Hypertension Research (2025) 48:2117–2118
https://doi.org/10.1038/s41440-025-02224-w

COMMENT

Extracardiac mechanisms of cardiac output affect unexplained dyspnea on exertion

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Keywords Dyspnea on exertion · Cardiopulmonary exercise test · Hypertension · Augmentation index

Received: 27 March 2025 / Accepted: 10 April 2025 / Published online: 25 April 2025
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Dyspnea, or shortness of breath, is a common symptom in clinical settings. There are many causes of dyspnea including respiratory disease, cardiovascular disease, and other conditions. It has been reported that in patients referred to a specialty clinic, approximately 35% of heart failure patients with preserved ejection fraction (HFpEF) had unexplained dyspnea on exertion [1]. We sometimes encountered hypertensive patients with unexplained dyspnea on exertion despite having controlled blood pressure and with extensive tests that were unremarkable. Exertion increases cardiac output in order to adapt the blood supply demand through controlling both cardiac and extracardiac mechanisms (Fig. 1) [2]. Heart rate and stroke volume are the main components of cardiac mechanisms in regulating the cardiac output, whereas cardiac output during exercise, in large part, depends on an extracardiac mechanism [2]. The preload and afterload are the components that constitute the extracardiac mechanism for regulating cardiac output. During physical activity, an increase in venous return towards the heart (preload) controls stroke volume, and decreased vascular resistance (afterload) in active muscles increases cardiac output [2, 3]. Several investigators have reported that extracardiac abnormalities are associated with exertional dyspnea and vascular function is impaired in HFpEF [2, 4, 5]. However, extracardiac mechanisms as the cause of dyspnea on exertion have been underrecognized in clinical settings.

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In this issue of the Hypertension Research, Skalska and colleagues reported the results of evaluation of the differences in central pulse pressure (cPP) and augmentation index (AIx) during a cardiopulmonary exercise test (CPET, personalized ramp protocol) between hypertensive females without dyspnea on exertion (non-dyspneic females, nDFs; $n = 27$) and hypertensive females with dyspnea on exertion (dyspneic females, DFs; $n = 25$) [6]. Applanation tonometry was performed before, during, and after the CPET. "Dyspnea on exertion" is defined as a subjective sensation of breathlessness or difficulty breathing during physical activity. Patients with heart failure, left ventricular ejection fraction <50%, chronic kidney disease, diabetes mellitus, history of lung disease, and other conditions precluding physical exercise were excluded from this study. There were no significant differences in baseline clinical characteristics including N-terminal pro-B-Type brain natriuretic peptide, echocardiography parameters, and AIx between the two groups. In the DFs group, AIx increased from 29 ± 10% at rest to 48 ± 37% after 3 min of exercise and then decreased to 21 ± 16% immediately after exercise, while AIx decreased from 27 ± 15% at rest to 21 ± 18% after 3 min of exercise and to 6 ± 23% immediately after exercise in nDFs. AIx was negatively correlated with peak heart rate, peak oxygen uptake, and peak cardiac output immediately after exercise. The results of this study showed that there were different AIx patterns in the DFs group and the nDFs group during the CPET. This study suggests that an abnormal response of AIx to exercise indicates that vascular function is impaired and blood vessels are unable to adapt to the demand for blood supply.

Although Skalska et al. suggested that utilizing the measurement of applanation tonometry (a measure of afterload) during a CPET is useful for identifying the impairment in hemodynamic adaptability in hypertensive females with unexplained dyspnea on exertion, effects of extracardiac abnormalities of preload reserve on exertional

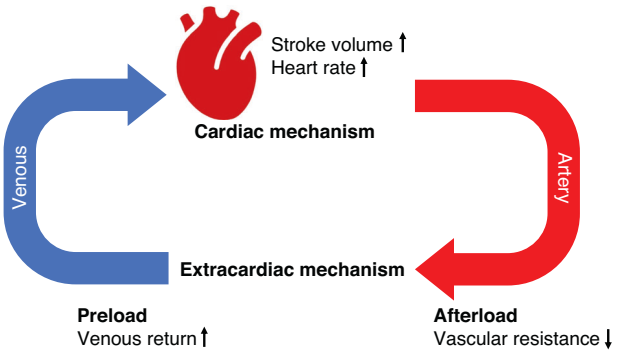

Fig. 1 Cardiac mechanisms and extracardiac mechanisms to increase cardiac output during exercise

dyspnea were not considered. Oldham et al. reported that 18% of unexplained exertional dyspnea patients without evidence of HFpEF have isolated preload failure [7]. They evaluated the effects of saline infusion on hemodynamics in some patients with preload failure by invasive CPET testing. Saline was administered before the invasive CPET to target a resting upright right atrial pressure of ≥5 mmHg. They found that 24% of the patients did not respond to volume loading with reduced peak cardiac output and maximum aerobic capacity during exercise. In non-responders, right atrial pressure and stroke volume did not increase during exercise. These findings suggest that there are some cases with the issue of preload failure in patients with unexplained exertional dyspnea. Limitation of exercise capacity that affects the quality of life has been under-recognized. The pathophysiology of HFpEF appears to be focused too much on the assessment of cardiac function. We should pay attention to not only on cardiac dysfunction but also conditions related to vascular failure to clarify the issues of unexplained dyspnea on exertion and to provide effective therapeutic approaches towards the best practice in cardiovascular health.

Acknowledgements We thank Farina Mohamad Yusoff, MD, PhD and Satoko Michiyama for their excellent secretarial assistance.

Funding This work was supported by JSPS KAKENHI (Grant Number JP19K17599) and Hirose Foundation, and Tsuchiya Foundation.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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References

1. Redfield MM, Borlaug BA. Heart Failure With Preserved Ejection Fraction: A Review. JAMA. 2023;329:827–38.
2. Fudim M, Sobotka PA, Dunlap ME. Extracardiac Abnormalities of Preload Reserve: Mechanisms Underlying Exercise Limitation in Heart Failure with Preserved Ejection Fraction, Autonomic Dysfunction, and Liver Disease. Circ Heart Fail. 2021;14:e007308.
3. Hsu S, Fang JC, Borlaug BA. Hemodynamics for the Heart Failure Clinician: A State-of-the-Art Review. J Card Fail. 2022;28:133–48.
4. Tooba R, Mayuga KA, Wilson R, Tonelli AR. Dyspnea in Chronic Low Ventricular Preload States. Ann Am Thorac Soc. 2021;18:573–81.
5. Kishimoto S, Kajikawa M, Maruhashi T, Iwamoto Y, Matsumoto T, Iwamoto A, et al. Endothelial dysfunction and abnormal vascular structure are simultaneously present in patients with heart failure with preserved ejection fraction. Int J Cardiol. 2017;231:181–7.
6. Skalska P, Kurpaska M, Banak M, Krzesiński P. Hypertensive women with dyspnea exhibit an unfavorable central blood pressure response to exercise. Hypertens Res. 2025. https://doi.org/10.1038/s41440-025-02171-6.
7. Oldham WM, Lewis GD, Opotowsky AR, Waxman AB, Systrom DM. Unexplained exertional dyspnea caused by low ventricular filling pressures: results from clinical invasive cardiopulmonary exercise testing. Pulm Circ. 2016;6:55–62.