

Research Article

Influence of the 2004 Mid Niigata Prefecture Earthquake in Japan on Plasma Brain Natriuretic Peptide Concentrations

Keizo Tsuchida, MD

Tsuchida Clinic of Internal Medicine and Cardiology, Niigata-ken, Japan

Kazuhiko Tanabe, MD

Tanabe Clinic, Niigata-ken, Japan

ABSTRACT

Background: The 2004 Mid Niigata Prefecture Earthquake struck the Chuetsu district of Niigata Prefecture in Japan on October 23, 2004 (6.8 on the Richter scale, 13 km in depth), following a lot of strong aftershocks for 20 days. This study investigated the change of plasma brain natriuretic peptide (BNP) on the earthquake, and the relationship between earthquake-induced stress and BNP.

Methods: This study included 529 outpatients (mean age: 69.8 years), whose BNP was measured within 4 weeks after the earthquake and additional 4 weeks after the former by immunoradiometric assay (Sionogi), and compared to BNP before the earthquake.

Results: The mean BNP 0-4 weeks after the earthquake was increased significantly by 18 pg/ml compared to BNP before the earthquake (Δ BNP), and fell to the former level 4-8 weeks after the earthquake (56→74→60 pg/ml, $p<0.0001$). BNP was increased significantly in patients with cardiac diseases ($n=218$)

(101→129→109 pg/ml, $p<0.0001$) and also in patients without cardiac diseases ($n=311$) (25→35→25 pg/ml, $p<0.0001$) and furthermore in healthy persons ($n=10$) (9→29→8 pg/ml, $p<0.0001$). BNP was increased not significantly in patients taking beta-blocker ($n=13$) (Δ BNP 19 pg/ml: 19→39→20 pg/ml, $p=0.0685$) but significantly in patients not taking it ($n=61$) (Δ BNP 25 pg/ml: 20→45→22 pg/ml, $p<0.0001$). Further, blood pressure, pulse rate and D-dimer were significantly increased right after the earthquake.

Conclusion: These results suggest that emotional and physical stress on earthquake stimulates sympathetic nerve system, and subsequently elevates blood pressure and heart rate, and so increases BNP levels. BNP is useful for evaluation of cardiac overload and dysfunction due to emotional and physical stress after the earthquake.

Keywords: Earthquake, Brain natriuretic peptide, Natural disaster, Stress, Sympathetic nerve system, D-dimer.

Introduction

On October 23, 2004 at 17:56, the 2004 Mid Niigata Prefecture Earthquake (6.8 on the Richter scale, 13 km in depth: Japan Meteorological Agency) struck the Chuetsu district of Niigata Prefecture in Japan, following a lot of strong aftershocks for 20 days. The earthquake casualties included 68 deaths and 4800 injuries. It has been estimated that over 100,000 people chose to take refuge in their cars or temporary shelters.

Earthquake-induced stress contributes to cardiovascular disease, such as coronary heart disease, stroke, heart failure, arrhythmia and so on.^{1,2} Plasma brain natriuretic peptide (BNP) concentration is known to have a positive correlation with the left ventricular end-diastolic pressure (LVEDP) and a negative correlation with the left ventricular ejection fraction (LVEF), so BNP level is measured in order to evaluate left ventricular function.³⁻⁶ BNP is now recognized as a reliable marker of cardiac dysfunction and cardiac overload.⁷⁻⁹ It seems that earthquake-induced stress has an influence on BNP level, but the change in BNP level on earthquake is unknown.

This study investigated the change in BNP level on the 2004 Mid Niigata Prefecture Earthquake in Japan, and

examined the relationship between earthquake-induced stress and BNP.

Materials and Methods

Subjects and Methods

This study included 529 outpatients, 232 men and 297 women (mean age 69.8 ± 11.5 years) in Tsuchida Clinic (located about 20 km from epicenter), whose BNP levels were measured within four weeks after the earthquake (0 to 4 weeks after the earthquake) and an additional four weeks after the former (4 to 8 weeks after the earthquake), and compared to BNP within one year prior to the earthquake (before the earthquake). Furthermore, BNP levels of 10 healthy persons were measured on 1, 2, 4, 8 weeks after the earthquake, and compared to BNP levels before the earthquake (at health check up). BNP levels were measured by the Immunoradiometric Assay method (IRMA) using a Shionoria BNP assay kit for the blood sample taken in a sitting position. The change of BNP level (Δ BNP) was calculated as : Δ BNP= (BNP within four weeks after the earthquake) – (BNP before the earthquake). In addition, blood pressure and pulse rate were measured simultaneously in 515 of 529 patients. And D-dimer levels were also measured simultaneously by a latex agglutination D-dimer testing (NS AUTO D-Dimer, Naska Co., Ltd.). Furthermore, we investigated the number of

Table 1: Characteristic of the study population.

Number of patients	529
Age (yr, mean±SD)	69.8±11.5
Men	232 (44%)
Underlying cardiovascular disease	218 (41%)
Hypertension	349 (66%)
Diabetes Mellitus	160 (30%)
Hyperlipidemia	213 (40%)
Previous stroke	22
Chronic heart failure	39
Hypertrophic cardiomyopathy	13
Dilated cardiomyopathy	5
Coronary heart disease	49
Old myocardial infarction	29
Angina pectoris	20
Valvular disease	35
Chronic atrial fibrillation	83
Paroxysmal atrial fibrillation	42
Previous pacemaker implantation op.	20
Paroxysmal supraventricular tachycardia	8

cardiovascular deaths and all-cause deaths before and after the earthquake for 3123 patients of the cohort study (named "BNP and Cardiovascular Events in General Practice").¹⁰

The patient characteristics are summarized in Table 1. No underlying cardiac disease could be demonstrated in 311 patients (ex. hypertension, diabetes mellitus, dyslipidemia without cardiac diseases), whereas underlying cardiac diseases were found in 218 patients: chronic heart failure (CHF) in 39 (CHF was defined when congestive heart failure had been diagnosed based on "Framingham criteria" up to that time); hypertrophic cardiomyopathy in 13; dilated cardiomyopathy in 5; old myocardial infarction in 29; angina pectoris in 20; valvular disease in 35; chronic atrial fibrillation in 83; paroxysmal atrial fibrillation in 42; previous pacemaker implantation op. in 20; paroxysmal supraventricular tachycardia in 8, and so on; including some patients with more than one disease. The study protocol was approved by the Ethic Committee of Tsuchida Clinic of Internal Medicine and Cardiology.

Statistical analysis

Values are shown as mean ± standard error (SE). BNP values were transformed into natural logarithms (ln BNP) to form normal distribution for analysis. Using the ln BNP, multi-comparison analyses were performed at three time points (before the earthquake, 0 to 4 weeks after the earthquake, 4 to 8 weeks after the earthquake) with Scheffe's analysis after one-way analysis of variance. Analysis for the change of BNP level (Δ BNP) about gender and age was performed using unpaired t-test. The relationship between the change of blood pressure and pulse rate and the change of BNP level, and between the change of D-dimer and the change of BNP level was performed using correlation and covariance analysis. All analyses were performed with the use of StatView (Version 5.0). Significance

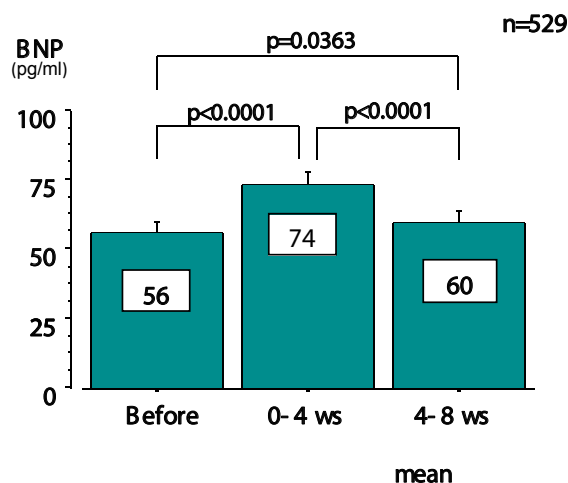


Figure 1: BNP level changes after the earthquake of a total of 529 patients. BNP : brain natriuretic peptide Before : within one year prior to the earthquake (before the earthquake) 0-4 ws : within four weeks after the earthquake (0 to 4 weeks after the earthquake) 4-8 ws : additional four weeks after the former (4 to 8 weeks after the earthquake)

* Repeated measures analysis of variance with Scheffe's analysis (BNP values were transformed into natural logarithms)

levels were $P < 0.05$ in these analyses.

Results

BNP level changes of a total of 529 patients after the earthquake

BNP level changes of a total of 529 patients after the earthquake are shown in Figure 1. The mean Δ BNP was 18 pg/ml (calculated from the values before the earthquake of 56 ± 4 pg/ml, 0-4 weeks after the earthquake of 74 ± 5 , and 4-8 weeks after the earthquake of 60 ± 4 pg/ml), showing a significant increase ($p < 0.0001$) 0-4 weeks after the earthquake and resumption of the former levels 4-8 weeks after the earthquake.

Regarding gender, 232 men had Δ BNP of 18 pg/ml ($64 \pm 8 \rightarrow 80 \pm 8 \rightarrow 69 \pm 8$ pg/ml, $p < 0.0001$), while 297 women had Δ BNP of 19 pg/ml ($50 \pm 4 \rightarrow 69 \pm 5 \rightarrow 53 \pm 4$ pg/ml, $p < 0.0001$). But Δ BNP showed no significant difference between men and women. Furthermore, as to age, 312 patients over 70 years old had Δ BNP of 20 pg/ml ($72 \pm 7 \rightarrow 93 \pm 7 \rightarrow 77 \pm 3$ pg/ml, $p < 0.0001$), while 217 patients under 70 years old had Δ BNP of 14 pg/ml ($33 \pm 3 \rightarrow 47 \pm 4 \rightarrow 36 \pm 2$ pg/ml, $p < 0.0001$). But Δ BNP showed no significant difference between over 70 years old and under 70 years old.

BNP level changes in patients with or without cardiac diseases and in healthy persons

Figure 2 showed that 218 patients with cardiac diseases had significant Δ BNP of 27 pg/ml ($100 \pm 9 \rightarrow 128 \pm 10 \rightarrow 108 \pm 9$ pg/ml, $p < 0.0001$), whereas 311 patients without cardiac diseases also had significant Δ BNP of 11 pg/ml ($25 \pm 1 \rightarrow 35 \pm 1 \rightarrow 25 \pm 1$ pg/ml, $p < 0.0001$). Investigating each cardiac disease (valvular disease, hypertrophic cardiomyopathy, old myocardial infarction and atrial fibrillation), BNP levels in almost all patients with cardiac diseases except CHF patients increased

significantly 0-4 weeks after the earthquake, and returned nearly to the former level 4-8 weeks after the earthquake (valvular disease: $135 \pm 20 \rightarrow 172 \pm 27 \rightarrow 152 \pm 21$ pg/ml, hypertrophic cardiomyopathy: $168 \pm 36 \rightarrow 238 \pm 48 \rightarrow 182 \pm 36$ pg/ml, old myocardial infarction: $46 \pm 7 \rightarrow 76 \pm 18 \rightarrow 55 \pm 8$ pg/ml, atrial fibrillation: $143 \pm 11 \rightarrow 167 \pm 14 \rightarrow 148 \pm 11$ pg/ml).

In the patients with CHF, significant elevation of BNP level remained still 4-8 weeks after the earthquake ($186 \pm 42 \rightarrow 234 \pm 43 \rightarrow 221 \pm 44$ pg/ml: Δ BNP 48 pg/ml, $p=0.0043$), and BNP fell to the former level for five months (Figure 3). Of 39 CHF patients, heart failure became worse in 10, and cerebral infarction was developed in 3, acute coronary syndrome in 3 and sudden death in one, during 6 months after the earthquake.

The course of BNP level changes in 10 healthy persons is shown in Figure 4. Ten healthy persons had significant Δ BNP of 20 pg/ml (9 ± 2 pg/ml $\rightarrow 29 \pm 2$ pg/ml, $p<0.0001$) and almost resumption of the former levels 2 weeks after the earthquake (11 ± 2 pg/ml, $p<0.0001$).

Influence of medication of beta-blocker on BNP level change after the earthquake

In the patients with hypertension who's BNP levels were less than 40 pg/ml before the earthquake, BNP level was increased

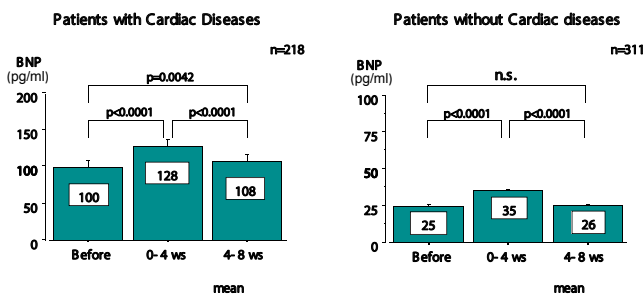


Figure 2: BNP level changes in patients with or without cardiac diseases.

* Repeated measures analysis of variance with Scheffe's analysis (BNP values were transformed into natural logarithms)

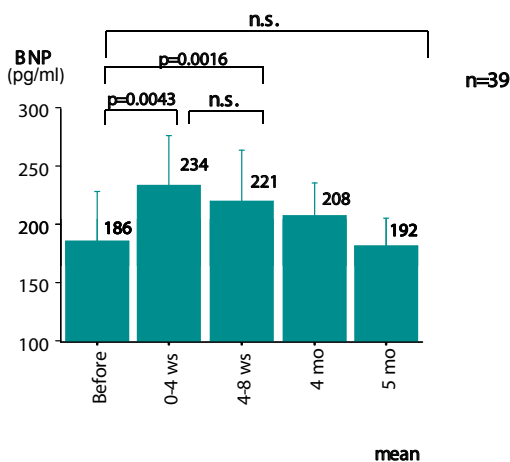


Figure 3: BNP level changes after the earthquake of 39 patients with CHF.

* Repeated measures analysis of variance with Scheffe's analysis (BNP values were transformed into natural logarithms)

significantly in patients not taking beta-blocker ($n=61$) (Δ BNP 25 pg/ml: $20 \pm 1 \rightarrow 45 \pm 4 \rightarrow 22 \pm 2$ pg/ml, $p<0.0001$), but not significantly in patients taking it ($n=13$) (Δ BNP 19 pg/ml: $19 \pm 3 \rightarrow 39 \pm 8 \rightarrow 20 \pm 4$ pg/ml, $p=0.0685$) (Figure 5).

Changes in Blood Pressure, Pulse Rate and D-dimer levels (Figure 6)

515 patients had significant elevation of systolic blood pressure of 4.7 mmHg (mean \pm SD: 136.6 ± 16.9 mmHg $\rightarrow 141.2 \pm 19.2$ mmHg $\rightarrow 135.4 \pm 18.2$ mmHg, $p<0.0001$), diastolic blood pressure of 4.8 mmHg (74.1 ± 10.1 mmHg $\rightarrow 78.8 \pm 10.8$ mmHg $\rightarrow 75.2 \pm 10.9$ mmHg, $p<0.0001$) and pulse rate of 1.6/min (66.8 ± 8.4 /min $\rightarrow 68.4 \pm 9.0$ /min $\rightarrow 67.7 \pm 8.2$ /min, $p<0.0001$). In addition, we analyzed to investigate the relationship between the change of blood pressure and pulse rate and the change of BNP level, but no significant correlation was seen.

Furthermore D-dimer increased significantly 0-4 weeks after the earthquake, and decreased 4-8 weeks after the earthquake (mean \pm SD: $0.34 \pm 0.51 \rightarrow 0.41 \pm 0.72 \rightarrow 0.39 \pm 0.54$, $p=0.0021$). But there was not significant correlation between the change of D-dimer and the change of BNP.

The number of cardiovascular deaths and all-cause deaths after the earthquake

The number of cardiovascular deaths within 6 months after the earthquake increased to 13, compared with 7 (5-9) in every 6 months of the prior 2 years before the earthquake (Figure 7). Of 13 cardiovascular deaths, heart failure was in 4, acute myocardial infarction and sudden death in 4, and stroke in 5. The number of all-cause deaths within six months after the

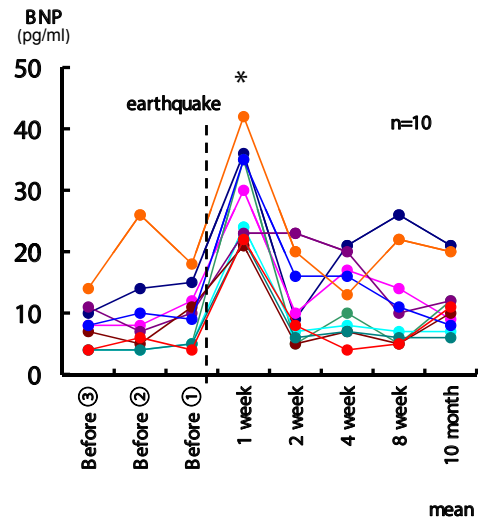


Figure 4: The course of BNP level changes in 10 healthy persons.

Before ① : 3 months before the earthquake (at health check up)

Before ② : 9 months before the earthquake (at health check up)

Before ③ : 15 months before the earthquake (at health check up)

1 week : 1 week after the earthquake 10 month : ten months after the earthquake

* $p<0.0001$ vs all others

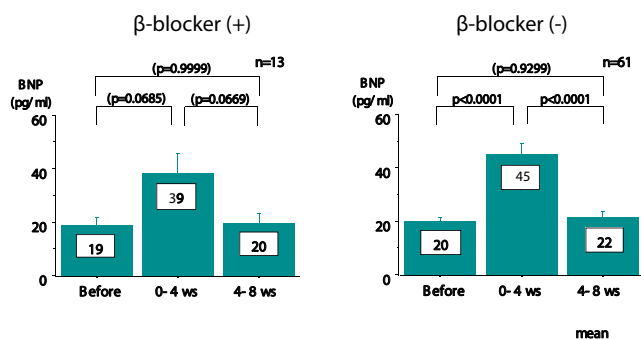


Figure 5: Influence of medication of beta-blocker on Δ BNP.

* Repeated measures analysis of variance with Scheffe's analysis (BNP values were transformed into natural logarithms)

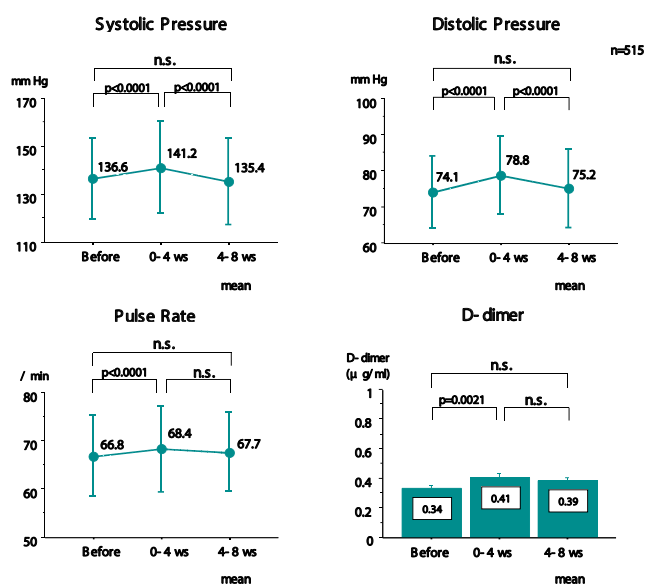


Figure 6: Changes in Blood Pressure, Pulse Rate and D-dimer levels.

earthquake markedly increased to 32, compared with 18 (14-20) in every 6 months of the prior 2 years before the earthquake. Of 19 non-cardiovascular deaths, pneumonia and other pulmonary diseases were in 8 patients, malignant neoplasm in 9 and others in 2. In addition, one patient (82 year old woman) was suspected to have developed 'Takotsubo' cardiomyopathy several hours after the earthquake, and three patients had deep vein thromboses during 2 months after the earthquake (further, 78 year old woman developed acute pulmonary embolism in one). But we could not clarify the association between change in BNP, blood pressure, pulse rate, D-dimer and mortality after the earthquake.

Discussion

Earthquake-induced stress contributes to various cardiovascular diseases, such as acute myocardial infarction, stroke, heart failure, arrhythmia and so on.^{1,11} Several reports have showed that the incidence of fatal and non-fatal cardiovascular events (both cardiac and cerebral) was increased at the time of the 1995 Hanshin-Awaji Earthquake.^{2,12,13} In addition, after the 2004 Mid Niigata Prefecture Earthquake, a considerable number of cases of 'Takotsubo' cardiomyopathy (probably caused by the emotional stress) and a number of acute pulmonary embolism (caused by deep vein thromboses) occurred.¹⁴⁻¹⁷

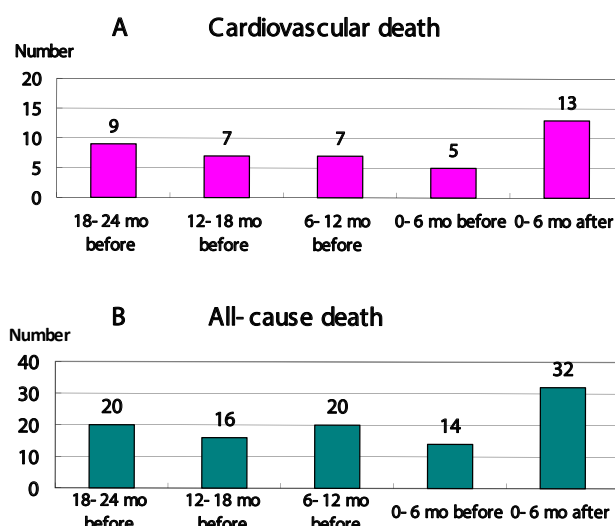


Figure 7: The number of cardiovascular death and all-cause death after the earthquake.

18-24 mo before : 18 to 24 months before the earthquake

0-6 mo after : 0 to 6 months after the earthquake

This study demonstrated that BNP was increased within four weeks after the earthquake significantly compared to BNP before the earthquake, and fell nearly to the former level additional 4 weeks after the earthquake, not only in the patients with cardiac diseases, but also in those without cardiac diseases and in healthy persons. Furthermore, in the patients with CHF, significant elevation of BNP continued for several months, and finally fell to the former level five months after the earthquake. In fact, in 26% of 39 CHF patients, heart failure became worse with additional therapy or hospitalization during 6 months after the earthquake.

BNP is now recognized as a reliable marker of cardiac dysfunction and a prognostic marker in the patients with cardiac diseases and in general population.^{6-10,18-20} It is known that the synthesis and secretion of BNP increase with ventricular wall stress (ex. left ventricular overload, left ventricular dysfunction), atrial wall stress (ex. atrial fibrillation), secretion of norepinephrine (NE), endothelin-1 (ET-1), angiotensin II and so on.^{3-6,21,22}

While we could not statistically solve the reason why BNP increases after a disaster like a major earthquake, we think that it could be; 1) increase of left ventricular overload (ex. due to elevated blood pressure and heart rate, etc.), and dysfunction (ex. development of acute coronary syndrome, 'Takotsubo' cardiomyopathy and pulmonary embolism, etc.).^{6,23-25} 2) sympathetic nervous activation, directly (excessive secretion of catecholamine) or indirectly (through elevation of blood pressure and heart rate, etc.).^{1,26} 3) increase of atrial wall stress (due to arrhythmia such as paroxysmal atrial fibrillation).^{21,27}

In this study, blood pressure and pulse rate increased also significantly right after the earthquake, compared to those before the earthquake, simultaneously with the elevations of BNP, whereas we could not find the relationship between changes of BNP and changes of blood pressure and heart rate. Further, this study showed that BNP levels after earthquake were significantly elevated in the patients with hypertension not

taking beta-blocker, but not significantly elevated in the patients taking it. These findings suggest that emotional and physical stress on earthquake stimulates sympathetic nerve system, and subsequently elevates blood pressure and heart rate, thereby increasing BNP levels.

Furthermore, earthquake-induced stress contributes also to arrhythmia and BNP levels are known to be elevated by arrhythmia (such as ventricular tachycardia, atrial tachycardia, atrial fibrillation, etc.).^{21,27-29} Therefore, the elevation of BNP levels after an earthquake may be also caused by arrhythmia.

D-dimer is an activation marker of both coagulation and subsequent fibrinolysis. The elevations of D-dimer levels are caused by deep vein thrombosis (and pulmonary infarction), aortic aneurysm, left atrial appendage thrombus due to atrial fibrillation (subsequently, cerebral embolism), acute myocardial infarction, 'Takotsubo' cardiomyopathy, etc., and BNP levels are also elevated with these cardiovascular diseases.

In this study, the CHF patients during 6 months after the earthquake have a tendency for worsening of heart failure, occurrence of cerebral infarction and acute coronary syndrome. Furthermore, the number of cardiovascular deaths and the number of all-cause deaths within six months after the earthquake were increased by about 2 times compared to those before the earthquake. There was a tendency for increase of the mortality from heart failure, acute myocardial infarction, stroke and pneumonia in the patients of this clinic during 6 months after the earthquake.

Conclusions

BNP level was increased significantly right after earthquake, not only in the patients with cardiac diseases, but also in the patients without cardiac diseases and in healthy persons. We suggest that emotional and physical stress after earthquake stimulates sympathetic nerve system and subsequently elevates blood pressure and heart rate, and so BNP levels increase. BNP is useful for evaluation of cardiac overload and dysfunction after the earthquake.

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ADDRESS FOR CORRESPONDENCE

Keizo Tsuchida, Tsuchida Clinic of Internal Medicine and Cardiology, 3-12-29 Kesajiro, Nagaoka-shi, Niigata-ken, 940-0033, Japan, Tel: +81-258-39-8888; Fax: +81-258-37-6822; e-mail: kalove@etude.ocn.ne.jp