Definitions for Hypertensive Response to Exercise

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Abstract: Broad evidence indicates that hypertensive response to exercise (HRE) is associated with future hypertension (aHT) at rest and cardiovascular morbidity and mortality. Nevertheless, a consensus on the definition of HRE is lacking and the comparability of the available data is difficult due to a wide variation of definitions used. This review aims to harmonize currently available definitions of HRE in normotensive and athletic populations and to propose a generally valid cut-off applicable in everyday clinical practice. A literature search on PubMed and Embase was conducted to assemble and analyze the most recent data. Various definitions of HRE were identified and linked with future cardiovascular diseases. Forty-one studies defined HRE at a peak systolic blood pressure (SBP) above or equal to 200 mmHg in men and 25 studies for 190 mmHg in women. Peak diastolic blood pressure (DBP) between 90 and 110 mmHg was reported in 14 studies, relative DBP increase in four. Eight studies defined HRE as SBP between 160 and 200 mmHg at 100 watts. 17 studies performed submaximal exercise testing, while two more looked at BP during recovery. A plethora of other definitions was identified. In athletes, total workload and average blood pressure during exercise were considerably higher. Based on the presented data, the most commonly used definition of HRE at peak exercise is 210/105 mmHg for men, 190/105 mmHg for women, and 220/210 mmHg for athletes. Furthermore, a uniform exercise testing protocol, a position statement by leading experts to unify the definition of HRE, and prospective studies are warranted to confirm these cut-offs and the associated morbidity and mortality.

Key Words: arterial hypertension, exercise, cardiovascular risk

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Aerobic exercise leads to an increase in systolic blood pressure (SBP) linearly proportional to exercise intensity in healthy individuals. In contrast, diastolic blood pressure (DBP) may remain the same, increase only slightly, or even decline.[1] Some individuals exhibit an abnormally exaggerated increase, known as hypertensive response to exercise (HRE). This is often observed in individuals without other clinical manifestations of cardiovascular diseases.[2] Currently, there is no consensus on normal blood pressure (BP) response during exercise in normotensive individuals and athletes.[3] Inconsistent definitions of HRE, lack of standardized testing and different study characteristics make it difficult to define HRE and its prognostic value for future arterial hypertension (aHT) at rest and cardiovascular events. Therefore, HRE has hardly been included in guidelines, and the actual prevalence is unclear.[3] A recent systematic review showed HRE was an independent risk factor for future aHT.[4] Other studies associated HRE with cardiac remodeling and cardiovascular diseases.[5] Similarly, HRE in athletes is not a normal finding and should be interpreted as a risk factor for developing aHT.[6] These findings support the clinical value of HRE in identifying individuals at higher risk for future cardiovascular events. However, HRE was defined in different heterogeneous ways.[7] This review aims to harmonize currently available definitions of HRE in normotensive individuals and athletes. Finally, we propose a valid general definition of HRE, which can be applied to clinical practice.

PATHOPHYSIOLOGY OF HRE IN DIFFERENT POPULATIONS

The American College of Sports Medicine (ACSM) and the American Heart Association (AHA) define a normal SBP increase by 10±2 mmHg per metabolic equivalent task (1MET = 3.5 mL/kg*min).[8] It has been reported that SBP and DBP at peak exercise, as well as the relative change in SBP during exercise (ΔSBP), was higher in men than in women and older patients.[9] It is essential to acknowledge that noninvasive methods can measure only SBP but not DBP reliably.[10] The pathophysiology of an abnormal BP response is still not fully clear.[1] BP is regulated by peripheral vascular resistance and cardiac output (CO, defined as heart rate (HR) × stroke volume).[11] At moderate to high-intensity exercise, the rise in cardiac output is primarily dependent on an increase in HR, whereas stroke volume typically reaches a plateau at 50–60% of maximal oxygen uptake. In physiological conditions, the average rise in SBP during effort is about 10 mmHg/MET.[11,12] Current evidence suggests that the determinants of HRE are multifactorial and gradually vary over time, shares the many mechanisms with aHT at rest, and are influenced by age, gender, and gene-environment interaction.[2,13] Figure 1 illustrates the mechanisms leading to HRE. According to some studies, the main mechanism leading to an excessive BP response is related to the inability to reduce peripheral vascular resistance during exercise, which is caused by an overreactive stimulation of the sympathetic nervous system, leading to impaired endothelial vasodilation.[2] According to animal models, the presence of peripheral artery disease exacerbates autonomic reflex responses thus leading to abnormal sympathetic responsiveness and abnormal responses to metabolic receptors, particularly under effort.[14] Further mechanisms imply an increased vascular stiffness of large arteries, endothelial dysfunction with insufficient nitric oxide (NO) production, and increased activation of the renin-angiotensin-aldosterone system and inflammation.[15] A reduced NO has been closely described in atherosclerosis, leading to an altered metabolic and cardiovascular homeostasis towards vasoconstriction and increased peripheric vascular resistance.[16] Similar alterations at a preclinical stage have been observer in otherwise normotensive patients with HRE.[2]

Increased angiotensin-II has been reported in individuals with HRE in relation to reduced NO signaling and increased oxidative stress.[2,15] As such, high-intensity, prolonged exercise may induce oxidative stress, tissue damage, and negatively influence vascular resistance.[17] Furthermore, an altered exercise pressor reflex may

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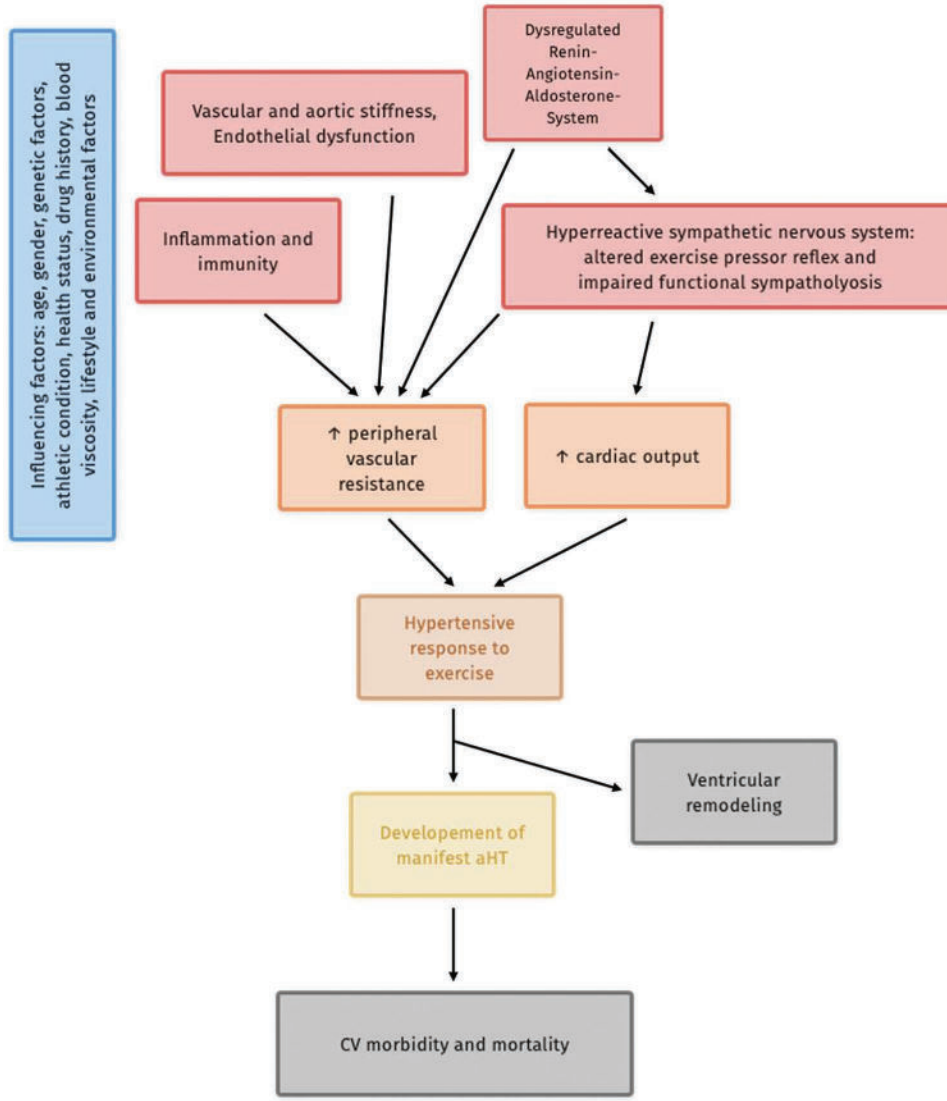

FIGURE 1. Pathological mechanisms leading to HRE. aHT, arterial hypertension, CV, cardiovascular.

contribute to an abnormal sympathetic nervous system activation.[18] To uphold BP during exercise, the blood flow is equalized between metabolically induced vasodilation in skeletal muscles and vasoconstriction in the spleen, liver, and kidneys. This exercise-induced pressor reflex is triggered by mechanical and metabolic stimuli originating from the skeletal muscle: it increases the sympathetic afferent nerve activity while reducing parasympathetic efferent nerve activity, thus resulting in vasoconstriction and increased HR and left ventricular (LV) contractility.[14] Chronically increased sympathetic tone can lead by downregulating α- and β-receptors to reduced cardiovascular responsiveness and structural alterations.[19] In the elderly, as well as in females, HRE is mainly related to increased vascular stiffness.[2] In particular, elder patients with HRE presented with a higher left ventricular diastolic and systemic arterial elastance, whereas younger patients had a higher relative ventricular wall thickness.[20] In support of these findings, impaired elastic properties of the aorta have been found in normotensive subjects presenting with HRE.[21]

BP cut-offs for HRE should be different for men and women. In women, HRE seems to be predominantly related to increased systemic vascular resistance and not to sympathetic activation.[20] Normally, women present high estrogen levels, which acts as a vasodilator in peripheral and coronary vessels.[22] Estrogen receptors, however, may undergo downregulation due to age, pregnancy, and menopause, thus increasing the aHT risk.[3] Of note, women are at higher risk of developing heart failure with preserved ejection fraction (HFpEF), which is typically characterized by LV diastolic impairment. This is largely due to a higher systemic arterial and LV stiffness, which could be demonstrated under effort in relation to HRE before the clinical onset of HFpEF.[23] Namely, HRE has been associated with LV hypertrophy, diastolic dysfunction, and reduced coronary perfusion: the increased peripheral BP in HRE augments afterload and LV wall stress, which in turn induces cardiac remodeling.[24] However, this association is still debated.[25] Furthermore, it is not fully understood if LV diastolic dysfunction is a cause or consequence of HRE. There is evidence that HRE promotes heart failure with preserved ejection fraction partially due to insufficient interaction between arterial elastance and LV end-systolic elastance (i.e., ventricular-arterial uncoupling).[20] In particular, ventricular-arterial uncoupling likely represents the main pathophysiological mechanisms underlying the long-term evolution of HRE in HFpEF, principally in the elderly, as discussed before.[20,23]

It is still debated if higher peak BP in athletes is due to physiological adaptation of the heart without pathophysiological significance.[26] Athletes achieve higher peak workloads, which is associated with higher normal BP values during exercise.[27] Cardiorespiratory fitness has been reported to be an independent factor influencing BP during exercise testing, leading to physiological adaptions in the cardiovascular, musculoskeletal, respiratory, endocrine, and immune system.[26,28] Athletes are known to have higher maximal oxygen uptake and lower peripheral vascular resistance.[27] With the increasing workload, CO increases nearly linearly, but is limited to a maximum capacity. The athlete's heart is associated with higher peak stroke volumes and therefore higher CO, and lower HR at submaximal workloads and rest.[11] Athletes with HRE attain higher workloads during exercise testing and present more LV remodeling compared to those without.[27] A prospective study followed-up young normotensive athletes for almost 7 years and found HRE as independent and significant predictor of future aHT.[6] Turmel et al. showed that athletes with HRE have higher SBP during exercise at different intensity levels and higher SBP during the 24-h ambulatory blood pressure monitoring (ABPM) compared with those without HRE.[29]

METHODS

A comprehensive search of the Pubmed and Embase databases for studies reporting definitions of HRE was conducted, yielding 63 studies of nonathletes and 14 of athletes. Cross-sectional, longitudinal studies and reviews were included. Only studies regarding adults and published in the English language were considered. Following information were extracted: study design, characteristics of participants (age, gender, health status, athletic condition), HRE cut-off values, BP measurement method, exercise testing protocol, cardiovascular outcomes, and the years of follow-up. Studies regarding isometric exercise and studies including participants with preexisting cardiovascular disease were excluded. Reports on pathophysiological mechanisms were analyzed.

RESULTS

A total of 63 studies were analyzed, with a total of 98,460 nonathletic study participants (mean age 42 years). Thirty prospective studies were individuated, with a mean follow-up of 10 years (Supplementary Table 1, http://links.lww.com/CIR/A49). In 16 studies, HRE was defined as SBP ≥210 mmHg for men and ≥190 mmHg for women at peak exercise, mirroring the cut-off values proposed in the Framingham study.[30] Eight studies defined HRE as peak SBP >200 mmHg in men. In 14 studies, abnormal peak DBP was defined as >90 and 110mmHg in both genders, while seven studies did not propose absolute cut-offs. Twelve studies proposed HRE cut-off values for both peak SBP and DBP, as follows: in men, four studies proposed ≥210/105 mmHg, one study ≥230/100 mmHg, another study, including both men and women, ≥225/90 mmHg, and other five studies considered HRE ≥190/105 mmHg in women. The lowest SBP cut-off used to define HRE was described by Lewis et al., with >180mmHg for men and women, according to the >80th percentile of individuals in the Framingham study.[30,31] However, the majority of the authors choose HRE cut-offs >90th or >95th percentile. Matthews defined HRE as a ΔSBP of >60 mmHg at 6.3 MET or >70 mmHg at 8.1 MET, while Lima proposed an increase in SBP >7.5 mmHg/MET.[32,33] Considering a workload of 100W, HRE was defined as a peak SBP >180 mmHg, >192 mmHg and >200 mmHg.[34–36] Nazar defined HRE as a peak SBP >200 mmHg at a workload <150 W in men.[12] Only one study defined HRE as a peak DBP >90 mmHg at 100 W.[37]

Besides the definition of HRE, some studies investigated the association of HRE with cardiovascular outcomes. Similarly to the cut-off proposed by Lewis, Jae reported a SBP >181 mmHg as significant and a relative SBP increase ≥52 mmHg during exercise as relevant predictors of aHT onset after a mean follow-up of 5 years.[38] Zanettini proposed an SBP variation of 11 mmHg/MET as an ideal cut-off to explore the longitudinal association between HRE and the incidence of aHT and hypertension-mediated organ damage, whereas a peak SBP of >190 mmHg in women and >210 mmHg in men as well as an SBP value >160 mmHg at 100W was identified as the best cut-off in term of sensitivity and specificity for the prediction of aHT.[39,40] Another study associated a rise of SBP >19.7 mmHg per minute of exercise with increased stroke risk.[41] In other studies, HRE was investigated as the difference between peak exercise BP and resting BP (ΔBP): Miyai found a ΔSBP of 33 to 59 mmHg as associated with a higher risk for future aHT, while Shim proposed a cut-off of 60 mmHg ΔSBP in men and 50 mmHg in women.[15,42] Mundal found a ΔSBP >48.5 mmHg at 100 watts (W) to be associated with a 1.5-fold increased risk of cardiovascular mortality.[36]

Further studies considered BP during recovery to define HRE and evaluated it as a suitable indicator for future cardiovascular diseases.[5,41]

A total of 14 studies investigated HRE in athletes. 5228 normotensive athletes (mean age 26.5 years) were reviewed (Supplementary Table 2, http://links.lww.com/CIR/A49). In some studies, the same cut-off values as proposed in the Framingham study and the recent AHA guidelines were utilized for athletes, as well:[11,30] as such, HRE was defined as a peak SBP ≥210 mmHg for men and ≥190 mmHg for women. Since these values were exceeded by 43% in male and 28% and female master athletes, an SBP cut-off of >247 mmHg and >214 mmHg, corresponding to the 97th percentile, was proposed.[43] An association between the SBP/MET-slope and the risk of future aHT was reported for athletes, too.[44] Although no gender differences were found for this association, the predictive value of the peak SBP/W-ratio was different in men as compared to women.[45] Following cut-off values were prospectively investigated: peak SBP >220 mmHg and/or peak DBP >85 mmHg for men, peak SBP >200 mmHg and/or peak DBP >80 mmHg for women.[6] Although, some studies failed to report any significant association with cardiac remodeling or metabolic dysfunction using these cut-offs, another study reported lower apo-A1 serum levels and, as such, a higher risk of cardiovascular diseases.[27,29,46] DBP cut-off values in athletes, ranging from 80 mmHg in females and 85 mmHg in males and >100 mmHg in both, were investigated in four studies. HRE was defined as a ΔDBP >10 mmHg from resting DBP in one study.[47] The association between HRE as defined by peak SBP and peak DBP are contrasting.[43,44] The detail of the studies defining HRE are summarized in Supplementary Table 1, http://links.lww.com/CIR/A49 for nonathletic individuals, and Supplementary Table 2, http://links.lww.com/CIR/A49 for athletes.

DISCUSSION

This narrative review analyzed overall 77 studies, including 98,460 normotensive, healthy individuals and 5228 athletes. Of all study participants, 74% and 85%, respectively, were male. We report overall an HRE definition as peak SBP >210 mmHg in men and 190mmHg in women and a peak DBP ≥110 mmHg for both.[9,11,13,19,25,37] We here present longitudinal observational studies and also considered a number of meta-analyses and studies on pathophysiological mechanisms of HRE. In the reviewed literature, we report some consistency in defining HRE as absolute peak BP values ≥210/105 mmHg in nonathletic men and ≥190/105 mmHg for women, while in athletes HRE should be pondered as ≥220/110 mmHg. The proposed HRE cut-off may have been influenced by participants' age and ethnicity: age-related increase of SBP, mainly related to atherosclerosis, is a well-described event. Furthermore, the heterogeneity of exercise protocols should be acknowledged, as

well. A step protocol (e.g., Bruce treadmill protocol) may yield more stable BP values than a ramp protocol on a bicycle ergometer.[11] The identification of a universally accepted definition of an HRE is necessary to distinguish between physiologic BP adaptation from pathologic conditions, to initiate appropriate treatment.

Defining HRE as an absolute BP cut-off assures easy usability in the clinical context and should be chosen wisely: Peak SBP values between 180–190 mmHg are problematically low and would significantly increase the incidence of HRE. On the other hand, values >230 mmHg are not sensible as they would miss many patients at risk for future aHT. A SBP >250 mmHg or DBP >115 mmHg or a drop in SBP of >10 mmHg are relative indications for terminating exercise testing, which should be acknowledged.[11] Further, there is still no consensus if DBP should be included in HRE, since it is difficult to reliably measure DBP noninvasively during exercise.[3] However, a direct correlation between direct and indirect DBP measurements at low and moderate exercise has been reported.[48]

Since a strong correlation between peak SBP and resting SBP has been reported, it has been debated, whether HRE may be solely a reflection of elevated BP at rest.[49] Anyhow, a significant increase in BP corrected for peak workload as compared to BP values at rest has been shown to significantly correlate with cardiovascular risk factors.[9,11] Nevertheless, there is currently insufficient evidence to define HRE as a ΔSBP or DBP value, although ΔBP and the pattern of BP variation during effort should be taken into consideration when interpreting absolute BP values.[5,11] The role of gender when reading peak BP values is not clear, yet. Both in healthy men and men with high cardiovascular risk factors, higher peak SBP were observed as compared to women.[1,9,43] This may be explained by higher estrogen levels in women, as well as different body composition and physiological cardiovascular adaption to exercise: pre-menopausal women have a reduced incidence of cardiovascular diseases compared to men at the same age.[45] After menopause, cardio-protective estrogen levels decreases, total arterial compliance diminishes, and systemic vascular resistance augments.[45]

It remains controversial if peak exercise testing predicts adverse cardiovascular outcomes better than performing at submaximal workloads.[50] Clinical circumstances, health status, the individual's familiarity with the exercise testing modality, and cardiovascular risk factors can influence peak exercise performance. Furthermore, it may be challenging to identify whether peak exercise testing was accomplished.[1] Several studies proposed measuring BP at 100W.[34–36,39] This workload may imitate everyday stress but may be unachievable for some and for individuals with higher CRF this level may be too low to offer adequate sensitivity. On the other hand, SBP cut-offs ranging 160–200 mmHg during submaximal exercise testing predict future aHT and adverse cardiovascular outcomes.[35,36,38,39] Recommendations for exercise testing and hypertension guidelines advocate considering workload when assessing SBP during exercise, but no specific approach is indicated.[11] There is evidence of a better prognostic value of peak SBP adjusted for workload as compared to SBP before exercise, at 100W and peak SBP alone.[51] The SBP/MET-slope may have a better predictive sensitivity as compared to other approaches.[52] It has to be noted that MET is calculated by standard, validated formulas validated by the ACSM, thus CO and oxygen uptake are estimated. Moreover, the achievable workload is affected by many factors. Based on gender and training status the SBP/W-ratio and peak SBP/W were proposed as more sensitive parameters: although male athletes showed a higher peak SBP, females had a significantly higher SBP/W-slope and ratio.[45] This significant difference may be due to a higher vasodilator reserve in male athletes. Furthermore, hormonal levels may have influenced these findings through alterations in substrate metabolism, body composition, thermoregulation, muscular strength, and tissue stiffness.[52]

In general, trained individuals present with a slower and steadier BP increase during exercise and achieved higher peak BP values than untrained individuals.[37] Athletes have a lower risk of developing aHT compared to untrained individuals, therefore it is reasonable to assume that higher peak BP in athletes is a compensatory mechanism to meet higher demands rather than dysfunction of the cardiovascular system.[13] Consequently, higher cut-off values for HRE should be chosen for athletes and they should be applicable to different sport disciplines.[43] Some authors associated lower VO_2max and HR values with negative cardiovascular outcomes.[28,53] However, to determine VO_2max cardiopulmonary exercise testing is required, which is costly and not always feasible in everyday clinical practice. Moreover, HR is affected by behavioral, dietary, and environmental factors and is thereby prone to misinterpretation.

Normal BP in the clinic, but an elevated BP at home is known as masked aHT.[3] There are data regarding the association between HRE and masked aHT, although a positive association for DBP was described.[48] This could have relevant clinical implications on screening for masked aHT without the use of 24h-ABPM. Prospective research is warranted on this subject.

Clinical perspective. If HRE is present, as illustrated in Figure 2, we suggest establishing lifestyle modifications first, in particular, weight control through a healthy diet and regular exercise. In the second step, periodical BP measurement and follow-up, including 24h-ABPM, should be implemented. In the current literature, there is no evidence to treat HRE with oral antihypertensive therapy.[1] Such a therapy should be prescribed when aHT is manifest, which may be detected at an early stage through frequent clinical evaluation.

In athletes, lifestyle modifications, such as weight loss if obese and healthier eating habits (e.g., salt and alcohol restriction), are often enough to ensure optimum BP control during exercise and at rest. Athletes with HRE should undergo 24-h-ABPM, perhaps even during training sessions and medical treatment of masked aHT or aHT should be implemented when nonpharmacologic strategies are insufficient.[13] However, we propose an individualized approach regarding age, gender, and cardiovascular risk factors as indicated.

LIMITATIONS

This narrative review has some limitations. First, it is limited to articles published in PubMed and Embase in the English language. Some minor studies might potentially be not included in our review. Second, only studies investigating adults, mostly white men, were included. A review of HRE in adolescents and children would be beyond the scope of this review. Age, gender, ethnicity, health status, and the indication for exercise testing varied and, consequently, the studies' inhomogeneity represents a significant limitation of this analysis. Several cross-sectional studies were included, therefore evidence of a temporal relationship between exposure and outcome is lacking.

CONCLUSION

We propose a standardized definition of HRE as peak exercise BP >210/105 mmHg in men, >190/105 mmHg in women, and >220/110 mmHg in athletes. To ensure adequate management of HRE standardized exercise testing protocols and further prospective randomized research is warranted to confirm these cut-offs and the associated morbidity and mortality. Particularly, more studies with women and athletes are required.

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CG was responsible for designing the review protocol, writing the report, screening potentially eligible studies, extracting and analyzing data, interpreting results, updating reference lists, and

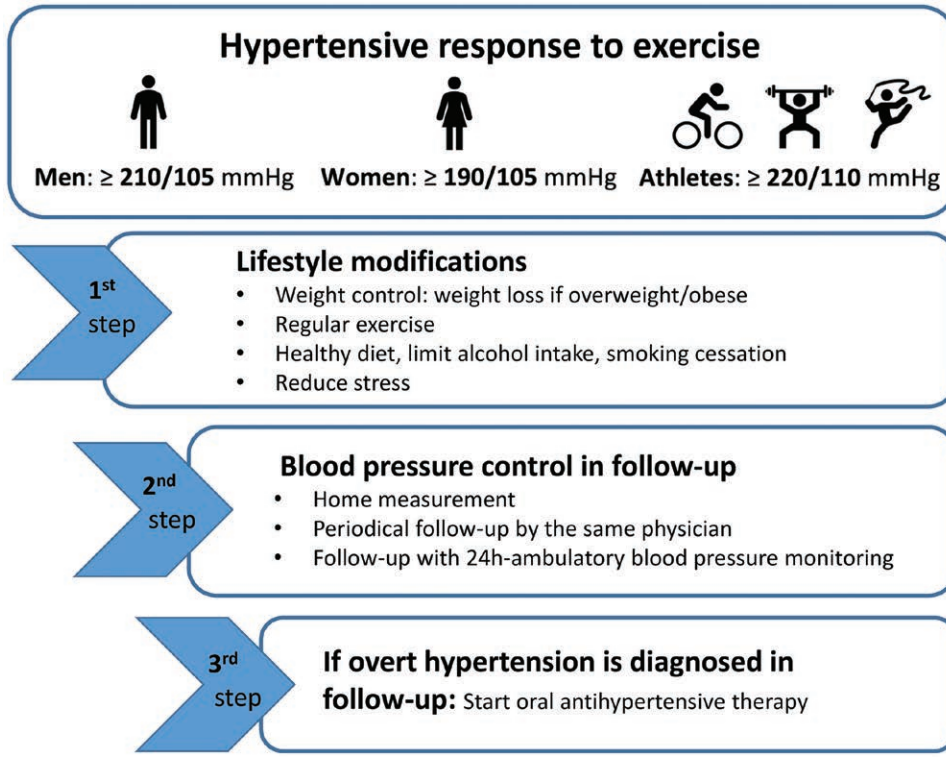

FIGURE 2. Treatment recommendations of HRE.

creating "Summary of findings" tables. MK contributed to writing the report, interpreting results, and providing feedback and important intellectual comments on the report. VAR contributed to designing the review protocol, screening potentially eligible studies, interpreting results, and providing feedback and important intellectual comments on the report. CS contributed to designing the review protocol, screening potentially eligible studies, interpreting results, and providing feedback and important intellectual comments on the report. SC contributed to designing the review protocol, screening potentially eligible studies, interpreting results, provided feedback and important intellectual comments on the report. DN contributed to designing the review protocol, screening potentially eligible studies, interpreting results, providing feedback and important intellectual comments on the report; and is taking final responsibility for this manuscript.

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