Possible Mechanisms Underlying Elevated Serum N-Terminal Pro-Brain Natriuretic Peptide in Healthy Japanese Subjects

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Background: The precise mechanisms underlying elevation of serum N-terminal pro-brain natriuretic peptide (NT-proBNP) in healthy subjects have not been fully clarified.

Methods and Results: In 2,844 Japanese healthy subjects with serum NT-proBNP <125 pg/mL, (1) brachial-ankle pulse wave velocity and (2) second peak of the peripheral systolic blood pressure minus diastolic blood pressure (pulse pressure 2 [PP2]), as markers of cardiac afterload; (3) fibrosis 4 score (FIB-4 score, a marker of liver fibrosis), as a marker of cardiac preload; and (4) ratio of the pre-ejection time to ejection time (PEP/ET), as a marker of cardiac systolic function, were measured. At the first examination, after the adjustments, log-transformed serum NT-proBNP was associated with PP2 and FIB-4 score, but not with PEP/ET. These parameters were successfully measured again after a 3-year interval in 1,978 subjects. On Pearson's correlation analysis, change in PP2 and FIB-4 score during the study period was significantly correlated with change in serum NT-proBNP (r=0.05, 0.09, respectively; P<0.01).

Conclusions: In apparently healthy Japanese subjects, both increased cardiac preload and increased cardiac afterload, but not impaired cardiac systolic function, may be associated with elevated serum NT-proBNP.

Key Words: Cardiac preload/afterload; Cardiac systolic function; NT-proBNP

Serum natriuretic peptide is a useful marker for the diagnosis of acute heart failure (HF). Moreover, it reflects the prognosis and allows prediction of the short- and long-term outcomes in patients with HF. According to the guidelines of the European Society of Cardiology and American Heart Association/American College of Cardiology Foundation, blood levels of natriuretic peptides, such as B-type natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP), are useful markers for the diagnosis, prediction of outcome and selection of treatment for HF. Cardiomyocyte stretching is the most important stimulus for the production of natriuretic peptide in the heart; therefore, cardiac systolic dysfunction, increased cardiac preload and/or increased cardiac afterload can increase the production of NT-proBNP. Recently, several prospective observational studies have reported that slightly elevated blood natriuretic peptide in the general population (i.e., a lower degree of elevation than in patients with HF) is a predictor of new-onset HF or of atrial fibrillation (AF). The precise mechanisms underlying elevation of the blood natriuretic peptide level in healthy subjects, however, which could be related to the risk of development of HF, have not yet been fully clarified.

The present study of cross-sectional and longitudinal assessments was conducted to examine the associations of elevated serum NT-proBNP with the abdominal compartment. This compartment might be associated with elevation of the cardiac preload, as assessed on measurement of the fibrosis 4 score (FIB-4 score), elevation of the cardiac afterload, as assessed on measurement of the pulse wave velocity and pulse wave analysis, and impairment of the cardiac systolic function, as assessed on measurement of the cardiac systolic time interval, in apparently healthy Japanese subjects.

Methods

A flow chart of the participant selection procedure is shown in Figure. Cross-sectional and longitudinal studies were conducted. The participants in this study were employees of a construction company. In Japan, all company employees are obligated to undergo annual health checkups. We used the data from the annual health checkups recorded in 2009 and 2012. The health checkup protocol has already been described. The health checkup examinations, including medical interview, physical examination, blood and urine examinations, blood pressure measurement (2 times), brachial-ankle pulse wave velocity...
Cardiac Preload and NT-proBNP

was automatically calculated by subtracting the ET from QS2.14,15

AI Measurements of the blood pressure and radial AI were performed after the participants had rested in the sitting position for at least 5 min. Blood pressure was measured in the right upper arm using the oscillometric method (HEM-907; Omron Healthcare, Kyoto, Japan). Immediately after this measurement, the left radial arterial waveform was recorded using an arterial applanation tonometry probe equipped with 40 micropiezo-resistive transducers (HEM-9010AI; Omron Healthcare). The HEM-9010AI device is programmed to automatically determine the pressure of the radial artery, to yield the optimal radial arterial waveform.16 Then, the first and second peaks of the peripheral systolic blood pressure (SBP1, a marker of the brachial blood pressure; and SBP2, a marker of the central systolic blood pressure) and peripheral diastolic blood pressure (DBP) were automatically detected using the fourth derivatives for each radial arterial waveform, and averaged. Radial AI, a marker of the central AI, was calculated as follows: (SBP2−DBP)/(SBP1−DBP)×100 (%).16 Pulse pressure 1 (PP1)=SBP1−DBP, and PP2=SBP2−DBP, a marker of the CPP, were also calculated.16

Laboratory Measurements
Fasting serum triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), creatinine (Cr), serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentration, and fasting plasma glucose were measured using enzymatic methods, and platelet count (PLT) was measured using the sheath flow method (Falco Biosystems, Tokyo, Japan). Serum NT-proBNP was determined on chemiluminescence immunoassay (Roche Diagnostic, Mannheim, Germany). All blood samples were obtained in the morning after the participants had fasted overnight on the same day to measure the blood

(baPWV), radial augmentation index (r-AI) and ratio of the pre-ejection time to ejection time (PEP/ET) were conducted in the morning after the participants had fasted overnight.

In 2009, 3,276 employees underwent annual checkup. Of these, 236 employees were excluded because of the following: presence of AF, past history of treatment for liver disease, chronic kidney disease, heart disease and/or stroke, ankle/brachial index (ABI) <0.9, and standard deviation of the radial AI ≥6%. Moreover, in 2009, we also excluded 196 employees with serum NT-proBNP >125 pg/mL and PEP/ET >0.43 or not measured at all. Based on Reant et al and Park et al,11,12 we excluded subjects with PEP/ET >0.43 given that this indicated cardiac systolic dysfunction. In other words, we excluded these subjects who had already developed HF or cardiac systolic dysfunction. Of the 2,844 employees, 1,999 were successfully followed up until 2012. The study was conducted with the approval of the Ethics Guidelines Committee of Tokyo Medical University.

Measurements
PWV, PEP and ET The baPWV was measured using a volume plethysmograph (Form/ABI; Colin, Komaki, Japan), in accordance with a previously described methodology.13 In brief, the brachial and post-tibial arterial pressures were measured using an oscillometric sensor. Measurements were recorded after the participants had rested for at least 5 min in the supine position in a temperature-controlled room (24–26°C) designed exclusively for this purpose. The ET was automatically measured from the foot to the dicrotic notch (equivalent to the incisura on the down-stroke of the aortic pressure waveform produced by closure of the aortic valves) of the pulse-volume waveform. The total electromechanical systolic interval (QS2) was measured from the onset of the QRS complex on the electrocardiogram to the first high-frequency vibrations of the aortic component of the second heart sound on the phonocardiogram. The PEP

Figure. Participant selection procedure. AI, augmentation index; ET, ejection time; NT-proBNP, N-terminal pro-brain natriuretic peptide; PEP, pre-ejection time.
pressure, baPWV and radial AI; FIB-4 score was calculated using the following formula: (age [years] × AST [U/L]) / (PLT [10^9/L] × ALT [U/L])^{1.17}. The result was primarily driven by the relationship between the cardiac afterload, as assessed on PP2, and FIB-4 and PEP/ET (Table 2). On multivariate regression analysis with adjustments, significant positive associations were also seen between r-AI, SBP2, PP2, FIB-4 and log BNP; in contrast, no significant association was seen between log BNP and PEP/ET (Table 2). Of the 2,844 participants, 1,999 successfully underwent measurement of the same parameters after a 3-year interval. baPWV, PP2, r-AI, FIB-4 and PEP/ET at the second examination were higher than at the first examination (Table 3). On Pearson’s correlation analysis, the change in serum NT-proBNP during the 3-year period was significantly positively correlated with the change in FIB-4 and in PP2 during the same period. Multivariate regression analysis with adjustment identified change in FIB-4 score as being significantly positively correlated with change in serum NT-proBNP during the 3-year study period (Table 4).

### Table 1. Clinical Subject Characteristics: First Examination

| Parameter                  | n      | 2,844 |
|----------------------------|--------|-------|
| Age (years)                | 45±9   |       |
| Men/Women                  |        | 2,407/437 (85/15) |
| BMI (kg/m²)                | 23.6±3 |       |
| Alcohol drinking (current) | 2,388 (84) |
| Alcohol intake (ethanol g/day) | 9.7±7.1 |
| Smoking (current)          | 703 (25) |
| SBP (mmHg)                 | 121±15 |
| DBP (mmHg)                 | 75±11  |
| Pulse rate (beats/min)     | 68±9   |
| Hb (g/L)                   | 145±13 |
| PLT (×10⁹/L)               | 231±49 |
| AST (U/L)                  | 22.8±9 |
| ALT (U/L)                  | 25.0±17 |
| TC (mmol/L)                | 5.3±0.9 |
| HDL-C (mmol/L)             | 1.7±0.5 |
| TG (mmol/L)                | 1.3±1.1 |
| FPG (mmol/L)               | 5.0±0.7 |
| Serum creatinine (μmol/L)  | 73±12  |
| Serum NT-pro BNP (pg/mL)   | 27±22  |
| baPWV (cm/s)               | 1,275±191 |
| r-AI (%)                   | 71±14  |
| SBP2 (mmHg)                | 108±16 |
| PP2 (mmHg)                 | 33±9   |
| FIB-4                      | 0.9±0.4 |
| PEP/ET                     | 0.3±0.04 |

Data given as n (%) or mean±SD. ALT, alanine aminotransferase; AST, aspartate aminotransferase; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; FIB-4, fibrosis 4; FPG, fasting plasma glucose; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PEP/ET, ratio of pre-ejection period to ejection time; PLT, platelet count; PP2, second peak of the radial pressure waveform minus first peak of the radial pressure waveform; r-AI, radial augmentation index; SBP, systolic blood pressure; SBP2, second peak of the radial pressure waveform; TC, total cholesterol; TG, triglycerides.

### Results

The present study is the first prospective observational study to assess the association of serum NT-proBNP with the abdominal compartment. This compartment might be associated with elevation of the cardiac preload, as assessed on FIB-4 score,9 cardiac afterload, as assessed on PP2, and cardiac systolic function, as assessed on PEP/ET, in healthy Japanese subjects. Elevated FIB-4 score and PP2, but not PEP/ET, were associated with elevated serum NT-proBNP. Moreover, change in serum NT-proBNP during the 3-year study period was associated with change in FIB-4 score during the same period.

### Discussion

Elevated serum BNP is a known predictor of the future development of HF. Therefore, studies to clarify the association of serum BNP with the pathophysiological abnormalities associated with the development of HF in its early stages are highly relevant. Cardiac wall stress induces synthesis of natriuretic peptide by the cardiac myocytes; thus, increased cardiac afterload is known to affect natriuretic peptide synthesis. Serum BNP has also been shown to be associated with the markers of cardiac afterload, such as PWV and/or AI, in the general population.18-20 In contrast, increased cardiac preload may directly affect the Akt pathway, which may then trigger the synthesis of the natriuretic peptide.21,22 Thus, both increased cardiac afterload and increased cardiac preload could be associated with elevated secretion of natriuretic peptide. Except in our previous study,23 the relationship between the cardiac preload and serum BNP/NT-proBNP has never been clarified in healthy subjects. In our previous study, conducted in the same cohort as that used for the present study, markers of the cardiac afterload (i.e., AI, PP2 and brachial-ankle PWV) and the abdominal compartment, which might be associated with elevation of the cardiac preload, as

### Table 2

| Parameter                  | n   | 2,407 |
|----------------------------|-----|-------|
| SBP (mmHg)                 | 121±15 |
| DBP (mmHg)                 | 75±11  |
| Pulse rate (beats/min)     | 68±9   |
| Hb (g/L)                   | 145±13 |
| PLT (×10⁹/L)               | 231±49 |
| AST (U/L)                  | 22.8±9 |
| ALT (U/L)                  | 25.0±17 |
| TC (mmol/L)                | 5.3±0.9 |
| HDL-C (mmol/L)             | 1.7±0.5 |
| TG (mmol/L)                | 1.3±1.1 |
| FPG (mmol/L)               | 5.0±0.7 |
| Serum creatinine (μmol/L)  | 73±12  |
| Serum NT-pro BNP (pg/mL)   | 27±22  |
| baPWV (cm/s)               | 1,275±191 |
| r-AI (%)                   | 71±14  |
| SBP2 (mmHg)                | 108±16 |
| PP2 (mmHg)                 | 33±9   |
| FIB-4                      | 0.9±0.4 |
| PEP/ET                     | 0.3±0.04 |

Statistical Analysis

All data are expressed as mean±SD. Differences in the variables between the first and second examinations were assessed using paired t-test or the McNemar test. Change in the variables during the study period was calculated by subtracting the values recorded at the first examination from those recorded at the second examination. Serum NT-proBNP was log-transformed for the analysis. The relationships between log-transformed serum NT-proBNP (log BNP) and the variables were assessed using Pearson’s correlation and multivariate linear regression analysis with adjustments for confounding covariates. The covariates adjusted for were age, body mass index (BMI), heart rate, SBP, Cr and hemoglobin. All the analyses were conducted using IBM/SPSS version 25.0 (IBM/SPSS, Chicago, IL, USA). The level of significance was set at P<0.05.

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assessed on FIB-4 score, were significantly associated with serum NT-proBNP.

**Serum BNP and Cardiac Systolic Function**
Cardiac afterload and preload affect cardiac systolic function. Patients with HF with preserved ejection fraction have lower serum BNP than those with HF with reduced ejection fraction. Even so, it has not been clarified in apparently healthy subjects as to whether elevated serum BNP is directly associated with abnormal cardiac preload and/or cardiac afterload, or if it is due to impaired cardiac systolic function. Nevertheless, serum BNP was not significantly correlated with left ventricular (LV) ejection fraction (LVEF) in the subjects who underwent diagnostic cardiac catheterization and did not have significant coronary artery stenosis or abnormal LV wall motion. In the present study, we showed that serum NT-proBNP was associated with the markers of the central hemodynamics and also with a marker of the cardiac preload, irrespective of the status of the cardiac systolic function, in healthy Japanese subjects. Thus, the present study suggests that in the early stages of the development of HF, increased cardiac afterload and preload are independently associated with elevated serum NT-proBNP, irrespective of cardiac systolic function status.

**Clinical Implications**
In healthy subjects in the present study, serum NT-proBNP was associated with the central hemodynamics and cardiac preload, rather than with cardiac systolic function. The clinical implication is that even in patients with normal cardiac systolic function, inappropriate control of the cardiac preload/afterload may increase the risk of HF. A recent epidemiological study showed that advanced age, high BMI, elevated SBP, increased heart rate, elevated serum Cr, smoking habit, presence of diabetes mellitus, history of coronary artery disease, and history of use of antihypertensive medication are all associated with an increased risk of HF. All of these factors are associated with increased arterial stiffness, which increases the cardiac afterload, and therapeutic lifestyle modifications can improve these risk factors. Therefore, further study is needed to clarify the benefits of therapeutic lifestyle modifications for preventing the development of HF via improvement of the arterial stiffness.

**Study Limitations**
The present study had several limitations. First, it was conducted in healthy Japanese subjects and most of the subjects were men; therefore, further studies are needed to examine the associations in other ethnic groups and in women. Second, subjects with a history of liver disease, heart disease and/or stroke were excluded from the present study, but the presence of these diseases was confirmed only on self-administered questionnaire survey, and not on quantitative examination. Third, non-invasive modalities (e.g., echocardiography, carotid ultrasound, elastography) can be used for assessment of the liver stiffness and cardiac systolic function, but we did not conduct the assessments using these modalities. Fourth, we used FIB-4 index as a marker of the cardiac preload and PEP/ET as a marker of the cardiac systolic function, but these associations have

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### Table 2. Correlations of Log-Transformed Serum NT-proBNP With Markers of Cardiac Afterload, Cardiac Preload, Cardiac Systolic Function at First Examination

| Pearson's correlation analysis | Variables | Correlation coefficient | P-value |
|-------------------------------|-----------|------------------------|---------|
| FIB-4                         | 0.23      | <0.01                  |         |
| baPWV                         | 0.03      | 0.08                   |         |
| r-AI                          | 0.28      | <0.01                  |         |
| SBP2                          | 0.07      | 0.01                   |         |
| PP2                           | 0.21      | <0.01                  |         |
| PEP/ET                        | -0.11     | <0.01                  |         |

| Multivariate linear regression analysis | Variables | Total R² | Standardized coefficient | Non-standardized coefficient (95% CI) | P-value |
|---------------------------------------|-----------|----------|--------------------------|-------------------------------------|---------|
| FIB-4‡                               | 0.21      | 0.09     | 0.18 (0.10–0.25)         | <0.01                               |         |
| SBP2‡                                | 0.21      | 0.21     | 0.01 (0.01–0.02)         | <0.01                               |         |
| FIB-4‡                               | 0.21      | 0.10     | 0.18 (0.11–0.26)         | <0.01                               |         |
| r-AI‡                                | 0.21      | 0.11     | 0.007 (0.004–0.009)      | <0.01                               |         |
| PP2‡                                 | 0.22      | 0.10     | 0.18 (0.11–0.26)         | <0.01                               |         |

†Variables were entered individually with the covariates used for adjustments in each model. ‡Both variables were entered simultaneously with the covariates used for adjustments in the same model. Basic covariates adjusted for: age, BMI, SBP, heart rate, Hb, creatinine. Abbreviations as in Table 1.
not been demonstrated on echocardiography or pulmonary artery catheterization. Fifth, we excluded subjects with PEP/ET >0.43; PEP/ET >0.43 is a useful marker of LVEF <35%. Therefore, subjects with mild cardiac systolic dysfunction (LVEF around 40%) could have been included in the present study. Sixth, in the present study, of the 2,844 participants at baseline, data of only 1,999 participants were available at the end of the study period, because some subjects moved from the company headquarters to branch offices, or due to layoff, retirement, and so forth.

Data given as n (%) or mean ± SD. Abbreviations as in Table 1.

| Table 3. Change in Subject Clinical Characteristics |
| Parameter | First examination | Second examination | P-value |
| n | 1,999 | 1,999 | |
| Age (years) | 44±8 | 47±8 | <0.01 |
| BMI (kg/m²) | 23.5±3 | 23.7±3 | <0.01 |
| Alcohol drinking (current) | 1.673 (84) | 1.666 (83) | 0.49 |
| Alcohol intake (ethanol g/day) | 9.7±7.0 | 17.0±17.0 | <0.01 |
| Smoking (current) | 483 (24) | 414 (21) | <0.01 |
| SBP (mmHg) | 120±15 | 119±15 | <0.01 |
| DBP (mmHg) | 74±11 | 72±11 | <0.01 |
| Pulse rate (beats/min) | 68±9 | 68±9 | <0.01 |
| Hb (g/L) | 145±13 | 144±12 | <0.01 |
| PLT (×10⁹/L) | 231±48 | 230±48 | <0.01 |
| AST (U/L) | 5.4±0.9 | 4.5±0.9 | <0.01 |
| ALT (U/L) | 1.7±0.5 | 1.7±0.4 | <0.01 |
| TC (mmol/L) | 24.9±18 | 25.3±18 | <0.01 |
| HDL-C (mmol/L) | 73±11 | 71±12 | <0.01 |
| Serum creatinine (μmol/L) | 5.9±0.6 | 5.4±0.7 | <0.01 |
| Serum NT-proBNP (pg/mL) | 1.259±176 | 1.285±195 | <0.01 |
| baPWV (cm/s) | 71±14 | 73±13 | <0.01 |
| r-AI (%) | 107±15 | 106±15 | <0.01 |
| PP2 (mmHg) | 32±8 | 34±9 | <0.01 |
| FIB-4 | 0.98±0.4 | 1.0±0.4 | <0.01 |
| PEPI/ET | 0.34±0.04 | 0.35±0.05 | <0.01 |

Medication history
Hypertension | 151 (8) | 212 (11) | <0.01 |
Dyslipidemia | 59 (3) | 104 (5) | <0.01 |
Diabetes mellitus | 46 (2) | 65 (3) | <0.01 |

Table 4. Significant Indicators of Change in Serum NT-proBNP

Pearson’s correlation analysis

| Correlation coefficient | P-value |
|------------------------|---------|
| δ FIB-4 | 0.09 | <0.01 |
| δ baPWV | −0.004 | 0.87 |
| δ r-AI | 0.02 | 0.35 |
| δ SBP2 | 0.04 | 0.06 |
| δ PP2 | 0.06 | 0.01 |
| δ PEP/ET | −0.14 | <0.01 |

Multivariate linear regression analysis

| Total R² | Standardized coefficient | Non-standardized coefficient (95% CI) | P-value |
|---------|--------------------------|-------------------------------------|---------|
| δ FIB-4 | 0.01 | 0.09 | 1.22 (0.68–1.75) | <0.01 |
| δ PP2 | 0.01 | 0.06 | 0.24 (0.05–0.42) | 0.01 |

Both variables were entered simultaneously in the same model. δ (delta), measurement at the second examination minus the measurement at the first examination. Abbreviations as in Table 1.
Conclusions
Not only cross-sectional, but also longitudinal associations were found between serum NT-proBNP and the markers of central hemodynamics and FIB-4 score in healthy Japanese subjects; no such association of serum NT-proBNP was observed with PEP/PT, a marker of cardiac systolic function. Thus, in middle-aged Japanese men without apparent HF, abnormal abdominal compartment, which might be associated with elevation of the cardiac preload, and cardiac afterload, rather than impaired cardiac systolic function, were associated with elevated serum NT-proBNP. Thus, abnormal abdominal compartment and cardiac afterload may serve as risk factors for the development of HF in the early stages.

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Disclosures
With regard to the employee data, the sponsor (Omron Health Care Company) assisted in the data formatting (i.e., the data of the brachial-ankle pulse wave velocity stored in the hard disc of the equipment used for measurement of the brachial-ankle pulse wave velocity was transferred to an Excel file). Other than this, however, the company played no role in the design or conduct of the study, that is, in the data collection, management, analysis or interpretation of the data, or in the preparation, review or approval of the manuscript. The authors declare no other conflicts of interest.

References
1. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347:161 – 167.
2. Wright GA, Struthers AD. Natriuretic peptides as a prognostic marker and therapeutic target in heart failure. Heart 2006; 92:149 – 151.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Kardiol Pol 2016; 74:1037 – 1147 (in Polish).
4. Writing Committee Members, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013; 128:e240 – e327.
5. Tokola H, Hautala N, Marttila M, Magga J, Pikkarainen S, Kerkela R, et al. Mechanical load-induced alterations in B-type natriuretic peptide gene expression. Can J Physiol Pharmacol 2001; 79:646 – 653.
6. Swetzler NK, Hetzel SJ, Skalski J, Velez M, Eggleston K, Mitchell GF. Left ventricular responses to acute changes in late systolic pressure augmentation in older adults. Am J Hypertens 2013; 26:866 – 871.
7. Ledwidge M, Gallagher J, Coulon C, Tallon E, O’Connell E, Dawkins I, et al. Natriuretic peptide-based screening and collaborative care for heart failure: The STOP-HF randomized trial. JAMA 2013; 310:66 – 74.
8. Whitman IR, Vittinghoff E, DeFilippi CR, Gottdiener JS, Alonso A, Patsy BM, et al. NT-proBNP as a mediator of the racial difference in incident atrial fibrillation and heart failure. J Am Heart Assoc 2019; 8:e010868.
9. Verbrugge FH, Dupont M, Steels P, Grieten L, Malbrain M, Tang WH, et al. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. J Am Coll Cardiol 2013; 62:485 – 495.
10. Tamiyama H, Nishikimi T, Matsumoto C, Kimura K, Odaira M, Shinka I, et al. Longitudinal changes in late systolic cardiac load and serum NT-proBNP levels in healthy middle-aged Japanese men. J Am Coll Cardiol 2010; 55:1979 – 1987.
11. Reant P, Dijsor M, Donal E, Mignon A, Ritter P, Bordachar P, et al. Systolic time intervals as simple echocardiographic parameters of left ventricular systolic performance: Correlation with ejection fraction and longitudinal two-dimensional strain. Eur J Echocardiogr 2010; 11:834 – 844.
12. Park KH, Park WJ, Han SJ, Kim HS, Jo SH, Kim SA, et al. Clinical meaning of the ratio of brachial pre-ejection period to brachial ejection time in patients with left ventricular systolic dysfunction. Int Heart J 2018; 59:566 – 572.
13. Tamiyama H, Hashimoto H, Tanaka H, Matsumoto C, Odaira M, Yamada J, et al. Continuous smoking and progression of arterial stiffening: A prospective study. J Am Coll Cardiol 2010; 55:1979 – 1987.
14. Chen SC, Chang JM, Tsai JC, Hsu PC, Lin TH, Su HM, et al. A new systolic parameter defined as the ratio of brachial pre-ejection period to brachial ejection time predicts overall and cardiovascular mortality in hemodialysis patients. Hypertens Res 2010; 33:492 – 498.
15. Su HM, Lin TH, Lee CS, Lee HC, Chu CY, Hsu PC, et al. Myocardial performance index derived from brachial-ankle pulse wave velocity: A novel and feasible parameter in evaluation of cardiac performance. Am J Hypertens 2009; 22:871 – 876.
16. Tamiyama H, Yamazaki M, Sagawa Y, Teraoka K, Shirota T, Miyawaki Y, et al. Synergistic effect of smoking and blood pressure on augmentation index in men, but not in women. Hypertens Res 2009; 32:122 – 126.
17. Loko MA, Castella L, Dabis F, Le Bail B, Winnock M, Coureau G, et al. Validation and comparison of simple noninvasive indexes for predicting liver fibrosis in HIV-HCV-coinfected patients: ANRS CO3 Aquitaine cohort. Am J Gastroenterol 2008; 103:1973 – 1980.
18. Levy D, Hwang SJ, Kayalar A, Benjamin EJ, Vasan RS, Parise H, et al. Associations of plasma natriuretic peptide, adrenomedullin, and homocysteine levels with alterations in arterial stiffness: The Framingham Heart Study. Circulation 2007; 115:3079 – 3085.
19. Kaji Y, Miyoshi T, Doi M, Hirohata S, Kamikawa S, Sakane K, et al. Augmentation index is associated with B-type natriuretic peptide in patients with paroxysmal atrial fibrillation. Hypertens Res 2009; 32:611 – 616.
20. Odaira M, Tamiyama H, Matsumoto C, Yoshida M, Shinka I, Nakata M, et al. Strength of relationships of the pulse wave velocity and central hemodynamic indices with the serum N-terminal fragment B-type natriuretic peptide levels in men: A worksite cohort study. Circ J 2012; 76:1928 – 1933.
21. Toischer K, Rokita AG, Unsold B, Zhu W, Kararigas G, Hoes AW, Tijssen JGP, et al. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. Circ J 2013; 77:485 – 495.