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REVIEW

Invasive haemodynamic assessment in heart failure with preserved ejection fraction

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Abstract

Despite the increasing prevalence and substantial burden of heart failure with preserved ejection fraction (HFpEF), which constitutes up to 50% of all heart failure cases, significant challenges persist in its diagnostic and therapeutic strategies. These difficulties arise primarily from the heterogeneous nature of the condition, the presence of various comorbidities and a wide range of phenotypic variations. Considering these challenges, current international guidelines endorse the utilization of invasive haemodynamic assessments, including resting and exercise haemodynamics, as the gold standard for enhancing diagnostic accuracy in cases where traditional diagnostic methods yield inconclusive results. These assessments are crucial not only for confirming the diagnosis but also for delineating the complex underlying pathophysiology, enabling the development of personalized treatment strategies, and facilitating the precise classification of HFpEF phenotypes. In this review, we summarize the haemodynamic changes observed in patients with HFpEF, comparing resting and exercise-induced parameters to those of normal subjects. Additionally, we discuss the current role of invasive haemodynamics in HFpEF assessment and highlight its utility beyond diagnosis, such as identifying HFpEF comorbidities, guiding phenotype-based personalized therapies and characterizing prognostication. Finally, we address the challenges associated with utilizing invasive haemodynamics and propose future directions, focusing on integrating these assessments into routine HFpEF care.

Keywords invasive haemodynamic assessment; heart failure with preserve ejection fraction

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Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is increasingly recognized as a significant public health issue, accounting for up to 50% of all HF cases.[1] In the United States, projections indicate a 46% increase in HF prevalence from 2012 to 2030, with an anticipated 8.5 million Americans affected by 2030, alongside a corresponding rise in healthcare costs.[2] The growing prevalence of HFpEF is primarily driven by an ageing population with an increasing burden of comorbidities such as hypertension, obesity and metabolic syndrome.[3]

Despite extensive efforts to establish definitive diagnostic criteria, diagnosing HFpEF is challenging, with a significant proportion of cases remaining inconclusive due to the complex underlying pathophysiologic mechanisms.[4] Some patients may not display apparent HF symptoms or lack physical signs of congestion. Up to 60% of patients with HFpEF confirmed by right heart catheterization (RHC) have normal natriuretic peptide levels.[5] Echocardiographic assessment is essential for HFpEF evaluation. However, the presence of grade 2 or 3 diastolic dysfunction [indicating elevated left ventricular (LV) filling pressure] albeit specific for HFpEF, lacks sensitivity.[6] Additionally, echocardiographic assessments of

diastolic dysfunction are essential for HFpEF evaluation but can be particularly challenging in patients with comorbid atrial fibrillation (AF) and calcific valvular disease, which are increasingly common in the ageing population and in those with HFpEF.[7] Considering these diagnostic challenges, invasive haemodynamic assessments remain the gold standard for distinguishing HFpEF from other conditions.[8]

This review aims to summarize the haemodynamic alterations and factors influencing haemodynamic changes in HFpEF patients compared with normal individuals. Then, we explore the utility of invasive haemodynamics in HFpEF diagnostic evaluation, phenotyping and prognostication. Finally, we address the challenges of implementing invasive haemodynamics in clinical practice and propose future directions for integrating these assessments into routine HFpEF care.

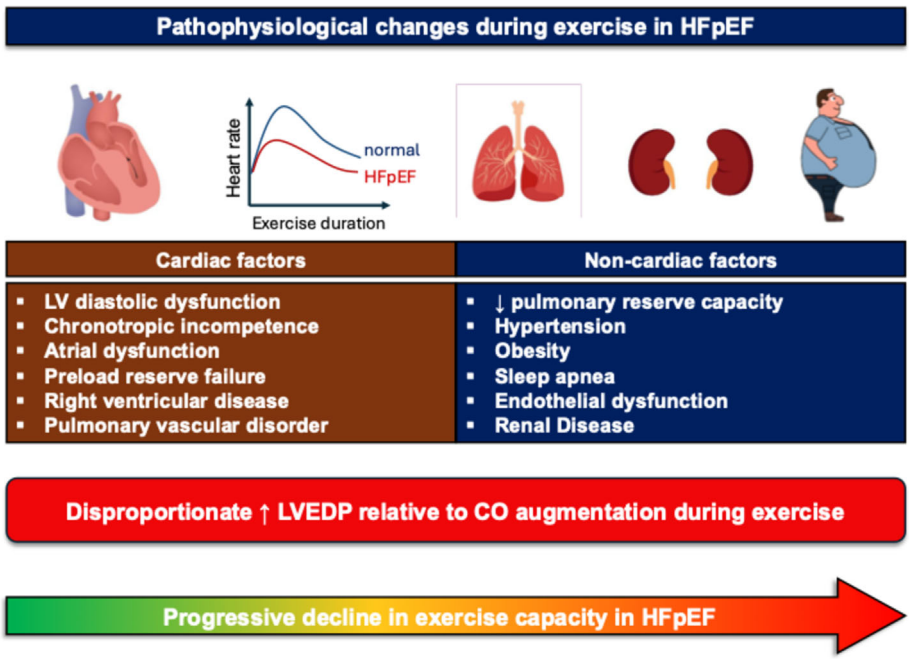
Haemodynamic alterations in HFpEF

Historically, the haemodynamic disturbance in HFpEF was primarily attributed to LV diastolic dysfunction, leading to elevated LV end-diastolic pressure (LVEDP) and congestion, similar to what is seen in HF with reduced ejection fraction.[9] However, it is now recognized that this is only a part of the explanation as shown in *Figure* 1. In HFpEF, haemodynamic derangement is caused by a complex interplay not only of LV diastolic dysfunction but also the involvement of subtle LV systolic dysfunction, atrial abnormalities, preload reserve failure and pulmonary vascular disorders, especially in the late stages of the disease, with one of these mechanisms potentially being more dominant in individual patients.[9] Moreover, non-cardiac factors, such as pre-existing comorbidities including obesity, sleep apnoea, hypertension, heightened systemic inflammatory responses leading to endothelial dysfunction and renal dysfunction, also significantly contribute to worsening clinical course.[10] In this section, we focus on changes in pulmonary artery wedge pressure (PAWP) as a surrogate for LVEDP during resting and exertional stages, as the severity of HFpEF progresses.

Resting haemodynamics

Patients with early stage of HFpEF are often asymptomatic or experience minimal symptoms, with normal cardiac size or only slight left atrial (LA) dilatation.[11] Resting haemodynamic profiles may appear normal (i.e., PAWP $<$ 15 mmHg), making HFpEF diagnosis challenging without provocative testing, for example, exercise. As the disease progresses, LV diastolic dysfunction worsens, leading to a significant increase in LVEDP. This long-standing rise in LVEDP causes pathological remodelling of the LA, resulting in elevated resting LA pressure due to the LV's reduced ability to function effectively as a vacuum.[12,13] LA failure, not infrequently associated with AF, may ensue, elevating mean LA pressure above LVEDP.[14] Consequently, this leads to an increase in PAWP, which reflects the haemodynamic load imposed by the left heart on the pul-

Figure 1 Pathophysiological changes during exercise: comparison between normal versus HFpEF patients. Abbreviations: CO, cardiac output; HFpEF, heart failure with preserved ejection fraction; LV, left ventricle; LVEDP, left ventricular end-diastolic pressure.



monary circulation.[15,16] Given that resting PAWP may be normal in early HFpEF, exercise testing plays a critical role in uncovering early haemodynamic changes.

Exercise haemodynamics

Exercise intolerance is considered a characteristic feature of HFpEF, often evident from the early stage due to reduced physiological reserve across multiple organ systems.[17,18] In response to exercise, an increase in cardiac preload due to blood volume recruitment from the legs and abdominal compartments can significantly enhance cardiac output (CO), as described by the Frank–Starling relationship.[19] Under normal conditions, CO augmentation during exercise does not result in a substantial change in LVEDP. However, it is a hallmark in patients with HFpEF that CO augmentation with increased cardiac preload during exercise occurs at the expense of a disproportionate rise in LVEDP despite having normal LVEDP at rest, as demonstrated in *Figure* 2. The maladaptive changes observed in HFpEF stem from LV diastolic dysfunction, compounded by chronotropic incompetence, subtle systolic dysfunction, LA dysfunction and other non-cardiac factors.[20–22] High PAWP at peak exercise, when patients reach exercise-limiting symptoms, is an essential diagnostic marker for HFpEF, serving as a surrogate for LVEDP.[17] PAWP has also been found to correlate well with LVEDP at rest and during exercise in populations suspected of HFpEF.[15] Additionally, a steep increase in PAWP relative to the rise in CO during exercise further supports the diagnosis of HFpEF.[17]

Invasive haemodynamic assessment for HFpEF diagnosis

Guidelines on invasive haemodynamic assessment for HFpEF

Current guidelines support the adoption of two distinct diagnostic scoring systems for HFpEF in clinical practice to guide the use of invasive haemodynamic assessment: (1) H_2FPEF score, a composite system developed by the Mayo Clinic, and (2) HFA-PEFF stepwise diagnostic algorithm, proposed by the Heart Failure Association (HFA) of the European Society of Cardiology (ESC).

The H_2FPEF score is a weighted system developed and validated using the gold-standard reference of invasive exercise haemodynamic measurements.[23] It is considered more practical for clinicians as it is based on simple clinical variables, focusing on patient comorbidities and echocardiographic parameters like pulmonary hypertension (PH) and LV filling pressures (E/e'). In contrast, the HFA-PEFF algorithm, derived from expert consensus, takes a stepwise approach, starting with a pretest clinical assessment and progressing to a comprehensive resting echocardiogram and natriuretic peptide measurements to calculate a likelihood score.[24] Both systems classify the likelihood of HFpEF as low, intermediate, or high. For patients with an intermediate likelihood (H_2FPEF 2–5 or HFA-PEFF 2–4), additional haemodynamic assessments, such as exercise stress echocardiography or invasive haemodynamic assessment, are recommended to further diagnose or rule out HFpEF[8,24,25] as shown in *Figure* 3.

Figure 2 Haemodynamic changes during exertion in HFpEF versus healthy individuals. Abbreviations: HFpEF, heart failure with preserved ejection fraction; LV, Left ventricle; PAWP, pulmonary artery wedge pressure.

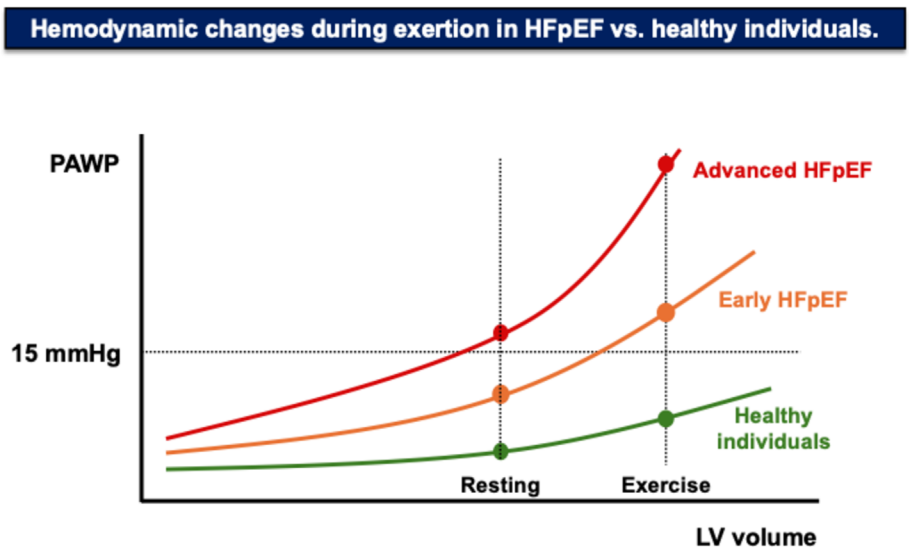
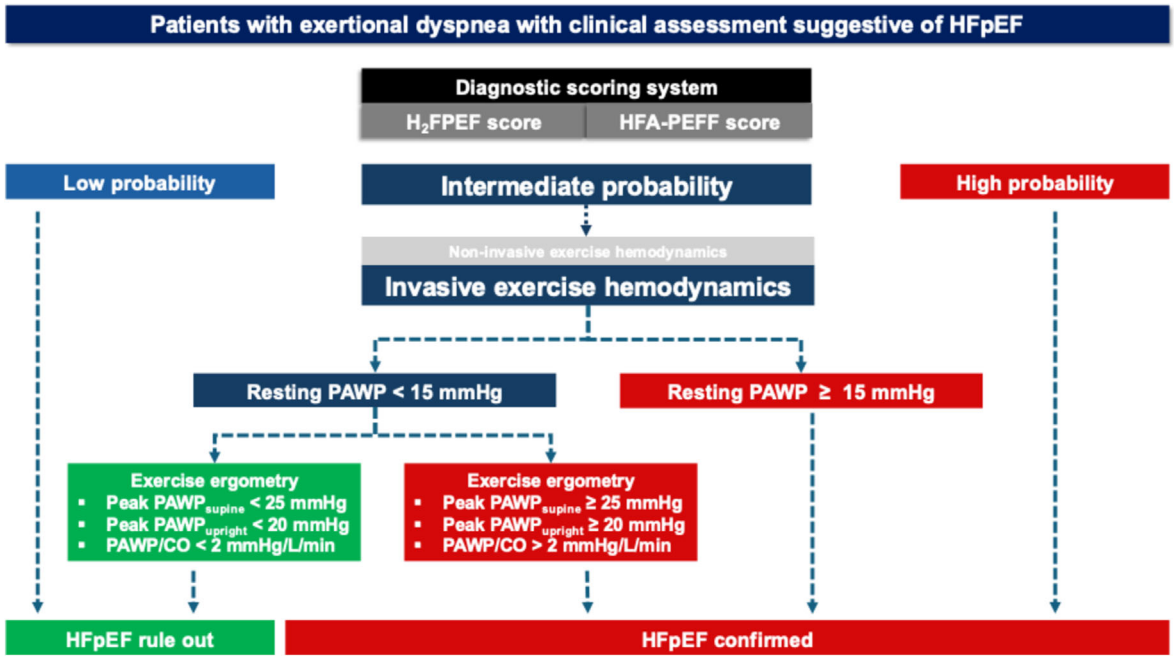


Figure 3 Strategic workflow for HFpEF diagnosis: from risk stratification to targeted case selection for invasive haemodynamic assessment. Abbreviations: CO, cardiac output; HFpEF, heart failure with preserved ejection fraction; PAWP, pulmonary artery wedge pressure.



It is important to note that there is ongoing debate about which scoring system is most effective for diagnosing HFpEF, as studies have shown conflicting results. Up to 40% of patients show discordant HFpEF probability estimates between the H_2FPEF and HFA-PEFF scores.[26] While some data indicate that the H_2FPEF score has superior discriminative ability, others suggest that the scores are comparable, with one study even reporting a higher AUC for the HFA-PEFF score[26–28] when validated against the gold-standard method of invasive haemodynamic assessment. These discrepancies likely arise from methodological differences, sample size, lack of appropriate control groups and variations in the criteria used to define HFpEF.[28] Given these limitations and the significant number of individuals falling into the intermediate categories, further testing, including invasive haemodynamics testing, is essential. Moreover, clinicians should use these scoring systems cautiously and thoroughly understand their limitations.[29] The choice of a scoring system should be guided by the specific clinical context, recognizing that no single system is perfect.

For patients with high clinical suspicion for HFpEF, invasive haemodynamic measurements might still be helpful for confirming the diagnosis, especially when the patient remains unresponsive to initial medical therapy. Although patients with advanced HFpEF might have overtly abnormal haemodynamics at rest, it is crucial for clinicians performing invasive haemodynamic assessment in patients with unexplained exertional dyspnoea to be able to implement exercise-provocative haemodynamic assessment in order to diagnose HFpEF in the early stage.[25,30]

Current practice of resting and exercise haemodynamics

For a general overview of resting and exercise RHC, the process begins with a resting RHC using a pulmonary artery catheter (Swan-Ganz catheter), with the patient in a supine position. The catheter is typically inserted through an upper-body venous access point (e.g., internal jugular or brachial vein), enabling cycle ergometer to test the lower body.[31] Considering respiratory variations, haemodynamics measurements are typically obtained at end-expiration and as mean values averaged over 5–10 s.[32] Following the resting RHC in supine position, the protocols vary across institutes but can be largely grouped into the supine or upright settings. In the supine protocol, passive leg raise (PLR) is generally performed before exercise as a simple way to augment cardiac preload and stress the LV.[33] This approach is particularly beneficial in settings where exercise testing equipment or expertise is unavailable. Data show that the increase in PAWP after PLR is more pronounced in patients with HFpEF compared with controls. Furthermore, elevated PAWP during PLR is associated with a corresponding increase in PAWP during exercise, which has prognostic relevance in HFpEF. While a PAWP $<$ 11 mmHg during PLR can help rule out HFpEF, a PAWP $\geq$ 19 mmHg strongly suggests the condition.[33] However, this threshold is not definitive and has not been endorsed as one of the diagnostic criteria in the guidelines.

The procedure then generally proceeds as these steps: (1) escalating exercise workload in either the supine or upright position; (2) simultaneous measurements of right atrial pressure (RAP), pulmonary artery pressure (PAP), PAWP and CO using either direct Fick method or thermodilution at each stage; and (3) gas exchange measurement if available.[30,34] Maximal exercise intensity is typically determined by the patient's level of exhaustion or respiratory exchange ratio if metabolic gas analyser is used.

Haemodynamic criteria for HFpEF diagnosis

The pathological rise in left heart filling pressure during exercise is a hallmark of HFpEF. While there is broad agreement that a resting PAWP of ≥15 mmHg, measured at end-expiration, indicates HFpEF,[24] a universal consensus on exercise haemodynamics criteria for diagnosing early HFpEF has not yet been established. Currently, two distinct sets of exercise haemodynamics criteria have been commonly used in clinical practice and research as shown in *Table* 1.

Peak PAWP

The first criterion, endorsed by international guidelines, defines HFpEF as a peak exercise PAWP ≥ 25 mmHg during supine position.[24] This is based on a pivotal study by Borlaug et al., which used a supine exercise protocol involving 55 patients with unexplained dyspnoea, normal ejection fraction, normal BNP and normal resting haemodynamics in order to define HFpEF.[35] The cutoff of ≥25 mmHg was established from earlier studies showing that normal individuals typically have peak PAWP values < 20–23 mmHg during supine exercise.[36] Subsequent data confirmed that elevated PAWP during exercise, specifically the ratio of peak exercise PAWP to body weight, is a significant predictor of long-term mortality among patients with early HFpEF.[37,38] In the upright position, a peak PAWP ≥ 20 mmHg during exercise is considered a pathological threshold for defining HFpEF.[15,39] This accounts for the physiological response where pulmonary pressures decrease slightly in the upright position compared with supine due to reduced venous return.

It is important to note a limitation of this criterion, as it is based on a single pressure measurement and does not account for varying exercise workload levels.[40] Additionally, emerging data suggest that even healthy individuals can exceed the PAWP threshold during exercise, and in physiologically advanced age, this parameter may also rise above the threshold.[31,41] This has led to the consideration of age-specific peak exercise PAWP cutoffs and the need for criteria that accounts for the workload achieved during exercise.

Table 1 Invasive haemodynamic criteria for diagnosing HFpEF.

At rest	PAWP ≥ 15 mmHg
During exercise	1. Peak exercise PAWP • ≥25 mmHg during supine exercise ergometry • ≥20 mmHg during upright exercise ergometry 2. PAWP/CO slope • >2 mmHg/L/min regardless of body positioning

Abbreviations: CO, cardiac output; HFpEF, heart failure with preserved ejection fraction; PAWP, pulmonary artery wedge pressure.

PAWP/CO slope

The second is a PAWP/CO slope > 2 mmHg/L/min, as defined by Eisman et al. during upright cycle ergometry, with CO derived using the direct Fick method.[42] This approach addresses the limitations of peak exercise PAWP measurement by considering the entire exercise workload, demonstrating superior diagnostic sensitivity and specificity for HFpEF and improved accuracy in risk prediction models.[6,39,42] The PAWP/CO slope > 2 mmHg/L/min was determined from a cohort of 175 patients, including healthy controls, those with HFpEF and elevated resting PAWP, and patients with unexplained dyspnoea but normal resting PAWP. Regression analysis was used to define the normative bounds and establish this cutoff, which was found to be more strongly associated with adverse cardiovascular outcomes in patients with early HFpEF compared with healthy controls. Considering measurement in supine position, the PAWP/CO slope > 2 mmHg/L/min remains valid for diagnosing HFpEF, although the slope tends to be slightly higher in HFpEF patients exercising in the supine position compared with the upright position.[43] While clinically useful, this diagnostic criterion has only been validated with direct Fick method and still needs validation with thermodilution CO measurement.[31]

The diagnostic accuracy of exercise haemodynamic criteria was evaluated in 57 patients with unexplained dyspnoea and intermediate HFpEF risk.[6] Peak PAWP and PAWP/CO slope agreed in 80% of cases, with the PAWP/CO slope more frequently identifying HFpEF. The discrepancy may be attributed to respiratory pressure variations during exertion, especially in obese and COPD patients.[44] Consequently, the PAWP/CO slope may be more reliable in patients prone to higher respiratory pressure variations, as it reduces the impact of single pressure measurements during exercise.

Supine versus upright positioning for exercise haemodynamic assessment in HFpEF

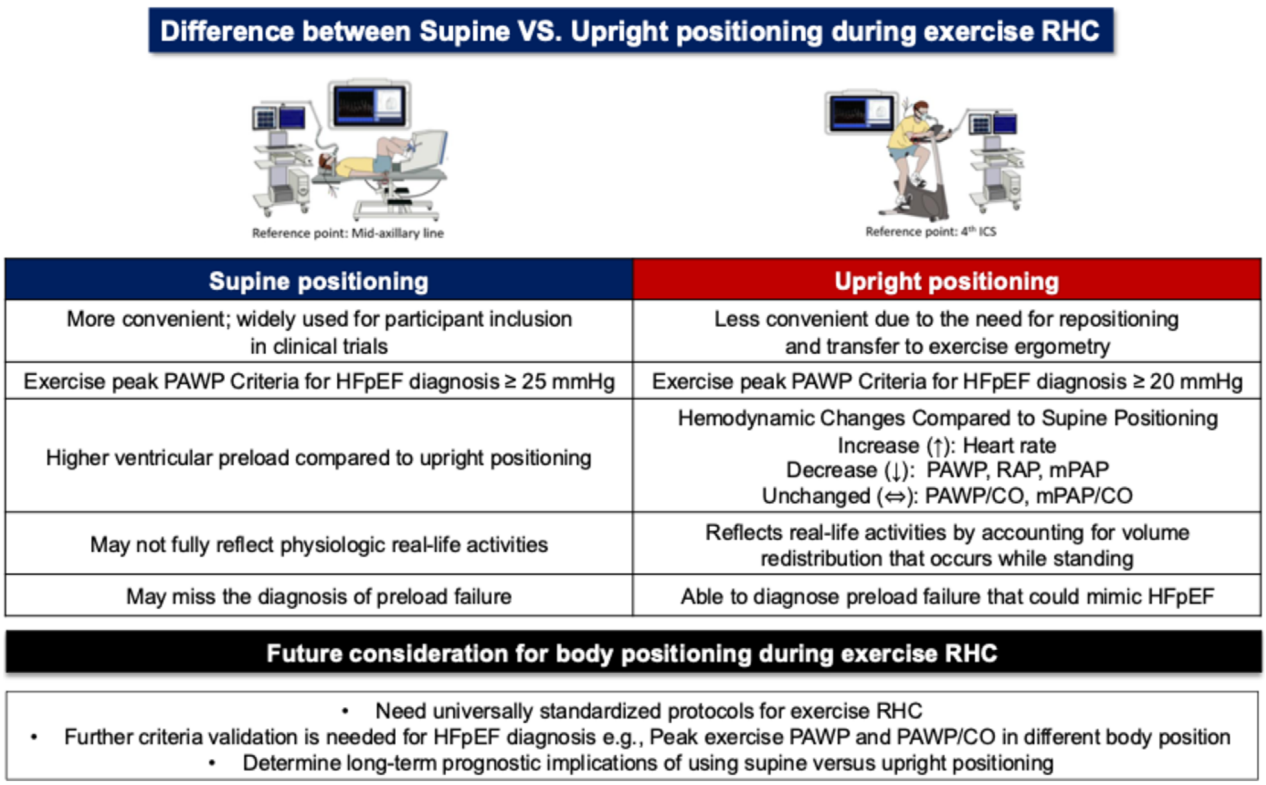
To date, there is no universally standardized protocol for the positioning for exercise haemodynamic assessment, with the choice between supine and upright positioning largely depending on the preference of the institution and operators. In the supine position, the legs are typically elevated at ≥30° angle from the bed to allow the use of a table-mounted ergometer without needing to transfer the patient from the catheterization table.[45] In contrast, the upright position, where the patient is seated at a 90° angle, re-

quires transferring the patient to a cycle ergometer. Due to the positional changes and the need to transfer patients during testing, especially in upright position exercise testing, current guidelines emphasize the importance of zeroing the pressure transducer at all positions to ensure that the zero-reference line is set at the level of the left atrium.[46]

It is important to acknowledge the distinct advantages and challenges associated with each positioning techniques as shown in *Figure* 4. The supine position offers the convenience of not requiring patient transfer, and some institutes may consider this approach to be safer and more efficient whereas upright positioning during exercise ergometry closely mirrors real-life activities, where preload reduction and changes in pulmonary haemodynamics occur while standing.[47] To explore this concept, volume redistribution, stressed blood volume during exercise and the impact of positional changes must be considered.[19,48] During exercise, both active and passive recruitment of stressed blood volume occur, leading to a rapid increase in CO driven by the expansion of stressed blood volume, an increase in HR and enhanced cardiac contractility. Compared with the supine position, the upright position results in lower venous return due to gravitational pooling of blood in the lower extremities, which reduces preload, stroke volume (SV) and, to a lesser extent, PAWP.[49] In contrast, the supine positioning increases venous return, raising preload and PAWP at baseline and during exercise, which may hypothetically lead to overdiagnosis of HFpEF. Although increase in both CO and PAWP with supine positioning could render relatively similar PAWP/CO slope in both supine and upright position, patients with HFpEF demonstrated higher PAWP/CO slope in the supine position compared with the upright position, a difference not observed in control subjects.[43] This suggests that while the slope can help distinguish HFpEF from controls, caution is necessary when comparing slopes between supine and upright positions, as they are not interchangeable.[43]

Testing positions also play a crucial role in evaluating preload failure, a condition linked to autonomic dysfunction that often mimics the symptoms of HFpEF.[50,51] In preload failure, right-sided filling does not adequately increase in response to exercise despite normal resting volumes. This leads to a blunted CO and an inability to meet circulatory demands.[52] Although the exact mechanism is unknown, preload failure is believed to be related to either dysregulation in autonomic control of central venous volume recruitment or peripheral muscle and venous insufficiency.[50] Testing in the upright position can worsen right sided underfilling in preload failure and this can be overlooked if exercise is performed only in

Figure 4 Difference between supine versus upright positioning during exercise RHC. Abbreviations: CO, cardiac output; HFpEF, heart failure with preserved ejection fraction; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; RHC, right heart catheterization.



the supine position. Patients with preload failure physiology can paradoxically present with a peak exercise PAWP exceeding the threshold for HFpEF diagnosis in the supine position..[50] In such cases, HFpEF specific treatments such as diuretics could be more harmful.

Because most institutes only perform exercise haemodynamic assessment in one position, the data on head-to-head comparison of haemodynamic measurements or diagnostic accuracy between supine and upright positioning are somewhat limited. Kirupaharan et al. explored the impact of body position (supine vs. upright) on invasive exercise haemodynamic testing in 17 patients with exercise intolerance and unexplained dyspnoea.[53] Patients were randomized to exercise either in the supine or upright position to a goal of 60 W followed by maximal exercise in the alternate position. The results showed that, in the upright position, RAP, mPAP and PAWP were significantly lower while heart rate was higher. However, the mPAP/CO and PAWP/CO slopes were not different between testing positions. The impact of testing positions on HFpEF diagnosis was not evaluated.

Invasive haemodynamic assessment in HFpEF beyond diagnosis

The importance of invasive haemodynamic testing extends beyond its pivotal role in HFpEF diagnosis, namely, in the management of patients with confirmed HFpEF. This is especially pertinent given recent therapeutic advances in HFpEF, where treatment strategies are increasingly tailored to specific phenotypes, enabling more targeted and personalized interventions.

Identification of concomitant pulmonary vascular disease

PH is commonly found in patients with HFpEF.[54] PH may develop either from the backward transmission of elevated LV filling pressures into the pulmonary circulation, leading to post-capillary PH [World Health Organization (WHO) group 2], or through pulmonary vascular remodelling (venular and arteriolar) as the disease progresses, resulting in increased pulmonary vascular resistance (PVR) and the development of pre-capillary PH.[55] PVR at rest, together with other haemodynamic markers of pulmonary vascular remodelling serve as poor prognostic indicator for long-term cardiovascular outcome.[56] Moreover, recent studies have identified a distinct phenotype within HFpEF, known as HFpEF with latent pulmonary vascular disease (PVD), which is characterized by having a normal resting PVR of <2 Wood units (WU) and a peak exercise PVR $>$ 1.74 WU during invasive haemodynamic testing.[57] In a study involving 86 HFpEF patients, latent PVD was identified in up to 21% of the cohort from supine exercise RHC.[58] These patients exhibited exercise limitations, impaired cardiac reserve and worse event-free survival compared with the overall HFpEF group.

Right HF and tricuspid regurgitation

HFpEF starts as a disease of the left heart but frequently ends with right HF. Right HF has been generally interpreted as an afterload-mediated event in HFpEF, secondary to severe PH with increased PVR, portending poor prognosis.[56] However, in recent years, it has become clear that also preload-mediated factors may contribute to right HF.[59]

From a haemodynamic perspective, not only PAWP, but also RAP is higher in HFpEF as compared with healthy controls and individuals with non-cardiac dyspnoea and generally doubles during exercise.[43] Thus, even when RA pressure is normal at rest, HFpEF patients may develop exercise-induced RA hypertension.[60] Exercise RA hypertension in HFpEF has been linked both to obesity with pericardial restraint due to excessive epicardial adipose tissue,[61] and to preload-related factors, including RA volume, stressed blood volume and the presence of severe TR.[60]

The development of permanent AF, frequently complicating HFpEF, may predispose to the above-mentioned alterations in preload. AF has been associated with volume overload, bi-atrial dilation and development of tricuspid regurgitation (TR), together with deterioration of echocardiographic metrics of RV function.[62,63] The tricuspid annulus lacks a strong fibrous support, thus facilitating its dilation in response to AF-mediated RA dilation, with consequent leaflet mal-coaptation and atrial-secondary TR.[64] Other potential mechanisms for TR development may include ventricular-functional TR, when severe PH complicates HFpEF, and TR secondary to leaflet interference due to cardiac implantable electronic devices.[65]

When severe TR develops, HFpEF patients may present with dysfunctional preload (higher stressed blood volume),[66] higher RA pressure at rest, higher ratio between RA pressure and PAWP, lower SV, lower LV transmural pressure and higher PVR, consistent with enhanced ventricular interdependence and pulmonary vascular and LV underfilling.[67] During supine exercise, they may display a steeper rise in RA pressure than in PAWP, blunted SV response and higher PVR.[67] In other words, enhanced interventricular dependence with low SV may impair LV filling in HFpEF, limiting the rate of increase of PAWP and of LV transmural pressure. At the same time, it may contribute to underfilling of the pulmonary vascular bed with resulting high PVR and a latent PVD profile.[58] The dependency of CO on chronotropic competence in this setting may suggest the opportunity of a less strict rate-control in HFpEF patients with TR, in line with the potential detrimental effects of beta-blockers in HFpEF.[68,69]

HFpEF haemodynamic phenotype-tailored therapy

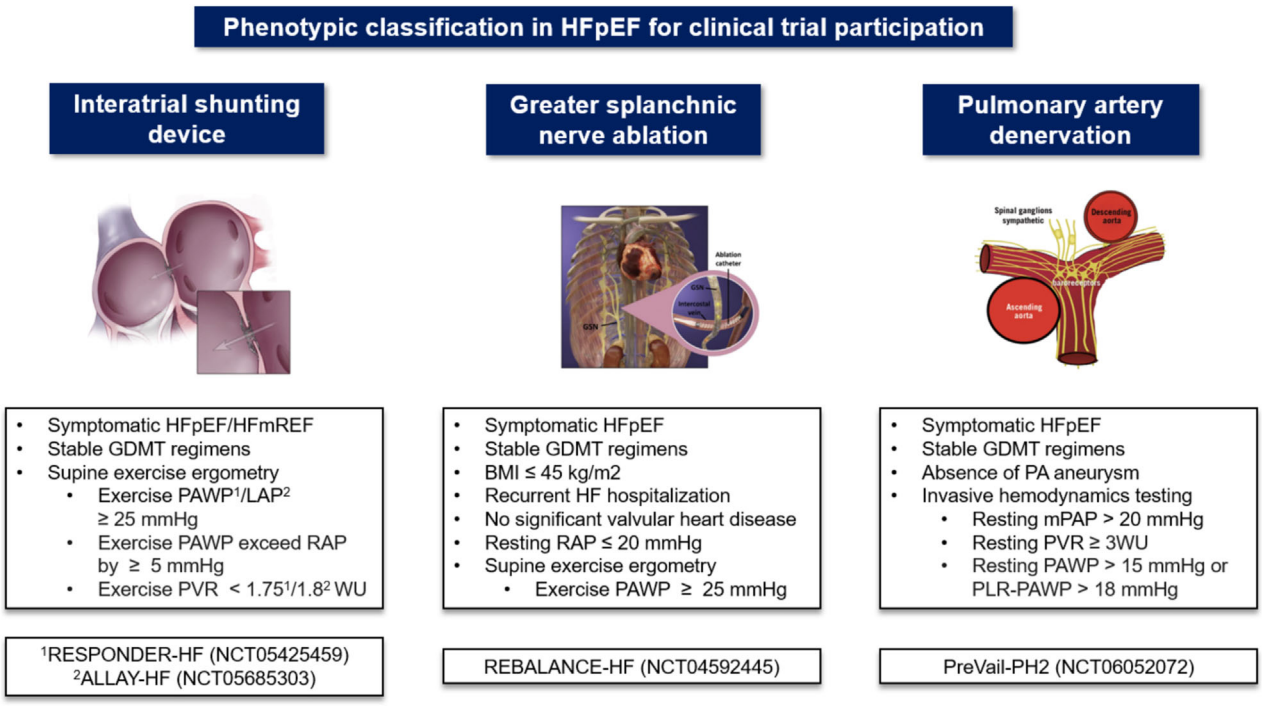
Given the limited effectiveness of pharmacological therapies in HFpEF, intervention-based therapies have emerged as a promising adjunctive approach, targeting structural and neurohormonal abnormalities that remain unaddressed by medications.[70,71] Therapeutic devices or interventions such as interatrial shunting, greater splanchnic nerve ablation and pulmonary artery denervation (PADN) require careful assessment through exercise invasive haemodynamic testing as shown in *Figure* 5. These novel strategies may improve outcomes in select patients and provide alternative options for better symptom control in those who refractory to medical treatment. Currently, most of these interventions are under clinical investigation and the invasive haemodynamic assessment plays a critical role in assessing the candidacy for clinical study participation.

Interatrial shunting devices

Several interatrial shunting devices, such as the Corvia shunt (Corvia Medical, Inc.), V-wave shunt (V-Wave Ltd.) and the no-implant shunt therapy (Alleviant Medical), have been developed to improve HF symptoms by offloading pressure from LA, hence lower PAWP, through artificially created left-to-right atrial shunt.[72] However, this redistribution comes with a trade-off of approximately a 25% increase in pulmonary blood flow, which may raise the risk of worsening PH and right-sided HF over time.[73] Therefore, in addition to confirming HFpEF with exercise haemodynamics testing (peak PAWP $\geq$ 25 mmHg), it is also crucial to assess the presence of a left-to-RAP gradient (exercise PAWP-RAP $\geq$ 5 mmHg) to ensure effective shunting while also minimizing the possibility of RV dysfunction or failure.

In the pivotal REDUCE LAP-HF II trial (A Study to Evaluate the Corvia Medical Inc. IASD System II to Reduce Elevated Left Atrial Pressure in Patients with Heart Failure), implantation of the Corvia shunting device in HF patients with EF $\geq$ 40% did not significantly impact the primary composite endpoint, which included cardiovascular death, stroke, HF events, and health status.[74] However, post-hoc analyses have revealed that HFpEF patients with latent PVD respond less favourably to atrial shunting therapy, experiencing worse outcomes such as increased HF event rates and poorer health status. In contrast, those without latent PVD demonstrated potential clinical benefits. This disparity may be due to a reduced left-to-RAP gradient or, in extreme circumstances, a reversal to right-to-left shunting in patients with latent PVD,

Figure 5 Phenotypic classification in HFpEF for clinical trial participation. RESPONDER-HF requires patients to have peak exercise PAWP $\geq$ 25 mmHg and exercise PVR $<$ 1.75 WU, while ALLAY-HF requires patients to have peak exercise LAP $\geq$ 25 mmHg and exercise PVR $<$ 1.8 WU. Abbreviations: BMI, body mass index; GDMT, guideline directed medical therapy; HF, heart failure; HFmREF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LAP, left atrial pressure; mPAP, mean pulmonary artery pressure; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; PLR, passive leg raising; PVR, pulmonary vascular resistance; RAP, right atrial pressure; WU, Wood unit.



resulting in less or non-effective shunting. These findings highlight the importance of exercise haemodynamic testing to phenotype those who benefit from advanced device-based therapy for HFpEF.

To address the challenge of latent PVD discovered in the REDUCE LAP-HF II trial, the ongoing RESPONDER-HF (Re-Evaluation of the Corvia Atrial Shunt Device in a Precision Medicine Trial to Determine Efficacy in Mildly Reduced or Preserved Ejection Fraction Heart Failure; NCT05425459) and ALLAY-HF (Safety and Efficacy of the Alleviant System for No-Implant Interatrial Shunt Creation in Patients with Chronic Heart Failure; NCT05685303) trials have been specifically designed.[7576] Both trials employ exercise haemodynamic testing to exclude HF patients with latent PVD, thus representing a critical step forward in refining the use of atrial shunt therapies.

Greater splanchnic nerve ablation

Greater splanchnic nerve ablation for volume management (SAVM) (Satera System, Axon Therapies) is based on the concept that exercise intolerance in HFpEF may partly result from inappropriate control of blood volume distribution.[77] Pathologic blood volume shifts into and out of the splanchnic vascular compartment can significantly alter cardiac haemodynamics and lead to sudden rises in LV filling pressures during exercise in those with HFpEF. By interrupting neural traffic through the right-sided greater splanchnic nerve, sympathetic activity to the splanchnic bed is reduced. This reduction may increase vascular compliance during exercise, lower pulmonary and cardiac filling pressures and improve exercise capacity. The REBALANCE-HF (Endovascular Ablation of the Right Greater Splanchnic Nerve in Subjects Having Heart Failure with Preserved Ejection Fraction: Feasibility Study; NCT04592445) is a phase 2, prospective, multicentre, randomized, double-blind, sham-controlled feasibility trial evaluating SAVM in patients with HFpEF who have peak exercise PAWP $\geq$ 25 mmHg.[78] The study demonstrated the safety of the SAVM, with a high likelihood of procedural success; however, no difference in the primary efficacy endpoint (reduction in legs-up and exercise PAWP at 1 month) between SAVM and sham group was observed. The exploratory responder analysis identified 47 of 90 randomized patients to be in the responder cohort. Interestingly, the responders tended to have lower E/A ratio (indicating less severe LV diastolic function), lower orthostatic pulse pressure change and greater ability to augment CO with exercise. Although participants in the responder group had no difference in PAWP change from baseline to 1 month between SAVM and sham, treatment with SAVM resulted in greater health status and exercise function at 12 months. Using haemodynamic profiles to identify responders for SAVM is critical for design and conduct of the confirmatory trial of SAVM in this population. It is also worth noting that that responsiveness to SAVM is closely tied to the capacity to maintain or increase CO during exercise or upon transitioning from supine to standing positions, evident through lower orthostatic pulse pressure change. This might suggest the importance of considering not only supine but also upright exercise haemodynamic data in the assessment of patient eligibility and treatment response.

Pulmonary artery denervation

PADN is being explored as a novel treatment for HF with combined pre- and post-capillary PH. In this population, increased LV filling pressure impairs the baroreflex mechanisms in the pulmonary arteries. This impaired baroreceptor reflex leads to pathological sympathetic stimulation, causing vasoconstriction and worsening PH. By reducing sympathetic activity, PADN aims to interrupt this reflex, decrease vasoconstriction and improve haemodynamics.[79–81] PreVail-PH2 trial [Pulmonary Artery DenerVation Clinical Study Using the Gradient Denervation System (Gradient Denervation Technologies) in Heart Failure Patients with Pulmonary Hypertension Group 2; NCT06052072] is a prospective, single-arm, multicentre study evaluating PADN in patients with EF $\geq$ 40%.[82] Participants must have a mean PAP $>$ 20 mmHg, PVR $\geq$ 3 WU at rest and PAWP $>$ 15 mmHg at rest or $>$18 mmHg with PLR. The trial aims to assess changes in PVR and evaluate the safety outcome of the procedure.

Haemodynamic monitoring in HFpEF

Remote PA monitoring plays a crucial role in the early detection of subclinical congestion, characterized by elevated LV filling pressures that occur weeks in advance before the onset of symptomatic decompensation.[83] This approach provides more sensitive indicators for predicting HF decompensation and guides decongestion therapy, which is particularly helpful for individuals with recurrent hospitalizations and those who experience fluctuations in volume status.

CardioMEMS HF System (Abbott) is an approved remote PAP monitoring device featuring an implanted wireless pressure sensor placed in the left pulmonary artery. It continuously measures systolic, diastolic and mean PAPs, as well as heart rate. Patients use a specialized pillow to remotely collect and automatically transmit these data to a secure database for review. This enables physicians to monitor PAP and, in turn, estimates cardiac filling pressures in real time, allowing for timely adjustments in HF treatment. The pivotal CHAMPION trial (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association Class III Heart Failure Patients) was a prospective, randomized, multicentre, single-blind study involving 550 HF patients with New York Heart Association class III across LVEF spectrum.[84] All participants had experienced HF hospitalization (HFH) within the previous year. The study found that HF management guided by the CardioMEMS system significantly reduced HFH at 6 months compared with the control

group, with a hazard ratio (HR) of 0.72 [95% confidence interval (CI) 0.60–0.85; $P = 0.002$]. In a prespecified subgroup of patients with LVEF greater than 50% (HFpEF), the reduction in HFH was more pronounced, with HR of 0.30 (95% CI 0.18–0.48; $P < 0.001$) over a 17.6 month follow-up.[85] Additionally, a meta-analysis of the three major RCTs comparing CardioMEMS versus control group confirmed a significant reduction in the combined endpoint of all-cause mortality, HF admissions and urgent HF events in patients with LVEF $>$ 40%.[86]

Current challenges and future considerations

Despite the recognized benefits of invasive exercise haemodynamic assessment in managing HFpEF, it is being used in routine clinical practice in a few specialized centres. This is primarily due to the need for specialized equipment, expertise and facilities capable of performing invasive exercise testing. These requirements impact the reproducibility of the test and highlight the necessity for well-developed infrastructure and expertise. Additionally, procedural approaches vary across institutions, including methods for obtaining PAWP readings, body positioning and diagnostic criteria. For example, while most centres measure PAWP at end-expiration, others average values over several respiratory cycles. Body positioning (supine vs. upright) also significantly affects cardiac preload, influencing resting and exercise haemodynamics, which may impact the accuracy of the diagnostic criteria and may not be used interchangeably.[43,53] Similarly, CO measurements validated using the Fick method as part of the current PAWP/CO criteria for HFpEF exercise haemodynamics may not be reliable when using thermodilution, as there is currently no supporting data for this comparison.[31] Additionally, preload failure, which mimics HFpEF and leads to exercise intolerance, can only be detected through upright exercise haemodynamic testing.[19] All of these factors affect the accuracy and generalizability of test results, emphasizing the need for standardized protocols to ensure reproducibility across laboratories.

To overcome these challenges, future efforts should focus on developing standardized workflows and achieving consensus to integrate invasive haemodynamic testing into routine clinical practice. Further studies are warranted to improve our understanding in the differences between testing in supine and upright positions. In the meantime, it is critical to consider testing in the upright position when there is a high suspicion for preload failure, although it is difficult to predict the scenario when HFpEF might mimic this condition. The standardization of invasive haemodynamic assessment is important not only for accurate diagnosis but also because emerging devices and interventions rely on data from invasive exercise haemodynamic testing to guide patient selection, ensuring the right individuals receive the right treatment.

Conflict of interest

Dr. Yaku received consulting fees from Omron. Dr. Gustafsson received consulting fees from Abbott, AstraZeneca, Pfizer, Ionis, Alnylam, Bayer, Boehringer-Ingelheim, FineHeart and Corwave. Dr Caravita received consulting fees from Alleviant and Janssen. Dr Fudim is supported by the NIH (1OT2HL156812-01; 1R01HL171305-01) and Doris Duke. He received consulting fees from Abbott, Ajax, Alio Health, Alleviant, Artha, Audicor, AxonTherapies, Bayer, Bodyguide, Bodyport, Boston Scientific, Broadview, Cadence, Cardioflow, Cardionomics, Coridea, CVRx, Daxor, Deerfield Catalyst, Edwards LifeSciences, Echosens, EKO, Feldschuh Foundation, Fire1, FutureCardia, Galvani, Gradient, Hatteras, HemodynamiQ, Impulse Dynamics, Intershunt, Medtronic, Merck, NIMedical, NovoNordisk, NucleusRx, NXT Biomedical, Orchestra, Pharmacosmos, PreHealth, Presidio, Procyreon, ReCor, Rockley, SCPharma, Shifamed, Splendo, Summacor, SyMap, Verily, Vironix, Viscardia and Zoll. All other authors have no relevant financial disclosures.

References

1. Shahim B, Kapelios CJ, Savarese G, Lund LH. Global public health burden of heart failure: an updated review. *Card Fail Rev* 2023;**9**:e11. doi:10.15420/cfr.2023.05
2. Bozkurt B, Ahmad T, Alexander KM, Baker WL, Bosak K, Breathett K, *et al*. Heart failure epidemiology and outcomes statistics: a report of the Heart Failure Society of America. *J Card Fail* 2023;**29**:1412-1451. doi:10.1016/j.cardfail.2023.07.006
3. Teramoto K, Teng T-HK, Chandramouli C, Tromp J, Sakata Y, Lam CSP. Epidemiology and clinical features of heart failure with preserved ejection fraction. *Card Fail Rev* 2022;**8**:e27. doi:10.15420/cfr.2022.06
4. Kapłon-Cieślicka A, Kupczyńska K, Dobrowolski P, Michalski B, Jaguszewski MJ, Banasiak W, *et al*. On the search for the right definition of heart failure with preserved ejection fraction. *Cardiol J* 2020;**27**:449-468. doi:10.5603/CJ.a2020.0124
5. Verbrugge FH, Omote K, Reddy YNV, Sorimachi H, Obokata M, Borlaug BA. Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. *Eur Heart J* 2022;**43**:1941-1951. doi:10.1093/eurheartj/ehab911
6. Baratto C, Caravita S, Soranna D, Faini A, Dewachter C, Zambon A, *et al*. Current limitations of invasive exercise hemodynamics for the diagnosis of heart failure with preserved ejection fraction. *Circ Heart Fail* 2021;**14**:e007555.

doi:10.1161/CIRCHEARTFAILURE.120.007555
7. Mancusi C, Basile C, Spaccarotella C, Gargiulo G, Fucile I, Paolillo S, *et al*. Novel strategies in diagnosing heart failure with preserved ejection fraction: a comprehensive literature review. *High Blood Press Cardiovasc Prev Off J Ital Soc Hypertens* 2024;**31**:127-140. doi:10.1007/s40292-024-00629-1
8. Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart failure with preserved ejection fraction: JACC scientific statement. *J Am Coll Cardiol* 2023;**81**:1810-1834. doi:10.1016/j.jacc.2023.01.049
9. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2014;**11**:507-515. doi:10.1038/nrcardio.2014.83
10. Gevaert AB, Boen JRA, Segers VF, Van Craenenbroeck EM. Heart failure with preserved ejection fraction: a review of cardiac and noncardiac pathophysiology. *Front Physiol* 2019;**10**:638. doi:10.3389/fphys.2019.00638
11. Harada T, Tada A, Borlaug BA. Imaging and mechanisms of heart failure with preserved ejection fraction: a state of the art review. *Eur Heart J Cardiovasc Imaging* 2024;jeae152. doi:10.1093/ehjci/jeae152
12. Ohara T, Niebel CL, Stewart KC, Charonko JJ, Pu M, Vlachos PP, *et al*. Loss of adrenergic augmentation of diastolic intra-LV pressure difference in patients with diastolic dysfunction: evaluation by color M-mode echocardiography. *JACC Cardiovasc Imaging* 2012;**5**:861-870. doi:10.1016/j.jcmg.2012.05.013
13. Reddy YNV, Obokata M, Egbe A, Yang JH, Pislaru S, Lin G, *et al*. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. *Eur J Heart Fail* 2019;**21**:891-900. doi:10.1002/ejhf.1464
14. Reddy YNV, El-Sabbagh A, Nishimura RA. Comparing pulmonary arterial wedge pressure and left ventricular end diastolic pressure for assessment of left-sided filling pressures. *JAMA Cardiol* 2018;**3**:453-454. doi:10.1001/jamacardio.2018.0318
15. Baratto C, Faini A, Gallone GP, Dewachter C, Perego GB, Bondue A, *et al*. Pulmonary artery wedge pressure and left ventricular end-diastolic pressure during exercise in patients with dyspnoea. *ERJ Open Res* 2023;**9**:750-2022. doi:10.1183/23120541.00750-2022
16. Freed BH, Daruwalla V, Cheng JY, Aguilar FG, Beussink L, Choi A, *et al*. Prognostic utility and clinical significance of cardiac mechanics in heart failure with preserved ejection fraction: importance of left atrial strain. *Circ Cardiovasc Imaging* 2016;**9**:e003754. doi:10.1161/CIRCIMAGING.115.003754
17. Guazzi M, Wilhelm M, Halle M, van Craenenbroeck E, Kemps H, de Boer RA, *et al*. Exercise testing in heart failure with preserved ejection fraction: an appraisal through diagnosis, pathophysiology and therapy—a clinical consensus statement of the Heart Failure Association and European Association of Preventive Cardiology of the European Society of Cardiology. *Eur J Heart Fail* 2022;**24**:1327-1345. doi:10.1002/ejhf.2601
18. Houstis NE, Eisman AS, Pappagianopoulos PP, Wooster L, Bailey CS, Wagner PD, *et al*. Exercise intolerance in heart failure with preserved ejection fraction: diagnosing and ranking its causes using personalized O_2 pathway analysis. *Circulation* 2018;**137**:148-161. doi:10.1161/CIRCULATIONAHA.117.029058
19. Fudim M, Sobotka PA, Dunlap ME. Extracardiac abnormalities of preload reserve: mechanisms underlying exercise limitation in heart failure with preserved ejection fraction, autonomic dysfunction, and liver disease. *Circ Heart Fail* 2021;**14**:e007308. doi:10.1161/CIRCHEARTFAILURE.120.007308
20. Phan TT, Shivu GN, Abozguia K, Davies C, Nassimizadeh M, Jimenez D, *et al*. Impaired heart rate recovery and chronotropic incompetence in patients with heart failure with preserved ejection fraction. *Circ Heart Fail* 2010;**3**:29-34. doi:10.1161/CIRCHEARTFAILURE.109.877720
21. Pandey A, Khera R, Park B, Haykowsky M, Borlaug BA, Lewis GD, *et al*. Relative impairments in hemodynamic exercise reserve parameters in heart failure with preserved ejection fraction: a study-level pooled analysis. *JACC Heart Fail* 2018;**6**:117-126. doi:10.1016/j.jchf.2017.10.014
22. Obokata M, Reddy YNV, Borlaug BA. Diastolic dysfunction and heart failure with preserved ejection fraction: understanding mechanisms with non-invasive methods. *JACC Cardiovasc Imaging* 2020;**13**:245-257. doi:10.1016/j.jcmg.2018.12.034
23. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 2018;**138**:861-870. doi:10.1161/CIRCULATIONAHA.118.034646
24. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, *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**:3297-3317. doi:10.1093/eurheartj/ehz641
25. Vaishnav J, Sharma K. A stepwise guide to the diagnosis and treatment of heart failure with preserved ejection fraction. *J Card Fail* 2022;**28**:1016-1030. doi:10.1016/j.cardfail.2021.12.013
26. Sanders-van S, Barandiarán A, Brunner-la HP, Henkens M, Weerts J, Knackstedt C, *et al*. The HFA-PEFF and H2 FPEF scores largely disagree in classifying patients with suspected heart failure with preserved ejection fraction. *Eur J Heart Fail* 2021;**23**:838-840. doi:10.1002/ejhf.2019
27. Reddy YNV, Kaye DM, Handoko ML, van de Bovenkamp AA, Tedford RJ, Keck C, *et al*. Diagnosis of heart failure with preserved ejection fraction among patients with unexplained dyspnea. *JAMA Cardiol* 2022;**7**:891-899. doi:10.1001/jamacardio.2022.1916
28. Fernandes-Silva MM. Diagnostic scores in heart failure with preserved ejection fraction. *ABC Heart Fail Cardiomyopathy* 2022;**2**:275-280. doi:10.36660/abchf.20220057
29. Kittleson MM, Panjrath GS, Amancherla K, Davis LL, Deswal A, Dixon DL, *et al*. 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol* 2023;**81**:1835-1878. doi:10.1016/j.jacc.2023.03.393
30. Hsu S, Fang JC, Borlaug BA. Hemodynamics for the heart failure clinician: a state-of-the-art review. *J Card Fail* 2022;**28**:133-148. doi:10.1016/j.cardfail.2021.07.012
31. Finet JE, Van Iterson EH, Wilson Tang WH. Invasive hemodynamic and metabolic evaluation of HFpEF. *Curr Treat Options Cardiovasc Med* 2021;**23**:32. doi:10.1007/s11936-021-00904-7
32. Rosenkranz S, Preston IR. Right heart catheterisation: best practice and pitfalls in pulmonary hypertension. *Eur Respir Rev* 2015;**24**:642-652. doi:10.1183/16000617.0062-2015
33. van de Bovenkamp AA, Wijkstra N, Oosterveer FPT, Vonk Noordegraaf A, Bogaard HJ, van Rossum AC, *et al*. The value of passive leg raise during right heart catheterization in diagnosing heart failure with preserved ejection fraction. *Circ Heart Fail* 2022;**15**:e008935. doi:10.1161/CIRCHEARTFAILURE.121.008935
34. Rajagopalan N, Borlaug BA, Bailey AL, Eckman PM, Guglin M, Hall S, *et al*. Practical guidance for hemodynamic assessment by right heart catheterization in management of heart failure. *JACC Heart Fail* 2024;**12**:1141-1156. doi:10.1016/j.jchf.2024.03.020
35. Borlaug BA, Nishimura RA, Sorajja P, Lam CSP, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail* 2010;**3**:588-595. doi:10.1161/CIRCHEARTFAILURE.109.930701
36. Thadani U, Parker JO. Hemodynamics at rest and during supine and sitting bicycle exercise in normal subjects. *Am J Cardiol* 1978;**41**:52-59. doi:10.1016/0002-9149(78)90131-5

37. Dorfs S, Zeh W, Hochholzer W, Jander N, Kienzle RP, Pieske B, *et al*. Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction. *Eur Heart J* 2014;**35**:3103-3112. doi:10.1093/eurheartj/ehu315
38. Omote K, Verbrugge FH, Sorimachi H, Omar M, Popovic D, Obokata M, *et al*. Central haemodynamic abnormalities and outcome in patients with unexplained dyspnoea. *Eur J Heart Fail* 2023;**25**:185-196. doi:10.1002/ejhf.2747
39. Ho JE, Zern EK, Wooster L, Bailey CS, Cunningham T, Eisman AS, *et al*. Differential clinical profiles, exercise responses, and outcomes associated with existing HFpEF definitions. *Circulation* 2019;**140**:353-365. doi:10.1161/CIRCULATIONAHA.118.039136
40. Naeije R, Vanderpool R, Dhakal BP, Saggar R, Saggar R, Vachiery JL, *et al*. Exercise-induced pulmonary hypertension: physiological basis and methodological concerns. *Am J Respir Crit Care Med* 2013;**187**:576-583. doi:10.1164/rccm.201211-2090CI
41. Wolsk E, Bakkestrøm R, Thomsen JH, Balling L, Andersen MJ, Dahl JS, *et al*. The influence of age on hemodynamic parameters during rest and exercise in healthy individuals. *JACC Heart Fail* 2017;**5**:337-346. doi:10.1016/j.jchf.2016.10.012
42. Eisman AS, Shah RV, Dhakal BP, Pappagianopoulos PP, Wooster L, Bailey C, *et al*. Pulmonary capillary wedge pressure patterns during exercise predict exercise capacity and incident heart failure. *Circ Heart Fail* 2018;**11**:e004750. doi:10.1161/CIRCHEARTFAILURE.117.004750
43. Baratto C, Caravita S, Soranna D, Dewachter C, Bondue A, Zambon A, *et al*. Exercise haemodynamics in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *ESC Heart Fail* 2022;**9**:3079-3091. doi:10.1002/ehf2.13979
44. Kovacs G, Avian A, Pienn M, Naeije R, Olschewski H. Reading pulmonary vascular pressure tracings. How to handle the problems of zero leveling and respiratory swings. *Am J Respir Crit Care Med* 2014;**190**:252-257. doi:10.1164/rccm.201402-0269PP
45. Montané B, Tonelli AR, Arunachalam A, Bhattacharyya A, Li M, Wang X, *et al*. Hemodynamic responses to provocative maneuvers during right heart catheterization. *Ann Am Thorac Soc* 2022;**19**:1977-1985. doi:10.1513/AnnalsATS.202201-077OC
46. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, *et al*. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2023;**61**:2200879. doi:10.1183/13993003.00879-2022
47. Berlier C, Saxer S, Lichtblau M, Schneider SR, Schwarz EI, Furian M, *et al*. Influence of upright versus supine position on resting and exercise hemodynamics in patients assessed for pulmonary hypertension. *J Am Heart Assoc Cardiovasc Cerebrovasc Dis* 2022;**11**:e023839. doi:10.1161/JAHA.121.023839
48. Yaku H, Fudim M, Shah S. Role of splanchnic circulation in the pathogenesis of heart failure: state-of-the-art review. *J Cardiol* 2024;**83**:330-337. doi:10.1016/j.jjcc.2024.02.004
49. Olufsen MS, Ottesen JT, Tran HT, Ellwein LM, Lipsitz LA, Novak V. Blood pressure and blood flow variation during postural change from sitting to standing: model development and validation. *J Appl Physiol Bethesda Md* 2005;**99**:1523-1537. doi:10.1152/japplphysiol.00177.2005
50. Rao VN, Kelsey MD, Blazing MA, Pagidipati NJ, Fortin TA, Fudim M. Unexplained dyspnea on exertion: The difference the right test can make. *Circ Heart Fail* 2022;**15**:e008982. doi:10.1161/CIRCHEARTFAILURE.121.008982
51. Oldham WM, Lewis GD, Opotowsky AR, Waxman AB, Systrom DM. Unexplained exertional dyspnea caused by low ventricular filling pressures: results from clinical invasive cardiopulmonary exercise testing. *Pulm Circ* 2016;**6**:55-62. doi:10.1086/685054
52. Tooba R, Mayuga KA, Wilson R, Tonelli AR. Dyspnea in chronic low ventricular preload states. *Ann Am Thorac Soc* 2021;**18**:573-581. doi:10.1513/AnnalsATS.202005-581CME
53. Kirupaharan P, Lane J, Melillo C, Paul D, Amoushref A, Abdi SA, *et al*. Impact of body position on hemodynamic measurements during exercise: a tale of two bikes. *Pulm Circ* 2024;**14**:e12334. doi:10.1002/pul2.12334
54. Baratto C, Caravita S, Vachiéry J-L. Pulmonary hypertension associated with left heart disease. *Semin Respir Crit Care Med* 2023;**44**:810-825. doi:10.1055/s-0043-1772754
55. Fayyaz AU, Edwards WD, Maleszewski JJ, Konik EA, DuBrock HM, Borlaug BA, *et al*. Global pulmonary vascular remodeling in pulmonary hypertension associated with heart failure and preserved or reduced ejection fraction. *Circulation* 2018;**137**:1796-1810. doi:10.1161/CIRCULATIONAHA.117.031608
56. Baratto C, Caravita S, Soranna D, Dewachter C, Bondue A, Zambon A, *et al*. An updated meta-analysis of hemodynamics markers of prognosis in patients with pulmonary hypertension due to left heart disease. *Pulm Circ* 2022;**12**:e12145. doi:10.1002/pul2.12145
57. Borlaug BA, Blair J, Bergmann MW, Bugger H, Burkhoff D, Bruch L, *et al*. Latent pulmonary vascular disease may Alter the response to therapeutic atrial shunt device in heart failure. *Circulation* 2022;**145**:1592-1604. doi:10.1161/CIRCULATIONAHA.122.059486
58. Caravita S, Baratto C, Filippo A, Soranna D, Dewachter C, Zambon A, *et al*. Shedding light on latent pulmonary vascular disease in heart failure with preserved ejection fraction. *JACC Heart Fail* 2023;**11**:1427-1438. doi:10.1016/j.jchf.2023.03.003
59. Caravita S, Iacovoni A, Senni M. The right side of the circulation in not secondary heart failure with preserved ejection fraction: an elephant in the room? *Eur J Heart Fail* 2021;**23**:1659-1661. doi:10.1002/ejhf.2294
60. Baratto C, Caravita S, Dewachter C, Faini A, Perego B, Bondue A, *et al*. Right heart adaptation to exercise in pulmonary hypertension: an invasive hemodynamic study. *J Card Fail* 2023;**29**:1261-1272. doi:10.1016/j.cardfail.2023.04.009
61. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation* 2017;**136**:6-19. doi:10.1161/CIRCULATIONAHA.116.026807
62. Hahn RT, Lindenfeld J, Böhm M, Edelmann F, Lund LH, Lurz P, *et al*. Tricuspid regurgitation in patients with heart failure and preserved ejection fraction: JACC state-of-the-art review. *J Am Coll Cardiol* 2024;**84**:195-212. doi:10.1016/j.jacc.2024.04.047
63. Obokata M, Reddy YNV, Melenovsky V, Pislaru S, Borlaug BA. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction. *Eur Heart J* 2019;**40**:689-697. doi:10.1093/eurheartj/ehy809
64. Florescu DR, Muraru D, Florescu C, Volpato V, Caravita S, Perger E, *et al*. Right heart chambers geometry and function in patients with the atrial and the ventricular phenotypes of functional tricuspid regurgitation. *Eur Heart J Cardiovasc Imaging* 2022;**23**:930-940. doi:10.1093/ehjci/jeab211
65. Davidson LJ, Tang GHL, Ho EC, Fudim M, Frisoli T, Camaj A, *et al*. The tricuspid valve: a review of pathology, imaging, and current treatment options: a scientific statement from the American Heart Association. *Circulation* 2024;**149**:e1223-e1238. doi:10.1161/CIR.0000000000001232
66. Rommel K-P, Besler C, Unterhuber M, Kresoja KP, Noack T, Kister T, *et al*. Stressed blood volume in severe tricuspid regurgitation: implications for transcatheter treatment. *JACC Cardiovasc Interv* 2023;**16**:2245-2258. doi:10.1016/j.jcin.2023.07.040
67. Baratto C, Caravita S, Corbetta G, Soranna D, Zambon A, Dewachter C, *et al*. Impact of severe secondary tricuspid regurgitation on rest and exercise hemodynamics of patients with heart failure and a preserved left ventricular

ejection fraction. *Front Cardiovasc Med* 2023;**10**:1061118. doi:10.3389/fcvm.2023.1061118
68. Silverman DN, Plante TB, Infeld M, Callas PW, Juraschek SP, Dougherty GB, *et al*. Association of β-blocker use with heart failure hospitalizations and cardiovascular disease mortality among patients with heart failure with a preserved ejection fraction: a secondary analysis of the TOPCAT trial. *JAMA Netw Open* 2019;**2**:e1916598. doi:10.1001/jamanetworkopen.2019.16598
69. Palau P, Seller J, Domínguez E, Sastre C, Ramón JM, de la Espriella R, *et al*. Effect of β-blocker withdrawal on functional capacity in heart failure and preserved ejection fraction. *J Am Coll Cardiol* 2021;**78**:2042-2056. doi:10.1016/j.jacc.2021.08.073
70. Salah HM, Levin AP, Fudim M. Device therapy for heart failure with preserved ejection fraction. *Cardiol Clin* 2022;**40**:507-515. doi:10.1016/j.ccl.2022.06.005
71. Wu Y, Song M, Wu M, Lin L. Advances in device-based treatment of heart failure with preserved ejection fraction: evidence from clinical trials. *ESC Heart Fail* 2024;**11**:13-27. doi:10.1002/ehf2.14562
72. Jagadeesan V, Gray WA, Shah SJ. Atrial shunt therapy for heart failure: an update. *J Soc Cardiovasc Angiogr Interv* 2023;**2**:101203. doi:10.1016/j.jscai.2023.101203
73. Obokata M, Reddy YNV, Shah SJ, Kaye DM, Gustafsson F, Hasenfuß G, *et al*. Effects of interatrial shunt on pulmonary vascular function in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2019;**74**:2539-2550. doi:10.1016/j.jacc.2019.08.1062
74. Shah SJ, Borlaug BA, Chung ES, Cutlip DE, Debonnaire P, Fail PS, *et al*. Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): a randomised, multicentre, blinded, sham-controlled trial. *Lancet Lond Engl* 2022;**399**:1130-1140. doi:10.1016/S0140-6736(22)00016-2
75. Study details|RESPONDER-HF Trial ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05425459. Accessed 13 Sep 2024.
76. Study details|Alleviant ALLAY-HF Study|ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05685303. Accessed 13 Sep 2024.
77. Fudim M, Engelman ZJ, Reddy VY, Shah SJ. Splanchnic nerve ablation for volume management in heart failure. *JACC Basic Transl Sci* 2022;**7**:319-321. doi:10.1016/j.jacbts.2022.02.005
78. Fudim M, Borlaug BA, Mohan RC, Price MJ, Fail P, Goyal P, *et al*. Endovascular ablation of the greater splanchnic nerve in heart failure with preserved ejection fraction: The REBALANCE-HF randomized clinical trial. *JAMA Cardiol* 2024;e242612. doi:10.1001/jamacardio.2024.2612
79. Chen S-L, Zhang F-F, Xu J, Xie DJ, Zhou L, Nguyen T, *et al*. Pulmonary artery denervation to treat pulmonary arterial hypertension: the single-center, prospective, first-in-man PADN-1 study (first-in-man pulmonary artery denervation for treatment of pulmonary artery hypertension). *J Am Coll Cardiol* 2013;**62**:1092-1100. doi:10.1016/j.jacc.2013.05.075
80. Salazar AM, al-Asad K, Prasad RM, Panama G, Banga S, Wilcox M. Pulmonary artery denervation as a new therapeutic option for pulmonary hypertension: a systematic review and meta-analysis. *Curr Probl Cardiol* 2023;**48**:101776. doi:10.1016/j.cpcardiol.2023.101776
81. Rothman AMK, Vachiery J-L, Howard LS, Mikhail GW, Lang IM, Jonas M, *et al*. Intravascular ultrasound pulmonary artery denervation to treat pulmonary arterial hypertension (TROPHY1): multicenter, early feasibility study. *JACC Cardiovasc Interv* 2020;**13**:989-999. doi:10.1016/j.jcin.2019.12.027
82. Study details|Pulmonary artery denervation clinical study using the gradient denervation system in heart failure patients with pulmonary hypertension group 2 (PreVail-PH2 study)|ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06052072. Accessed 13 Sep 2024.
83. Veenis JF, Brugts JJ. Remote monitoring of chronic heart failure patients: invasive versus non-invasive tools for optimising patient management. *Neth Heart J* 2020;**28**:3-13. doi:10.1007/s12471-019-01342-8
84. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, *et al*. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet Lond Engl* 2011;**377**:658-666. doi:10.1016/S0140-6736(11)60101-3
85. Adamson PB, Abraham WT, Bourge RC, Costanzo MR, Hasan A, Yadav C, *et al*. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. *Circ Heart Fail* 2014;**7**:935-944. doi:10.1161/CIRCHEARTFAILURE.113.001229
86. Clephas PRD, Radhoe SP, Boersma E, Gregson J, Jhund PS, Abraham WT, *et al*. Efficacy of pulmonary artery pressure monitoring in patients with chronic heart failure: a meta-analysis of three randomized controlled trials. *Eur Heart J* 2023;**44**:3658-3668. doi:10.1093/eurheartj/ehad346