



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

Lavinia Del Punta¹ · Nicolò De Biase¹ · Alessio Balletti¹ · Francesco Filidei¹ · Alessandra Pieroni¹ · Silvia Armenia¹ · Alessandro Mengozzi¹ · Matteo Mazzola¹ · Valerio Di Fiore¹ · Frank Lloyd Dini² · Javier Rosada³ · Agostino Virdis¹ · Stefano Taddei¹ · Nicola Riccardo Pugliese¹ · Stefano Masi¹

Received: 23 September 2021 / Accepted: 23 November 2021
© The Author(s) 2022

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) $\geq 50\%$ [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.it

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- α , interleukin-1, and interleukin-6), growth factors (i.e. transforming growth factor- β) 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 Δ B-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 exercise. 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 $\dot{V}O_2 \leq 20.0$ 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 $\dot{V}O_2$
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 $\dot{V}O_2$ ($p < 0.05$).
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 $\dot{V}O_2$ ($p < 0.045$), higher vascular resistance ($p < 0.010$) in AH vs controls. Significant correlation between systemic vascular resistance and peak $\dot{V}O_2$ ($r = -0.72$, $p < 0.04$).
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 $\dot{V}O_2$ ($p < 0.03$), steeper peak $\dot{V}O_2/\dot{V}O_{2\max}$ ($p < 0.03$) 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 ²) + 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 $\dot{V}O_2$ 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 $\dot{V}O_2$, $\Delta\dot{V}O_2/\text{diff}$ 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 HFpEF); 81% with AH. CPET-ESE	To analyse mechanisms behind effort intolerance within the HF spectrum.	Peak $\dot{V}O_2$ 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 $\dot{V}O_2$ (adjusted $R^2 = 0.76$, $p < 0.001$).
Nedeljkovic 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 $\dot{V}O_2$ ($p < 0.001$) and O_2 pulse in AH ($p < 0.05$); higher $VE/\dot{V}CO_2$ slope and $PetCO_2$ in HFpEF ($p < 0.01$).

ACC: American College of Cardiologists; AH: arterial hypertension; AHA: American Heart Association; AT: anaerobic threshold; $\Delta\dot{V}O_2/\text{diff}$: arterio-venous oxygen difference; CPET: cardiopulmonary exercise testing; E/e' : ratio of transmural 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; HFpEF: 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; $\dot{V}CO_2/\dot{V}O_2$: respiratory exchange ratio; $VE/\dot{V}CO_2$: minute ventilation/carbon dioxide production; $\dot{V}O_2$: 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/VCO_2 slope in patients with HFrEF, seeking to determine whether the percentage of predicted VE/VCO_2 slope could have a greater prognostic power compared to traditional VE/VCO_2 slope [79]. Indeed, percent-predicted VE/VCO_2 slope allowed for a refined prognostic stratification in patients with severe HFrEF (peak $\text{VO}_2 < 14 \text{ ml/min/kg}$) compared to the absolute VE/VCO_2 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.

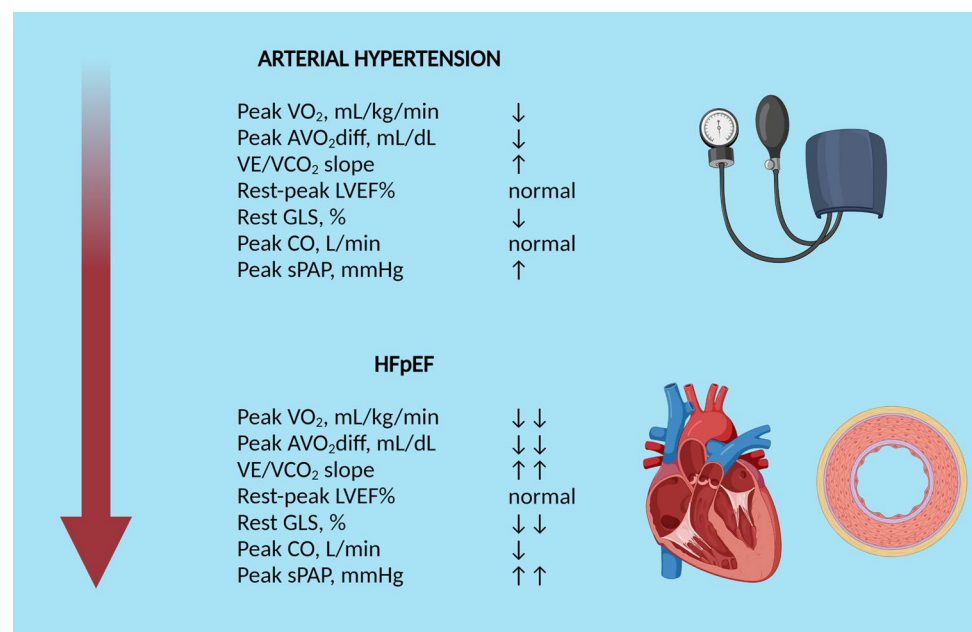
4 The Transition from Subclinical Alterations to Heart Failure: The Role of Combined Cardiopulmonary Echocardiography Stress Test

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 $>200/110 \text{ mmHg}$ [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. *AVO₂diff* 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/VCO₂* ventilatory equivalent for carbon dioxide, *VO₂* 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 VO_2 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_2 diff [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 (PETCO₂), 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,

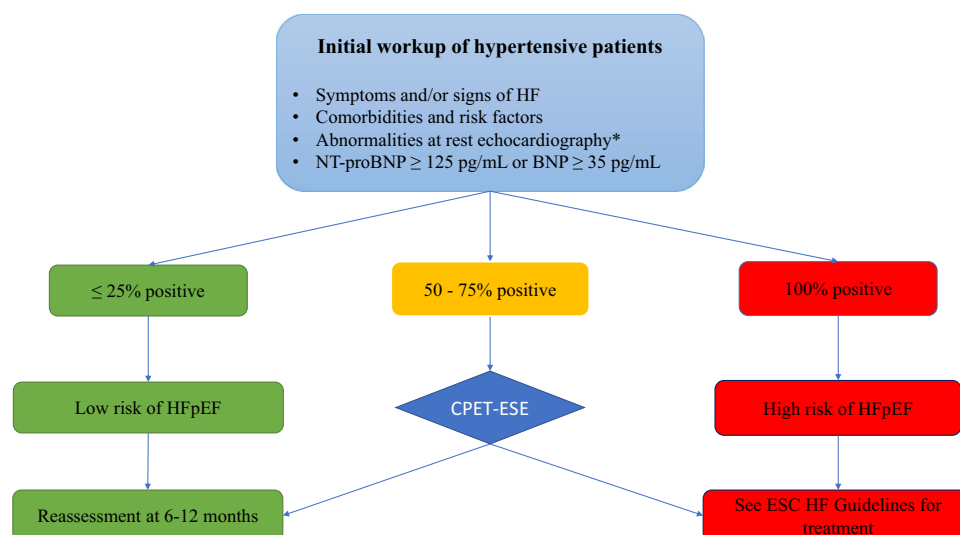


Fig. 2. Tentative flow chart showing how combined cardiopulmonary and echocardiography stress test can help stratify risk and probability of HFpEF in the setting of AH. CPET-ESE derived parameters suggestive of HFpEF are not listed in the flow chart, but all are discussed within the text and summarized in Fig. 1. *According to current Guidelines: left ventricular mass index ≥ 95 g/m² (female), ≥ 115 g/

m² (male); relative wall thickness > 0.42 ; left atrium volume index > 34 mL/m² (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.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

References

1. Chow CK, Teo KK, Rangarajan S, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *JAMA*. 2013;310:959–68. <https://doi.org/10.1001/jama.2013.184182>.
2. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force

- for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *Eur Heart J*. 2018;39:3021–104. <https://doi.org/10.1097/HJH>.
3. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: Lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. *Lancet*. 2014;383:1899–911. [https://doi.org/10.1016/S0140-6736\(14\)60685-1](https://doi.org/10.1016/S0140-6736(14)60685-1).
4. Bozkurt B, Aguilar D, Deswal A, et al (2016) Contributory Risk and Management of Comorbidities of Hypertension, Obesity, Diabetes Mellitus, Hyperlipidemia, and Metabolic Syndrome in Chronic Heart Failure: A Scientific Statement from the American Heart Association
5. McDonagh TA, United C, Gardner RS, et al (2021) 2021 ESC-Guidelines for the diagnosis and treatment of acute and chronic heart failure Developed. *Eur Heart J* 1–128. <https://doi.org/10.1093/eurheartj/ehab368>
6. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the american college of cardiology foundation/american heart association task force on practice guidelines. *Circulation*. 2013. <https://doi.org/10.1161/CIR.0b013e31829e8776>.
7. Pugliese NR, Paneni F, Mazzola M, et al. Impact of epicardial adipose tissue on cardiovascular hemodynamics, metabolic profile, and prognosis in heart failure. *Eur J Heart Fail*. 2021. <https://doi.org/10.1002/EJHF.2337>.
8. Nesti L, Pugliese NR, Sciuto P, et al. Mechanisms of reduced peak oxygen consumption in subjects with uncomplicated type 2 diabetes. *Cardiovasc Diabetol*. 2021;20:124. <https://doi.org/10.1186/s12933-021-01314-6>.
9. Pugliese NR, Mazzola M, Fabiani I, et al. Haemodynamic and metabolic phenotyping of hypertensive patients with and without heart failure by combining cardiopulmonary and

- echocardiographic stress test. *Eur J Heart Fail.* 2020;22:458–68. <https://doi.org/10.1002/ehjhf.1739>.
10. Pugliese NR, Fabiani I, Santini C, et al. Value of combined cardiopulmonary and echocardiography stress test to characterize the haemodynamic and metabolic responses of patients with heart failure and mid-range ejection fraction. *Eur Heart J Cardiovasc Imaging.* 2019;20:828–36. <https://doi.org/10.1093/ehjci/jez014>.
 11. Pugliese NR, Fabiani I, Mandoli GE, et al. Echo-derived peak cardiac power output-to-left ventricular mass with cardiopulmonary exercise testing predicts outcome in patients with heart failure and depressed systolic function. *Eur Heart J Cardiovasc Imaging.* 2019;20:700–8. <https://doi.org/10.1093/ehjci/jez172>.
 12. Pugliese NR, De Biase N, Conte L, et al. Cardiac reserve and exercise capacity: insights from combined cardiopulmonary and exercise echocardiography stress testing. *J Am Soc Echocardiogr.* 2020. <https://doi.org/10.1016/j.echo.2020.08.015>.
 13. Pugliese NR, De Biase N, Gargani L, et al. Predicting the transition to and progression of heart failure with preserved ejection fraction: a weighted risk score using bio-humoral, cardiopulmonary, and echocardiographic stress testing. *Eur J Prev Cardiol.* 2020. <https://doi.org/10.1093/eurjpc/zwaa129>.
 14. Guazzi M, Bandera F, Ozemek C, et al. Cardiopulmonary exercise testing: what is its value? *J Am Coll Cardiol.* 2017;70:1618–36. <https://doi.org/10.1016/j.jacc.2017.08.012>.
 15. Pugliese NR, De Biase N, Balletti A, et al (2021) Characterisation of haemodynamic and metabolic abnormalities in the heart failure spectrum: the role of combined cardiopulmonary and exercise echocardiography stress test. *Minerva Cardiol Angiol.* <https://doi.org/10.23736/S2724-5683.21.05743-4>
 16. Nesti L, Pugliese NR, Sciuto P, Natali A. Type 2 diabetes and reduced exercise tolerance: a review of the literature through an integrated physiology approach. *Cardiovasc Diabetol.* 2020;19:134.
 17. Nwabuo CC, Vasan RS. Pathophysiology of hypertensive heart disease: beyond left ventricular hypertrophy. *Curr Hypertens Rep.* 2020. <https://doi.org/10.1007/s11906-020-1017-9>.
 18. Pugliese NR, Masi S, Taddei S. The renin-angiotensin-aldosterone system: a crossroad from arterial hypertension to heart failure. *Heart Fail Rev.* 2019. <https://doi.org/10.1007/s10741-019-09855-5>.
 19. Burchfield JS, Xie M, Hill JA. Pathological ventricular remodeling: mechanisms: Part 1 of 2. *Circulation.* 2013;128:388–400. <https://doi.org/10.1161/CIRCULATIONAHA.113.001878>.
 20. Messerli FH, Rimoldi SF, Bangalore S. The transition from hypertension to heart failure: contemporary update. *JACC Hear Fail.* 2017;5:543–51. <https://doi.org/10.1016/j.jchf.2017.04.012>.
 21. Fabiani I, Pugliese NR, La Carrubba S, et al. Interactive role of diastolic dysfunction and ventricular remodeling in asymptomatic subjects at increased risk of heart failure. *Int J Cardiovasc Imaging.* 2019;35:1231–40. <https://doi.org/10.1007/s10554-019-01560-6>.
 22. Sciarretta S, Palano F, Tocci G, et al. Antihypertensive treatment and development of heart failure in hypertension: a Bayesian network meta-analysis of studies in patients with hypertension and high cardiovascular risk. *Arch Intern Med.* 2011;171:384–94. <https://doi.org/10.1001/archinternmed.2010.427>.
 23. Schelbert EB, Fridman Y, Wong TC, et al. Temporal relation between myocardial fibrosis and heart failure with preserved ejection fraction: Association with baseline disease severity and subsequent outcome. *JAMA Cardiol.* 2017;2:995–1006. <https://doi.org/10.1001/jamacardio.2017.2511>.
 24. Guzik TJ, Touyz RM. Oxidative stress, inflammation, and vascular aging in hypertension. *Hypertension.* 2017;70:660–7. <https://doi.org/10.1161/HYPERTENSIONAHA.117.07802>.
 25. Heymans S, González A, Pizard A, et al. Searching for new mechanisms of myocardial fibrosis with diagnostic and/or therapeutic potential. *Eur J Heart Fail.* 2015;17:764–71. <https://doi.org/10.1002/ehjhf.312>.
 26. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol.* 2013;62:263–71. <https://doi.org/10.1016/j.jacc.2013.02.092>.
 27. Mohammed SF, Hussain S, Mirzoyev SA, et al. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation.* 2015;131:550–9. <https://doi.org/10.1161/CIRCULATIONAHA.114.009625>.
 28. Kozáková M, Galetta F, Gregorini L, et al. Coronary vasodilator capacity and epicardial vessel remodeling in physiological and hypertensive hypertrophy. *Hypertension.* 2000;36:343–9. <https://doi.org/10.1161/01.HYP.36.3.343>.
 29. Hamasaki S, Al Suwaidi J, Higano ST, et al. Attenuated coronary flow reserve and vascular remodeling in patients with hypertension and left ventricular hypertrophy. *J Am Coll Cardiol.* 2000;35:1654–60. [https://doi.org/10.1016/S0735-1097\(00\)00594-5](https://doi.org/10.1016/S0735-1097(00)00594-5).
 30. Kaess BM, Rong J, Larson MG, et al. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA.* 2012;308:875–81. <https://doi.org/10.1001/2012.jama.10503>.
 31. Lüers C, Trippel TD, Seeländer S, et al. Arterial stiffness and elevated left ventricular filling pressure in patients at risk for the development or a previous diagnosis of HF—a subgroup analysis from the DIAST-CHF study. *J Am Soc Hypertens.* 2017;11:303–13. <https://doi.org/10.1016/j.jash.2017.03.006>.
 32. Kuznetsova T, D’Hooge J, Kloch-Badelek M, et al. Impact of hypertension on ventricular-arterial coupling and regional myocardial work at rest and during isometric exercise. *J Am Soc Echocardiogr.* 2012;25:882–90. <https://doi.org/10.1016/j.echo.2012.04.018>.
 33. Melenovsky V, Borlaug BA, Rosen B, et al. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban baltimore community. the role of atrial remodeling/dysfunction. *J Am Coll Cardiol.* 2007;49:198–207. <https://doi.org/10.1016/j.jacc.2006.08.050>.
 34. Borlaug BA, Melenovsky V, Redfield MM, et al. Impact of arterial load and loading sequence on left ventricular tissue velocities in humans. *J Am Coll Cardiol.* 2007;50:1570–7. <https://doi.org/10.1016/j.jacc.2007.07.032>.
 35. Ikonomidis I, Katsanos S, Triantafyllidi H, et al. Pulse wave velocity to global longitudinal strain ratio in hypertension. *Eur J Clin Invest.* 2019;49: e13049. <https://doi.org/10.1111/eci.13049>.
 36. Ikonomidis I, Tzortzis S, Triantafyllidi H, et al. Association of impaired left ventricular twisting-untwisting with vascular dysfunction, neurohumoral activation and impaired exercise capacity in hypertensive heart disease. *Eur J Heart Fail.* 2015;17:1240–51. <https://doi.org/10.1002/ehjhf.403>.
 37. O’Rourke MF, Safar ME (2005) Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertens (Dallas, Tex 1979)* 46:200–204. <https://doi.org/10.1161/01.HYP.0000168052.00426.65>
 38. Pugliese NR, Fabiani I, La Carrubba S, et al. Prognostic value of a tissue doppler index of systodiastolic function in patients with asymptomatic heart failure. *J Cardiovasc Echogr.* 2018. https://doi.org/10.4103/jeecho.jeecho_59_17.
 39. Dini FL, Fabiani I, Miccoli M, et al. Prevalence and determinants of left ventricular diastolic dysfunction in obese subjects and the role of left ventricular global longitudinal strain and mass normalized to height. *Echocardiography.* 2018;35:1124–31. <https://doi.org/10.1111/echo.13890>.

40. Pugliese NR, Fabiani I, La Carrubba S, et al. Classification and prognostic evaluation of left ventricular remodeling in patients with asymptomatic heart failure. *Am J Cardiol.* 2017;119:71–7. <https://doi.org/10.1016/j.amjcard.2016.09.018>.
41. Fabiani I, Pugliese NR, Conte L, et al. Incremental prognostic value of a complex left ventricular remodeling classification in asymptomatic for heart failure hypertensive patients. *J Am Soc Hypertens.* 2017;11:412–9. <https://doi.org/10.1016/j.jash.2017.05.005>.
42. Shah SJ, Lam CSP, Svedlund S, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. *Eur Heart J.* 2018;39:3439–50. <https://doi.org/10.1093/eurheartj/ehy531>.
43. Hage C, Svedlund S, Saraste A, et al. Association of coronary microvascular dysfunction with heart failure hospitalizations and mortality in heart failure with preserved ejection fraction: a follow-up in the PROMIS-HFpEF study. *J Card Fail.* 2020;26:1016–21. <https://doi.org/10.1016/j.cardfail.2020.08.010>.
44. Rush CJ, Berry C, Oldroyd KG, et al. Prevalence of coronary artery disease and coronary microvascular dysfunction in patients with heart failure with preserved ejection fraction. *JAMA Cardiol.* 2021. <https://doi.org/10.1001/jamacardio.2021.1825>.
45. Drazner MH, Rame JE, Marino EK, et al. Increased left ventricular mass is a risk factor for the development of a depressed left ventricular ejection fraction within five years: the cardiovascular health study. *J Am Coll Cardiol.* 2004;43:2207–15. <https://doi.org/10.1016/j.jacc.2003.11.064>.
46. Drazner MH. The progression of hypertensive heart disease. *Circulation.* 2011;123:327–34. <https://doi.org/10.1161/CIRCULATIONAHA.108.845792>.
47. Dini FL, Galeotti GG, Terlizzese G, et al. Left ventricular mass and thickness: why does it matter? *Heart Fail Clin.* 2019;15:159–66. <https://doi.org/10.1016/j.hfc.2018.12.013>.
48. Perrone-Filardi P, Coca A, Galderisi M, et al. Noninvasive cardiovascular imaging for evaluating subclinical target organ damage in hypertensive patients: a consensus article from the European Association of Cardiovascular Imaging, the European Society of Cardiology Council on Hypertension and the Eur. J Hypertens. 2017;35:1727–41. <https://doi.org/10.1097/HJH.0000000000001396>.
49. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging.* 2015;16:233–71. <https://doi.org/10.1093/ehjci/jev014>.
50. Sicari R, Cortigiani L. The clinical use of stress echocardiography in ischemic heart disease. *Cardiovasc Ultrasound.* 2017;15:1–16. <https://doi.org/10.1186/s12947-017-0099-2>.
51. Fabiani I, Pugliese NR, Galeotti GG, et al. The added value of exercise stress echocardiography in patients with heart failure. *Am J Cardiol.* 2019;123:1470–7. <https://doi.org/10.1016/j.amjcard.2019.02.008>.
52. Obokata M, Kane GC, Reddy YNV, et al. Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. *Circulation.* 2017;135:825–38. <https://doi.org/10.1161/CIRCULATIONAHA.116.024822>.
53. Donal E, Lund LH, Oger E, et al. Value of exercise echocardiography in heart failure with preserved ejection fraction: a sub-study from the KaRen study. *Eur Heart J Cardiovasc Imaging.* 2016;17:106–13. <https://doi.org/10.1093/ehjci/jev144>.
54. Lancellotti P, Pellikka PA, Budts W, et al. The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging.* 2016;17:1191–229. <https://doi.org/10.1093/ehjci/jev190>.
55. Rudski LG, Gargani L, Armstrong WF, et al. Stressing the cardiopulmonary vascular system: the role of echocardiography. *J Am Soc Echocardiogr.* 2018;31:527–550.e11. <https://doi.org/10.1016/j.echo.2018.01.002>.
56. Ha J-W, Andersen OS, Smiseth OA. Diastolic Stress Test Invasive and Noninvasive Testing. *JACC Cardiovasc Imaging.* 2019. <https://doi.org/10.1016/j.jcmg.2019.01.037>.
57. Pieske B, Tschöpe C, De Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J.* 2019;40:3297–317.
58. Coiro S, Simonovic D, Deljanin-Ilic M, et al. Prognostic value of dynamic changes in pulmonary congestion during exercise stress echocardiography in heart failure with preserved ejection fraction. *Circ Hear Fail.* 2020. <https://doi.org/10.1161/CIRCHEARTFAILURE.119.006769>.
59. Reddy YNV, Carter RE, Obokata M, et al. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation.* 2018;138:861–70. <https://doi.org/10.1161/CIRCULATIONAHA.118.034646>.
60. Sharifov OF, Gupta H. What is the evidence that the tissue doppler index e/e' reflects left ventricular filling pressure changes after exercise or pharmacological intervention for evaluating diastolic function? a systematic review. *J Am Heart Assoc.* 2017. <https://doi.org/10.1161/JAHA.116.004766>.
61. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr.* 2009;10:165–93. <https://doi.org/10.1093/ejehocardiography/jep007>.
62. Nedeljkovic IVANA, Banovic M, Stepanovic J, et al. The combined exercise stress echocardiography and cardiopulmonary exercise test for identification of masked heart failure with preserved ejection fraction in patients with hypertension. *Eur J Prev Cardiol.* 2016;23:71–7. <https://doi.org/10.1177/2047487315604836>.
63. Gargani L. Lung ultrasound: a new tool for the cardiologist. *Cardiovasc Ultrasound.* 2011. <https://doi.org/10.1186/1476-7120-9-6>.
64. Miglioranza MH, Gargani L, Sant'Anna RT, et al. Lung ultrasound for the evaluation of pulmonary congestion in outpatients: a comparison with clinical assessment, natriuretic peptides, and echocardiography. *JACC Cardiovasc Imaging.* 2013;6:1141–51. <https://doi.org/10.1016/j.jcmg.2013.08.004>.
65. Picano E, Scali MC, Ciampi Q, Lichtenstein D. Lung ultrasound for the cardiologist. *JACC Cardiovasc Imaging.* 2018;11:1692–705. <https://doi.org/10.1016/j.jcmg.2018.06.023>.
66. Scali MC, Zagatina A, Ciampi Q, et al. Lung ultrasound and pulmonary congestion during stress echocardiography. *JACC Cardiovasc Imaging.* 2020. <https://doi.org/10.1016/j.jcmg.2020.04.020>.
67. Weber KT, Kinasevitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation.* 1982;65:1213–23. <https://doi.org/10.1161/01.CIR.65.6.1213>.
68. Mancini DM, Eisen H, Kussmaul W, et al. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation.* 1991;83:778–86.
69. Shimaie J, Sherez J, Aviram G, et al. Determinants of effort intolerance in patients with heart failure: combined echocardiography and cardiopulmonary stress protocol. *JACC Hear Fail.* 2015;3:803–14. <https://doi.org/10.1016/j.jchf.2015.05.010>.

70. Guazzi M, Adams V, Conraads V, et al. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation*. 2012;126:2261–74. <https://doi.org/10.1161/CIR.0b013e31826fb946>.
71. Reddy YNV, Olson TP, Obokata M, et al. Hemodynamic correlates and diagnostic role of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. *JACC Hear Fail*. 2018;6:665–75. <https://doi.org/10.1016/j.jchf.2018.03.003>.
72. Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American heart association. *Circulation*. 2010;122:191–225. <https://doi.org/10.1161/CIR.0b013e3181e52e69>.
73. Del Buono MG, Arena R, Borlaug BA, et al. Exercise intolerance in patients with heart failure: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;73:2209–25. <https://doi.org/10.1016/j.jacc.2019.01.072>.
74. Dhakal BP, Malhotra R, Murphy RM, et al. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. *Circ Hear Fail*. 2015;8:286–94. <https://doi.org/10.1161/CIRCHEARTFAILURE.114.001825>.
75. Houstis NE, Eisman AS, Pappagianopoulos PP, et al. Exercise intolerance in heart failure with preserved ejection fraction: diagnosing and ranking its causes using personalized O₂ pathway analysis. *Circulation*. 2018;137:148–61. <https://doi.org/10.1161/CIRCULATIONAHA.117.029058>.
76. Guazzi M. Stress echocardiography combined with cardiopulmonary exercise testing: opening a new window into diagnosis of heart failure with preserved ejection fraction. *Eur J Prev Cardiol*. 2016;23:67–70. <https://doi.org/10.1177/2047487315607076>.
77. Arena R, Myers J, Abella J, et al. Development of a ventilatory classification system in patients with heart failure. *Circulation*. 2007;115:2410–7. <https://doi.org/10.1161/CIRCULATIONAHA.107.686576>.
78. Lewis GD, Shah RV, Pappagianopolas PP, et al. Determinants of ventilatory efficiency in heart failure: the role of right ventricular performance and pulmonary vascular tone. *Circ Hear Fail*. 2008;1:227–33. <https://doi.org/10.1161/CIRCHEARTFAILURE.108.785501>.
79. Salvioni E, Corrà U, Piepoli M, et al. Gender and age normalization and ventilation efficiency during exercise in heart failure with reduced ejection fraction. *ESC Hear Fail*. 2020;7:371–80. <https://doi.org/10.1002/ehf2.12582>.
80. Paulus WJ. H2FPEF Score: at last, a properly validated diagnostic algorithm for heart failure with preserved ejection fraction. *Circulation*. 2018;138:871–3. <https://doi.org/10.1161/CIRCULATIONAHA.118.035711>.
81. Pimenta E, Calhoun DA. Resistant hypertension: incidence, prevalence, and prognosis. *Circulation*. 2012;125:1594–6. <https://doi.org/10.1161/CIRCULATIONAHA.112.097345>.
82. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American heart association. *Circulation*. 2013;128:873–934. <https://doi.org/10.1161/CIR.0b013e31829b5b44>.
83. Reddy YNV, Andersen MJ, Obokata M, et al. Arterial stiffening with exercise in patients with heart failure and preserved ejection fraction. *J Am Coll Cardiol*. 2017;70:136–48. <https://doi.org/10.1016/j.jacc.2017.05.029>.
84. Modesti PA, Olivo G, Pestelli F, et al. Peripheral vascular resistance limits exercise functional capacity of mild hypertensives. *Angiology*. 1999. <https://doi.org/10.1177/000331979905000605>.
85. Modesti PA, Olivo G, Pestelli F, et al. Anaerobic metabolism in hypertensive patients during exercise stress test. *Am J Hypertens*. 1994;7:469–73. <https://doi.org/10.1093/ajh/7.5.469>.
86. Smith DHG, Neutel JM, Graettinger WF, et al. Impact of left ventricular hypertrophy on blood pressure responses to exercise. *Am J Cardiol*. 1992;69:225–8. [https://doi.org/10.1016/0002-9149\(92\)91309-R](https://doi.org/10.1016/0002-9149(92)91309-R).
87. Brubaker PH, Kitzman DW. Chronotropic incompetence: causes, consequences, and management. *Circulation*. 2011;123:1010–20. <https://doi.org/10.1161/CIRCULATIONAHA.110.940577>.
88. Zweerink A, van der Lingen ALCJ, Handoko ML, et al. Chronotropic incompetence in chronic heart failure. *Circ Hear Fail*. 2018;11:e004969.
89. Celic V, Tadic M, Suzic-Lazic J, et al. Two- and three-dimensional speckle tracking analysis of the relation between myocardial deformation and functional capacity in patients with systemic hypertension. *Am J Cardiol*. 2014;113:832–9. <https://doi.org/10.1016/j.amjcard.2013.11.031>.
90. Belyavskiy E, Morris DA, Url-Michitsch M, et al. Diastolic stress test echocardiography in patients with suspected heart failure with preserved ejection fraction: a pilot study. *ESC Hear Fail*. 2019;6:146–53. <https://doi.org/10.1002/ehf2.12375>.
91. Guazzi M, Arena R. The impact of pharmacotherapy on the cardiopulmonary exercise test response in patients with heart failure: a mini review. *Curr Vasc Pharmacol*. 2009;7:557–69. <https://doi.org/10.2174/157016109789043955>.
92. Halle M, Schöbel C, Winzer EB, et al. A randomized clinical trial on the short-term effects of 12-week sacubitril/valsartan vs. enalapril on peak oxygen consumption in patients with heart failure with reduced ejection fraction: results from the ACTIVITY-HF study. *Eur J Heart Fail*. 2021. <https://doi.org/10.1002/ehf2.2355>.