



Review Article

Impact of exaggerated blood pressure response in normotensive individuals on future hypertension and prognosis: Systematic review according to PRISMA guideline



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ABSTRACT

Purpose: Arterial hypertension (aHT) is the leading risk factor for morbidity and mortality worldwide. Blood pressure (BP) deviation at rest is well defined and accompanies risk for cardiovascular events and cardiovascular mortality. A growing body of evidence emphasises that an exaggerated blood pressure response (EBPR) in cardiopulmonary exercise testing (CPET) could help to identify seemingly cardiovascular healthy and normotensive subjects, who have an increased risk of developing aHT and cardiovascular events in the future.

Materials and methods: The PubMed online database was searched for published studies reporting exercise-related BP and both the risk of aHT and cardiovascular events in the future.

Results: We identified 18 original studies about EBPR in CPET, which included a total of 35,151 normotensive individuals for prediction of new onset of aHT in the future and 11 original studies with 43,012 enrolled subjects with the endpoint of cardiovascular events in the future.

Although an EBPR under CPET is not well defined, a large number of studies emphasise that EBPR in CPET is associated with both new-onset aHT and cardiovascular events in the future.

Conclusions: A growing number of studies support the hypothesis that EBPR in CPET may be a diagnostic tool to identify subjects with an elevated risk of developing aHT and cardiovascular events in the future.

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1. Introduction

Arterial hypertension (aHT) is the leading cardiovascular risk factor for morbidity and mortality worldwide [1–3].

In industrialised countries, the prevalence of aHT is growing with age and overweight [4]. In the United States, approximately 78 million adults suffer from aHT [5]. Prevalence of aHT in Germany was assessed as 10–35% in the 3 decades between 30th and 60th life-year and over 65% in people older than 60 years [6].

A large number of studies have emphasised that cardiovascular morbidity and mortality reveal a continuous relationship with both systolic and diastolic blood pressure (BP) [7–9]. The relationship between BP and cardiovascular events seems to be less strong for coronary artery disease (CAD) events than for stroke [7,8]. Therefore, stroke is the most important and a directly aHT-related complication [7,8]. It has been estimated that aHT is responsible for 7.6 million deaths per year worldwide [4].

Furthermore, both systolic and diastolic BP have shown an independent relationship with heart failure, atrial fibrillation, aortic dissection, atherosclerosis with peripheral artery disease, cognitive impairment, retinopathy and renal disease [2,4,7]. Therefore, aHT is a major risk factor for most of the cardiovascular and related diseases [2,7].

Diagnosis of aHT by resting BP is well defined, with systolic BP values of ≥ 140 mmHg and diastolic BP values of ≥ 90 mmHg [10]. A growing body of evidence indicates that aHT-related organ damage occurs beyond these boundaries [10,11]. Therefore, clinicians and scientists are searching for sensitive and specific diagnostic tools and methods to identify patients, who are at an increased risk of developing aHT and are at risk of the subsequent organ damage [10]. Although an increased exercise capacity was identified as a powerful predictor of mortality [12], several studies suggested that an exaggerated BP response (EBPR) in standard exercise testing could be one of these sensitive diagnostic tools [10].

1.1. Definition of arterial hypertension

BP is the product of cardiac output and vascular resistance [13,14]. Therefore, elevated BP is the result of changes of at least one of these factors [14].

According to the current ESC guidelines for the management of aHT [1] systolic BP values of ≥ 140 mmHg and diastolic BP values of ≥ 90 mmHg at rest were categorised as hypertensive BP values (Table 1) [1,7]. However, recent studies have suggested that organ damage occurs when individuals are progressing towards aHT and therefore are still in the normotensive BP range [10]. BP shows a continuous relationship with the risk of cardiovascular events starting at systolic and diastolic BP levels even as low as 115–110 mmHg and 75–70 mmHg, respectively [4,7,15]. Despite adverse events in cases of acute hypertensive BP deviation, such as bleeding in acute hypertensive crises, diseases from secondary causes develop mostly not in short term, but in longer follow-up periods (FU). These may occur approximately 10 years after the onset of aHT [4]. The SPRINT trial [16] emphasised the importance of a good BP management in aHT. Better BP adjustment towards a mean systolic BP value of 121 mmHg in patients with aHT was associated with a lower rate of cardiovascular events and better survival in comparison to those aHT patients with adjusted mean BP values of 136 mmHg [16].

For risk stratification of patients with aHT, the development of endorgan damage should also be taken into account, in addition to elevated systolic and diastolic BP values [2].

1.2. Prevalence of hypertension

aHT is the most prevalent cardiovascular disease in the industrialised world [10] and is a powerful risk factor for fatal and non-fatal cardiovascular events [15,17]. The World Health Organisation (WHO) estimated the worldwide overall prevalence of raised BP in adults ≥ 25 years as approximately 40% in the year 2008 [18]. It has been estimated that approximately 1 billion people suffer from uncontrolled aHT and 7.6 million deaths annually are BP related worldwide [18]. The reported regional prevalence of aHT varies around the world [18,19]. While a high prevalence has been reported in Africa for example, a lower prevalence was found in North America [18]. Men had a slightly higher prevalence than women worldwide [18].

Importantly, prevalence of aHT is growing with age and obesity in industrialised countries [4]. In the United States, approximately 78 million adults had an elevated BP [5]. In contrast to reports 20

Table 1
Definitions and classification of blood pressure levels (mmHg) and arterial hypertension categories according to the current ESC-Guideline for the management of arterial hypertension [1,7].

Categories	Systolic blood pressure		Diastolic blood pressure
Optimal	<120 mmHg	and	<80 mmHg
Normal	120–129 mmHg	and/or	80–84 mmHg
High-normal	130–139 mmHg	and/or	85–89 mmHg
Grade 1 hypertension	140–159 mmHg	and/or	90–99 mmHg
Grade 2 hypertension	160–179 mmHg	and/or	100–109 mmHg
Grade 3 hypertension	>180 mmHg	and/or	>110 mmHg
Isolated systolic hypertension	>140 mmHg	and	<90 mmHg

years ago, aHT prevalence is once again rising in the United States [17,20].

The connection between the growing burden of aHT with increasing age is well known [5,20,21]. Hajjar and Kotchen [20] reported a 1.3-fold increase in aHT prevalence with every life-year [20]. The prevalence of aHT increased age-dependently. While 10–35% of the citizens in Germany between 30th and 60th life-year had aHT, the percentage increases to >65% in people aged 60 years and older [6]. Due to its high prevalence, the increased risk of BP-related diseases and organ damage, aHT is undisputedly an important factor in public health [19]. Despite this, awareness about aHT is low, with plenty of scope for improvement [20]. In summary, aHT is an important public health challenge in economically developed and developing countries around the world [19].

1.3. Age-dependent changes of normal blood pressure values

Studies have found a physiological increase in BP as ageing progresses [21–23]. At birth, the systolic and diastolic BP values are on average at 70 mmHg and 50 mmHg, respectively [21,23]. BP values, especially systolic BP, tend to rise progressively through the childhood and adolescence [21–23]. BP is substantially determined by body weight; the BP in childhood strongly predicts adult BP [22,23]. Subjects aged ≥ 70 years reach an average systolic BP value of 140 mmHg [21]. The diastolic BP values also tend to increase in ageing, but the increase is less steep compared to systolic BP rise [21]. After the 50th life-year, diastolic mean BP either increases only slightly or may even decline [21]. These described changes reflect the normal course of BP changes during the ageing process [21]. In cases of aHT, a rise in BP could be detected in every time period of life and could reach distinctly higher BP values than in non-aHT cases.

1.4. Pathophysiology of arterial hypertension

The majority of patients (more than 90%) with aHT present with essential aHT [4]. The pathomechanism of essential aHT is multifactorial [4,7]. A combination of genetic and environmental factors such as diet, salt intake, physical or psychological stress, smoking and endocrinal factors have been assumed to be important in the development of aHT [4,7,13]. Patients with aHT often show a family history of high BP in relatives, suggesting that inheritance plays an essential role in the pathogenesis of this disorder [7]. Commonly, polygenic heritability underlies essential aHT, but in some individuals monogenic rare forms such as glucocorticoid-remediable aldosteronism or Liddle's syndrome may be identified [7].

In humans, BP changes have been detected in specialised strain sensitive baro-receptors, localised in the carotids and the thoracic aorta [13,24]. Baro-receptors are activated if BP increases [13,24] and signals are sent to the brainstem via afferent nerves, leading to adaptations of sympathetic and parasympathetic nerve system activity [13]. By the adjustment of heart rate, cardiac output and peripheral vascular resistance, BP can be effectively and immediately regulated. These regulators are coordinated by the central nervous system [13]. In older individuals the reduced elastic properties of the aorta and the carotids could lead to elevated BP values [4,25,26]. In addition, aHT patients have been shown to have higher catecholamine levels than controls [24].

In the minority of the patients with aHT (less than 10%), occurrence is based on secondary causes such as renal parenchymal diseases, renovascular hypertension in stenosis of renal arteria, obstructive sleep apnoea, pheochromocytoma, primary aldosteronism, Cushing's syndrome, Liddle syndrome, coarctation of the aorta and, last but not least, the important group of drug-

induced aHT by substances such as oral contraceptives, non-steroidal anti-inflammatory drugs, erythropoietin, cocaine, amphetamines, erythropoietin and cyclosporines [7]. Other rare causes of secondary aHT are acromegalia, thyroidal dysfunctions, hyperparathyroidism, dysbalances in mineralcorticoids, Gordon syndrome and renin productive tumours [27].

1.5. The physiological exaggerated blood pressure response

In stress situations BP increases from resting to stress level depending on exercise intensity and stressor [7,13,28]. Both physical stresses caused by physical activity (dynamic or static exercise) and psychological/mental stress lead to an incline of BP levels [7]. The rise of BP levels is a reaction to the increase of the metabolic demands of the involved organs, especially the musculature [29]. Haemodynamic BP responses to exercises depend on cardiac output and peripheral resistance [30]. Cardiac output is boosted to supply the increased demand for oxygenated blood and nutrition of the active regions of the body [29]. The rise in cardiac output dominates over the reduction in vascular resistance [29] and, as a consequence, exercise results in an elevation of mean arterial pressure [29]. During physical activities BP increases in dynamic as well as static exercise, whereby the increase in the BP is more pronounced for systolic than for diastolic BP [1]. During these activities, both heart rate and BP increase generally to an exercise-dependent and predetermined individual limit [7,30].

Cardiopulmonary exercise testing (CPET) is routinely performed to assess cardiovascular risk and to elicit cardiovascular abnormalities that are commonly not present at rest [29,31]. It provides valuable diagnostic and prognostic information in individuals with and without cardiovascular and pulmonary diseases [29,30,32]. Of particular note, it is a longstanding and powerful tool used to identify a suspected CAD or an aggravation of CAD [33].

CPET usually comprises dynamic exercise, either on bicycle, ergometer or treadmill [1,28]. The measurement of brachial BP before, during and after CPET is a fundamental component of the exercise stress test [29]. Although no standard values or consensus exists, the normal systolic BP response in progressive CPET consists of an increase of approximately 7–10 mmHg per 25 W rise in workload [28]. In general, the BP responses at submaximal as well as maximal efforts and during the recovery phase depend on age, sex and physical condition [28]. Expected maximal BP values in ergometry bicycle testing are about 200/100 mmHg in healthy untrained adults in the general population [14] and 215/105 mmHg in those individuals older than 50 years [14]. These values are therefore important reference points for daily clinical practice [14]. Notably, only systolic BP values may be reliably measured with the standard, non-invasive methods and not the diastolic values [1].

1.6. What is an exaggerated blood pressure response?

Although systolic BP values ≥ 250 mmHg and diastolic BP values ≥ 120 mmHg have been defined as stopping criteria for bicycle ergometry CPET [14,34,35], currently there is no consensus on normal BP response during dynamic CPET [1,28,29,36]. An assessment should be made on an individual basis when the CPET should be stopped. This should take any comorbidities and suspected disease into account [14]. Especially, in athletes, who exceed these thresholds within their normal sports practice, cessation of CPET at this rigid recommended threshold (250/120 mmHg) may limit the level of diagnostic power of the test to evaluate the athlete's cardiovascular fitness [14,28,35]. In very fit and powerful athletes, higher BP values could be physiological and likely reached during competition as well as CPET [14].

Besides CPET for suspected CAD or an aggravation in known CAD, CPET has been used to identify subjects with an abnormal BP response, with the idea that these individuals have a masked hypertension or will develop aHT in the future [35]. This phenomenon has been termed as EBPR or exercise hypertension [1,37,38].

Individual variability in BP response triggered by specific stressors has been investigated with regard to the prediction of new onset of aHT manifestation, target organ damage, incident cardiovascular disease, cardiovascular events and/or mortality [7]. While it is well known, that abnormally low BP values during exercise are generally associated with poor prognosis related to cardiac dysfunction [29], study results have pointed out that EBPR in normotensive subjects at rest may be associated with the development of aHT, cardiovascular events and mortality in the future [1,39–41].

Although this phenomenon of EBPR to CPET is relatively common in the physicians' routine, especially in Western countries [42], only little emphasis is placed on the results due to a lack of information about its clinical relevance [29]. However, results using EBPR to predict future aHT and cardiovascular outcome are conflicting [7]. While several studies have reported an independent significant risk for the development of aHT [7,37,39,43,44], cardiovascular events and mortality [45], others did not [7,46]. In contrast to the very well defined categories of deviation in resting BP [7], grading of exercise-related BP elevation-response is not very well defined [7,10,14,28,36]. A systolic peak BP of ≥ 210 mmHg for men and ≥ 190 mmHg for women has been defined as a hypertensive test result or respectively as EBPR in a number of studies, but other definitions are also used for an EBPR [1,29,36–38,44,47]. In the ACC/AHA 2002 guideline update for exercise testing a systolic peak BP of >214 mmHg was defined as EBPR in CPET [35]. Others have defined EBPR as values of systolic BPs exceeding the 90th to 95th percentile of the study population [36].

2. Research methods and reporting

This review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA-P) guidelines [48]. In order to comply with the principles of these guidelines, we tried to avoid selective reporting by collating all relevant data that conformed to the pre-specified eligibility criteria and answered our specific research question: Does an EBPR have

clinical relevance in individuals for the prediction of cardiovascular events, mortality and aHT in the future?

2.1. Eligibility criteria for this review

Studies were selected according to the criteria outlined below.

2.1.1. Study design

We included original studies of prospective and retrospective study design and existing reviews about EBPR in CPET in our review. A schematic diagram of the literature search procedure used in this review is shown in Fig. 1.

2.1.2. Participants

The study participants were adult humans with an age of at least 18 years. For the endpoint of new onset of aHT, studies concerning patients with pre-existing aHT were excluded. Moreover, studies that included patients with CAD and status post valve surgery were excluded, except for those studies about cardiovascular diseases with a cardiovascular healthy control group or subjects under suspicion of cardiovascular disease without confirmation of cardiovascular disease. Those studies were considered for inclusion. Moreover, treatment studies about the effects of antihypertensive drugs in CPET were excluded from this review.

2.1.3. Endpoints

Endpoints important for decision-making and inclusion of these studies about EBPR in CPET were cardiovascular events, cardiovascular death, all-cause mortality and aHT in the future.

2.2. Information sources

Literature search strategies comprised using medical subject headings (MeSH) and text words related to EBPR in CPET. We conducted a search in the PubMed search platform up to November 2015.

Search strategies consisted of the terms of “exaggerated blood pressure response”&“future hypertension”, “exercise blood pressure response”&“future hypertension”, “exercise blood pressure”&“hypertension”, “exercise hypertension”, “exercise”&“induced”&“systemic hypertension”, “exaggerated

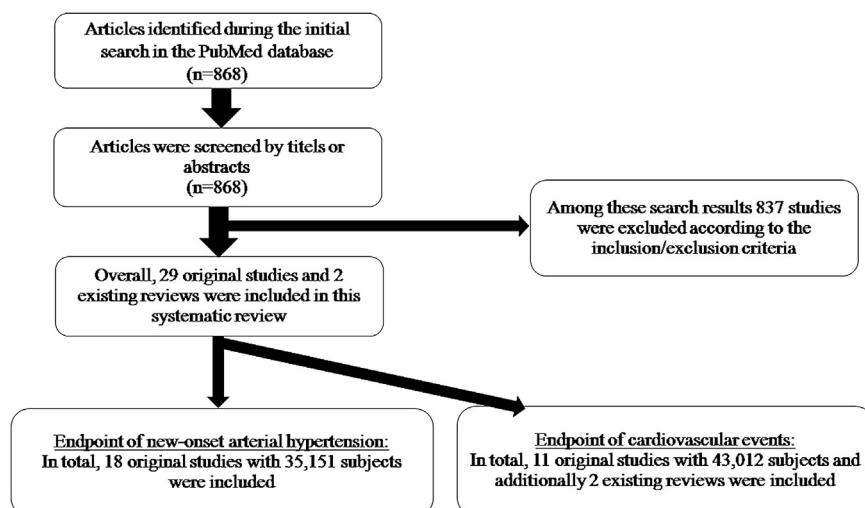


Fig. 1. PRISMA flow diagram: schematic diagram of literature search and selection for articles included in this systematic review.

Table 2

Overview of studies included in this review reporting about exercise blood pressure in normotensive individuals and new-onset arterial hypertension in the future. Abbreviations: aHT: arterial hypertension; EBPR: exaggerated blood pressure response; CPET: cardiopulmonary exercise testing.

Study	Subjects' characteristics	Number of enrolled subjects	Study design (original/review)	Definition of exaggerated blood pressure response during CPET	Study outcome parameters	Follow-up period	Outcomes
Sharabi et al. [57]	Normotensive men	190	Original	BP response >200/100 mmHg	Development of aHT in the future	5.7 years on average	aHT in the future was significantly more often in subjects with EBPR (22.0% vs. 2.6%, $p < 0.0001$)
Lorbeer et al. [58]	Normotensive participants	661	Original	Systolic peak BP response >210 mmHg in men and >190 mmHg in women at 100 W level	Development of aHT in the future	5 years	EBPR predicted incident aHT significantly with cut-off systolic peak BP response >210 mmHg in men and >190 mmHg in women
Farah et al. [59]	Normotensive individuals	30	Original	≥ 210 mmHg systolic peak pressure	aHT in the future	2 years in median	EBPR was predictive for aHT in the future
Miyai et al. [51]	Normotensive men	239	Original	Upper quartile	aHT in the future	5.1 years	EBPR was associated with 2.3-fold risk of new-onset of aHT in the future
Odahara et al. [56]	Healthy normotensive men	815	Original	Systolic peak BP >250 mmHg or diastolic peak BP >120 mmHg	aHT in the future	7 years	EBPR was associated with 2.3-fold risk of aHT in the future
Nakashima et al. [55]	Young healthy adults (mean age 19 years)	214	Original	No cut-off values defined	aHT in the future	12 years on average	Systolic peak BP immediately after exercise was associated with systolic BP in the future
Berger et al. [49]	Normotensive middle-aged adults	7082	Original	Quartiles of exercise BP	aHT in the future	5 years	BP response was associated with aHT in the future
Singh et al. [44]	Normotensive men and women	2310	Original	Age-adjusted BP value greater than 95th percentile	aHT in the future	8 years	EBPR was associated with 4.2-fold risk of future aHT in men and 2.2-fold risk in women
Wilson and Meyer [43]	Non-hospital population with normal resting BP	3820	Original	$\geq 225/90$ mmHg	aHT in the future	32 months on average	EBPR was associated with a 2.3-fold higher risk of aHT in the future
Dlin et al. [52]	Subjects without history of aHT or renal disease	5098	Original	Systolic peak BP of ≥ 200 mmHg and/or diastolic peak BP of ≥ 90 mmHg	aHT in the future	5.8 years	EBPR was a predictor of future aHT
Chaney and Eyman [60]	Normotensive male patients without unstable angina pectoris, congestive heart failure and serious arrhythmia	100	Original	No cut-off values defined	aHT in the future	14 years	Resting BP and BP during exercise were both predictors of aHT in the future
Holmqvist et al. [61]	Patients without aHT	352	Original	No cut-off values defined	aHT in the future	10–12 years	Systolic BP before exercise, maximal systolic BP during exercise and the systolic BP at 100 W workload were significant single predictors of future aHT
Lima et al. [46]	Normotensive individuals	188	Original	Systolic peak BP ≥ 220 mmHg	aHT in the future	3.5 years	EBPR was not an independent predictor for aHT in the future

blood pressure response to exercise”, “dynamic exercise as predictors of systemic hypertension”, “prognostic blood pressure increase during exercise stress testing”, “masked hypertension exercise”, “peak systolic blood pressure”&“exercise”.

Only studies in English or German language were included in this systematic review.

3. Results

3.1. Overview of the literature search results

The initial search in the PubMed database revealed a total of 868 articles. All of these studies were screened by their titles or abstracts. Among these search results, 837 studies were excluded according to the inclusion/exclusion criteria mentioned above, leaving 29 original studies and 2 existing reviews for the systematic review. These studies were included to answer the main question of the review.

In total, 18 original studies with 35,151 enrolled normotensive subjects were included for the endpoint of new-onset aHT in the future. For the endpoint cardiovascular events, 11 original studies with 43,012 subjects and an additional 2 existing reviews were included in this systematic review. An overview about the included studies for both endpoints is presented in [Tables 2 and 3](#).

There was a wide variability in study design and participants' characteristics, including age and fitness level, and in the criteria used to define an EBPR [\[29\]](#).

3.2. Endpoint of new-onset aHT in the future

In total, nine articles reported the results of eight study cohorts with more than 1000 included individuals included in this systematic review with regard to the endpoint.

Berger et al. [\[49\]](#) followed 7082 asymptomatic, normotensive middle-aged adults for 5 years after CPET at baseline. The cumulative probability of new onset of aHT during the FU increased significantly with increasing quartiles of BP during exercise. BP during exercise was significantly associated with future development of aHT [\[49\]](#).

Miyai et al. [\[50\]](#) investigated in 1033 non-medicated men with bicycle ergometry at baseline, and the association between EBPR and development of aHT in an average FU of 4.7 years [\[50\]](#). 15.4% of the individuals had new-onset of aHT during this FU [\[50\]](#). The cumulative incidence of aHT increased progressively with higher percentiles of systolic and diastolic BP response ($p < 0.01$) [\[50\]](#). The adjusted increase in relative risk of development of aHT in respect of EBPR was 3.8-fold compared to those men, who showed no EBPR at baseline [\[50\]](#).

In another additional article, Miyai et al. [\[51\]](#) reported that an EBPR in CPET, defined as the upper quartile of measurements, was associated with 2.3-fold risk of new onset of aHT in the future in individuals with high-normal BP (5.1 year FU) [\[51\]](#).

In the Framingham Spring Study, 1026 men and 1284 women, who were normotensive at baseline assessment, were followed for 8 years [\[44\]](#). An EBPR was defined as an age-adjusted BP value >95th percentile. An excessive diastolic BP during treadmill CPET was associated with 4.2-fold risk of future aHT in men and 2.2-fold risk in women [\[44\]](#). Moreover elevated systolic recovery BP values were predictive for development of future aHT in men [\[44\]](#).

Wilson and Meyer [\[43\]](#) traced 3395 men and 425 women of a non-hospital population with normal resting BP over an average period of 32 months after baseline assessment of treadmill CPET [\[43\]](#). Patients with an EBPR of $\geq 225/90$ mmHg revealed a 2.3-fold increase in risk of developing aHT in the future, compared with those who had lower peak BP during CPET [\[43\]](#).

Table 2 (Continued)

Study	Subjects' characteristics	Number of enrolled subjects	Study design (original/review)	Definition of exaggerated blood pressure response during CPET	Study outcome parameters	Follow-up period	Outcomes
Matthews et al. [10]	Healthy normotensive men	5386	Original	Systolic BP increase from rest to exercise BP level at 5 min treadmill exercise >60 mmHg	aHT in the future	4–15 years	EBPR was associated with 3.0-fold risk of future aHT
Miyai et al. [50]	Men without known aHT or medication	1033	Original	Percentiles of systolic and diastolic BP response during exercise	aHT in the future	4.7 years	Cumulative incidence of aHT increased progressively with higher percentiles of systolic and diastolic BP response
Jae et al. [53]	Cardiovascular healthy normotensive men	3742	Original	Calculated cut-off values of EBPR were 181 mmHg for systolic and 52 mmHg for diastolic EBPR	aHT in the future	5-year on average	Systolic peak BP (AUC = 0.644) and relative BP increase (AUC = 0.549) were predictors of incident aHT with computed cut-off values of 181 mmHg and 52 mmHg, respectively
Manolio et al. [54]	Normotensive young adults	3741	Original	Systolic peak BP response of ≥ 210 mmHg in men and ≥ 190 mmHg in women	aHT in the future	5 years	Subjects with EBPR had 5 mmHg higher systolic and 1 mmHg higher diastolic BP at follow-up ($p < 0.005$) and carried a 1.7-fold higher risk for future aHT
Allison et al. [62]	Healthy, asymptomatic subjects with normal resting BP	150	Original	Systolic peak BP >214 mmHg	Cardiovascular events and aHT in the future	7.7 years	EBPR was not a significant predictor for death or cardiovascular events, but for aHT in the future

Table 3

Overview of studies included in this review reporting about exercise blood pressure and cardiovascular events in the future. *Abbreviations:* aHT: arterial hypertension; EBPR: exaggerated blood pressure response; CAD: coronary artery disease; CPET: cardiopulmonary exercise testing.

Study	Subject characteristics	Number of enrolled subjects	Study design (original/review)	Definition of exaggerated blood pressure response during CPET	Study outcome parameters	Follow-up period	Outcomes
Allison et al. [62]	Healthy, asymptomatic subjects with normal resting BP	150	Original	Systolic peak BP >214 mmHg	Cardiovascular events and aHT in the future	7.7 years	EBPR was not a significant predictor for death or cardiovascular events, but for aHT in the future
Kjeldsen et al. [67]	Middle-aged healthy men	1999	Original	No cut-off values defined	Cardiovascular mortality	21 years on average	Supine systolic BP and 6 min systolic BP at 600 kpm/min were identified as independent predictors of cardiovascular death, but not maximal systolic BP during CPET
Kurl et al. [70]	Population-based sample of men without CAD, antihypertensive medication or prior stroke	1026	Original	No cut-off values defined	Stroke in the future	10.4 years	Systolic BP rise during exercise and percent maximum systolic BP at 2 min rest after exercise were strongly and independently associated with stroke events in the future
Laukkanen et al. [41]	Middle-aged men without history of CAD	1731	Original	Maximal systolic BP of >230 mmHg	MI in the future	12.7 years on average	EBPR was associated with 2.5-fold risk for MI
Laukkanen and Rauramaa [40]	Middle-aged men without history of CAD	1731	Original	Systolic peak BP >195 mmHg	Sudden cardiac death	12.7 years on average	EBPR was associated with sudden cardiac death
Kohl et al. [63]	Apparently healthy subjects	26,621	Original	Quartiles	All-cause mortality, risk of cardiovascular disease, coronary heart disease death	8.1 years on average	All-cause mortality increases with systolic peak BP quartiles in CPET compared to lowest quartiles
Weiss et al. [68]	Asymptomatic normotensive participants	6578	Original	Systolic peak BP during exercise >180/90 mmHg	Cardiovascular death	20 years	EBPR carried higher risk of cardiovascular death
Mundal et al. [64]	Middle-aged healthy men	1999	Original	Increment of systolic BP of 48.5 mmHg or systolic peak BP >200 mmHg	Cardiovascular mortality	31,984 patient-years	EBPR was associated with 1.5-fold risk to die from cardiovascular causes
Mundal et al. [65]	Middle-aged healthy men	1999	Original	Increment of systolic BP of 48.5 mmHg or systolic peak BP >200 mmHg	Mortality from MI	31,984 patient-years	EBPR was a strong predictor for mortality caused by MI
Filipovsky et al. [69]	Middle-aged men without known hypertension	4907	Original	No cut-off was determined	Cardiovascular mortality	17 years	Systolic peak BP during CPET was associated with cardiovascular mortality
Kjeldsen et al. [66]	Middle-aged healthy men	1999	Original	Systolic peak BP response \geq 200 mmHg	Cardiovascular mortality, mortality caused by MI	16 years on average	EBPR was associated with 2-fold risk of dying from cardiovascular causes and from MI
Smith et al. [71]	Healthy volunteers with normotensive BP at rest	34,873	Review	Varied from study to study	Cardiovascular events and cardiovascular death	Varied from study to study	EBPR predicted cardiovascular events and cardiovascular death

Table 3 (Continued)

Study	Subject characteristics	Number of enrolled subjects	Study design (original/review)	Definition of exaggerated blood pressure response during CPET	Study outcome parameters	Follow-up period	Outcomes
Schultz et al. [38]	Individuals without significant CAD	46,314	Review	Varied from study to study	Cardiovascular events and cardiovascular death in the future	Mean follow-up of 15.2 years	EBPR at baseline with moderate exercise intensity levels carried a 1.4-fold higher risk of cardiovascular events and mortality

Results from Dlin et al. [52] emphasised that EBPR during exercise (defined as systolic peak BP ≥ 200 mmHg and/or diastolic peak BP ≥ 90 mmHg) was a strong predictor of aHT in the future (FU of 5.8 years) in 5098 subjects without history of aHT or renal disease [52], and 10.6% of the subjects with EBPR in CPET developed an aHT in the FU [52].

In the study of Matthews et al. [10], 5386 healthy normotensive men were traced for 4–15 years FU [10]. Males with an EBPR (defined as a change in systolic BP from rest to exercise at 5 min of treadmill test >60 mmHg) had a 3.0-fold risk to develop an aHT in the future [10].

Jae et al. [53] tested 3742 cardiovascular healthy normotensive men with treadmill exercise testing at baseline [53]. During an average 5-year FU, aHT was diagnosed in 9.7% [53]. Systolic peak BP (AUC=0.644) and relative BP increase (AUC=0.549) were predictors of incident aHT with cut-off values of 181 mmHg and 52 mmHg, respectively [53]. Systolic peak BP values >181 mmHg and relative BP increase >52 mmHg were associated with a 1.54-fold and a 1.44-fold increase in risk of developing aHT in the future [53].

In the study of Manolio et al. [54], 3741 normotensive young adults, who underwent treadmill CPET at baseline, were followed up for 5 years [54]. EBPR (defined as systolic peak BP ≥ 210 mmHg in men and ≥ 190 mmHg in women) was found in 687 individuals [54]. Subjects with EBPR revealed a 5-mmHg higher systolic and a 1-mmHg higher diastolic BP at FU ($p < 0.005$) and carried a 1.7-fold higher risk of developing aHT compared to those without EBPR in CPET ($p < 0.001$) [54]. After multivariable adjustment, EBPR was connected with a 2.14 mmHg increase systolic BP after 5 years [54].

Moreover, nine further studies with less than 1000 enrolled subjects were additionally included in this review.

Nakashima et al. [55] followed 214 young adults over a FU of 12 years. Systolic peak BP immediately after exercise at baseline was strongly associated with the systolic BP in the future [55].

In the prospective study of Odahara et al. [56], which included 815 healthy normotensive men, with EBPR (defined as systolic peak BP >250 mmHg or diastolic peak BP >120 mmHg) was associated with 2.3-fold increased risk of aHT in the future [56].

In the study of Sharabi et al. [57], 190 men without known aHT were followed for an average FU of 5.7 years. Among these subjects with EBPR to CPET (with peak BP values $>200/100$ mmHg) significantly more subjects developed an aHT in comparison with those without EBPR (22.0% vs. 2.6%, $p < 0.0001$).

Lorbeer et al. [58] identified an EBPR of >210 mmHg and >190 mmHg systolic peak BP as the optimal cut-off values to predict incident aHT in 5 year FU [58].

In addition, Farah et al. [59] confirmed in their small prospective study, that an EBPR during CPET was predictive for aHT in the future.

Chaney and Eyman [60] investigated the three predictors of transient high BP at rest and during dynamic and isometric exercise for predicting development of aHT in the future [60]. One-hundred male, normotensive patients without unstable angina

pectoris, congestive heart failure and serious arrhythmia, were tested at baseline by treadmill and handgrip dynamometer [60]. In the FU of 14 years 16% were diagnosed with aHT [60]. The best single predictor for aHT in the future was resting diastolic BP, followed closely by handgrip, diastolic and treadmill diastolic peak BP. Best prediction was reached with a combination of resting diastolic BP and handgrip diastolic peak BP [60].

In the study by Holmqvist et al. [61] of 352 normotensive patients, systolic BP before exercise, maximal systolic BP during exercise and systolic BP at 100-W workload were significant single predictors of future aHT during a 10–12-year FU [61].

In contrast, the results of the study by Lima et al. [46] showed that 188 normotensive individuals showed that EBPR (defined as systolic peak BP at least 220 mmHg) during CPET (treadmill testing) was not an independent prediction factor for the development of aHT during the FU of 3.5 years [46].

Allison et al. [62] observed the development of new-onset aHT and cardiovascular events in 150 healthy, asymptomatic, normotensive subjects, with an EBPR ≥ 214 mmHg systolic peak BP (in treadmill testing) during a mean FU of 7.7 years. This was in comparison to the same number of age- and gender-matched controls with an exercise systolic peak BP of 170–192 mmHg [62]. Thirteen controls and 37 subjects with EBPR had diagnosed an aHT during FU [62]. In multivariable regression, EBPR was a significant predictor for new onset of aHT with an odds ratio of 2.41 ($p = 0.02$) [62].

3.3. Endpoint of cardiovascular events in the future

Overall, 11 original research articles investigating six study cohorts about this endpoint were included in our review.

Kohl et al. [63] described in their large study of about $>26,000$ apparently healthy participants, that the all-cause mortality (stratified by quartiles of maximal systolic BP in CPET) was significantly higher in the upper quartiles compared to lowest quartile. Similar results were found for the risk of cardiovascular events and mortality due to CAD [63].

Overall, four different articles were published on a cohort of 1999 middle-aged healthy men. Mundal et al. [64] found a strong association between EBPR (defined as an increment of systolic BP >48.5 mmHg ($=2$ SD)) and cardiovascular mortality in the future [64]. In another study by the same authors, EBPR was a strong and independent predictor of mortality from myocardial infarction (MI) in the future [65]. Kjeldsen et al. [66] observed that individuals with an EBPR during CPET (defined as systolic peak BP ≥ 200 mmHg) had a twofold increased risk of dying from cardiovascular causes and MI during FU of 16 years [66]. In another paper, Kjeldsen et al. [67] traced the outcome of these 1999 healthy men after an FU of 21 years [67]. Supine systolic BP, 6 min systolic BP level at the starting workload of 600 kpm/min (approximately 100 W) and maximal systolic BP during exercise were investigated to predict cardiovascular death [67]. Both supine systolic BP (risk ratio [RR] 1.4, $p = 0.029$) and 6 min systolic BP at 600 kpm/min (RR

1.4, $p=0.017$) were identified as independent predictors of cardiovascular death, but not maximal systolic BP during exercise testing [67]. Interestingly, the results of this study emphasised that systolic BP response at a moderate intensity of exercise testing carries more information about mortality in the future than systolic BP values at maximal exercise levels (in contrast to testing for CAD) [67].

Weiss et al. [68] reported that an EBPR was accompanied by a higher risk of cardiovascular death in asymptomatic normotensive participants in the future, but this association became non-significant after adjustment for BP at rest [68].

Additionally, Filipovsky et al. [69] detected an association between systolic peak BP during CPET and cardiovascular mortality during FU of 17 years [69].

In a study of 150 healthy, asymptomatic and normotensive subjects, with an EBPR (defined as ≥ 214 mmHg systolic peak BP) and the same number of age- and gender-matched controls with exercise systolic peak BP of 170–192 mmHg, Allison et al. [62] observed that major cardiovascular events such as cardiovascular death, MI, stroke, coronary angioplasty or coronary bypass graft surgery occurred in 5 controls and in 10 individuals with EBPR [62]. The RR for EBPR for the prediction of a major cardiovascular event was 3.6 ($p=0.03$) compared to controls [62], but in multivariable regression, EBPR failed to be a significant predictor for death or cardiovascular events [62].

Kurl et al. [70] reported on a population-based sample of 1026 men without CAD, antihypertensive medication or prior stroke at baseline. In these individuals, a systolic BP rise during exercise and maximum systolic BP 2 min after exercise were both strongly and independently associated with the risk of stroke during the FU (10.4 years) [70]. Males with a systolic BP rise of more than 19.7 mmHg per minute during exercise had a 2.3-fold higher risk of stroke (ischaemic and haemorrhagic), and a 2.3-fold increased risk of ischaemic stroke compared to those with lower systolic BP response [70]. Systolic BP at 2 min recovery divided by peak

exercise systolic BP was strongly associated with 4.6-fold increased risk of any stroke, and 5.2-fold risk of ischaemic stroke [70].

Laukkanen et al. [41] investigated in 1731 middle-aged men without history of CAD with cycle ergometric CPET the prognosis in respect to development of MI during a FU of 12.7 years on average [41]. In this cohort, 188 MI events were counted during FU [41]. An EBPR of maximal systolic BP of >230 mmHg at baseline was associated with a 2.5-fold risk for MI in the future [41]. In one further study, Laukkanen and Rauramaa [40] reported that an EBPR with a systolic peak BP >195 mmHg was associated with higher mortality compared to those subjects with a systolic peak BP response <175 mmHg during CPET in men [40].

In a pooled outcome analysis, which studied the results of 14 studies, Smith et al. [71] reported that exercise hypertension predicted cardiovascular events and cardiovascular death in healthy volunteers with normotensive BP at rest [71]. In contrast, subjects with known heart disease, EBPR in CPET but normotensive BP values at rest, showed no higher mortality or even lesser mortality [71].

The meta-analysis by Schultz et al. [38], who reviewed 12 longitudinal studies with 46,314 individuals without significant CAD, showed that subjects with EBPR at baseline and at moderate exercise intensity levels carried a 1.4-fold higher risk of cardiovascular events and mortality during an FU of approximately 15 years [38]. Each 10-mmHg increase in systolic BP during moderate exercise intensity was connected with a 4% increase in cardiovascular events and mortality [38]. Systolic BP at maximum workload was not significantly associated with poorer outcome [38].

4. Discussion

In this systematic review, comprising data from 29 original research studies and 2 existing review articles, the majority of research papers confirmed an association between EBPR and both new onset of aHT and cardiovascular events in the future.

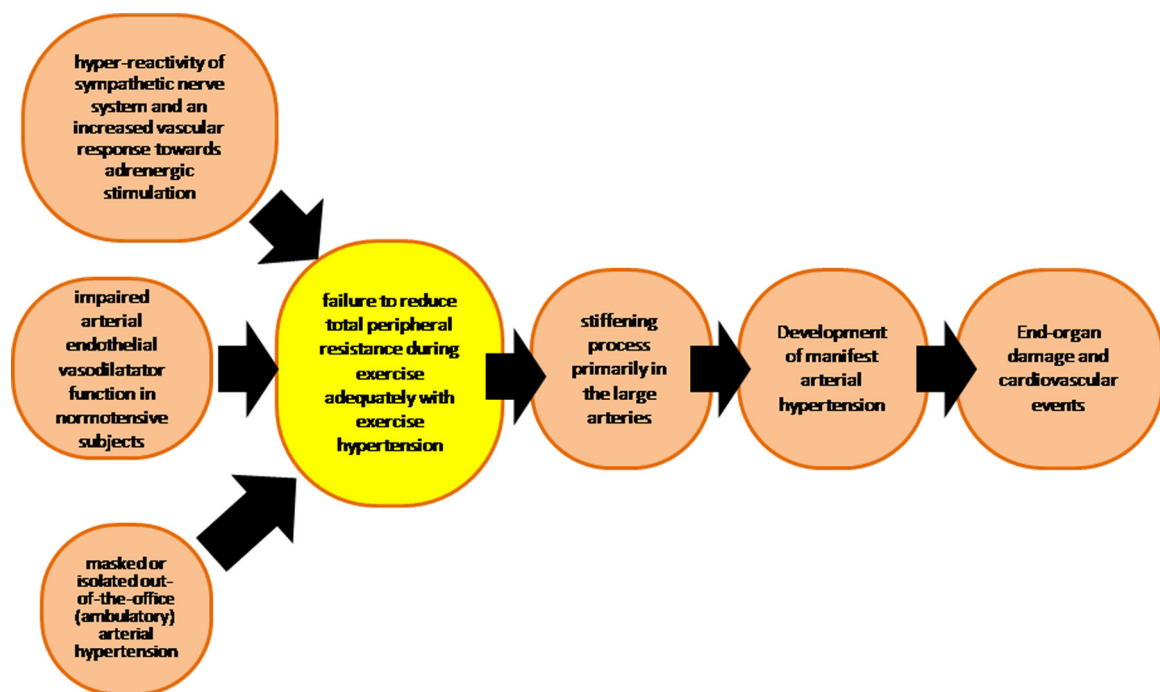


Fig. 2. Assumed pathomechanism of exercise hypertension and the development of manifest arterial hypertension, end-organ damage and cardiovascular events in the future.

Among the articles with the endpoint of new onset of aHT in the future, 17/18 (94.4%) of the articles included, showed a significant association between an EBPR and this endpoint. The relative risk of developing an aHT in the future was increased in subjects with EBPR in CPET between 1.4- and 4.2-fold higher, in comparison to those individuals without EBPR.

The relative risk for cardiovascular events was increased in individuals with EBPR in CPET between 1.4- and 3.0-fold higher compared to subjects without EBPR. Of the 11 original research articles, 6 different study cohorts were included, and associations between EBPR and cardiovascular events were found in 4 cohorts (66.6%). In one study, the association did not remain significant after adjustment for BP at rest, and in another study the association was not significant in multivariate regression; however, the risk ratio revealed a higher risk for cardiovascular events in subjects with EBPR.

Similarly, EBPR was also associated with cardiovascular events in some studies concerning patients with cardiovascular diseases such as CAD and aHT. Gupta et al. [37] investigated the prognosis of such subjects with CPET in 6145 men using exercise treadmill testing [37]. Subjects with EBPR (defined as exercise-induced increase in systolic BP ≥ 44 mmHg) had a higher cardiovascular mortality (13.7% vs. 8.2%, $p < 0.001$). After adjustment for assessed baseline variables, EBPR remained associated with a 1.2-fold increase in mortality risk ($p < 0.05$, FU of > 6 years) in a multivariate regression model [37]. However, not all studies could confirm the relationship between EBPR and cardiovascular events in the future. Bouzas-Mosquera Mdel et al. [72] did not find a significant association between EBPR in CPET and future stroke events in patients with known or suspected CAD and with and without known aHT [72]. Additionally, Smith et al. [71] reported in their review that patients with heart diseases and EBPR in CPET showed no higher mortality or even lesser mortality than those without EBPR [71].

In this review, we avoided the inclusion of the studies with known CAD in cardiovascular patients, due to our concern with the disparities in these studies. CAD seems to be such an important trigger for future cardiovascular events that EBPR caused by preliminary disease stages of other diseases becomes masked and insignificant in comparison to CAD.

The underlying pathomechanism of an EBPR in CPET in normotensive individuals is poorly understood [38]. Although exercise hypertension seems likely to be multifactorial, study results have emphasised that an impaired arterial endothelial vasodilator function in normotensive individuals may be an important causative factor [51,57,73–75] (Fig. 2). This failure to adequately reduce total peripheral resistance during exercise might be caused by initial structural cardiovascular abnormalities leading to arterial adaptations and potentially the development of aHT in the future [51,73]. This is supported by a hyper-reactivity of sympathetic nerve system and an increased vascular response towards adrenergic stimulation accompanied with thickening of the arteriolar wall [51]. The stiffening process occurs primarily in the large arteries [38].

Another explanation is a metabolic defect in those patients with EBPR in CPET, seen in higher levels of fasting glucose and triglycerides, total cholesterol, reduced glucose tolerance values and higher body mass index [57,76,77].

In addition, a growing body of evidence emphasises that EBPR in CPET helps to unmask an underlying masked or isolated out-of-the-office (ambulatory) aHT [11,29,77–80]. Masked aHT means normal office BP values, but elevated out-of-the-office (ambulatory) BP results [11,77,80]. This phenomenon is probably not so rare, because single point-BP-measurements at rest ‘in-the-office’ can fail to detect elevated BP measurements, even if the majority of the time the BP may be elevated. Some studies confirmed in subjects

with normotensive BP ‘at-the-office’, that those with EBPR in CPET had significantly higher average 24 h systolic and diastolic BP mean values compared to those without EBPR [79,80]; EBPR was associated with masked aHT [77,81].

In addition, studies showed an association between EBPR in exercise testing and an increase in left ventricular mass and hypertrophy [82–89]. However, this association was confounded by age in one of these studies, as well as resting BP and body mass [82].

With respect to EBPR, some points merit closer contemplation. Interestingly, studies found on the one hand that BP during exercise was strongly associated with BP values at rest, and patients with EBPR had significantly higher BP values at rest [90]. On the other hand, EBPR in CPET were rarely reproducible [91]. These findings seem to be conflicting.

Another important point is that studies comparing maximum workload and systolic BP during CPET in normotensive untrained and trained subjects, found a significant higher workload and systolic peak BP in trained compared to untrained participants [92]. This is critical in the evaluation of EBPR in CPET. Therefore, individuals’ fitness levels should be taken into account in the evaluation of EBPR results with regard to aHT and cardiovascular events in the future [92].

Within the published studies, a wide variety in study design, outcome measurements, FU, exercise modalities, exercise intensities and enrolled participants’ characteristics have been used. In addition, the lack of consensus about the definition of an EBPR in CPET complicates the interpretation and the comparison of the data. We identified 16 different definitions of EBPR in the 29 original studies included in this review. In addition, rigid BP limits for definition of EBPR without age adjustment or gender differentiation are connected with problems. The increased systolic BP in ergometric CPET is related to some factors, which influence the BP response significantly [1,45]. Such factors are pre-exercise BP levels, arterial stiffness, obesity, fitness, gender and age [1,45]. The above-mentioned points may be reasons that the current guidelines for the management of aHT provide no information about the management of exercise hypertension [38]. Although aHT is the world-leading risk factor for mortality and is ranked third as a cause of disability-adjusted life-years [3], the importance of an EBPR remains unclear.

An isolated EBPR in (endurance) CPET was identified as a risk factor for development of aHT in the future and was therefore pointed out as a prognostic factor in normotensive individuals without history of aHT [1,14]. Additionally, adequate aHT control is important to avoid organ damage and complications, but despite these crucial factors, the implications for treatment of such an EBPR in CPET and its prognostic significance remain widely unclear [1]. In some patient groups a higher BP during CPET may be connected with an indeed better prognosis, such as in individuals aged 75 years and older and patients with heart failure, in whom higher systolic BP response leads to a better cardiac function [1].

In summary, routine CPET to predict future hypertension is not recommended by the 2013 ESH/ESC Guidelines for the management of aHT [1]. But, what is the implication of EBPR during CPET in normotensive cardiovascular healthy subjects? Data from the studies analysed in this review have led us to suggest that EBPR in apparently healthy normotensive individuals could be a screening method to identify pre-morbid conditions as well as masked or borderline aHT [57]. However, identification of those normotensive individuals with EBPR in CPET may allow preventive changes in lifestyle such as body weight reduction, salt-restricted diet and endurance sports to delay or avoid development of aHT and its associated complications [35]. While there is no recommendation for medical antihypertensive treatment of such an EBPR in subjects with normal resting BP, EBPR in CPET should be considered as an

indication for ambulatory blood pressure monitoring to identify masked hypertension with exclusively ambulatory increased BP values [1,29].

5. Conclusions

Although an EBPR under CPET is not well defined, a large number of studies emphasise that EBPR in CPET is associated with both new-onset aHT and cardiovascular events in the future. A growing body of evidence supports the hypothesis that EBPR may be a diagnostic tool to identify subjects with an elevated risk to develop aHT and cardiovascular events in the future.

Conflict of interests

The authors declare no conflict of interests.

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