A huge earthquake hardened arterial stiffness monitored with cardio-ankle vascular index

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Short title: CAVI reflects emotional stress of the artery

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Abstract

Rationale

The incidence of cardiovascular events increases after a big earthquake, but the mechanism is not fully understood. Cardio-ankle vascular index (CAVI) reflects the stiffness of the artery from the origin of the aorta to ankles and is independente from blood pressure.

Objective

To determine the effect of a major earthquake on CAVI in healthy volunteers and in patients with cardiovascular risks.

Methods and results

Our hospital was situated about 300 km from the epicenter of the earthquake. In study 1, healthy volunteers were included. In study 2, patients with cardiovascular factors were included. In study 1, the mean CAVI was 7.3±1.0 just after the earthquake. After 7-14 days, the mean CAVI decreased to 6.8±1.1 (compared to 1st time, $p < 0.05$). Furthermore, the CAVI value 30 days after the earthquake was 7.0±1.1. The blood pressure did not change during 30 days. In study 2, the mean CAVI 12 and 6 months before the earthquake were 8.95±0.76 and 8.99±0.83, respectively. The CAVI was 9.34±1.0 just after the earthquake and decreased to 8.83±0.76 6

months later (compared to after earthquake, $p<0.05$). The blood pressure was increased a little at the time of earthquake, but was not significantly different, compared to that before the earthquake.

Conclusions

CAVI was increased in healthy people and also in patients with cardiovascular risks just after the earthquake, even far away from the epicenter.

Key words

CAVI, earthquake, emotional stress, arterial stiffness, cardiovascular event

Introduction

It is known that the frequency of cardiovascular events increases just after a huge earthquake.[1-3] When the Hanshin-Awaji earthquake occurred in 1995, an epidemiological survey about cardiovascular events was made by Kario. He reported that earthquake-induced stress increased blood pressure and blood viscosity determinants in a group of hypertensive elderly subjects after the Hanshin-Awaji earthquake magnitude 7.2. [4,5]

Another study reported a direct association between a measure of β2-adrenergic receptor functioning and stress-induced hemostatic changes.[6] Acute mental stress may trigger a hypercoagulable state evidenced by increasing thrombin activity and by increasing fibrin turnover.[6] These mechanisms may be involved in the occurrence of cardiovascular events. However, the role of vascular stress associated with earthquakes is not clear.

Arterial stiffness might provide valuable information about arterial wall conditions, which include arteriosclerosis and contraction of arterial smooth muscles. It is reported that increased arterial stiffness is an important risk factor for cardiovascular morbidity and mortality. [7, 8, 9]

One problem is that there have not been suitable markers reflecting arterial stiffness. Pulse wave velocity is a traditional marker of arterial wall stiffness, but it depends on blood pressure at measuring time. In 2006, a new arterial wall stiffness parameter, the cardio-ankle vascular stiffness index (CAVI), was developed. CAVI is a parameter that reflects the stiffness of the aorta, femoral artery, and tibial artery as a whole. One conspicuous feature is its independence from blood pressure at measuring time.[10] CAVI increases with age and in many arteriosclerotic diseases, such as coronary artery disease,[11-15] carotid arteriosclerosis,[12] chronic kidney disease, [16] and cerebral infarction.[17]

On March 11th, 2011, an earthquake of magnitude 9.0 occurred on the Pacific coast of Tohoku, Honshu Island, Japan, at 14:46 local time (the Great East Japan Earthquake). It was followed by a series of powerful aftershocks, with 31 earthquakes of magnitude larger than 6 in 3 days. As shown in Figure 1, our institute (Toho University Sakura Medical Center Hospital) was situated about 300 km away from the epicenter. The building was strongly shaken and part of a wall collapsed. An unusual crisis occurred in our town.

To examine the possibility that arterial stiffness of the people would be increased, we started to measure vascular stiffness of healthy volunteers and also those of the patients with cardiovascular risks using CAVI just after the earthquake. As for the patients, the cases whose

CAVI values were measured twice in the previous year were selected. Blood pressure change was also examined in both groups.

Subjects and Methods

We show the design of the study in Figure 2. There were two study groups. The first study group (Study 1) included 43 healthy volunteers. CAVI was measured 3 times (1st time: day 1 after the earthquake. 2nd time: day between7 to 14. 3rd time: day 30). After measurement of CAVI, we performed a blood test and questionnaire survey. We investigated the serum adrenalin and noradrenaline levels. The contents of the questionnaire survey included sleeping time before examination day, the distance from the epicenter to the hometown, marital status, presence of children, and a confirmation of the safety of the family.

The second study group (Study 2) included 32 patients with cardiovascular risk factors from the outpatient clinics. CAVI was measured 4 times (1st time: 12 months before the earthquake. 2nd time: 6 months before. 3rd time: 1 to 5 days after. 4th time: 6 months later).

Table 1 shows the characteristics of the subjects. In study 1, subjects consisted of 23 doctors, 17 nurses, and 3 laboratory technicians. In study 2, subjects consisted of 32 patients whose CAVI was measured regularly in the past. As shown in Table 1, the average age and body mass index (BMI) in subjects of study 1 were lower than that of study 2. Cases in study 2, were taking several drugs including antihypertensive agents (calcium channel blocker, 68.8%; angiotensin 2 receptor blockers, 53.1%; angiotensin-converting enzyme inhibitor, 9.4%; alpha blocker, 6.3%; beta blocker, 15.6%; thiazide, 21.9%).

The serum adrenaline and noradrenaline levels were performed after measurement of CAVI. A blood sample was collected from the brachial veins after 10 minutes of bed rest. Serum was stored at -80°C. Adrenaline and noradrenaline were determined by Mitsubishi Chemical Medicine, Tokyo, Japan.

Measurement of cardio–ankle vascular index

CAVI was measured using a VaSera1500 (Fukuda Denshi Co. Ltd., Tokyo, Japan). The methods were described previously.[10] Briefly, cuffs were applied to bilateral upper arms and ankle, with the subject supine and the head held in the midline position. Examinations were performed after resting for 10 min. To detect brachial and ankle pulse waves with cuffs, a low cuff pressure of 30–50 mmHg was used to ensure the minimal effect of cuff pressure on hemodynamics. Blood pressure was measured thereafter.

CAVI is determined by the following equation:

$$CAVI = a\{ (2p/\Delta P) \times \ln(Ps/Pd)P_{WV}^2\} + b,$$

Where Ps and Pd are systolic and diastolic blood pressure, PWV is pulse wave velocity from the origin of aorta to the junction of the tibial artery with the femoral artery, ΔP is Ps-Pd, p is blood density, and a and b are constants. The equation is derived from Bramwell-Hill's equation and the stiffness parameters β, and CAVI was adjusted for blood pressure based on the stiffness parameters β.

The VaSera was equipped with both measurement and calculation systems, and automatically calculated CAVI. We used right CAVI for analysis at this time. The average coefficient of variation of CAVI is 3.8%, which is sufficiently low for clinical usage and indicates that CAVI has good reproducibility.[10]

Statistical analysis

Continuous variables are expressed as mean ± SD. Categorical variables are expressed as a proportion or percentage. Statistical analysis was performed using an SPSS software package (PASW Statistics 18, Chicago, IL, USA). One-way ANOVA was performed to determine whether the differences among groups were statically significant and the Tukey test was used for post hoc comparisons. We examined the association between nominal scale and ⊿CAVI by using the correlation ratio. Pearson's correlation was performed to determine with metric scale and ⊿CAVI. Statistical significance was established at a level of $p < 0.05$.

Results

In study 1, as shown in Figure 3, the mean CAVI was 7.3±1.0 at the 1st measurement. The mean CAVI was 6.8±1.1 at the 2nd time, and 3rd time data was 7.0±1.1. We had a significantly differences between 1st measurement and 2nd measurement ($p < 0.05$). From these results, it is suggested that CAVI might be increased just after a huge earthquake, even though the previous values were not measured.

The mean systolic blood pressure was 122.7±18.5 mmHg at the 1st measurement. The 2nd time it was 123.8±18.3 mmHg, and the 3rd time it was 123.2±18.3 mmHg. The mean diastolic blood pressure was 75.7±15.8 mmHg at the 1st measurement. The 2nd time it was 78.4±15 mmHg. And at the 3rd time it was 76.2±16.3 mmHg. Essentially, there were no changes significantly in the blood pressure between 3 measurements.

The mean heart rate was 70.1±10.5 b.p.m. at the 1st measurement. The 2nd time was 68.3±9.8

b.p.m., and the 3rd time was 74.1±13. 6 b.p.m.. There were no changes significantly in the heart rate between 3 measurements.

In study 1, we investigated the serum adrenaline and noradrenaline levels after the earthquake. Blood test was done following measurement of CAVI. The serum adrenaline level was 18.8 ± 8.6 pg/ml at the 1st measurement. The 2nd time it was 12.9 ± 5.9 pg/ml. And at the 3rd time it was 15. 9 ± 10.0 pg/ml. There was not a significant change in the serum adrenaline level between them. The serum noradrenaline level was 292.9 ± 119.5 pg/ml at the 1st measurement. The 2nd time it was 278.8 ± 185.5 pg/ml. And at the 3rd time it was 301.8 ± 129.7 pg/ml. There was not a significant change in the serum noradrenaline level too.

In addition, we investigated the correlation between ⊿CAVI and the various clinical factors as shown in Table 2. We defined the value that subtracted the 2nd measurement of CAVI from the 1st measurement as ⊿ CAVI. A relationship of ⊿CAVI with blood pressure was not observed.
We examined the association between CAVI and the nominal scale such as the marital status, with or without children and confirmation of the safety of family by using the correlation ratio. The persons who were not able to do confirmation of the safety of family had a significant change of ⊿ CAVI ($P<0.015$). The others did not show a significant change.

In study 2, as shown in Figure 4, the mean CAVI was 8.95±0.76 at the 1st measurement (12 months before the earthquake). The mean CAVI was 8.99±0.83 the 2nd time (6 months before the earthquake). The mean CAVI was 9.34±1.0 at the 3rd time, just after the earthquake. The mean CAVI was 8.83±0.76 at the 4th time (6 months after the earthquake) There were significantly difference between 3rd time and 4th time ($p<0.05$). CAVI was increased just after the earthquake. The mean systolic blood pressure was 133.4±20.2 mmHg at the 1st measurement. The 2nd time was 135.2±22.1 mmHg, the 3rd time was 139.5±22.2 mmHg, and the 4th time was 133±19.8 mmHg. Significant changes were not observed.

The mean diastolic blood pressure was 78.8±11.5 mmHg at the 1st measurement. The 2nd time was 80.5±12.6 mmHg, the 3rd time was 83.2±11.4 mmHg, and the 4th time was 79.5±9.0 mmHg. Significant changes were not observed too.

The mean heart rate was 60.7±13.2 b.p.m. at the 1st measurement. The 2nd time was 66.6±13.2 b.p.m., the 3rd time was 71.8±14.7 b.p.m., and the 4th time was 67.6±12.0 b.p.m.. Significant changes were not observed.
In addition, we investigated the correlation between ⊿CAVI and the clinical parameters as

shown in Table 3. We defined the value that subtracted the 3rd measurement of CAVI from the 2nd measurement as ⊿ CAVI in this time. We were not able to find any parameters that had a significant correlation with ⊿CAVI. And we could not show a significant differences between ⊿CAVI and the various medication.

In 23 patients with the arteriosclerosis risk factors, blood tests were made 4 times. The changes of total cholesterol levels were as follows, 199±38,200±38,200±26 and 192±30 respectively. Triglyceride levels were 131±48,155±74,150±68 and 140±54 respectively. HDL cholesterol levels were as follows,53±14,53±13,54±13 and 53±13 respectively. LDL cholesterol levels were as follows,112±35,112±38,116±35 and 114±23 respectively. Glucose levels were as follows, 121±37,137±56,142±55 and 128±48 respectively. HbA1c (JDS) levels were as follows,6.0±0.5,6.2±1.1,6.3±1.3 and6.3±1.2 respectively. We were not able to find a significant change in these factors.

Discussion

The 2011 earthquake on the Pacific coast of Tohoku (the Great East Japan Earthquake) provided an unusual opportunity to investigate the relationship between emotional stress and arterial stiffness. In both healthy people (Study 1) and the patients with cardiovascular risks (Study 2), CAVI was supposed to be increased just after the earthquake compared with those values before and after a few months. These results suggest that the earthquake increased the stiffness of the artery monitored with CAVI. The factors responsible for this were analyzed in healthy people as shown in Table 1. There were no significant contributing factors for raising CAVI including blood pressure, distance of the diameter from the home town, and sleeping time, except the confirmation of the safety of the relatives. So, unexpectedly, emotional stress seemed to have an important role in stress to the artery.

Systolic and diastolic blood pressure did not change in healthy people and in patients with cardiovascular risk factors. These results suggest that CAVI might be a more sensitive marker for stress from earthquakes on the human body than blood pressure.

The meaning of increased CAVI just after an earthquake, was unclear until now. But, it is reported that cardiovascular events increased after a big disaster. [1-4] We investigated the incidence of death rates in our town. As shown in Figure 5, the number of deaths in our town in the following month (April, 2011) increased compared with those in April during several previous years. And the number of patients, who were hospitalized into our hospital with acute coronary syndrome, takotsubo cardiomyopathy, and cerebral bleeding just after the earthquake, increased by about 40~50%, compared with those during March and April in 2010 and in 2009

(data not shown). Although the precise incidence of cardiovascular disease in the whole town was not reported, the possibility that enhanced CAVI might be related to the high occurrence of cardiovascular diseases, could not be denied.

Acute enhanced arterial stiffness itself might contribute to the rupture of a vulnerable atherosclerotic plaque, and subsequent coronary artery thrombosis.[18-22] The precise mechanism must be investigated in the future.

As for the mechanism by which CAVI was increased, many factors might be involved. It is reported that CAVI decreased, when alpha-adrenoceptor blocker, doxazosin was administered, indicating that CAVI was composed of organic stiffness and smooth muscle cell contraction, and that the latter is controlled by cathecholamine.[23] We investigated the serum cathecholamine levels in healthy volunteers. We could not show the significant difference about them.
It is difficult to explain that CAVI increase caused by the earthquake is a result of the change in serum adrenaline level alone. Besides the sympathetic nerve system, angiotensin II, serotonin, endothelin, nitrogen oxide (NO) and cortisol which is a major stress hormone[24] are known to be involved in vascular stiffness.
The World Cup soccer 2006 has been shown to provoke levels of stress sufficient to increase the incidence of Acute coronary syndrome (ACS). German group reported that stress-induced ACS was associated with a profound increase of inflammatory and vasoconstrictive mediators. Receiver-operating characteristic analysis displayed high performance of both MCP-1 and ET-1 as a measure to discriminate between stress-induced ACS and ACS controls.[25]
Higher cortisol, a major stress hormone, and stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis may also be significant. There are some reports about earthquake and higher cortisol level.[26,27]
Further study is required in cases of natural disaster.

As for blood pressure, remarkable increases in systolic and diastolic blood pressure were not observed in healthy people and also in patients with cardiovascular risk factors. Kario reported that blood pressure was increased in the Hanshin-Awaji big earthquake. And, it has been reported that the alpha-1 selective receptor blocker, doxazosin, decreased blood pressure efficiently.[28] The reason why CAVI was not increased by the Great East Japan Earthquake in the people of our town might be due to the difference of the distances from the epicenter of the earthquake. Our study was performed at 300 km from the epicenter of the earthquake. But, from another point of view, it might be also mentioned that arterial stiffness monitored by CAVI could be changed much more sensitively than the changes in the blood pressure.

Study limitations

1. There are no data for CAVI in the healthy volunteers before the earthquake.
2. The precise number of cardiovascular events in the area were not clear. Only the number of the patients in our hospital was investigated.
3. The death rate in Sakura city in April, 2011 was increased compared with those of previous years, but the cause of those deaths was not clarified.

Conclusions

The Great East Japan Earthquake increased CAVI-monitored arterial stiffness in both healthy people and patients with cardiovascular risk factors, whereas blood pressures did not change significantly. The acute increase in arterial stiffness might be an important risk factor for cardiovascular morbidity and mortality after a big disaster.[8] This finding could play a key role in solving the cause of cardiovascular events after a disaster. The mechanism for it needs further studies.

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Disclosures

All authors declare that they have no conflicts of interest.

Author`s contribution

K. Shimizu as a first author made the literature search with Pub Med, and discussed research design with M. Takahashi and K. Shirai.

K. Shimizu wrote figures, study design, data collection, data analysis, data interpretation and writing.

M. Takahashi contributed to the design and implementation of the study; collection and assembly of data.

K. Shirai contributed to the design and implementation of the study; collection and assembly of data; interpretation of results; and drafting of the report.

The institutional review board of Toho University Sakura Medical Center approved the study, and we began research after obtaining informed consent from all participants in accordance with the Declaration of Helsinki.

We had no statistical consultation or assistance.

All authors have reviewed the article and agree with its contents.

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Table 1. Characteristics of the subjects

Variable	Study 1 Healthy volunteers		Study 2 Patients	
Total number	43		32	
Male/Female	26 / 17		22/10	
Age (years)	33.4±10.5	(30.1–36.6)	64.5±7.4	(61.8-67.2)
Height (cm)	168.0±8.6	(165.4-170.7)	163.5±8.0	(160.7-166.4)
Body weight (kg)	66.3±12.9	(62.3-70.2)	66.8±9.5	(63.4-70.2)
BMI (kg/m^2)	23.4±3.7	(22.3-24.5)	25.0±3.1	(23.8-26.1)
SBP (mmHg)	123.5±15.3	(118.0-129.0)	133.2±19.8	(126.1-140.4)
DBP (mmHg)	75.4±11.9	(71.1-79.7)	79.5±9.0	(76.3-82.8)
HR (beats min^{-1})	75.1±12.0	(70.8-79.4)	67.6±12.0	(63.3-71.9)
Risk factors				
Stroke	0(0)		3(9.4)	
CAD	0(0)		7(21.9)	
Dyslipidemia	0(0)		27(84.4)	
DM	0(0)		14(43.8)	
Current smoker	7(16.3)		10(31.3)	
Previous medication				
Antihypertensive agents	0(0)		27(84.4)	
CCBs	0(0)		22(68.8)	

ARBs	0(0)	17(53.1)
ACE inhibitors	0(0)	3(9.4)
α-Blockers	0(0)	2(6.3)
β-Blockers	0(0)	5(15.6)
Diuretics	0(0)	7(21.9)
Antiplatelet agents	0(0)	14(43.8)
Statins	0(0)	15(46.9)
Antidiabetic agents	0(0)	9(28.1)

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; CAD, coronary artery disease; DM, diabetes millets; CCB, calcium channel blockers; ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme

Data are shown as number of patients (%) or mean ± S.D. (95% C.I.)

Table 2. Correlation between ⊿CAVI and each clinical parameter in Study 1.

Variable	r	p
Age	-0.127	0.416
Height	-0.079	0.613
Body weight	0.024	0.877
BMI	0.087	0.578
⊿SBP	-0.180	0.248
⊿DBP	-0.046	0.768
⊿HR	-0.139	0.373
Sleeping time before examination day	0.115	0.513
Distance from the hometown	0.073	0.643

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate

We defined the value that subtracted the 2nd measurement from the 1st measurement as ⊿CAVI, ⊿SBP, ⊿DBP, and ⊿HR.

Table 3. Correlation between ⊿CAVI and each clinical parameter in Study 2.

Variable	r	p
Age	-0.108	0.557
Height	0.171	0.350
Body weight	0.327	0.068
BMI	0.235	0.196
⊿SBP	0.035	0.851
⊿DBP	0.078	0.671
⊿HR	0.099	0.590

Abbreviations: BMI. body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.
We defined the value that subtracted the 2nd measurement from the 3st measurement as ⊿CAVI, ⊿SBP, ⊿DBP and ⊿HR.

Figure legends

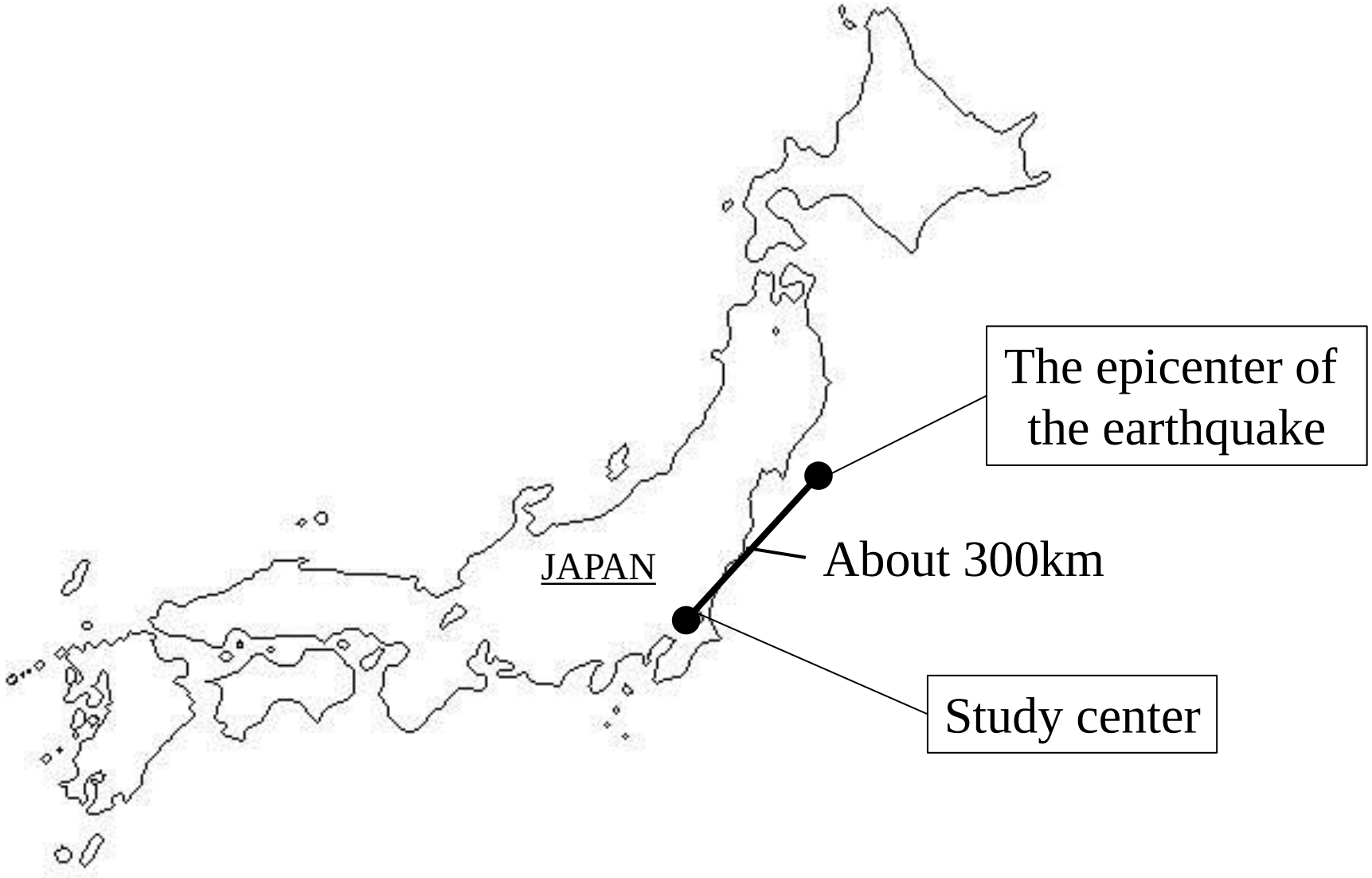
Figure 1: Geographical relationship between the epicenter and the study center. Our study center is located 300 km away from the epicenter.

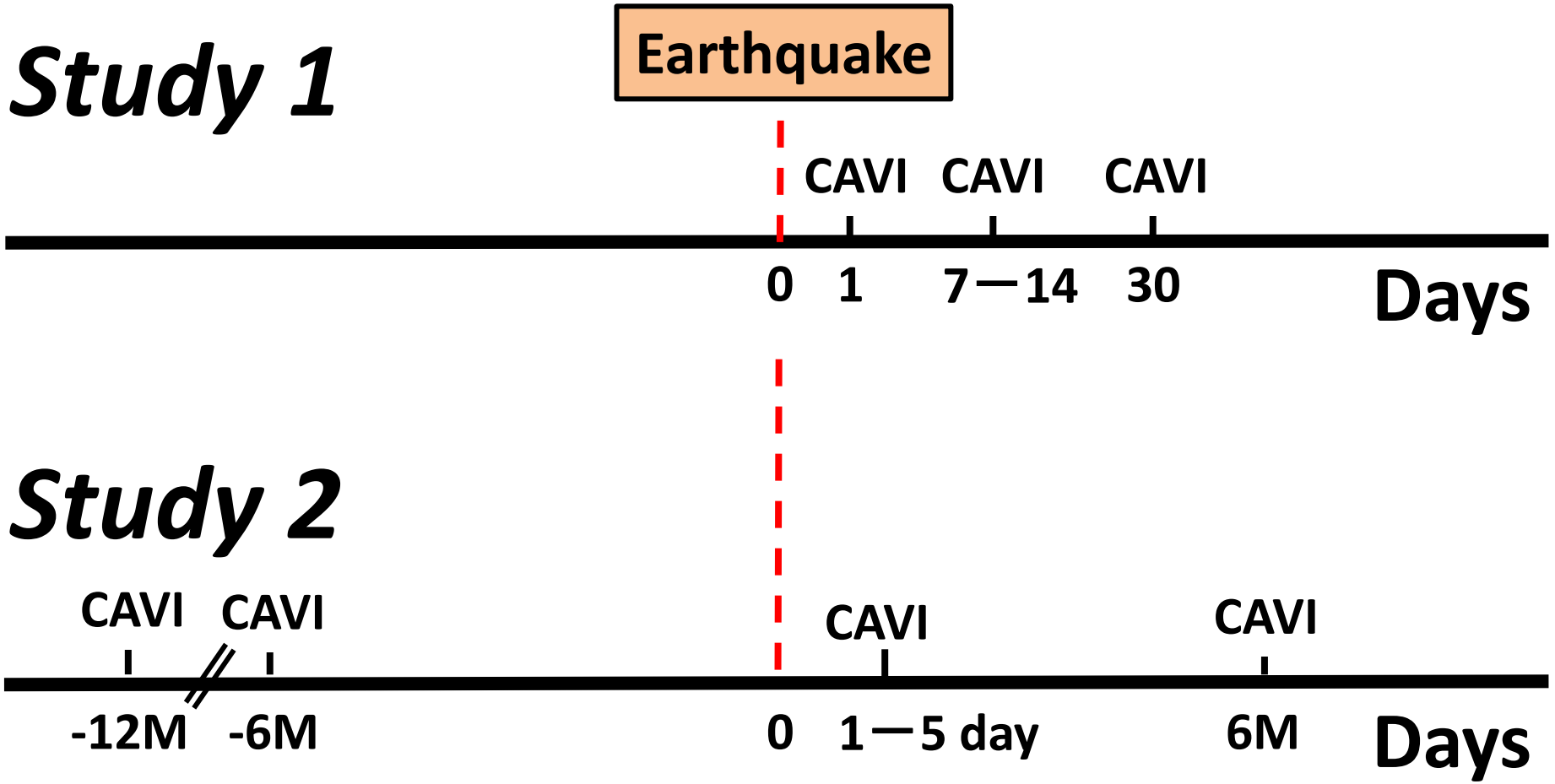
Figure 2: Study design. CAVI, cardio-ankle vascular stiffness index.

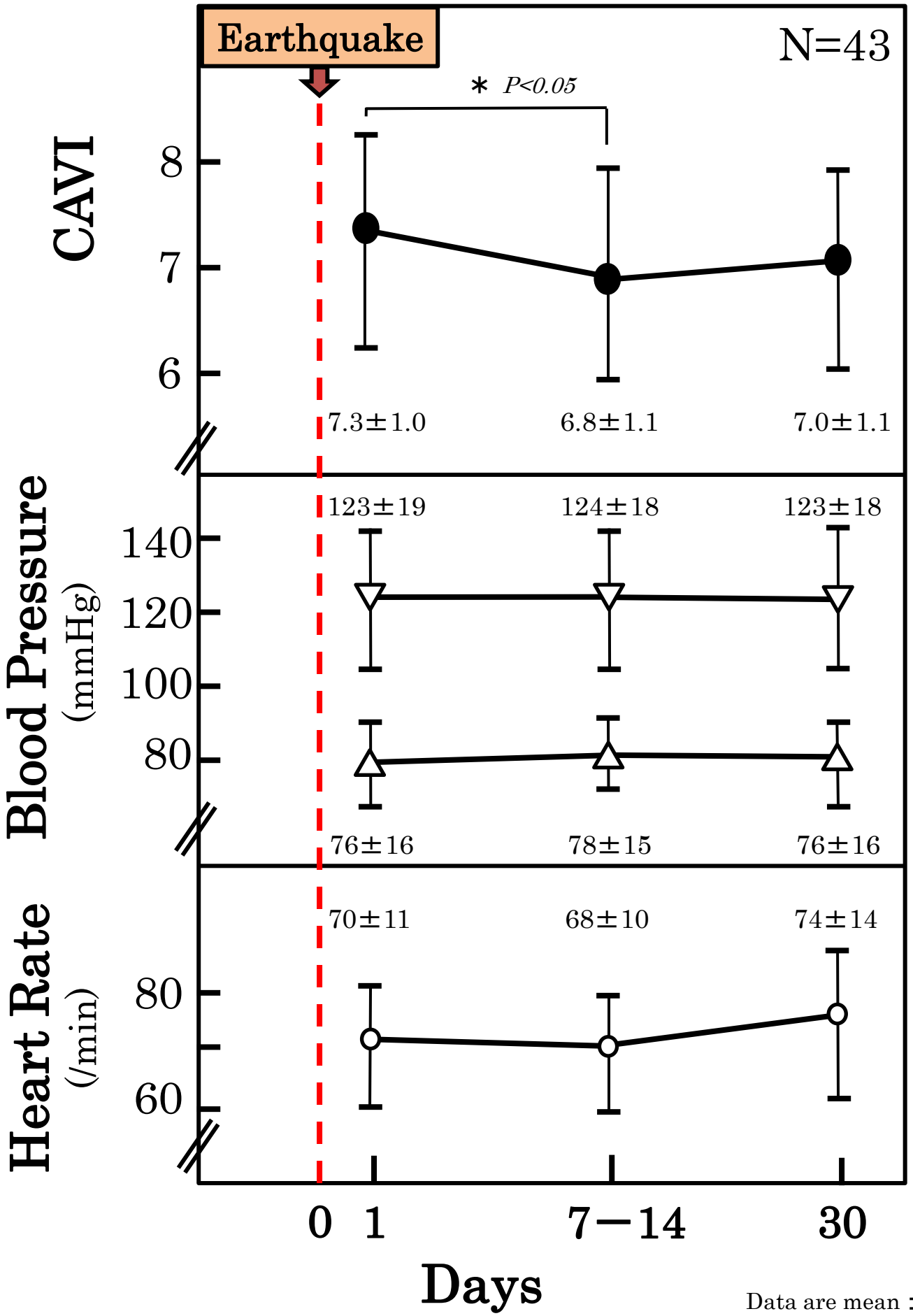
Figure 3: Changes in cardio-ankle vascular stiffness index (CAVI), blood pressure, and heart rate in healthy volunteers.
*p: Tukey-Kramer methods post-one-way repeated measures ANOVA.

Figure 4: Changes in cardio-ankle vascular stiffness index (CAVI), blood pressure, and heart rate in patients with cardiovascular risk factors.
*p: Tukey-Kramer methods post-one-way repeated measures ANOVA.

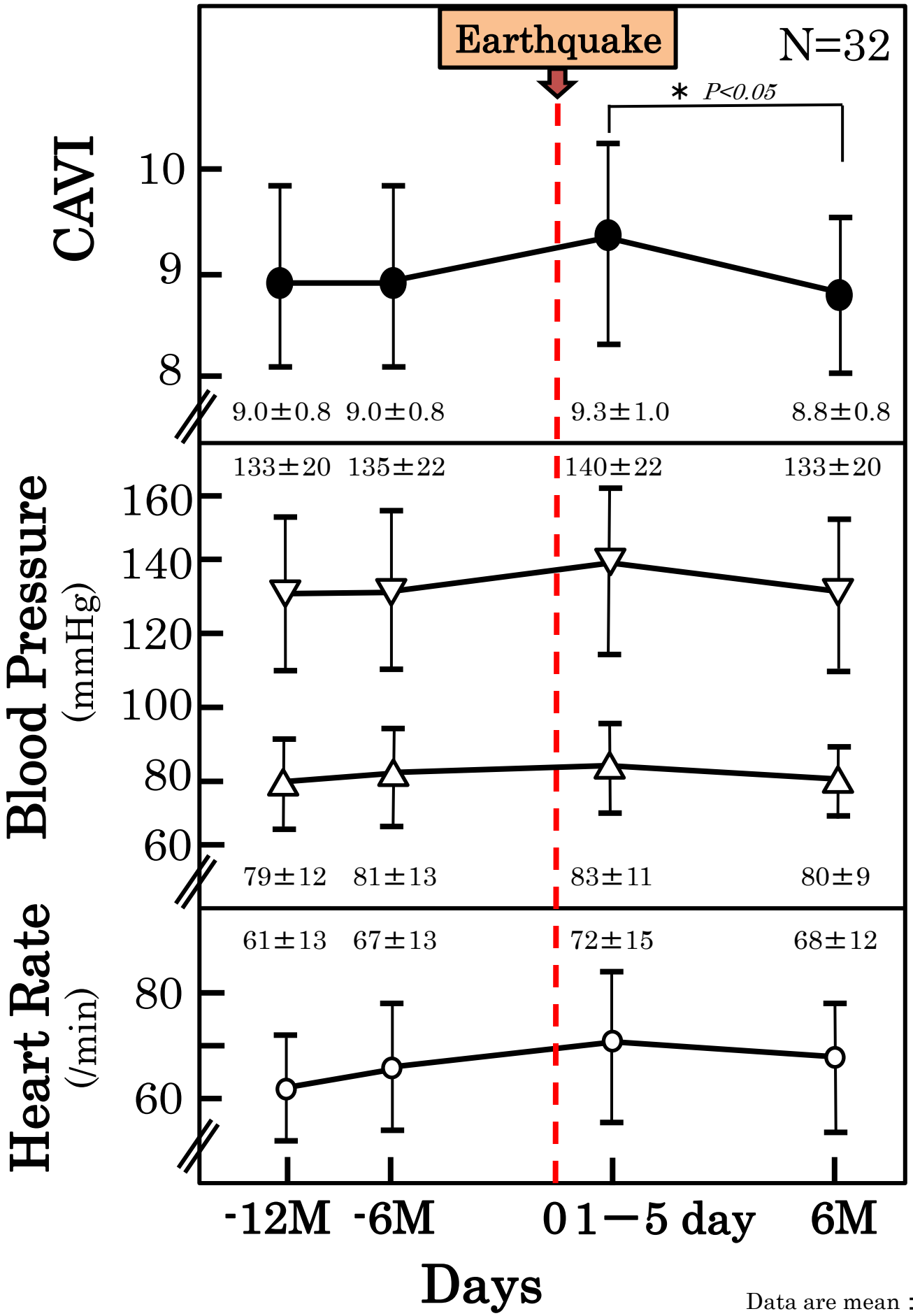
Figure 5: Changes in the fatalities of Sakura city


The epicenter of the earthquake
About 300km
JAPAN
Study center

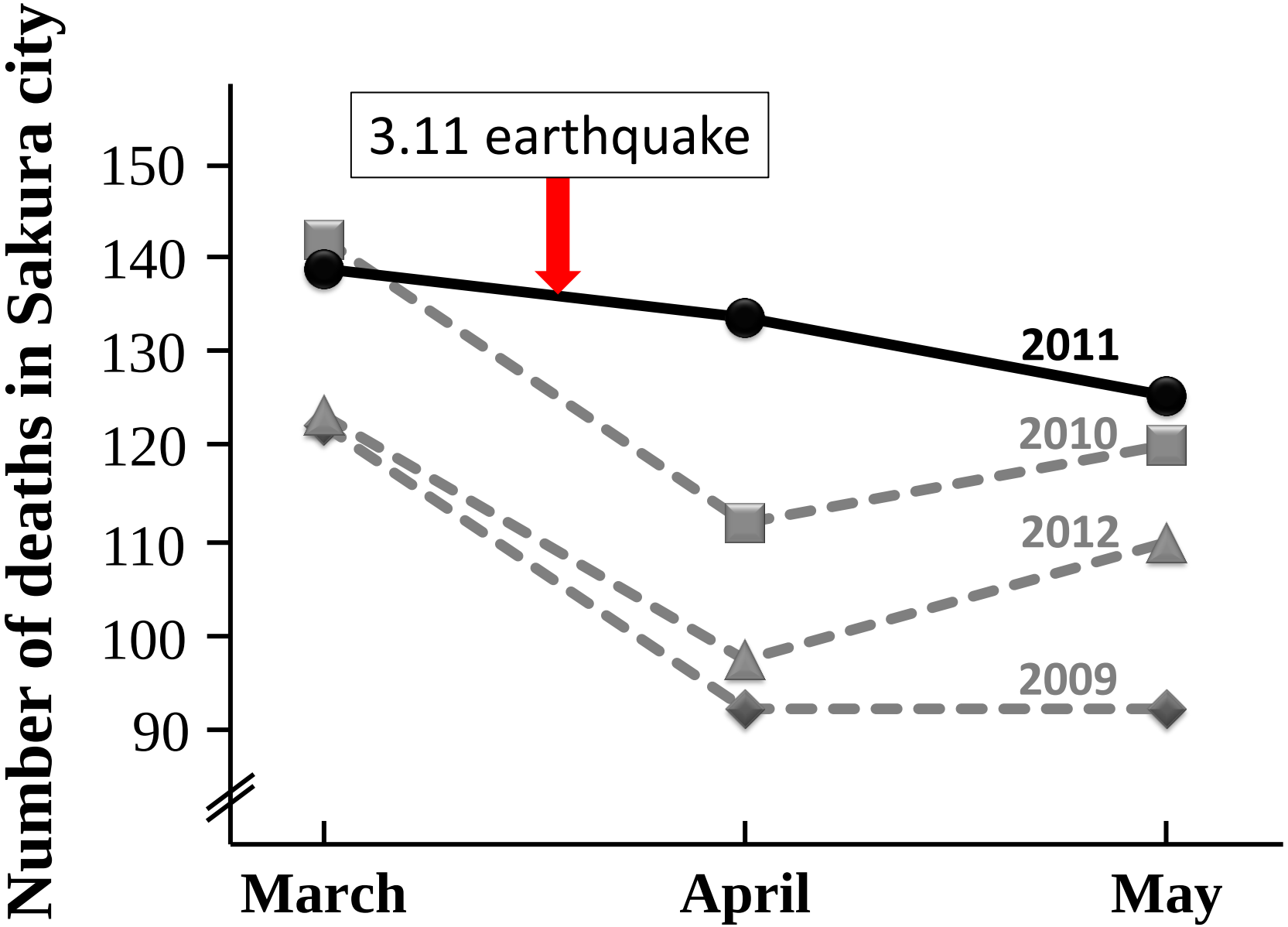

Study 1
Earthquake
CAVI
CAVI
CAVI
0
1
7—14
30
Days
Study 2
CAVI
CAVI
CAVI
CAVI
-12M
-6M
0
1—5 day
6M
Days



Data are mean ±S.D.



Data are mean ±S.D.


Number of deaths in Sakura city
150
140
130
120
110
100
90
3.11 earthquake
2011
2010
2012
2009
March
April
May