Review

Clinical and Prognostic Value of Exaggerated Blood Pressure Response to Exercise

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Abstract

The hypertensive response to exercise testing, defined as exaggerated blood pressure response (EBPR), has been documented to be independently associated with unhealthy conditions, carrying an increased risk of future hypertension, cardiovascular (CV) morbidity and mortality. In treated hypertensives, EBPR is a marker of uncontrolled hypertension, a condition previously undetected by office blood pressure (BP) measurements at rest; EBPR may also detect masked hypertension, a phenotype characterized by normal BP values in the medical environment but elevated home or ambulatory BP monitoring (ABPM). The aim of the present review is to provide a comprehensive and up-dated information on the clinical importance of EBPR targeting the following issues: (I) definition and prevalence; (II) underlying mechanisms; (III) clinical correlates and association with subclinical organ damage; (IV) predictive value; (V) clinical decision making.
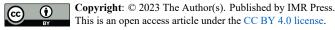
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1. Introduction

In both normotensive and hypertensive individuals, physical exercise, either dynamic or isometric, carried out in the clinical setting for cardiovascular (CV) diagnostics, is associated to significant blood pressure (BP) variations, in particular sharp increments in systolic BP (SBP) and variable changes in diastolic BP (DBP), that may either decrease, increase or remain unchanged [1,2]. In physiological conditions, BP changes during exercise are the result of the rise in cardiac output in response to the increased oxygen demand from working muscles via activation of the adrenergic tone [3,4]. The electrocardiography (ECG)-monitored stress test for assessing cardiopulmonary fitness is routinely performed by means of dynamic exercise with a progressive workload. In response to the rapid increase in physical activity, stroke volume and heart rate are boosted by increased sympathetic activity and a vasodilation occurs at the level of arterioles supplying the exercising muscles, thus leading to a decrease in systemic vascular resistances [5].

Stress ECG testing with measurement of BP at incremental stages of exercise intensity is a validated non-invasive diagnostic tool carried out worldwide in cardiology practice [6,7]. Measuring BP response to physical exercise during stress ECG testing represents a key procedure, as abnormal responses in terms of BP increases or decreases provide relevant information in addition to conventional ECG and clinical diagnostic criteria [8,9]. In addition to dynamic exercise, other stimuli such as mental stress, cold stress and handgrip represent an alternative method for evaluating exaggerated pressure reactivity [10]. Exaggerated BP response (EBPR) to these stimuli has been also associated with poor prognosis; our review, however, will focus on the abnormal pressure reactivity to exercise ECG-testing [11].

Consistent evidence indicates that hypertensive response to exercise testing is independently associated with several CV risk factors and, more importantly, with an increased likelihood of CV morbidity and mortality [12–15]. The strength of this association is more evident when EBPR occurs in the early stages of test or during submaximal exercise [16,17]. Of note, EBPR in treated hypertensives may be seen as a marker of uncontrolled hypertension previously undetected by office BP measurements at rest [18]. On the other hand, EBPR in normotensive individuals may be a marker of masked hypertension and predictor of future hypertension [19,20]. This review aimed to summarise available evidence about the clinical relevance of EBPR will be focused on the following issues: (I) definition and prevalence; (II) mechanisms; (III) clinical correlates and association with subclinical organ damage; (IV) prognostic value; (V) clinical management.

2. Definition and Prevalence

Several definitions of EBPR during treadmill and bicycle exercise testing have been reported in the literature; this may be relate to the lack of consensus about the 'threshold' value of exercise BP defining this phenotype. This uncertainty is also reflected by the different recommendations issued by the Cardiology and Sports Medicine guidelines. The American Heart Association (AHA) guidelines define EBPR as systolic peak BP >210 mmHg in men and >190 mmHg in women, and/or diastolic peak >90 mmHg in both sexes; the corresponding thresholds recommended by the European Society of Cardiology (ESC) guidelines are systolic peak >220 mmHg in men, >200 mmHg in women and/or diastolic peak >85 mmHg in men, >80 mmHg in women [21,22]. At difference, the American College Sports Medicine (ACSM) guidelines suggest a non-sex specific BP threshold (i.e., systolic peak BP >225 mmHg and/or diastolic peak BP >90 mmHg) [23] (Table 1). Different definitions of EBPR are based on SBPs values exceeding either the 90th or 95th percentile of the study population. Recently, age- and sex-specific peak SBP 90th percentiles have been used to assess the risk of CV morbidity and mortality associated with EBPR [24].

Table 1. Blood pressure diagnostic cut-offs recommended by guidelines to define exaggerated blood pressure response to exercise.

Guidelines	Blood pressure cut-offs	
	Men	Women
American Heart Association	210/90 mmHg	190/90 mmHg
European Society of Cardiology	220/85 mmHg	200/80 mmHg
American College Sports Medicine	225/90 mmHg	

A meta-analysis of 12 studies revealed that EBPR may be defined over a wide interval of SBP values ranging from 180 to 275 mmHg [25]. A further source of heterogeneity of EBPR diagnostic criteria is the intensity of physical exercise. Differences in protocol, type of exercise (i.e., bicycle, treadmill), age, gender, degree of physical activity of the individuals examined (i.e., sedentary, trained, athletes) and comorbidities are major determinants of variability among studies. A consequence of the lack of consensus about EBPR definition is the difficulty in comparing and interpreting data provided by the studies. It is worth noting that EBPR may occur in both normotensive individuals with no known history of hypertension and in treated hypertensive patients. Thus, the variable prevalence of EBPR reported in current literature may be related to numerous factors including threshold values used to define this phenotype, demographic (i.e., age, sex, ethnicity) and clinical characteristics of the populations studied. In the Southall and Brent Revisited (SABRE) study, including 659 older adults, EBPR (i.e., SBP ≥210 mmHg in men and >190

mmHg in women and/or DBP ≥110 mmHg in both sexes) was found in 31% of normotensive and 23% of hypertensive participants with controlled resting BP [26]. The EXERTION study (Exercise Stress Test Collaboration) based on the results of clinical stress testing recorded from multiple hospitals in Australia and including 13.268 subjects (aged 53 ± 13 years, 9% with type 2 diabetes) who completed the Bruce treadmill protocol, showed that EBPR overall prevalence at stage 3 in participants with 'normal' pre-exercise BP (<140/90 mmHg) was 6.4% [13]. In a large cohort of 1167 competitive athletes of any age without known arterial hypertension, EBPR prevalence rates varied from 6.8 to 19.6% according to ACSM and ESC guidelines, respectively [27]. It is therefore evident that EBPR during physical exercise may affect a significant fraction of individuals with normal BP at rest, EBPR prevalence ranging from 5 to 30%.

3. Mechanisms

Although the complex pathophysiological mechanisms of EBPR remain poorly defined, growing evidence on this issue has been collected in individuals with and without CV diseases. The multiple factors implicated in EBPR development include genetic background, endothelial function, large artery stiffness, arterial baroreflex sensitivity and neurohormonal response to exercise (Fig. 1). Emerging findings suggest that exaggerated BP and sympathetic responses to physical stimuli may reflect a deranged neural-cardiovascular control in young adults with a genetic predisposition to hypertension [28]. A greater increase in BP and muscle sympathetic nerve activity in response to static exercise has been described in young otherwise healthy adults with a family history of hypertension as compared to controls matched for age, BP and heart rate [29]. Endothelium-dependent vasodilation in large arteries represents a key adaptive response to systolic wall shear stress occurring during physical exercise [30]. Thus, endothelial dysfunction by impairing the physiological vasodilation that counterbalances the increased shear stress, may trigger EBPR. Numerous studies during the last two decades have documented an association of EBPR with endothelial dysfunction, aortic stiffness and enhanced angiotensin II rise at exercise peak [31,32]. Stewart *et al.* [33] measured endothelial vasodilator function, assessed as brachial artery flow-mediated vasodilation (FMD), in untreated individuals with high normal BP or mild hypertension. The authors documented that FMD was the only independent correlate of the difference between resting and maximal pulse pressure in both sexes.

Increased arterial stiffness resulting in a reduced buffer function of large arteries may, in turn, enhance excessive BP increments during exercise. A recent study carried out in 92 untreated normotensive men without a history of CV disease revealed that, compared with individuals with a normal response, those with an EBPR exhibited
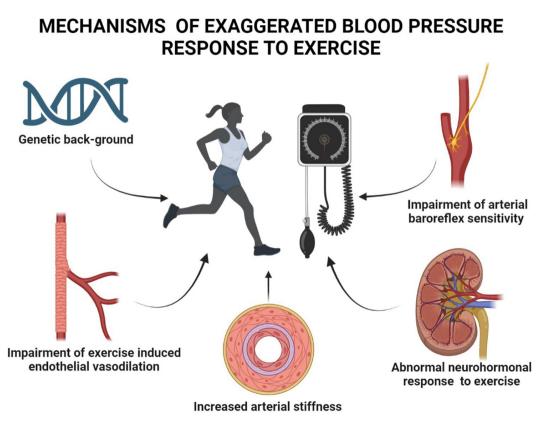
MECHANISMS OF EXAGGERATED BLOOD PRESSURE RESPONSE TO EXERCISE

Fig. 1. Mechanisms and factors implicated in the development of exaggerated blood pressure response to exercise.

a significantly higher brachial-ankle pulse wave velocity (1412 ± 158 vs 1250 ± 140 cm/s), after adjusting for several confounders [34]. Activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system during exercise and their involvement in EBPR has been reported by different research groups [35,36]. In particular, greater increases in angiotensin II levels during exercise have been reported in individuals with EBPR when compared to age and gender matched controls with normal BP response [37]. The parallel increase in norepinephrine and epinephrine observed in the study by Shim *et al.* [37] supports the view that both RAAS and sympathoadrenal system mutually interact in determining BP changes during physical exercise. The increased activity of both systems leading to peripheral arterial vasoconstriction may contribute to EBPR during exercise [38]. In this regard, studies conducted in hypertensive patients, in individuals with high-normal BP as well as in elderly men have suggested that hyper-activation of muscle chemoreceptors may attenuate functional sympatholysis, enhancing the vasoconstriction, which, in combination with increased cardiac output, is responsible of EBPR [39,40]. Finally, it should be emphasized that the mechanisms of EBPR vary in relation to the intensity of exercise. The largest part of evidence about the relationship between EBPR and outcomes is based on observations made at moderate workloads. BP recorded during submaximal exercise is likely indicative of BP variations during daily life as reflects the usual dynamic ac-

tivities [25]. Of note, BP at peak of maximal exercise may represent a confounding factor for prognostic predictions, as these protocols usually select individuals with elevated cardiopulmonary fitness and, therefore, at lower CV risk [41].

4. Clinical Correlates

Main research lines addressing the factors associated with EBPR have investigated the relationship between masked hypertension and BP changes during exercise. Masked hypertension is a condition characterized by normal BP values measured in the medical environment but elevated home or ambulatory BP monitoring (ABPM) values [42]. This term was coined in the early 2000's by Pickering *et al.* [43] in order to define a hypertensive status not identified by routine office BP measurements. Since then, a large body of evidence has accumulated on the adverse clinical and prognostic significance of masked hypertension. Numerous cross-sectional and longitudinal investigations demonstrated that, compared to normotensive individuals, those with masked hypertension have an increased risk of hypertension-mediated organ damage, CV morbidity and mortality substantially overlapping that of sustained hypertensive patients [44–46]. The pathophysiological mechanisms underlying these observations are related to the fact that out-of-office BP, either monitored at home or in dynamic conditions over 24 h, has a closer relationship with CV events and a greater predictive value for adverse out-

comes compared to office BP [47]. One of the first studies to investigate the relationship between masked hypertension and EBPR was published a decade ago by Sharman *et al.* [48]. Among 72 non-diabetic individuals free of CV disease with EBPR to maximal treadmill exercise (i.e., SBP $\geq$210 mmHg in men and $\geq$190 mmHg in women and/or DBP $\geq$105 mmHg in both sexes), the authors found that out-of-office hypertension, defined as daytime BP values $\geq$135/85 mmHg during 24 h ABPM, was present in the majority of the study population (58%). The prevalence of masked hypertension detected in studies conducted with similar protocols in both non-diabetic and diabetic subjects varied between 28 and 41% of the population study, thus indicating that excessive BP elevation induced by exercise occurs more frequently in individuals with hypertension unrecognized by office BP measurements [49,50].

The presence of subclinical target organ damage in individuals with normal office BP at rest has been proven to be associated with EBPR; in particular, left ventricular hypertrophy (LVH) or concentric remodelling have been related to this abnormal BP phenotype. In a pioneering study performed in 1978 including participants to Framingham Heart Study free of CV disease and not taking any antihypertensive or CV medication, individuals with an EBPR to exercise exhibited a 10% higher LV mass than those with normal SBP responses to exercise [51]. In the previously mentioned study by Sharman *et al.* [48] patients with EBPR had significantly higher values of LV mass index (41.5 $\pm$ 8.7 vs 35.9 $\pm$ 8.5 g/m$^{2.7}$) and relative wall thickness (0.42 $\pm$ 0.09 vs 0.37 $\pm$ 0.06) than their counterparts with normal exercise BP. The association between EBPR and LVH has also been reported in the competitive sport setting. In a large cohort of 1137 athletes (mean age 21 years; 35% females) without known arterial hypertension, LVH was approximately two-fold more frequent in athletes with EBPR, defined by ACSM guidelines, than in counterparts without EBPR [27].

5. Prognostic Significance

Two lines of research, based on prospective studies, investigated the predictive significance of EPBR targeting its association with: (I) new-onset hypertension and (II) fatal and non-fatal CV events.

The Coronary Artery Risk Development in Young Adults (CARDIA) study was the first investigation to address the association between EBPR and incident hypertension in 3741 normotensive individuals undergoing treadmill testing [52]. EBPR was found in 687 participants (18%) who exhibited 5 mmHg higher SBP and 1 mmHg higher DBP; after a 5-year follow-up period ($p < 0.005$); these subjects were 1.70 times more likely to develop hypertension than those with normal BP response ($p < 0.001$). Although the increase in SBP associated with EBPR, after adjusting for major confounders, was small (1 to 3 mmHg), these sustained increments over time may result in a signifi-

cant increased incidence of hypertension. In the late 1990s, the Framingham Heart Study provided a new piece of information on the relation of EBPR during graded treadmill test with the risk of future hypertension [53]. Over 8 years of follow-up new onset hypertension occurred in 28% of men and 16% of women. Interestingly, the most important exercise predictor of new-onset hypertension in both sexes was DBP recorded at peak exercise rather than SBP. Furthermore, a delayed recovery SBP response also predicted incident hypertension in men. The prognostic significance of EBPR to exercise has recently been addressed in different ethnic and clinical settings. In a study performed in a Japanese cohort totalling 733 male middle-aged individuals, SBP measured at the end of a 10-year follow-up period was more closely related to exercise SBP ($\beta = 0.271$, $p < 0.001$) than to resting SBP ($\beta = 0.148$, $p < 0.001$) [54]. Office BP after 10 years was 123 $\pm$ 12/79 $\pm$ 7 mmHg in individuals with low SBP response to exercise ($<$180 mmHg), 127 $\pm$ 13/81 $\pm$ 8 mmHg in those with moderate response (180–199 mmHg), and 134 $\pm$ 15/84 $\pm$ 10 mmHg in the group with high response ($\geq$200 mmHg).

The value of EBPR in predicting future hypertension has also been demonstrated in the setting of athletes which, by definition, includes healthy subjects trained to perform intense physical activity. One hundred and forty-one normotensive athletes with EBPR to exercise were compared to 141 normotensive athletes with normal BP response matched for gender, age, body size, and type of sport [55]. A total of 19 athletes belonging to EBPR group developed hypertension (13.5%) compared with 5 of the normal BP response group (6.5%) during a mean follow-up period of 6.5 years.

Finally, moving from single studies to meta-analysis, the findings of a systematic review by Keller *et al.* [56] based on 18 prospective and retrospective studies including 35,151 healthy normotensive participants undergoing cardiopulmonary testing revealed a significant association between EBPR to exercise (systolic, diastolic or both) and new onset hypertension over a follow-up period lasting between 2 and 14 years regardless of the wide heterogeneity of the criteria used to define the EBPR.

The notion that EBPR in otherwise normotensive individuals may represent a risk factor for cardiovascular disease has been known for over thirty years. The Paris Prospective Study was among the first to investigate this topic by analysing the data collected in 4907 normotensive healthy middle-aged men over a mean followed-up period of 17 years [15]. The magnitude of exercise-induced SBP elevation was significantly associated with incident CV events and all-cause death, regardless of several major confounders including LVH. The value of SBP recorded during the maximal stress test for prediction of all-causes mortality, CV disease, and coronary heart disease was assessed in a large population-based sample of 20,387 men and 6234 women living in Dallas during a 8-year follow-up

period [57]. In men, the adjusted risks of all-cause mortality for quartiles 3 and 4 of maximal SBP, compared to the lowest quartile, were: 1.36 (1.01–1.85), and 1.37 (0.98–1.92), respectively. This was also the case for the risk of CV disease and coronary morbidity and mortality. Similar findings for all-cause and CV mortality were observed in women across maximal SBP quartiles. Recently, the Oslo Ischemia Study provided further evidence of a positive association between the magnitude of BP responses to moderate exercise and the risk of CV disease and mortality [58].

Unlike the above mentioned studies, a recent report by Zafrir *et al*. [59], based on a retrospective analysis of 14,792 individuals followed for over 6 years, showed that the excessive increase in SBP during exercise did not predict CV disease and mortality after adjustment for confounding factors. Of note, when the SBP quartiles measured during the stress test were taken into account, the analysis documented that individuals belonging to the highest quartile were at higher risk than those in the lowest quartile.

A couple of meta-analyses have confirmed the unfavourable prognostic significance of EBPR. Pooled data from 12 studies including 46,314 individuals without overt cardiac disease suggested that the hypertensive response to an exercise of moderate intensity carried a 36% higher rate of CV events and mortality (95% CI 1.02–1.83, $p = 0.04$) compared to normal BP response [17]. The meta-analysis by Perçuku *et al*. [25], carried out in 47,188 normotensive individuals from 8 studies, showed that individuals with EBPR to exercise had a greater risk of CV death and coronary disease (HR: 1.36, $p < 0.001$) [25]. Finally, the predictive value of EBPR with respect to specific outcomes, such as coronary artery disease, sudden cardiac death and stroke, deserves to be briefly commented. The participants to the Gothemburg Study with EBPR exhibited a significant increased risk of stroke but not of myocardial infarction [60]. On the contrary, an association between EBPR and incident acute coronary syndrome and myocardial infarction was reported in the meta-analysis by Perçuku *et al*. [25]. Among the Framingham Offspring Study participants (n = 2066, mean age 58 years, 53% women) higher DBP and lower pulse pressure values during submaximal treadmill test were associated with an increased risk of heart failure over a median follow-up of 16.8 years [61]. Laukkanen *et al*. [62] failed to find an independent relationship between SBP during recovery from a symptom-limited exercise and sudden cardiac death after adjiusting for resting SBP and other CV risk factors.

6. Clinical Management

EBPR documented during exercise in normotensive subjects without history of hypertension and in treated hypertensives may require further diagnostic investigations, bearing in mind, however, that this BP phenotype is not a fully reproducible clinical trait. Grossman *et al*. [63], evaluating the data of exercise tests performed during annual health examinations for five consecutive years in 69 normotensive patients with high normal BP levels, found that only 11 patients (21.5%) out of the whole baseline EBPR group exhibited the same abnormal BP response during subsequent tests. Although limited data on EBPR reproducibility over time do not allow to correctly estimate the clinical relevance of this BP phenotype, the significance of EBPR in single patients should be evaluated in order to exclude both masked hypertension or uncontrolled masked hypertension. A comprehensive diagnostic approach in these patients should include BP measurements out-side the office environment (preferentially in dynamic conditions with the ABPM) and the search for subclinical hypertension mediated organ damage [64]. Available evidence of an association between EBPR, elevated ABPM values and/or target organ damage such as concentric remodelling, LVH, increased arterial stiffness, and carotid atherosclerosis should direct the clinician to plan a therapeutic intervention based on lifestyle modifications and drug treatment [65–67]. A large body of evidence supports the view that regular physical activity may favourably affect endothelial function, sympathetic activity, arterial stiffness and consequently BP levels both in normotensive individuals and hypertensive patients. Lifestyle modification programs consisting of aerobic exercise and diet counselling have been shown to reduce exercise-induced SBP elevation, improve arterial stiffness and nitric oxide bioavailability even in short-term studies (i.e., 12 weeks) [68]. Of note, the reversibility of EBPR to exercise was found to be less evident in elderly patients [69]. Nonetheless, non-pharmacological treatment of hemodynamic changes associated with EBPR represents the first mandatory step in sedentary overweight/obese individuals without history of hypertension. As for antihypertensive treatment, this option should be considered when EBPR is associated with masked hypertension, according to guideline recommendations. In treated patients with normal office BP at rest, but elevated BP during exercise, optimal treatment strategies are still uncertain [70]. As RAAS activation and increased adrenergic tone may affect vascular and myocardial responses to exercise, angiotensin converting enzyme inhibitors, angiotensin receptor antagonists and beta-blockers are the drugs of choice for hypertensive patients with EBPR [71]. Furthermore, it is useful to underline that in diabetic patients the improvement of metabolic profile may reduce and even normalize EBPR [72]. In addition, the insulin sensitizer rosiglitazone has been reported to play a beneficial effect on resting BP as well as on BP response to exercise in men with type 2 diabetes mellitus and coronary artery disease, especially in those with EBPR [73]. Finally, weight loss after bariatric surgery, a treatment increasingly used in morbid obesity, has been shown to effectively reduce the high prevalence of EBPR in these patients [74]. It is worth mentioning, however, that evidence on the effects of non-pharmacological and pharmacological interventions on CV outcomes in patients with EBPR is still lacking.

7. Conclusions

EBPR detected during ECG stress test is a common condition both in normotensive individuals without a known history of hypertension and in treated hypertensives with normal resting BP. Growing evidence suggests that EBPR is related to several CV risk factors such as endothelial and large artery dysfunction, increased sympathetic tone, metabolic alterations and obesity [75]. In clinical perspectives, EBPR may be regarded as a marker of multiple conditions, including masked hypertension, poor BP control, subclinical target organ damage and adverse CV outcomes [76,77]. When this condition is ignored, CV risk is underestimated in a large proportion of the population undergoing stress testing, thus contributing to the increased burden of CV diseases with their public health consequences. It should be underlined, however, that some methodological and clinical aspects of this condition remain poorly defined, in particular clinical indications of stress test, diagnostic criteria of EBPR and screening criteria of individuals to unmask this condition. Furthermore, the role of EBPR treatment as an effective therapeutic target for reducing CV risk remains to be clarified. Thus, further studies are needed to investigate this important issue in order to prevent CV complications associated with EBPR.

Author Contributions

CC and MT conceived and designed the review; CC drafted the manuscript; AF and EG contributed to the collection and analysis of literature, prepared figures and tables; CS and GG provided substantial revision of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Guido Grassi is serving as one of the Editorial Board members of this journal. We declare that Guido Grassi had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Carl J. Lavie.

References

[1] Heimark S, Eitzen I, Vianello I, Bøtker-Rasmussen KG, Mamen A, Hoel Rindal OM, *et al*. Blood Pressure Response and Pulse Arrival Time During Exercise Testing in Well-Trained Individuals. Frontiers in Physiology. 2022; 13: 863855.

[2] Alvarez-Pitti J, Herceg-Čavrak V, Wójcik M, Radovanović D, Brzeziński M, Grabitz C, *et al*. Blood pressure response to exercise in children and adolescents. Frontiers in Cardiovascular Medicine. 2022; 9: 1004508.

[3] Bingel A, Messroghli D, Weimar A, Runte K, Salcher-Konrad M, Kelle S, *et al*. Hemodynamic Changes During Physiological and Pharmacological Stress Testing in Patients With Heart Failure: A Systematic Review and Meta-Analysis. Frontiers in Cardiovascular Medicine. 2022; 9: 718114.

[4] Richards JC, Luckasen GJ, Larson DG, Dinenno FA. Role of α-adrenergic vasoconstriction in regulating skeletal muscle blood flow and vascular conductance during forearm exercise in ageing humans. The Journal of Physiology. 2014; 592: 4775–4788.

[5] Gifford J, Kofoed J, Leach O, Wallace T, Dorff A, Hanson BE, *et al*. Impact of Interrepetition Rest on Muscle Blood Flow and Exercise Tolerance during Resistance Exercise. Medicina. 2022; 58: 822.

[6] Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, *et al*. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013; 128: 873–934.

[7] Colquhoun D, Freedman B, Cross D, Fitzgerald B, Forge B, Hare DL, *et al*. Clinical Exercise Stress Testing in Adults (2014). Heart, Lung & Circulation. 2015; 24: 831–837.

[8] Schultz MG, Sharman JE. Exercise Hypertension. Pulse. 2014; 1: 161–176.

[9] Costa EC, Browne RAV, Câmara M, Macêdo GAD, Lucena BEB, Vianna LC, *et al*. Immediate post-exercise blood pressure and arterial stiffness in hypertensive and normotensive older females. Journal of Clinical Hypertension. 2022; 24: 704–712.

[10] Delaney EP, Greaney JL, Edwards DG, Rose WC, Fadel PJ, Farquhar WB. Exaggerated sympathetic and pressor responses to handgrip exercise in older hypertensive humans: role of the muscle metaboreflex. American Journal of Physiology. Heart and Circulatory Physiology. 2010; 299: H1318–1327.

[11] Chaney RH, Eyman RK. Blood pressure at rest and during maximal dynamic and isometric exercise as predictors of systemic hypertension. The American Journal of Cardiology. 1988; 62: 1058–1061.

[12] Miyai N, Arita M, Morioka I, Takeda S, Miyashita K. Ambulatory blood pressure, sympathetic activity, and left ventricular structure and function in middle-aged normotensive men with exaggerated blood pressure response to exercise. Medical Science Monitor. 2005; 11: CR478–484.

[13] Schultz MG, Otahal P, Kovacevic A, Roberts-Thomson P, Stanton T, Hamilton-Craig C, *et al*. Type-2 Diabetes and the Clinical Importance of Exaggerated Exercise Blood Pressure. Hypertension. 2022; 79: 2346–2354.

[14] Moore MN, Climie RE, Otahal P, Schultz MG. Exercise blood pressure and cardiovascular disease risk: a systematic review and meta-analysis of cross-sectional studies. Journal of Hypertension. 2021; 39: 2395–2402.

[15] Filipovský J, Ducimetière P, Safar ME. Prognostic significance of exercise blood pressure and heart rate in middle-aged men. Hypertension. 1992; 20: 333–339.

[16] Greaney JL, Farquhar WB. Skeletal muscle contraction triggers rapid onset pressor responses in cardiovascular disease. The Journal of Physiology. 2012; 590: 5933–5934.

[17] Schultz MG, Otahal P, Cleland VJ, Blizzard L, Marwick TH, Sharman JE. Exercise-induced hypertension, cardiovascular events, and mortality in patients undergoing exercise stress testing: a systematic review and meta-analysis. American Journal of Hypertension. 2013; 26: 357–366.

[18] Chant B, Bakali M, Hinton T, Burchell AE, Nightingale AK, Paton JFR, *et al*. Antihypertensive Treatment Fails to Control Blood Pressure During Exercise. Hypertension. 2018; 72: 102–109.

[19] Koletsos N, Dipla K, Triantafyllou A, Gkaliagkousi E, Sachpekidis V, Zafeiridis A, *et al*. A brief submaximal isometric exercise test 'unmasks' systolic and diastolic masked hypertension. Journal of Hypertension. 2019; 37: 710–719.

[20] Huang Z, Sharman JE, Fonseca R, Park C, Chaturvedi N, Davey Smith G, *et al*. Masked hypertension and submaximal exercise blood pressure among adolescents from the Avon Longitudinal Study of Parents and Children (ALSPAC). Scandinavian Journal of Medicine & Science in Sports. 2020; 30: 25–30.

[21] Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, *et al*. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013; 128: 873–934.

[22] Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, *et al*. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. European Heart Journal. 2021; 42: 17–96.

[23] Currie KD, Floras JS, La Gerche A, Goodman JM. Exercise Blood Pressure Guidelines: Time to Re-evaluate What is Normal and Exaggerated? Sports Medicine. 2018; 48: 1763–1771.

[24] Hedman K, Lindow T, Cauwenberghs N, Carlén A, Elmberg V, Brudin L, *et al*. Peak exercise SBP and future risk of cardiovascular disease and mortality. Journal of Hypertension. 2022; 40: 300–309.

[25] Perçuku L, Bajraktari G, Jashari H, Bytyçi I, Ibrahimi P, Henein MY. Exaggerated systolic hypertensive response to exercise predicts cardiovascular events: a systematic review and meta-analysis. Polish Archives of Internal Medicine. 2019; 129: 855–863.

[26] Jones S, Schultz MG, Park C, Tillin T, Chaturvedi N, Hughes AD. Antihypertensive treatment effect on exercise blood pressure and exercise capacity in older adults. Journal of Hypertension. 2022; 40: 1682–1691.

[27] Keller K, Hartung K, Del Castillo Carillo L, Treiber J, Stock F, Schröder C, *et al*. Exercise Hypertension in Athletes. Journal of Clinical Medicine. 2022; 11: 4870.

[28] Greaney JL, Matthews EL, Wenner MM. Sympathetic reactivity in young women with a family history of hypertension. American Journal of Physiology. Heart and Circulatory Physiology. 2015; 308: H816–H822.

[29] Matthews EL, Greaney JL, Wenner MM. Rapid onset pressor response to exercise in young women with a family history of hypertension. Experimental Physiology. 2017; 102: 1092–1099.

[30] Shi W, Liu H, Cao L, He Y, Su P, Chen J, *et al*. Acute effect of high-intensity interval exercise on vascular endothelial function and possible mechanisms of wall shear stress in young obese males. Frontiers in Physiology. 2022; 13: 966561.

[31] Downey RM, Liao P, Millson EC, Quyyumi AA, Sher S, Park J. Endothelial dysfunction correlates with exaggerated exercise pressor response during whole body maximal exercise in chronic kidney disease. American Journal of Physiology-Renal Physiology. 2017; 312: F917–F924.

[32] Baycan ÖF, 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. Hypertension Research. 2022; 45: 1653–1663.

[33] Stewart KJ, Sung J, Silber HA, Fleg JL, Kelemen MD, Turner KL, *et al*. Exaggerated exercise blood pressure is related to impaired endothelial vasodilator function. American Journal of Hypertension. 2004; 17: 314–320.

[34] Miyai N, Shiozaki M, Terada K, Takeshita T, Utsumi M, Miyashita K, *et al*. Exaggerated blood pressure response to exercise is associated with subclinical vascular impairment in healthy normotensive individuals. Clinical and Experimental Hypertension. 2021; 43: 56–62.

[35] Kim D, Ha J. Hypertensive response to exercise: mechanisms and clinical implication. Clinical Hypertension. 2016; 22: 17.

[36] Kim C, Park Y, Chun MY, Kim Y. Exercise-induced hypertension is associated with angiotensin II activity and total nitric oxide. Medicine. 2020; 99: e20943.

[37] Shim CY, Ha J, Park S, Choi E, Choi D, Rim S, *et al*. Exaggerated blood pressure response to exercise is associated with augmented rise of angiotensin II during exercise. Journal of the American College of Cardiology. 2008; 52: 287–292.

[38] Saltin B, Mortensen SP. Inefficient functional sympatholysis is an overlooked cause of malperfusion in contracting skeletal muscle. The Journal of Physiology. 2012; 590: 6269–6275.

[39] Vongpatanasin W, Wang Z, Arbique D, Arbique G, Adams-Huet B, Mitchell JH, *et al*. Functional sympatholysis is impaired in hypertensive humans. The Journal of Physiology. 2011; 589: 1209–1220.

[40] Choi H, Stebbins CL, Lee O, Nho H, Lee J, Chun J, *et al*. Augmentation of the exercise pressor reflex in prehypertension: roles of the muscle metaboreflex and mechanoreflex. Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme. 2013; 38: 209–215.

[41] Schultz MG, La Gerche A, Sharman JE. Cardiorespiratory Fitness, Workload, and the Blood Pressure Response to Exercise Testing. Exercise and Sport Sciences Reviews. 2022; 50: 25–30.

[42] Cuspidi C, Sala C, Tadic M, Grassi G. When office blood pressure is not enough: the case of masked hypertension. American Journal of Hypertension. 2019; 32: 225–233.

[43] Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. Hypertension. 2002; 40: 795–796.

[44] Cuspidi C, Facchetti R, Quarti-Trevano F, Sala C, Tadic M, Grassi G, *et al*. Incident Left Ventricular Hypertrophy in Masked Hypertension. Hypertension. 2019; 74: 56–62.

[45] Pierdomenico SD, Pierdomenico AM, Coccina F, Clement DL, De Buyzere ML, De Bacquer DA, *et al*. Prognostic Value of Masked Uncontrolled Hypertension. Hypertension. 2018; 72: 862–869.

[46] Zhang D, Guo Q, An D, Li Y, Wang J. A comparative meta-analysis of prospective observational studies on masked hypertension and masked uncontrolled hypertension defined by ambulatory and home blood pressure. Journal of Hypertension. 2019; 37: 1775–1785.

[47] Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, *et al*. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. Circulation. 2005; 111: 1777–1783.

[48] Sharman JE, Hare JL, Thomas S, Davies JE, Leano R, Jenkins C, *et al*. Association of masked hypertension and left ventricular remodeling with the hypertensive response to exercise. American Journal of Hypertension. 2011; 24: 898–903.

[49] Akilli H, Kayrak M, Arıbas A, Tekinalp M, Ayhan SS, Gündüz M, *et al*. The relationship between exercise capacity and masked hypertension in sedentary patients with diabetes mellitus. Clinical and Experimental Hypertension. 2014; 36: 9–16.

[50] 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. Clinical and Experimental Hypertension. 2010; 32: 560–568.

[51] Lauer MS, Levy D, Anderson KM, Plehn JF. Is there a relationship between exercise systolic blood pressure response and left ventricular mass? The Framingham Heart Study. Annals of In-

ternal Medicine. 1992; 116: 203–210.

[52] Manolio TA, Burke GL, Savage PJ, Sidney S, Gardin JM, Oberman A. Exercise blood pressure response and 5-year risk of elevated blood pressure in a cohort of young adults: the CARDIA study. American Journal of Hypertension. 1994; 7: 234–241.

[53] Singh JP, Larson MG, Manolio TA, O'Donnell CJ, Lauer M, Evans JC, et al. Blood pressure response during treadmill testing as a risk factor for new-onset hypertension. The Framingham heart study. Circulation. 1999; 99: 1831–1836.

[54] Ito K, Iwane M, Miyai N, Uchikawa Y, Mugitani K, Mohara O, et al. Exaggerated exercise blood pressure response in middle-aged men as a predictor of future blood pressure: a 10-year follow-up. Clinical and Experimental Hypertension. 2016; 38: 696–700.

[55] Caselli S, Serdoz A, Mango F, Lemme E, Vaquer Seguì A, Milan A, et al. High blood pressure response to exercise predicts future development of hypertension in young athletes. European Heart Journal. 2019; 40: 62–68.

[56] 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. Advances in Medical Sciences. 2017; 62: 317–329.

[57] Kohl HW, Nichaman MZ, Frankowski RF, Blair SN. Maximal exercise hemodynamics and risk of mortality in apparently healthy men and women. Medicine and Science in Sports and Exercise. 1996; 28: 601–609.

[58] Falk RS, Mariampillai JE, Prestgaard EE, Heir T, Bodegård J, Robsahm TE, et al. The Oslo Ischaemia Study: cohort profile. BMJ Open. 2021; 11: e049111.

[59] Zafrir B, Aker A, Asaf Y, Saliba W. Blood pressure response to treadmill exercise test and the risk for future cardiovascular events and new onset hypertension. Journal of Hypertension. 2021; 40: 143–152.

[60] Giang KW, Hansson P, Mandalenakis Z, Persson CU, Grimby G, Svärdsudd K, et al. Long-term risk of stroke and myocardial infarction in middle-aged men with a hypertensive response to exercise: a 44-year follow-up study. Journal of Hypertension. 2021; 39: 503–510.

[61] Carneiro HA, Song RJ, Lee J, Schwartz B, Vasan RS, Xanthakis V. Association of Blood Pressure and Heart Rate Responses to Submaximal Exercise With Incident Heart Failure: The Framingham Heart Study. Journal of the American Heart Association. 2021; 10: e019460.

[62] Laukkanen JA, Willeit P, Kurl S, Mäkikallio TH, Savonen K, Ronkainen K, et al. Elevated systolic blood pressure during recovery from exercise and the risk of sudden cardiac death. Journal of Hypertension. 2014; 32: 659–666.

[63] Grossman A, Cohen N, Shemesh J, Koren-Morag N, Leibowitz A, Grossman E. Exaggerated blood pressure response to exercise is not associated with masked hypertension in patients with high normal blood pressure levels. Journal of Clinical Hypertension. 2014; 16: 277–282.

[64] Mizuno R, Fujimoto S, Saito Y, Yamazaki M. Clinical impor-

tance of detecting exaggerated blood pressure response to exercise on antihypertensive therapy. Heart. 2016; 102: 849–854.

[65] Cuspidi C. Is exaggerated exercise blood pressure increase related to masked hypertension? American Journal of Hypertension. 2011; 24: 861.

[66] Jae SY, Fernhall B, Heffernan KS, Kang M, Lee M, Choi YH, et al. Exaggerated blood pressure response to exercise is associated with carotid atherosclerosis in apparently healthy men. Journal of Hypertension. 2006; 24: 881–887.

[67] Haarala A, Kähönen E, Koivistoinen T, Pälve K, Hulkkonen J, Tikkakoski A, et al. Pulse wave velocity is related to exercise blood pressure response in young adults. The Cardiovascular Risk in Young Finns Study. Blood Pressure. 2020; 29: 256–263.

[68] Michishita R, Ohta M, Ikeda M, Jiang Y, Yamato H. Effects of Lifestyle Modification on an Exaggerated Blood Pressure Response to Exercise in Normotensive Females. American Journal of Hypertension. 2017; 30: 999–1007.

[69] Jones S, Schultz MG, Park C, Tillin T, Chaturvedi N, Hughes AD. Antihypertensive treatment effect on exercise blood pressure and exercise capacity in older adults. Journal of Hypertension. 2022; 40: 1682–1691.

[70] Chant B, Bakali M, Hinton T, Burchell AE, Nightingale AK, Paton JFR, et al. Antihypertensive Treatment Fails to Control Blood Pressure During Exercise. Hypertension. 2018; 72: 102–109.

[71] Mert KU, Şener E, Yılmaz AS, Mert GÖ, Yetmiş F, Dural M, et al. The association of exaggerated hypertensive response to exercise and beta-blockers use in hypertensives. Clinical and Experimental Hypertension. 2020; 42: 707–713.

[72] Yardley JE, MacMillan F, Hay J, Wittmeier K, Wicklow B, MacIntosh AC, et al. The blood pressure response to exercise in youth with impaired glucose tolerance and type 2 diabetes. Pediatric Exercise Science. 2015; 27: 120–127.

[73] Piché M, Laberge A, Brassard P, Arsenault BJ, Bertrand OF, Després J, et al. Rosiglitazone lowers resting and blood pressure response to exercise in men with type 2 diabetes: A 1-year randomized study. Diabetes, Obesity & Metabolism. 2018; 20: 1740–1750.

[74] Sénéchal-Dumais I, Auclair A, Leclerc J, Poirier P. Effect of bariatric surgery on blood pressure response to exercise in a severely obese population. Blood Pressure Monitoring. 2021; 26: 357–363.

[75] Tzemos N, Lim PO, MacDonald TM. Exercise blood pressure and endothelial dysfunction in hypertension. International Journal of Clinical Practice. 2009; 63: 202–206.

[76] Aung SM, Güler A, Güler Y, Karabay CY, Akdemir I. Two-dimensional speckle-tracking echocardiography-based left atrial strain parameters predict masked hypertension in patients with hypertensive response to exercise. Blood Pressure Monitoring. 2017; 22: 27–33.

[77] Małek ŁA, Jankowska A, Greszata L. Mild Left Ventricular Hypertrophy in Middle-Age Male Athletes as a Sign of Masked Arterial Hypertension. International Journal of Environmental Research and Public Health. 2022; 19: 10038.