.022	0.270	0.811	0.231	0.303	-0.180	0.575	1.000	-0.584	-0.052
Δ temp. differ.	0.153	-0.045	-0.066	0.064	-0.219	0.509	0.325	-0.584	1.000	0.061
mean moist.	-0.236	-0.324	-0.038	-0.351	-0.259	-0.098	-0.005	-0.052	0.061	1.000

<Standard for Diagnosis of Acute Myocardial Infarction>

The patients who fulfill all the following items A-C or those who correspond to D are diagnosed to be suffering from acute myocardial infarction.

A. Clinical symptoms such as chest oppression lasting for more than 30 min.

B. Ischemic stigmata such as Q wave, ST elevation, and coronary T appearing in ECG with temporal change.

C. Myocardium-derived enzymes such as MB-CK, CPK, GOT, and LDH increasing more than three-fold over the normal upper limit, with temporal change after the occurrence.

D. Fresh localized necrotic myocardial areas are recognized in postmortem examination.

Out of 686 cases, 581 myocardial infarctions occurred somewhere in the Kamikawa Basin (Asahikawa, Aibetsu, Higashikawa, Higashikagura, Pippu, Tohma, Takasu) and the day of occurrence was able to be confirmed.

(2) Methods

a) The 581 occurrences were individually classified by month (every month is corrected to have 30.44 days), and the fluctuation of occurrence was analyzed with chi square test.

b) Out of these 581 occurrences, 269 occurrences in the cold periods were chosen. Two occurrences of the disease happened on 24 days. The 245 days with one or two occurrences of acute myocardial infarction comprised the A1 group. As the control A2 group, 245 days were selected by random sampling out of 1410 days without occurrences of acute myocardial infarction.

In order to make canonical discriminant

analysis, the data set of 10 meteorological factors was input in a personal computer (NEC, PC-9801RA2)⁹. The analysis was made between A1 and A2 groups, then the F value and the first correlation ratio was calculated.

c) B1 group was composed of 37 days with outdoor occurrences in the cold periods of the past 10 years, and B2 group was composed of 37 control days chosen by random sampling out of the days without occurrences. Canonical discriminant analysis was made in the same manner applying 10 factors between B1 and B2 groups.

d) To estimate the regional difference, data collected in Yamagata were utilized. In accordance with data from the Yamagata District Meteorological Observatory⁸, a cold period in this district was defined as when the average temperature was 3°C or less (from 9 Dec. to 19 Mar.). On the basis of the diagnostic standard described before, 177 patients with myocardial infarction were hospitalized in the Yamagata Prefectural Central Hospital from 1983 to 1985. Forty six days with occurrences in the cold periods of these 3 years were detected and comprised the C1 group. To make a control C2 group, 46 days without occurrences were extracted randomly. Canonical discriminant analysis was done in the same way mentioned above applying 10 meteorological factors between C1 and C2 groups.

1-2 Results

a) Figure 1 shows the histograms of incidence of acute myocardial infarction by month in the 10 years. The fluctuation in monthly incidence was analyzed with chi square test. The value of

Fig.2. Bihourly incidence of acute myocardial infarction by the time of occurrence (n = 562). The value of chi square is 38.99 ($p < 0.01$).

χ^2 was 12.96 ($p > 0.25$).

b) Table I shows the correlation matrix of 10 meteorological factors of the 245 days with occurrences. Canonical discriminant analysis on A1 and A2 groups revealed the F value of $F = 0.0003 \ll F_9^1(0.25) = 1.51$, and the first correlation ratio of $\eta^2 = 0.03\%$. The equation to calculate the first canonical variate was;

$$Z_1 = 0.0010X_1 - 0.0009X_2 - 0.0010X_3 + 0.0017X_4 + 0.0018X_5 + 0.0015X_6 + 0.0004X_7 + 0.0003X_8 + 0.0005X_9 + 0.0003X_{10} - 0.3437$$

c) Canonical discriminant analysis on B1 and B2 groups revealed the F value of $F = 0.0155 \ll F_9^1(0.25) = 1.51$, and the first correlation ratio of $\eta^2 = 1.53\%$. The equation to calculate the first canonical variate was;

$$Z_2 = -0.0007X_1 - 0.0006X_2 - 0.0006X_3 - 0.0005X_4 + 0.0018X_5 + 0.0017X_6 + 0.0015X_7 + 0.0015X_8 + 0.0004X_9 + 0.0004X_{10} - 0.4818$$

d) Canonical discriminant analysis on C1 and C2 groups revealed the F value of $F = 0.0098 \ll F_9^1(0.25) = 1.51$, and the first correlation ratio of $\eta^2 = 0.97\%$. The equation to calculate the first canonical variate was;

$$Z_3 = -0.0001X_1 + 0.0013X_2 + 0.0010X_3 + 0.0012X_4 - 0.0004X_5 + 0.0021X_6 + 0.0020X_7 + 0.0020X_8 + 0.0022X_9 - 0.0000X_{10} - 1.1197$$

The first canonical variates calculated in these 3 equations were significantly small, and the number of the groups was two. So, the second canonical variates were not obtained, and scatter diagrams were not drawn.⁹

2. Bihourly Incidence of Acute Myocardial Infarction by Time of Occurrence

—Assessment of Circadian Rhythm—

2-1 Subjects and Methods

(1) Subjects

The time and situation just before the occurrence of acute myocardial infarction was inquired of each patient (when the patient was unconscious, somebody else who witnessed the occurrence was asked). The time when the patient began to feel subjective chest symptoms lasting for more than 30 min was regarded as the time of occurrence.

Of the 581 patients who were admitted to the Asahikawa Municipal Hospital from 1976 to 1985 with attacks of acute myocardial infarction somewhere in the Kamikawa Basin and who fulfilled the diagnostic standard described before, 19 were excluded from the present analysis. This was due to the following 3 conditions; ① asymptomatic myocardial infarction, ② unstable angina which transitted into myocardial infarction over integration of attacks, ③ detailed interview was impossible because the patient was unconscious and there was no bystander at the occurrence of the infarction.

Even if the time of occurrence was somewhat uncertain, patients giving the time of occurrence with deviation less than one hour, such as "between 8 and 9 o'clock" were included in the analysis.

A total of 562 patients (430 men and 132 women, between 30 and 88 of age, and 62.6 years old on average) were subjected to the analysis.

(2) Methods

a) In order to analyze statistically the time of occurrence of myocardial infarction, the 24 hours of the day were divided into 12 blocks of 2 hours each, and bihourly incidence between each block was evaluated by chi square test.

b) Bihourly incidences in each year of the past 10 years (120 data in total) were processed with a personal computer (NEC, PC-9801RA2) for autocorrelative analysis. The obtained values were then used for the calculation of power spectral analysis.¹⁰

c) In order to analyze the incidence of acute myocardial infarction from the point of physical

Fig.3. Bihourly incidence of acute myocardial infarction by the time of occurrence in each year from 1976 to 1985 (n = 562).

Fig.4. Power spectral analysis of bihourly incidence of acute myocardial infarction in 10 years (n = 562).

activity just before the occurrence, the 562 patients were divided into 2 groups; those who had acute myocardial infarction at rest (any of sleeping, watching TV, reading, sitting, or lying without sleeping) and those who had the disease on effort (moving or working). Bihourly incidence in each group was analyzed with chi square test and power spectral analysis in the same ways

as described above.

2-2 Results

a) Figure 2 shows bihourly incidence of acute myocardial infarction by the time of occurrence for 562 patients. The maximum incidence was observed between 20.00 and 22.00 showing 69 occurrences, while the minimum incidence was observed between 4.00 and 6.00 showing 29 occurrences. The highest peak was observed between 20.00 and 24.00, and the second highest between 8.00 and 12.00, while a trough appeared between 4.00 and 6.00 and also between 16.00 and 18.00. On the whole, the histogram showed a two-peak distribution with peaks in the morning and night. The transition in frequency between each block was analyzed with chi square test, and was statistically significant with $\chi^2 = 38.99$ ($p < 0.01$).

b) Figure 3 shows bihourly incidence of myocardial infarction in each year of the past 10 years. Power spectral analysis of the incidence in these 120 blocks was made. As shown in Fig. 4, when power is plotted on the vertical axis and cycle/day on the horizontal axis, the maximum value of power was observed at the point of 2 cycles/day.

c) Figure 5 shows bihourly incidence by the time of occurrence in each of the 2 groups; one group consisting of 253 cases occurred at rest, and the other group consisting of 309 patients whose myocardial infarction occurred on effort. Both groups showed significant variation in frequency giving $\chi^2 = 35.38$ and 96.65

Fig.5. Bihourly incidence of acute myocardial infarction in two groups subdivided dependent on the physical activity at the occurrence. The values of chi square for the occurrence at rest and on effort are 35.38 and 96.65 respectively ($p < 0.01$).

respectively ($p < 0.01$). The group who showed occurrence at rest had a peak incidence at midnight, while the group with occurrence on effort had it late in the morning. In the group of occurrence on effort, most patients had been engaged in no more than daily activity, and only 23 patients had their occurrences during heavy labor such as snow-removal work or bearing a heavy load.

Figure 6 and 7 show the results of power spectral analyses in the two groups. The occurrence at rest group tended to have a rhythm of 1 cycle/day, while the occurrence on effort group tended to have rhythm of 2 cycles/day.

3. Discussion

3-1 Influences of Meteorological factors on the Occurrence of Acute Myocardial Infarction

When a patient with ischemic heart disease is exposed to cold abruptly, the values of hematocrit, platelet count and blood viscosity are increased, and the resistance of coronary arteries gets enhanced.^{11,12} In northern Europe and in high latitudes, the frequency and mortality of acute myocardial infarction have been validated significantly higher in winter than in summer,

Fig.6. Power spectral analysis of bihourly incidence of acute myocardial infarction occurred at rest in 10 years ($n = 253$).

Fig.7. Power spectral analysis of bihourly incidence of acute myocardial infarction occurred on effort in 10 years ($n = 309$).

and there has been a seasonal fluctuation in the frequency and mortality of this disease.¹³⁻¹⁶ So we can suppose the positive influence of cold on the occurrence of myocardial infarction. In

some reports the frequency and mortality of acute myocardial infarction were high when the temperature was low,¹⁷⁻¹⁹ but in other reports no relation was found between the temperature and the occurrence or mortality of myocardial infarction.^{15,20,21}

In this study, we found no significant fluctuation in monthly incidence of myocardial infarction. This result might be attributable to the mild climate of the Kamikawa Basin compared with the cooler climate of northern Europe. The extension of protective facilities against cold in the Kamikawa Basin could be another reason for this result.

Ten meteorological factors were selected for the multivariate analysis in this report. Since the average wind velocity through the year is as low as 1.5 m/sec in Asahikawa,⁸ the velocity of the wind was excluded from the 10 factors selected. No suitable factor was found to influence the effect of a cold front on the occurrence of myocardial infarction. The mean atmospheric pressure, officially announced by the Meteorological Observatory, is the mean value of 4 consecutive measurements, and does not seem to reflect the exact daily fluctuation of atmospheric pressure. A report that deaths from ischemic heart disease had been increased for 8 days after a snowstorm suggests the importance of longtime meteorological changes on the occurrence of myocardial infarction.²² To save the efficiency of analytic procedures in this study, however, differences in the 4 types of temperatures between the day of occurrence and the previous day were employed, and no more consideration was paid to long-term meteorological changes.

The F values and the first correlation ratios in canonical discriminant analyses were 0.0003 and 0.03% on A1 and A2 groups, 0.0155 and 1.53% on B1 and B2 groups respectively. These values disclosed that the 10 meteorological factors in the Kamikawa Basin were unable to discriminate between the day with and without occurrence of myocardial infarction, whether the occurrence of the disease was outdoors or not.

In Yamagata, it is a little warmer than in the Kamikawa Basin, but the inhabitants are easily subjected to the influence of outdoor temperature because of insufficient construction of houses against heavy snow and incomplete facilities against cold.²³ So the referential analysis was performed to evaluate the influence of the meteorological factors on the occurrence of

acute myocardial infarction in the cold periods in Yamagata. The F value and the first correlation ratio obtained in canonical discriminant analysis on C1 and C2 groups were 0.0098 and 0.97%. There was no indication that the meteorological factors influenced on the occurrence of acute myocardial infarction in Yamagata.

Throughout several statistical analyses, it was recognized that the occurrence of myocardial infarction had no monthly fluctuation, nor was it influenced by the 10 meteorological factors in the cold period.

3-2 Circadian Rhythm of the Occurrence of Acute Myocardial Infarction

In Japan, an early study on 381 patients with acute myocardial infarction reported that the highest frequency of occurrence was observed between 18.00 and 24.00 and that 32.0% of all the occurrences came under this interval.²⁴ In that study, labor or stress in the daytime, maladjustment to the change in daily meteorological conditions, unstable autonomic nervous system, and sudden metabolic change after overeating were speculated to trigger the occurrence of the disease. Recently, however, Sumiyoshi et al²⁵ in their report on 750 patients with myocardial infarction pointed out that the highest frequency of occurrence was observed between 6.00 and 8.00 and between 19.00 and 22.00.

There are several reports on the time of occurrence of myocardial infarction in Europe and America since 1980.²⁶⁻³² Most of these reports indicate that the frequency of occurrence was highest between 6.00 and 12.00,²⁷⁻³² and that the second highest frequency was observed sometimes between 18.00 and 24.00.^{27,29-32} In 1985, we also obtained the result that the frequency of occurrence of this disease was highest between 8.00 and 12.00 and between 20.00 and 24.00 in a study of 276 patients.³³

From these results mentioned above, it can be estimated that the occurrence of myocardial infarction has a circadian fluctuation. However, few reports have clarified circadian rhythm by means of power spectral analysis.^{29,34} In this study, we attempted to make a power spectral analysis to assess the circadian rhythm of the occurrence of acute myocardial infarction in 562 patients. The result that the largest peak was observed at the rhythm of 2 cycles/day has revealed circadian rhythm in the occurrence of myocardial infarction.

Many factors are considered conventionally to trigger the obstruction of a stenotic coronary

artery. For example, blood pressure, platelet count, platelet aggregation, and vasospasticity are well-known factors with a circadian rhythm of 1 cycle/day in a living body^{4,5,7,35}. On the other hand, noradrenaline is dependent on the change of sympathetic nervous activity and has a rhythm of 2 cycles/day^{36,37}.

The total 562 patients in this study were subdivided into two groups according to physical activity just before the occurrence; one group consisted of patients whose myocardial infarction occurred at rest and the other group consisted of those whose infarction occurred on effort. Although significant fluctuations of the occurrences were recognized, the peaks of frequency were observed at different periods of the day in these two groups. Power spectral analyses showed that the former group had a rhythm of 1 cycle/day, while the latter group had a rhythm of 2 cycles/day. From a viewpoint of physical activity, it can be supposed that the overall circadian rhythm of 2 cycles/day is made up of these two different but overlapping rhythms, even though there is no reference of analysis concerning this viewpoint.

Although this study did not specify the triggering factor of occurrence at rest, some factors with circadian rhythm of 1 cycle/day mentioned above may be related. Rocco et al³⁸ observed a rhythm of 1 cycle/day in monitoring electrocardiological spontaneous ST depression in patients with ischemic heart disease.

Ganelina et al³⁰ showed that the excretion of catecholamine in human urine increased between 9.00 and 12.00 and between 18.00 and 21.00, no matter what the pattern of work hours was. A circadian rhythm of blood noradrenaline level has been verified^{36,37}. Putting all references including the result of this study together, it might be inferred that sympathetic nervous activity could participate in triggering the occurrence of acute myocardial infarction.

We analyzed the influences of two factors, which were suspected to be transient risk factors of myocardial infarction, on the occurrence of the disease. Multivariate analysis revealed that the 10 selected meteorological factors did not discriminate between the days with occurrences and the days without occurrences in the cold periods. Power spectral analysis showed rhythm of 2 cycles/day as to the time of occurrence. These results indicate that weather plays little role in triggering acute myocardial infarction, while biological intrinsic rhythm may influence

the occurrence of this disease to some extent.

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