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REVIEW ARTICLE

Arterial Hypertension and Cardiopulmonary Function: The Value of a Combined Cardiopulmonary and Echocardiography Stress Test

Lavinia Del Punta[1] · Nicolò De Biase[1] · Alessio Balletti[1] · Francesco Filidei[1] · Alessandra Pieroni[1] · Silvia Armenia[1] · Alessandro Mengozzi[1] · Matteo Mazzola[1] · Valerio Di Fiore[1] · Frank Lloyd Dini[2] · Javier Rosada[3] · Agostino Virdis[1] · Stefano Taddei[1] · Nicola Riccardo Pugliese[1] · Stefano Masi[1]

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Abstract
Arterial hypertension (AH) is a global burden and the leading risk factor for mortality worldwide. Haemodynamic abnormalities, longstanding neurohormonal and inflammatory activation, which are commonly observed in patients with AH, promote cardiac structural remodeling ultimately leading to heart failure (HF) if blood pressure values remain uncontrolled. While several epidemiological studies have confirmed the strong link between AH and HF, the pathophysiological processes underlying this transition remain largely unclear. The combined cardiopulmonary-echocardiography stress test (CPET-ESE) represents a precious non-invasive aid to detect alterations in patients at the earliest stages of HF. The opportunity to study the response of the cardiovascular system to exercise, and to differentiate central from peripheral cardiovascular maladaptations, makes the CPET-ESE an ideal technique to gain insights into the mechanisms involved in the transition from AH to HF, by recognizing alterations that might be silent at rest but influence the response to exercise. Identifications of these subclinical alterations might allow for a better risk stratification in hypertensive patients, facilitating the recognition of those at higher risk of evolution towards established HF. This may also lead to the development of novel preventive strategies and help tailor medical treatment. The purpose of this review is to summarise the potential advantages of using CPET-ESE in the characterisation of hypertensive patients in the cardiovascular continuum.

Keywords Arterial hypertension · Heart failure · Cardiopulmonary exercise test, exercise stress echocardiography

1 Introduction

Arterial hypertension (AH) is a public health burden, with an overall prevalence in adults estimated around 30–45% [1], making it a major preventable cause of cardiovascular disease and all-cause mortality worldwide [2]. A major contribution to the morbidity and mortality related to AH derives from heart failure (HF), for which AH represents the leading risk factor [3, 4]. Hypertensive patients show a five- to six-fold higher risk of developing HF than healthy subjects, and lifetime HF risk grows directly proportional to blood pressure [5]. The presence of AH before the HF-related symptoms represents the most prevalent risk factor in heart failure with preserved ejection fraction (HFpEF), which is defined, according to current guidelines, by left ventricular ejection fraction (LV EF) ≥ 50% [5]. Indeed, hypertensive patients fall into stage A-HFpEF, according to the American College of Cardiology Foundation/American Heart Association classification (AHA/ACC), while those with AH-associated asymptomatic cardiac structural and/or function alterations fall into Stage B-HFpEF [6].

To tailor preventive and therapeutic interventions, a complete understanding of the mechanisms underlying the transition from HF stages A-B to clinical HF (AHA/ACC Stage C) would be of utmost importance. Cardiopulmonary-echocardiography stress test (CPET-ESE) is currently used

Lavinia Del Punta and Nicolò De Biase equally contributed.

Nicola Riccardo Pugliese and Stefano Masi joint last authorship.

✉ Stefano Masi
stefano.masi@unipi.i

[1] Department of Clinical and Experimental Medicine, University of Pisa, Via Roma, 67, 56126 Pisa, Italy

[2] Centro Medico Sant'Agostino, Milan, Italy

[3] Fourth Unit of Internal Medicine, University Hospital of Pisa, Pisa, Italy

to detect early alterations in patients with a definite diagnosis of HF, differentiating central from peripheral abnormalities in the cardiopulmonary response to physical exercise [7–12]. However, the opportunity to study the entire cardiovascular system under exercise makes the CPET-ESE equally effective in highlighting initial alterations induced by hypertension and shared with HF, thus identifying early and long-acting pathways that might account for the transition between the two clinical conditions [13]. As a matter of fact, CPET-ESE has recently demonstrated an additional predictive value in patients with subclinical HF compared to the two techniques taken individually, independently from bio-humoral, clinical and instrumental parameters evaluated at rest [14–16]. Several biomarkers of cardiac function bear prognostic significance in patients with overt HF, among which the N-terminal pro-B type natriuretic peptide (NT-proBNP) is the most used, according to current Guidelines [5]. However, these biomarkers are often normal in subjects in ACC/AHA HF stages A-B, including those with AH, and therefore cannot be used to evaluate the risk of transition towards more advanced HF Stages. Indeed, a multiparametric score including NT-proBNP and CPET-ESE derived parameters has been recently proposed as an accurate prognostic tool to predict HF hospitalization and cardiovascular death in Stage C-HFpEF, as well as to identify the subjects in Stages A and B at risk of transition towards more advanced HF Stages [13].

2 Pathophysiology

AH leads to progressive cardiovascular alterations through several different processes. Longstanding pressure overload on the LV is the first well-known mechanism of damage, which brings about structural remodeling and ultimately LV concentric hypertrophy (LVH). All of these alterations are often globally referred to as "hypertensive heart disease", even if there is no unanimous agreement on the definition [17, 18]. Commonly, diastolic dysfunction (usually assessed by echocardiography) is the first manifestation of this pathological process, discernible in early, mild AH even before the development of LVH [19–21]. This notwithstanding, it is worth noting that hypertensive heart disease is also characterized by underhanded systolic dysfunction, even before the onset of clinical HF [12].

A network metanalysis by Sciarretta et al. [22] investigated the impact of different antihypertensive therapies in the prevention of HF, concluding that diuretics seem the most effective class of drugs in preventing the transition from AH to overt HF. Nevertheless, pressure overload is only one of the numerous mechanisms involved in the development of HF. Structural alteration of small coronary arteries, with increased collagen deposition and fibrosis (i.e. microvascular disease), is a key feature of cardiac chamber damage, detectable in the early stages of hypertensive heart disease [23]. Chronic hyperactivation of neurohormonal pathways (i.e. renin-angiotensin-aldosterone system) has a pivotal role in AH, as does the persistent increase of proinflammatory cytokines (tumor necrosis factor-alpha, interleukin-1, and interleukin-6), growth factors (i.e. transforming growth factor-beta) and reactive oxygen species [18, 24]. This miscellaneous humoral environment leads to myocardial fibrosis, coronary microvascular endothelial inflammation, and rarefaction [25–27]. This, in turn, reduces coronary flow reserve, which is also impaired by diminished vasodilatory capacity [28], elevation in LV diastolic filling pressure and compression of subendocardial microcirculation due to increased LV wall thickness [29]. In a vicious circle, the inability to satisfy increased oxygen demand (associated with LVH) predisposes to ischemia and further fibrosis and remodeling [18].

The longstanding neurohormonal and inflammatory activation also impacts considerably on the remodeling and stiffening of systemic arteries, which is a crucial feature in the pathophysiology of AH. Increased arterial stiffness causally contributes to isolated systolic hypertension [30], leading to both ventricular-arterial uncoupling and microvascular damage [31–33]. There is a strong correlation between LV diastolic function, assessed by tissue Doppler imaging-derived mitral annular velocity in early diastole (e'), and indices of arterial afterload (i.e. arterial elastance, arterial compliance, systemic vascular resistance) or vascular stiffness (i.e. pulse wave velocity) both in healthy ageing and in hypertensive patients with or without HF [34]. Moreover, pulse wave velocity is related to abnormal myocardial deformation in systole, assessed by speckle tracking echocardiography (STE) [35] and to increased serum levels of biomarkers of collagen turnover (suggesting excessive myocardial collagen deposition). Beyond its impact on LV function and structure, the increased pulsatile energy transmitted by stiff vessels to the microvascular system promotes remodeling of the small vessels, which might further impair coronary flow reserve at the cardiac level and oxygen extraction in the periphery [36]. Finally, the microvascular disease promoted by increased arterial stiffness is responsible for the damage of target organs such as the brain and the kidney [37]. Due to these synergetic mechanisms, and in parallel with LVH development, AH is thought to progress towards HFpEF [38–41], which is indeed characterised by impaired LV systo-diastolic function, reduced exercise capacity and a high prevalence of peripheral and coronary microvascular dysfunction [42–44].

On the other hand, AH can also lead to HF with LV EF < 40% (HFrEF) [5]. The Cardiovascular health study demonstrated that LVH is a strong predictor of depressed ventricular function and acts as a direct or indirect predecessor of systolic deterioration through chronic myocardial ischemia

[45]. Indeed, comorbidities commonly associated with AH, such as obesity, chronic kidney disease and anemia, can lead to volume overload and thus contribute to LV dilation [20]. Therefore, end-stage hypertensive heart disease can result in dilated cardiomyopathy. Furthermore, the development of acute ischemic events, facilitated by the co-existence of AH and coronary atherosclerosis, is another frequent circumstance that can cause the progression of hypertensive heart disease towards dilated cardiomyopathy [40, 46, 47].

3 Combined Cardiopulmonary-Echocardiography Stress Test

Transthoracic echocardiography has a well-known role in the clinical assessment of hypertensive patients, both to detect LV remodeling and to evaluate the response of cardiac structural and functional alterations to antihypertensive medications [2, 40]. 2D-derived resting LV mass and geometry and left atrial dimension have been used traditionally in the stratification of cardiovascular risk, while further evaluation of LV diastolic and systolic function can be assessed by echo-Doppler and STE [48]. Noteworthy, the latter technique—namely, STE-derived global longitudinal strain (GLS)—has shown to be more reliable than LV EF in evaluating inapparent abnormalities in myocardial contractile function [49]. However, physical exercise can stress cardiopulmonary homeostasis and unmask pathological hemodynamic changes still unapparent at rest, allowing a better characterisation of the transition from AH to HF (Table 1).

In hypertensive patients, ESE finds its main application in risk stratification and in the diagnosis of myocardial ischemia [50]. However, this technique has also been successfully used in the last years to gain insight into cardiovascular mechanisms underpinning effort intolerance in patients in different subsets of HF, from Stages A-B to overt HF [51–53]. ESE can integrate the assessment of cardiac function analysed at rest through the evaluation of chamber geometry and volumes, LV systolic and diastolic function, left atrial structure and function, and valvular function during exercise [54].

Progressive impairment of cardiac mechanics and/or coronary flow reserve can result in the absence of contractile reserve, defined as the inability to increase LVEF $\geq$ 7.5% from rest to peak exercise [55]. Subclinical LV contractile dysfunction can be evaluated by tissue Doppler imaging-derived systolic mitral annulus tissue velocity (s') [12] and STE-derived GLS [55]. On the other hand, early (E) to late (A) diastolic transmitral flow velocity ratio is part of the routine assessment of diastolic function both at rest and during exercise, together with the ratio of transmitral flow velocity to mitral annular velocity in early diastole (E/e') [56]. The latter, in particular, correlates well with LV filling pressure when assessed at rest. Resting E/e' > 15 represents a major criterion in the diagnostic workup of HFpEF [57], as well as a powerful prognostic indicator in this population [58, 59]. However, albeit peak effort E/e' > 15 is deemed to express a stress-induced increase in LV filling pressure, doubts have been recently raised regarding the technical feasibility and reliability of this parameter during exercise [60]. The evaluation of diastole is integrated with the estimation of systolic pulmonary arterial pressure (sPAP), which is calculated by adding estimated right atrial pressure to measured tricuspidal regurgitation velocity [61]. An inappropriate increase in sPAP indicates a pulmonary hypertensive response to physical or pharmacological stress [54], which is common in AH and is usually associated with increased LV filling pressure [9, 62].

ESE can be easily combined with lung ultrasound, which allows for the assessment of extravascular lung water, as revealed by the presence of B-lines [63, 64]. An increase in the number of B-lines during exercise, rather than their absolute number at a given moment, indicates cardiogenic extravascular lung water accumulation, which is likely due to increased filling pressures [65, 66]. In a recent study involving patients in AHA/ACC HF Stages A/B (81% of which had AH), those with higher peak-rest ΔB-lines (i.e., more severe exercise-induced pulmonary congestion) were at higher risk of transition towards manifest HFpEF after a two-year follow-up [13].

The combination of ESE with CPET can provide important additional information on the systemic and pulmonary response to exercice. CPET has been increasingly recognised as a reliable tool in assessing aerobic fitness due to the possibility to analyse in a non-invasive and multiparametric fashion the cardiovascular, respiratory and metabolic response to exercise [14]. Oxygen consumption (VO_2) was the first exercise-derived parameter used to categorise HFrEF [67]; a decade later, Mancini et al. proposed peak VO_2 as a prognostic risk factor for cardiovascular death in patients with advanced HFrEF [68]. However, increasing evidence suggests that effort intolerance is as common in patients with chronic, stable HFpEF as it is in subjects with HFrEF [7, 10, 12, 69]. Current Clinical Recommendations discuss the possibility of converting measured peak VO_2 to percent-predicted to account for age and sex differences [70]. However, recently the reliability of this parameter compared to peak VO_2 in HFpEF has been questioned [71].

CPET can detect impairment in aerobic metabolism by evaluating the anaerobic threshold (AT), which identifies the physiological switch to mainly anaerobic metabolism [72]. Earlier AT denotes a principal role of anaerobic metabolism during exercise, and this finding characterises both physical deconditioning and HF [73]. The increased amount of time spent in anaerobic conditions appears to be related to

Table 1. CPET, ESE and the combined CPET-ESE approach in the analyses of cardiopulmonary response to exercise in hypertensive patients with and without HFpEF.

Study	Setting	Aims	Results
CPET and/or ESE separately			
Belyavsky et al, 2018	19 pts with AH, 13 pts with suspected HFpEF + 19 healthy controls. CPET, ESE	To assess the potential usefulness of ESE in patients with suspected HFpEF	HFpEF during exercise defined as exertional dyspnoea and peak $VO_2 \leq 20.0$ mL/min/kg Increased sensitivity (72.7%) combining TRV during exercise and E/e' compared to the sole peak E/e' (sensitivity 45.5%) in the diagnosis of subclinical HFpEF
Ikonomidis et al, 2015 [36]	320 pts with AH + 160 matched controls. CPET (subgroup of 80 pts), baseline echocardiography, pulse wave velocity	To assess the relationship between LV and vascular function, exercise capacity and bio-humoral parameters (NT-proBNP, markers of collagen metabolism)	Significant correlation between STE-derived parameters of myocardial deformation and coronary flow reserve, pulse wave velocity, LV mass, and systolic blood pressure ($p < 0.05$). All these parameters were impaired in AH pts and related with increased NT-proBNP and reduced peak VO_2
Celic et al., 2014 [89]	51 untreated AH pts, 49 well-controlled AH pts, 52 uncontrolled AH pts + and 50 matched controls. CPET, baseline echocardiography	To assess the relationship between impaired left ventricular deformation and exercise capacity in patients with AH	STE-derived parameters of myocardial deformation significantly decreased in patients with untreated AH and related with peak VO_2 ($p < 0.05$).
Modesti et al., 1999 [84]	25 pts with AH and no LVH + 10 matched controls CPET, baseline echocardiography, angiocardioscintigraphy	To evaluate the role of systemic vascular resistance in effort intolerance	Lower peak VO_2 ($p < 0.045$), higher vascular resistance ($p < 0.010$) in AH vs controls. Significant correlation between systemic vascular resistance and peak VO_2 ($r =$ -0.72, p<0.04).
Modesti et al., 1994 [85]	21 pts with AH + 19 matched controls CPET	Using CPET to evaluate anaerobic metabolism in AH	Earlier AT, lower peak VO_2 ($p < 0.03$), steeper peak VCO_2/VO_2 ($p < 0.03$) in AH vs controls.
Smith et al., 1992 [86]	65 male pts with AH and LVH (i.e. LV mass by height index exceeded 163 g/m) + 35 matched controls CPET, baseline echocardiography	To evaluate the correlation between LVH and blood pressure during exercise	There was an inverse relation between LVH and SBP during exercise ($r = -0.34$; $p = 0.005$). Lower peak VO_2 and blunted increase in heart rate at peak in AH vs controls ($p < 0.05$)
Combined CPET-ESE			
Pugliese et al., 2020 [9]	63 pts with AH and 50 with HFpEF-AH + 32 matched controls. CPET-ESE	To identify early CPET-ESE alterations in the transition to HFpEF.	Significantly reduced VO_2, AVO_2diff and GLS in pts with AH versus controls ($p < 0.0001$). Significantly increased peak E/e' and B-lines in AH ($p < 0.0001$).
Pugliese et al., 2020 [12]	113 pts in AHA/ACC A-B stage, 244 in AHA/ACC C-stage (101 HFpEF, 143 HFrEF); 81% with AH. CPET-ESE	To analyse mechanisms behind effort intolerance within the HF spectrum.	Peak VO_2 significantly decrease from controls to stage A-B and C ($p < 0.0001$). Peak S', peak TAPSE/sPAP, LA reservoir strain/E/e' at low load were independent predictors of peak VO_2 (adjusted $R^2 = 0.76$, $p < 0.001$).
Nedelijkovic et al., 2016 [62]	87 pts with AH, exertional dyspnoea and normal resting LV. CPET-ESE	To analyse the value of CPET-ESE in unmasking HFpEF.	No differences at rest between AH pts with and without HFpEF, except for lower e' and higher sPAP in pts with HFpEF. Significantly higher VO_2 ($p < 0.001$) and O_2 pulse in AH ($p < 0.05$); higher VE/VCO_2 slope and $PetCO_2$ in HFpEF ($p < 0.01$).

ACC: American College of Cardiologists; AH: arterial hypertension; AHA: American Heart AssociationAT: anaerobic threshold; AVO_2diff: arterio-venous oxygen difference; CPET: cardiopulmonary exercise testing; E/e': ratio of transmitral flow velocity to mitral annular velocity in early diastole; ESE: echocardiography stress test; GLS: global longitudinal strain; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LA: left atrial; LV: left ventricular; LVH: left ventricular hypertrophy; NT-proBNP: N-terminal pro-B natriuretic peptide; O_2: oxygen; $PetCO_2$: end-tidal pressure of carbon dioxide; SBP: systolic blood pressure; sPAP: systolic pulmonary artery pressure; STE: speckle tracking echocardiography; TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspidal regurgitation velocity; VCO_2/VO_2: respiratory exchange ratio; VE/VCO_2: minute ventilation/carbon dioxide production; VO_2: oxygen consumption

impaired oxygen extraction [74]. Indeed, VO_2 depends on cardiac output (CO; i.e., heart rate times stroke volume) and oxygen extraction by peripheral tissues (i.e., arteriovenous oxygen difference [AVO_2diff]), as summarised by Fick's principle [15]. Thus, VO_2 is the physiological result of the interplay between central (CO) and peripheral (AVO_2diff) components. The physiological increase in AVO_2diff during exercise is blunted in the whole spectrum of HF, probably due to microvascular and mitochondrial impairment in AHA/ACC A-B stages and C-HFpEF [12, 75], with the additional contribution of cardiac cachexia and sarcopenia in advanced HFrEF [73]. Noteworthy, AVO_2diff can be assessed only through invasive catheterisation or estimated by CPET-ESE from Fick's principle as VO_2/CO. Indeed, although CPET allows a global analysis of VO_2 during exercise, only a concurrent invasive hemodynamic evaluation by cardiac catheterisation or with imaging techniques such as ESE allows distinguishing its central and peripheral determinants [76]. For this reason, in the last years, the integrated CPET-ESE evaluation has been revealed to be a precious tool to refine the characterisation of patients with HF or at risk of developing it [12–16, 51] (Fig. 1).

The ventilatory equivalent for carbon dioxide (VE/VCO_2) is another crucial parameter evaluated by CPET, as it demonstrated robust prognostic power in HF, even in submaximal levels of effort, in contrast to other CPET parameters such as VO_2 [14, 77, 78]. VE/VCO_2 is an index of ventilation/perfusion matching in the lung and describes the increase in minute ventilation for any given amount of CO_2 generated from cellular respiration. It is determined by CO_2 production, the physiological dead space to tidal volume ratio (V_D/V_T) and the arterial CO_2 partial pressure, with higher values (i.e., a steeper slope) indicating ventilation/perfusion mismatch. The V_D/V_T ratio and the end-tidal partial pressure of CO_2 also reflect ventilatory control and ventilation/perfusion matching during exercise. Furthermore, the latter provides a reliable non-invasive estimation for arterial CO_2 partial pressure. Recently, Salvioni et al. proposed an equation to predict VE/VCO2 slope in patients with HFrEF, seeking to determine whether the percentage of predicted VE/VCO2 slope could have a greater prognostic power compared to traditional VE/VCO2 slope [79]. Indeed, percent-predicted VE/VCO2 slope allowed for a refined prognostic stratification in patients with severe HFrEF (peak VO2 < 14 ml/min/kg) compared to the absolute VE/VCO2 slope value. However, such an equation has yet to find wider application, even in the research setting.

Notably, impaired ventilation and ventilation/perfusion mismatch correlated with increased B-lines in a cohort of patients across the whole HF spectrum [9].

Despite the promising evidence derived by the combined approach in patients with HF, this technique has some limitations worthy of being mentioned. Compared with rest echocardiographic and clinical evaluation, CPET-ESE is more time-consuming, more expensive, and requires specialized equipment and personnel.

4 The Transition from Subclinical Alterations to Heart Failure: The Role of Combined Cardiopulmonary Echocardiography Stress Test

Despite the importance of risk stratification and preventive interventions in hypertensive patients, and despite the tight pathophysiological connection between AH with HFpEF [18], only scarce attention has been given to the systematic analysis of the transition from one condition to the other. Moreover, many typical comorbidities of HFpEF (e.g., AH, obesity and diabetes mellitus) cluster together and are all involved in the pathophysiology of HF, making it difficult for the clinician to discern the contribution of each of these conditions and their associated cardiovascular and pulmonary alterations in the development and progression of the disease [15, 16].

As CPET-ESE is an expensive and time-consuming technique, patient selection is mandatory and should be driven by clinical judgment. Thus, hypertensive patients experiencing symptoms and signs suggestive of HF, such as dyspnea, fatigue and ankle swelling, should first undergo a comprehensive evaluation, including standard rest echocardiography and natriuretic peptides measurement (Fig. 2). HF-specific quality of life questionnaires (e.g., the Kansas City Cardiomyopathy Questionnaire), scores based on clinical and rest echocardiographic parameters (e.g., H2FPEF and HFA-PEFF [57, 80]), and submaximal exercise tests (e.g., the 6-minute walk test) can be used in clinical practice but are scarcely reliable for patients at intermediate probability. For those falling in this "grey zone", the combined CPET-ESE approach could offer a better pathophysiological characterization, supporting or ruling out the diagnosis of HFpEF. Noteworthy, subjects with resistant hypertension represent a subgroup at higher risk of transition toward HF [81] and likely candidates for the CPET-ESE examination when clinically indicated. However, it must be noted that exercise testing might be contraindicated in those with resting BP >200/110 mmHg [82].

In an interesting paper by Melenovsky et al., resting vascular (i.e. brachial and carotid pressures, total arterial resistance, arterial elastance) and conventional LV diastolic parameters (i.e. E-wave, A-wave, deceleration time, and e' at both mitral annular insertions) were able to detect early cardiovascular maladaptations in hypertensive subjects with LVH compared to healthy controls [33]. Invasive hemodynamic assessment of arterial function at rest and during exercise confirmed those results,

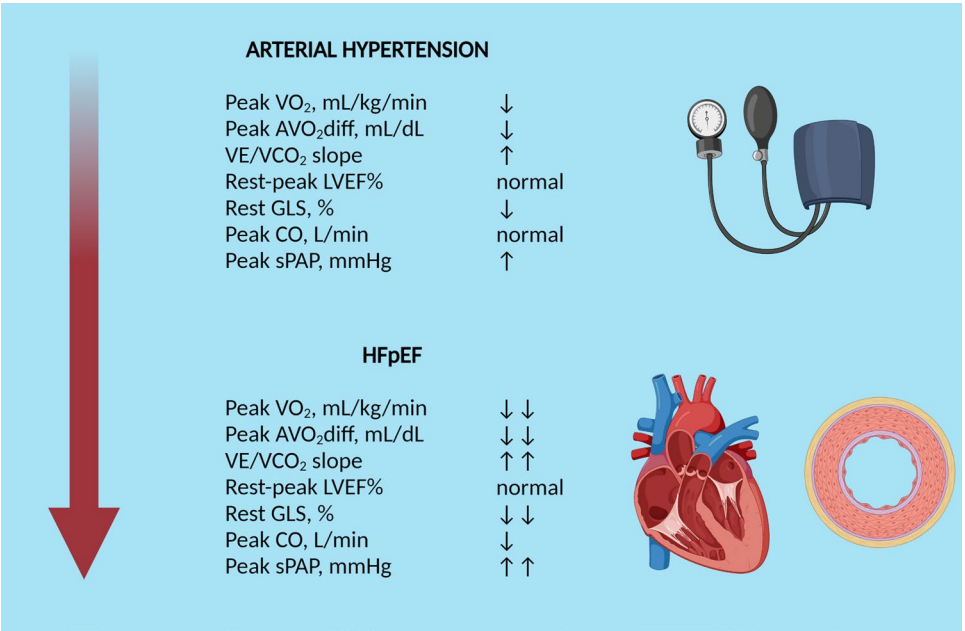

Fig. 1. The combined CPET-ESE approach to evaluate the cardiopulmonary response to exercise in hypertensive patients with and without HFpEF. Bottom images depict left ventricular hypertrophy and arterial thickening, which are characterizing features of HFpEF. *AVO_2diff* arteriovenous oxygen difference, *CO* cardiac output, *CPET-ESE* cardiopulmonary-echocardiography stress test, *GLS* global longitudinal strain, *HFpEF* heart failure with preserved ejection fraction, *LV EF* left ventricular ejection fraction, *sPAP* systolic pulmonary arterial pressure, *VE/VCO_2* ventilatory equivalent for carbon dioxide, *VO_2* oxygen consumption

unmasking significant exercise-induced impairment in arterial compliance and vasodilatory response to nitrate infusion in HFpEF and AH [9, 83]. Such alterations can lead to a reduced peak VO_2, an earlier AT and a steeper VCO_2/VO_2 in hypertensive patients [84, 85]. It has been recently observed that, despite peak VO2 appears more severely impaired in hypertensive subjects with HFpEF than in isolated AH, the two populations share similar signs of low peripheral oxygen extraction in terms of impaired AVO_2diff [9]. However, there is also evidence of central alterations to exercise intolerance in AH, as demonstrated by a mildly reduced peak heart rate than healthy subjects [86]. Indeed, chronotropic incompetence (i.e., insufficient increase in HR during exercise) is a common feature in the HF spectrum and a strong predictor of cardiac and all-cause mortality [87, 88] Moreover, hypertensive patients present with preserved CO increase during exercise, but they show subtle alterations in regional myocardial deformation (e.g. STE-derived GLS) that are significant compared to healthy controls [9]. The correlation between STE-derived myocardial deformation parameters and impaired exercise capacity is well established [24, 33]. Nedeljkovic et al. studied hypertensive patients with and without HFpEF, showing similar echocardiographic parameters at rest in the two populations, except for a lower e' and higher sPAP in subjects with HFpEF, suggesting that peak E/e' could unmask HFpEF. Indeed, subjects with pathologically high E/e' had significantly steeper VE/VCO_2 slope and reduced partial pressure of end-tidal carbon dioxide ($PETCO_2$), another marker of ventilatory/perfusion mismatch [62]. Similar data were observed by Belyavskiy et al., highlighting how the evaluation of tricuspid regurgitation velocity during exercise—and thus, indirectly, of pulmonary artery pressures—could better detect patients with HFpEF, compared with the sole peak E/e' ratio [90]. Moreover, the mild elevation of sPAP observed during exercise in subjects with AH and HFpEF was revealed to be consistent with a steeper VE/VCO_2 slope and increased peak B-lines [9].

These results suggest that exercise can elicit subclinical pulmonary congestion even in patients with isolated AH and before overt HFpEF occurs, providing a more accurate risk stratification and potentially a more personalised therapy.

Several studies analysed the impact of medical therapy on the CPET response in patients with HF [91, 92]. As far as we know, the combined approach has not been used for this purpose in HF nor AH, possibly due to its relatively recent introduction in the research setting. In the future, the application of CPET-ESE might also spread to the evaluation of the response to pharmacological therapy.

5 Conclusions

AH is a global burden and the leading risk factor for HFpEF. Given its capacity to detect early functional alterations, CPET-ESE could give more insight into the clinical stages towards HF and allow a better risk stratification in hypertensive patients. As identifying early cardiopulmonary alterations in AH may suggest novel preventive strategies and help clinicians tailor medical treatment,

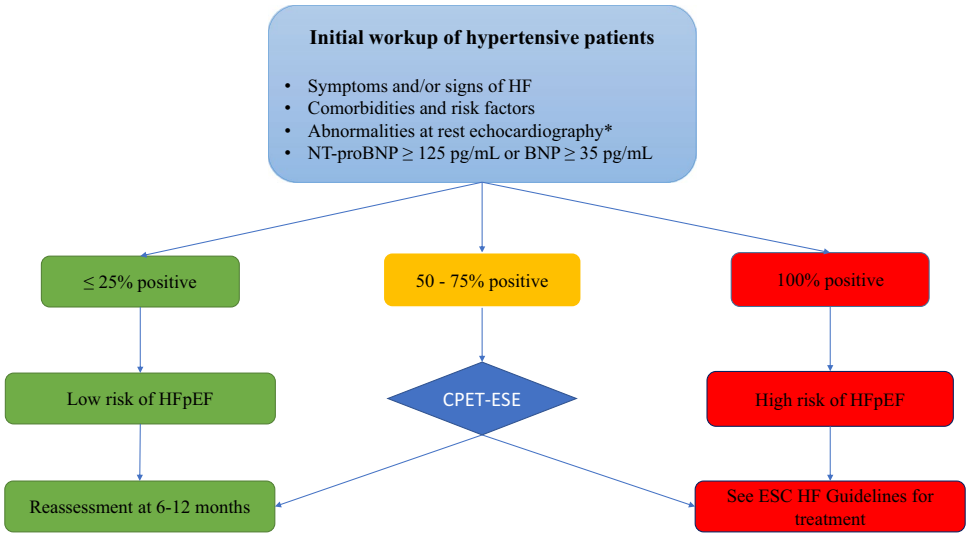

Fig. 2. Tentative flow chart showing how combined cardiopulmonary and echocardiography stress test can help stratify risk and probability of HFpEF in the setting of AH. CPET-ESE derived parameters suggestive of HFpEF are not listed in the flow chart, but all are discussed within the text and summarized in Fig. 1. *According to current Guidelines: left ventricular mass index ≥ 95 g/m^2 (female), ≥ 115 g/m^2 (male); relative wall thickness > 0.42; left atrium volume index > 34 mL/m^2 (sinus rhythm); E/e' ratio > 9; pulmonary artery systolic pressure > 35 mmHg; tricuspid regurgitation velocity > 2.8 m/s. *BNP* brain natriuretic peptide, *ESC* European Society of Cardiology, *HF* heart failure, *HFpEF* heart failure with preserved ejection fraction, *NT-proBNP* N-terminal pro-B type natriuretic peptide

further investigations are needed to confirm the value of CPET-ESE in the clinical arena.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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