Int J Heart Fail. 2020 Jul;2(3):195-203
https://doi.org/10.36628/ijhf.2020.0005
pISSN 2636-154X·eISSN 2636-1558

International Journal of Heart Failure
IJHF

Original Article

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

Hyemoon Chung, MD, PhD[1], Sung Wan Kim, MD, PhD[2], Hyung Oh Kim, MD[1], Jung Myung Lee, MD, PhD[1], Jong Shin Woo, MD, PhD[1], Jin Bae Kim, MD, PhD[1], Soo Joong Kim, MD, PhD[1], Weon Kim, MD, PhD[1], Kwon Sam Kim, MD, PhD[1], and Woo-Shik Kim, MD, PhD[1]

[1]Cardiovascular Division, Department of Internal Medicine, School of Medicine, Kyung Hee University, Seoul, Korea
[2]Department of Otorhinolaryngology-Head and Neck Surgery, School of Medicine, Kyung Hee University, Seoul, Korea

Received: Feb 27, 2020
Revised: Apr 12, 2020
Accepted: Apr 20, 2020

Correspondence to
Woo-Shik Kim, MD, PhD
Cardiovascular Division, Department of Internal Medicine, School of Medicine, Kyung Hee University, 23 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, Korea.
E-mail: wskim1125@khu.ac.kr

ORCID iDs
Hyemoon Chung
https://orcid.org/0000-0002-5615-6245
Sung Wan Kim
https://orcid.org/0000-0002-6100-8634
Hyung Oh Kim
https://orcid.org/0000-0003-2157-441X
Jung Myung Lee
https://orcid.org/0000-0002-1904-5335
Jong Shin Woo
https://orcid.org/0000-0003-0535-1742
Jin Bae Kim
https://orcid.org/0000-0002-0293-0901
Soo Joong Kim
https://orcid.org/0000-0001-6969-3229
Weon Kim
https://orcid.org/0000-0003-1264-9870
Woo-Shik Kim
https://orcid.org/0000-0002-3345-1137

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.[1-5] OSA might

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Chung H, Kim SW, Kim KS, Kim WS; Data curation: Chung H, Kim SW, Kim HO, Kim JB; Formal analysis: Chung H, Woo JS, Kim KS, Kim WS; Investigation: Chung H, Lee JM, Kim SJ, Kim W, Kim KS, Kim WS; Methodology: Chung H, Kim WS; Project administration: Chung H, Kim WS; Resources: Chung H, Kim SW, Kim WS; Software: Chung H; Supervision: Chung H, Kim SW, Kim HO, Lee JM, Woo JS, Kim JB, Kim SJ, Kim W, Kim KS, Kim WS; Validation: Chung H, Kim WS; Visualization: Chung H; Writing - original draft: Chung H; Writing - review & editing: Chung H, Kim SW, Kim WS.

be associated with cardiac and arterial damage, which leads to adverse cardiovascular outcomes.[6] 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.[7,10] A previous study reported the relationship between OSA and reduced coronary flow reserve (CFR).[11] There are several physiological contributors to cardiac function, such as ventricular size, contractile function, and afterload.[12,13] 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.[13,18]

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.[19] 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.[20] 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/m^2 in males, ≤95 gm/m^2 in females, and RWT ≤0.42)', 'eccentric hypertrophy (LVMI >115 gm/m^2 in males, >95 gm/m^2 in females, and RWT ≤0.42)', 'concentric remodeling (LVMI ≤115 gm/m^2 in males, ≤95 gm/m^2 in females, and RWT >0.42)' and 'concentric hypertrophy (LVMI >115 gm/m^2 in males, >95 gm/m^2 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. Here, end-systolic pressure was calculated by (2×systolic blood pressure+diastolic blood pressure)/3.[13)21)] 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.

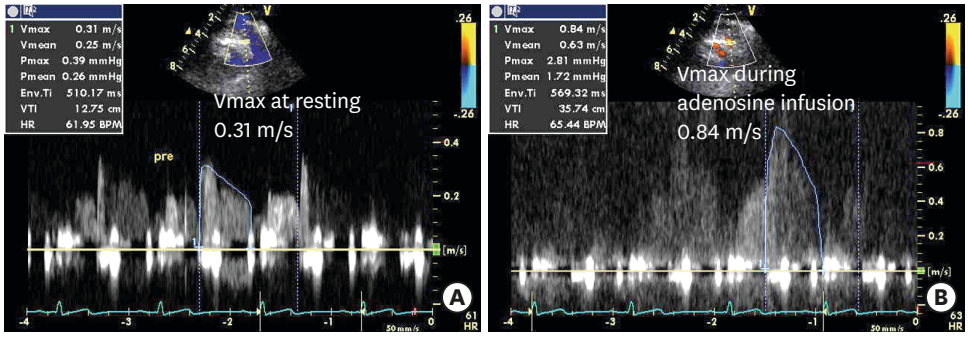

Figure 1. A representative case of CFR measurement demonstrated peak velocity of distal left anterior descending coronary artery (A) at resting and (B) during adenosine infusion. CFR was calculated as follows: peak coronary flow velocity during adenosine infusion (measured as B)/peak coronary flow velocity at resting (measured as A). CFR = coronary flow reserve; VTI = velocity time integral; HR = hazard ratio.

https://doi.org/10.36628/ijhf.2020.0005

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 (25.2)	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
$LSaO_2$ (%)	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; $LSaO_2$ = lowest O2 saturation; ODI = oxygen disturbance index; OSA = obstructive sleep apnea; SBP = systolic blood pressure; RDI = respiratory disturbance index.

https://doi.org/10.36628/ijhf.2020.0005

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	0.524
LVMI (g/m^2)	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/m^2)	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′	8.2±2.1	7.7±2.0	0.128
DT (ms)	191±41	188±42	0.630
Ed (1/mL)	0.16±0.06	0.15±0.06	0.404
ESP (mmHg)	104.01±11.83	100.78±18.03	0.117
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
VVI	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.

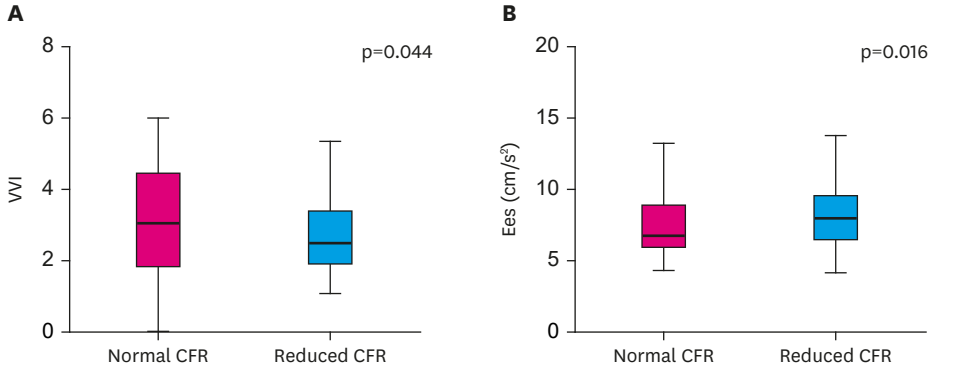

Figure 2. Comparison of (A) VVI and (B) Ees between the normal CFR group and the reduced CFR group. The solid bar in the box represents the median value.
CFR = coronary flow reserve; VVI = ventricular-vascular coupling index; Ees = left ventricular end-systolic elastance.

VVI using transthoracic echocardiography. The assessment of CFR by transthoracic Doppler echocardiography has been reported as a useful method in previous studies.[26)27)] 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

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	0.136
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	0.054–3.709	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.

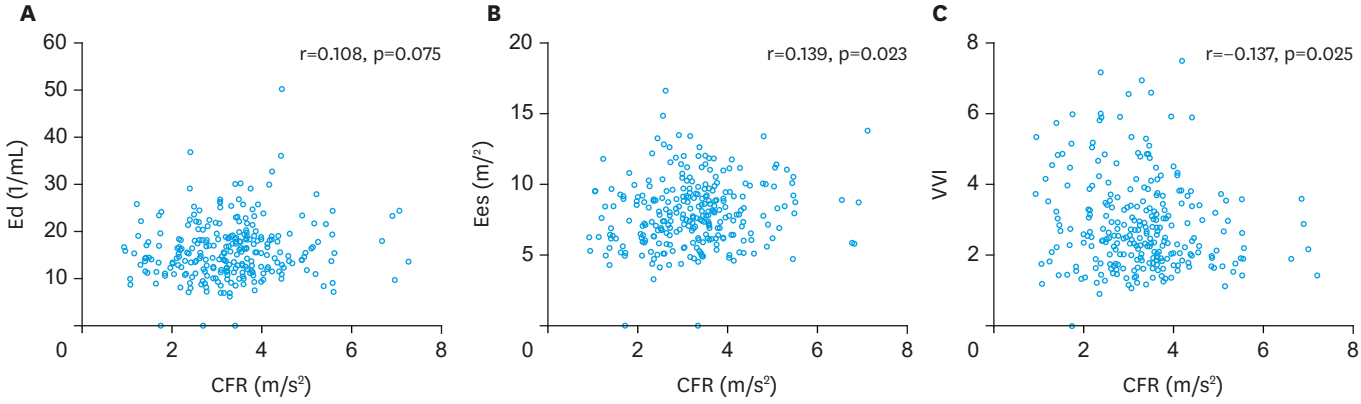

Figure 3. Correlation between CFR and (A) Ed, (B) Ees and (C) VVI.
CFR = coronary flow reserve; Ed = left ventricular end-diastolic elastance index; Ees = left ventricular end-systolic elastance; VVI = ventricular-vascular coupling index.

pressure-volume curve, previous reports measured these parameters using a single beat-derived method with Doppler echocardiography.[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.[29)] VVI represents afterload-adjusted contractility, reflecting the efficiency of the cardiovascular system,[13)] and it is well known to predict cardiovascular outcomes.[12)30)] OSA is associated with increased cardiovascular mortality and morbidity via various pathways.[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.[32)] And repetitive hypoxia/reoxygenation during transient cessation of breathing promotes generation of reactive oxygen species, inflammation and reduced nitric oxide availability.[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.[32)] Microvascular inflammation induced fibrosis and cardiomyocyte stiffening lead to diastolic dysfunction, pathophysiology of heart failure with preserved EF (HFpEF).[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.[35)] Therefore, cardiovascular disease

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.

REFERENCES

1. Hung J, Whitford EG, Parsons RW, Hillman DR. Association of sleep apnoea with myocardial infarction in men. Lancet 1990;336:261-4.
PUBMED | CROSSREF
2. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002;165:1217-39.
PUBMED | CROSSREF
3. Butt M, Dwivedi G, Khair O, Lip GY. Obstructive sleep apnea and cardiovascular disease. Int J Cardiol 2010;139:7-16.
PUBMED | CROSSREF
4. Lee CH, Sethi R, Li R, et al. Obstructive sleep apnea and cardiovascular events after percutaneous coronary intervention. Circulation 2016;133:2008-17.
PUBMED | CROSSREF
5. Johnson KG, Johnson DC. Frequency of sleep apnea in stroke and TIA patients: a meta-analysis. J Clin Sleep Med 2010;6:131-7.
PUBMED | CROSSREF
6. Shantsila A, Shantsila E, Butt M, Khair OA, Dwivedi G, Lip GY. Ventricular-arterial coupling in obstructive sleep apnea. J Am Soc Hypertens 2014;8:624-9.
PUBMED | CROSSREF
7. Blomster JI, Svedlund S, U Westergren H, Gan LM. Coronary flow reserve as a link between exercise capacity, cardiac systolic and diastolic function. Int J Cardiol 2016;217:161-6.
PUBMED | CROSSREF
8. Snoer M, Monk-Hansen T, Olsen RH, et al. Coronary flow reserve as a link between diastolic and systolic function and exercise capacity in heart failure. Eur Heart J Cardiovasc Imaging 2013;14:677-83.
PUBMED | CROSSREF
9. Rigo F, Gherardi S, Galderisi M, et al. The prognostic impact of coronary flow-reserve assessed by Doppler echocardiography in non-ischaemic dilated cardiomyopathy. Eur Heart J 2006;27:1319-23.
PUBMED | CROSSREF
10. Anantharam B, Janardhanan R, Hayat S, et al. Coronary flow reserve assessed by myocardial contrast echocardiography predicts mortality in patients with heart failure. Eur J Echocardiogr 2011;12:69-75.
PUBMED | CROSSREF
11. Wang N, Li SB, Zhao LS, et al. Relationship between obstructive sleep apnea and coronary microcirculatory function among patients with cardiac syndrome X. Coron Artery Dis 2014;25:35-9.
PUBMED | CROSSREF

12. Ky B, French B, May Khan A, et al. Ventricular-arterial coupling, remodeling, and prognosis in chronic heart failure. J Am Coll Cardiol 2013;62:1165-72.
PUBMED | CROSSREF
13. Her AY, Kim JY, Choi EY, et al. Value of ventricular stiffness index and ventriculoarterial interaction in patients with nonischemic dilated cardiomyopathy. Circ J 2009;73:1683-90.
PUBMED | CROSSREF
14. Borlaug BA, Kass DA. Ventricular-vascular interaction in heart failure. Cardiol Clin 2011;29:447-59.
PUBMED | CROSSREF
15. Borlaug BA, Kass DA. Invasive hemodynamic assessment in heart failure. Heart Fail Clin 2009;5:217-28.
PUBMED | CROSSREF
16. Borlaug BA, Kass DA. Ventricular-vascular interaction in heart failure. Heart Fail Clin 2008;4:23-36.
PUBMED | CROSSREF
17. Neumann T, Vollmer A, Schaffner T, Hess OM, Heusch G. Diastolic dysfunction and collagen structure in canine pacing-induced heart failure. J Mol Cell Cardiol 1999;31:179-92.
PUBMED | CROSSREF
18. Ishihara H, Yokota M, Sobue T, Saito H. Relation between ventriculoarterial coupling and myocardial energetics in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1994;23:406-16.
PUBMED | CROSSREF
19. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39.e14.
PUBMED | CROSSREF
20. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440-63.
PUBMED | CROSSREF
21. Choi EY, Choi BW, Kim SA, et al. Patterns of late gadolinium enhancement are associated with ventricular stiffness in patients with advanced non-ischaemic dilated cardiomyopathy. Eur J Heart Fail 2009;11:573-80.
PUBMED | CROSSREF
22. Pepine CJ, Anderson RD, Sharaf BL, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. J Am Coll Cardiol 2010;55:2825-32.
PUBMED | CROSSREF
23. Murthy VL, Naya M, Taqueti VR, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. Circulation 2014;129:2518-27.
PUBMED | CROSSREF
24. Stenström I, Maaniitty T, Uusitalo V, et al. Frequency and angiographic characteristics of coronary microvascular dysfunction in stable angina: a hybrid imaging study. Eur Heart J Cardiovasc Imaging 2017;18:1206-13.
PUBMED | CROSSREF
25. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 2017;13:479-504.
PUBMED | CROSSREF
26. Voci P, Pizzuto F, Mariano E, Puddu PE, Chiavari PA, Romeo F. Measurement of coronary flow reserve in the anterior and posterior descending coronary arteries by transthoracic Doppler ultrasound. Am J Cardiol 2002;90:988-91.
PUBMED | CROSSREF
27. Lee DH, Youn HJ, Choi YS, et al. Coronary flow reserve is a comprehensive indicator of cardiovascular risk factors in subjects with chest pain and normal coronary angiogram. Circ J 2010;74:1405-14.
PUBMED | CROSSREF
28. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community-based study. Circulation 2005;112:2254-62.
PUBMED | CROSSREF
29. Chantler PD. Arterial ventricular uncoupling with age and disease and recoupling with exercise. Exerc Sport Sci Rev 2017;45:70-9.
PUBMED | CROSSREF

30. Milewska A, Minczykowski A, Krauze T, et al. Prognosis after acute coronary syndrome in relation with ventricular-arterial coupling and left ventricular strain. Int J Cardiol 2016;220:343-8.
PUBMED | CROSSREF
31. Pack AI, Gislason T. Obstructive sleep apnea and cardiovascular disease: a perspective and future directions. Prog Cardiovasc Dis 2009;51:434-51.
PUBMED | CROSSREF
32. Morra S, Roubille F. Obstructive sleep apnoea: from respiratory events to coronary microvascular dysfunction. Acta Cardiol 2018;73:319-24.
PUBMED | CROSSREF
33. Atkeson A, Jelic S. Mechanisms of endothelial dysfunction in obstructive sleep apnea. Vasc Health Risk Manag 2008;4:1327-35.
PUBMED | CROSSREF
34. Ter Maaten JM, Damman K, Verhaar MC, et al. Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation. Eur J Heart Fail 2016;18:588-98.
PUBMED | CROSSREF
35. Baguet JP, Barone-Rochette G, Tamisier R, Levy P, Pépin JL. Mechanisms of cardiac dysfunction in obstructive sleep apnea. Nat Rev Cardiol 2012;9:679-88.
PUBMED | CROSSREF