Relationship of pulmonary function with myocardial microdamage and oxidative stress in the Japanese population without a history of cardiopulmonary disease

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Abstract
An association between pulmonary and cardiovascular impairment has been reported, but studies are lacking that focus on individuals without advanced impairment in the pulmonary or cardiovascular system. We aimed to investigate the relationship between myocardial microdamage and reduced pulmonary function in the Japanese population without a history of cardiopulmonary disease and to assess whether oxidative stress links the 2 features.

We enrolled patients undergoing an annual health check-up and measured serum high-sensitivity cardiac troponin I (hs-cTnI) and derivatives of reactive oxygen metabolites (d-ROM) to evaluate myocardial microdamage and oxidative stress. To assess pulmonary function, we calculated forced vital capacity as a percentage of predicted value, forced expiratory volume in 1 second as a percentage of predicted value, and the ratio of forced expiratory volume in 1 second to forced vital capacity. Possible associations between each parameter of pulmonary function, hs-cTnI, and d-ROM were cross-sectionally investigated.

The study included 1265 participants (57 ± 2 years). In multivariate regression analysis, the forced vital capacity as a percentage of predicted value was inversely associated with hs-cTnI levels after adjustment for possible confounders. In another multivariate model, all indices of pulmonary function were inversely correlated with d-ROM levels. We observed similar relationships in a multivariate regression model that included hs-cTnI and d-ROM simultaneously as independent variables. Levels of d-ROM and hs-cTnI also were significantly associated.

These results highlight an inverse association of pulmonary function with hs-cTnI and d-ROM in the Japanese population without a history of cardiopulmonary disease. The findings suggest that in individuals without obvious cardiovascular and pulmonary diseases, reduced pulmonary function could reflect myocardial microdamage, at least in part through increased oxidative stress.

Abbreviations:
BP = blood pressure, COPD = chronic obstructive pulmonary disease, d-ROM = derivatives of reactive oxygen metabolites, FEV1 = forced expiratory volume in 1 second, FEV1%-predicted = forced expiratory volume in 1 second as a percentage of predicted value, FVC = forced vital capacity, FVC%-predicted = forced vital capacity as a percentage of predicted value, hs-cTnI = high-sensitivity cardiac troponin I.

Keywords: derivatives of reactive oxygen metabolites, high-sensitivity cardiac troponin I, myocardial microdamage, oxidative stress, pulmonary function
1. Introduction

Pulmonary function decreases with age, and a decline in pulmonary function is associated with all-cause mortality and cardiovascular death.[11–41] In addition, increasing evidence supports a link between pulmonary diseases and future cardiovascular events, including heart failure and atherosclerotic cardiovascular disease.[5,6] Most studies investigating the association between pulmonary and cardiovascular diseases have focused on chronic obstructive pulmonary disease (COPD).[7–10] This common pulmonary condition involves airflow limitation and is a leading cause of mortality and morbidity.[11–12] Increased oxidative stress and subsequent inflammation in the respiratory tract are relevant to development of COPD and to the pathways involved in the vascular endothelial damage that leads to atherosclerotic cardiovascular disease.[13–16] Thus, increased oxidative stress may be the pathway common between pulmonary and cardiovascular diseases. Our fundamental hypothesis is that the reduction in pulmonary function could reflect myocardial microdamage through increased oxidative stress.

Myocardial constitutive cardiac troponins are released into the circulation in patients with myocardial infarction,[17,18] and these levels are frequently used for detecting myocardial damage in patients with acute coronary syndrome.[17,18] However, myocardial damage also is often observed in non-ischemic myocardial disease, including heart failure and cardiomyopathy.[17–20] A slight increase in circulating cardiac troponins indicates myocardial microdamage that may asymptotically progress through non-ischemic mechanisms such as cardiac overload caused by elevated blood pressure (BP) and inflammation.[21–23] Recently developed high-sensitivity assays for the detection of cardiac troponins have enabled diagnosis of myocardial microdamage.[19,24] In the present study, we aimed to investigate the relationships among reduced pulmonary function, myocardial microdamage, and oxidative stress in individuals without obvious cardiovascular and pulmonary diseases in the Japanese population.

2. Methods

For this study, we enrolled individuals attending their annual physical check-up. Possible associations between pulmonary function, myocardial microdamage, and oxidative stress were cross-sectionally investigated. The study protocol was approved by the ethics committees of Enshu Hospital, and the study was performed in accordance with the principles of the Declaration of Helsinki. Each participant gave written informed consent before participation in the study.

2.1. Participants

Subjects who visited Enshu Hospital in 2015 for an annual health check-up were screened for eligibility for inclusion. Those who had renal insufficiency (estimated glomerular filtration rate <30 mL/min/1.73 m²), cancer, active inflammatory disease, a history of cardiovascular disease (stroke, myocardial infarction, heart failure), or pulmonary disease were excluded. We also excluded Subjects with obvious ST segment or T wave abnormality, pacemaker implantation, or frequent arrhythmia (such as atrial fibrillation and atrial flutter) on the standard 12-lead electrocardiogram. Because high-intensity physical activity can influence high-sensitivity cardiac troponin I (hs-cTnI) levels, participants who engaged in hard physical labor or high-intensity exercise were also excluded.

For laboratory measurements, we took blood samples early in the morning after an overnight fast and measured serum concentrations of hs-cTnI. For systolic and diastolic BP measurements, we used the non-dominant arm and a validated oscillometric technique (HEM-7070; Omron Corporation, Kyoto, Japan) with the subject in a seated position. Of 3 consecutive BP measurements taken at 2-minutes intervals, we recorded the mean of the second and third measurements as the BP. Subjects who were taking antihypertensive medications or with systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg were defined as having hypertension.[25] Those taking lipid-lowering medications or with high-density lipoprotein cholesterol <40 mg/dL, low-density lipoprotein cholesterol ≥140 mg/dL, or triglycerides ≥150 mg/dL were defined as having dyslipidemia,[26] Patients taking blood glucose-lowering medication or presenting a fasting plasma glucose level ≥126 mg/dL were defined as having diabetes.[27]

2.2. Biochemical analysis

We used standard laboratory assays for all biochemical tests, including determination of serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. To measure circulating levels of hs-cTnI, we used the ARCHITECT high-sensitivity troponin I assay according to the manufacturer’s instructions (Abbott, Tokyo, Japan). Serum levels of derivatives of reactive oxygen metabolites (d-ROM) were measured to evaluate oxidative stress, as described previously.[28] Briefly, serum samples were mixed with acetate buffer pH 4.8 in a cuvette, and a chromogenic substrate (N,N-diethyl p-phenyldiamine) was added to the mixture. Samples were immediately incubated in the analyzer for 5 minutes, after which absorbance was recorded at 505 nm, with d-ROM levels expressed in Carratelli units.

2.3. Assessment of pulmonary function

For assessing pulmonary function, we applied standard spirometric techniques using the MICROspiro HI-801 device (Chest Corp., Tokyo, Japan). We measured forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1), using spirometry, and evaluated the resulting data by calculating FVC as a percentage of the predicted value (FVC%-predicted), FEV1 as a percentage of the predicted value (FEV1%-predicted), and the ratio of FEV1 to FVC (FEV1/FVC). Participants whose FEV1/FVC was <70% were diagnosed as having COPD according to the definition of Global Initiative for Chronic Obstructive Lung Disease.[19]

2.4. Statistical analysis

Data were analyzed using IBM SPSS Statistics 19 (IBM Corp., Chicago, IL). Dichotomous variables (sex and smoking status) were assigned values of 0 (female and non-smoker) or 1 (male and smoker). Data with a normal distribution are expressed as means ± standard deviation, and data that were not normally distributed (hs-cTnI) as medians with interquartile ranges, evaluated after log transformation. Comparisons among multiple subgroups were made using 1-way analysis of variance. Multivariate regression analyses and multivariable logistic
Table 1
Characteristics of all the study participants (N = 1265).

| Variables                  | All participants | Quartile 1: hsc-TnI<1.6 (pg/mL) | Quartile 2: 1.6<hsc-TnI<2.4 (pg/mL) | Quartile 3: 2.4<hsc-TnI<3.6 (pg/mL) | Quartile 4: 3.6<hsc-TnI< (pg/mL) | P-value (ANOVA) |
|----------------------------|------------------|---------------------------------|-----------------------------------|---------------------------------|-------------------------------|-----------------|
| Age (yr)                   | 57.4±11.7        | 48.8±10.0                       | 55.4±8.8                          | 60.6±10.3                       | 64.4±10.4                    | <.0001          |
| Body mass index (kg/m²)    | 22.6±3.2         | 21.9±3.1                        | 22.7±3.3                          | 22.8±3.3                        | 23.0±3.2                     | <.001           |
| Male sex, n (%)            | 808 (63.9)       | 154 (50.3)                      | 202 (62.9)                        | 207 (67.4)                      | 245 (74.0)                   | .0001           |
| Current smoker, n (%)      | 258 (20.4)       | 70 (22.9)                       | 73 (22.7)                         | 62 (20.2)                       | 53 (16.0)                    | .104            |
| Systolic BP (mmHg)         | 118±11           | 117±13                          | 120±13                            | 125±14                          | 128±14                       | <.0001          |
| Diastolic BP (mmHg)        | 68±8             | 27±9                            | 74±9                              | 76±9                            | 76±9                         | <.0001          |
| Pulse rate (bpm)           | 64±9             | 64±9                            | 64±9                              | 63±9                            | 63±9                         | <.0001          |
| Creatinine (mg/dL)         | 0.79±0.17        | 0.75±0.14                       | 0.78±0.14                         | 0.80±0.16                       | 0.83±0.21                    | <.0001          |
| HDL-C (mg/dL)              | 62±16            | 64±16                           | 61±16                             | 60±16                           | 60±15                        | <.01            |
| LDL-C (mg/dL)              | 123±28           | 118±28                          | 124±28                            | 127±26                          | 126±27                       | <.001           |
| Triglyceride (mg/dL)       | 99±56            | 94±52                           | 112±69                            | 108±56                          | 104±44                       | .0001           |
| FPG (mg/dL)                | 94±14            | 93±17                           | 96±14                             | 96±14                           | 99±18                        | <.0001          |
| hs-cTnI (pg/mL)            | 2.4[1.6–3.6]     | 1.1[0.8–1.4]                    | 1.9[1.8–2.1]                      | 2.8[2.6–3.1]                    | 5.2[4.1–7.5]                 | <.0001          |
| d-ROM (Carratelli unit)    | 355.7±60.0       | 351.7±60.6                      | 353.1±61.4                        | 353.6±58.8                      | 363.6±58.6                   | <.05            |
| Pulmonary function         |                  |                                 |                                   |                                 |                               |                 |
| FVC%-predicted (%)         | 107.3±16.9       | 112.2±15.2                      | 108.4±15.3                        | 107.7±16.0                      | 101.4±18.8                   | <.0001          |
| FEV1%-predicted (%)        | 104.2±16.3       | 103.4±14.2                      | 103.6±15.6                        | 106.3±15.9                      | 102.9±18.9                   | .050            |
| FEV1/FVC (%)               | 78.8±7.6         | 80.9±6.8                        | 78.9±6.8                          | 78.3±6.2                        | 77.4±9.7                     | <.0001          |
| Complications              |                  |                                 |                                   |                                 |                               |                 |
| Hypertension, n (%)        | 379 (30.0)       | 36 (11.8)                       | 69 (21.5)                         | 111 (36.2)                      | 163 (90.6)                   | <.0001          |
| Dyslipidemia, n (%)        | 621 (49.1)       | 113 (36.9)                      | 159 (49.5)                        | 175 (57.0)                      | 174 (52.6)                   | <.0001          |
| Diabetes mellitus, n (%)   | 96 (7.6)         | 13 (4.2)                        | 24 (7.5)                          | 18 (5.9)                        | 41 (12.4)                    | <.001           |
| Obesity, n (%)             | 244 (19.3)       | 39 (12.7)                       | 66 (20.6)                         | 61 (19.9)                       | 78 (23.6)                    | <.01            |
| Medications                |                  |                                 |                                   |                                 |                               |                 |
| ACE inhibitor or ARB, n (%)| 172 (13.6)       | 17 (5.6)                        | 29 (9.0)                          | 48 (15.6)                       | 78 (23.6)                    | <.0001          |
| Beta-blocker, n (%)        | 14 (1.1)         | 1 (0.3)                         | 3 (0.9)                           | 4 (1.3)                         | 6 (1.8)                      | .334            |
| Calcium channel blocker, n (%)| 186 (14.7) | 15 (4.9)                        | 32 (10.0)                         | 53 (17.3)                       | 86 (26.0)                    | <.0001          |
| Diuretics, n (%)           | 19 (1.5)         | 0 (0)                           | 3 (0.9)                           | 5 (1.6)                         | 11 (3.3)                     | .01             |
| Lipid-lowering drug, n (%) | 175 (13.8)       | 24 (7.8)                        | 43 (13.4)                         | 46 (15.0)                       | 62 (18.7)                    | <.01            |
| Hypoglycaemic drug, n (%)  | 73 (5.8)         | 7 (2.3)                         | 17 (5.3)                          | 15 (4.9)                        | 34 (10.3)                    | <.001           |
| Antithrombotic agent, n (%)| 25 (2.0)         | 0 (0)                           | 3 (0.9)                           | 9 (2.9)                         | 13 (3.9)                     | <.01            |

Data are presented as mean±SD, median [interquartile range], or n (%). Percent predicted values were expressed as 100 × observed/predicted values. Obesity was diagnosed by body mass index ≥25 kg/m². Comparisons among subgroups (quartiles) were assessed using ANOVA.

ACE = angiotensin-converting enzyme. ANOVA = 1-way analysis of variance. ARB = angiotensin receptor blocker. BP = blood pressure. d-ROM = derivatives of reactive oxygen metabolites. FEV1%-predicted = FEV1 as a percentage of predicted value. FEV1/FVC = ratio of FEV1 to FVC. FEV1 = forced expiratory volume in 1 s. FPG = fasting plasma glucose. FVC%-predicted = FVC as a percentage of predicted value. FVC = forced vital capacity. HDL-C = high-density lipoprotein cholesterol. hs-cTnI = high-sensitivity cardiac troponin I. LDL-C = low-density lipoprotein cholesterol.

regression analyses were performed as appropriate. A 2-tailed P <.05 was considered significant.

3. Results

We enrolled 1265 subjects (808 [63.9%] men and 457 [36.1%] women) (Table 1), including 258 current smokers (20.4% of the total).

In multivariate regression analysis, the FVC%-predicted was inversely associated with levels of hsc-TnI after adjustment for possible confounders including medications. Neither FEV1%-predicted nor FEV1/FVC showed a significant association with hsc-TnI levels, however (Table 2). In our multivariate regression analyses investigating possible associations between each parameter of pulmonary function and d-ROM levels, in several adjusted models, we found an inverse association of FVC %-predicted, FEV1%-predicted, and FEV1/FVC with levels of d-ROM (Table 3). We also found a significant association between levels of d-ROM and hsc-TnI after adjustment for possible confounders (Table 4). To identify factors showing significant associations with higher levels of hsc-TnI, we conducted multivariable logistic regression analyses that included each parameter of pulmonary function and d-ROM simultaneously as independent variables, with the endpoint of the upper quartile of hsc-TnI (Table 3). The analysis revealed that both d-ROM and FVC%-predicted were independently associated with higher levels of hsc-TnI. On the other hand, systolic or diastolic BP was independently associated with hsc-TnI levels but not with d-ROM levels or each parameter of pulmonary function (Supplementary Table 1, http://links.lww.com/MD/762, Supplementary Table 2, http://links.lww.com/MD/E763, and Supplementary Table 3, http://links.lww.com/MD/E764).

To identify factors showing significant associations with each parameter of pulmonary function, we also performed multivariate regression analyses that included hsc-TnI and d-ROM simultaneously as independent variables. The results identified significant inverse associations of hsc-TnI and d-ROM with FVC%-predicted, but only d-ROM was inversely associated with FEV1%-predicted or FEV1/FVC (Table 6).
Among the enrolled participants, 106 (8.4%) met the criteria for a COPD diagnosis. Results of multivariate regression analyses were similar for a subgroup of subjects without COPD (data not shown).

4. Discussion

The main findings of the present study are

(1) an inverse association of FVC%-predicted with hs-cTnI levels;
(2) an inverse association of FVC%-predicted, FEV1%-predicted, and FEV1/FVC with d-ROM levels;
(3) a significant association between d-ROM and hs-cTnI; and
(4) a significant association of both hs-cTnI and d-ROM with FVC%-predicted when they were simultaneously included as independent variables, but an inverse association of only d-ROM with FEV1%-predicted or FEV1/FVC.

These findings are in line with our hypothesis that in the Japanese population without a history of cardiopulmonary disease, reduced pulmonary function could reflect myocardial microdamage through increased oxidative stress.

Potential relationships between myocardial damage and pulmonary function have been described before but largely only in patients with COPD.[29–32] Circulating levels of cardiac troponins are elevated in stable COPD and increase progressively with deteriorating COPD.[29,33] Predicting mortality with this disease. However, in the Japanese population without a history of cardiopulmonary disease, predictors of the relationship of pulmonary function and myocardial microdamage have not been established. The present study revealed that FVC%-predicted and FEV1%-predicted are separately significantly associated with hs-cTnI and/or d-ROM in the Japanese population without a history of cardiopulmonary disease. In addition, these significant associations persisted even after exclusion of individuals with COPD. These results indicate that the pathways that lead to cardiovascular and pulmonary impairments interact even in the early stages.

The mechanism underlying the close association between pulmonary function and myocardial microdamage is unclear, but 1 potential factor is increased oxidative stress. In the present study, we observed significant associations between the levels of d-ROM and hs-cTnI and between d-ROM and FVC%-predicted or FEV1%-predicted. Indeed, increased oxidative stress is a key factor in pulmonary damage and impairment of pulmonary function.[34–36] Although the link between oxidative stress and myocardial damage has not been established, our previous study suggested a close association between the 2.[29] In addition, increased oxidative stress plays a significant role in atherosclerosis,[28,36–39] which may in turn elevate cardiac load through...
increased cardiovascular damage. Thus, oxidative stress could be a common mechanism between pulmonary and cardiovascular diseases, including vascular and myocardial damage.\textsuperscript{11,34,35,40}

To the best of our knowledge, few previous reports have assessed FVC and myocardial damage in the Japanese population without a history of cardiopulmonary disease. In general, FVC is accepted as an index evaluating restrictive pulmonary dysfunction but not obstructive pulmonary dysfunction, and it decreases with age.\textsuperscript{1,10} A decline in FVC has been reported to be predictive of hypertension and heart failure\textsuperscript{12,13,15,20} which are both associated with elevated circulating cardiac troponin levels.\textsuperscript{20,41,42} Because circulating levels of cardiac troponin are thought to be predictive of future cardiovascular events\textsuperscript{43} the inverse association we found between FVC%-predicted and hs-cTnI in the Japanese population without a history of cardiopulmonary disease in this study indicates that pulmonary function impairment could increase risk for future cardiovascular disease, even in apparently healthy individuals.

Influences of oxidative and antioxidative factors are generally balanced in physiological conditions; however, excessive production of reactive oxygen species (ROS) introduces an imbalance between oxidative and antioxidative capacity and increases oxidative stress.\textsuperscript{34,35,38,43} ROS production has shown to link with pathological conditions such as pulmonary and

### Table 4

Results of multivariate regression analysis showing the association of derivatives of reactive oxygen metabolites and high-sensitivity cardiac troponin I in all participants (N = 1265).

| Variable | Dependent variables: d-ROM | Unadjusted | Adjusted Model 1 | Adjusted Model 2 | Adjusted Model 3 |
|----------|----------------------------|------------|-----------------|-----------------|-----------------|
| hs-cTnI  | Coefficient (β) [95% CI]  | 0.063 [0.008–0.118] | <.05 | 0.079 [0.018–0.139] | <.05 | 0.085 [0.023–0.145] | <.01 |

Adjusted Model 1 was adjusted for age, body mass index, sex, smoking status, systolic blood pressure, pulse rate, creatinine, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and fasting plasma glucose.

Adjusted Model 2 was further adjusted for possible confounders in medications in addition to adjusted Model 1. ACE inhibitor or ARB, beta-blocker, calcium channel blocker, diuretics, lipid-lowering drug, hypoglycaemic drug, and antithrombotic agent were considered as possible confounders in medications and were included into adjustment models.

CI = confidence interval, d-ROM = derivatives of reactive oxygen metabolites, hs-cTnI = high-sensitivity cardiac troponin I.

### Table 5

Results of multivariable logistic regression analysis including each parameter of pulmonary function and derivatives of reactive oxygen metabolites with the endpoint of high-sensitivity cardiac troponin I in all participants (N = 1265).

#### 1) Analysis using forced vital capacity % predicted as an index of pulmonary function

| Variable | Adjusted Model 1 | Adjusted Model 2 | Adjusted Model 3 |
|----------|-----------------|-----------------|-----------------|
| d-ROM (Carr. unit) | Odds ratio (95% CI) | P-value | Odds ratio (95% CI) | P-value | Odds ratio (95% CI) | P-value |
| FVC%-predicted (%) | 1.002 (1.001–1.004) | .05 | 1.004 (1.001–1.006) | <.01 | 1.004 (1.001–1.006) | <.01 |

#### 2) Analysis using forced expiratory volume in 1 s % predicted as an index of pulmonary function

| Variable | Adjusted Model 1 | Adjusted Model 2 | Adjusted Model 3 |
|----------|-----------------|-----------------|-----------------|
| d-ROM (Carr. unit) | Odds ratio (95% CI) | P-value | Odds ratio (95% CI) | P-value | Odds ratio (95% CI) | P-value |
| FEV1%-predicted (%) | 1.003 (1.001–1.005) | .099 | 1.004 (1.001–1.006) | <.01 | 1.004 (1.001–1.006) | <.01 |

#### 3) Analysis using forced expiratory volume in 1 s to forced vital capacity ratio as an index of pulmonary function

| Variable | Adjusted Model 1 | Adjusted Model 2 | Adjusted Model 3 |
|----------|-----------------|-----------------|-----------------|
| d-ROM (Carr. unit) | Odds ratio (95% CI) | P-value | Odds ratio (95% CI) | P-value | Odds ratio (95% CI) | P-value |
| FEV1/FVC | 0.968 (0.952–0.985) | .001 | 1.002 (0.983–1.022) | .844 |

Percent predicted value was expressed as 100 × observed/predicted value.

Derivatives of reactive oxygen metabolites and FVC%-predicted were simultaneously included as independent variables in all models conducted in Analysis 1.

Derivatives of reactive oxygen metabolites and FEV1%-predicted were simultaneously included as independent variables in all models conducted in Analysis 2.

Adjusted Model 1 was adjusted for age, body mass index, sex, smoking status, systolic blood pressure, pulse rate, creatinine, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and fasting plasma glucose in addition to Model 1.

Adjusted Model 3 was further adjusted for possible confounders in medications in addition to Model 2.

ACE inhibitor or ARB, beta-blocker, calcium channel blocker, diuretics, lipid-lowering drug, hypoglycaemic drug, and antithrombotic agent were considered as possible confounders in medications and were included into adjustment models.

CI = confidence interval, d-ROM = derivatives of reactive oxygen metabolites, FVC = forced vital capacity, FEV1%-predicted = FEV1 as a percentage of predicted value, FEV1 = forced expiratory volume in 1 s, FEV1/FVC = ratio of FEV1 to FVC, FEV1 = forced expiratory volume in 1 s, FVC = forced vital capacity, hs-cTnI = high-sensitivity cardiac troponin I.
Results of multivariate regression analysis showing independent correlation of pulmonary function with high-sensitivity cardiac troponin I and derivatives of reactive oxygen metabolites in all participants (N = 1265).

### 1) Analysis using forced vital capacity % predicted as an index of pulmonary function

| Variable | Adjusted Model 1 | Adjusted Model 2 | Adjusted Model 3 |
|----------|------------------|------------------|------------------|
|          | Coefficient (β) [95% CI] | P-value | Coefficient (β) [95% CI] | P-value | Coefficient (β) [95% CI] | P-value |
| hs-cTnl  | -0.208 [-0.261 to -0.154] | <.0001 | -0.072 [-0.134 to -0.009] | <.05 | -0.064 [-0.127 to -0.001] | <.05 |
| d-ROM   | -0.090 [-0.144 to -0.037] | .001  | -0.102 [-0.159 to -0.045] | .001  | -0.106 [-0.163 to -0.049] | .001  |

### 2) Analysis using forced expiratory volume in 1 s % predicted as an index of pulmonary function

| Variable | Adjusted Model 1 | Adjusted Model 2 | Adjusted Model 3 |
|----------|------------------|------------------|------------------|
|          | Coefficient (β) [95% CI] | P-value | Coefficient (β) [95% CI] | P-value | Coefficient (β) [95% CI] | P-value |
| hs-cTnl  | -0.023 [-0.078 to 0.032] | .405  | -0.047 [-0.112 to 0.019] | .161  | -0.041 [-0.106 to 0.025] | .228  |
| d-ROM   | -0.037 [-0.092 to 0.019] | .195  | -0.088 [-0.148 to -0.029] | <.01  | -0.091 [-0.150 to -0.032] | <.01  |

### 3) Analysis using forced expiratory volume in 1 s to forced vital capacity ratio as an index of pulmonary function

| Variable | Adjusted Model 1 | Adjusted Model 2 | Adjusted Model 3 |
|----------|------------------|------------------|------------------|
|          | Coefficient (β) [95% CI] | P-value | Coefficient (β) [95% CI] | P-value | Coefficient (β) [95% CI] | P-value |
| hs-cTnl  | -0.175 [-0.231 to -0.122] | <.0001 | 0.001 [-0.062 to 0.062] | .983  | 0.001 [-0.061 to 0.063] | .950  |
| d-ROM   | -0.048 [-0.101 to 0.008] | .287  | -0.080 [-0.115 to -0.023] | <.05  | -0.061 [-0.116 to -0.003] | <.05  |

Percent predicted value was expressed as 100 x observed/predicted value.

High-sensitivity cardiac troponin I and derivative of reactive oxygen metabolites were simultaneously included as independent variables in all models.

Adjusted Model 2 was adjusted for age, body mass index, sex, smoking status, systolic blood pressure, pulse rate, creatinine, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and fasting plasma glucose in addition to Model 1.

Adjusted Model 3 was further adjusted for possible confounders in medications in addition to Model 2.

ACE inhibitor or ARB, beta-blocker, calcium channel blocker, diuretics, lipid-lowering drug, hypoglycaemic drug, and antithrombotic agent were considered as possible confounders in medications and were included into adjustment models.

CI = confidence interval, d-ROM = derivative of reactive oxygen metabolites, FVC%-predicted = FVC as a percentage of predicted value, FVC = forced vital capacity, FEV1%-predicted = FEV1 as a percentage of predicted value, FEV1 = forced expiratory volume in 1 s, FVC = forced vital capacity, hs-cTnl = high-sensitivity cardiac troponin I.

### 5. Limitations

The present study has several limitations, and the findings should thus be interpreted with caution. First, the design was cross-sectional, and the study participants were a heterogeneous group. Second, we did not capture causal relationships among pulmonary function, hs-cTnl, and d-ROM, and in vivo studies should evaluate the mechanisms underlying the close association among pulmonary damage, myocardial microdamage, and oxidative stress. Third, enrolled participants were asymptomatic and without ST-T abnormality on electrocardiograms, but ischemic heart disease cannot be completely excluded. For definitive conclusions, further studies are needed that include a larger population, a longitudinal design, and detailed clinical examinations.

### 6. Future directions

The present study highlights an inverse association of pulmonary function with hs-cTnl and d-ROM in the Japanese population without a history of cardiopulmonary disease. In addition to the elevated BPs, the reduced pulmonary function should raise concern about myocardial microdamage even in those who are asymptomatic. Measurement of oxidative stress marker d-ROM...
may be useful for evaluating cardiopulmonary impairment among apparently healthy individuals.

7. Conclusions

The results of this Japanese population study revealed inverse associations of pulmonary function with hs-cTnI and d-ROM. These findings indicate that in individuals without obvious cardiovascular and pulmonary diseases, reduced pulmonary function, especially decreased FVC%-predicted, could reflect myocardial microdamage at least in part because of increased oxidative stress.

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