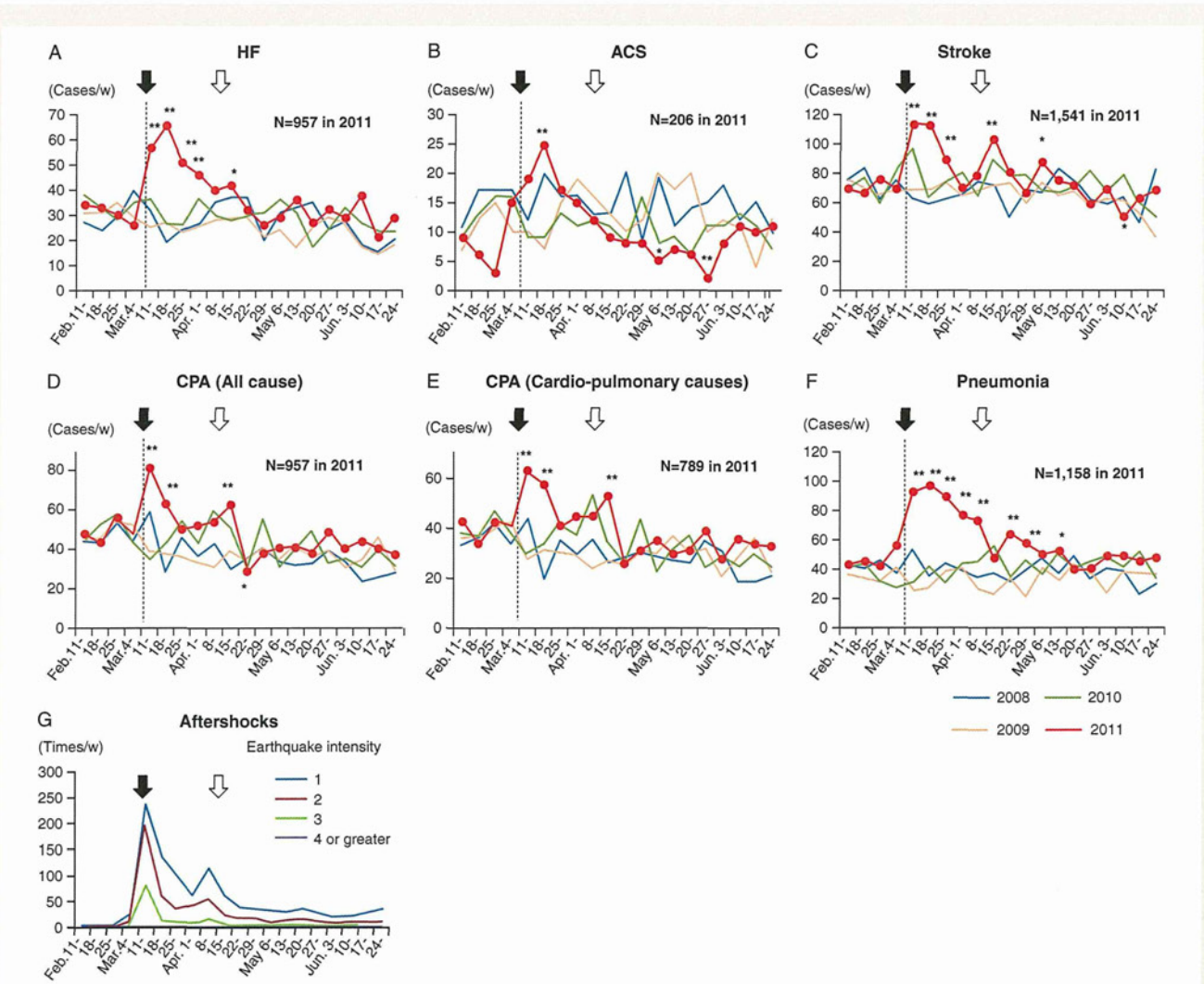

Figure 2 Time course of weekly occurrences of the diseases. (*A–F*) Weekly occurrences of heart failure (HF), stroke, cardiopulmonary arrest (CPA), and pneumonia were significantly increased after the Earthquake. $*P < 0.05$ and $**P < 0.01$. (*G*) The weekly counts of aftershocks observed in the Miyagi Prefecture with a seismic intensity of 1.0 or greater on the Japanese scale. The seismic intensity of the major Earthquake of 11 March 2011 was 7 in the Miyagi Prefecture. The number in the panels indicates the total number of the patients in 2011. Black arrows indicate the occurrence of the Great East Japan Earthquake (magnitude of 9.0, 11 March 2011) and white arrows indicate the largest aftershock (magnitude of 7.0, 11 April 2011).

for cerebral infarction but not for intracranial haemorrhage (see Supplementary material online, *Figure S2*). The number of aftershocks in the Miyagi Prefecture was frequent during the 6 weeks after the Earthquake, and the second peak was noted at the large aftershock on 7 April 2011 (magnitude of 7.0) (*Figure 2G*). When compared with the previous 3 years, the significant increases in the occurrence of HF and pneumonia were prolonged for more than 6 weeks after the Earthquake in 2011 (*Figure 2A* and *F*). On the other hand, the time course of the occurrences of stroke and CPA was shown by the second peak, corresponding to the distribution of the aftershocks (*Figure 2C–E*). We also observed that the rapid increase in the occurrence of ACS was followed by a significant decline (*Figure 2B*). Similarly, the occurrence of CPA showed a significant increase after the large aftershock followed by a rapid decline (*Figure 2D* and *E*). Those results by the Poisson regression stepwise analysis were comparable with those by the full Poisson regression analysis without stepwise methods (data not shown).

The subgroup analyses of the 2011 data showed that age, sex, or residence area did not significantly influence the occurrences of CVDs after the Earthquake (*Figure 4*). In contrast, a significant influence of residence area was noted only for pneumonia with a high occurrence in the seacoast (tsunami) area, although sex and age again had no effect (*Figure 4*).

Discussion

The novel findings of the present study are as follows: (i) the occurrences of CVDs and pneumonia were all significantly increased after the Great East Japan Earthquake in 2011 when

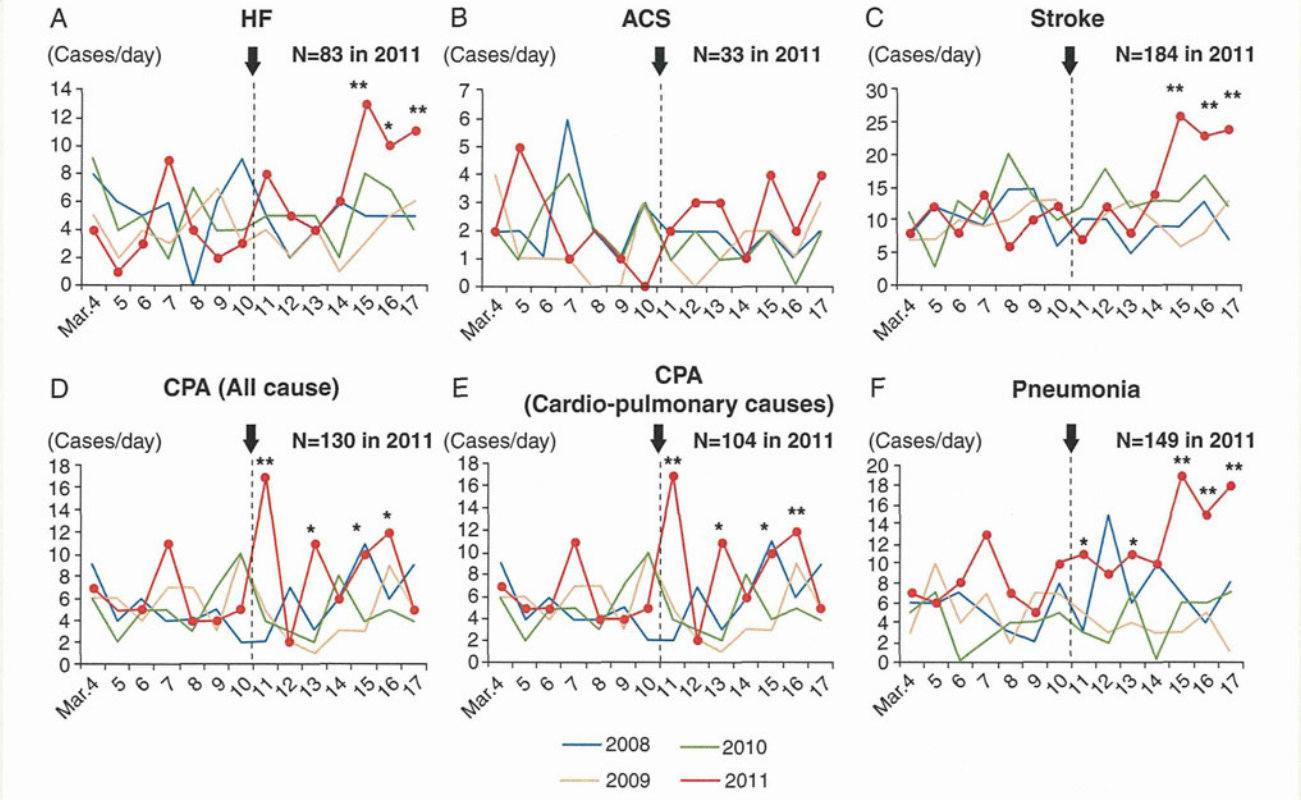

Figure 3 Daily occurrences of the diseases before and after the Earthquake. (*A–F*) Daily occurrences of heart failure (HF), stroke, cardiopulmonary arrest (CPA), and pneumonia were significantly increased after the Earthquake. *$P < 0.05$ and **$P < 0.01$. The number in the panels indicates that for 4 weeks before and after the Earthquake. Black arrows indicate the occurrence of the Great East Japan Earthquake (magnitude of 9.0, 11 March 2011).

compared with the previous 3 years (2008–10), (ii) the occurrences of HF and pneumonia were then gradually decreased, whereas the occurrences of ACS, stroke, and CPA were rapidly decreased when compared with those of HF and pneumonia, (iii) the occurrences of CVDs were increased independent of age, sex, or residence area, and (iv) the increase in the occurrence of pneumonia was higher in the seacoast (tsunami) area than in the inland area. To the best of our knowledge, this is the first report that demonstrates the mid-term courses of the occurrences of major CVDs and pneumonia after a great earthquake in the large-scale population. Especially, it provides the first evidence that the occurrence of HF was markedly increased for a long period after the Earthquake.

Increased occurrences of cardiovascular diseases and pneumonia

In the present study, we observed that the occurrences of HF, ACS, stroke, CPA, and pneumonia were all significantly increased after the Great East Japan Earthquake. Although previous studies demonstrated that the occurrences of acute myocardial infarction, stroke, and CPA were increased after earthquakes,[5,8,9,12–14] no study has ever demonstrated the increase in the occurrence of HF. The Earthquake forced many people in the Miyagi Prefecture to take shelter and/or to live without distribution of daily necessities, lifelines (e.g. water and electric supplies), and medicines. To make the situation worse, they were afflicted by the frequent aftershocks (the aftershocks with a seismic intensity of 1.0 or greater occurred 1025 times from 11 March to 7 April) and the freezing temperature (the average temperature in Sendai City was 3.8°C in March 2011) (*Table 1*). In these situations, where people are forced to extreme physical/mental stresses, CVDs may be caused by the activated sympathetic nervous system.[15,16] A transient increase in blood viscosity after an earthquake was observed only in those with high stress (e.g. move to shelter and loss of family member), which may increase the occurrences of ACS, stroke, and CPA.[17]

Increased occurrence of heart failure

When compared with the previous reports (*Table 1*),[5–9,12,14,18] one of the novel findings of the present study is the significant increase in the occurrence of HF, for which several factors may be involved. The activated sympathetic nervous system in the Great East Japan Earthquake should have elevated blood pressure and heart rate, as previously reported after large earthquakes.[15,19] Furthermore, the discontinued logistics distribution caused by the Earthquake resulted in insufficient delivery of regular medications,

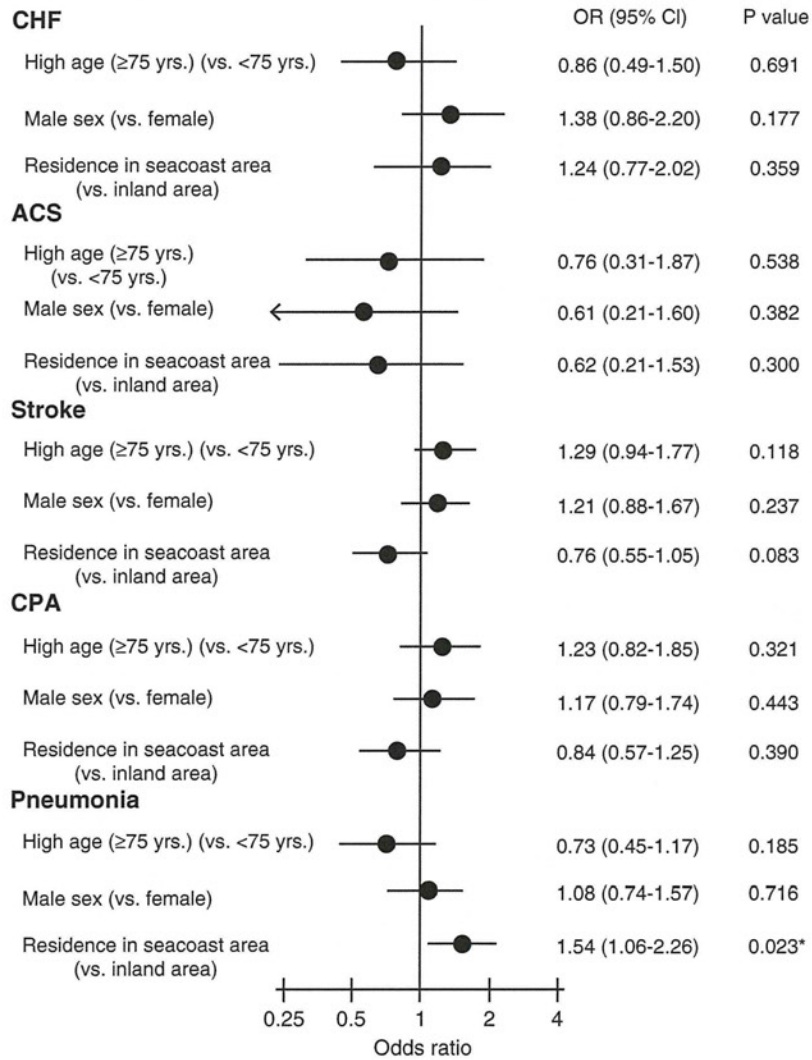

Figure 4 Subgroup analyses regarding age, sex, and residence area. We first counted the occurrence of each variable in the 4 weeks before and after the Earthquake and subsequently calculated the odds ratio. No significant influences of age, sex, or residence area were noted for the occurrences of cardiovascular diseases and pneumonia, except for the influence of the seacoast residence on the occurrence of pneumonia. HF, heart failure; ACS, acute coronary syndrome; CPA, cardiopulmonary arrest; OR, odds ratio; 95%CI, 95% confidential interval.

such as antihypertensive drugs and antithrombotic drugs, which can increase cardiovascular events as reported previously.[20] Moreover, these situations forced people to use preserved foods with high salt, and not fresh food, which also can elevate blood pressure and worsen HF.[21–23] It has been reported that high-salt intake under mental stress elevates blood pressure to a greater extent than normal conditions, thus easily worsening HF.[24,25] Additionally, the recent study has demonstrated that antecedent hypertension is associated with the increased occurrence of HF.[26] Furthermore, the recent report from our institute demonstrated that self-monitoring blood pressure was significantly elevated after the Earthquake.[27] Recently, we also have reported that the Earthquake increases the occurrence of ventricular tachyarrhythmia and hospitalization from worsening of HF among the patients with implantable cardiac defibrillators.[28] One of the well-known factors that worsen HF is infection including pneumonia, which was significantly increased after the Earthquake as shown in the present study. Taken together, we consider that discontinuation of drugs, increased salt intake, activated sympathetic nervous system, blood pressure elevation, and increased occurrences of tachyarrhythmia and infections were likely involved in the increased occurrence of HF after the Great East Japan Earthquake.

Time course of occurrences of the diseases

Unlike HF and pneumonia that showed a gradual decline for more than 6 weeks after the Earthquake, the weekly occurrence of ACS and CPA showed significant increases followed by decreases within 2–3 weeks after the Earthquake. Furthermore, the immediate

increase in the occurrence of the disease on the day of the Earthquake was noted only for CPA. The similar tendency was reported for sudden cardiac deaths related to atherosclerotic CVD after the Northridge Earthquake, although the observational period was very short (7 days)[12] when compared with the present study (16 weeks). These results suggest that the physical and/or mental stress induced by the Earthquake first facilitated CPA events, while other CVDs were due to the catastrophe occurring later on (tsunami, break down of lifelines, low temperatures, etc.). However, in the present catastrophic situation, the emergency care system itself was severely damaged for both ambulance transport and ambulance personnel availability, where the patients with CPA had a priority for ambulance transport. Thus, such a logistic factor may also have been involved in the present results. Furthermore, the onset patterns of CPA and stroke showed the second peak after the largest aftershock, suggesting that unstabilization of atherosclerotic plaques[29] and an increase in blood pressure were accelerated by the Earthquake[27] with a resultant increase followed by a decrease in the occurrence, an interesting and important difference when compared with other diseases.

Predictors for increased occurrences of cardiovascular diseases and pneumonia

Little information is available about the impacts of age and sex on the occurrences of CVDs and pneumonia after an earthquake. Although the age of all transported patients in 2011 was significantly higher than that in the previous 3 years, the age of the patients with CVDs and pneumonia was comparable with the previous 3 years, suggesting less impact of age and sex on the increased occurrences of CVDs and pneumonia (*Figure 3*).

Importantly, although the Earthquake-induced tsunami directly and seriously affected the people in the seacoast area, but not those in the inland area, the increased occurrences of CVDs after the Earthquake were comparable between the two areas. Similar indirect effects of a disaster on CVDs in a remote area have been reported in the World Trade Center Disaster in 2001, where the blood pressure of people living in Mississippi was equally elevated as that of those living in New York City.[30] These results indicate that the impact of life-threatening events, such as the Great Earthquake, could trigger CVDs even in areas distant from the disaster area. However, a certain number of people who suffered damage from the tsunami migrated from the seacoast area to the inland area after the Earthquake, which might have attenuated the influence of the tsunami on the occurrence of the diseases examined. In contrast, the increased occurrence of pneumonia was higher in the seacoast area than in the inland area, which can be explained by aspiration pneumonia in drowned people and/or the large amount of sludge carried by the tsunami.

Study limitations

Several limitations should be mentioned for the present study. First, in the present study, we analysed the occurrences of the diseases based on the initial diagnoses on the ambulance transport records that were made by attending doctors. Although the diagnoses were made based on physical examination, ECG, chest X-ray, echocardiography, and laboratory test, the process of the diagnoses were not standardized in the present study. Although this method might reduce the accuracy of diagnoses, the rate of definitive diagnosis at admission in the emergency rooms was comparable among the 4 years studied, and the process of diagnosis was the same throughout the study period. However, in our emergency medical system, we were unable to examine the accuracy of diagnoses in emergency rooms, especially in the catastrophic situations after the Earthquake. Secondly, some people were forced to move from the seacoast area to the inland area after the Earthquake. However, we have no data on how many people moved from the seacoast area to the inland area. This could have affected the increased occurrences of CVDs in the inland area. Thirdly, we do not have background data on the patients who were diagnosed as having HF, including clinical characteristics and underlying heart disease.[31,32] We are now prospectively following the patients with HF in our cohort study in the Tohoku area[33] and we will report the clinical outcomes of those patients in the future. Fourthly, we have no data regarding the number of patients who visited hospitals by themselves without the use of ambulance. We also were unable to exclude the effects of traffic disruption by the Earthquake that might have affected the use of ambulance. Fifthly, the Miyagi Prefecture is located next to the Fukushima Prefecture where the nuclear power plant accident occurred; however, the influence of the nuclear accident was minimal in our Miyagi Prefecture. Sixthly, although ACS and stroke are similarly and strongly associated with atherosclerosis, we were unable to elucidate the mechanism for the different time courses between them. This issue remains to be examined in future studies. Seventhly, we have no data regarding prior medications in each patient, which might have affected the occurrence of CVDs. Eighthly, because the diagnosis of ACS was not based on coronary angiograms, but on ECG, echocardiography, and blood test, which made it difficult to diagnose Takotsubo cardiomyopathy. Finally, we have no data that can differentiate CPA of cardiac causes from CPA of pulmonary causes.

Clinical implications

We consider that the increased occurrences of CVDs in the Great East Japan Earthquake may have been caused by the following multiple factors: (i) the activated sympathetic nervous system by physical and mental stresses, (ii) insufficient medications, (iii) increased salt intake from preserved foods, and (iv) elevated blood pressure and viscosity; however, further studies are required to elucidate the mechanisms of disaster-related CVDs.

Conclusions

The present study demonstrates that the East Japan Earthquake Disaster has significantly increased the occurrences of CVDs, including the first observation of the increased occurrence of HF, independent of age, sex, area of residence.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

We appreciate the Miyagi Medical Association (president: Dr Junzo Ito) and the Fire Departments of the Miyagi Prefecture (chiefs of the 12 Fire Departments: Fumio Takahashi, Kosaburo Hoshi, Makoto Suzuki, Masaichi Tsunoda, Mutsuo Takahashi, Shinichi Konno, Shiro Otomo, Syoichi Chiba, Takao Sakurai, Teruo Sugahara, Toshiji Omatsu, and Yasushi Shiga) for collaboration in this study. We thank E. Ishida, M. Takahashi, A. Tsunoda, and Y. Hamada for their valuable contributions to this study.

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Conflict of interest: none declared.

References

1. Monthly Report on Earthquake and Volcanoes in Japan. Meteorological Agency, 2011.
2. The Report on Damage from the East Japan Earthquake. National Police Agency, 2012.
3. 2010's National Census. Ministry of Internal Affairs and Communications, 2012.
4. Ogawa K, Tsuji I, Shiono K, Hisamichi S. Increased acute myocardial infarction mortality following the 1995 Great Hanshin-Awaji earthquake in Japan. *Int J Epidemiol* 2000;**29**:449–455.
5. Tsuchida M, Kawashiri MA, Teramoto R, Takata M, Sakata K, Omi W, Okajima M, Takamura M, Ino H, Kita Y, Takegoshi T, Inaba H, Yamagishi M. Impact of severe earthquake on the occurrence of acute coronary syndrome and stroke in a rural area of Japan. *Circ J* 2009;**73**:1243–7.
6. Watanabe H, Kodama M, Okura Y, Aizawa Y, Tanabe N, Chinushi M, Nakamura Y, Nagai T, Sato M, Okabe M. Impact of earthquakes on Takotsubo cardiomyopathy. *J Am Med Assoc* 2005;**294**:305–7.
7. Watanabe H, Kodama M, Tanabe N, Nakamura Y, Nagai T, Sato M, Okabe M, Aizawa Y. Impact of earthquakes on risk for pulmonary embolism. *Int J Cardiol* 2008;**129**:152–4.
8. Suzuki S, Sakamoto S, Miki T, Matsuo T. Hanshin-Awaji earthquake and acute myocardial infarction. *Lancet* 1995;**345**:981.
9. Suzuki S, Sakamoto S, Koide M, Fujita H, Sakuramoto H, Kuroda T, Kintaka T, Matsuo T. Hanshin-Awaji earthquake as a trigger for acute myocardial infarction. *Am Heart J* 1997;**134**:974–7.
10. Inoue K, Suwa S, Ohta H, Itoh S, Maruyama S, Masuda N, Sugita M, Daida H. Heart fatty acid-binding protein offers similar diagnostic performance to high-sensitivity troponin T in emergency room patients presenting with chest pain. *Circ J* 2011;**75**:2813–20.
11. McCullagh P, Nelder JA. *Generalized Linear Models*. London, New York: Chapman & Hall Ltd, 1999.
12. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. *N Engl J Med* 1996;**334**:413–9.
13. Meisel SR, Kutz I, Dayan KI, Pauzner H, Chetboun I, Arbel Y, David D. Effect of Iraqi missile war on incidence of acute myocardial infarction and sudden death in Israeli civilians. *Lancet* 1991;**338**:660–1.
14. Takakura R, Himeno S, Kanayama Y, Sonoda T, Kiriyama K, Furubayashi T, Yabu M, Yoshida S, Nagasawa Y, Inoue S, Iwao N. Follow-up after the Hanshin-Awaji earthquake: diverse influences on pneumonia, bronchial asthma, peptic ulcer and diabetes mellitus. *Intern Med* 1997;**36**:87–91.
15. Esler M, Kaye D. Sympathetic nervous system activation in essential hypertension, cardiac failure and psychosomatic heart disease. *J Cardiovasc Pharmacol* 2000; **35**:S1–S7.
16. Grippo AJ, Johnson AK. Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from pre-clinical disease models. *Stress* 2009;**12**:1–21.
17. Kario K, Matsuo T, Kobayashi H, Yamamoto K, Shimada K. Earthquake-induced potentiation of acute risk factors in hypertensive elderly patients: possible triggering of cardiovascular events after a major earthquake. *J Am Coll Cardiol* 1997; **29**:926–33.
18. Zhang XQ, Chen M, Yang Q, Yan SD, Huang dJ. Effect of the Wenchuan earthquake in China on hemodynamically unstable ventricular tachyarrhythmia in hospitalized patients. *Am J Cardiol* 2009;**103**:994–7.
19. Azuma T, Seki N, Tanabe N, Saito R, Honda A, Ogawa Y, Suzuki H. Prolonged effects of participation in disaster relief operations after the Mid-Niigata earthquake on increased cardiovascular risk among local governmental staff. *J Hypertens* 2010;**28**:695–702.
20. Corrao G, Parodi A, Nicotra F, Zambon A, Merlino L, Cesana G, Mancia G. Better compliance to antihypertensive medications reduces cardiovascular risk. *J Hypertens* 2011;**29**:610–8.
21. Fukui S, Fukumoto Y, Suzuki J, Saji K, Nawata J, Tawara S, Shinozaki T, Kagaya Y, Shimokawa H. Long-term inhibition of Rho-kinase ameliorates diastolic heart failure in hypertensive rats. *J Cardiovasc Pharmacol* 2008;**51**:317–26.
22. Fukui S, Fukumoto Y, Suzuki J, Saji K, Nawata J, Shinozaki T, Kagaya Y, Watanabe J, Shimokawa H. Diabetes mellitus accelerates left ventricular diastolic dysfunction through activation of the renin-angiotensin system in hypertensive rats. *Hypertens Res* 2009;**32**:472–80.
23. Miura Y, Fukumoto Y, Sugimura K, Oikawa M, Nakano M, Tatebe S, Miyamichi S, Satoh K, Shimokawa H. Identification of new prognostic factors of pulmonary hypertension. *Circ J* 2010;**74**:1965–71.
24. Damgaard M, Goetze JP, Norsk P, Gadsbøll N. Altered sodium intake affects plasma concentrations of BNP but not proBNP in healthy individuals and patients with compensated heart failure. *Eur Heart J* 2007;**28**:2726–31.
25. Sawai A, Ohshige K, Yamasue K, Hayashi T, Tochikubo O. Influence of mental stress on cardiovascular function as evaluated by changes in energy expenditure. *Hypertens Res* 2007;**30**:1019–27.
26. Felšöci M, Pařenica J, Spinar J, Vítovec J, Widimský P, Linhart A, Fedorco M, Málek F, Cíhalík C, Miklík R, Jarkovský J. Does previous hypertension affect outcome in acute heart failure? *Eur J Intern Med* 2011;**22**:591–6.
27. Satoh M, Kikuya M, Ohkubo T, Imai Y. Acute and subacute effects of the great East Japan earthquake on home blood pressure values. *Hypertension* 2011; **58**:e193–4.
28. Nakano M, Kondo M, Wakayama Y, Kawana A, Hasebe Y, Shafee MA, Fukuda K, Shimokawa H. Increased incidence of tachyarrhythmias and heart failure hospitalization in patients with implanted cardiac devices after the Great East Japan Earthquake Disaster. *Circ J* 2012;**76**:1283–1285.
29. Libby P, Okamoto Y, Rocha VZ, Folco E. Inflammation in atherosclerosis: transition from theory to practice. *Circ J* 2010;**74**:213–20.
30. Gerin W, Chaplin W, Schwartz JE, Holland J, Alter R, Wheeler R, Duong D, Pickering TG. Sustained blood pressure increase after an acute stressor: the effects of the 11 September 2001 attack on the New York City World Trade Center. *J Hypertens* 2005;**23**:279–84.
31. Aoki T, Fukumoto Y, Sugimura K, Oikawa M, Satoh K, Nakano M, Nakayama M, Shimokawa H. Prognostic impact of myocardial interstitial fibrosis in non-ischemic heart failure. Comparison between preserved and reduced ejection fraction heart failure. *Circ J* 2011;**75**:2605–13.
32. Tatebe S, Fukumoto Y, Sugimura K, Miyamichi-Yamamoto S, Aoki T, Miura Y, Nochioka K, Satoh K, Shimokawa H. Clinical significance of reactive post-capillary pulmonary hypertension in patients with left heart disease. *Circ J* 2012; **76**:1235–1244.
33. Shiba N, Nochioka K, Miura M, Kohno H, Shimokawa H, Investigators C. Trend of westernization of etiology and clinical characteristics of heart failure patients in Japan—first report from the CHART-2 study. *Circ J* 2011; **75**:823–33.

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Original article

Coronary perivascular fibrosis is associated with impairment of coronary blood flow in patients with non-ischemic heart failure

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ABSTRACT

Background: Although myocardial interstitial fibrosis has been considered to play a pathogenic role in chronic heart failure (HF), the role of perivascular fibrosis, another form of fibrosis, remains to be elucidated.

Methods: We examined 64 consecutive patients with non-ischemic HF caused by hypertrophic cardiomyopathy (HCM, $n=16$), hypertensive heart disease (HHD, $n=11$), or dilated cardiomyopathy (DCM, $n=37$), diagnosed by both cardiac catheterization and endomyocardial biopsy (right ventricular side of the interventricular septum) in the Tohoku University Hospital between January 2001 and April 2009. We calculated the collagen volume fraction (CVF) and perivascular fibrosis ratio (PFR) in biopsy samples and also examined Thrombolysis in Myocardial Infarction (TIMI) frame count to evaluate coronary blood flow.

Results: There was no significant correlation between CVF and PFR ($r^2=0.0007$). Although CVF was comparable among HCM, HHD, and DCM (1.11 ± 1.04, 1.89 ± 1.61, and 1.41 ± 1.48, respectively), PFR was significantly higher in HCM than in DCM (1.78 ± 1.09 vs. 1.23 ± 0.44, $p<0.05$). PFR was not correlated with cardiac function parameters, such as left ventricular (LV) ejection fraction, cardiac output, LV end-diastolic pressure, LV end-diastolic volume, aortic pressure, or pulmonary artery pressure. However, PFR was significantly correlated with coronary flow in the left anterior descending coronary artery (as evaluated by TIMI frame count) ($r^2=0.3351$, $p<0.0001$, in all-cases combined population), but not with that in the left circumflex or right coronary artery. This correlation remained significant in a logistic regression model tested in 7 variables (body mass index, PVR, CVF, presence of hypertension, dyslipidemia, diabetes mellitus, and atrial fibrillation).

Conclusions: These results indicate that coronary perivascular fibrosis is associated with the impairment of coronary blood flow although not associated with interstitial fibrosis or cardiac function, suggesting that it can be a new therapeutic target to improve coronary microcirculation.

Introduction

Chronic heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorders, including coronary artery disease, hypertensive heart disease, myocardial disease, and valvular heart disease [1], where not only HF with reduced ejection fraction (HFrEF) but also HF with preserved ejection fraction (HFpEF) are substantially involved [2–4]. Indeed, HFrEF and HFpEF respectively account for approximately half of chronic HF patients [5–8].

In HF patients, coronary flow reserve is impaired during the acute phase of HF and is strongly correlated with mortality [9,10]. Coronary microvascular dysfunction has been recognized as an important contributor to impaired coronary blood flow [11], which occurs not only in coronary artery disease, but also in various myocardial diseases, such as hypertension, hypertrophic cardiomyopathy (HCM) and infiltrative heart disease (e.g. Anderson–Fabry cardiomyopathy) [11]. Also, it has been reported that myocardial diseases are associated with abnormal coronary microvascular structures such as thickened wall and proliferation of vascular smooth muscle cells [11]. However, the correlation between organic and functional coronary microvascular abnormalities has not been well documented.

Thrombolysis in Myocardial Infarction (TIMI) frame count is a simple, objective, and quantitative index of coronary blood flow, and has been reported to increase not only in myocardial infarction

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[12], but also in coronary microvascular dysfunction [11,13–15]. It is important to exclude the contribution of organic coronary artery disease when evaluating coronary blood flow and microvascular dysfunction in HF patients. In the present study, we thus aimed to examine the impact of perivascular fibrosis on coronary microvascular dysfunction in patients with chronic and non-ischemic HF by using TIMI frame count.

Methods

The ethical committees of Tohoku University Hospital approved the study protocol and all patients provided written informed consent.

Study subjects

We examined 132 consecutive patients with stages B/C/D chronic HF defined by the American College of Cardiology/American Heart Association 2005 Guidelines [1,4], caused by non-ischemic HF, including hypertrophic cardiomyopathy (HCM, $n=45$), hypertensive heart disease (HHD, $n=25$), or dilated cardiomyopathy (DCM, $n=62$) enrolled in our database, who were hospitalized at our hospital and underwent both cardiac catheterization and endomyocardial biopsy (right ventricular side of the interventricular septum) to diagnose the etiology of HF from January 2001 to April 2009. In the present study, 68 out of the 132 patients were excluded; 66 for the absence of coronary arteries in the biopsy samples and 2 for significant coronary artery disease. Finally, we enrolled the remaining 64 patients, including 16 HCM, 11 HHD, and 37 DCM patients.

Data collection

Baseline demographic data, hemodynamic data obtained by catheterization, medications, and comorbidities (hypertension, diabetes mellitus, dyslipidemia, and atrial fibrillation) were obtained from their medical records. Hypertension was diagnosed by the use of antihypertensive drugs and/or systolic blood pressure $\geq$130 mmHg and/or diastolic blood pressure $\geq$80 mmHg. Diabetes mellitus was diagnosed by the use of anti-diabetic drugs, fasting glucose $\geq$110 mg/dl, and/or glucose $\geq$200 mg/dl 2 h after a 75 g oral glucose tolerance test. Dyslipidemia was diagnosed by the use of lipid-lowering drugs and/or elevated lipid levels, defined as plasma low-density lipoprotein (LDL) cholesterol $\geq$140 mg/dl, triglycerides $\geq$150 mg/dl, or high-density lipoprotein (HDL) <40 mg/dl. The hemodynamic parameters obtained by cardiac catheterization included left ventricular ejection fraction (LVEF), LV end-diastolic volume index (LVEDVI), aortic pressure (AoP), LV end-diastolic pressure (LVEDP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO) and cardiac index (CI). Before cardiac catheterization, we measured serum levels of hemoglobin, brain natriuretic peptide (BNP), creatinine, and high-sensitivity C-reactive protein (hsCRP), and estimated creatinine clearance (eGFR) by Cockroft–Gault formula.

Histological analysis of biopsy samples

The acquisition, fixation, and staining of myocardial biopsy samples was previously described [16]. Collagen volume fraction (CVF), as an index of myocardial interstitial fibrosis, was calculated and averaged in representative fields containing no endocardium or blood vessel, as previously described [16].

Furthermore, we have analyzed images of the stained sections using ImageJ 1.45 s (W. Rasband, NIH, Bethesda, MD, USA, http://imagej.nih.gov/ij/, 1997–2012, 400×) to determine perivascular fibrosis around arteries, expressed as perivascular fibrosis ratio (PFR) (Fig. 1). PFR was defined as the area of perivascular fibrosis divided by the area of the vascular wall, averaged over all quantifiable images of arteries taken from a section [17] (mean, 1.72 ± 0.84 quantifiable images of arteries). All histological evaluation was performed by a single well-trained observer without knowing whose samples were analyzed.

Determination of delayed enhancement on cardiac magnetic resonance imaging

Out of the 64 patients enrolled, 27 also underwent cardiac magnetic resonance (CMR) imaging using a 1.5-T CMR system (Siemens Magnetom, Erlangen, Germany). Delayed enhancement images captured 15 min after intravenous injection of gadolinium were used to determine the presence of delayed enhancement [18–20].

Evaluation of coronary blood flow

Coronary blood flow was quantified by a single well-trained observer in a blind manner, using TIMI frame count (TFC) method [12]. TFC was determined separately for the left anterior descending (LAD) and circumflex coronary artery (LCx), and the right coronary artery (RCA), according to the method described by Gibson et al. [12]. We calculated corrected TFC (CTFC) for LAD by dividing TFC by 1.7, in order to adjust that for LCx and RCA [12]. All coronary angiograms were obtained before endomyocardial biopsy at a speed of 15 frames/s. To be universally comparable, TFCs and CTFCs were converted to a frame acquisition rate of 30 frames/sec by multiplying by 2.0 [15].

Statistical analysis

Continuous variables were presented as mean $\pm$ SD. Comparison of 2 groups was made by unpaired t-test for continuous variables and Pearson's chi-square test for categorical variables. Comparison among 3 groups was made by ANOVA test. A multivariate analysis was conducted to examine the effectors of CTFC for LAD, using a logistic regression model, in which the following were included as variables: body mass index (BMI), PFR, CVF, and the presence of comorbidities (hypertension, dyslipidemia, diabetes mellitus, and atrial fibrillation). A p-value less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

There were no statistically significant differences among the 3 groups in age, gender, or BMI (Table 1). Expectedly, the prevalence of hypertension was significantly higher in the HHD group compared with the other 2 groups (Table 1). The DCM group had a higher prevalence of atrial fibrillation than the HCM group (Table 1). LVEF was the highest in the HCM group (Table 1).

Coronary perivascular fibrosis and myocardial interstitial fibrosis

Although there was no significant difference in myocardial interstitial CVF among the 3 groups (Fig. 2A), PFR was significantly more severe in the HCM group than in the DCM group (Fig. 2B). No correlation was observed between CVF and PFR in all-cases combined population (Fig. 2C) or in each group (Fig. 2D–F). Of the 27 patients who underwent CMR, 16 presented delayed enhancement and PFR was comparable between the patients with and those without delayed enhancement (1.18 ± 0.67 vs. 1.55 ± 0.78, $p=0.21$).

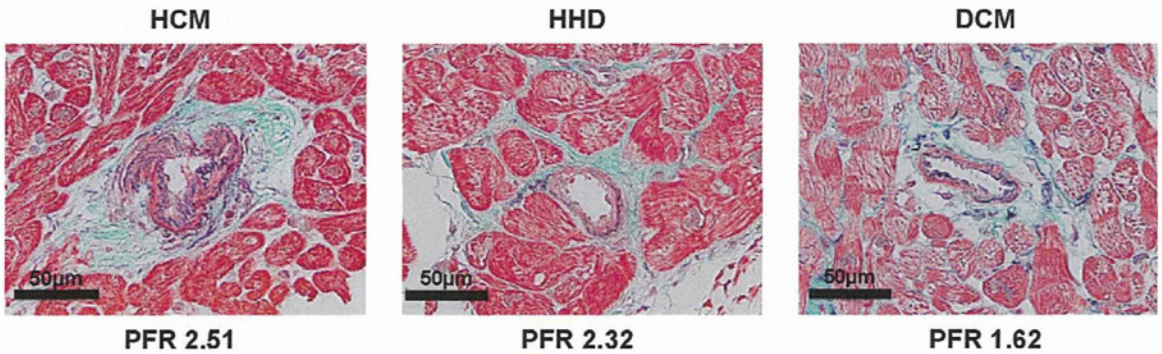

Fig. 1. Representative histology of perivascular fibrosis. Perivascular fibrosis in hypertrophic cardiomyopathy (HCM) (left), hypertensive heart disease (HHD) (middle), and dilated cardiomyopathy (DCM) (right) patients, stained in blue by Elastica–Masson staining. Scale bar, 50 μm.

Coronary perivascular fibrosis and cardiac function

PFR was not significantly correlated with LVEF ($r^2 = 0.0003$, $p = 0.90$), CO ($r^2 = 0.0095$, $p = 0.45$), LVEDP ($r^2 = 0.0042$, $p = 0.62$), LVEDV ($r^2 = 0.0019$, $p = 0.75$), systolic and diastolic AoP ($r^2 = 0.0038$, $p = 0.63$; $r^2 = 0.0102$, $p = 0.43$, respectively), systolic or diastolic PAP ($r^2 = 0.0102$, $p = 0.43$; $r^2 = 0.0072$, $p = 0.51$, respectively), in all-cases combined population as well as in each group. The prognosis was comparable between mild and severe perivascular fibrosis groups (divided by the median of 1.255), for all-cause death (log-rank test, $p = 0.49$) or cardiac events, including cardiac or sudden death and admission for HF (log-rank test, $p = 0.29$), as was the case with patient characteristics such as gender, age, BMI, comorbidities, medication, and laboratory data (data not shown).

Perivascular fibrosis and TIMI frame count

TFCs measured in each group are shown in Table 2. There were no significant differences among the 3 groups in each coronary artery. Importantly, PFR was significantly correlated with CTFCs for LAD (Fig. 3A), but not with those for LCx or RCA (Fig. 3B and C). The correlation between PFR and CTFC for LAD was also observed in each group (Fig. 3D–F). Multivariate analysis was performed using a logistic regression model to examine the difference between high and low CTFC for LAD (divided by median of 21.18, with median attributed into the lower group) with 7 comorbidities, demonstrating that only PFR and atrial fibrillation were significantly correlated with CTFC for LAD (Table 3). PFR in patients with and without atrial fibrillation were comparable (1.42 ± 0.53 vs. 1.45 ± 0.91, $p = 0.92$).

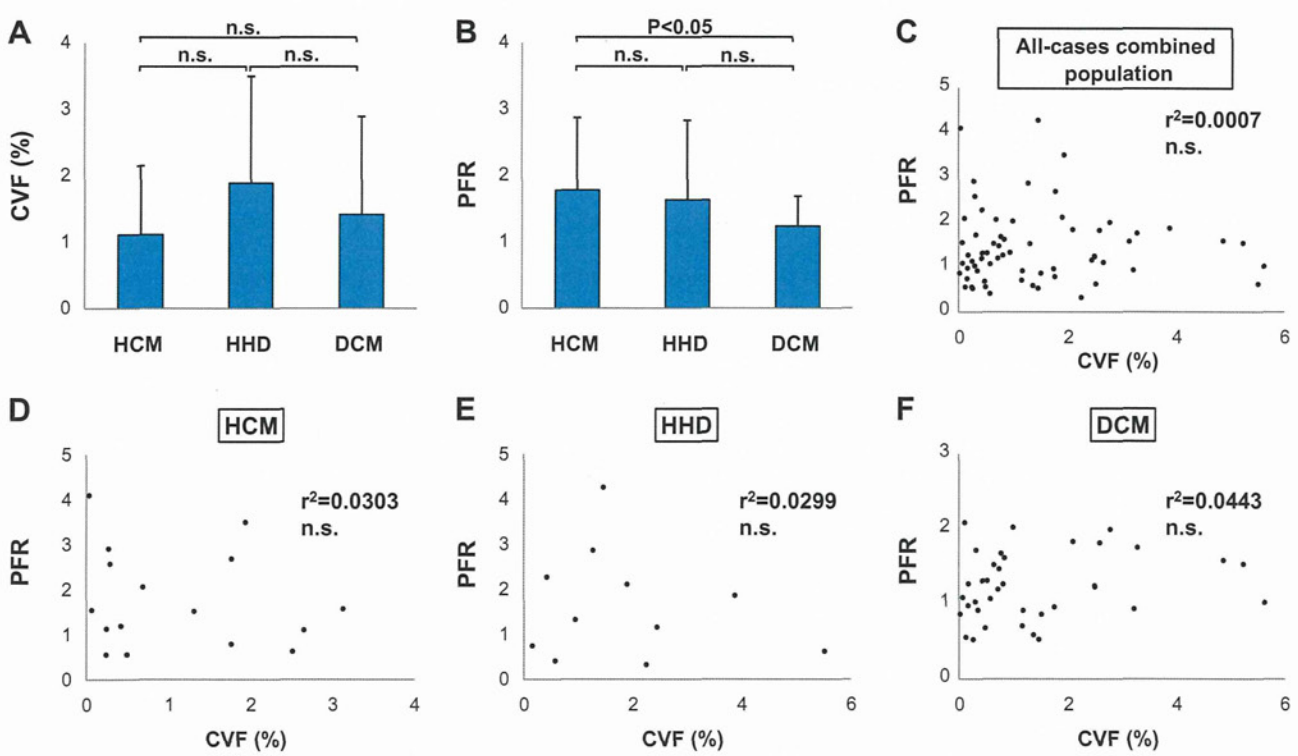

Fig. 2. Interstitial collagen volume fraction and perivascular fibrosis ratio. (A) Interstitial collagen volume fraction (CVF) was not significantly different among the 3 groups. (B) Perivascular fibrosis ratio (PFR) was higher in the HCM group than in the DCM group. (C) No correlation was observed between CVF and PFR in all-cases combined population ($r^2 = 0.0007$, $p = 0.84$), HCM (D), HHD (E), or DCM (F). HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; DCM, dilated cardiomyopathy.

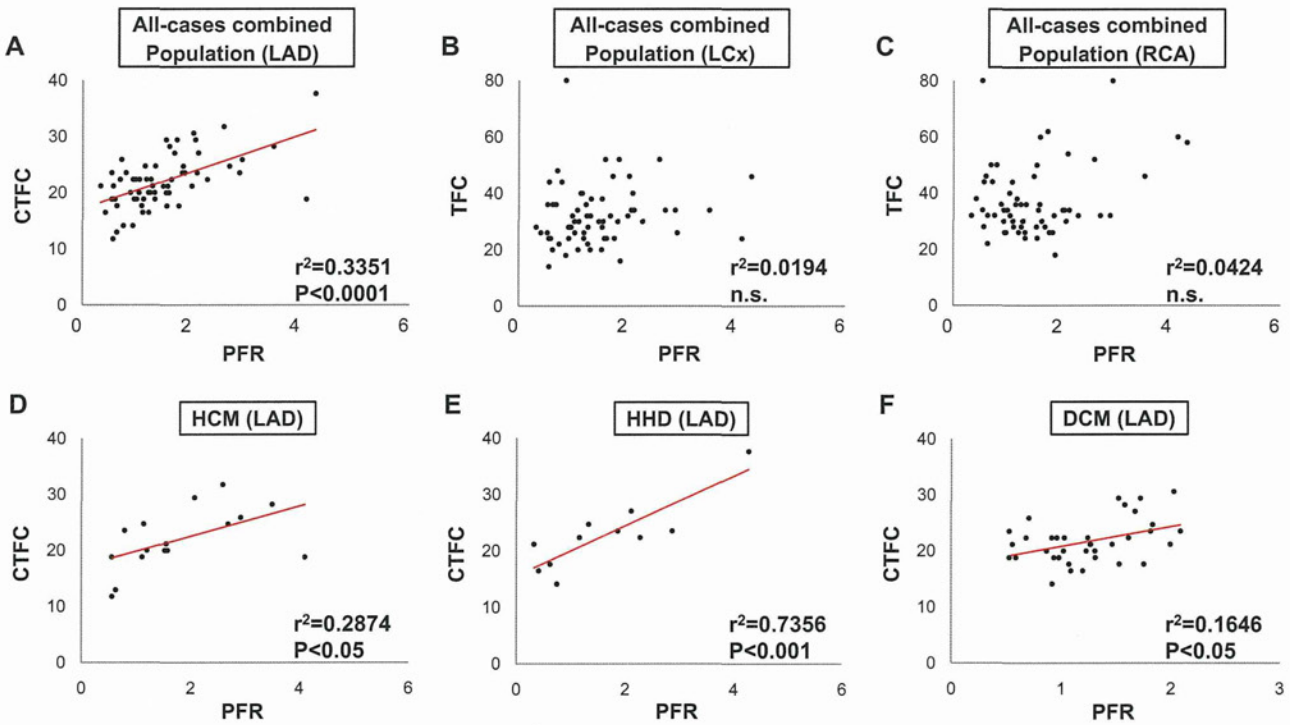

Fig. 3. Correlation between perivascular fibrosis ratio and thrombolysis in myocardial infarction (TIMI) frame counts (TFC). (A) Significant correlation was noted between perivascular fibrosis ratio (PFR) and corrected TIMI frame count (CTFC) for the left anterior descending coronary artery (LAD) in all study population ($r^2 = 0.3351$, $p < 0.0001$), but not for the left circumflex coronary artery (LCx) (B) ($r^2 = 0.0194$, $p = 0.27$) or the right coronary artery (RCA) (C) ($r^2 = 0.0424$, $p = 0.11$). A correlation between PFR and CTFCs for LAD was also noted in each HCM (D), HHD (E), and DCM group (F), respectively. HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; DCM, dilated cardiomyopathy.

Discussion

The novel findings of the present study are as follows: (1) although interstitial CVF was comparable among the HCM, HHD, and DCM groups, perivascular fibrosis was more severe in the HCM group than in the DCM group; (2) PFR was independent of CVF; and (3) PFR was significantly correlated with CTFC for LAD. To the best of our knowledge, this is the first report that demonstrates the histopathological impact of perivascular fibrosis of small coronary arteries on impaired coronary blood flow in non-ischemic HF patients. Thus, the present results suggest that impaired coronary microcirculation could be caused not only by vascular remodeling, endothelial dysfunction, and microvascular spasm [11,21], but also by perivascular fibrosis.

Coronary perivascular fibrosis and interstitial myocardial fibrosis

Several studies have shown that myocardial collagen content is correlated with LV stiffness [22,23] and is involved in the progression of HF [24–26]. We also have recently demonstrated that CVF is correlated with LVEDP in HFrEF and is an important predictor of poor prognosis [16]. Previous studies using autopsy samples have demonstrated that interstitial CVF was higher in HCM than in HHD [27,28] and that ventricular fibrosis in HCM is known to concentrate in the ventricular septum, whereas it is equally distributed in the septum and the LV free wall in HHD [27]. The present study demonstrates that interstitial CVF was comparable between HCM and HHD, probably because our biopsy samples were obtained from the ventricular septum. Compared with interstitial myocardial fibrosis, not much attention has been paid to the possible importance of perivascular fibrosis in the pathogenesis of non-ischemic HF.

As demonstrated in the present study, neither CVF nor delayed enhancement on CMR was correlated with perivascular fibrosis. Furthermore, no correlation was observed between PFR and cardiac function such as LVEF, CO, or LVEDP. These results suggest that coronary perivascular fibrosis occurs independently of interstitial myocardial fibrosis or cardiac function.

Coronary perivascular fibrosis and coronary blood flow

TFC is a simple, effective and quantitative index of coronary blood flow that is able to detect coronary microvascular dysfunction [11–15]. The present study demonstrates for the first time the significant correlation between PFR and CTFC for LAD, indicating that perivascular fibrosis is substantially associated with the impairment of coronary blood flow in patients with non-ischemic HF.

In the present study, PFR in biopsy samples from the septum was associated with CTFC for LAD, but not TFC for LCx or RCA. This finding appears to be reasonable as blood flow in the septum is supplied mainly by LAD [29]. As the present study indicated, PFR in the area supplied by LAD was significantly associated with CTFC. Thus, if we could examine PFR in the free walls supplied by LCx or RCA, PFR in such areas might be associated with TFC in the corresponding areas. Conversely, this finding also suggests that the evaluation of perivascular fibrosis of the septum does not reflect that of the whole heart.

In addition to PFR, the presence of atrial fibrillation, which was irrelevant to PFR, was also significantly correlated with CTFC for LAD, a consistent finding with the previous study that atrial fibrillation was associated with increased coronary resistance and impaired myocardial blood flow [30]. The present study did not show that hypertension, diabetes mellitus, and dyslipidemia were related to CTFC for LAD, probably due to the limited number of patients in the present study.

Table 1
Patient characteristics.

	HCM ($n=16$)	HHD ($n=11$)	DCM ($n=37$)	Notes
Male gender	13 (81)	8 (73)	27 (75)	
Age (years)	55.9 ± 12.4	53.4 ± 14.9	55.5 ± 13.5	
BMI (kg/m^2)	24.2 ± 4.0	25.6 ± 4.8	24.7 ± 4.2	
Hypertension	5 (31)	11 (100)	17 (46)	*,‡
Diabetes mellitus	2 (13)	5 (45)	6 (16)	‡
Dyslipidemia	2 (13)	3 (27)	10 (27)	
Atrial fibrillation	1 (6)	1 (9)	14 (38)	†
Medication				
ACEI	6 (38)	6 (55)	22 (59)	
ARB	2 (13)	8 (73)	13 (35)	*,‡
β-blocker	10 (63)	9 (82)	26 (70)	
Diuretics	0 (0)	3 (27)	21 (57)	†
Spironolactone	2 (13)	1 (9)	11 (30)	
Warfarin	2 (13)	2 (18)	18 (49)	†
CCB	7 (44)	6 (55)	4 (11)	†,‡
Antiplatelet	4 (25)	4 (36)	10 (27)	
Statin	0 (0)	1 (9)	9 (24)	†
Amiodarone	0 (0)	0 (0)	4 (11)	
Laboratory data				
Hemoglobin (g/dl)	14.4 ± 1.4	14.3 ± 1.9	14.3 ± 1.6	
hsCRP (mg/dl)	0.10 ± 0.14	0.15 ± 0.14	0.15 ± 0.17	
BNP (pg/ml)	218.7 ± 247.3	50.7 ± 33.9	240.6 ± 373.3	*
LDL (mg/dl)	77.8 ± 62.8	89.7 ± 75.0	85.2 ± 74.8	
HDL (mg/dl)	56.7 ± 23.5	39.3 ± 9.4	42.0 ± 12.5	*,†
TG (mg/dl)	130.9 ± 91.9	143.9 ± 65.2	138.3 ± 74.4	
Glucose (mg/dl)	94.5 ± 25.8	110.9 ± 19.5	106.4 ± 30.6	
CCr (ml/min)	89.4 ± 34.4	95.5 ± 24.2	93.8 ± 37.7	
Hemodynamic data				
LVEDVI (ml/m^2)	72.5 ± 18.3	72.7 ± 19.0	111.8 ± 28.0	†,‡
EF (%)	71.2 ± 10.1	54.4 ± 4.9	36.8 ± 11.8	*,†,‡
mAoP (mmHg)	103.8 ± 17.5	120.2 ± 19.7	98.8 ± 17.8	*,‡
LVEDP (mmHg)	16.6 ± 5.7	10.3 ± 5.1	10.6 ± 4.1	*,†
mPAP (mmHg)	19.9 ± 4.5	20.9 ± 7.0	18.9 ± 5.3	
PCWP (mmHg)	11.3 ± 6.2	9.3 ± 5.0	9.0 ± 5.3	
Cardiac output (L/min)	4.7 ± 1.0	5.9 ± 1.7	4.6 ± 1.4	*,‡
Cardiac index (L min^{-1} m^{-2})	2.7 ± 0.4	3.3 ± 0.6	2.7 ± 0.7	*,‡
Morphometric data				
CVF (%)	1.11 ± 1.04	1.89 ± 1.61	1.41 ± 1.48	
PFR	1.78 ± 1.09	1.63 ± 1.20	1.24 ± 0.45	†
All-cause death	1 (6)	0 (0)	2 (5)	
Cardiac events				
Cardiac or sudden death	0 (0)	0 (0)	2 (5)	
Admission for HF	2 (13)	0 (0)	3 (8)	

Results are presented as mean ± SD or n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CCB, calcium channel blocker; CCr, creatinine clearance; CVF, collagen volume fraction; DCM, dilated cardiomyopathy; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; HDL, high-density lipoprotein; HF, heart failure; HHD, hypertensive heart disease; hsCRP, high-sensitive C-reactive protein; LDL, low-density lipoprotein; LVEDP, left ventricular end-diastolic pressure; LVEDVI, left ventricular end-diastolic volume index; mAoP, mean aortic pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PFR, perivascular fibrosis ratio; TG, triglyceride.

* $p<0.05$, HCM vs. HHD.

† $p<0.05$, HCM vs. DCM.

‡ $p<0.05$, HHD vs. DCM.

Table 2
Thrombolysis in myocardial infarction frame counts.

Coronary artery	HCM ($n=16$)	HHD ($n=11$)	DCM ($n=37$[a])	p-Value
LAD (corrected)	21.91 ± 5.48	22.78 ± 6.23	21.67 ± 3.87	n.s.
LCx	29.63 ± 3.80	31.82 ± 8.55	33.30 ± 11.82	n.s.
RCA	39.50 ± 15.22	34.72 ± 9.39	38.72 ± 14.64	n.s.

Results are presented as mean ± SD. HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; DCM, dilated cardiomyopathy; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; n.s., not statistically significant.

[a] Data of LAD in one DCM case and that of RCA in another DCM case failed to be obtained.

Table 3
Logistic regression model for factors of corrected thrombolysis in myocardial infarction frame count for the left anterior descending coronary artery.

Variables	p-Value	Odds ratio (95% CI)
Hypertension	0.23	
Dyslipidemia	0.21	
Diabetes mellitus	0.63	
Atrial fibrillation	0.02	5.78 (1.33–30.53)
Body mass index (kg/m^2)	0.20	
PFR	<0.002	3.28 (1.52–9.00) per 1.0 increase
CVF (%)	0.81	

95% CI, 95% confidence interval; PFR, perivascular fibrosis ratio; CVF, collagen volume fraction.

Heart failure and coronary blood flow

It has been reported that coronary blood flow is impaired in aortic valve diseases because coronary blood flow depends on hemodynamic changes [31] and that coronary blood flow is determined by heart rate, peak stress, and ventricular performance in cardiomyopathy with normal coronary angiogram [32]. Coronary microvascular dysfunction has attracted much attention as a contributor to impaired coronary blood flow in various etiologies of HF [11]. The presence of microvascular dysfunction after acute myocardial infarction is now considered to be an important prognostic factor [33]. Coronary flow reserve, as an indicator of coronary blood flow, has been demonstrated to be impaired during acute phase of HF, and to be strongly correlated with the mortality of HF patients [9,10]. Thus, it is important to improve coronary blood flow in non-ischemic HF patients as well and to pay much attention to perivascular fibrosis as it is an important determinant of coronary blood flow.

Study limitations

Several limitations should be mentioned for the present study. First, coronary arteries in biopsy samples were partially crushed during the procedure, which might have affected the quantitative analyses of perivascular fibrosis, although we did not use the lumen area for the present analysis. Furthermore, myocardial biopsy samples from healthy controls were not available for apparent ethical reasons. Second, we only examined the role of perivascular fibrosis quantity but not its quality. Indeed, it has been reported that not only the quantity but also the quality of interstitial myocardial fibrosis (e.g. cross-linking and type I/III collagen ratio) are important determinants of myocardial stiffness [34–36]. Future studies are required to address this issue. Third, we used TFC method to evaluate coronary blood flow because we did not directly evaluate coronary flow velocity with a flow wire. This was based on the previous studies that TFC well represents coronary flow velocity [12,15,37,38]. Fourth, we were unable to elucidate the mechanisms and factors related to perivascular fibrosis. This issue should also be examined in future studies. Finally, the present study was an observational study with a relatively small number of patients. The relatively small numbers of all-cause deaths and admissions (Table 1) prevented us from investigating whether perivascular fibrosis has a prognostic impact. This issue also should be addressed in future studies with a large number of patients, including the effects of drugs to modulate perivascular fibrosis.

In conclusion, we were able to demonstrate that coronary perivascular fibrosis is significantly associated with impairment of coronary blood flow in non-ischemic HF patients. Thus, coronary perivascular fibrosis can be a new therapeutic target to improve coronary microcirculation in HF.

Disclosures

None.

Acknowledgments

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References

[1] Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009;119:e391–479.

[2] Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, Brosnihan B, Morgan TM, Stewart KP. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 2002;288:2144–50.

[3] Redfield MM, Jacobsen SJ, Burnett Jr JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194–202.

[4] Miura Y, Fukumoto Y, Shiba N, Miura T, Shimada K, Iwama Y, Takagi A, Matsusaka H, Tsutsumi T, Yamada A, Kinugawa S, Asakura M, Okamatsu S, Tsutsui H, Daida H, et al. Prevalence and clinical implication of metabolic syndrome in chronic heart failure. Circ J 2010;74:2612–21.

[5] Cleland JG, Cohen-Solal A, Aguilar JC, Dietz R, Eastaugh J, Follath F, Freemantle N, Gavazzi A, van Gilst WH, Hobbs FD, Korewicki J, Madeira HC, Preda I, Swedberg K, Widimsky J. Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey. Lancet 2002;360:1631–9.

[6] Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006;355:260–9.

[7] Shiba N, Watanabe J, Shinozaki T, Koseki Y, Sakuma M, Kagaya Y, Shirato K. Analysis of chronic heart failure registry in the Tohoku district: third year follow-up. Circ J 2004;68:427–34.

[8] Shiba N, Nochioka K, Miura M, Kohno H, Shimokawa H. Trend of westernization of etiology and clinical characteristics of heart failure patients in Japan—first report from the CHART-2 study. Circ J 2011;75:823–33.

[9] Neishi Y, Akasaka T, Tsukiji M, Kume T, Wada N, Watanabe N, Kawamoto T, Kaji S, Yoshida K. Reduced coronary flow reserve in patients with congestive heart failure assessed by transthoracic Doppler echocardiography. J Am Soc Echocardiogr 2005;18:15–9.

[10] Anantharam B, Janardhanan R, Hayat S, Hickman M, Chahal N, Bassett P, Senior R. Coronary flow reserve assessed by myocardial contrast echocardiography predicts mortality in patients with heart failure. Eur J Echocardiogr 2011;12:69–75.

[11] Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med 2007;356:830–40.

[12] Gibson CM, Cannon CP, Daley WL, Dodge Jr JT, Alexander Jr B, Marble SJ, McCabe CH, Raymond L, Fortin T, Poole WK, Braunwald E. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996;93:879–88.

[13] Sun H, Fukumoto Y, Ito A, Shimokawa H, Sunagawa K. Coronary microvascular dysfunction in patients with microvascular angina: analysis by TIMI frame count. J Cardiovasc Pharmacol 2005;46:622–6.

[14] Zalewski J, Zmudka K, Musialek P, Zajdel W, Pieniazek P, Kadzielski A, Przewlocki T. Detection of microvascular injury by evaluating epicardial blood flow in early reperfusion following primary angioplasty. Int J Cardiol 2004;96:389–96.

[15] Kunadian V, Harrigan C, Zorkun C, Palmer AM, Ogando KJ, Biller LH, Lord EE, Williams SP, Lew ME, Ciaglo LN, Buros JL, Marble SJ, Gibson WJ, Gibson CM. Use of the TIMI frame count in the assessment of coronary artery blood flow and microvascular function over the past 15 years. J Thromb Thrombolysis 2009;27:316–28.

[16] Aoki T, Fukumoto Y, Sugimura K, Oikawa M, Satoh K, Nakano M, Nakayama M, Shimokawa H. Prognostic impact of myocardial interstitial fibrosis in non-ischemic heart failure—comparison between preserved and reduced ejection fraction heart failure. Circ J 2011;75:2605–13.

[17] Higashi M, Shimokawa H, Hattori T, Hiroki J, Mukai Y, Morikawa K, Ichiki T, Takahashi S, Takeshita A. Long-term inhibition of Rho-kinase suppresses angiotensin II-induced cardiovascular hypertrophy in rats in vivo: effect on endothelial NAD(P)H oxidase system. Circ Res 2003;93:767–75.

[18] Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, Klocke FJ, Bonow RO, Judd RM. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 2000;343:1445–53.

[19] Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O, Bundy J, Finn JP, Klocke FJ, Judd RM. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation 1999;100:1992–2002.

[20] Nojiri A, Hongo K, Kawai M, Komukai K, Sakuma T, Taniguchi I, Yoshimura M. Scoring of late gadolinium enhancement in cardiac magnetic resonance imaging can predict cardiac events in patients with hypertrophic cardiomyopathy. J Cardiol 2011;58:253–60.

[21] Mohri M, Koyanagi M, Egashira K, Tagawa H, Ichiki T, Shimokawa H, Takeshita A. Angina pectoris caused by coronary microvascular spasm. Lancet 1998;351:1165–9.

[22] Diez J, Querejeta R, Lopez B, Gonzalez A, Larman M, Martinez Ubago JL. Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. Circulation 2002;105:2512–7.

[23] van Heerebeek L, Hamdani N, Handoko ML, Falcao-Pires I, Musters RJ, Kupreishvili K, Ijsselmuiden AJ, Schalkwijk CG, Bronzwaer JG, Diamant M, Borbely A, van der Velden J, Stienen GJ, Laarman GJ, Niessen HW, et al. Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension. Circulation 2008;117:43–51.

[24] Hein S, Arnon E, Kostin S, Schonburg M, Elsasser A, Polyakova V, Bauer EP, Klovekorn WP, Schaper J. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: structural deterioration and compensatory mechanisms. Circulation 2003;107:984–91.

[25] Graham HK, Trafford AW. Spatial disruption and enhanced degradation of collagen with the transition from compensated ventricular hypertrophy to symptomatic congestive heart failure. Am J Physiol Heart Circ Physiol 2007;292:H1364–72.

[26] Watanabe S, Shite J, Takaoka H, Shinke T, Tanino Y, Otake H, Matsumoto D, Ogasawara D, Sawada T, Hirata K, Yokoyama M. Predictive importance of left ventricular myocardial stiffness for the prognosis of patients with congestive heart failure. J Cardiol 2011;58:245–52.

[27] Tanaka M, Fujiwara H, Onodera T, Wu DJ, Hamashima Y, Kawai C. Quantitative analysis of myocardial fibrosis in normals, hypertensive hearts, and hypertrophic cardiomyopathy. Br Heart J 1986;55:575–81.

[28] Shirani J, Pick R, Roberts WC, Maron BJ. Morphology and significance of the left ventricular collagen network in young patients with hypertrophic cardiomyopathy and sudden cardiac death. J Am Coll Cardiol 2000;35:36–44.

[29] James TN, Burch GE. Blood supply of the human interventricular septum. Circulation 1958;17:391–6.

[30] Range FT, Schafers M, Acil T, Schafers KP, Kies P, Paul M, Hermann S, Brisse B, Breithardt G, Schober O, Wichter T. Impaired myocardial perfusion and perfusion reserve associated with increased coronary resistance in persistent idiopathic atrial fibrillation. Eur Heart J 2007;28:2223–30.

[31] Hongo M, Goto T, Watanabe N, Nakatsuka T, Tanaka M, Kinoshita O, Yamada H, Okubo S, Sekiguchi M. Relation of phasic coronary flow velocity profile to clinical and hemodynamic characteristics of patients with aortic valve disease. Circulation 1993;88:953–60.

[32] Weiss MB, Ellis K, Sciacca RR, Johnson LL, Schmidt DH, Cannon PJ. Myocardial blood flow in congestive and hypertrophic cardiomyopathy: relationship to peak wall stress and mean velocity of circumferential fiber shortening. Circulation 1976;54:484–94.

[33] Yasuda S, Shimokawa H. Acute myocardial infarction: the enduring challenge for cardiac protection and survival. Circ J 2009;73:2000–8.

[34] Kass DA, Bronzwaer JG, Paulus WJ. What mechanisms underlie diastolic dysfunction in heart failure? Circ Res 2004;94:1533–42.

[35] Fukui S, Fukumoto Y, Suzuki J, Saji K, Nawata J, Tawara S, Shinozaki T, Kagaya Y, Shimokawa H. Long-term inhibition of Rho-kinase ameliorates diastolic heart failure in hypertensive rats. J Cardiovasc Pharmacol 2008;51:317–26.

[36] Asif M, Egan J, Vasan S, Jyothirmayi GN, Masurekar MR, Lopez S, Williams C, Torres RL, Wagle D, Ulrich P, Cerami A, Brines M, Regan TJ. An advanced glycation endproduct cross-link breaker can reverse age-related increases in myocardial stiffness. Proc Natl Acad Sci USA 2000;97:2809–13.

[37] Bickel C, Rupprecht HJ, Maimaitiming A, Welk I, Blankenberg S, Krummenauer F, Meyer J. The superiority of TIMI frame count in detecting coronary flow changes after coronary stenting compared to TIMI Flow Classification. J Invasive Cardiol 2002;14:590–6.

[38] Gibson CM, Murphy S, Menown IB, Sequeira RF, Greene R, Van de Werf F, Schweiger MJ, Ghali M, Frey MJ, Ryan KA, Marble SJ, Giugliano RP, Antman EM, Cannon CP, Braunwald E. Determinants of coronary blood flow after thrombolytic administration TIMI Study Group. Thrombolysis in myocardial infarction. J Am Coll Cardiol 1999;34:1403–12.

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RAPID COMMUNICATION

Effect of the Great East Japan Earthquake on Cardiovascular Diseases

– Report From the 10 Hospitals in the Disaster Area –

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Background: We reported an increased occurrence of cardiovascular diseases (CVDs) after the Great East Japan Earthquake by examining ambulance records, but it had to be confirmed by cardiologists.

Methods and Results: We enrolled patients admitted to the cardiology department of the 10 hospitals in the disaster area from 4 weeks prior to 15 weeks after March 11 in the years 2008–2011 (n=14,078). The weekly occurrence of several CVDs, including heart failure (HF), pulmonary thromboembolism (PTE) and infectious endocarditis (IE), was sharply and significantly increased after the Earthquake.

Conclusions: The Disaster caused significantly increases in the occurrence of HF, PTE and IE. (*Circ J* 2013; **77:** 490–493)

Key Words: Cardiovascular disease; Disasters; Great East Japan Earthquake

We examined ambulance records from Miyagi prefecture and reported that the occurrence of cardiovascular diseases (CVDs), including heart failure (HF), acute coronary syndrome (ACS), stroke, and cardiopulmonary arrest, had increased after the Great East Japan Earthquake (magnitude 9.0 on March 11, 2011).[1] However, because the ambulance records were made in the emergency rooms by doctors who were not always cardiologists, our findings had to be confirmed by cardiologists in the disaster area. Furthermore, we did not examine the incidence of pulmonary thromboembolism (PTE), infectious endocarditis (IE) or takotsubo cardiomyopathy in that previous study because those diagnoses require a professional approach.[1]

In this study, we examined the medical records made by cardiologists to determine whether the occurrence of CVDs, including HF, acute myocardial infarction (AMI), PTE, IE and takotsubo cardiomyopathy, had increased after the Earthquake.

Methods

The ethical committees of Tohoku University Hospital and participating hospitals approved the protocol of the present study.

Study Population and Participating Hospitals

We enrolled all patients admitted to the cardiology department of the 10 hospitals in Miyagi prefecture from 4 weeks prior to 15 weeks after the Earthquake in 2011 and in the corresponding periods in 2008, 2009 and 2010 (n=14,078). We also col-

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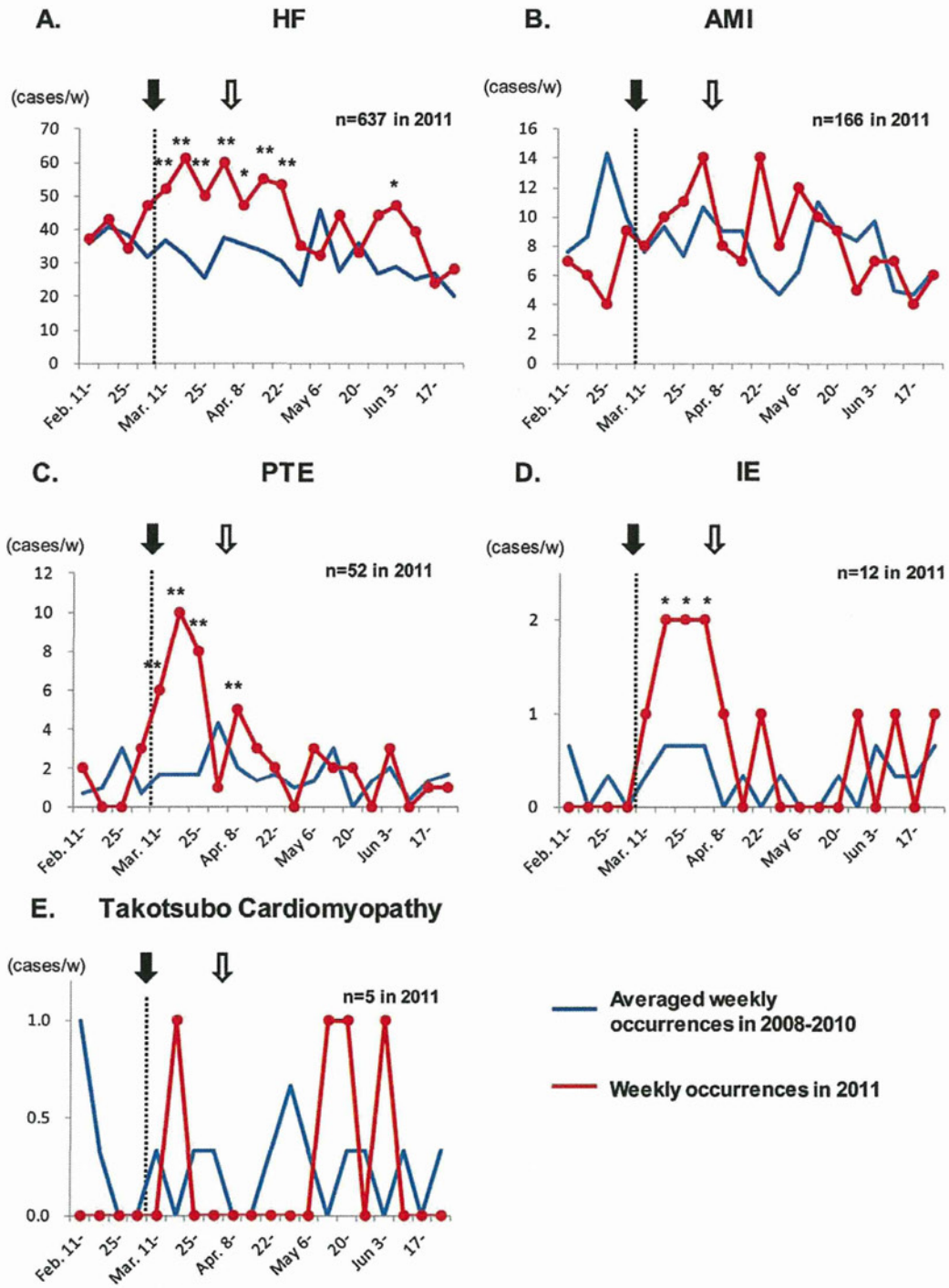

Figure 1. Weekly occurrence of cardiovascular diseases: (**A**) heart failure (HF), (**B**) acute myocardial infarction, (**C**) pulmonary thromboembolism (PTE), (**D**) infectious endocarditis (IE) and (**E**) takotsubo cardiomyopathy. HF, PTE and IE were significantly increased after the Earthquake. *P<0.05, **P<0.01. Black arrows indicate the occurrence of the Great East Japan Earthquake (magnitude 9.0, March 11, 2011), and white arrows indicate the largest aftershock (magnitude 7.2, April 7, 2011).

lected additional information about the date of admission, sex and age of the patients from the medical insurance database. We defined the 3 hospitals facing the Pacific Ocean as those in the seacoast area with direct assault by the tsunamis, and the remaining 7 hospitals as those in the inland (remote) area.

Definition of the Diseases

All definitive diagnoses of the patients were confirmed at discharge by cardiologists and classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). We also collected the diag-

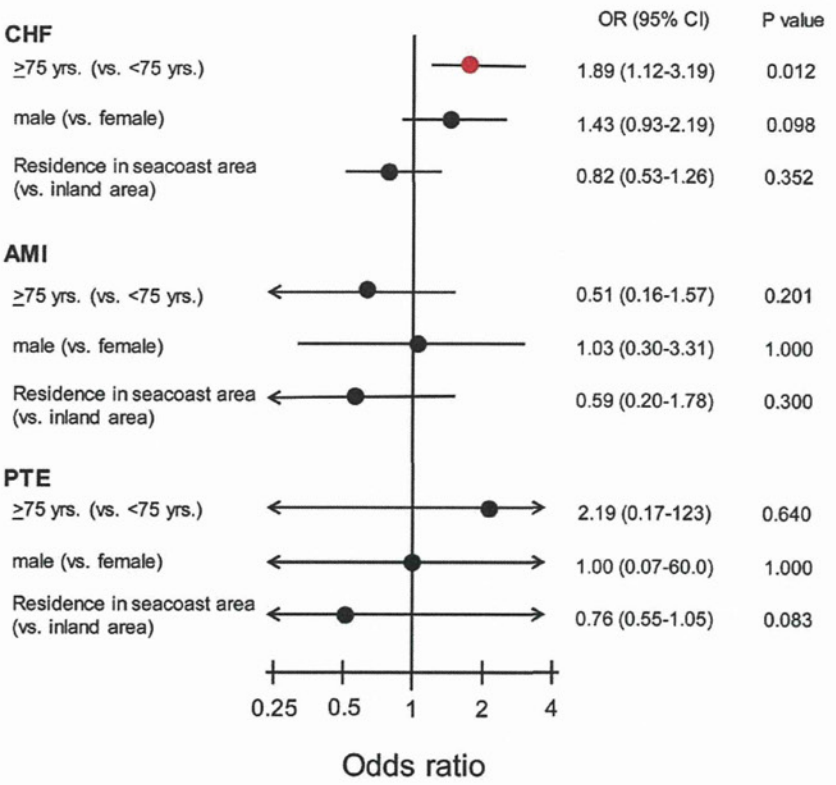

Figure 2. Effect of age, sex and area of residence on increased occurrence of cardiovascular diseases. We first counted the occurrence of each variable in the 4 weeks before and after the Earthquake in 2011, and subsequently calculated the odds ratio. No significant influence of age, sex or residence area was noted, except for the influence of high age on the occurrence of HF. Because there was no patient with IE or takotsubo cardiomyopathy before the Earthquake in 2011, we were unable to calculate the odds ratio of these 2 diseases. *P<0.05. AMI, acute myocardial infarction; HF, heart failure; PTE, pulmonary thromboembolism; OR, odds ratio; 95% CI, 95% confidence interval.

nosis at discharge from the medical insurance database as the ICD-10 code, comprising I-50.0 (HF), I-21.0–I-21.9 (AMI), I-26.0–I-26.9 (PTE), I-33.0–I-33.9 (IE) and takotsubo cardiomyopathy (I-51.8).

Statistical Analysis

We used a Poisson regression model to assess differences in the variables between 2011 and the previous 3 years.[1] Furthermore, as previously reported,[1] we calculated the odds ratio with the 4-week occurrence in 2011 before and after the Earthquake in terms of age (<75 or ≥75 years), sex, and area of residence (inland vs. seacoast). Continuous variables are expressed as mean±SD. All statistical analyses were performed using R 2.15.0 (www.r-project.org/). All P values were 2-sided, and P<0.05 was considered to be statistically significant.

Results

The number of patients enrolled in the study for 2008, 2009, 2010 and 2011 was 3,190, 3,582, 3,752 and 3,554, respectively. In 2011, the prevalence of male sex was significantly lower (62.2%, 61.75, 59.95 and 58.8% in 2008, 2009, 2010 and 2011, respectively, P=0.014) and age (years) was significantly higher (68.8±13.9, 69.5±13.9, 70.4±14.2, and 71.2±14.2 in 2008, 2009, 2010 and 2011, respectively, P<0.05).

The weekly occurrence of each of HF, PTE and IE was significantly increased after the Earthquake (**Figures 1A,C,D**). We also noted a mild but insignificant peak of the weekly occurrence of AMI after the Earthquake (**Figure 1B**). There were very few cases of takotsubo cardiomyopathy, even after the Earthquake (**Figure 1E**). The significant increase in the weekly occurrence of HF was prolonged for 7 weeks after the Earthquake in 2011 (**Figure 1A**), whereas the time course of PTE showed a second peak at the largest aftershock (magnitude 7.2 on April 7, 2011).

The subgroup analyses showed that among the 3 factors examined (age, sex, and area of residence), only higher age (>75 years) significantly influenced the occurrence of HF but not that of AMI or PTE (**Figure 2**). Because there was no patient with IE or takotsubo cardiomyopathy for 4 weeks before the Earthquake in 2011, we were unable to calculate the odds ratio of either disease.

Discussion

In the present study of cardiologists records, as compared with our recent study using ambulance records,[1] we were able to demonstrate the following: (1) a sharp and sustained (over 7 weeks) increase in the occurrence of HF after the Earthquake, (2) a sharp but transiently increased occurrence of both PTE and IE after the Earthquake, and (3) a tendency for the occurrence of AMI to be increased, but not that of takotsubo cardiomyopathy, after the Earthquake.

Increased Occurrences of CVD

The present study demonstrated a significant increase in the occurrence of both HF and PTE, consistent with the findings of our recent study[1] and another study,[2] and of IE, which was a novel finding not reported previously.[3–8]

The Earthquake forced many people in the Miyagi prefecture to take shelter and/or to live without daily necessities, services, and medicines. Disaster situations can increase the occurrence of CVDs through physical and mental stresses.[9] Furthermore, a prolonged stressful situation can suppress the immune sys-

tem,[10] leading to increased rates of infectious diseases, such as IE.

Activation of the sympathetic nervous system of people involved in the present disaster would have elevated both blood pressure and heart rate, as previously reported.[9,11] The report by Satoh et al has also demonstrated that self-monitored blood pressure significantly increased after the Earthquake.[12] Furthermore, we recently reported that the Earthquake increased the occurrence of ventricular tachyarrhythmias among patients with an implantable cardiac defibrillator.[13] Thus, we consider that an activated sympathetic nervous system, elevated blood pressure, and increased occurrence of tachyarrhythmias were all involved in the increased occurrence of HF during and after the Great East Japan Earthquake.

Although people in temporary accommodation were supplied with information and compression stockings, the increased occurrence of PTE after the Earthquake was not prevented.[3] The occurrence of severe PTE, with resultant improved mortality from PTE, may have been decreased; however, further studies regarding the effects of preventive practice for PTE are needed.

In the present study, the occurrence of AMI also tended to increase after the Earthquake, and in our recent study there was a significant increase in the occurrence of ACS (AMI plus unstable angina).[1] Unlike in a previous report,[3] we did not observe an increased occurrence of takotsubo cardiomyopathy. The reasons for the discrepancy remains to be examined in future studies.

Effects of Age, Sex and Location of Hospitals on CVDs

In the present study, no significant influence of age, sex or area of residence was noted for CVDs, except for the influence of higher age on the occurrence of HF, which suggested that the Earthquake had a greater effect on elderly people.

Although the tsunami directly and seriously affected the seacoast area, the increased occurrence of CVDs after the Earthquake was comparable between the seacoast and inland areas. Similar indirect effects of a disaster on CVD occurrence were reported after the World Trade Center Disaster in 2001, whereby the blood pressure of people in Mississippi was equally elevated as in those in New York City.[14] These results indicate that life-threatening events, such as a great earthquake, can trigger CVDs even in remote areas.

The limitations of this study include the lack of detailed patient data, such as clinical characteristics and underlying heart disease. In order to prospectively observe the long-term prognosis of the patients, we are following the HF patients in a cohort in the Tohoku area,[15] which had been established 2.5 years before the Earthquake.

Conclusions

The Great East Japan Earthquake Disaster significantly increased the occurrence of CVDs, including HF, PTE and IE. Elderly patients with HF were significantly more affected by the Earthquake.

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Disclosures

None.

References

1. Aoki T, Fukumoto Y, Yasuda S, Sakata Y, Ito K, Takahashi J, et al. The Great East Japan Earthquake Disaster and cardiovascular diseases. *Eur Heart J* 2012; **33:** 2796–2803.
2. Watanabe H, Kodama M, Tanabe N, Nakamura Y, Nagai T, Sato M, et al. Impact of earthquakes on risk for pulmonary embolism. *Int J Cardiol* 2008; **129:** 152–154.
3. Watanabe H, Kodama M, Okura Y, Aizawa Y, Tanabe N, Chinushi M, et al. Impact of earthquakes on takotsubo cardiomyopathy. *JAMA* 2005; **294:** 305–307.
4. Suzuki S, Sakamoto S, Miki T, Matsuo T. Hanshin-Awaji Earthquake and acute myocardial infarction. *Lancet* 1995; **345:** 981.
5. Suzuki S, Sakamoto S, Koide M, Fujita H, Sakuramoto H, Kuroda T, et al. Hanshin-AwajiEearthquake as a trigger for acute myocardial infarction. *Am Heart J* 1997; **134:** 974–977.
6. Leor J, Poole WK, Kloner RA. Sudden cardiac death triggered by an earthquake. *N Engl J Med* 1996; **334:** 413–419.
7. Zhang XQ, Chen M, Yang Q, Yan SD, Huang DJ. Effect of the wenchuan earthquake in china on hemodynamically unstable ventricular tachyarrhythmia in hospitalized patients. *Am J Cardiol* 2009; **103:** 994–997.
8. Tsuchida M, Kawashiri MA, Teramoto R, Takata M, Sakata K, Omi W, et al. Impact of severe earthquake on the occurrence of acute coronary syndrome and stroke in a rural area of Japan. *Circ J* 2009; **73:** 1243–1247.
9. Esler M, Kaye D. Sympathetic nervous system activation in essential hypertension, cardiac failure and psychosomatic heart disease. *J Cardiovasc Pharmacol* 2000; **35:** S1–S7.
10. Segerstrom SC, Miller GE. Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. *Psychol Bull* 2004; **130:** 601–630.
11. Kario K. Disaster hypertension: Its characteristics, mechanism, and management. *Circ J* 2012; **76:** 553–562.
12. Satoh M, Kikuya M, Ohkubo T, Imai Y. Acute and subacute effects of the Great East Japan Earthquake on home blood pressure values. *Hypertension* 2011; **58:** e193–e194.
13. Nakano M, Kondo M, Wakayama Y, Kawana A, Hasebe Y, Shafee MA, et al. Increased incidence of tachyarrhythmias and heart failure hospitalization in patients with implanted cardiac devices after the Great East Japan Earthquake Disaster. *Circ J* 2012; **76:** 1283–1285.
14. Gerin W, Chaplin W, Schwartz JE, Holland J, Alter R, Wheeler R, et al. Sustained blood pressure increase after an acute stressor: The effects of the 11 September 2001 attack on the New York City World Trade Center. *J Hypertens* 2005; **23:** 279–284.
15. Shiba N, Nochioka K, Miura M, Kohno H, Shimokawa H, CHART-2 Investigators. Trend of westernization of etiology and clinical characteristics of heart failure patients in Japan: First report from the Chart-2 Study. *Circ J* 2011; **75:** 823–833.