Reduced Coronary Flow Reserve Is Associated with Impaired Ventricular-vascular Interaction in Patients with Obstructive Sleep Apnea

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ABSTRACT

Background and Objectives: Obstructive sleep apnea (OSA) is associated with cardiac and arterial damage and adverse cardiovascular outcomes. We aimed to determine whether coronary flow reserve (CFR), which represents microvascular dysfunction, might be associated with the ventricular-vascular coupling index (VVI), which represents the afterload-adjusted contractility in patients with OSA.

Methods: We enrolled 281 patients (257 males; mean age, 43±11 years) with newly diagnosed OSA. Transthoracic echocardiography was performed, and adenosine-associated CFR was measured in the left anterior descending coronary artery. We evaluated the differences between the patients with normal CFR ≥2.5 and reduced CFR <2.5. VVI was calculated using the effective arterial elastance (Ea) and left ventricular (LV) end-systolic elastance (Ees) as follows: 10×Ea/Ees.

Results: The normal CFR group (n=214) showed increased Ees (7.28±2.31 vs. 8.14±2.33 mmHg/mL, p=0.016) and preserved VVI (3.17±1.53 vs. 2.78±1.20, p=0.044) compared with the reduced CFR group (n=67). There were no differences in LV dimension, LV ejection fraction, left atrial-volume index, E/e’, left atrial strain and LV global longitudinal strain between the 2 groups (all p>0.05). CFR was significantly correlated to Ees (r=0.139; p=0.023) and VVI (r=-0.137; p=0.025).

Conclusions: Reduced CFR is associated with decreased Ees and impaired VVI in OSA patients. It suggests the necessity of more intensive observation in OSA patients with reduced CFR to improve cardiovascular outcomes.

Keywords: Obstructive sleep apnea; Coronary arteries; Heart contractility

INTRODUCTION

Obstructive sleep apnea (OSA) is a common condition that affects at least 10% of the general population and 40% to 60% of patients with cardiovascular disease. OSA might...
Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
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be associated with cardiac and arterial damage, which leads to adverse cardiovascular outcomes. Although the mechanism of cardiovascular pathophysiology is not well-established in patients with OSA, it is important to identify the mechanism responsible for the cardiac dysfunction and detect asymptomatic patients with subclinical cardiac dysfunction in OSA. Microvascular dysfunction is a subclinical pathologic condition, and it is known to be associated with cardiac function and cardiovascular events. A previous study reported the relationship between OSA and reduced coronary flow reserve (CFR). There are several physiological contributors to cardiac function, such as ventricular size, contractile function, and afterload. Cardiovascular prognosis can be affected by the vulnerability to a loading condition, which is determined by ventricular stiffness, ventricular-vascular interaction, as well as left ventricular (LV) ejection fraction (EF) itself.

We aimed to investigate whether CFR might be associated with the ventricular-vascular coupling index (VVI), which represents the afterload-adjusted contractility in OSA patients.

METHODS

Study population
This retrospective observational study was performed from May 2009 to July 2012 in a single tertiary referral hospital. A total of 281 subjects (257 males; mean age, 43±11 years) who were diagnosed with OSA and confirmed by polysomnographic study were consecutively enrolled in this study. CFR was measured in all patients. The study protocol was approved by the Institutional Review Board of the Kyung Hee University Medical Center, Seoul, Korea (approval No. 2020-05-030) and complied with the Declaration of Helsinki. Informed consent was waived.

Conventional echocardiography and echo-Doppler-derived hemodynamic parameters
A routine standard echocardiography study was performed to measure the following systolic and diastolic parameters. LV end-diastolic volume and LV end-systolic volume were measured with the biplane Simpson’s method, and LV EF was calculated. LV mass was measured by Devereux’s methods as recommended by the American Society of Echocardiography. LV mass index (LVMi) was calculated as LV mass/body surface area (BSA). Relative wall thickness (RWT) was calculated as twice the posterior wall thickness at end-diastole divided by the LV end-diastolic dimension. LV geometry was reported as ‘normal (LVMi ≤115 gm/m² in males, ≤95 gm/m² in females, and RWT ≤0.42)’, ‘eccentric hypertrophy (LVMi >115 gm/m² in males, >95 gm/m² in females, and RWT ≥0.42)’, ‘concentric remodeling (LVMi ≤115 gm/m² in males, ≤95 gm/m² in females, and RWT >0.42)’ and ‘concentric hypertrophy (LVMi >115 gm/m² in males, >95 gm/m² in females and RWT >0.42)’. Left atrial (LA) volume was measured at the end-systole by the ellipsoidal method, and LA volume index was calculated as LA volume/BSA. Peak early (E) and late (A) diastolic mitral inflow velocities were measured in the apical 4-chamber view. Tissue Doppler interrogation was performed in the septal mitral annulus in the apical 4-chamber view followed by measurement of the peak systolic mitral annulus velocity (s’) and early diastolic mitral annulus peak velocity (e’). The ratio of E/e’ was calculated. LV wall thickness was measured in parasternal short axis view. From the echocardiographic data, LV end-diastolic elastance index (Ed) was calculated as E/e’/stroke volume, LV end-systolic elastance (Ees) as end-systolic pressure/LV end-systolic volume, arterial elastance (Ea) as end-systolic pressure/stroke volume, and VVI as 10×Ea/Ees.

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Ees. Here, end-systolic pressure was calculated by \((2 \times \text{systolic blood pressure} + \text{diastolic blood pressure})/3\).\(^{13,20}\) LV global longitudinal strain and LA strain were also measured.

**CFR**

We measured coronary flow velocity before and after adenosine infusion. We acquired the optimal image at the modified apical 2-chamber view, between a 2- and 3-chamber view, and coronary flow velocity was measured at the distal left ascending artery (LAD). For hyperemia, adenosine was infused (140 μg·kg\(^{-1}\)·min\(^{-1}\); BC World Pharm Co. Ltd., Seoul, Korea) over 4 minutes. CFR was determined by the ratio of peak velocity in hyperemia divided by the peak velocity at resting as follows: peak coronary flow velocity in hyperemia/peak coronary flow velocity at resting (Figure 1). Reduced CFR below 2.0 to 2.5 was used as the diagnostic criteria for microvascular dysfunction in previous studies.\(^{22-24}\) Therefore, all patients were divided into 2 groups: normal CFR group (CFR ≥2.5, n=214) and reduced CFR group (CFR <2.5, n=67).

**Polysomnographic study**

All patients underwent an overnight polysomnographic study that was administered by a single sleep technician. According to the scoring rule of the American Academy of Sleep Medicine,\(^{25}\) Apnea-hypopnea index (AHI, events/hour), hypopnea index (HI, events/hour), respiratory disturbance index (RDI, events/hour), oxygen disturbance index (ODI, events/hour), and the lowest O\(_2\) saturation (LSaO\(_2\), percent) were measured. The severity of OSA was defined as follows: AHI equal to or over 5 and less than 15, mild; AHI equal to or over 15 and less than 30, moderate; and AHI equal to or over 30, severe.

**Statistical analysis**

Continuous variables that were normally distributed are reported as the mean±standard deviation or a 95% confidence interval (CI). Student’s t-test was used to compare the means of continuous variables that were approximately normally distributed between the 2 groups. If the assumption of normality was violated, Wilcoxon rank-sum test was used. Normality was determined using the Kolmogorov-Smirnov goodness of fit-test. Categorical variables were reported as count (percentage) and compared using Fisher’s exact test. Pearson’s correlation analysis was used for the univariate analysis to find the determinants of reduced CFR. In addition, univariate and multivariate logistic regression analyses were used to identify association with decreased CFR (<2.5). The SPSS statistical package (IBM Corp., Armonk, NY, USA) was used to perform all statistical evaluations. A 2-tailed p value <0.05 was considered statistically significant.

**Figure 1.** A representative case of CFR measurement demonstrated peak velocity of distal left anterior descending coronary artery (A) at resting and (B) during adenosine infusion. CFR was calculated as follows: peak coronary flow velocity during adenosine infusion (measured as B)/peak coronary flow velocity at resting (measured as A). 

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RESULTS

Baseline characteristics according to CFR
The patients’ baseline and echocardiographic characteristics are shown in Tables 1 and 2. The mean age of the enrolled patients was 43±11 years, and 257 patients (92%) were male. The mean CFR value was 3.26±1.13. The presence of diabetes and dyslipidemia were similar between the 2 groups. There was no difference in the severity of OSA, ODI, and RDI between the 2 groups. Hypertension was more prevalent in the normal CFR group compared with the reduced CFR group (28.5% vs. 11.9%, respectively; p=0.009). There was no intergroup difference in LV dimension, LA volume index and E/e'. Ea was not different between 2 groups (2.07±0.62 vs. 2.12±0.76 mmHg/mL, p=0.638). Ees was lower in the reduced CFR group compared with the normal CFR group (7.28±2.31 vs. 8.14±2.33 mmHg/mL, respectively; p=0.016), and VVI was higher in the reduced CFR group compared with the normal CFR group (3.17±1.53 vs. 2.78±1.20, respectively; p=0.044) (Figure 2). Using univariate and multivariate regression analysis, hypertension and VVI was significantly associated with reduced CFR (<2.5) (Table 3). Multivariate logistic regression analysis showed that hypertension and VVI were significantly associated with reduced CFR after adjusting age, sex, smoking, diabetes and dyslipidemia, components of metabolic syndrome which could affect CFR. VVI was associate with reduced CFR with an odds ratio of 1.266 (95% CI, 1.004–1.596; p=0.046).

Association between CFR and hemodynamic parameters
CFR was significantly correlated to Ees (r=0.139; p=0.023) and VVI (r=−0.137; p=0.025) using a univariate analysis. The correlation between CFR and Ed was not statistically significant (r=0.108; p=0.075) (Figure 3).

DISCUSSION

This study reports the major finding regarding the cardiovascular hemodynamic characteristics in OSA: CFR is related to VVI in patients with OSA. We noninvasively measured both CFR and

| Table 1. Baseline characteristics |
|----------------------------------|
| Characteristics                  | Normal CFR group (n=214) | Reduced CFR group (n=67) | p value |
| Age (years)                      | 43±11                    | 43±10                    | 0.880   |
| Male                             | 195 (91.1)               | 62 (92.5)                | 0.808   |
| Body mass index (kg/m²)          | 1.9±0.2                  | 1.8±0.1                  | 0.848   |
| Severity of OSA                  |                          |                          | 0.584   |
| Severe (AHI ≥30)                 | 82 (38.3)                | 22 (32.8)                |         |
| Moderate (15≤ AHI <30)           | 78 (36.4)                | 24 (35.8)                |         |
| Mild (5≤ AHI <15)                | 54 (25.3)                | 21 (31.3)                |         |
| RDI (event/hour)                 | 20.6±16.7                | 19.9±16.4                | 0.800   |
| ODI (event/hour)                 | 28.9±19.8                | 26.6±20.0                | 0.400   |
| LSaO₂ (%)                        | 81.3±7.3                 | 83.3±6.3                 | 0.047   |
| Hypertension                     | 61 (28.5)                | 8 (11.9)                 | 0.009   |
| Diabetes                         | 8 (3.7)                  | 4 (6.0)                  | 0.489   |
| Dyslipidemia                     | 7 (3.3)                  | 1 (1.5)                  | 0.685   |
| Smoking                          | 86 (40.2)                | 35 (52.2)                | 0.091   |
| SBP (mmHg)                       | 119±14                   | 117±14                   | 0.444   |
| DBP (mmHg)                       | 75±9                     | 75±10                    | 0.943   |
| HR (beats/min)                   | 74±7                     | 74±7                     | 0.817   |

Values are presented as number (%) or mean±standard deviation.
AHI = apnea-hypopnea index; DBP = diastolic blood pressure; CFR = coronary flow reserve; HR = heart rate; LSaO₂ = lowest O₂ saturation; ODI = oxygen disturbance index; OSA = obstructive sleep apnea; SBP = systolic blood pressure; RDI = respiratory disturbance index.
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Table 2. Echocardiographic characteristics

| Characteristics       | Normal CFR group (n=214) | Reduced CFR group (n=67) | p value |
|-----------------------|--------------------------|--------------------------|---------|
| LV EDD (mm)           | 48.9±4.0                 | 49.5±4.1                 | 0.319   |
| LV ESD (mm)           | 31.3±3.7                 | 32.0±3.5                 | 0.154   |
| PWTd (mm)             | 9.6±1.3                  | 9.7±1.2                  | 0.312   |
| IVTd (mm)             | 9.3±1.3                  | 9.5±1.2                  | 0.594   |
| LVMi (g/m²)           | 87.1±17.5                | 90.8±17.3                | 0.134   |
| RWT                   | 0.39±0.06                | 0.40±0.06                | 0.547   |
| LV geometry           |                          |                          | 0.048   |
| Normal                | 140 (65.4)               | 40 (59.7)                |         |
| Concentric remodeling | 65 (31.7)                | 19 (28.4)                |         |
| Eccentric hypertrophy | 2 (1.0)                  | 5 (7.5)                  |         |
| Concentric hypertrophy| 7 (3.4)                  | 3 (4.5)                  |         |
| LV EF (%)             | 64±6                     | 64±6                     | 0.896   |
| LA volume index (mL/m²)| 20.2±5.8                 | 20.9±5.8                 | 0.395   |
| E velocity (cm/s)     | 65.7±15.6                | 65.8±13.2                | 0.987   |
| A velocity (cm/s)     | 58.2±25.8                | 56.2±14.2                | 0.334   |
| e′ velocity (cm/s)    | 8.5±2.6                  | 8.9±2.4                  | 0.292   |
| a′ velocity (cm/s)    | 9.3±2.0                  | 9.4±2.0                  | 0.898   |
| s′ velocity (cm/s)    | 7.9±1.4                  | 8.0±1.3                  | 0.683   |
| E/e′                  | 6.2±2.1                  | 7.7±2.0                  | 0.128   |
| DT (ms)               | 191±41                   | 188±42                   | 0.630   |
| Ed (t/mL)             | 0.16±0.06                | 0.15±0.06                | 0.404   |
| ESP (mmHg)            | 104.01±111.83            | 100.78±18.03             | 0.177   |
| Ea (mmHg/mL)          | 2.07±0.62                | 2.12±0.76                | 0.638   |
| Ees (mmHg/mL)         | 8.14±2.33                | 7.28±2.31                | 0.016   |
| VTI                    | 2.78±1.20                | 3.17±1.53                | 0.044   |
| LA strain (%)         | 44.2±13.7                | 44.5±12.4                | 0.887   |
| LV GLS (%)            | −19.5±2.2                | −19.7±2.2                | 0.695   |

Values are presented as number (%) or mean±standard deviation.

CFR = coronary flow reserve; DT = deceleration time; Ea = arterial elastance; Ed = left ventricular diastolic elastance; EDD = end-diastolic dimension; E/e′ = the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e′); Ees = left ventricular end-systolic elastance; EF = ejection fraction; ESD = end-systolic dimension; ESP = end-systolic pressure; GLS = global longitudinal strain; IVTd = end-diastolic interventricular thickness; LA = left atrial; LV = left ventricular; LVMi = left ventricular mass index; PWTd = end-diastolic left ventricular posterior wall thickness; RWT = relative wall thickness; VVI = ventricular-vascular coupling index.

Figure 2. Comparison of (A) VVI and (B) Ees between the normal CFR group and the reduced CFR group. The solid bar in the box represents the median value.

CFR = coronary flow reserve; VVI = ventricular-vascular coupling index; Ees = left ventricular end-systolic elastance.

VVI using transthoracic echocardiography. The assessment of CFR by transthoracic Doppler echocardiography has been reported as a useful method in previous studies. Although echo-Doppler-derived hemodynamic parameters for ventricular stiffness and the end-systolic ventricular-vascular interaction were conventionally measured with an invasive method using a
pressure-volume curve, previous reports measured these parameters using a single beat-derived method with Doppler echocardiography.\textsuperscript{(13,28)}

Coupling between the heart and the arterial system is a crucial determinant of cardiovascular performance, because their interaction influences the efficiency of transfer of stroke volume to the circulation.\textsuperscript{(29)} VVI represents afterload-adjusted contractility, reflecting the efficiency of the cardiovascular system,\textsuperscript{(13)} and it is well known to predict cardiovascular outcomes.\textsuperscript{(12,30)} OSA is associated with increased cardiovascular mortality and morbidity via various pathways.\textsuperscript{(31)} Microvascular dysfunction is suggested as one of the mechanism of OSA-related ischemic heart disease and cardiovascular events. Intrathoracic negative pressure increases the LV wall stress, which stimulate increase of the vascular tone. Persistent increased vascular tone drives chronic vascular adaptation by structural remodeling.\textsuperscript{(32)} And repetitive hypoxia/reoxygenation during transient cessation of breathing promotes generation of reactive oxygen species, inflammation and reduced nitric oxide availability.\textsuperscript{(33)} OSA increases release of cytokines via inflammatory state, which induce local production of growth factors such as transforming growth factor beta. That stimulates smooth muscle cells of the media layer to proliferation, and this condition contributes to vascular remodeling. Consequently, vascular remodeling impairs endothelial function.\textsuperscript{(32)} Microvascular inflammation induced fibrosis and cardiomyocyte stiffening lead to diastolic dysfunction, pathophysiology of heart failure with preserved EF (HfP EF).\textsuperscript{(34)} In the present study, the reduced CFR group demonstrated lower Ees and higher VVI compared with the normal CFR group. Decreased arterial compliance may result in impaired ventricular-vascular coupling and reduced coronary flow. OSA increases both coronary artery disease and heart failure.\textsuperscript{(35)} Therefore, cardiovascular disease

### Table 3. Univariate and multivariate logistic analysis for association with CFR <2.5

| Characteristics | Univariate | Multivariate |
|-----------------|------------|--------------|
|                 | OR         | 95% CI       | p value | OR         | 95% CI       | p value |
| Age (per year)  | 0.998      | 0.974–1.023  | 0.886   | 1.001      | 0.973–1.030  | 0.925   |
| Male            | 0.828      | 0.297–2.309  | 0.718   | 0.882      | 0.266–2.923  | 0.837   |
| Smoking         | 1.628      | 0.938–2.827  | 0.083   | 1.610      | 0.860–3.014  | 0.336   |
| HTN             | 0.340      | 0.153–0.754  | 0.008   | 0.340      | 0.138–0.839  | 0.019   |
| DM              | 1.635      | 0.476–5.610  | 0.435   | 1.507      | 0.357–6.361  | 0.577   |
| Dyslipidemia    | 0.448      | 0.054–7.309  | 0.457   | 0.501      | 0.055–4.535  | 0.539   |
| VVI             | 1.252      | 1.004–1.560  | 0.046   | 1.266      | 1.004–1.596  | 0.046   |

CFR = coronary flow reserve; CI = confidence interval; DM = diabetes mellitus; HTN = hypertension; OR = odds ratio; VVI = ventricular-vascular coupling index.

### Figure 3. Correlation between CFR and (A) Ed, (B) Ees and (C) VVI.

CFR = coronary flow reserve; Ed = left ventricular end-diastolic elastance index; Ees = left ventricular end-systolic elastance; VVI = ventricular-vascular coupling index.
in patients with OSA may share a similar pathophysiology with HFpEF. Clarification of the pathophysiological mechanism could improve cardiovascular outcomes by prevention and early intervention of cardiac damage in patients with OSA and subclinical cardiac conditions.

Microvascular dysfunction is often a subclinical phenomenon, so overt clinical manifestations of cardiac disease are not seen in most patients. Impaired ventricular-vascular coupling is a crucial mechanism of HFpEF, and the contribution of OSA in cardiovascular disease may share this mechanism. Among OSA patients, those with reduced CFR could tend to develop heart failure and cardiovascular disease. Early detection in this subgroup of patients is important, and we suggest that medication for microvascular dysfunction, such as nitrate or trimetazidine, could improve cardiovascular disease in these patients. However, further study is needed to evaluate the efficacy of these medications for OSA patients.

In conclusion, OSA is associated with adverse cardiovascular outcomes, although the mechanism is not clear. In the present study, decreased CFR was associated with impaired ventricular-vascular coupling, which is an important factor in the pathophysiology of HFpEF. Early detection and close observation or therapeutic interruption may improve cardiovascular outcomes in special populations with microvascular dysfunction, but further research is needed.

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