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ORIGINAL ARTICLE

Lower Framingham risk score and the absence of hypertension are associated with the morning peak in the circadian variation of ST-elevation myocardial infarction onset

Hiroki Usuku[1,4], Yasuhiro Izumiya[1], Seigo Sugiyama[1], Sunao Kojima[1], Satoshi Araki[1], Kazumasa Kurogi[2], Nobuyasu Yamamoto[2], Yukio Ando[3] and Hisao Ogawa[1]

There are few studies analyzing the influences of coronary risk factors on the circadian variation of ST-elevation myocardial infarction (STEMI). Between 2008 and 2011, 293 patients were admitted to Miyazaki Prefectural Nobeoka Hospital with STEMI. The onset time of STEMI was identified in 280 patients (age, 70.5 ± 11.7 years; male subjects, 68%; hypertension (HT), 80%; diabetes mellitus, 28%; current smoking (cSM), 33%; Framingham risk score (FRS), 8.77 ± 3.28). The day was divided into six 4-h periods, with the morning peak between 0800 and 1200 hours. The frequency of HT was significantly lower in the morning incidence group than in the nighttime incidence group. Multivariate logistic regression analysis revealed that the prevalence of HT was the only independent variable associated with the morning peak of STEMI (odds ratio (OR), 0.43; 95% confidence interval (95% CI), 0.23–0.83; $P=0.01$) and that cSM was significantly associated with the nighttime peak of STEMI (OR, 1.96; 95% CI, 1.01–3.80; $P=0.04$). A comprehensive evaluation using the FRS showed that the FRS was significantly lower in the morning incidence group than in the nighttime incidence group and the other time incidence group (7.95 ± 3.47 *vs.* 9.14 ± 2.89 *vs.* 9.06 ± 3.25, $P<0.01$), and that having a lower FRS was associated with the morning peak of STEMI (OR, 1.12; 95% CI, 1.02–1.21; $P=0.01$). A lower FRS and non-HT status are associated with the morning peak in the circadian variation of STEMI onset. The morning incidence of STEMI might be affected by pathogenic factors other than the classic coronary risk factors.
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INTRODUCTION

Circadian variation in the frequency of the onset of myocardial infarction (MI) has been described in a number of studies, with a first peak in the morning and a second peak in the late evening.[1–3] Analysis of the circadian variations is important to clarify the triggering mechanisms of MI. Coronary risk factors, including hypertension (HT), diabetes mellitus (DM), dyslipidemia and smoking are reported to influence the autonomic nerve system.[4–8] Alterations in sympathovagal balance affect the time of myocardial ischemia onset.[9] Therefore, it is rational to speculate that coronary risk factors affect the circadian variation of the onset of ischemic heart diseases. However, limited information is available regarding the relationships between coronary risk factors and the circadian variation of MI.

The Framingham risk score (FRS) is based on the number and severity of coronary risk factors. The FRS is most widely used to predict coronary artery disease over a 10-year period.[10] However, little has been reported on the association between the FRS and the circadian variation of MI. The aim of this study was to evaluate the associations of coronary risk factors and FRS with ST-elevation myocardial infarction (STEMI) onset time.

METHODS

Study setting and population

We conducted this study at Miyazaki Prefectural Nobeoka Hospital, Japan. A total of 293 patients with STEMI were admitted to the hospital within 24 h of symptom onset between April 2008 and March 2011. The diagnosis of STEMI was as follows: (a) ischemic symptoms, (b) ST-segment elevation >0.1 mV in

[1]Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan; [2]Department of Cardiovascular Medicine, Miyazaki Prefectural Nobeoka Hospital, Miyazaki, Japan and [3]Department of Laboratory Medicine, Kumamoto University hospital, Kumamoto, Japan
[4]Current address: Department of Cardiovascular Medicine, Kumamoto Chuo Hospital, 1-5-1, Tainoshima, Minami-ku, Kumamoto city 862-0965, Japan
Correspondence: Dr H Usuku, Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto city 860-8556, Japan.
E-mail: h-usuku@kumachu.gr.jp
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at least one standard or two precordial leads and (c) more than twofold elevation in the creatine kinase-MB level.[11] The time of STEMI onset was determined by the attending physician on the basis of a patient's self-report. The time of STEMI onset was not definitively identified in 13 patients; therefore, 280 patients were analyzed in this study.

Evaluation of circadian variation and definitions of clinical characteristics

The standard hourly profile of STEMI onset was obtained over a 24-h period. We divided the day into six 4-h periods (0000–0400, 0400–0800, 0800–1200, 1200–1600, 1600–2000 and 2000–2400 hours) to clarify the peaks of STEMI onset. Next, to evaluate the relationship between a morning or nighttime incidence of STEMI and clinical characteristics, we divided the patients into three groups according to the time of day of STEMI onset: morning incidence (0800–1200 hours), nighttime incidence (2000–2400 hours) and other time incidence (0000–0400, 0400–0800, 1200–1600 and 1600–2000 hours).

Clinical characteristics were defined as follows: obesity, body mass index $\geqslant 25\,kg\,m^{-2}$; HT, patients' self-reports of a history of systolic blood pressure (BP) $\geqslant 140$ mm Hg and/or diastolic BP $\geqslant 90$ mm Hg and/or prior use of antihypertensive agents, including β-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers; DM, patients' self-reports of a history of hemoglobin A1c $\geqslant 6.5\%$ and fasting plasma glucose $\geqslant 126\,mg\,dl^{-1}$ or casual plasma glucose $\geqslant 200\,mg\,dl^{-1}$ and/or use of insulin or diabetes drugs; dyslipidemia, patients' self-reports of a history of statin use, low-density lipoprotein cholesterol $\geqslant 140\,mg\,dl^{-1}$, triglycerides $\geqslant 150\,mg\,dl^{-1}$ and/or high-density lipoprotein cholesterol $<40\,mg\,dl^{-1}$; renal impairment, estimated glomerular filtration rate $<60\,ml\,min^{-1}$ per $1.73\,m^2$; total/subtotal occlusion, coronary stenosis $\geqslant 99\%$ by coronary angiography; multivessel disease, two or three vessels with coronary artery disease; and preserved left ventricular ejection fraction, left ventricular ejection fraction $\geqslant 50\%$ (left ventricular ejection fraction was measured by echocardiography using a modified Simpson method).

Data collection

Blood samples were obtained from patients upon admission to our hospital, and a physical examination was performed, including measurements of blood pressure and heart rate, when patients left the emergency room.

Statistical analysis

A χ^2 goodness-of-fit test was performed to test the uniformity of the distribution of patients among the time periods. When this test showed significant differences, a one-sided binominal test was performed to examine whether the frequency of STEMI was higher than the expected rate. The FRS was calculated on the basis of seven risk factors: age, gender, BP, DM, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and current smoking (cSM).[10] We used the Kruskal–Wallis test or the χ^2-test for comparisons of patient clinical characteristics among the time periods. We used the Bonferroni test to perform pairwise comparisons for variables with global significance. The independent variables associated with each period of STEMI were assessed by logistic regression analysis. The following variables were incorporated first into the univariate logistic regression analysis model: age, gender, prior MI, Killip class, obesity, HT, DM, dyslipidemia, cSM, renal impairment, aspirin use, antihypertensive medication use (including calcium-channel blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and β-blockers), statin use, exertion-induced STEMI, attack while eating, attack when taking a bath, outside attack, left anterior descending artery lesion, total/subtotal occlusion, multivessel disease, percutaneous coronary intervention therapy, reperfusion, preserved left ventricular ejection fraction and time from onset to admission. Variables with P-values <0.05 were incorporated into the multivariate logistic regression analysis model.

Logistic regression analysis was then used to evaluate the association between the FRS and a morning or nighttime peak of STEMI incidence. Analyses were conducted with SPSS version 17.0. Statistical significance was defined as $P<0.05$.

RESULTS

Circadian variation of STEMI

The circadian variation of STEMI in this study population showed two peaks: one definite morning peak at ~0900 hours and a broad peak at ~2300 hours (Figure 1a). When we divided the day into six 4-h periods, there were significant differences in patient distribution among the time periods ($P<0.01$, Figure 1b). In this analysis, we observed a peak in the number of patients between 0800 and 1200 hours (77/280, 28%, $P<0.01$).

Clinical characteristics of the study population

The baseline characteristics, coronary risk factors, baseline hemodynamics, prior medications, laboratory findings and situation at the time of STEMI onset of the study population are presented in Table 1. The frequency of HT in the morning incidence group was significantly lower than that in the nighttime incidence group. Peak creatine kinase-MB in the morning incidence group was significantly lower than that in the other time incidence group. The rates of exertion-induced STEMI and outside attack were significantly higher in the morning incidence group than in the nighttime incidence group and other time incidence group. There were no significant differences among the three groups in baseline hemodynamics or prior medication.

Echocardiographic and angiographic findings

There were no significant differences in the echocardiographic findings among the three groups (Table 2). The rate of total/subtotal occlusion was significantly lower in the morning incidence group than

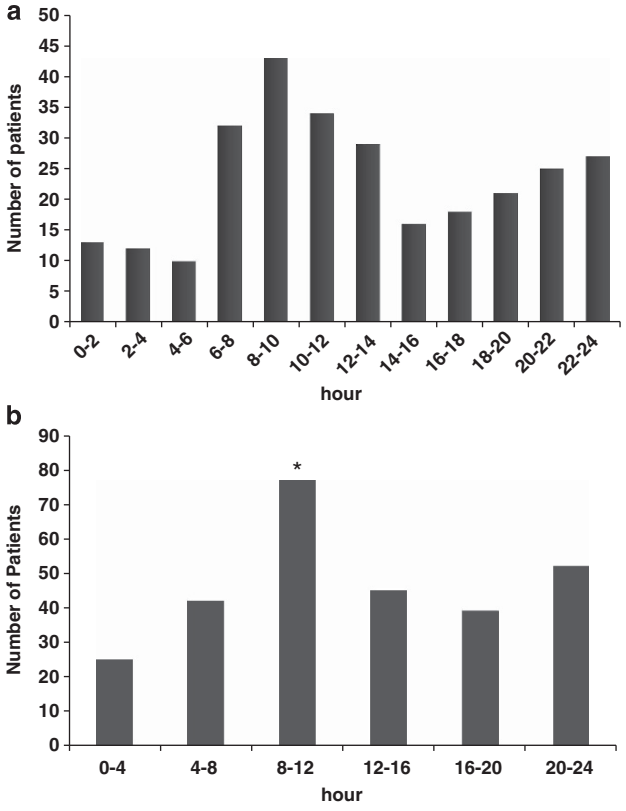

Figure 1 The circadian variation of the onset of ST-elevation myocardial infarction (STEMI) for the total study population obtained at 2-h intervals (**a**) and 4-h intervals (**b**). *$P<0.05$ by a one-sided binominal test. A full color version of this figure is available at the *Hypertension Research* journal online.

Table 1 Baseline characteristics and coronary risk factors, baseline hemodynamics, prior medications, laboratory findings and situation at the time of STEMI onset among the morning incidence group, nighttime incidence group and other time incidence group

Variables	*Morning incidence group (n = 77)*	*Nighttime incidence group (n = 52)*	*Other time incidence group (n = 151)*	P-*value*
Baseline characteristics and coronary risk factors				
Age, years	70.8 ± 12.5	69.1 ± 11.8	70.8 ± 11.2	0.62
Male gender, *n* (%)	52 (68)	36 (67)	101 (67)	0.95
Prior MI, *n* (%)	7 (9)	0 (0)	14 (9)	0.08
Killip (II–IV), *n* (%)	14 (18)	13 (25)	25 (17)	0.40
BMI, kg m^{-2}	22.8 ± 3.3	23.6 ± 3.5	23.3 ± 3.1	0.23
HT, *n* (%)	52 (68)*	45 (87)	126 (83)	<0.01
DM, *n* (%)	17 (22)	17 (33)	44 (29)	0.37
Dyslipidemia, *n* (%)	55 (71)	36 (69)	101 (67)	0.78
cSM, *n* (%)	20 (26)	24 (46)	48 (32)	0.05
Baseline hemodynamics				
Systolic BP, mm Hg	127.3 ± 30.7	137.2 ± 36.0	133.4 ± 32.8	0.23
Diastolic BP, mm Hg	76.4 ± 18.5	81.0 ± 22.5	81.6 ± 23.0	0.13
Heart rate, beats per min	72.2 ± 20.7	73.6 ± 25.3	75.8 ± 24.3	0.40
Prior medications				
Aspirin, *n* (%)	19 (25)	9 (17)	31 (21)	0.59
Anti-HT agents, *n* (%)	31 (40)	26 (50)	77 (51)	0.27
CCB, *n* (%)	21 (27)	20 (38)	51 (34)	0.38
ACEI/ ARB, *n* (%)	20 (26)	15 (29)	46 (30)	0.76
β-blocker, *n* (%)	5 (6)	3 (6)	13 (9)	0.73
Statin, *n* (%)	15 (19)	4 (8)	20 (13)	0.16
Laboratory findings				
Total cholesterol, mg dl^{-1}	194.0 ± 42.9	190.7 ± 38.5	196.3 ± 44.8	0.86
Triglyceride, mg dl^{-1}	148.5 ± 164.1	110.1 ± 50.5	130.3 ± 110.4	0.73
HDL cholesterol, mg dl^{-1}	47.9 ± 12.9	44.5 ± 11.2	46.9 ± 13.4	0.40
LDL cholesterol, mg dl^{-1}	120.0 ± 39.4	124.2 ± 32.6	123.4 ± 37.0	0.73
HbA1c, (%)	6.22 ± 1.18	6.45 ± 1.38	6.30 ± 1.29	0.80
eGFR, ml min^{-1} per 1.73 m^2	60.2 ± 21.9	63.0 ± 22.7	57.2 ± 22.2	0.33
Peak CK-MB, ng ml^{-1}	188.4 ± 176.5†	207.8 ± 204.3	243.7 ± 190.9	0.04
Situation at the time of STEMI onset				
Exertion	20 (26)*,†	0 (0)‡	20 (13)	<0.01
Eating, (%)	5 (6)	4 (8)	5 (3)	0.36
Taking a bath, (%)	2 (3)	1 (2)	7 (5)	0.57
Outside, (%)	29 (38)*,†	3 (6)‡	24 (16)	<0.01

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium-channel blocker; CK-MB, creatine kinase-MB; cSM, current smoking; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HT, hypertension; LDL, low-density lipoprotein; MI, myocardial infarction.
P-values were obtained using the Kruskal–Wallis test and the χ^2-test.
*$P<0.05$ *vs.* nighttime incidence group by the Bonferroni test.
†$P<0.05$ *vs.* other time incidence group by the Bonferroni test.
‡$P<0.05$ *vs.* other time incidence group by the Bonferroni test.

in the other time incidence group. The time from onset to admission tended to be shorter in the morning incidence group than in the nighttime incidence group and in the other time incidence group.

Factors associated with the morning and nighttime peaks of STEMI

The multivariate logistic regression analysis revealed that the prevalence of HT, outside attack and the rate of total/subtotal occlusion were independently associated with the morning peak of STEMI (odds ratio (OR); 0.43, 95% confidence interval (95% CI); 0.23–0.83, $P = 0.01$, OR; 3.13, 95% CI; 1.34–7.35, $P < 0.01$ and OR; 0.25, 95% CI; 0.10–0.59, $P < 0.01$, Table 3). In contrast, the multivariate logistic regression analysis also revealed that the frequency of cSM, outside attack and time from onset to admission were significantly associated with the nighttime peak of STEMI (OR; 1.96, 95% CI; 1.01–3.80, $P = 0.04$, OR; 0.19, 95% CI; 0.06–0.66, $P < 0.01$ and OR; 1.00, 95% CI; 1.00–1.00, $P = 0.02$, Table 4).

Subgroup analysis

We observed a morning peak and a nighttime peak in the HT group, but the peaks were not significantly higher than the incidence during the remainder of the day (Supplementary Figures 1A and B). However, we observed a significant morning STEMI peak in the non-HT

Table 2 Echocardiographic findings, angiographic findings and management and therapy among the morning incidence group, nighttime incidence group and other time incidence group

Variables	*Morning incidence group (n = 77)*	*Nighttime incidence group (n = 52)*	*Other time incidence group (n = 151)*	P-*value*
Echocardiographic findings				
Left ventricular EF, (%)	56.8 ± 10.4	55.5 ± 12.3	54.6 ± 11.0	0.54
Aortic stenosis, *n* (%)	3 (4)	3 (6)	4 (3)	0.59
Mitral regurgitation, *n* (%)	5 (7)	2 (4)	16 (11)	0.25
Angiographic findings				
Total/subtotal occlusion, *n* (%)	62 (82)†	48 (92)	143 (95)	<0.01
	2 (3)	1 (2)	8 (5)	0.43
LMT lesion, *n* (%)	30 (39)	26 (50)	70 (47)	0.51
LAD lesion, *n* (%)	32 (42)	26 (50)	59 (39)	0.41
Multi vessels disease, n (%) management and therapy				
Onset to admission time (min)	180.1 ± 166.1	357.0 ± 382.9	246.4 ± 285.9	0.09
Door to balloon time (min)	73.0 ± 47.2	76.3 ± 24.5	82.0 ± 39.3	0.06
IABP (%)	13 (17)	7 (52)	18 (12)	0.23
PCI (%)	75 (97)	52 (100)	148 (98)	0.53
Reperfusion (%)	73 (94)	51 (98)	147 (97)	0.50

Abbreviations: EF, ejection fraction; IABP, intra-aortic balloon pumping; LMT, left main trunk; LAD, left anterior descending artery; PCI, percutaneous coronary intervention.
P-values were obtained using the Kruskal–Wallis test and the χ^2-test.
†$P<0.05$ *vs.* other time incidence group by the Bonferroni test.

group (44%, 25/57, $P<0.01$, Supplementary Figure 1C and D). We defined hypertension as high BP and/or prior use of antihypertensive agents. Thus, we divided the HT patients into two groups: the antihypertensive agent group and the non-antihypertensive agent group. The circadian variation of STEMI onset was similar between the antihypertensive agent group and the non-antihypertensive agent group (Supplementary Figures 1E–H). The rate of morning STEMI incidence did not differ between the antihypertensive agent group and non-antihypertensive agent group (23% *vs.* 22%, $P=0.89$).

There was a nighttime STEMI peak in the cSM group, but it was not significant (Supplementary Figures 2A and B). In contrast, we observed a significant morning STEMI peak in the non-SM group (57/188, 30%, $P<0.01$, Supplementary Figures 2C and D).

In patients with DM, there was no significant peak in the circadian variation of STEMI (Supplementary Figures 3A and B). However, we observed a significant morning STEMI peak in the non-DM group (60/202, 30%, $P<0.01$, Supplementary Figures 3C and D).

FRS and morning or nighttime STEMI incidence

Finally, we comprehensively evaluated the relationships between coronary risk factors and the circadian variation of STEMI incidence using the FRS. The FRS was significantly lower in the morning incidence group than in the nighttime incidence group and the other time incidence group (7.95 ± 3.47 *vs.* 9.14 ± 2.89 *vs.* 9.06 ± 3.25, $P<0.01$, Figure 2). Logistic regression analysis revealed that a lower FRS was significantly associated with the morning STEMI peak (OR; 1.12, 95% CI; 1.02–1.21, $P=0.01$).

Table 3 Factors associated with the morning peak of STEMI

	Univariate analysis		*Multivariate analysis*	
	OR (95% CI)	P-*value*	*OR (95% CI)*	P-*value*
High age (⩾ 65 years) (+)	1.26 (0.71–2.24)	0.43		
Male (+)	1.00 (0.57–1.76)	0.99		
Prior MI (+)	1.35 (0.52–3.48)	0.54		
Killip (II–IV) (+)	0.97 (0.49–1.90)	0.92		
Obesity (+)	0.89 (0.48–1.65)	0.71		
HT (+)	0.39 (0.21–0.72)	<0.01	0.43 (0.23–0.83)	0.01
DM (+)	0.66 (0.36–1.22)	0.19		
Dyslipidemia (+)	1.20 (0.68–2.14)	0.53		
cSM (+)	0.64 (0.36–1.15)	0.13		
Renal impairment (+)	0.78 (0.46–1.32)	0.36		
Aspirin (+)	1.33 (0.71–2.47)	0.37		
Anti-HT agents (+)	*0.65 (0.38–1.10)*	*0.11*		
CCB (+)	0.69 (0.39–1.23)	0.21		
ACEI/ARB (+)	0.81 (0.45–1.47)	0.49		
β-blocker (+)	0.81 (0.29–2.29)	0.69		
Statin (+)	1.79 (0.89–3.64)	0.11		
Exertion-induced attack (+)	3.21 (1.61–6.39)	<0.01	1.45 (0.55–3.84)	0.45
Attack while eating (+)	1.50 (0.49–4.62)	0.48		
Attack when taking a bath (+)	0.65 (0.14–3.13)	0.59		
Outside attack (+)	3.94 (2.13–7.28)	<0.01	3.13 (1.34–7.35)	<0.01
LAD lesion (+)	0.74 (0.44–1.27)	0.28		
Total/subtotal occlusion, *n* (%)	0.26 (0.11–0.59)	<0.01	0.25 (0.10–0.59)	<0.01
Multi vessel disease (+)	1.00 (0.59–1.71)	1.00		
PCI therapy (+)	0.56 (0.09–3.43)	0.53		
Reperfusion (+)	0.46 (0.12–1.76)	0.26		
Preserved LVEF (+)	1.41 (0.76–2.61)	0.27		
Time from onset to admission (per 1 min)	1.00 (1.00–1.00)	0.08		

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium-channel blocker; CI, confidence interval; cSM, current smoking; DM, diabetes mellitus; HT, hypertension; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; OR, odds ratio.
P-values were obtained using logistic regression analysis.

DISCUSSION

We report three new findings. First, the absence of HT and a lower rate of total/subtotal occlusion were associated with the morning STEMI peak. Second, cSM was associated with the nighttime STEMI peak. Third, a lower FRS was associated with the morning STEMI peak. These data indicate that coronary risk factors affect the circadian variation of STEMI onset and that the morning STEMI incidence might be affected by pathogenic factors other than the classic coronary risk factors. In addition, our study showed that the patient situations at the time of STEMI onset differed among the time periods.

Circadian variation in the frequency of onset of STEMI could be affected by various clinical factors. In the present study, we documented a significant morning STEMI peak in the non-HT group. In contrast, the morning STEMI peak was not significant in the HT group. When we divided the HT patients into two groups, the antihypertensive agent group and the non-antihypertensive agent group, there was no significant difference in the morning STEMI

Table 4 Factors associated with the nighttime peak of STEMI

	Univariate analysis		*Multivariate analysis*	
	OR (95% CI)	P-*value*	*OR (95% CI)*	P-*value*
High age (⩾ 65 years) (+)	0.64 (0.34–1.19)	0.16		
Male (+)	1.00 (0.58–2.11)	0.77		
Prior MI (+)	*Not selected*			
Killip (II–IV) (+)	1.62 (0.79–3.31)	0.19		
Obesity (+)	1.11 (0.56–2.19)	0.77		
HT (+)	1.81 (0.77–4.25)	0.18		
DM (+)	1.33 (0.70–2.55)	0.39		
Dyslipidemia (+)	1.04 (0.54–1.99)	0.91		
cSM (+)	2.02 (1.09–3.73)	0.03	1.96 (1.01–3.80)	0.04
Renal impairment (+)	1.01 (1.00–1.02)	0.16		
Aspirin (+)	0.74 (0.34–1.62)	0.45		
Anti-HT agents (+)	*1.10 (0.60–2.01)*	*0.75*		
CCB (+)	1.35 (0.72–2.51)	0.35		
ACEI/ARB (+)	0.99 (0.51–1.92)	0.97		
β-blocker (+)	0.71 (0.20–2.51)	0.60		
Statin (+)	0.46 (0.16–1.35)	0.16		
Exertion-induced attack (+)		*Not selected*		
Attack while eating (+)	1.82 (0.55–6.04)	0.33		
Attack when taking a bath (+)	0.48 (0.06–3.85)	0.49		
Outside attack (+)	0.20 (0.06–0.68)	<0.01	0.19 (0.06–0.66)	<0.01
LAD lesion (+)	1.25 (0.68–2.28)	0.47		
Total/subtotal occlusion, *n* (%)	1.23 (0.40–3.75)	0.72		
Multi vessel disease (+)	1.51 (0.82–2.76)	0.19		
PCI therapy (+)		*Not selected*		
Reperfusion (+)	1.86 (0.23–15.16)	0.56		
Preserved LVEF (+)	1.33 (0.70–2.55)	0.39		
Time from onset to admission (per 1 min)	1.00 (1.00–1.00)	0.01	1.00 (1.00–1.00)	0.02

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium-channel blocker; CI, confidence interval; cSM, current smoking; DM, diabetes mellitus; HT, hypertension; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; OR, odds ratio.
P-values were obtained using logistic regression analysis.

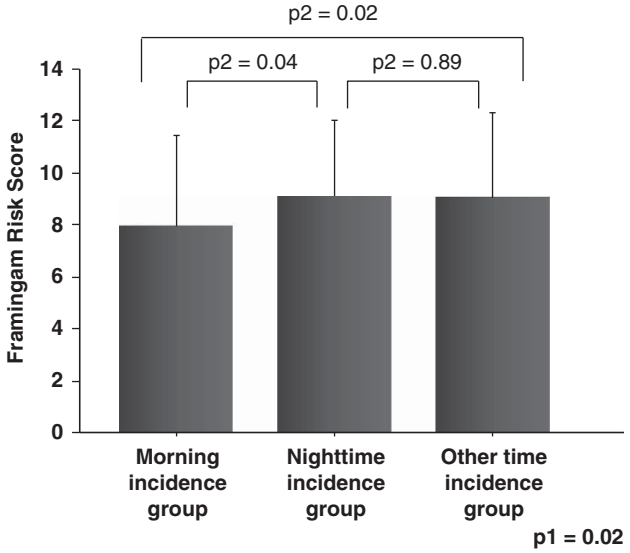

Figure 2 Comparison of the FRS between the morning incidence group and the other time incidence group. The p1 value was obtained by the Kruskal–Wallis test, and the p2 values were obtained by the Bonferroni test. A full color version of this figure is available at the *Hypertension Research* journal online.

incidence rate between these groups. This result indicates that the circadian variation of STEMI is not affected by antihypertensive agents but by HT itself. Patients with HT show alterations in the rhythm and pattern of blood pressure oscillation, including a non-dipper pattern.[12,13] In addition, BP variation appears to be closely related to sympathetic nervous system activity because plasma catecholamine levels decrease with nocturnal BP and increase with the morning BP elevation.[14] The morning STEMI peak is significantly associated with hemodynamic changes[15,16] and neurohumoral factors.[17,18] Thus, we believed that the disturbance of hemodynamic changes and the sympathetic nervous system by HT would decrease the morning incidence of STEMI in patients with HT. Because other factors such as platelet aggregation and coagulation also trigger morning MI,[19–21] the morning STEMI peak may be present even in patients with HT.

Our study showed that the prevalence of DM was not significantly associated with the morning incidence of STEMI. However, we observed a significant morning STEMI peak in the non-DM group, and there was no significant morning STEMI peak in the DM group. In patients with DM, hemodynamic status and the autonomic nervous system are disturbed.[22,23] Thus, we hypothesized that DM might affect the circadian variation of STEMI by disturbing hemodynamic status and the autonomic nervous system. However, we did not observe an association between DM and the morning STEMI incidence because the number of patients in our study was too small.

It is well known that smoking is an important risk factor for atherosclerosis development,[24,25] coronary vascular disease[26,27] and coronary spasm.[28] Because coronary spasm is one of the triggers of acute myocardial infarction (AMI), particularly during the morning hours,[29,30] we anticipated that smoking would increase the morning incidence of STEMI. However, our study indicates that smoking is not associated with the morning STEMI peak but that it is associated with the nighttime STEMI peak. This result is congruent with those reported by Kinjo.[31] In general, the nighttime AMI peak is affected by socioeconomic factors, such as mental stress[32] and overtime work.[33] Thus, we speculated that socioeconomic factors in current smokers would be potent triggers of the nighttime onset of STEMI. Patients with AMI treated during off hours have a worse clinical outcome than patients treated during duty hours.[34] Modification of socioeconomic factors, including smoking cessation, might improve the quality of care and lead to a better clinical outcome of STEMI.

Many studies have evaluated the circadian variation of coronary vascular disease by dividing the day into four 6-h periods.[2,35] However, some studies have divided the day into six 4-h periods to evaluate the circadian variation of coronary vascular disease.[31,36] In addition, some studies have reported that the morning peak of AMI starts at 0800 hours and lasts until 1100 or 1200 hours.[2,37] Our study also showed that the rate of STEMI between 0800 and 1200 hours was the highest (Figures 1a and b). Moreover, the rate of effort attack was higher in the period between 800 and 1200 hours compared with the other periods. These results suggest that exercise might be one of the triggers of STEMI onset, particularly in the morning hours (800–1200 hours). We speculated that the triggers of STEMI onset differ between

the early morning hours (600–800 hours) and the morning hours (800–1200 hours).

Accumulation of coronary risk factors is important to predict coronary vascular events.[10,38] The FRS is a comprehensive reflection of coronary risk factors. Thus, the FRS is widely used to predict coronary vascular events.[10] In the present study, we found a significant association between a lower FRS and the morning incidence of STEMI. This result suggests that morning-onset STEMI occurs even in patients with only a few coronary risk factors and that the morning incidence of STEMI might be affected by unestablished pathogenic factors in addition to its atherosclerotic pathogenesis. Thus, we believe that analyzing the circadian variation of STEMI using the FRS provides additional important clinical information. Regarding other pathogenic factors, the involvement of platelet aggregation, coagulation and coronary spasm should be considered. Platelet aggregation and coagulation are known to be important triggers of MI onset. Moreover, platelet aggregation and plasminogen activator inhibitor-1 (one of the coagulation factors) activity are elevated in the morning hours.[19–21] We speculate that the morning incidence of STEMI might be more affected by coagulation or platelet aggregation than atherosclerotic pathogenesis. In addition, coronary spasm is recognized as one of the triggers of AMI, particularly in Asian people,[29] and it occurs most frequently in the morning hours.[30] Our study also showed that the rate of total/subtotal occlusion was lower in the morning incidence group than in the other time incidence group, suggesting that the morning incidence of STEMI might be affected by coronary spasm. Morning MI was triggered by many non-atherosclerotic factors such as exercise, platelet aggregation, coagulation and coronary spasm. Therefore, morning-onset MI tends to occur even in patients with a lower FRS.

Study limitations

First, this was a retrospective study, and it was therefore difficult to establish a cause–effect relationship. Second, this study was a single-center study, and only 77 patients were included in the morning incidence group. Therefore, a bias related to the sample size may have influenced our findings. Third, the time from onset to admission tended to be shorter in the morning incidence group than in the nighttime incidence group and in the other time incidence group. The occlusion status of the culprit artery may therefore have been influenced by the time since the onset.

CONCLUSION

A lower FRS and non-HT status are associated with the morning peak in the circadian variation of STEMI onset. The morning incidence of STEMI might be affected by pathogenic factors other than the classic coronary risk factors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)