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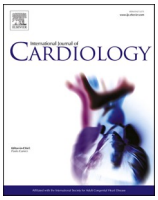

Physical exercise in hypertensive heart disease: From the differential diagnosis to the complementary role of exercise

Maria Concetta Pastore [a,1], Luna Cavigli [a,1], Gabriele Olivoni [a], Francesco Morrone [a], Francesca Amati [b], Egidio Imbalzano [c], Andrea Rinaldi [d], Riccardo Liga [e], Anna Vittoria Mattioli [f], Pietro Scicchitano [g,1], Antonio Curcio [h], Francesco Barillà [i], Michele Ciccarelli [j], Viviana Maestrini [k], Pasquale Perrone Filardi [l], Flavio D'Ascenzi [a,*,2], Matteo Cameli [a,2], On behalf of the Working Group on Hypertension, Prevention and Peripheral Circulation of the Italian Society of Cardiology

[a] Department of Medical Biotechnologies, Division of Cardiology, University of Siena, Siena, Italy
[b] Department of Cardiology, University of Bari, Bari, Italy
[c] Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
[d] Unit of Cardiology, Department of Experimental, Diagnostic and Specialty Medicine-DIMES, University of Bologna, Sant'Orsola-Malpighi Hospital, IRCCS, Bologna, Italy
[e] Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy
[f] Department of Quality of Life Sciences, University of Bologna, Italy
[g] Cardiology Department, Hospital "F. Perinei", Altamura, (BA), Italy
[h] Division of Cardiology, Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Rende, Italy
[i] Department of Systems Medicine, Tor Vergata University, 00133 Rome, Italy
[j] Cardiovascular Research Unit, Department of Medicine and Surgery, University of Salerno, Salerno, Italy
[k] Institute of Sports Medicine and Science, Rome, Italy
[l] Department of Advanced Biomedical Sciences, Italian Society of Cardiology, Federico II University of Naples, Naples, Italy

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ABSTRACT

Arterial hypertension (AH) is one of the most common pathologic conditions and uncontrolled AH is a leading risk factor for cardiovascular disease and mortality. AH chronically causes myocardial and arterial remodelling with hemodynamic changes affecting the heart and other organs, with potentially irreversible consequences leading to poor outcomes. Therefore, a proper and early treatment of AH is crucial after the diagnosis. Beyond medical treatment, physical exercise also plays a therapeutic role in reducing blood pressure, given its potential effects on sympathetic tone, renin-angiotensin-aldosterone system, and endothelial function. International scientific societies recommend physical exercise among lifestyle modifications to treat AH in the first stages of the disease. Moreover, some studies have also shown its usefulness in addition to drugs to reduce blood pressure further. Therefore, an accurate, personalized exercise prescription is recommended to optimize the prevention and treatment of hypertension. On the other hand, uncontrolled AH in athletes requires proper risk stratification and careful evaluation to practice competitive sports safely. Moreover, the differential diagnosis between hypertensive heart disease and athlete's heart is sometimes challenging and requires a careful and comprehensive interpretation in order not to misinterpret the clinical findings.

The present review aims to discuss the relationship between hypertensive heart disease and physical exercise, from diagnostic tools to prevention and treatment strategies.

* Corresponding author at: Department of Medical Biotechnologies, Division of Cardiology, University of Siena, Viale M. Bracci, 16 53100 Siena, Italy.
E-mail address: flavio.dascenzi@unisi.it (F. D'Ascenzi).
[1] *The first two authors equally contributed to the preparation of the manuscript*
[2] *The last two authors equally contribute to the manuscript as senior authors*

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1. Introduction

Arterial hypertension (AH) affects over one billion people worldwide, and its prevalence is continuously increasing [1,2]. It is the leading risk factor for cardiac or stroke-related death. However, there are still gaps in diagnosing and treating this pathologic condition. In 2018, the rate of people with disease awareness, treatment, and control of AH was only 43.5%, 20.6%, and 5.3%, respectively [3].

Hypertensive heart disease (HHD) is characterized by myocardial and arterial remodelling and fibrosis, with hemodynamic impairment that progressively leads to cardiac and renal failure and increased risk for cardiovascular (CV) events. On the contrary, the reduction and treatment of AH prevents heart attack, stroke, kidney, and other organ damage [4,5]. A good blood pressure (BP) control, defined as systolic BP (sBP) below 140 mmHg and diastolic BP (dBP) below 90 mmHg, is associated with delay or regression of target organ damage and improvement in quality of life [6].

After diagnosis, people in early phases of HHD or patients who do not reach sufficient BP control with pharmacologic therapy, those with a persistent moderate increase of BP with low adherence to poli-pill therapy, could benefit from adjuvant therapy in the way of lifestyle modifications, and particularly the regular practice of aerobic exercise [1,7,8]. Indeed, regular physical activity (PA) induces a reduction in BP via neuro-humoral, vascular and structural adaptations, with immediate effects after the first training sessions [9]. Several studies have reported reductions of 5–15 mmHg in sBP and 4–9 mmHg in dBP in individuals with essential hypertension following aerobic exercise programs lasting 4–12 weeks [10].

International scientific societies have recognized the role of PA in lifestyle intervention recommended for CV risk prevention and treatment of risk factors [11,12]. However, as stated in the latest European Society of Cardiology (ESC) guidelines for sports cardiology [13] and CV prevention [14], PA should be individually assessed and prescribed in terms of frequency, intensity, duration, time, type, volume, and progression [15,16]. Accordingly, a recent consensus document from the European Association of Preventive Cardiology (EAPC) and the ESC Council on Hypertension, based on the evidence derived from 34 meta-analyses, encourages more frequent use of personalized exercise prescription to optimize lifestyle interventions for the prevention and treatment of AH [2].

The present review aims to highlight the relationship between HHD and physical exercise, from prevention and diagnosis to treatment.

2. Left ventricular hypertrophy: diagnostic framework in HHD

AH, especially with uncontrolled BP values, often causes left ventricular hypertrophy (LVH), which is considered a sign of hypertension-mediate organ damage [17]. LVH is a phenotype characterizing several heart diseases and physiological adaptations: HHD, aortic stenosis, Fabry disease, cardiac amyloidosis, hypertrophic cardiomyopathy (HCM), and athlete's heart are the most recurring causes of LVH, sometimes posing challenges for the differential diagnosis [18,19]. Furthermore, early identification of pathological LVH caused by HHD permits prompt medical treatment to stop or slow down adverse myocardial remodelling [11].

According to the most recent ESC guidelines, clinical examination and electrocardiogram (ECG) are recommended in all patients with suspected AH [11]. The ECG has a good specificity in identifying LVH: the Cornell voltage product was reported as the criterion with the best sensitivity (25%) and high specificity (75%) in identifying LVH, but, in many cases, this is not sufficient to obtain a certain diagnosis [20]. Other ECG features in HHD are left axis deviation (QRS > -30°), left anterior hemiblock, left bundle branch block and left ventricular (LV) repolarization abnormalities [20,21].

Nevertheless, echocardiography is an essential diagnostic test for estimating LVH and LV mass according to its wide availability and high sensitivity [11,22]. LVH is defined as an increased LV mass index (LVMI) >95 g/m in women and >115 g/m in men [22]. Differential diagnosis is fundamental among the conditions leading to LVH, such as HHD, athlete's heart, and cardiomyopathies, and an accurate description of LVH is crucial in this context, primarily based on the estimation of LV wall thickness and the characteristics of LVH[20]. For instance, LVH is usually concentric and symmetric in the healthy athlete; conversely, it is typically septal and is associated with aortic dilatation in an athlete suffering from HHD, while it is asymmetric in HCM [23,24].

A comprehensive echocardiographic exam should include the evaluation of systolic and diastolic function indexes. The athlete's heart usually has a normal or supranormal diastolic function, while the diastolic function may be impaired in HHD [20,25]. Also, tissue Doppler imaging has a key role in this setting: athletes are more likely to present normal values of s', e', and E/e', contrary to hypertensive patients [20,25]. Notably, the reduction of diastolic function showed by tissue Doppler parameters is a premature sign of HHD, and the E/e' ratio also has a prognostic value in AH [26].

Speckle tracking echocardiography (STE) could play a fundamental role in the differential diagnosis of LVH: it is easy to use, highly feasible, and repeatable. Particularly, LV global longitudinal strain (GLS) could be impaired in HHD, and the basal septum usually exhibits a reduction of longitudinal strain values since this is the first zone that suffers from pressure overload [27]. On the contrary, in the athlete's heart, GLS is normal and, usually, myocardial segments do not show subtle dysfunction [28]. Finally, the evaluation of left atrial (LA) size and function is important in HHD: indeed, LA volume indexed in these patients is generally increased, with LA strain analysis demonstrating a reduction of LA reservoir function, contrary to athletes, showing LA dilatation but normal atrial function, or healthy controls, exhibiting normal LA size and function [29] (Table 1). Unfortunately, the differential diagnosis is even more challenging when the clinical evaluation refers to an athlete

Table 1
Differential diagnosis between athlete's heart and hypertensive heart disease.

Athlete's heart	Hypertensive heart disease
Electrocardiography (ECG)	
Possible ECG signs of LV hypertrophy	Possible ECG modification: • signs of LV hypertrophy • LBBB • T-wave inversion in the inferolateral leads • ST-T segment "strain" • intrinsicoid deflection, P-wave terminal force in V1, P-wave dispersion
Cardiac imaging (echocardiography, cardiac magnetic resonance)	
Possible imaging (echocardiography, cardiac magnetic resonance) findings: • LV hypertrophy with regression after detraining • Atrial dilation • Balanced biventricular remodelling • Balanced biatrial remodelling • Normal diastolic function • Normal LV cavity pressure • Normal atrial function	Possible imaging (echocardiography, cardiac magnetic resonance) findings: • LV hypertrophy • LV thickness normalization after treatment • Aortic dilation • Reduction of LV function • Diastolic dysfunction • Raised LV filling pressures • Atrial dilation • Reduced atrial function • Reduced LV and/or LA deformation • Patchy late gadolinium enhancement
Exercise test	
Normal blood pressure response to exercise test	Exercise-induced hypertension
Cardiopulmonary exercise test	
Normal response to cardiopulmonary exercise test	Peak V_{O2} lower than predicted at cardiopulmonary exercise test

ECG, electrocardiogram; LA, left atrium; LBBB, left bundle branch block; LV, left ventricle; V_{O2}, oxygen consumption.

with unknown HHD: indeed, in these cases, the effects of sports practice may mitigate the pathological echocardiographic findings usually identified in sedentary patients with HHD, such as diastolic dysfunction, and should be taken into account for an appropriate interpretation.

Cardiac magnetic resonance (CMR) is the gold standard method to define LV mass, LVH and myocardial tissue characterization, particularly when ECG, clinical examination and conventional echocardiography are inconclusive and may further support the clinical interpretation [30]. The presence and localization of late gadolinium enhancement (LGE) may further support an appropriate interpretation of LVH. Indeed, approximately 50–65% of HCM patients show LGE with two major distribution patterns: patchy intramural within the hypertrophied segments or right ventricular insertion point LGE [31]. Then, high native T1 may be found in hypertrophic and non-hypertrophic segments, with native T1 values correlated with the extent of the LV mass [31]. Conversely, in patients with HHD, the pattern of LVH is typically concentric, within a non-specific, non-ischemic LGE pattern (reported in around 50% of the patients) and a slight increase in T1 mapping values [31]. Particularly, LGE shows a patchy pattern that has been documented in 45% of patients with HHD, possibly related to both myocardial interstitial fibrosis and coronary microangiopathy. Importantly, studies conducted on LGE in triathletes showed that LGE revealed focal non-ischemic myocardial fibrosis in triathletes who had higher peak exercise systolic BP (213 ± 24 mmHg vs 194 ± 26 mmHg; $p < 0.05$), suggesting that myocardial fibrosis could be possibly related to exercise-induced hypertension and myocardial hypertrophy [32].

LVH can be the clinical expression of infiltrative disorders. These conditions can be suspected based on typical clinical features already evident in the resting ECG of the patients (e.g. low QRS voltages) [33]; however, CMR may provide further insights into the characterization of LVH.

On the other hand, physiological training-induced LVH is typically accompanied by enlarged cardiac chamber size and increased LV wall thickness and mass in the absence of LGE, except for minor LGE at the right ventricular inferior insertion point. Mapping technique may also be useful in addition to standard tissue characterization [34–37].

While imaging plays a pivotal role in characterizing LVH, an appropriate interpretation of imaging data relies on a comprehensive assessment, including the evaluation of the response during exercise. Exercise testing can provoke or identify an hypertensive response to exercise. Cardiopulmonary exercise testing (CPET) permits the assessment of exercise-induced hypertension and, above all, the exercise capacity by adding ventilatory gas-exchange measurements [38]. Indeed, untreated hypertensive patients and patients with uncontrolled AH had significantly lower peak oxygen consumption (V_{O2}) than controls and well-controlled AH; moreover, a significant negative correlation between BP and peak V_{O2} has been demonstrated [39]. Peak V_{O2} was similar between athletes with optimal and normal BP but significantly lower in athletes with high normal BP and AH [39]. The decreased maximal oxygen consumption reflects an impaired oxygen delivery to muscles that may be due to sympathetic overactivity, vasoconstriction, and a consequent reduction of blood flow in the skeletal muscle [40]. These conditions lead to impaired glucose uptake and insulin resistance and a failure to reduce peripheral resistance during exercise in patients with AH that might limit exercise capacity, with or without changes in the stroke volume [40]. Therefore, the staging of hypertension according to the BP level, on the one hand, and the effects of BP on cardiopulmonary capacity, on the other, may be coupled for further risk stratification and diagnosis [37].

3. The role of physical exercise and training in the early phases of HHD

It is widely known that a sedentary lifestyle may be considered an independent CV risk factor, while exercise training is now well-recognized in the prevention and treatment of HHD[14]. Importantly, exercise training may be used as an alternative to medication in patients with pre-hypertension or newly diagnosed hypertension [14]. The available literature, which was resumed by 17 meta-analyses and a systematic review (with an overall number of 594.129 individuals), describes a direct effect of PA on BP reduction among adults with normal BP, prehypertension, and hypertension, with the magnitude of the BP response to PA varying across different resting BP values: indeed, PA showed greater benefits in adults with prehypertension than in those normal BP[41], in terms of BP reduction. Moreover, an inverse dose-response relationship between PA and incident hypertension among non-hypertensive adults was demonstrated, with PA also reducing the risk of CV disease progression among adults with hypertension [41]. Furthermore, a meta-analysis including 391 randomized controlled trials (RCTs), 197 of which evaluated exercise intervention and 194 antihypertensive treatments, showed that all types of exercise and all classes of antihypertensive medications were effective in lowering baseline sBP [42].

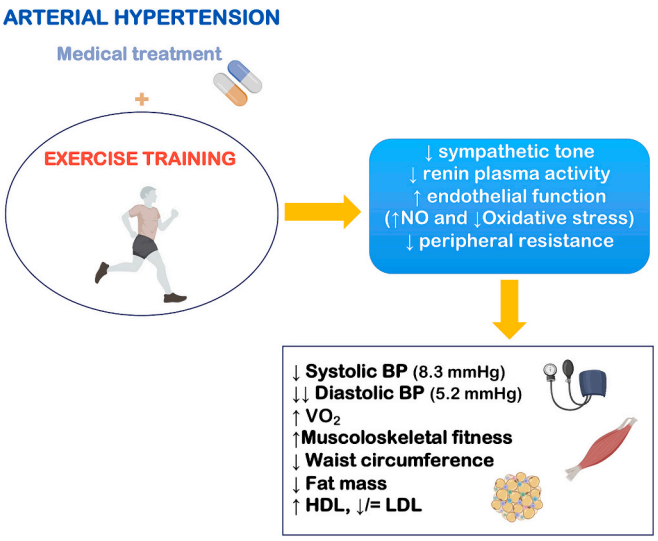

Fig. 1. Central illustration. Mechanism of reduction of blood pressure in hypertensive patients undergoing physical exercise.

Exercise practice is recommended by the European and American Cardiology Societies to prevent or reduce the incidence of CV mortality and morbidity, with a minimum of 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity aerobic training [13].

Aerobic exercise has greater effectiveness in preventing and treating HHD [43] among the various forms of exercise. Different mechanisms are involved in aerobic exercise's effects on BP (Fig. 1). First of all, a reduction in sympathetic tone leads to a greater reduction in daytime BP than in nighttime BP when the sympathetic tone is physiologically lower [44]. Then, a reduction in renin plasma activity potentiates the effects on BP, and this often causes a greater drop in BP in hypertensive patients than in normotensive patients [45]. Another mechanism is the potentiation of endothelial function through the effects on oxygen free radicals [46]: aerobic exercise can counteract oxidative stress by increasing nitric oxygen bioavailability and reducing superoxide levels, thus reducing BP levels [47,48].

Hypertensive adults performing aerobic exercise weekly for months experienced a lowering of BP with a reduction of 8.3 and 5.2 mmHg for office sBP and dBP, respectively [49]. Moreover, moderate-to-high intensity exercise was associated with significant effects on sBP and dBP, and higher benefits were obtained with a greater duration of the training program [50,51].

Therefore, according to the currently available literature, regular exercise should be strongly encouraged in hypertensive patients who should be aware of the importance of this lifestyle change to control blood pressure.

4. The combined treatment of hypertension

The latest ESC guidelines for managing AH recommend lifestyle changes as the first treatment, among which regular aerobic exercise takes a relevant place, along with salt restriction, moderate consumption of alcohol, high consumption of vegetables and fruits, and weight reduction [11]. Then, the 2021 ESC guidelines for CV prevention recommended lifestyle intervention for high-normal BP (130–139/ 85–89 mmHg) or higher; for grade 1 hypertension, to start medical treatment based on absolute CV risk, estimated lifetime benefit, and the presence of hypertensive mediated organ damage (class IC), while for grade 2 or higher, to start treatment with drugs (class IA) [14], together with lifestyle interventions.

However, achieving the BP target may not be easy, also in patients with a first diagnosis of AH, and often requires more than one drug, affecting the patient's adherence to medical therapy, particularly in case of drug-related unfavourable effects [11]. Due to its positive effects on endothelium and CV events in patients with hypertension, the adjunctive use of aerobic exercise to medications may improve the CV risk factor profile and complement the BP-lowering effects of medical treatment, thus reducing the dose of a drug required [52,53]. The current ESC guidelines on CV prevention state that lifestyle interventions are indicated for all patients with high-normal BP or mild hypertension because they can delay the need for drug treatment or complement its BP-lowering effect [14].

A recent meta-analysis including 15 studies and 910 patients with AH showed that exercise significantly reduced 24-h BP (sBP/dBP: −5.4/−3.0 mmHg; [95% CI, −9.2; −1.6]/[−5.4; −0.6]) and also daytime (sBP/dBP: −4.5/−3.2 mmHg [−6.6; −2.3]/[−4.8;−1.5]) and nighttime ambulatory BP (sBP/dBP, −4.7/−3.1 mmHg [−8.4; −1.0]/ [−5.3; −0.9]) in patients taking anti-hypertensive medications (all $P < 0.05$). Notably, only aerobic exercise provided substantial benefits ($P < 0.05$) [54]. Moreover, a randomized controlled trial conducted in patients with resistant hypertension (which was defined as a BP ≥140/90 mmHg despite 3 antihypertensive agents or a blood pressure controlled by ≥4 antihypertensive agents) randomized hypertensive patients to participate or not in an 8-to-12-week exercise program: exercise significantly decreased daytime ambulatory sBP and dBP by 6 ± 12 and 3 ± 7 mmHg, respectively ($P = 0.03$ each); regular exercise also reduced BP on exertion and increased physical performance, assessed by maximal oxygen uptake and lactate curves [55].

Similarly, in a recent RCT by Lopes et al., a 12-week aerobic exercise program reduced 24-h BP by 7.1 mmHg (95% CI, −12.8;-1.4; $P = 0.02$) and daytime ambulatory BP (sBP/dBP: −8.4/−5.7 mmHg [95% CI -14.3;-2.5/;-9.0; −2.4; $P = 0.006$/ $P = 0.001$) as well as systolic office BP (−10.0 mmHg; 95% CI, −17.6; −2.5; $P = 0.01$) in patients with resistant hypertension [51].

This should encourage clinicians to recommend people with AH, especially those who require more than two antihypertensive drugs to achieve BP control, practicing aerobic exercise, and prescribe a personalized exercise program to improve patient adherence to therapy and quality of life.

5. Sports eligibility and disqualification in athletes with hypertension

AH can be detected during the clinical evaluation of athletes [56]. Identifying hypertensive individuals is essential in pre-participation screening to assess sports eligibility and the type of sport allowed and to set up appropriate management and follow-up [13,56–59]. Despite being considered healthy by definition, even top-level professional athletes during the pre-participation screening can be diagnosed: in 1058 Olympic athletes, 3.8% had hypertension [60]. Notably, most of the athletes with hypertension are males with no significant differences in terms of sport practiced [61], with a relevant impact of family history and overweight. Performing a CV risk stratification is fundamental in the hypertensive subject, evaluating the BP levels at rest and during exercise, the presence of other risk factors and organ damage (LV hypertrophy, diastolic dysfunction, ultrasound evidence of arterial wall thickening or atherosclerotic plaque, hypertensive retinopathy, increased serum creatinine) and associated clinical conditions to classify individuals at low, moderate, high or very high CV risk [62].

When BP is uncontrolled, temporary restriction from competitive sports is recommended, except for skill sports, and the maximal exercise test should be postponed until resting BP is controlled [13,56]. When BP is well controlled, eligibility may be granted for all sports in individuals with low or moderate CV risk [13,56]. In individuals with a high-risk CV profile with a well-controlled BP, participation in all competitive sports is possible, except for the most intensive power disciplines such as discus/javelin throwing, shot-putting, and weightlifting [13,56]. However, eligibility must be assessed on a case-by-case basis, depending on the type and severity of the associated clinical condition and target organ damage [13,56].

Regular follow-up is recommended during sports participation depending on the severity of hypertension and the risk category [13]. The American Heart Association stated that stage 1 hypertension, without target-organ damage, should not limit eligibility for any competitive sport, while athletes suffering from stage 2 hypertension should be restricted from high-static sports, such as weightlifting until hypertension is controlled [63,64]. If hypertension is present parallel to another CV disease, eligibility for competitive sports participation should be based on the type and severity of the associated condition [63,64]. Notably, in most professional athletes, lifestyle modifications were sufficient to achieve optimal control of blood pressure values [61].

Some individuals are normotensive at rest with an exaggerated BP response to exercise (>220/85 mmHg for males and 200/80 mmHg for females) [65]. An abnormally high BP response to exercise testing is an independent and significant predictor of incident hypertension, increased CV events and mortality, independently of age, gender, resting BP, and cardiac risk factors [66,67]. Therefore, a complete clinical evaluation, including ECG and echocardiography, evaluation of CV risk profile, identification and correction of risk factors, and lifestyle modification, should be performed in athletes with an exaggerated BP response to exercise, even if the athletes are normotensive at rest [66]. Moreover, the Italian cardiological guidelines for competitive sports eligibility (COCIS) [68] suggest performing blood/urine sample tests for baseline evaluation and monitoring of hypertensive athletes' including creatinine, estimated glomerular renal function, urinary albumin and albumin/creatinine ratio to detect possible renal involvement, uric acid, glucose and cholesterol dosage for a complete evaluation of cardiovascular risk profile.

Non-pharmacological measures should be considered as the first step in managing hypertension in athletes, including weight control, cessation of smoking, reduced intake of salt, supplements, and alcohol, and the use of anti-inflammatory drugs and anabolic steroids agents [13,56,66]. This approach is usually considered inappropriate for competitive athletes because they are assumed to have a low-risk profile and are instinctively believed to represent the healthy lifestyle model. However, even professional top-level athletes are not immune from most CV risk factors, with dyslipidemia and increased waist circumference affecting a substantial proportion of individuals (32% and 25%, respectively) and with a small minority presenting a high CV risk profile, largely expression of lifestyle and related to modifiable CV risk factors [60]. Aerobic exercise programs should complement the individual's training schedule. If drug therapy is required, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and calcium channel blockers (dihydropyridines) are the preferred choice as they do not affect performance capacity and are not on the doping list [13,56,69]. Diuretics can cause electrolyte imbalances and increase the risk of dehydration, particularly in hot environments or events that tend to raise core body temperature over a prolonged period [69]; moreover, they are prohibited as they can mask banned substances and could be

Table 2
Summary of the recommendations about the use of antihypertensive drugs in athletes.

Drug class	Recommended: YES/NO	Reasons to recommend/not recommend
ACE inhibitors / ARB	YES	-do not affect performance capacity -not on the WADA prohibited list
	NO for women in reproductive years	-potential teratogenicity
Calcium channel blockers (dihydropyridines)	YES	-do not affect performance capacity -not on the WADA prohibited list
Diuretics	NO	- electrolyte imbalances and increase the risk of dehydration - mask performance/enhancing drugs (included in the WADA prohibited list) - could be used to accelerate weight loss for competitive sports in which weight criteria are used to determine qualification (included in the WADA prohibited list)
Alpha-blockers	NO	may decrease physical endurance performance
Beta-blockers	Only in selected cases	-induce bradycardia, impair aerobic exercise performance - included in the WADA prohibited list for some competitive skill disciplines requiring control of tremors (e.g., archery, shooting)

WADA, World Anti-doping Agency.

used for accelerated weight loss for sports in which weight criteria are used to determine qualification for participation [13,56,69]. Alpha-blockers may decrease physical endurance performance, while beta-blockers induce bradycardia, usually reduce exercise capacity, and are considered doping in certain sports disciplines requiring increased fine motor control since they can improve performance by lowering tremors (e.g., shooting) [13,56,69] (see Table 2).

6. Conclusions

Appropriate clinical data interpretation is essential for the differential diagnosis between athlete's heart and HHD. A possible coexistence of both conditions requires tailored management and treatment. The interplay between physical training and hypertension is not limited to the differential diagnosis but extends to the combined role that PA and therapy have in the appropriate management of patients with HDD. Accordingly, exercise should be tailored and prescribed in patients with HDD as a first-line therapy or in addition to pharmacological treatment. More evidence in large-scale randomized controlled trials is needed to delineate personalized exercise programs as an effective therapy in patients with HHD.

CRediT authorship contribution statement

Maria Concetta Pastore: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Conceptualization. **Luna Cavigli:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization. **Gabriele Olivoni:** Writing – original draft. **Egidio Imbalzano:** Writing – review & editing. **Andrea Rinaldi:** Writing – review & editing. **Riccardo Liga:** Writing – review & editing. **Anna Vittoria Mattioli:** Writing – review & editing. **Pietro Scicchitano:** Writing – review & editing. **Antonio Curcio:** Writing – review & editing. **Francesco Barillà:** Writing – review & editing. **Michele Ciccarelli:** Writing – review & editing. **Viviana Maestrini:** Writing – review & editing. **Pasquale Perrone Filardi:** Writing – review & editing. **Flavio D'Ascenzi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization. **Matteo Cameli:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization.

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