Hypertension Research (2022) 45:2028–2029
https://doi.org/10.1038/s41440-022-01058-0

COMMENT

Pathophysiology of the exaggerated blood pressure response to exercise

Akihiro Tokushige[1,2] · Mitsuru Ohishi[1,2]

Received: 2 August 2022 / Revised: 28 August 2022 / Accepted: 29 August 2022 / Published online: 7 October 2022

Persistent hypertension leads to the onset, progression, and recurrence of various cardiovascular diseases, a decreased quality of life, and an increased risk of mortality [1]. In developed countries, age and obesity contribute to the prevalence of hypertension [2]. It is estimated that 43 million people in Japan, or one in three people, have hypertension, which is responsible for 7.6 million deaths annually worldwide [2]. Furthermore, studies show that systolic blood pressure (SBP) and diastolic blood pressure (DBP) have independent relationships with heart failure, atrial fibrillation, aortic dissection, atherosclerosis with peripheral arterial disease, renal disease, dementia, and retinopathy [2, 3]. Thus, hypertension is a major risk factor for most cardiovascular and related diseases [3].

Individuals without resting hypertension but with an exaggerated blood pressure response (EBPR) present with end-organ damage (e.g., albuminuria, left ventricular hypertrophy, diastolic dysfunction), similar to those with sustained hypertension. Estimates of the prevalence are uncertain because the threshold for exercise-induced hypertension is undefined. The prevalence in several healthy study cohorts of varying age, sex, and ethnicity was estimated at 3–4%, while other studies of healthy individuals have reported prevalence rates of up to 18% [4]. However, the overestimation of exercise blood pressure is higher in patients with established coronary artery disease (CAD) risk factors, such as type 2 diabetes (>50%) and masked hypertension (>40%), than in those without these conditions. A growing body of evidence helps identify healthy individuals without apparent cardiovascular disease or normotensive individuals who present an increased risk of developing hypertension and cardiovascular events in the future. In a systematic review by Keller et al., the definition of EBPR in cardiopulmonary exercise testing (CPET) was unclear; however, multiple studies showed that EBPR in CPET was associated with new onset of hypertension and future cardiovascular events [5]. Flow-mediated dilation (FMD) examines the relationship between higher SBP during submaximal intensity exercise and increased arterial stiffness and decreased endothelial function. However, the association between CAD and the exaggerated blood pressure response to exercise (EBPE) is not entirely clear, as there are limited data linking early markers of atherosclerosis to EBPE. Additionally, the association between EBPE and biomarkers of coronary microvascular dysfunction (MVD) and inflammation is not known in detail.

Although previous studies have shown that the coronary flow velocity reserve (CFVR) is reduced in patients with various manifestations of hypertension, no studies have assessed MVD in patients with EBPE using echocardiography for vascular impairment. In their latest study, Baycan et al. reported that patients with EBPE showed signs of coronary MVD in addition to endothelial dysfunction and subclinical atherosclerosis [6]. This was a single-center, cross-sectional study of patients aged 20–80 years with symptoms of chest pain who underwent an exercise stress test on a treadmill. Patients with EBPE had a higher carotid intima-media thickness and a significantly lower FMD than patients without EBPE. In addition, patients with EBPE had significantly higher office and 24-h mean SBP and DBP than those without EBPE. A limitation described by the authors is that it is difficult to understand whether these results are specific to EBPE or applicable to all patients with hypertension or mild hypertension. However, EBPE remains a significant predictor of CFVR after adjusting for 24-h ambulatory blood pressure measurements, and it is reasonable to assume that EBPE itself is associated with MVD. However, while comparing patients with and without EBPE, there were no significant differences in high-sensitivity C-reactive protein (hs-CRP) or copeptin levels, which are markers of vascular inflammation. This could

✉ Akihiro Tokushige
akihiro@m3.kufm.kagoshima-u.ac.jp

[1] Department of Cardiovascular Medicine and Hypertension, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan

[2] Department of Prevention and Analysis of Cardiovascular Diseases, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan

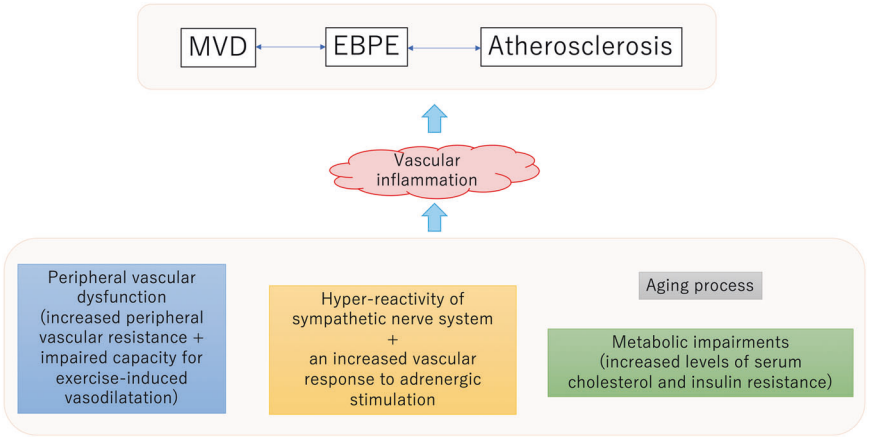

Fig. 1 Assumed pathophysiology of the exaggerated blood pressure response to exercise

be because the subjects were young, averaging ~37 years of age, and diseases that promote atherosclerosis were excluded. This could have prevented detection.

However, the underlying pathophysiology of EBPE is poorly understood. Wilson et al. found that total peripheral resistance was not sufficiently reduced in patients with EBPE to compensate for increased cardiac output during exercise [7]. Thus, EBPE can be partially explained by increased peripheral vascular resistance and an impaired capacity for exercise-induced vasodilation. These responses of peripheral vascular function are attributed to sympathetic nervous system hyperactivity and increased vascular response to adrenergic stimulation or microvascular wall thickening, which alters the ability to respond to vasoconstrictive stimuli [8]. Another explanation is the presence of metabolic abnormalities in patients with EBPE on CPET, such as high fasting glucose, triglycerides, and total cholesterol levels, low glucose tolerance, and high obesity rates [9–11]. Vascular inflammation is also considered a pathophysiological intermediate linking EBPE and atherosclerosis. Previous studies revealed that inflammatory biomarkers, such as hs-CRP and interleukin-6, are correlated with peak SBP during exercise [12] (Fig. 1).

Thus, although the mechanism of elevated blood pressure during exercise may be related to a variety of factors, the results of various clinical trials suggest that microvascular impairment is associated with an increased risk of mortality, even in the absence of obvious significant epicardial coronary stenosis. Evidence of abnormal microvascular function in EBPE may be a useful screening marker for future cardiovascular event risk. Further investigation of the long-term outcomes of patients with EBPE is needed to verify whether it leads to an improved prognosis.

Compliance with ethical standards

Conflict of interest AT has no conflicts of interest to declare. MO is a member of Hypertension Research' Editorial Team.

References

1. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2159–219.
2. Sacks FM, Campos H. Dietary therapy in hypertension. N Engl J Med. 2010;362:2102–12.
3. Schmieder RE. End organ damage in hypertension. Dtsch Arztebl Int. 2010;107:866–73.
4. Le VV, Mitiku T, Sungar G, Myers J, Froelicher V. The blood pressure response to dynamic exercise testing: a systematic review. Prog Cardiovasc Dis. 2008;51:135–60.
5. Keller K, Stelzer K, Ostad MA, Post F. Impact of exaggerated blood pressure response in normotensive individuals on future hypertension and prognosis: systematic review according to PRISMA guideline. Adv Med Sci. 2017;62:317–29.
6. Baycan OF, Çelik FB, Güvenç TS, Atıcı A, Yılmaz Y, Konal O, et al. Coronary flow velocity reserve is reduced in patients with an exaggerated blood pressure response to exercise. Hypertens Res. 2022;45:1653–63.
7. Wilson MF, Sung BH, Pincomb GA, Lovallo WR. Exaggerated pressure response to exercise in men at risk for systemic hypertension. Am J Cardiol. 1990;66:731–6.
8. Kavey RE, Kveselis DA, Gaum WE. Exaggerated blood pressure response to exercise in children with increased low-density lipoprotein cholesterol. Am Heart J. 1997;133:162–8.
9. Sharabi Y, Ben-Cnaan R, Hanin A, Martonovitch G, Grossman E. The significance of hypertensive response to exercise as a predictor of hypertension and cardiovascular disease. J Hum Hypertens. 2001;15:353–6.
10. Mundal R, Kjeldsen SE, Sandvik L, Erikssen G, Thaulow E, Erikssen J. Clustering of coronary risk factors with increasing blood pressure at rest and during exercise. J Hypertens. 1998;16:19–22.
11. Kayrak M, Bacaksiz A, Vatankulu MA, Ayhan SS, Kaya Z, Ari H, et al. Exaggerated blood pressure response to exercise—a new portent of masked hypertension. Clin Exp Hypertens. 2010;32:560–8.
12. Hamer M, Steptoe A. Vascular inflammation and blood pressure response to acute exercise. Eur J Appl Physiol. 2012;112:2375–9.