Original Article

A Huge Earthquake Hardened Arterial Stiffness Monitored with Cardio-Ankle Vascular Index

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Aims: The incidence of cardiovascular events increases after a large earthquake, but the mechanism is not fully understood. The cardio-ankle vascular index (CAVI) reflects the stiffness of the artery from the origin of the aorta to the ankles and is independent of blood pressure. To determine the effect of a major earthquake on CAVI in healthy volunteers and in patients with cardiovascular risks.

Methods and Results: Our hospital is situated about 300 km from the epicenter of the earthquake that occurred in Japan in 2011. 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 had decreased to 6.8 ± 1.1 (compared to first measurement, p < 0.05). Furthermore, the CAVI value 30 days after the earthquake was 7.0 ± 1.1. The blood pressure did not change during these 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 had decreased to 8.83 ± 0.76 6 months later (compared to after the earthquake, p < 0.05). The blood pressure increased slightly at the time of earthquake, but was not significantly different from before the earthquake.

Conclusions: CAVI increased in healthy people and also in patients with cardiovascular risks just after the earthquake, even far 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 earthquake1-3). When the Hanshin-Awaji earthquake, magnitude 7.2, 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 subjects4, 5). Another study reported a direct association between a measure of β2-adrenergic receptor functioning and stress-induced hemostatic changes6). Acute mental stress may trigger a hypercoagulable state, evidenced by increasing thrombin activity and by increasing fibrin turnover6). 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 atherosclerosis and the contraction of arterial smooth muscles. It is reported that increased arterial stiffness is an important risk factor for cardiovascular morbidity and mortality7-9). 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 the measuring time. In 2006, a new arterial wall stiffness parameter was developed, the cardio-ankle vascular stiffness index (CAVI). 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.
nation day, the distance from the epicenter to the hometown, marital status, children, and confirmation of the safety of the family.

The second study group (Study 2) included 32 patients with cardiovascular risk factors from 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 in study 1 were lower than in study 2. Patients 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%).

Serum adrenaline and noradrenaline were measured after 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. Briefly, cuffs were applied to bilateral upper arms and ankles, 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.

Subjects and Methods

The study design is shown in Fig. 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: between day 7 to 14; 3rd time: day 30). After measuring CAVI, we performed a blood test and questionnaire survey and investigated the serum adrenalin and noradrenaline levels. The contents of the questionnaire survey included sleeping time before the examination, the distance from the epicenter to the hometown, marital status, children, and confirmation of the safety of the family.

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 >6 in 3 days. As shown in Fig. 1, our institute (Toho University Sakura Medical Center Hospital) was situated about 300 km from the epicenter. The building was shaken strongly and part of a wall collapsed; therefore, an unusual crisis occurred in our town.

To examine the possibility that arterial stiffness would have increased, we started to measure vascular stiffness in healthy volunteers and also in patients with cardiovascular risks using CAVI just after the earthquake. For the patients, those whose CAVI values had been measured twice in the previous year were selected. Blood pressure change was also examined in both groups.

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

Fig. 2. Study design. CAVI, cardio-ankle vascular stiffness index.
CAVI Reflects Emotional Stress on the Artery

CAVI is determined by the following equation:

$$\text{CAVI} = a \cdot \left( \frac{2 \rho}{\Delta P} \times \ln \left( \frac{P_s}{P_d} \right) \right) \cdot PWV^2 + b,$$

Where $P_s$ and $P_d$ are systolic and diastolic blood pressure, $PWV$ is pulse wave velocity from the origin of the aorta to the junction of the tibial artery with the femoral artery, $\Delta P$ is $P_s - P_d$, $\rho$ is blood density, and $a$ and $b$ are constants. The equation is derived from Bramwell-Hill’s equation and the stiffness parameter $\beta$, and CAVI was adjusted for blood pressure based on stiffness parameter $\beta$.

The VaSera was equipped with both measurement and calculation systems, and automatically calculated CAVI. Right CAVI was used for analysis. The average coefficient of variation of CAVI is 3.8%, which is sufficiently low for clinical usage and indicates that CAVI has good reproducibility16.

Statistical Analysis

Continuous variables are expressed as the 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 the nominal scale and $\Delta$CAVI using the correlation ratio. Pearson’s correlation was performed to determine with a metric scale and $\Delta$CAVI. Statistical significance was established at a level of $p<0.05$.

Results

In study 1, as shown in Fig. 3, the mean CAVI
The 1st measurement, 68.3 ± 9.8 b.p.m. the 2nd time, and 74.1 ± 13.6 b.p.m. the 3rd time. There were no significant changes in the heart rate among the 3 measurements.

In study 1, we investigated serum adrenaline and noradrenaline levels after the earthquake. A blood test was performed following CAVI measurement. Serum adrenaline was 18.8 ± 8.6 pg/mL at the 1st measurement, 12.9 ± 5.9 pg/mL the 2nd time, and 15.9 ± 10.0 pg/mL the 3rd time. There was no significant change in serum adrenaline among these measurements. Serum noradrenaline was 292.9 ± 119.5 pg/mL at the 1st measurement, 278.8 ± 185.5 pg/mL the 2nd time, and 301.8 ± 129.7 pg/mL the 3rd time. There was also no significant change in serum noradrenaline.

was 7.3 ± 1.0 at the 1st measurement, 6.8 ± 1.1 the 2nd time, and 7.0 ± 1.1 the 3rd time. There were significant differences between 1st and 2nd measurements (p < 0.05). These results suggested that CAVI might increase 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, 123.8 ± 18.3 mmHg the 2nd time, and 123.2 ± 18.3 mmHg the 3rd time. The mean diastolic blood pressure was 75.7 ± 15.8 mmHg at the 1st measurement, 78.4 ± 15 mmHg the 2nd time, and 76.2 ± 16.3 mmHg the 3rd time. Essentially, there were no significant changes in the blood pressure among the 3 measurements.

The mean heart rate was 70.1 ± 10.5 b.p.m. at the 1st measurement, 68.3 ± 9.8 b.p.m. the 2nd time, and 74.1 ± 13.6 b.p.m. the 3rd time. There were no significant changes in the heart rate among the 3 measurements.

In study 1, we investigated serum adrenaline and noradrenaline levels after the earthquake. A blood test was performed following CAVI measurement. Serum adrenaline was 18.8 ± 8.6 pg/mL at the 1st measurement, 12.9 ± 5.9 pg/mL the 2nd time, and 15.9 ± 10.0 pg/mL the 3rd time. There was no significant change in serum adrenaline among these measurements. Serum noradrenaline was 292.9 ± 119.5 pg/mL at the 1st measurement, 278.8 ± 185.5 pg/mL the 2nd time, and 301.8 ± 129.7 pg/mL the 3rd time. There was also no significant change in serum noradrenaline.
In addition, we investigated the correlation between \( \triangle \text{CAVI} \) and the various clinical factors, as shown in Table 2. \( \triangle \text{CAVI} \) was defined by subtracting the 2nd measurement of CAVI from the 1st measurement. No relationship of \( \triangle \text{CAVI} \) with blood pressure was observed.

The association was examined between CAVI and the various clinical factors, such as the marital status, with or without children and confirmation of the safety of family by using the correlation ratio.

Individuals who were not able to confirm the safety of their family had a significant change of \( \triangle \text{CAVI} \) \((p < 0.015) \). The others did not show a significant change.

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

The mean diastolic blood pressure was 78.8 ± 11.5 mmHg at the 1st measurement, 80.5 ± 12.6 mmHg the 2nd time, 83.2 ± 11.4 mmHg the 3rd time, and 79.5 ± 9.0 mmHg the 4th time. No significant changes were observed.

The mean heart rate was 60.7 ± 13.2 b.p.m. at the 1st measurement, 66.6 ± 13.2 b.p.m. the 2nd time, 71.8 ± 14.7 b.p.m. the 3rd time, and 67.6 ± 12.0 b.p.m. the 4th time. No significant changes were observed.

In addition, we investigated the correlation between \( \triangle \text{CAVI} \) and the clinical parameters, as shown in Table 3. \( \triangle \text{CAVI} \) was defined by subtracting the 3rd measurement of CAVI from the 2nd measurement. No parameters were found that had a significant correlation with \( \triangle \text{CAVI} \), and there were no significant differences between \( \triangle \text{CAVI} \) and the various medications.

In 23 patients with arteriosclerosis risk factors, blood tests were performed 4 times. The changes of total cholesterol were as follows: 199 ± 38, 200 ± 38, 200 ± 26 and 192 ± 30, respectively.

Triglyceride was 131 ± 48, 155 ± 74, 150 ± 68 and 140 ± 54, respectively. HDL cholesterol was as follows: 53 ± 14, 53 ± 13, 54 ± 13 and 53 ± 13, respectively. LDL cholesterol was as follows: 112 ± 35, 112 ± 38, 116 ± 35 and 114 ± 23, respectively. Glucose was as follows: 121 ± 37, 137 ± 56, 142 ± 55 and 128 ± 48, respectively. HbA1c (JDS) was as follows: 6.0 ± 0.5, 6.2 ± 1.1, 6.3 ± 1.3 and 6.3 ± 1.2, respectively. No significant change was found 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 patients with cardiovascular risks (Study 2), CAVI was thought to have increased just after the earthquake compared with the values before and after a few months. The results suggest that the earthquake increased the stiffness of the artery monitored with CAVI. The factors responsible were analyzed in healthy people, as shown in Table 1. There were no significant contributing factors raising CAVI, including blood pressure, distance of the epicenter from the home town, and sleeping time, except for confirmation of the safety of relatives. Unexpectedly, emotional stress seemed to play an important role in stress on 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 has been reported that cardiovascular events increased after a major disaster\(^{1-10}\). We therefore investigated the incidence of death rates in our town. As shown in Fig. 5, the number of deaths in our town in the following

<table>
<thead>
<tr>
<th>Variable</th>
<th>( r )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.127</td>
<td>0.416</td>
</tr>
<tr>
<td>Height</td>
<td>-0.079</td>
<td>0.613</td>
</tr>
<tr>
<td>Weight</td>
<td>0.024</td>
<td>0.877</td>
</tr>
<tr>
<td>BMI</td>
<td>0.087</td>
<td>0.578</td>
</tr>
<tr>
<td>( \triangle \text{SBP} )</td>
<td>-0.180</td>
<td>0.248</td>
</tr>
<tr>
<td>( \triangle \text{DBP} )</td>
<td>-0.046</td>
<td>0.768</td>
</tr>
<tr>
<td>( \triangle \text{HR} )</td>
<td>-0.139</td>
<td>0.373</td>
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<tr>
<td>Sleeping time before examination day</td>
<td>0.115</td>
<td>0.513</td>
</tr>
<tr>
<td>Distance from the hometown</td>
<td>0.073</td>
<td>0.643</td>
</tr>
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</table>

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 \( \triangle \text{CAVI} \), \( \triangle \text{SBP} \), \( \triangle \text{DBP} \), and \( \triangle \text{HR} \).
As for the mechanism by which CAVI increased, many factors might be involved. It is reported that CAVI decreased when alpha-adrenoceptor blocker, doxazosin, was administered, indicating that CAVI involves organic stiffness and smooth muscle cell contraction, and that the latter is controlled by catecholamine\(^2\). We investigated serum catecholamine levels in healthy volunteers but found no significant difference.

It is difficult to state that the CAVI increase caused by the earthquake is a result of the change in the serum adrenaline level alone. In addition to the sympathetic nerve system, angiotensin \(\text{II}\), serotonin, endothelin, nitrogen oxide (NO) and cortisol, which

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**Fig. 4.** Changes in cardio-ankle vascular stiffness index (CAVI), blood pressure, and heart rate in patients with cardiovascular risk factors.

*\(^p\): Tukey-Kramer post-one-way repeated measures ANOVA.

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<table>
<thead>
<tr>
<th>Days</th>
<th>CAVI</th>
<th>Blood Pressure (mmHg)</th>
<th>Heart Rate (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5 day</td>
<td>9.3±1.0</td>
<td>135±22</td>
<td>83±11</td>
</tr>
<tr>
<td>6M</td>
<td>8.8±0.8</td>
<td>133±20</td>
<td>80±9</td>
</tr>
<tr>
<td>1-5 day</td>
<td>9.0±0.8</td>
<td>140±22</td>
<td>72±15</td>
</tr>
<tr>
<td>-12M</td>
<td>9.0±0.8</td>
<td>133±20</td>
<td>67±13</td>
</tr>
<tr>
<td>-6M</td>
<td>9.0±0.8</td>
<td>135±22</td>
<td>61±13</td>
</tr>
</tbody>
</table>

Data are mean ±S.D.

month (April, 2011) increased compared with in April in several previous years. In addition, the number of patients who were admitted to our hospital with acute coronary syndrome, takotsubo cardiomyopathy, and cerebral bleeding just after the earthquake, increased by about 40-50% compared with March and April in 2010 and 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 rejected.

Acute enhanced arterial stiffness itself might contribute to the rupture of vulnerable atherosclerotic plaque, and subsequent coronary artery thrombosis\(^{18-22}\). The precise mechanism must be investigated in the future.
CAVI reflects emotional stress on the artery

Table 3. Correlation between $\Delta$CAVI and each clinical parameter in Study 2

<table>
<thead>
<tr>
<th>Variable</th>
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<th>$p$</th>
</tr>
</thead>
<tbody>
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<td>Age</td>
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<tr>
<td>Height</td>
<td>0.171</td>
<td>0.350</td>
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<tr>
<td>Weight</td>
<td>0.327</td>
<td>0.068</td>
</tr>
<tr>
<td>BMI</td>
<td>0.235</td>
<td>0.196</td>
</tr>
<tr>
<td>ΔSBP</td>
<td>0.035</td>
<td>0.851</td>
</tr>
<tr>
<td>ΔDBP</td>
<td>0.078</td>
<td>0.671</td>
</tr>
<tr>
<td>ΔHR</td>
<td>0.099</td>
<td>0.590</td>
</tr>
</tbody>
</table>

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 3rd measurement as $\Delta$CAVI, $\Delta$SBP, $\Delta$DBP and $\Delta$HR.

is a major stress hormone$^{24}$, are known to be involved in vascular stiffness.

The soccer World Cup in 2006 was shown to provoke levels of stress sufficient to increase the incidence of acute coronary syndrome (ACS). A German group reported that stress-induced ACS was associated with a profound increase of inflammatory and vasoconstrictive mediators. Receiver-operating characteristic analysis displayed the high performance of both MCP-1 and ET-1 as measures 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 have been reports about earthquakes and a higher cortisol level$^{26,27}$. Further study is required in cases of natural disaster.

As for blood pressure, marked increases in systolic and diastolic blood pressure were not observed in healthy people or in patients with cardiovascular risk factors. Kario reported that blood pressure increased after 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 different distances from the epicenter of the earthquake. Our study was performed 300 km from the epicenter; however, from another point of view, it should also be mentioned that arterial stiffness monitored by CAVI can change much more sensitively than changes in 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 was not clear. Only the number of patients in our hospital was investigated.
3. The death rate in Sakura city in April, 2011 was increased compared with previous years, but the causes of those deaths were 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 pressure did not change significantly. The acute increase in arterial stiffness might be an important risk factor for cardiovascular morbidity and mortality after a major disaster$^{8}$. This finding could play a key role in solving the cause of cardiovascular events after a disaster. The mechanism needs further study.

Acknowledgments

We thank the staff of Toho University Sakura Medical Center for cooperating with our study during the confusing situation after the Great East Japan Earthquake.

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Disclosures

All authors declare that they have no conflicts of interest.

Authors’ Contributions

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

K. Shimizu developed the 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 report.

We had no statistical consultation or assistance.

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

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