Issue 4 | 2019-20

Access the content online at:
http://collections.medengine.com/cardiology/best-of-heart-failure/

Best of Heart Failure

LUMINARY EDUCATION

- Recently Approved Pharmacologic Agents to Improve Outcomes in Heart Failure
- New Perspectives and Future Directions in the Treatment of Heart Failure
- Usefulness and Clinical Relevance of Left Ventricular Global Longitudinal Systolic Strain in Patients with Heart Failure with Preserved Ejection Fraction
- Heart Failure with Preserved Ejection Fraction: the Missing Pieces in Diagnostic Imaging
- Current Challenges in Sudden Cardiac Death Prevention

CONNECT THE DOTS

- Subclinical Hypothyroidism and the Development of Heart Failure: an Overview of Risk and Effects on Cardiac Function
- Pulmonary Hypertension in Advanced Heart Failure: assessment and Management of the Failing RV and LV

Springer Healthcare Education

Vasodilating β blocker that

Understands the heart better

cardivas

(Carvedilol Tablets 3.125/6.25/12.5/25 mg)

THE RIGHT CHOICE for Improved Survival

In Heart Failure

Inapure

Ivabradine Tablets 5 mg

Control Heart Rate In a Pure Way

Best of Heart Failure

Contents

Step by step procedure for online viewing:

1. Go to http://collections.medengine.com/cardiology/best-of-heart-failure/ or scan QR code.
2. Web page of the issue will open on the screen.
3. View and read the PDF version online.
4. The PDF file can be downloaded too for offline reading.

October 2019

Springer Healthcare

This edition is published by Springer Nature India Private Limited.

Registered Office: 7th Floor, Vijaya Building, 17, Barakhamba Road, New Delhi 110 001, India.
T: +91 11 4575 5888
www.springerhealthcare.com

Part of the Springer Nature group

Printed & bound by: Balaji Art, India.

Recently Approved Pharmacologic Agents to Improve Outcomes in Heart Failure

David C. Booth and Navin Rajagopalan

Introduction and Background

Over the past 5 years, two novel FDA-approved agents for the treatment of heart failure have been introduced, the angiotensin receptor-neprilysin inhibitor (ARNi), sacubitril/valsartan (Entresto), and the funny current (I_f) inhibitor ivabradine (Corlanor). Prior to the approval of these agents, hemodynamic optimization – using vasodilators including hydralazine and isosorbide [1, 4, 5] – and neuro-humoral inhibition, combining angiotensin-converting enzyme inhibition, ß-blockade, and mineralocorticoid-receptor antagonism [2, 3, 6–11], have been the evidence-based pharmaceutical approaches to improve outcome in chronic systolic heart failure. The majority of the agents tested in the referenced trials rested on a background of proven hemodynamic benefit. There is a relative paucity of published hemodynamic data for sacubitril/valsartan and ivabradine, as randomized trials for these agents in systolic heart failure have been endpoint-driven. This chapter summarizes the outcome data, quality of life results, and available hemodynamic data for these two drugs. Other modalities which have been shown to improve survival in systolic heart failure include the implantable cardioverter defibrillator, cardiac resynchronization therapy, and left ventricular assist device implantation, but these are not discussed here.

Rationale and Research Leading to Sacubitril/Valsartan

Heart failure activates the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS), leading to vasoconstriction and increased sympathetic tone, in turn resulting in downregulation of the ß-receptors. Activation of RAAS leads to increased secretion of angiotensin II and aldosterone, which also results in increased ADH secretion. These neurohormonal maladaptations result in fluid retention, perpetuating the cycle of heart failure. ACE inhibition, or angiotensin receptor blockade, ß-blockade, and mineralocorticoid antagonism modulate the effects of the SNS and RAAS.

Since the early 1980s, the natriuretic peptide system (NPS) began to receive attention as a potential target in heart failure treatment. Within the NPS are three hormones, atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP),

D. C. Booth (✉)
The Gill Heart and Vascular Institute, University of Kentucky Medical Center, Lexington, KY, USA
e-mail: dcbooth@email.uky.edu

N. Rajagopalan
Heart Failure/Cardiac Transplant Program, The Gill Heart and Vascular Institute, Lexington, KY, USA
e-mail: n.rajagopalan@uky.edu

A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_8

and C-type atrial natriuretic peptide (CNP). While CNP is secreted from endothelial cells and cardiac fibroblasts and has vasodilatory and anti-remodeling effects, ANP and BNP are secreted, respectively, from the atria and the ventricles, are released in response to fiber stretch and volume overload and promote diuresis, natriuresis, and vasodilation, counteracting the maladaptive effects of SNS and RAAS activation [12]. With the development of angiotensin receptor blockers, which exert their effects primarily at the Type 1 angiotensin II receptor, there was hope that a more specific RAAS antagonist would result in further survival improvement in heart failure outcomes. However, while the Valsartan Heart Failure Trial (Val HeFT) [13] (2001) demonstrated reduced heart failure hospitalizations, leading to an FDA-approved indication in heart failure, overall mortality in the valsartan and placebo groups was similar. The demonstration of the beneficial effects of the natriuretic peptides led to the development of human recombinant BNP, namely nesiritide, which was FDA-approved for use in 2001 on the basis of improvement in dyspnea in decompensated heart failure. However, a larger randomized trial released in 2011, the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) [14], demonstrated no improvement in dyspnea, 30-day mortality, or readmission rates in the nesiritide group. Hypotension was significant in the nesiritide group. As a result, nesiritide is used rarely in practice today, but natriuretic peptide levels remain well established as biomarkers.

Research efforts have been directed at toward identifying agents that could inhibit the enzyme that breaks down endogenous natriuretic peptides, namely, neprilysin. Neprilysin (NEP) is a neutral endopeptidase, and its inhibition increases bioavailability of natriuretic peptides, bradykinin, and substance P, resulting in natriuretic, vasodilatatory, and anti-proliferative effects. The natural hypothesis was that combined inhibition of the RAAS and NEP would result in a better heart failure treatment (Fig. 8.1). This led to the development of omapatrilat, a combined ACEi/NEPi. Several trials of the agent were conducted in heart failure, culminating in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) Trial [15] in patients with NYHA Functional Class II–IV heart failure. While post hoc analyses appeared to demonstrate potential benefit, there was an increased incidence of life-threatening angioedema, which was substantiated in a subsequent study of the agent in hypertension. These results effectively thwarted ACEi-NPi as a treatment in heart failure.

An important advantage of ARBs over ACE is is that ARBs do not block the degradation of bradykinin, the principal instigator of cough, a side effect noted in at least 10% of patients on an ACE, and do not cause angioedema which can occur in about 0.1% of patients on an ACE [16]. Omapatrilat was subsequently demonstrated to inhibit an enzyme responsible for bradykinin metabolism. A logical solution to the adverse effects of omapatrilat was to combine an ARB with an NEPi, termed ARNI or angiotensin receptor-neprilysin inhibitor – LCZ696, Sacubitril/Valsartan. Sacubitril is a prodrug which is converted in the body to sacubitrilat, which inhibits neprilysin and thereby the degradation of NPs. A Phase III trial [17] published in 2010 comparing sacubitril/valsartan to valsartan showed greater reduction in systolic, diastolic, and pulse pressures with sacubitril/valsartan. The Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction (PARAMOUNT) Trial [18], published in 2012 was a Phase II randomized trial that assessed NT-proBNP after 12 weeks of sacubitril/valsartan compared to valsartan in patients with heart failure with preserved left ventricular ejection fraction (HFpEF). At 12 weeks, NT-proBNP was significantly lower in the sacubitril/valsartan group, and an echocardiographic reduction in left atrial volume and size was also demonstrated. The NT-proBNP lowering effect appeared to be independent of a blood pressure lowering effect of the drug.

Published in 2014, the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial randomized 8399 patients with HFrEF (LVEF $\leq$40%) and NYHA Class II–IV symptoms to sacubitril/valsartan 200 mg PO BID or enalapril 10 mg PO BID (the

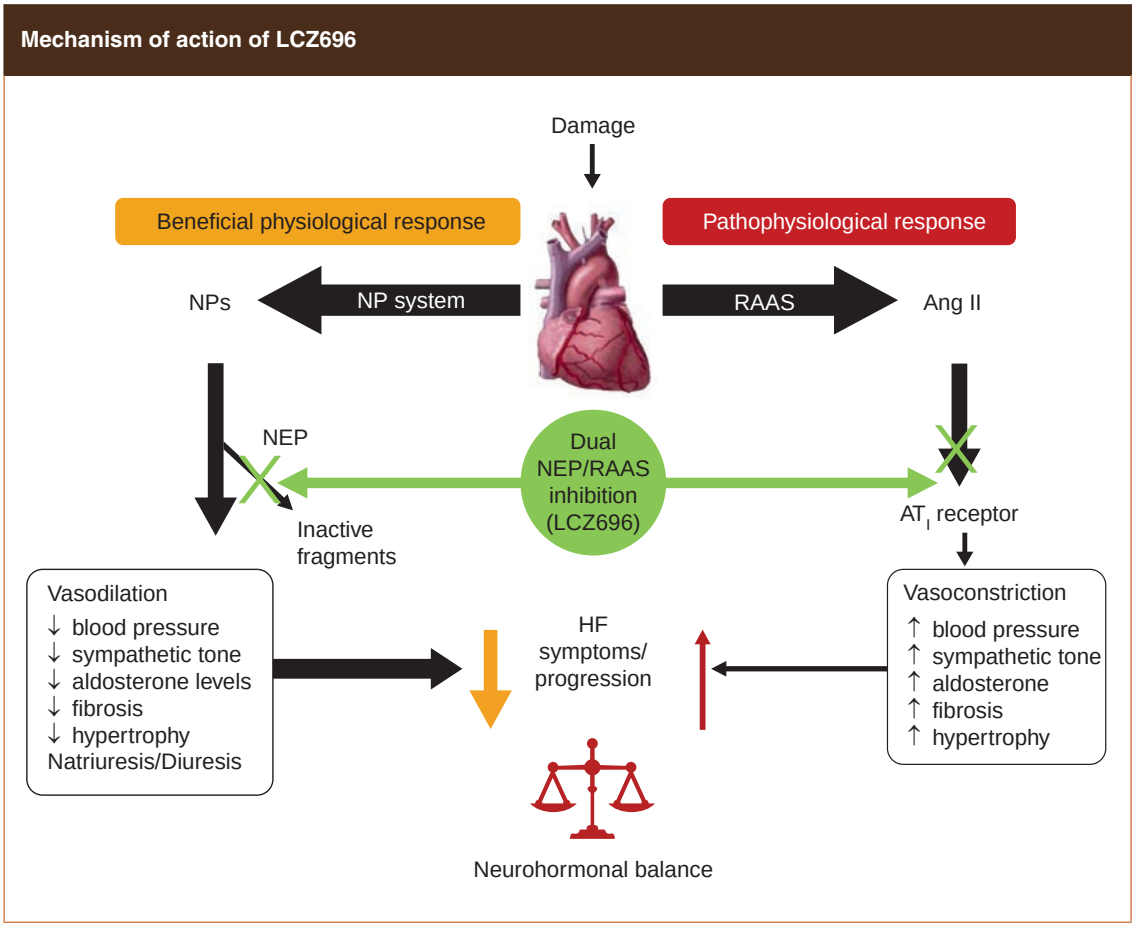


Fig. 8.1 Angiotensin receptor-neprilysin inhibitors have the potential to modulate two counter-regulatory neurohormonal systems in HF: the renin-angiotensin-aldosterone system and natriuretic peptide system. ANG angiotensin, AT1 angiotensin type 1, HF heart failure, NP natriuretic peptide, RAAS renin-angiotensin-aldosterone system. (Indian Heart Journal Volume 70, Supplement 1, July 2018, Pages S102–S110)

goal dose from CONSENSUS and SOLVD), in addition to standard therapy for chronic systolic heart failure. The majority of the study population was receiving ß-blockers and mineralocorticoid antagonists. The primary end point of the trial was the combination of death from cardiovascular causes and heart failure hospitalization. There being insufficient Phase II safety data for sacubitril/valsartan, the PARADIGM protocol stipulated safety and tolerability run-ins for all participants in the trial. If participants tolerated both sacubitril/valsartan and enalapril, they were randomly assigned to the two study arms. This approach allowed assessment not only of the end point of the trial but also provided safety and tolerability data. The study was stopped early, after median follow-up of 27 months, when the study met the prespecified cutoff for significant benefit. The ARNI combination resulted in a 20% decrease in the primary end point, HR = 0.80, $P < 0.001$, giving a Number Needed to Treat of 21. The study drug also reduced the individual components of the combined end point, death from cardiovascular cause by 20% and heart failure hospitalizations by 21%, both $p < 0.001$. All-cause mortality in the sacubitril/valsartan arm was reduced by 16%, HR = 0.84, $p < 0.001$. While sacubitril/valsartanb resulted in 14% experiencing hypotension as compared to 9% in the enalapril arm, the discontinuation rate was not significantly different (sacubitril/valsartan 0.9%, enalapril 0.7%). No significant difference was noted in the occurrence of non-serious angioedema between the two groups.

In secondary analyses, sacubitril/valsartan demonstrated clinical benefits in other indices of heart failure progression, including improved NYHA class, reduced need for intensification of medical treatment, and reduction in the need for emergency department visits, intensive care, and inotropic support. Other findings from PARADIGM-HF include significantly lower NT-proBNP and troponin levels in the sacubitril/valsartan group, significant reduction in the incidence of sudden cardiac death and death from worsening heart failure independent of cardioverter defibrillation implantation, and a nonsignificant reduction in the need for left ventricular assist device implantation and cardiac transplantation. The PARADIGM-HF investigators also carried out a comparison of the sacubitril/valsartan arm with the treatment arms of the SOLVD Trial (enalapril) and the CHARM-Alternative Trial [19] (candesartan) and found substantial relative risk reductions for both the composite end point and for cardiovascular death. Using the Kansas City Cardiomyopathy Questionnaire, the PARADIGM-HF investigators [20] demonstrated remarkable improvement in physical and social activity limitations with sacubitril/valsartan compared to enalapril. The largest improvements were reported in household chores ($p < 0.001$) and sexual relationships ($p = 0.002$); these benefits persisted through 36 months of assessment. In another secondary analysis [21], the PARADIGM-HF investigators found the frequency of episodes of hyperkalemia to be significantly greater in the enalapril arm compared to ARNI, (3.1 versus 2.2 incidents per 100 patient-years, HR = 1.37, CI 1.06–1.76, $p = 0.02$) for patients already taking a mineralocorticoid antagonist.

Criticisms of the PARADIGM-HF Trial include that the study was predominantly white (66%), male (78%), and enrolled predominantly NYHA Functional Class II (70%) patients. Only 5% of the study population was black, perhaps limiting the ability of the study to accurately detect the incidence of angioedema. It has also been suggested that the enalapril dose in PARADIGM-HF was too low [22]. Narrowly defined, only patients with systolic heart failure and an ejection fraction of ≤35% would be candidates for the drug, based on PARADIGM-HF entry criteria. An additional criticism is that neprilysin has been shown to have a role in maintaining homeostasis of amyloid-ß peptide, raising the issue that a neprilysin inhibitor might lead to increased deposits of this protein in brain [11]. However, in a randomized, double-blind trial measuring sacubitril/valsartan levels in cerebrospinal fluid in healthy human subjects [23], sacubitril/valsartan did not cause changes in aggregable amyloid β isoforms compared with placebo, despite achieving CSF concentrations of a metabolite of sacubitril/valsartan sufficient to inhibit neprilysin.

The Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON-HF Trial) [24], a prospective randomized trial of the impact of sacubitril/valsartan in HFpEF, has completed enrollment and has an estimated study completion date of March 15, 2019 (clinicaltrials.gov). Serial cognitive testing is being carried out in PARAGON-HF in an effort to assess the impact of sacubitril/valsartan on cognition.

In summary, in prespecified measures of nonfatal clinical deterioration of heart failure, the PARADIGM-HF investigators demonstrated that the combination of sacubitril/valsartan prevented the clinical progression of surviving heart failure patients more effectively than did enalapril alone [25]. On the basis of the PARADIGM-HF Trial, sacubitril/valsartan was FDA-approved in July 2015 to reduce the risk of death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II–IV) and reduced ejection fraction.

The comParIson Of sacubitril/valsartaN versus Enalapril on Effect on nt-pRo-bnp in patients stabilized from an acute Heart Failure (PIONEER-HF) trial (PMID:30415601) enrolled 881 patients with heart failure with reduced ejection fraction who were hospitalized for acute decompensated heart failure at 129 sites in the United States. After hemodynamic stabilization, patients were randomly assigned to receive either sacubitril–valsartan (target dose, 97 mg of sacubitril with 103 mg of valsartan twice daily) or enalapril (target dose, 10 mg twice daily). The primary efficacy outcome was the time-averaged proportional change in the N-terminal pro–B--type natriuretic peptide (NT-proBNP) concentra-

tion from baseline through weeks 4 and 8. Key safety outcomes were the rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema.

The investigators noted that time-averaged reduction in the NT-proBNP concentration was significantly greater in the sacubitril–valsartan group than in the enalapril group. In addition, the two drugs appeared to be equally safe; the rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly. In an analysis of exploratory clinical outcomes, the in-hospital initiation of sacubitril–valsartan therapy was associated with a lower rate of rehospitalization for heart failure at 8 weeks than enalapril therapy.

Pharmacokinetics of Sacubitril/Valsartan

Absorption of sacubitril/valsartan is rapid, with maximum levels of sacubitril, sacubitrilat, and valsartan all achieved by 2–3 h [26]. With twice-daily dosing, steady-state concentrations are reached within 3 days. Sacubitril is eliminated as predominantly sacubitrilat by the kidney, while valsartan is eliminated by the biliary route. In heart failure patients, area under the concentration-time curves for sacubitril, sacubitrilat, and valsartan was higher. Renal impairment had no impact on sacubitril or valsartan, but increased the area under the concentration-time curve for sacubitrilat. Moderate hepatic impairment increased the area under the concentration-time curve of valsartan and sacubitrilat approximately two-fold. Regarding drug-drug interactions, sacubitril/valsartan increased plasma concentrations of atorvastatin. Pharmacokinetics of the drug were not affected by age, sex, or ethnicity.

Hemodynamic Impact of Sacubitril/Valsartan

Surprisingly little specific functional and hemodynamic data are available regarding sacubitril/valsartan. A post hoc analysis of the PARAGIGM-HF demonstrated that the drug was effective at reducing cardiovascular death and heart failure hospitalization across the spectrum of left ventricular ejection fraction (LVEF), when assessed in stepwise 5-point reductions in LVEF [27]. Addition of sacubitril/valsartan in patients with advanced systolic heart failure may be a useful strategy to improve hemodynamics and to potentially facilitate the transitioning from intravenous HF therapies.

Ivabradine

Background and Pharmacology

The search for a direct sinoatrial node inhibitor began four decades ago. Ivabradine was the first drug specifically developed as a heart rate lowering agent, and in Europe was initially considered for the treatment of angina pectoris. Sinoatrial myocytes have the capacity to develop slow diastolic depolarizations, driving membrane voltage toward the threshold for initiating an action potential (Fig. 8.2). Sinoatrial node activity involves several ionic currents flowing through channels, including the funny or hyperpolarization-activated cyclic nucleotide-gated channel that regulates the I_f current, so-called for its unusual properties compared with other channels at the time of its discovery. The I_f current is carried across the sarcolemma by both sodium and potassium ions, is directly activated by cyclic adenosine monophosphate (cAMP), and is related to I_h neuronal channels. Ivabradine has substantial selectivity for inhibiting the I_f channel at doses that allow heart rate slowing [28]. Studies in experimental models have demonstrated that ivabradine has a pure heart rate lowering effect, does not affect LV contractile state [29], and does not have negative lusitropic properties. In healthy volunteers, equipotent doses of ivabradine (30 mg) and propranolol (40 mg) had similar effects on heart rate and heart rate variability, whereas propranolol was associated with significant systolic and mean blood pressure lowering, and a greater decrease in cardiac output measured noninvasively, compared to ivabradine, placebo, or both [30]. Under fasting conditions, peak plasma ivabradine concentrations are reached in approximately

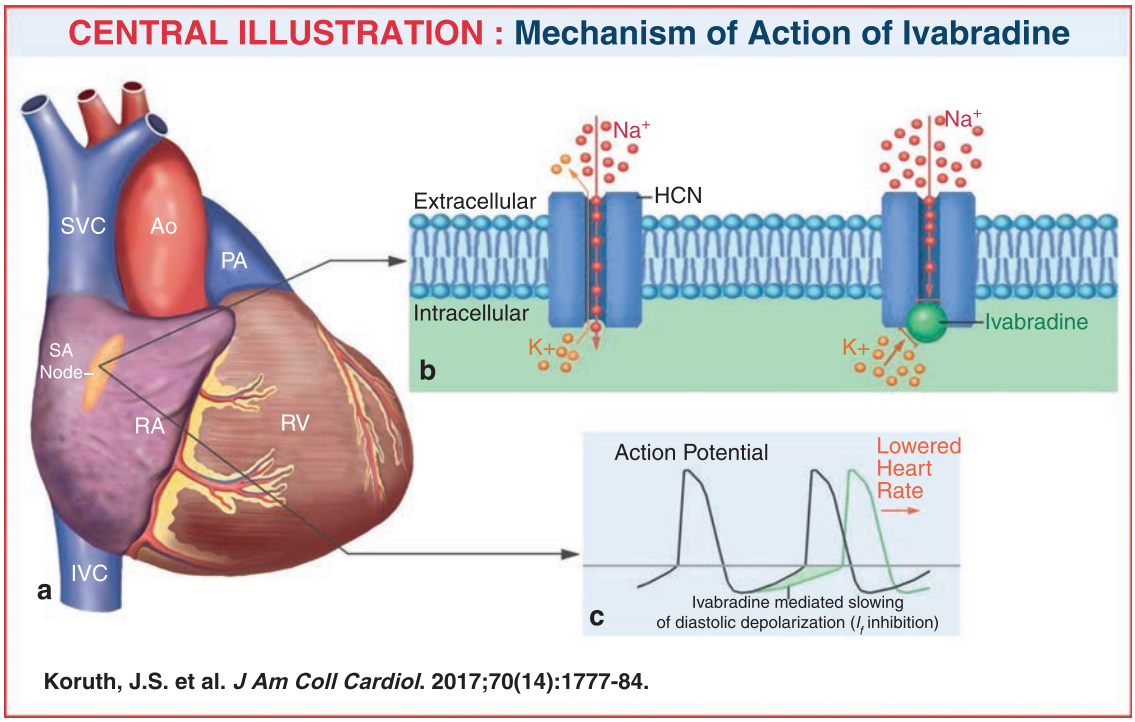


Fig. 8.2 Ivabradine's primary mechanism of action on cardiac tissue is on the sinoatrial (SA) node, which occupies a predominantly subepicardial position at the junction of the superior vena cava (SVC) and the right atrium (RA). (**a**) Heart with position of the Sinoatrial (SA) node. (**b**) In the sinoatrial node, ivabradine blocks the intracellular aspect of the hyperpolarization-activated cyclic nucleotide-gated (HCN) transmembrane channel, which is responsible for the transport of sodium (Na^+) and potassium (K^+) ions across the cell membrane, in the open state. This results in the inhibition of the inward funny current ($\mathbf{I_f}$), which is specifically activated at hyperpolarized membrane potentials. (**c**) By selectively inhibiting $\mathbf{I_f}$, there is a reduction in the slope of diastolic depolarization of the pacemaker action potential (shaded region) and an increase in the duration of diastole, without altering other phases of the action potential. This results in heart rate reduction. Ao aorta, IVC inferior vena cava, PA pulmonary artery, RV right ventricle. (PMID:28958335)

1 hour. Food delays absorption by approximately 1 hour but appears to increase plasma levels of the drug. Ivabradine is extensively metabolized in the liver. The excretion of ivabradine and its metabolites is both renal and hepatic. The half-life of ivabradine and its metabolites requires twice-daily dosing. There is no direct effect of ivabradine on the QT interval. Phosphenes, the off-target effect of ivabradine, are bright sensations not mediated by retinal stimuli, due to effects on hyperpolarization-activated channels in the retina.

While ivabradine was initially targeted as a drug for heart rate control, randomized data failed to demonstrate a significant advantage in patents with stable coronary artery disease without clinical heart failure [31]. Similarly, ivabradine compared to placebo did not significantly improve the change in physical limitation score at 1 year in patients with anginas pectoris [32], although ivabradine patients had better angina scores compared to placebo on the Seattle Angina Questionnaire on every visit to 36 months. Ivabradine did not result in significant exercise tolerance testing benefit, compared to low-dose atenolol, and no advantage was noted when added to full-dose amlodipine [33, 34].

Because of the documented beneficial effect of heart rate lowering in heart failure with reduced ejection fraction, ivabradine was tested in this setting, beginning with the Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease and Left Ventricular Dysfunction (BEAUTIFUL) Trial [35], a randomized double-blind, placebo-controlled trial of

10,917 patients. Enrollment characteristics included LVEF <40%, 85% NYHA Class II and III, 83% male, and 87% were taking ß-blockers. At a median of 19 months of follow-up, no difference was found between the ivabradine and placebo groups for the composite end point of cardiovascular death, hospitalization for myocardial infarction (MI), or hospitalization for worsening heart failure. A subgroup analysis of 14% of patients with activity-limiting angina had reduction in hospitalization for MI and borderline reduction in the composite end point ($p = 0.05$); the difference was statistically significant for patients in this subgroup with baseline heart rate ≥ 70 [36].

To investigate the potential benefits on ischemia seen in this subgroup, the SIGNIFY [37] Trial was undertaken, enrolling 19,102 patients with stable coronary artery disease who did not have clinical heart failure. This study again enrolled predominantly male patients; 75% had angina pectoris, and the mean LV ejection fraction was 56%. While heart rate was significantly reduced by ivabradine, there was no significant benefit of ivabradine on the primary composite end point of cardiovascular death or nonfatal MI after median follow-up of 28 months. When the prespecified subgroup with activity-limiting angina was analyzed for the composite outcome, there was in fact evidence of harm with ivabradine therapy; an absolute increase in the composite end point of 1.1% ($p = 0.02$). The reason or reasons for this adverse outcome remain unclear, but the conclusion to be drawn from trials of ivabradine in angina pectoris without LV systolic dysfunction is that no benefit occurs, and even though there may be symptomatic improvement, those patients appear to be at greater risk of an adverse effect of the drug.

The Systolic Heart Failure Treatment with the I_f-inhibitor Ivabradine (SHIFT) Trial [38] randomized 6505 patients with ischemic and nonischemic heart failure, NYHA Class II–IV but predominantly Class II–III, LVEF ≤35%, to ivabradine or placebo. The trial randomized no patients from the United States; most patients were male, 89% taking ß-blockers, 91% ACEi or ARB, 60% aldosterone antagonists, 22% a digitalis preparation. More than two-thirds achieved the target dose of 7.5 mg ivabradine twice daily. Compared to placebo, the composite end point of cardiovascular death or first hospitalization for heart failure was significantly reduced (hazard ratio 0.82, $p < 0.0001$, driven primarily by reduction in HF hospitalization) (Fig. 8.3) Trends were detected for less benefit in patients also receiving ß-blockers and greater benefit for nonischemic patients. There were significant improvements in the NYHA Class and Kansas City Cardiomyopathy Questionnaire summary scores [39]. When patients with baseline heart rate ≥70 from BEAUTIFUL and SHIFT were pooled, no significant impact on mortality could be demonstrated. An echo substudy [40] from SHIFT of 275 patients demonstrated a small but significant increase on LVEF after 8 months of ivabradine therapy (4 ± 10%, $p = 0.004$).

Shortcomings of the SHIFT Trial include that 25% of trial participants were not taking a ß-blocker for HRrEF and that ivabradine did not significantly reduce any end point in patients with baseline HR ≤ 75 bpm. Whereas trials of carvedilol, metoprolol succinate, and bisoprolol demonstrated consistent survival benefit, a similar heart rate reduction by ivabradine resulted in no all-cause survival benefit. Another SHIFT subgroup analysis demonstrated that a statistically significant improvement for the primary end point occurred only for patients <50% of target ß-blocker doses [41]. Thus, ivabradine appeared to exert a beneficial effect only in patients who were also being treated with ß-blockers in whom a heart rate goal of ≤75 bpm had not been achieved. Regarding adverse effects, ivabradine increased the frequency of bradycardia, both asymptomatic and symptomatic, was associated with an increased incidence of atrial fibrillation, and resulted in some ivabradine withdrawals due to phosphenes, which resolved upon discontinuation of drug. The 1.7% increase in the risk of atrial fibrillation noted in pooled BEAUTIFUL and SHIFT data underscore the importance of observing patients on ivabradine for this rhythm disturbance, especially in view of the negative prognostic impact of atrial fibrillation on systolic heart failure. The FDA approved ivabradine in April 2015 for patients with HFrEF

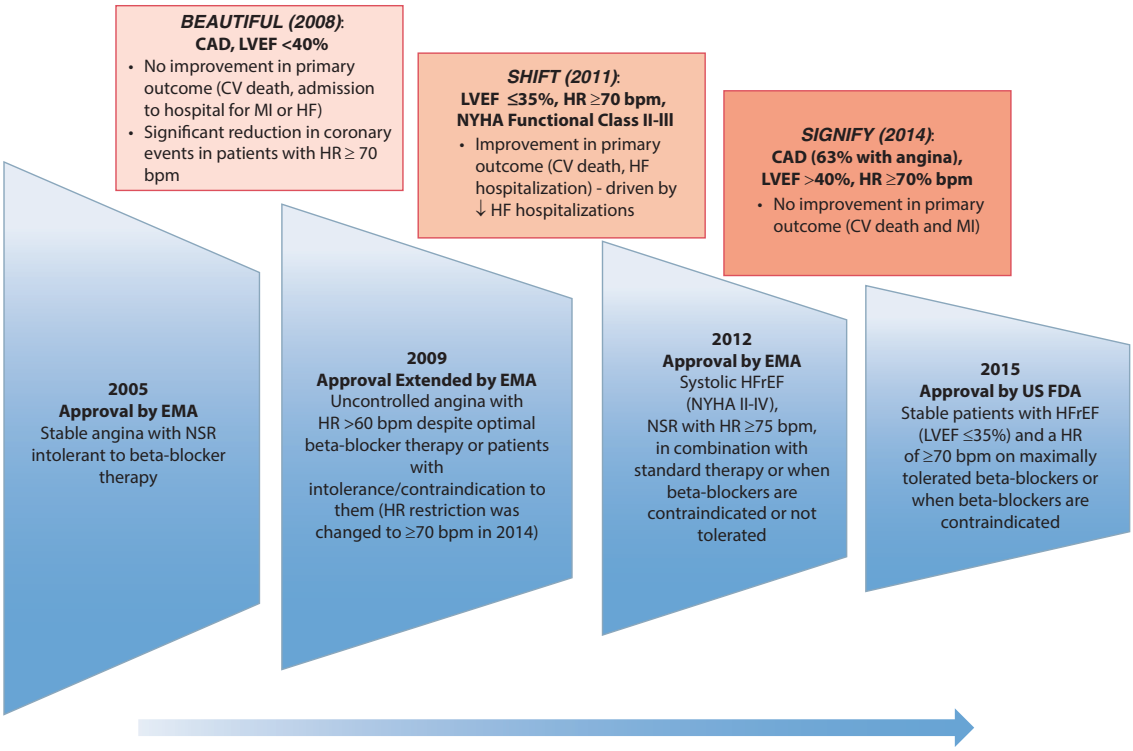


Fig. 8.3 Approval timeline of ivabradine across Europe and the United States. The indications for the use of ivabradine have evolved over time and differ based on region. Since it was first approved for use in angina by the European Medicines Agency (EMA) in 2005, the findings of several randomized controlled trials have resulted in expanded indications to include select heart failure patients and only recent approval by the US Food and Drug Administration (FDA) for this indication. BEAUTIFUL Morbidity-Mortality Evaluation of the I_f-Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventricular Dysfunction, CAD coronary artery disease, CV cardiovascular, HFrEF heart failure with reduced ejection fraction, LVEF left ventricular ejection fraction, MI myocardial infarction, NYHA New York Heart Association, NSR normal sinus rhythm, SHIFT Systolic Heart Failure Treatment with the I_f-Inhibitor Ivabradine Trial, SIGNIFY Study Assessing the Morbidity-Mortality Benefits of the I_f-Inhibitor Ivabradine in Patients With Coronary Artery Disease. (PMID:28958335)

with LVEF ≤35% on a ß-blocker at the maximum tolerated dose, with HR ≥ 70 bpm (Fig. 8.4). The drug is contraindicated in patients with sinus node dysfunction or atrioventricular block. The FDA approval underscores the prerequisite for guideline-based treatment with maximally tolerated ß-blockers proven effective in HFrEF. In such patients in whom HR remains >70–75 beats per minute, the addition of ivabradine is reasonable. For patients with HFrEF who are proven intolerant of ß-blockers, treatment with ivabradine appears reasonable, keeping in mind that while ivabradine results in decreased heart rate, the exact mechanism of benefit remains uncertain.

Questions remain regarding the efficacy of ivabradine. From a recent meta-analysis of the ivabradine trials [42], the authors concluded that while use of ivabradine in patients with HFrEF in sinus rhythm with HR ≥ 70 to reduce HF hospitalization was supported by the literature, the strength of the evidence was such that more widespread adoption of ivabradine in HF would require additional randomized trials. Recent guideline updates [43] emphasize adherence to the ivabradine FDA package indication.

On the other hand, the guidelines advise that for any patient in NYHA Class II–IV HFrEF not on an ARNI, the threshold to consider discontinuing an ACEi or ARB in favor of sacubitril/valsartan should be low [44]. The number of women and ethnicities different from white in many of the foregoing trials is low enough that one might

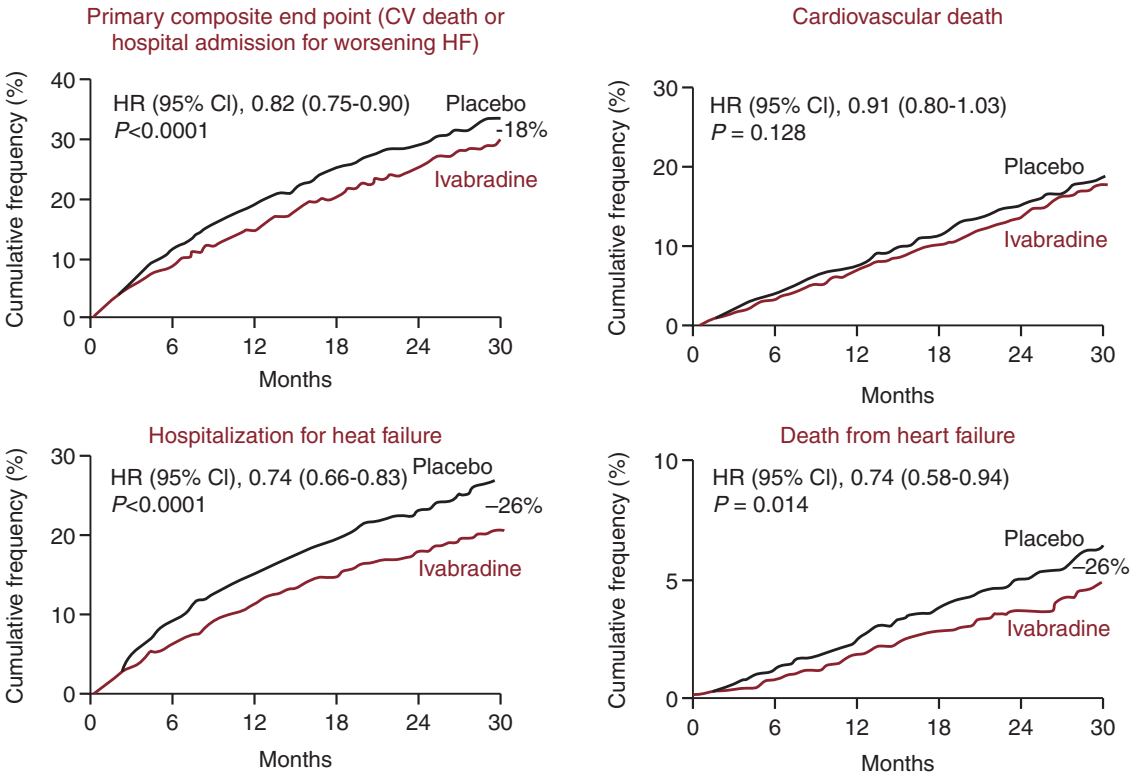


Fig. 8.4 Kaplan-Meier cumulative event curves for different end points in SHIFT. Primary composite outcome (**Panel A**); cardiovascular mortality or heart failure hospitalization and its two components cardiovascular mortality (**Panel B**); heart failure hospitalizations (**Panel C**) and heart failure deaths (**Panel D**) in the ivabradine and the placebo arms. CV cardiovascular, HF heart failure, SHIFT Systolic Heart Failure Treatment with the I_f-Inhibitor Ivabradine Trial. (Swedberg et al.; SHIFT Investigators. Lancet. 2010;376:875–885)

question scientific efficacy of these agents in these populations. For further guidance on the use of sacubitril/valsartan and ivabradine, the reader is referred to the 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure [43] and the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment [44].

References

1. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. N Engl J Med. 1986;314:1547–52.
2. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. N Engl Med. 1987;316:1429–35.
3. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325:293–302.
4. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med. 1991;325:303–10.
5. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med. 2004;351:2049–57.
6. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344:1651–8.
7. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). Lancet. 1999;353:2001–7.
8. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. N Engl J Med. 1999;341:709–17.
9. Kagawa CM, Sturtevant FM, Van Arman CG. Pharmacology of a new steroid that blocks salt

activity of aldosterone and desoxycorticosterone. J Pharm Exp Ther. 1959;126:123–30.
10. Zannad F, McMurray JJ, Frum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364:11–21.
11. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997;336:525–33.
12. Srikanth Y, Aronow WS, Mondal P, Chabbott DR. The evolution of natriuretic peptide augmentation in management of heart failure and the role of sacubitril/valsartan. Arch Med Sci. 2017;13:1207–16.
13. Cohn JN, Tognoni G, for the Valsartan Trial Investigators. A randomized trial of the angiotensin receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001;345:1667–1675.
14. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med. 2011;365:32–43.
15. Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation. 2002;106:920–6.
16. Braunwald E. The path to an angiotensin receptor neprilysin inhibitor in the treatment of heart failure. J Am Coll Cardiol. 2015;65:1029–41.
17. Ruilope LM, Dukat A, Bohm M, et al. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. Lancet. 2010;375:1255–66.
18. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 2012;380:1387–95.
19. Young JB, Dunlap ME, Pfeffer MA, et al. Mortality and morbidity reduction with candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. Circulation. 2004;110:2618–26.
20. Chandra A, Lewis EF, Claggett BL, et al. Effects of sacubitril/valsartan on physical and social activity limitations in patients with heart failure: a secondary analysis of the PARADIGM-HF trial. JAMA Cardiol. 2018;3:498–505. https://doi.org/10.1001/jamacardio.2018.0398 . Published online April 4.
21. Desai AS, Vardeny O, Claggett B, et al. Reduced risk of hyperkalemia during treatment of heart failure with mineralocorticoid receptor antagonists by use of sacubitril/valsartan compared with enalapril: a secondary analysis of the PARADIGM-HF trial. JAMA Cardiol. 2017;2:79–85.
22. Bernardez-Pereira S, Ramires FJA, de Melo RFT, Pereira-Barretto AC. Was the enalapril dose too low in the PARADIGM-HF trial? Cardiol Rev. 2018; https://doi.org/10.1097/CRD.0000000000000193. [Epub ahead of print]
23. Langenickel TH, Tsubouchi C, Ayalasomayajula S, et al. The effect of LCZ696 (sacubitril/valsartan) on amyloid-ß concentrations in cerebrospinal fluid in healthy subjects. Br J Clin Pharmacol. 2016;81:878–90.
24. Solomon SD, Rizkala AR, Gong J, et al. Angiotensin receptor neprilysin inhibition in heart failure with preserved ejection fraction: rationale and design of the PARAGON-HF Trial. JACC Heart Fail. 2017;5:471–82.
25. Packer M, McMurray JJ, Desai AS, et al. Angiotensin receptor neprilysin inhibition compared to enalapril on the risk of clinical progression in surviving patients with heart failure. Circulation. 2015;131:54–61.
26. Ayalasomayajula S, Langenickel T, Pal P, et al. Clinical pharmacokinetics of sacubitril/valsartan (LCZ696): a novel angiotensin receptor neprilysin inhibitor. Clin Pharmacokinet. 2017;56:1461–78.
27. Solomon SD, Claggett B, Desai AS, et al. Influence of ejection fraction on outcomes and efficacy of sacubitril/valsartan (LCZ696) in heart failure with reduced ejection fraction. The prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure (PARADIGM-HF) trial. Circ Heart Fail. 2016;9:e002744.
28. Sulfi S, Timmis AD. Ivabradine – the first selective sinus node I_f channel inhibitor in the treatment of stable angina pectoris. Int J Clin Pract. 2006;60:222–8.
29. Vilaine JP, Bidouard JP, Lesage L, et al. Anti-ischemic effects of ivabradine, a selective heart rate-reducing agent, in exercise-induced myocardial ischemia in pigs. J Cardiovasc Pharmacol. 2003;42:688–96.
30. Joannides R, Moore N, Iacob M, et al. Comparative effects of ivabradine, a selective heart rate lowering agent, and propranolol on systemic and cardiac haemodynamics at rest and during exercise. Br J Clin Pharmacol. 2006;61:127–37.
31. Borer JS, Fox K, Jaillon P, et al. Antianginal and antiischemic effects of ivabradine, and I_f inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. Circulation. 2003;107:817–23.
32. Tendera M, Chassany O, Ferrari R, et al. Quality of life with ivabradine in patients with angina pectoris. The study assessing the morbidity and mortality benefits of the I_f inhibitor ivabradine in patients with stable coronary artery disease quality of life substudy. Circ Cardiovasc Qual Outcomes. 2016;9:31–8.
33. Tardif JC, Ponikowski P, Kahan T, et al. Efficacy of the I_f current inhibitor ivabradine in patients with chronic stable angina receiving beta blocker therapy: a 4-month, randomize, placebo-controlled trial. Eur Heart J. 2009;30:540–8.
34. European Medicines Agency. Ivabradine: European public assessment report – scientific discussion. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000597/WC500043587.pdf
35. Fox K, Ford I, Steg PG, et al. Ivabradine for patients with stable coronary artery disease and left-

ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet. 2008;372:807–16.
36. Fox K, Ford I, Steg PG, et al. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. Eur Heart J. 2009;30: 2337–45.
37. Fox K, Ford I, Steg PG, et al. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med. 2014;371:1091–9.
38. Swedberg K, Komaida M, Bohm M, Borer JS, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled trial. Lancet. 2010;376:875–85.
39. Ekman I, Chassany O, Komajda M, et al. Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: results from the SHIFT study. Eur Heart J. 2011;32:2395–404.
40. Tardif JC, O'Meara E, Komajda M, SHIFT Investigators, et al. Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy. Eur Heart J. 2011;32:2507–15.
41. Böhm M, Borer J, Ford I, et al. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. Clin Res Cardiol. 2013;102:11–22.
42. Narayanan MA, Reddy YNV, Baskaran J, et al. Ivabradine in the treatment of systolic heart failure – a systematic review and meta-analysis. World J Cardiol. 2017;9:182–90.
43. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017;70:776–803.
44. Yancy CW, Januzzi JL, Allen LA, et al. 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2018;71:201–30.

Heart Failure Reviews
https://doi.org/10.1007/s10741-019-09829-7

New perspectives and future directions in the treatment of heart failure

Pierpaolo Pellicori[1] · Muhammad Javed Iqbal Khan[1] · Fraser John Graham[1] · John G. F. Cleland[1,2]

Abstract
The management of heart failure has changed significantly over the last 30 years, leading to improvements in the quality of life and outcomes, at least for patients with a substantially reduced left ventricular ejection fraction (HFrEF). This has been made possible by the identification of various pathways leading to the development and progression of heart failure, which have been successfully targeted with effective therapies. Meanwhile, many other potential targets of treatment have been identified, and the list is constantly expanding. In this review, we summarise planned and ongoing trials exploring the potential benefit, or harm, of old and new pharmacological interventions that might offer further improvements in treatment for those with HFrEF and extend success to the treatment of patients with heart failure with preserved left ventricular ejection fraction (HFpEF) and other heart failure phenotypes.

Keywords Heart failure · Treatment · Trials · HFpEF · HFrEF

Introduction

Heart failure and its management have changed dramatically over the last 30 years. In the 1980s, patients were included in clinical trials of heart failure based purely on the clinical opinion of the investigator with no objective criteria to confirm the diagnosis. The patients were younger and had fewer comorbidities but a broad range of left ventricular ejection fraction (LVEF) compared with contemporary trials; quality of life was often poor and mortality rate high. Fluid retention, causing peripheral oedema and breathlessness, was the main therapeutic target. Digoxin and diuretics were the only available medical treatments, sometimes accompanied with bed rest and fluid restriction.

Subsequently, objective criteria such as LVEF and, more recently, natriuretic peptides were required to select patients for trials. Initially, trials targeted vasoconstriction, using nitrates and hydralazine [1], and pathologically activated neuro-hormonal systems, using angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers and mineralocorticoid antagonists (MRAs). These trials provided evidence that, for heart failure with reduced LVEF (HFrEF), treatment could improve ventricular function, symptoms and signs, as well as morbidity and mortality [2–5]. More recently, other targets and novel treatments have been identified for HFrEF. Ivabradine, an agent that slows the rate of sinus node discharge and therefore heart rate, improved ventricular function, symptoms and morbidity for patients who do not achieve a heart rate < 70 bpm on a beta-blocker; for those with a heart rate > 75 bpm or who were not treated with a beta-blocker, mortality was also reduced [6, 7]. Patients with HFrEF in sinus rhythm with a QRS duration > 130 msec benefitted from cardiac resynchronization therapy (CRT) [8, 9] with improvements in cardiac function, symptoms, morbidity and mortality. Patients who were at low risk of dying for any reason other than an arrhythmia benefitted from an implantable cardioverter-defibrillator (ICD) although its utility is currently being called into question [10, 11]. The development of dedicated specialist HF teams has also been of great importance to inform patients of their diagnosis, prognosis and need for

✉ Pierpaolo Pellicori
pierpaolo.pellicori@glasgow.ac.uk

[1] Robertson Institute of Biostatistics and Clinical Trials Unit, University of Glasgow, University Avenue, Glasgow G12 8QQ, UK

[2] National Heart & Lung Institute and National Institute of Health Research Cardiovascular Biomedical Research Unit, Royal Brompton & Harefield Hospitals, Imperial College, London, UK

therapy, to improve the implementation of and adherence to treatment and to facilitate titration of medications to target doses, all of which leads to greater patient-satisfaction and better long-term outcomes [12].

Despite these successes, the 'war' on heart failure is far from won. For patients hospitalised with worsening heart failure aged less than 75 years, mortality at 1 year may be as high as 20% and up to 40% in those aged > 85 years [13]. For patients with stable HFrEF who survive the initial 6 months after diagnosis and are enrolled in contemporary clinical trials, the annual risk of the composite of hospitalisation for heart failure or mortality is about 10% [14]. Outcome amongst patients who do not participate in clinical trials is much worse [15]. Older patients and those with a recent episode of decompensation despite guideline-recommended therapy who require intensification of therapy have a much worse prognosis. Disappointingly, many patients do not receive, and therefore cannot benefit from, guideline-recommended therapy [16, 17].

More appropriate use of investigations and less complex diagnostic algorithms are likely to reveal that there are many undiagnosed cases of heart failure in the community, particularly with preserved left ventricular (LV) ejection fraction (HFpEF) [18], a condition for which some insist no effective therapy exists as yet, although treatment with a thiazide diuretic and ACE inhibitor exerted remarkable benefits in the HYVET trial in a group of patients many of whom undoubtedly had undeclared HFpEF [19]. Of note, the European Society of Cardiology (ESC) heart failure registry suggested little difference in the therapies applied to patients with HFrEF and HFpEF in clinical practice; perhaps clinicians are sometimes wiser than the guidelines they are asked to follow [20].

The age-adjusted incidence of heart failure may be fairly stable but the total number of patients who will develop heart failure will rise substantially in the next few decades as the proportion of people aged > 60 years increases [21]. Nowadays, many people survive the onset of cardiovascular disease for long periods. Treatment of hypertension, diabetes, chronic kidney disease, atrial fibrillation and ischaemic heart disease might delay the onset of heart failure, but procrastination is not the same as prevention. It is likely that most people with cardiovascular disease will develop heart failure before they die [22, 23]. Strategies to diagnose and treat heart failure before it becomes clinically overt require much more research investment [24]. An increased awareness of what is important to older people may identify novel outcomes and treatments and define the future role of palliative care and euthanasia.

Enormous amounts of routinely collected personal health records, biochemical and imaging data are now available for novel analytical approaches such as machine-learning and artificial intelligence that will identify novel pathways leading to heart failure and redefine its epidemiology in the next decade (Fig. 1). The definition as well as management of heart failure might be transformed, with care and services personalised to the individual patient's needs.

Currently, there are many ongoing trials exploring the potential for benefit, or harm, of old and new treatments that might improve the management of HF: summarising novel pharmacological interventions is the purpose of this review; space precludes an in-depth review of devices (electrical, mechanical or valve) or biological interventions (other than influenza vaccination) although key trials are shown in the Table 1 (and in supplementary Table 1, if they aim to enrol fewer than 200 patients).

Neuro-endocrine interventions

Augmentation of natriuretic and other peptides: sacubitril/valsartan

One of the key therapeutic successes for heart failure has been the inhibition of neuro-endocrine pathways with ACE-Is, ARBs, MRAs and beta-blockers. Recently, a new class of agents, angiotensin receptor neprilysin inhibitors (ARNI), has proved superior to ACE-Is for the treatment of HFrEF [14]. Neprilysin inhibitors retard the degradation of many peptides, including atrial (ANP) and B-type natriuretic peptides (BNP) and vasoactive intestinal polypeptide, which have diuretic, vasodilator and inotropic properties [25, 26]. In the Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF) trial, initiation of sacubitril/valsartan for patients with either new-onset or chronic HFrEF ($n = 881$) during the in-hospital recovery phase after an acute decompensation was as safe as initiating enalapril, but led to a greater, and earlier (within 1 week), reduction in plasma concentrations of NT-proBNP, which was sustained until the end of 8 weeks follow-up [27]. A reduction in a composite of serious HF-related adverse clinical events was also observed [28]. However, about 20% of surviving patients discontinued treatment with either ACEi or ARNI and only 55% achieved guideline-recommended doses of the ARNI [27]. In the PRIME trial ($n = 118$), patients with HF, an LVEF < 50% and functional mitral regurgitation (MR) who were randomised to sacubitril/valsartan had a greater reduction in the effective regurgitant orifice area (EROA) compared with valsartan alone at 12 months follow-up [29]. Other trials are currently ongoing in specific populations with HFrEF, including those with symptoms at rest (NCT02816736), or an elevated pulmonary artery pressure (NCT02788656) or in Japan (NCT02468232).

The Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON; NCT01920711) is a randomised, double-blind, event-driven trial comparing the efficacy and safety of

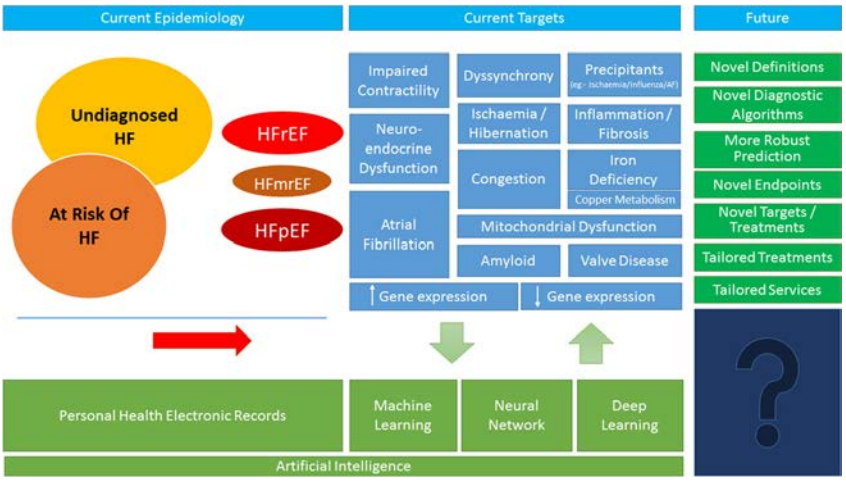


Fig. 1 The present and future of heart failure. Conventionally, the prevalence of heart failure is thought to be about 1.5% in the adult population. However, it might be substantially greater than that, as many cases remain undiagnosed, particularly amongst older people, and are usually only identified when symptoms are severe enough to require hospital admission. Several ongoing trials target different pathways that might contribute to disease progression. Success provides tentative insights into the likely mechanisms of progression, although off-target effects may lead to serendipitous effects (this is probably true of most effective treatments for heart failure). There may be many reasons for failure other than the lack of importance of the targeted mechanism. This may include a smaller than anticipated benefit with consequent lack of power, lack of target engagement, a mechanism that is important but only works in a specific subgroup (e.g., heart rate reduction in sinus rhythm) or one that is overwhelmed by competing risks (e.g., rivaroxaban 2.5 mg bd for advanced heart failure in sinus rhythm). Processing large volumes of routinely collected electronic health records using novel analytical approaches, such as artificial intelligence and machine learning, will provide new insights into disease classification, mechanisms of progression and therapeutic targets. Epidemiology, definition and management of heart failure are likely to be transformed in the next decade, with care and services matched to the individual patient's needs in a "precision-medicine" approach

valsartan vs sacubitril/valsartan in patients with HFpEF that has enrolled 4822 patients (mean age 73 ± 8 years, median NT-proBNP 911 (interquartile range 464–1610) pg/mL, > 2/3 in sinus rhythm) [30]. The results should be reported later in 2019. PARALLAX (NCT03066804) is another large (> 2,000 patients) randomised, double-blind trial of patients with HFpEF, comparing sacubitril/valsartan with a control group (the investigator can chose whether this is an ACE-I, an ARB or neither, in which case patients assigned to the control group receive placebo); the effect on plasma NT-proBNP and exercise capacity after 24 weeks of treatment and safety are the main outcomes of interest.

Concerns exist that the inhibition of *neprilysin* could interfere with breakdown of beta amyloid (βA) peptides, which might accumulate in the brain and contribute to the development of Alzheimer's disease. The PERSPECTIVE trial (NCT02884206) is currently recruiting ~ 500 patients with HF and LVEF > 40%, to investigate whether chronic administration of sacubitril/valsartan for 3 years leads to a decline in cognitive function when compared with valsartan alone.

Management of hyperkalaemia: patiromer and sodium zirconium cyclosilicate

Currently, based on the evidence provided by clinical trials, guidelines recommend that ACEi, ARB and MRA should not be initiated if serum potassium is > 5.0 mmol/L (5.2 mmol/L for ARNI) and that doses should be reduced or treatment stopped if serum potassium is > 5.5 mmol/L. Accordingly, many patients with HFrEF do not receive guideline-recommended doses of these agents [16, 17, 31]. Older patients, those with type-2 diabetes mellitus and those with renal dysfunction are more likely to develop hyperkalaemia [32]. Patients who fail to achieve guideline-recommended doses of these medications due to hyperkalaemia have a worse prognosis, but this may be because of concomitant renal dysfunction or hypotension.

Patiromer and sodium zirconium cyclosilicate are novel oral treatments that bind potassium in the gastrointestinal (GI) tract and rapidly normalise serum potassium concentrations. Whether their use will allow doctors to prescribe and patients to achieve guideline-recommended doses of RAASi more often and whether this will improve outcomes are now being investigated. Results of substantial trials are not expected before 2021.

Vasodilators: vericiguat and nitroxyl

Nitric oxide (NO) activates soluble guanylate cyclase (sGC), causing an elevation of intracellular cyclic guanosine monophosphate (cGMP) in vascular and non-vascular tissues, such as the myocardium and kidney. In heart failure, production of NO is reduced and its degradation is increased, leading to an increase in systemic and pulmonary arteriolar and venous tone, thereby increasing the after-load and pre-load on the failing myocardium [33]. Vericiguat is an oral sGC

Table 1 Ongoing trials in heart failure (HF). Only trials planned to recruit > 200 participants with HF are shown

Name	ClinicalTrials.gov identifier	Expected completion	Phase	Participants	HF phenotype	Recruitment status
Willingness to participate	NCT03840499	2022	NA	400	All	A
Neuro-endocrine interventions						
Augmentation of natriuretic and other peptides: sacubitril/valsartan						
PARAGON	NCT01920711	2019	3	4822	HFpEF	T
PARALLEL-HF	NCT02468232	2020	3	225	HFrEF	T
PERSPECTIVE	NCT02884206	2022	3	520	HFpEF	A
PARALLAX	NCT03066804	2019	3	2500	HFpEF	A
HFN-LIFE	NCT02816736	2020	4	400	Severe HFrEF	A
Management of hyperkalaemia: patiromer and sodium zirconium cyclosilicate (SCZ)						
DIAMOND (patiromer)	NCT03888066	2022	3	2388	HFrEF	Not yet A
RELIEHF (patiromer)	?	2022/2024	4	400/2000	All	Not yet A
PRIORITIZE HF (SZC)	NCT03532009	Suspended	2	280	HFrEF	A
Vasodilators: vericiguat						
VICTORIA	NCT02861534	2020	3	4872	HFrEF	T
Vitality-HFpEF	NCT03547583	2020	2	735	HFpEF	A
Vasodilators: nitroxyl						
STANDUP-AHF	NCT03016325	2019	2	310	HFrEF	A
Inotropic agents						
Omecamtiv mecarbil						
GALACTIC-HF	NCT02929329	2021	3	8000	HFrEF	A
METEORIC-HF	NCT03759392	2021	3	270	HFrEF	Not yet A
Levosimendan						
LeoDOR	NCT03437226	2019	3	264	HFrEF	A
Digoxin						
DIG-START-AHF	NCT02544815	2019	3	1500	AHF	A
DECISION	NCT03783429	2024	4	982	LVEF < 50%	Not yet A
Recombinant human neuregulin-1 β						
	NCT03388593	2023	3	1600	HFrEF	A
Congestion						
Ultrasound guided treatment for congestion						
JECICA	NCT02892227	2019	NA	250	AHF	A
CAVA-ADHF	NCT03140566	2019	NA	388	AHF	A
Device guided treatment for congestion						
GUIDE-HF	NCT03387813	2023	NA	3600	HFrEF and HFpEF	A

Table 1 (continued)

Name	ClinicalTrials.gov identifier	Expected completion	Phase	Participants	HF phenotype	Recruitment status
Torasemide						
TRANSFORM-HF	NCT03296813	2022	3	6000	HFrEF	A
Acetazolamide						
ADVOR	NCT03505788	2021	4	519	WHF	A
Other combinations of diuretic						
CLOROTIC	NCT01647932	2019	4	304	AHF	A
Spironolactone						
SPIRRIT	NCT02901184	2022	3	3200	HFpEF	A
SPIRIT-HF	2017-000697-11*	?	3	1300	HFmrEF/HFpEF	A
SGLT2i						
Empagliflozin						
EMPERIAL-R	NCT03448419	2019	3	300	HFrEF	A
EMPERIAL-P	NCT03448406	2019	3	300	HFpEF	A
EMMY	NCT03087773	2020	3	476	HF (post AMI)	A
EMPEROR-P	NCT03057951	2021	3	6000	HFpEF	A
EMPEROR-R	NCT03057977	2020	3	2850	HFrEF	A
Sotagliflozin						
SOLOIST-WHF	NCT03521934	2021	3	4000	HFrEF and T2DM	A
Dapagliflozin						
PRESERVED-HF	NCT03030235	2019	4	320	HFpEF	A
DAPA-HF	NCT03036124	2019	3	4744	HFrEF	T
DEFINE-HF	NCT02653482	2019	4	263	HFrEF	T
DELIVER	NCT03619213	2021	3	4700	HFpEF	A
Intravenous iron						
IRONMAN	NCT02642562	2021	3	1300	HFrEF	A
HEART-FID	NCT03037931	2022	3	3014	HFrEF	A
FAIR-HF2	NCT03036462	2020	4	1200	HFrEF	A
FAIR-HFpEF	NCT03074591	2019	2	200	HFpEF	A
Affirm-HF	NCT02937454	2019	4	1100	AHF (LVEF < 50%)	A
Micronutrients: copper, selenium and co-enzyme Q10						
Q10	NCT03133793	2020	2	250	HFpEF	A
TRACER-HF	NCT03875183	2021	2	200	HFrEF	Not yet A
Pulmonary hypertension and right ventricular dysfunction						
Treprostinil						
	NCT03037580	2020	3	310	HFpEF and PHT	A
Macitentan						
SERENADE	NCT03153111	2020	2	300	HFpEF and RV Dysfunction and PHT	A

Table 1 (continued)

Name	ClinicalTrials.gov identifier	Expected completion	Phase	Participants	HF phenotype	Recruitment status
Cardiac amyloidosis						
Tafamidis-long term	NCT02791230	2024	3	1400	NA	A
Influenza vaccination						
RCT-IVVE	NCT02762851	2020	4	5000	NYHA II-IV	A
INVESTED	NCT02787044	2021	4	9300	HFrEF	A
Hydralazine and metformin						
DANHEART	NCT03514108	2023	4	1500	HFrEF	A
Devices and others						
AdaptResponse	NCT02205359	2023	NA	3700	Adaptive CRT and HFrEF	A
APAF-CRT	NCT02137187	2021	2–3	1830	Atrio-ventricular junction ablation for AF and HF	A
REVIVED-BCIS2	NCT01920048	2022	3	700	IHD and HFrEF (Revasc)	A
GUIDE-CMR	NCT01918215	2023	NA	428	ICD v ILR for HF and LVEF 35–50%	A
RESET-ICD	NCT03494933	2021	NA	2030	CRT-P vs CRT-D	A
RESHAPE-HF2	NCT02444338	2021	NA	420	MR and HFrEF	A
ADVENT-HF	NCT01128816	2020	4	860	Sleep apnoea and LVEF < 45%	A
PURE-HF	NCT03161158	2021	NA	864	HF and severe congestion (venous ultrafiltration)	A

Smaller trials are summarised in Table 1 supplementary

*EUDRACT number

HFrEF, heart failure with reduced left ventricular ejection fraction (LVEF); *HFpEF*, heart failure with preserved left ventricular ejection fraction; *HFmrEF*, heart failure with mid-range left ventricular ejection fraction; *AF*, atrial fibrillation; *MR*, mitral regurgitation; *IHD*, ischaemic heart disease; *T2DM*, type 2 diabetes; *ICD*, implantable cardioverter-defibrillator; *ILR*, implantable loop recorder; *CRT*, cardiac resynchronization therapy; *PHT*, pulmonary hypertension; *AHF*, acute heart failure; *AMI*, acute myocardial infarction; *A*, active recruitment; *T*, recruitment terminated

stimulator which increases cGMP production. Phase 2 trials showed that vericiguat is well tolerated in patients with HFrEF [34]. A large (~4,500 patients) phase 3 trial (VICTORIA; NCT02861534) is currently evaluating whether vericiguat improves morbidity and mortality compared with placebo in patients with chronic HFrEF [35].

Nitroxyl is a second-generation donor of nitric oxide that causes vasodilatation and may have inotropic effects, which are only partially mediated by an increase in cGMP [36]. A phase 2 trial (STAND-UP; NCT03016325) is currently evaluating the safety and efficacy (changes in NT-proBNP and symptoms) of 48-h infusion of nitroxyl in 310 patients admitted with decompensated HFrEF. Smaller mechanistic trials are investigating its effects on cardiac and renal function.

Inotropic agents

Omecamtiv mecarbil, levosimendan, digoxin and recombinant human neuregulin-1

Omecamtiv mecarbil (OM) is a cardiac myosin activator that alters the kinetics of actin/myosin cross-bridges, prolonging the duration of the systole and, thus, stroke volume, without increasing ATP consumption [37]. Phase II trials showed that IV administration of OM in patients with acutely decompensated HFrEF had the expected haemodynamic effects but no clear clinical benefit [38]. In The Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF) trial, oral OM given for 20 weeks was safe and reduced LV size and plasma concentrations of NT-proBNP levels; the latter effect persisted for 4 weeks after treatment withdrawal suggesting that long-term favourable structural remodelling had occurred [39]. The Phase II trial programme has repeatedly shown small increases in serum troponin concentrations, raising concerns about safety that, so far, appears unfounded. Increases in troponin appear unrelated to any clinical evidence of myocardial ischaemia or adverse outcomes. A large (n ~ 8,000) phase III trial of patients with chronic HFrEF (with 25% planned to be enrolled during a hospitalisation for an episode of decompensation) is nearing completion of enrolment and should report in 2021 (GALACTIC-HF; NCT02929329).

Levosimendan, a vasodilator and calcium sensitiser, has been used to treat refractory HF in many countries despite two large neutral trials conducted in patients with acute HF and a large trial of an oral formulation in patients with chronic severe HF that showed reductions in NT-proBNP and an improvement in QoL but did not otherwise improve outcome [40, 41]. Recently, small trials have explored the effects of giving levosimendan intermittently to patients with chronic severe HFrEF and shown that this can reduce plasma concentrations of NT-proBNP [42]. Larger trials are now attempting to determine whether this strategy can improve symptoms, exercise capacity, morbidity and mortality in patients with HFrEF.

Neuregulin-1 proteins are important for the development and function of cardiac myocytes. Small phase II studies reported that recombinant human neuregulin-1 improved haemodynamics and promoted reverse LV remodelling in patients with HFrEF [43, 44]. A phase III study is currently testing whether, compared to placebo, use of daily (for 10 days) IV infusions, followed by weekly boluses, of recombinant human neuregulin-1 is feasible, safe and effective in reducing mortality in Chinese patients with mild to moderate chronic HFrEF.

Digoxin may be the oldest medicine still prescribed for heart failure, but controversies persist about its benefits. In the DIG trial, conducted before many current HF treatments were available, digoxin did not reduce mortality compared to placebo, although it did reduce HF hospitalisations by 28%. A retrospective analysis suggested that patients with serum concentrations of digoxin of 0.5–0.9 ng/mL were more likely to benefit [45, 46]. A prospective, randomised, placebo-controlled trial is testing whether lower doses of digoxin, guided by measurements of its plasma concentrations (0.5–0.9 ng/mL), will reduce HF hospitalisations and cardiovascular death in ~ 1,000 symptomatic patients with chronic HF and a reduced or mid-range LVEF (< 50%) (NCT03783429).

Congestion

Congestion is an important cause of the symptoms and signs of HF, leads to adverse atrial and ventricular remodelling, arrhythmias and worsening renal function and is associated with poor outcomes [47, 48]. Controlling congestion is a key therapeutic goal in the management of heart failure. However, clinical identification of congestion is challenging, unless severe. Up to 50% of outpatients with HF who were considered to be clinically dry had sub-clinical congestion on ultrasound, either in the pulmonary interstitium (lung B-lines) or in the intra-vascular space, as measured by a distended inferior vena cava (IVC). Sub-clinical congestion was associated with a poor outcome [49, 50]. Whether treatment guided by ultrasound assessments is feasible and effective for the management of congestion in patients with HF is currently being explored in several small- to medium-sized trials. Biomarker-guided management of congestion has met with mixed success, largely because treatment was similarly effective in each arm [51]. A large trial (GUIDE-HF; NCT03387813) is currently investigating whether pulmonary artery pressure monitoring using a small implanted device can help guide treatment of congestion.

Torasemide, acetazolamide and other diuretics

Loop diuretics are the most potent diuretic agents, and furosemide is the most widely used in patients with HF. However, other loop diuretics, such as bumetanide and torasemide, are either better absorbed or delivered more reliably to the renal tubule. Meta-analysis of small randomised trials and observational studies suggests that torasemide might be superior to furosemide, but no substantial randomised trial has yet compared these two agents [52–54]. TRANSFORM-HF (NCT03296813) is an ongoing, multi-centre, unblinded, trial that will randomise, prior to discharge, ~ 6000 patients admitted with decompensated heart failure to long-term treatment with oral torasemide or furosemide to investigate effects on morbidity and mortality.

Other options for treating resistant congestion in patients HF exist, such as combining different classes of diuretics, but their safety and efficacy have been rarely tested in clinical trials [55]. Most of the sodium filtered by kidneys is reabsorbed in the proximal tubule of the nephron. Acetazolamide, a carbonic anhydrase inhibitor, should decrease the amount of sodium reabsorbed in the proximal nephron and enhance the distal effects of loop diuretics. The Acetazolamide in Decompensated heart failure with Volume OveRload (ADVOR) is a randomised, double-blind, placebo-controlled trial which will test whether combining acetazolamide with a loop diuretic is more successful in achieving decongestion in ~ 500 patients admitted with HF and signs of fluid overload [56].

Sodium glucose co-transporter 2 inhibitors

Although not everyone would agree that it is the principal mechanism of action of sodium glucose co-transporter 2 inhibitors (SGLT2i), there is little doubt that diuresis contributes to their effects in HF. SGLT2i reduce glucose reabsorption in the proximal nephron, increasing delivery of glucose and sodium to the distal nephron and inducing an osmotic diuresis. Whether SGLT2i have additional metabolic effects on the heart and kidney by inhibiting carbonic anhydrase or increasing the availability of ketones as a metabolic substrate for the myocardium is uncertain [57]. Empagliflozin reduced all-cause mortality and hospitalisation for heart failure in patients with type 2 diabetes mellitus (T2DM) and ischaemic heart disease (IHD) [58]. Trials of canagliflozin and dapagliflozin also suggested a reduction in hospitalisations for HF [59–61]; although the relative risk reduction was substantial, the absolute benefits were very small, creating uncertainty about whether they are clinically meaningful. Interestingly, the programme of phase III trials for HF has not required patients to have T2DM and has enrolled a broad range of patients with HFrEF and HFpEF as well as in-patients and out-patients. The first of these trials is likely to report in 2019 (DAPA-HF) [62].

Intravenous iron

Up to 50% of patients with HF have iron deficiency (ID), with or without anaemia. ID is associated with adverse outcomes, even in the absence of anaemia, and is a potential target of treatment [63]. Oral iron is widely available and cheap but only a small amount of oral iron can be absorbed in a day (perhaps 2–10 mg/day compared with a total deficiency of > 1,000 mg) and many patients have GI intolerance to oral iron. Oral iron absorption may be impaired in heart failure, possibly due to increased secretion of hepatic hepcidin, but even if it is not, oral supplementation would take many months to correct iron deficiency [64]. Modern preparations of IV iron are safe and well tolerated and improve symptoms and exercise capacity in patients with HFrEF. An individual patient meta-analysis from four randomised controlled trials including 839 patients with HFrEF and ID, of whom 504 were randomised to IV ferric carboxymaltose, suggests that short-term (mean follow-up 31 weeks) treatment could also reduce HF hospitalisations when compared with placebo. However, the analysis included very few cardiovascular ($n = 34$) or other ($n = 4$) deaths and does not prove long-term safety [65]. Four substantial (> 1000 patients) randomised trials are currently investigating whether different formulations of IV iron (either iron isomaltoside or ferric carboxymaltose) improve morbidity and mortality in patients with chronic or acute HF. These trials have included far more patients and recorded far more events than the published evidence but have not yet been stopped for benefit. Phase II trials are also investigating the potential benefits of IV iron on symptoms, exercise tolerance and quality of life of patients with HFpEF and ID (NCT03074591).

Copper, selenium and co-enzyme Q10

Heart failure may be accompanied by high plasma copper concentrations but myocardial copper depletion. There is evidence from both animal models and a limited amount of human data that copper chelation may be beneficial [66]. However, an alternative view is that low doses of the chelating agent trientine might facilitate copper redistribution to tissues. This concept is currently being tested in a 200-patient, dose-ranging trial (NCT03875183).

Co-enzyme Q10 is an essential component of the mitochondrial electron transport chain and both co-enzyme Q10 and selenium have an important role in many metabolic processes. Lower plasma concentrations of Q10 and selenium have been associated with adverse outcomes in heart failure [67–69]. Two trials showed a reduction in mortality with co-enzyme Q10 supplements for patients with or at high-risk of heart failure and a broad range of LVEF [70, 71]. Randomised controlled trials are underway.

Other trials

Pulmonary hypertension and right ventricular dysfunction

Pulmonary hypertension (PHT) is common, especially in patients with advanced heart failure, due to a combination of left atrial hypertension, pulmonary arteriolar hypertrophy and pulmonary vasoconstriction. Small trials have shown that sildenafil, a selective inhibitor of type 5 phosphodiesterase, might improve haemodynamics and exercise performance in patients with HFrEF and PHT; other trials should report soon [72]. In HFpEF, sildenafil was not beneficial [73]. The effects of treprostinil, a synthetic analogue of prostacyclin with potent vasodilator properties, on exercise capacity and NT-proBNP are currently under investigation in a trial ($n \sim 300$) of HFpEF and PHT. However, trials in patients with HFrEF were stopped for harm. The safety, and effect on NT-proBNP levels of macitentan, an antagonist/blocker of endothelin receptors, will be also studied in 300 patients with HFpEF complicated by PHT or right ventricular dysfunction (SERENADE, NCT03153111).

Amyloidosis

Accumulation of wild-type or variant transthyretin amyloid occurs when fibrils become unstable and misfold. Recent reports suggest that 15–20% of patients with HFpEF may have TTR amyloidosis. These patients have a poor outcome and may not respond to conventional treatments [74]. A recent trial showed that treatment with tafamidis, which binds to transthyretin, preventing tetramer dissociation and amyloidogenesis, improves symptoms, quality of life and exercise capacity and reduces cardiovascular hospitalisations and mortality in patients with transthyretin amyloid cardiomyopathy [75]. The costs of tafamidis are currently prohibitive, preventing large-scale uptake. However, demonstration of the effectiveness of treatment will lead to changes in diagnostic pathways (at least to identify patients who may not benefit from some treatments or for selection into clinical trial even if treatment is unaffordable). In due course, the cost of tafamidis will fall.

Influenza vaccination

Influenza might be an important precipitant of HF hospitalisations [76]. A recent observational study from Denmark suggested that influenza vaccination might be associated with better outcomes in patients with heart failure, but it also reported that a large proportion (> 40%) of patients with heart failure do not receive influenza vaccination, which might reflect lack of evidence arising from trials and therefore weak recommendations from guidelines [77]. Two large trials investigating the ability of influenza vaccinations to reduce morbidity and mortality should report in the next few years. The Influenza Vaccine To Prevent Adverse Vascular Events (RCT-IVVE) will randomise ~ 5,000 patients with HF globally. The INfluenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure (INVESTED) will compare high-dose trivalent influenza vaccine vs standard-dose quadrivalent influenza vaccine in almost 10,000 patients with a recent myocardial infarction or hospitalisation for HF.

Conclusions

Over the last 30 years, various pathways leading to the development and progression of heart failure have been identified and successfully targeted with effective therapies. This has improved the quality of life and survival for millions of individuals with HFrEF, globally. Hopefully, new treatments will offer further improvements and extend these successes to the treatment of HFpEF and other specific causes and phenotypes of HF. New concepts of how HF should be defined combined with new analytical approaches using large data-sets will reshape its epidemiology and offer new therapeutic targets. However, old age rather than cardiac dysfunction may be the next great barrier to overcome.

Compliance with ethical standards

Conflict of interest Dr. Cleland reports personal fees from Johnson & Johnson; grants and personal fees from Amgen; personal fees from AstraZeneca; grants and personal fees from Bayer; grants and personal fees from Bristol Myers Squibb; personal fees from GSK; grants, personal fees and non-financial support from Medtronic; personal fees from Myokardia; grants, personal fees and non-financial support from Novartis; grants and personal fees from Philips; grants and non-financial support from Pharmacosmos; grants and non-financial support from PharmaNord; personal fees from Sanofi; personal fees from Servier; grants and personal fees from Stealth Biopharmaceuticals; grants and personal fees from Torrent Pharmaceuticals; and grants, personal fees and non-financial support from Vifor.

Dr. Pellicori has received support for travel from Novartis and Vifor.

References

1. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH, Goldman S, Cobb FR, Shah PM, Saunders R, Fletcher RD, Loeb HS, Hughes VC, Baker B (1986) Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med 314:1547–1552

2. The CONSENSUS Trial Study Group (1987) Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 316:1429–1435
3. The SOLVD Investigators (1991) Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 325:293–302
4. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH (1996) The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 334:1349–1355
5. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J (1999) The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 341:709–717
6. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L (2010) SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 376:875–885
7. Cleland et al. Effect of ivabradine on mortality in patients with heart failure and a reduced left ventricular ejection fraction not receiving a beta-blocker: an analysis from SHIFT. Eur Heart J, Volume 38, Issue suppl_1, August 2017, ehx501.246
8. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L, Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators (2005) The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 352:1539–1549
9. Cleland JG, Abraham WT, Linde C, Gold MR, Young JB, Claude Daubert J, Sherfesee L, Wells GA, Tang AS (2013) An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. Eur Heart J 34:3547–3556
10. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M (1996) Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 335:1933–1940
11. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjær H, Brandes A, Thøgersen AM, Gustafsson F, Egstrup K, Videbæk R, Hassager C, Svendsen JH, Høfsten DE, Torp-Pedersen C, Pehrson S, DANISH Investigators (2016) Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 375: 1221–1230
12. Blue L, Lang E, McMurray JJ, Davie AP, McDonagh TA, Murdoch DR, Petrie MC, Connolly E, Norrie J, Round CE, Ford I, Morrison CE (2001) Randomised controlled trial of specialist nurse intervention in heart failure. BMJ. 323:715–718
13. Cleland JG, McDonagh T, Rigby AS, Yassin A, Whittaker T, Dargie HJ, National Heart Failure Audit Team for England and Wales (2011) The national heart failure audit for England and Wales 2008-2009. Heart. 97:876–886
14. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR (2014) Angiotensin-neprilysin inhibition versus enalapril in heart failure. PARADIGM-HF Investigators and Committees. N Engl J Med 371:993–1004
15. Clark AL, Lammiman MJ, Goode K, Cleland JG (2009) Is taking part in clinical trials good for your health? A cohort study. Eur J Heart Fail 11:1078–1083
16. Pellicori P, Urbinati A, Shah P, MacNamara A, Kazmi S, Dierckx R, Zhang J, Cleland JGF, Clark AL (2017) What proportion of patients with chronic heart failure are eligible for sacubitril-valsartan? Eur J Heart Fail 19:768–778
17. Greene SJ, Fonarow GC, DeVore AD, Sharma PP, Vaduganathan M, Albert NM, Duffy CI, Hill CL, McCague K, Patterson JH, Spertus JA, Thomas L, Williams FB, Hernandez AF, Butler J (2019) Longitudinal titration of medical therapy for heart failure with reduced ejection fraction: CHAMP-HF registry. J Am Coll Cardiol. https://doi.org/10.1016/j.jacc.2019.02.015
18. van Riet EE, Hoes AW, Limburg A, Landman MA, van der Hoeven H, Rutten FH (2014) Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. Eur J Heart Fail 16:772–777
19. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ, HYVET Study Group (2008) Treatment of hypertension in patients 80 years of age or older. N Engl J Med 358:1887–1898
20. Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozdz J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavoliuniene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L (2013) Heart Failure Association of the ESC. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 15:1173–1184
21. Curtis LH, Whellan DJ, Hammill BG, Hernandez AF, Anstrom KJ, Shea AM, Schulman KA (2008) Incidence and prevalence of heart failure in elderly persons, 1994-2003. Arch Intern Med 168:418–424
22. Torabi A, Cleland JG, Khan NK, Loh PH, Clark AL, Alamgir F, Caplin JL, Rigby AS, Goode K (2008) The timing of development and subsequent clinical course of heart failure after a myocardial infarction. Eur Heart J 29:859–870
23. Torabi A, Rigby AS, Cleland JG (2009) Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. J Am Coll Cardiol 55:79–81
24. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, Allison M, Hemingway H, Cleland JG, McMurray JJV, Rahimi K (2018) Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet 391:572–580
25. Good JM, Peters M, Wilkins M, Jackson N, Oakley CM, Cleland JG (1995) Renal response to candoxatrilat in patients with heart failure. J Am Coll Cardiol 25:1273–1281
26. Packer M, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau JL, Swedberg K (2002) Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation. 106:920–926
27. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R, Braunwald E, PIONEER-HF Investigators (2019) Angiotensin-neprilysin inhibition in acute decompensated heart failure. N Engl J Med 380:539–548
28. Morrow DA, Velazquez EJ, DeVore AD, Desai AS, Duffy CI, Ambrosy AP, Gurmu Y, McCague K, Rocha R, Braunwald E (2019) Clinical outcomes in patients with acute decompensated heart failure randomly assigned to sacubitril/valsartan or enalapril in the PIONEER-HF trial. Circulation. https://doi.org/10.1161/CIRCULATIONAHA.118.039331
29. Kang DH, Park SJ, Shin SH, Hong GR, Lee S, Kim MS, Yun SC, Song JM, Park SW, Kim JJ (2019) Angiotensin receptor neprilysin

inhibitor for functional mitral regurgitation. Circulation. 139:1354–1365

30. Solomon SD, Rizkala AR, Lefkowitz MP, Shi VC, Gong J, Anavekar N, Anker SD, Arango JL, Arenas JL, Atar D, Ben-Gal T, Boytsov SA, Chen CH, Chopra VK, Cleland J, Comin-Colet J, Duengen HD, Echeverría Correa LE, Filippatos G, Flammer AJ, Galinier M, Godoy A, Goncalvesova E, Janssens S, Katova T, Køber L, Lelonek M, Linssen G, Lund LH, O'Meara E, Merkely B, Milicic D, Oh BH, Perrone SV, Ranjith N, Saito Y, Saraiva JF, Shah S, Seferovic PM, Senni M, Sibulo AS Jr, Sim D, Sweitzer NK, Taurio J, Vinereanu D, Vrtovec B, Widimský J Jr, Yilmaz MB, Zhou J, Zweiker R, Anand IS, Ge J, CSP L, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, Van Veldhuisen DJ, Zannad F, Zile MR, McMurray JJV (2018) Baseline characteristics of patients with heart failure and preserved ejection fraction in the PARAGON-HF trial. Circ Heart Fail 11(7): e004962
31. Beusekamp JC, Tromp J, van der Wal HH, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Metra M, Ng LL, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zwinderman AH, Rossignol P, Zannad F, Voors AA, van der Meer P (2018) Potassium and the use of renin-angiotensin-aldosterone system inhibitors in heart failure with reduced ejection fraction: data from BIOSTAT-CHF. Eur J Heart Fail 20:923–930
32. Michel A, Martín-Pérez M, Ruigómez A, García Rodríguez LA (2015) Risk factors for hyperkalaemia in a cohort of patients with newly diagnosed heart failure: a nested case-control study in UK general practice. Eur J Heart Fail 17:205–213
33. Stasch JP, Pacher P, Evgenov OV (2011) Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease. Circulation. 123:2263–2273
34. Gheorghiade M, Greene SJ, Butler J, Filippatos G, Lam CS, Maggioni AP, Ponikowski P, Shah SJ, Solomon SD, Kraigher-Krainer E, Samano ET, Müller K, Roessig L, Pieske B, SOCRATES-REDUCED Investigators and Coordinators (2015) Effect of vericiguat, a soluble guanylate cyclase stimulator, on natriuretic peptide levels in patients with worsening chronic heart failure and reduced ejection fraction: the SOCRATES-REDUCED randomized trial. JAMA 314:2251–2262
35. Armstrong PW, Roessig L, Patel MJ, Anstrom KJ, Butler J, Voors AA, Lam CSP, Ponikowski P, Temple T, Pieske B, Ezekowitz J, Hernandez AF, Koglin J, O'Connor CM (2018) A Multicenter, randomized, double-blind, placebo-controlled trial of the efficacy and safety of the oral soluble guanylate cyclase stimulator. The VICTORIA Trial JACC Heart Fail 6:96–104
36. Tita C, Gilbert EM, Van Bakel AB, Grzybowski J, Haas GJ, Jarrah M, Dunlap SH, Gottlieb SS, Klapholz M, Patel PC, Pfister R, Seidler T, Shah KB, Zieliński T, Venuti RP, Cowart D, Foo SY, Vishnevsky A, Mitrovic V. A Phase 2a dose-escalation study of the safety, tolerability, pharmacokinetics and haemodynamic effects of BMS-986231 in hospitalized patients with heart failure with reduced ejection fraction. Eur J Heart Fail 2017;19:1321–1332
37. Cleland JG, Teerlink JR, Senior R, Nifontov EM, Mc Murray JJ, Lang CC, Tsyrlin VA, Greenberg BH, Mayet J, Francis DP, Shaburishvili T, Monaghan M, Saltzberg M, Neyses L, Wasserman SM, Lee JH, Saikali KG, Clarke CP, Goldman JH, Wolff AA, Malik FI (2011) The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure: a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial. Lancet. 378(9792):676–683
38. Teerlink JR, Felker GM, McMurray JJV, Ponikowski P, Metra M, Filippatos GS, Ezekowitz JA, Dickstein K, JGF C, Kim JB, Lei L, Knusel B, Wolff AA, Malik FI, Wasserman SM, ATOMIC-AHF Investigators (2016) Acute treatment with omecamtiv mecarbil to increase contractility in acute heart failure: the ATOMIC-AHF study. J Am Coll Cardiol 67:1444–1455
39. Teerlink JR, Felker GM, McMurray JJ, Solomon SD, Adams KF Jr, Cleland JG, Ezekowitz JA, Goudev A, Macdonald P, Metra M, Mitrovic V, Ponikowski P, Serpytis P, Spinar J, Tomcsányi J, Vandekerckhove HJ, Voors AA, Monsalvo ML, Johnston J, Malik FI, Honarpour N, COSMIC-HF Investigators (2016) Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): a phase 2, pharmacokinetic, randomised, placebo-controlled trial. Lancet 388:2895–2903
40. Nieminen MS, Cleland JG, Eha J, Belenkov Y, Kivikko M, Põder P, Sarapohja T (2008) Oral levosimendan in patients with severe chronic heart failure –the PERSIST study. Eur J Heart Fail 10: 1246–1254
41. Packer M, Colucci W, Fisher L, Massie BM, Teerlink JR, Young J, Padley RJ, Thakkar R, Delgado-Herrera L, Salon J, Garratt C, Huang B, Sarapohja T (2013) REVIVE Heart Failure Study Group. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. JACC Heart Fail 1:103–111
42. Comín-Colet J, Manito N, Segovia-Cubero J, Delgado J, García Pinilla JM, Almenar L, Crespo-Leiro MG, Sionis A, Blasco T, Pascual-Figal D, Gonzalez-Vilchez F, Lambert-Rodríguez JL, Grau M, Bruguera J (2018) LION-HEART Study Investigators. Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: the LION-HEART multicentre randomised trial. Eur J Heart Fail 20: 1128–1136
43. Jabbour A, Hayward CS, Keogh AM, Kotlyar E, McCrohon JA, England JF, Amor R, Liu X, Li XY, Zhou MD, Graham RM, Macdonald PS (2011) Parenteral administration of recombinant human neuregulin-1 to patients with stable chronic heart failure produces favourable acute and chronic haemodynamic responses. Eur J Heart Fail 13:83–92
44. Gao R, Zhang J, Cheng L, Wu X, Dong W, Yang X, Li T, Liu X, Xu Y, Li X, Zhou M (2010) A Phase II, randomized, double-blind, multicenter, based on standard therapy, placebo-controlled study of the efficacy and safety of recombinant human neuregulin-1 in patients with chronic heart failure. J Am Coll Cardiol 55:1907–1914
45. Ahmed A, Rich MW, Love TE, Lloyd-Jones DM, Aban IB, Colucci WS, Adams KF, Gheorghiade M (2006) Digoxin and reduction in mortality and hospitalization in heart failure: a comprehensive post hoc analysis of the DIG trial. Eur Heart J 27(2):178–186
46. Ahmed A, Pitt B, Rahimtoola SH, Waagstein F, White M, Love TE, Braunwald E (2008) Effects of digoxin at low serum concentrations on mortality and hospitalization in heart failure: a propensity-matched study of the DIG trial. Int J Cardiol 123:138–146
47. Pellicori P, Cleland JG, Zhang J, Kallvikbacka-Bennett A, Urbinati A, Shah P, Kazmi S, Clark AL (2016) Cardiac dysfunction, congestion and loop diuretics: their relationship to prognosis in heart failure. Cardiovasc Drugs Ther 30:599–609
48. Pellicori P, Kallvikbacka-Bennett A, Dierckx R, Zhang J, Putzu P, Cuthbert J, Boyalla V, Shoaib A, Clark AL, Cleland JG (2015) Prognostic significance of ultrasound-assessed jugular vein distensibility in heart failure. Heart. 101:1149–1158
49. Pellicori P, Clark AL, Kallvikbacka-Bennett A, Zhang J, Urbinati A, Monzo L, Dierckx R, Anker SD, Cleland JGF (2017) Non-invasive measurement of right atrial pressure by near-infrared spectroscopy: preliminary experience. A report from the SICA-HF study. Eur J Heart Fail 19:883–892
50. Pellicori P, Shah P, Cuthbert J, Urbinati A, Zhang J, Kallvikbacka-Bennett A, Clark AL, Cleland JGF (2019) Prevalence, pattern and clinical relevance of ultrasound indices of congestion in outpatients with heart failure. Eur J Heart Fail. https://doi.org/10.1002/ejhf.1383

51. Felker GM, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, Januzzi JL Jr, Mark DB, Piña IL, Passmore G, Whellan DJ, Yang H, Cooper LS, Leifer ES, Desvigne-Nickens P, O'Connor CM (2017) Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. JAMA. 318:713–720
52. Mentz RJ, Hasselblad V, DeVore AD, Metra M, Voors AA, Armstrong PW, Ezekowitz JA, Tang WH, Schulte PJ, Anstrom KJ, Hernandez AF, Velazquez EJ, O'Connor CM (2016) Torsemide versus furosemide in patients with acute heart failure (from the ASCEND-HF trial). Am J Cardiol 117:404–411
53. DiNicolantonio JJ (2012) Should torsemide be the loop diuretic of choice in systolic heart failure? Futur Cardiol 8:707–728
54. Miles JA, Hanumanthu BK, Patel K, Chen M, Siegel RM, Kokkinidis DG (2019) Torsemide versus furosemide and intermediate-term outcomes in patients with heart failure: an updated meta-analysis. J Cardiovasc Med (Hagerstown). https://doi.org/10.2459/JCM.0000000000000794
55. Jentzer JC, DeWald TA, Hernandez AF (2010) Combination of loop diuretics with thiazide-type diuretics in heart failure. J Am Coll Cardiol 56:1527–1534
56. Mullens W, Verbrugge FH, Nijst P, Martens P, Tartaglia K, Theunissen E, Bruckers L, Droogne W, Troisfontaines P, Damman K, Lassus J, Mebazaa A, Filippatos G, Ruschitzka F, Dupont M (2018) Rationale and design of the ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial. Eur J Heart Fail 20:1591–1600
57. Packer M, Anker SD, Butler J, Filippatos G, Zannad F (2017) Effects of sodium-glucose cotransporter 2 inhibitors for the treatment of patients with heart failure: proposal of a novel mechanism of action. JAMA Cardiol 2:1025–1029
58. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE, EMPA-REG OUTCOME® trial investigators (2016) Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. Eur Heart J 37:1526–1534
59. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW, CREDENCE Trial Investigators (2019) Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. https://doi.org/10.1056/NEJMoa1811744
60. Rådholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, Fulcher G, Barrett TD, Shaw W, Desai M, Matthews DR, Neal B (2018) Canagliflozin and heart failure in type 2 diabetes mellitus. Circulation. 138:458–468
61. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RHM, Kuder J, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Bonaca MP, Ruff CT, Desai AS, Goto S, Johansson PA, Gause-Nilsson I, Johanson P, Langkilde AM, Raz I, Sabatine MS, Wiviott SD (2019) Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation. https://doi.org/10.1161/CIRCULATIONAHA.119.040130
62. McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sabatine MS, Sjöstrand M, Solomon SD, DAPA-HF Committees and Investigators (2019) A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). Eur J Heart Fail. https://doi.org/10.1002/ejhf.1432
63. Cleland JG, Zhang J, Pellicori P, Dicken B, Dierckx R, Shoaib A, Wong K, Rigby A, Goode K, Clark AL (2016) Prevalence and outcomes of anemia and hematinic deficiencies in patients with chronic heart failure. JAMA Cardiol 1:539–547
64. Lewis GD, Malhotra R, Hernandez AF, McNulty SE, Smith A, Felker GM, Tang WHW, LaRue SJ, Redfield MM, Semigran MJ, Givertz MM, Van Buren P, Whellan D, Anstrom KJ, Shah MR, Desvigne-Nickens P, Butler J, Braunwald E, NHLBI Heart Failure Clinical Research Network (2017) Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: the IRONOUT HF randomized clinical trial. JAMA 317:1958–1966
65. Anker SD, Kirwan BA, van Veldhuisen DJ, Filippatos G, Comin-Colet J, Ruschitzka F, Lüscher TF, Arutyunov GP, Motro M, Mori C, Roubert B, Pocock SJ, Ponikowski P (2018) Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. Eur J Heart Fail 20:125–133
66. Zhang S, Liu H, Amarsingh GV, Cheung CC, Hogl S, Narayanan U, Zhang L, McHarg S, Xu J, Gong D, Kennedy J, Barry B, Choong YS, Phillips AR, Cooper GJ (2014) Diabetic cardiomyopathy is associated with defective myocellular copper regulation and both defects are rectified by divalent copper chelation. Cardiovasc Diabetol 13:100
67. McMurray JJ, Dunselman P, Wedel H, Cleland JG, Lindberg M, Hjalmarson A, Kjekshus J, Waagstein F, Apetrei E, Barrios V, Böhm M, Kamenský G, Komajda M, Mareev V, Wikstrand J, CORONA Study Group (2010) Coenzyme Q10, rosuvastatin, and clinical outcomes in heart failure: a pre-specified substudy of CORONA (controlled rosuvastatin multinational study in heart failure). J Am Coll Cardiol 56:1196–1204
68. Alehagen U, Alexander J, Aaseth J (2016) Supplementation with selenium and coenzyme Q10 reduces cardiovascular mortality in elderly with low selenium status. A secondary analysis of a randomised clinical trial. PLoS One 11:e0157541
69. Alexanian I, Parissis J, Farmakis D, Pantziou C, Ikonomidis I, Paraskevaidis I, Ioannidou S, Sideris A, Kremastinos D, Lekakis J, Filippatos G (2014) Selenium contributes to myocardial injury and cardiac remodeling in heart failure. Int J Cardiol 176:272–273
70. Morisco C, Trimarco B, Condorelli M (1993) Effect of coenzyme Q10 therapy in patients with congestive heart failure: a long-term multicenter randomized study. Clin Investig 71(8 Suppl):S134–S136
71. Mortensen SA, Rosenfeldt F, Kumar A, Dolliner P, Filipiak KJ, Pella D, Alehagen U, Steurer G, Littarru GP, Q-SYMBIO Study Investigators (2014) The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. JACC Heart Fail 2:641–649
72. Cooper TJ, Guazzi M, Al-Mohammad A, Amir O, Bengal T, Cleland JG, Dickstein K (2013) Sildenafil in Heart failure (SilHF). An investigator-initiated multinational randomized controlled clinical trial: rationale and design. Eur J Heart Fail 15:119–122
73. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL, Deswal A, Stevenson LW, Givertz MM, Ofili EO, O'Connor CM, Felker GM, Goldsmith SR, Bart BA, McNulty SE, Ibarra JC, Lin G, Oh JK, Patel MR, Kim RJ, Tracy RP, Velazquez EJ, Anstrom KJ, Hernandez AF, Mascette AM, Braunwald E, RELAX Trial (2013) Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 309:1268–1277
74. González-López E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, Bornstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P (2015)

Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J 36:2585–2594

75. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C, ATTR-ACT Study Investigators (2018) Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 379:1007–1016
76. Kytömaa S, Hegde S, Claggett B, Udell JA, Rosamond W, Temte J, Nichol K, Wright JD, Solomon SD, Vardeny O (2019) Association of influenza-like illness activity with hospitalizations for heart failure: the atherosclerosis risk in communities study. JAMA Cardiol. https://doi.org/10.1001/jamacardio.2019.0549
77. Modin D, Jørgensen ME, Gislason G, Jensen JS, Køber L, Claggett B, Hegde SM, Solomon SD, Torp-Pedersen C, Biering-Sørensen T (2019) Influenza vaccine in heart failure. Circulation. 139:575–586

Heart Failure Reviews
https://doi.org/10.1007/s10741-019-09853-7

Usefulness and clinical relevance of left ventricular global longitudinal systolic strain in patients with heart failure with preserved ejection fraction

Carsten Tschöpe[1,2,3,4] · Michele Senni[5]

Abstract
In recent years, several studies have shown the usefulness and clinical relevance of left ventricular global longitudinal systolic strain (GLS) in different cardiovascular diseases. In line with this, the role of GLS in patients with heart failure with preserved ejection fraction (HFpEF) has achieved great importance in this predominant form of heart failure in the last years. In this regard, GLS has shown to be not only a sensitive parameter to detect subtle myocardial abnormalities but also a parameter of clinical and prognostic relevance in patients with HFpEF. In this review, we analyze the current evidence concerning the clinical relevance of GLS in patients with HFpEF and we discuss the potential usefulness of GLS in this complex and heterogeneous condition for which so far no effective therapy exists.

Keywords Global longitudinal strain · Heart failure · Echocardiography

Pathophysiological basis of LV longitudinal systolic dysfunction in HFpEF-comorbidities

It is well known that comorbid conditions such as type 2 diabetes, obesity, hypertension, history of coronary artery disease (CAD), and severe LV hypertrophy are characterized by causing interstitial fibrosis of the LV [1–7] affecting primarily the subendocardial layer of the LV [3–6]. In addition, several studies have evidenced the pivotal role of the subendocardial LV function (i.e., the longitudinal function of the LV) on the performance of the LV [8–11]. Accordingly, fibrotic processes of the LV, as a consequence of elevated rates of the abovementioned comorbidities, affect primarily the subendocardial fibers of the LV (i.e., the longitudinal systolic function of the LV) with minimal alterations of the midmyocardial and subepicardial LV fibers (i.e., LV circumferential, radial, and transverse systolic and diastolic functions), because the subendocardial cardiac fibers are particularly sensitive to the deleterious effects of fibrosis [3–6, 12, 13]. In line with this, several studies have also demonstrated a significant alteration of the longitudinal systolic and diastolic function of the LV in hypertensive, diabetic, obese, and CAD patients, despite a preserved LVEF [14–21]. In effect, Morris et al. in a HFpEF cohort characterized by high rates of these comorbid conditions found that 76% of these patients had LV longitudinal systolic dysfunction (i.e., LV subendocardial dysfunction), whereas almost 100% presented preserved LV circumferential, radial, transverse, and rotational systolic function (i.e., LV midmyocardial and subepicardial functions) [22]. In agreement with these findings, several studies have also evidenced a significant alteration of the longitudinal contractile function of the LV in subjects with HFpEF [23–30].

Pathophysiological mechanisms linked to an impaired LV longitudinal systolic function in HFpEF

While patients with HFpEF have principally impaired longitudinal contractile function of the LV with consequent

✉ Carsten Tschöpe
carsten.tschoepe@charite.de

1 Department of Internal Medicine and Cardiology, Charité - Universitätsmedizin Berlin, Campus Virchow Klinikum Augustenburgerplatz 1, 13353 Berlin, Germany

2 German Center for Cardiovascular Research (DZHK), Berlin, Germany

3 Berlin Institute of Health (BIH), Berlin, Germany

4 Berlin Center for Regenerative Therapies (BCRT), Campus Virchow Klinikum (CVK), Berlin, Germany

5 Cardiology Division, Cardiovascular Department, Papa Giovanni XXIII Hospital, Bergamo, Italy

low myocardial systolic performance, these patients are characterized by having normal LVEF. Accordingly, compensatory mechanisms to counteract this myocardial systolic dysfunction of the LV are activated. In this respect, Wang et al. [31] demonstrated that a preserved LV twist is the main compensatory mechanism that allows counteracting the longitudinal systolic dysfunction of the LV in HFpEF patients and thus maintaining a normal LVEF [31]. According to these findings, Morris et al. found that 100% of subjects with HFpEF had a normal LV rotational systolic function, which could act as a regulatory mechanism in order to balance a longitudinal LV systolic dysfunction in these patients [22]. Notwithstanding, in patients with HFpEF, this compensatory mechanism would not be enough to maintain a normal stroke volume or cardiac output during exercise. In this regard, a number of studies have demonstrated that patients with HFpEF have a significant decrease of the stroke volume or cardiac output during exercise as compared with healthy subjects [32–38], as a result of concentric LV remodeling, chronotropic incompetence, impaired arterial vasodilation, and/or reduced cardiac energetic reserve [32–39]. Accordingly, one of the mechanisms by which HFpEF patients could present an inefficient rise at exercise of the stroke volume and/or cardiac output could be in part due to an impaired LV longitudinal systolic function. Moreover, it is important to note that Wang et al. [40] found that an abnormal GLS during exercise was an independent predictor of the occurrence of all-cause death and HF hospitalization in patients with HFpEF [40].

Potential mechanisms linking an impaired LV longitudinal systolic function with the exertional dyspnea in HFpEF patients

Several investigations have highlighted the central role of LV diastolic dysfunction in the pathophysiology of HFpEF [41, 42]. In addition, several studies have shown that the symptomatology of patients with HFpEF is associated not only with LV diastolic dysfunction but also with an impaired LV longitudinal systolic function [22–25, 43]. The systolic and diastolic longitudinal functions of the LV cannot be interpreted as independent functions, since they are part of the same myocardial functional process [44]. Accordingly, both the diastolic and systolic longitudinal dysfunctions of the LV could contribute to the symptomatology of patients with HFpEF, i.e., elevation of LV filling pressures with subsequent dyspnea. In this respect, several studies, using strain imaging measurements demonstrated that both the diastolic and systolic LV longitudinal dysfunctions, even with normal LVEF, are significantly linked to elevated LV filling pressures [45–47].

Although elevated LV filling pressures have been implicated as one of the major mechanisms underlying HFpEF [48, 49], other studies have shown that additional pathophysiological processes, such as an impaired cardiac output reserve, could be involved in the development of the symptoms of patients with HFpEF [32–38]. In this regard, Borlaug et al. and Haykowsky et al. demonstrated that a diminished response of the cardiac output to the exercise is strongly associated with the reduced functional capacity during the effort in patients with HFpEF [32, 38]. Accordingly, as it happens in patients with HF and reduced LVEF [50], in patients with HFpEF, the perfusion of peripheral and respiratory muscles could decrease because of a low cardiac output (as a result in part of an impaired LV longitudinal systolic function), with consequent fatigue, breathlessness, and reduced functional capacity during exercise.

Usefulness and clinical relevance of LV global longitudinal systolic strain in HFpEF

Unlike systolic heart failure, HFpEF is characterized by a normal LV systolic function measured by Simpson's biplane method [51–54]. While it is correct, recent studies using GLS have suggested that the longitudinal systolic function of the LV is altered in HFpEF [23, 24, 29–31, 55–72]. In effect, a recent meta-analysis based on twenty-one studies (2100 HFpEF patients and 1974 controls) has confirmed that patients with HFpEF have significantly lower LV longitudinal systolic function than asymptomatic controls and that a longitudinal systolic dysfunction of the LV is common among HFpEF patients [28]. Accordingly, based on the findings of this meta-analysis, it is possible to confirm that the longitudinal systolic function of the LV as measured by GLS is altered in high proportion of patients with HFpEF.

While several studies have analyzed the association of GLS with cardiovascular outcomes in patients with HFpEF [28, 40, 55, 65, 66, 73–79], only 2 studies were multicentric, enrolled large number of patients, and had a high number of events (Table 1) [66, 73]. Accordingly, we consider that further large multicenter studies with the aim to confirm the prognostic role of abnormal GLS in HFpEF are warranted.

Clinical perspectives

Several clinical trials in HFpEF have been conducted with the aim of restoring LV diastolic dysfunction in subjects with HFpEF and thereby improving the prognosis of these patients

Table 1 Association of LV global longitudinal systolic strain (GLS) with outcomes in HFpEF

Study	Primary endpoint	Events (*n*)	Dichotomous analysis abnormal GLS HR (95%CI) Univariate	Dichotomous analysis abnormal GLS HR (95%CI) Multivariate	Continuous analysis GLS 1SD or 1% decrease HR (95%CI) Univariate	Continuous analysis GLS 1SD or 1% decrease HR (95%CI) Multivariate
Shah et al. [66]	CV death or HF hospitalization or aborted cardiac arrest	115	2.26 (1.53–3.34)	2.14 (1.26–3.66)	1.13 (1.08–1.19)	1.14 (1.04–1.24)
Donal et al. [73, 80]¥	Total death or HF hospitalization	177	Not reported	1.94 (1.22–3.07)	Not reported	Not reported
Pellicori et al. [81]	CV death or HF hospitalization	62	Not reported	Not reported	1.09 (1.00–1.19)	0.99 (0.90–1.11)
Freed et al. [82]	CV hospitalization or death	115	Not reported	Not reported	1.25 (1.03–1.52)	1.17 (0.95–1.43)
Obokata et al. [83]	CV death, nonfatal MI, and HF exacerbation	29	Not reported	Not reported	0.99 (0.87–1.13)	Not reported
Stampehl et al. [65]*	CV death or HF hospitalization	17	Not reported	Not reported	Not reported	Not reported
Wang et al. [40]#	Total death or HF hospitalization	43	Not reported	Not reported	Not reported	Not reported
DeVore et al. [55]≠	Total death or all-cause of hospitalization	35	Not reported	Not reported	Not reported	Not reported
Buggey et al. [84]**	Total death or all-cause of hospitalization	164	Not reported	Not reported	1.03 (0.99–1.08)	1.03 (0.98–1.08)

GLS indicates global LV longitudinal systolic strain (i.e., average longitudinal peak systolic strain from ≥ 12 LV segments). CV indicates cardiovascular. MI indicates myocardial infarction

¥ Donal et al. did not find any link between GLS and cardiovascular outcomes at 28 months in a continuous Cox proportional hazards regression analysis in 356 patients (univariate analysis: *p* value 0.1406; multivariate analysis: *p* value 0.1192; the HR of this analysis was not reported) [73]. However, in a post hoc analysis of this data in 348 patients [80], an abnormal GLS (< 16% in absolute values) was significantly linked to the combined endpoint total mortality or HF hospitalization at 18 months (HR 1.94 [1.22–3.07]), but an abnormal GLS was not linked to mortality-only at 18 months (HR 1.56 [0.84–2.89])

*Stampehl et al. found in a dichotomous univariate Cox proportional hazards regression analysis that an abnormal GLS (> − 15%) was linked to worse cardiovascular outcomes (chi-square 4.0, *p* 0.04; the HR of this analysis was not reported). In addition, patients with events had significantly lower GLS than those without events (− 11.6 ± 0.4% vs. − 16.5 ± 0.5%, *p* 0.03) [65]

Wang et al. did not find any link in a continuous logistic regression analysis between GLS at rest and cardiovascular outcomes (the HR of this analysis was not reported). In line with this, patients with events had similar values of GLS at rest than those without events (− 17.5 ± 3.7% vs. − 18.8 ± 2.9%, $p > 0.05$). However, GLS during exercise was significantly linked to cardiovascular outcomes (univariate analysis: HR 0.81 [0.72–0.92], $p < 0.01$; multivariate analysis: HR 0.79 [0.67–0.91], $p < 0.01$) in a continuous logistic regression analysis. In addition, patients with events had significantly lower GLS during exercise than those without events (− 18.2 ± 3.9% vs. − 21.4 ± 3.9%; *p* 0.001) [40]

≠ DeVore et al. did not find any link between the tertiles of GLS and a composite endpoint of time to death or all-cause hospitalization (*p* value 0.952) [55]

**Buggey et al. did not find any link between GLS and a composite endpoint of death or hospitalization at 1 year [84]

[80–86]. However, so far, no therapy has reduced the mortality in patients with HFpEF [80–86]. For this reason, new or additional pathophysiological processes should be also targeted in the treatment of this complex and heterogeneous disease [81, 87].

In the present review, it has been highlighted that by using GLS, it is possible to detect a longitudinal systolic dysfunction of the LV in patients with HFpEF. Thus, HFpEF should be considered not only as a pathophysiologic process of isolated LV diastolic dysfunction but also as a disorder with LV longitudinal systolic abnormalities. Hence, we consider that treatments destined to improve both the systolic and the diastolic longitudinal dysfunctions of the LV in patients with HFpEF could be of potential clinical and therapeutic relevance for this complex and heterogeneous cardiovascular disease for which so far no effective therapy exists.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Brilla CG, Funck RC, Rupp H (2000) Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. Circulation 102:1388–1393
2. Horwich TB, Fonarow GC (2010) Glucose, obesity, metabolic syndrome, and diabetes relevance to incidence of heart failure. J Am Coll Cardiol. 55:283–293
3. Hittinger L, Patrick T, Ihara T, Hasebe N, Shen YT, Kalthof B, Shannon RP, Vatner SF (1994) Exercise induces cardiac dysfunction in both moderate, compensated and severe hypertrophy. Circulation. 89:2219–2231
4. Marcos-Alberca P, García-Fernández MA, Ledesma MJ, Malpica N, Santos A, Moreno M, Bermejo J, Antoranz JC, Desco M (2002) Intramyocardial analysis of regional systolic and diastolic function in ischemic heart disease with Doppler tissue imaging: role of the different myocardial layers. J Am Soc Echocardiogr. 15:99–108
5. Chan J, Hanekom L, Wong C, Leano R, Cho GY, Marwick TH (2006) Differentiation of subendocardial and transmural infarction using two-dimensional strain rate imaging to assess short-axis and long-axis myocardial function. J Am Coll Cardiol. 48:2026–2033
6. Kang SJ, Lim HS, Choi BJ, Choi SY, Hwang GS, Yoon MH, Tahk SJ, Shin JH (2008) Longitudinal strain and torsion assessed by two-dimensional speckle tracking correlate with the serum level of tissue inhibitor of matrix metalloproteinase-1, a marker of myocardial fibrosis, in patients with hypertension. J Am Soc Echocardiogr. 21: 907–911
7. González A, López B, Querejeta R, Zubillaga E, Echeverría T, Díez J (2010) Filling pressures and collagen metabolism in hypertensive patients with heart failure and normal ejection fraction. Hypertension. 55:1418–1424
8. Martinez DA, Guhl DJ, Stanley WC, Vailas AC (2003) Extracellular matrix maturation in the left ventricle of normal and diabetic swine. Diabetes Res Clin Pract. 59:1–9
9. Carlsson M, Ugander M, Mosén H, Buhre T, Arheden H (2007) Atrioventricular plane displacement is the major contributor to left ventricular pumping in healthy adults, athletes, and patients with dilated cardiomyopathy. Am J Physiol Heart Circ Physiol. 292: H1452–H1459
10. Cameli M, Lisi M, Mondillo S, Padeletti M, Ballo P, Bigio E, Marchetti L, Biagioli B (2011) Prediction of stroke volume by global left ventricular longitudinal strain in patients undergoing assessment for cardiac transplantation. J Crit Care 26(4):433.e13–433.e20
11. Wang J, Khoury DS, Thohan V, Torre-Amione G, Nagueh SF (2007) Global diastolic strain rate for the assessment of left ventricular relaxation and filling pressures. Circulation. 115:1376–1383
12. Pope AJ, Sands GB, Smaill BH, LeGrice IJ (2008) Three-dimensional transmural organization of perimysial collagen in the heart. Am J Physiol Heart Circ Physiol. 295:H1243–H1252
13. Lumens J, Delhaas T, Arts T, Cowan BR, Young AA (2006) Impaired subendocardial contractile myofiber function in asymptomatic aged humans, as detected using MRI. Am J Physiol Heart Circ Physiol. 291:H1573–H1579
14. Fang ZY, Leano R, Marwick TH (2004) Relationship between longitudinal and radial contractility in subclinical diabetic heart disease. Clin Sci (Lond). 106:53–60
15. Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH (2004) Alterations of left ventricular myocardial characteristics associated with obesity. Circulation. 110:3081–3087
16. Ng AC, Delgado V, Bertini M, van der Meer RW, Rijzewijk LJ, Shanks M, Nucifora G, Smit JW, Diamant M, Romijn JA, de Roos A, Leung DY, Lamb HJ, Bax JJ (2009) Findings from left ventricular strain and strain rate imaging in asymptomatic patients with type 2 diabetes mellitus. Am J Cardiol. 104:1398–1401
17. Shivu GN, Abozguia K, Phan TT, Ahmed I, Weaver R, Narendran P, Stevens M, Frenneaux M (2009) Increased left ventricular torsion in uncomplicated type 1 diabetic patients: the role of coronary microvascular function. Diabetes Care. 32:1710–1712
18. Kouzu H, Yuda S, Muranaka A, Doi T, Yamamoto H, Shimoshige S, Hase M, Hashimoto A, Saitoh S, Tsuchihashi K, Miura T, Watanabe N, Shimamoto K (2011) Left ventricular hypertrophy causes different changes in longitudinal, radial, and circumferential mechanics in patients with hypertension: a two-dimensional speckle tracking study. J Am Soc Echocardiogr. 24:192–199
19. Hittinger L, Shannon RP, Kohin S, Manders WT, Kelly P, Vatner SF (1990) Exercise-induced subendocardial dysfunction in dogs with left ventricular hypertrophy. Circ Res. 66:329–343
20. Saito M, Khan F, Stoklosa T, Iannaccone A, Negishi K, Marwick TH (2016) Prognostic implications of LV strain risk score in asymptomatic patients with hypertensive heart disease. JACC Cardiovasc Imaging. 9:911–921
21. Kosmala W, Sanders P, Marwick TH (2017) Subclinical myocardial impairment in metabolic diseases. JACC Cardiovasc Imaging. 10: 692–703
22. Morris DA, Boldt LH, Eichstadt H, Ozcelik C, Haverkamp W (2012) Myocardial systolic and diastolic performance derived by 2-dimensional speckle tracking echocardiography in heart failure with normal left ventricular ejection fraction. Circ Heart Fail. 5: 610–620
23. Liu YW, Tsai WC, Su CT, Lin CC, Chen JH (2009) Evidence of left ventricular systolic dysfunction detected by automated function imaging in patients with heart failure and preserved left ventricular ejection fraction. J Card Fail. 15:782–789
24. Morris DA, Gailani M, Vaz Pérez A, Blaschke F, Dietz R, Haverkamp W, Ozcelik C (2011) Left atrial systolic and diastolic dysfunction in heart failure with normal left ventricular ejection fraction. J Am Soc Echocardiogr. 24:651–662
25. Morris DA, Gailani M, Vaz Pérez A, Blaschke F, Dietz R, Haverkamp W, Özcelik C (2011) Right ventricular myocardial systolic and diastolic dysfunction in heart failure with normal left ventricular ejection fraction. J Am Soc Echocardiogr. 24:886–897
26. Brucks S, Little WC, Chao T, Kitzman DW, Wesley-Farrington D, Gandhi S, Shihabi ZK (2005) Contribution of left ventricular diastolic dysfunction to heart failure regardless of ejection fraction. Am J Cardiol. 95:603–606
27. Pavlopoulos H, Nihoyannopoulos P (2008) Abnormal segmental relaxation patterns in hypertensive disease and symptomatic diastolic dysfunction detected by strain echocardiography. J Am Soc Echocardiogr. 21:899–906
28. Morris DA, Ma XX, Belyavskiy E, Radhakrishnan AK, Kropf M, Kraft R, Frydas A, Osmanoglou E, Marquez E, Donal E, Edelmann E, Tschöpe C, Pieske B, Pieske-Kraigher E (2017) Left ventricular longitudinal systolic function analysed by 2D speckle-tracking echocardiography in heart failure with preserved ejection fraction: a meta-analysis. Open Heart. 4(2):e000630
29. Kraigher-Krainer E, Shah AM, Gupta DK, Santos A, Claggett B, Pieske B, Zile MR, Voors AA, Lefkowitz MP, Packer M, McMurray JJ, Solomon SD, PARAMOUNT Investigators (2014) Impaired systolic function by strain imaging in heart failure with preserved ejection fraction. J Am Coll Cardiol 63:447–456
30. Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, Frenneaux M, Sanderson JE (2009) The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist and longitudinal motion. J Am Coll Cardiol. 54:36–46
31. Wang J, Khoury DS, Yue Y, Torre-Amione G, Nagueh SF (2008) Preserved left ventricular twist and circumferential deformation, but depressed longitudinal and radial deformation in patients with diastolic heart failure. Eur Heart J. 29:1283–1289

32. Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, Kass DA (2006) Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation. 114:2138–2147
33. Ennezat PV, Lefetz Y, Maréchaux S, Six-Carpentier M, Deklunder G, Montaigne D, Bauchart JJ, Mounier-Véhier C, Jude B, Nevière R, Bauters C, Asseman P, de Groote P, Lejemtel TH (2008) Left ventricular abnormal response during dynamic exercise in patients with heart failure and preserved left ventricular ejection fraction at rest. J Card Fail. 14:475–480
34. Phan TT, Abozguia K, Nallur Shivu G, Mahadevan G, Ahmed I, Williams L, Dwivedi G, Patel K, Steendijk P, Ashrafian H, Henning A, Frenneaux M (2009) Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency. J Am Coll Cardiol. 54:402–409
35. Borlaug BA, Olson TP, Lam CS, Flood KS, Lerman A, Johnson BD, Redfield MM (2010) Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol. 56:845–854
36. Maeder MT, Thompson BR, Brunner-La Rocca HP, Kaye DM (2010) Hemodynamic basis of exercise limitation in patients with heart failure and normal ejection fraction. J Am Coll Cardiol. 56: 855–863
37. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM (2010) Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail. 3:588–595
38. Haykowsky MJ, Brubaker PH, John JM, Stewart KP, Morgan TM, Kitzman DW (2011) Determinants of exercise intolerance in elderly heart failure patients with preserved ejection fraction. J Am Coll Cardiol. 58:265–274
39. Maciver DH, Townsend M (2008) A novel mechanism of heart failure with normal ejection fraction. Heart. 94:446–449
40. Wang J, Fang F, Wai-Kwok Yip G, Sanderson JE, Feng W, Xie JM, Luo XX, Lee AP, Lam YY (2015) Left ventricular long-axis performance during exercise is an important prognosticator in patients with heart failure and preserved ejection fraction. Int J Cardiol. 178: 131–135
41. Zile MR, Baicu CF, Gaasch WH (2004) Diastolic heart failure: abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med. 350:1953–1959
42. Westermann D, Kasner M, Steendijk P, Spillmann F, Riad A, Weitmann K, Hoffmann W, Poller W, Pauschinger M, Schultheiss HP, Tschöpe C (2008) Role of left ventricular stiffness in heart failure with normal ejection fraction. Circulation. 117:2051–2060
43. Morris DA, Vaz Perez A, Blaschke F, Eichstädt H, Ozcelik C, Haverkamp W (2012) Myocardial systolic and diastolic consequences of left ventricular mechanical dyssynchrony in heart failure with normal left ventricular ejection fraction. Eur Heart J Cardiovasc Imaging. 13:556–567
44. Takamura T, Dohi K, Onishi K, Tanabe M, Sugiura E, Nakajima H, Ichikawa K, Nakamura M, Nobori T, Ito M (2010) Left ventricular contraction-relaxation coupling in normal, hypertrophic, and failing myocardium quantified by speckle-tracking global strain and strain rate imaging. J Am Soc Echocardiogr. 23:747–754
45. Dokainish H, Sengupta R, Pillai M, Bobek J, Lakkis N (2008) Assessment of left ventricular systolic function using echocardiography in patients with preserved ejection fraction and elevated diastolic pressures. Am J Cardiol. 101:1766–1771
46. Nguyen JS, Lakkis NM, Bobek J, Goswami R, Dokainish H (2010) Systolic and diastolic myocardial mechanics in patients with cardiac disease and preserved ejection fraction: impact of left ventricular filling pressure. J Am Soc Echocardiogr. 23:1273–1280
47. Dokainish H, Sengupta R, Pillai M, Bobek J, Lakkis N (2008) Usefulness of new diastolic strain and strain rate indexes for the estimation of left ventricular filling pressure. Am J Cardiol. 101: 1504–1509
48. Zile MR, Gaasch WH, Carroll JD, Feldman MD, Aurigemma GP, Schaer GL, Ghali JK, Liebson PR (2001) Heart failure with a normal ejection fraction: is measurement of diastolic function necessary to make the diagnosis of diastolic heart failure? Circulation. 104:779–782
49. Zile MR, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, Aranda JM Jr, Abraham WT, Smart FW, Stevenson LW, Kueffer FJ, Bourge RC (2008) Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation. 118:1433–1441
50. Tumminello G, Guazzi M, Lancellotti P, Piérard LA (2007) Exercise ventilation inefficiency in heart failure: pathophysiological and clinical significance. Eur Heart J. 28:673–678
51. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbély A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL (2007) How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 28:2539–2550
52. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL (2013) 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. J Am Coll Cardiol. 62:e147–e239
53. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD (2016) Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 17: 1321–1360
54. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members; Document Reviewers (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 18:891–975
55. DeVore AD, McNulty S, Alenezi F, Ersboll M, Vader JM, Oh JK, Lin G, Redfield MM, Lewis G, Semigran MJ, Anstrom KJ, Hernandez AF, Velazquez EJ (2017) Impaired left ventricular global longitudinal strain in patients with heart failure with preserved ejection fraction: insights from the RELAX trial. Eur J Heart Fail. 19:893–900
56. Tops LF, Delgado V, Marsan NA, Bax JJ (2017) Myocardial strain to detect subtle left ventricular systolic dysfunction. Eur J Heart Fail 19:307–313
57. Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K, Hoffmann W, Poller W, Schultheiss HP, Pauschinger M, Tschöpe C (2007) Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative

Doppler-conductance catheterization study. Circulation. 116:637–647
58. Bruch C, Grude M, Müller J, Breithardt G, Wichter T (2005) Usefulness of tissue Doppler imaging for estimation of left ventricular filling pressures in patients with systolic and diastolic heart failure. Am J Cardiol. 95:892–895
59. Yip GW, Zhang Q, Xie JM, Liang YJ, Liu YM, Yan B, Lam YY, Yu CM (2011) Resting global and regional left ventricular contractility in patients with heart failure and normal ejection fraction: insights from speckle-tracking echocardiography. Heart. 97:287–294
60. Liao ZY, Peng MC, Yun CH, Lai YH, Po HL, Hou CJ, Kuo JY, Hung CL, Wu YJ, Bulwer BE, Yeh HI, Tsai CH (2012) Relation of carotid artery diameter with cardiac geometry and mechanics in heart failure with preserved ejection fraction. J Am Heart Assoc. 1:e003053
61. Abe H, Caracciolo G, Kheradvar A, Pedrizzetti G, Khandheria BK, Narula J, Sengupta PP (2013) Contrast echocardiography for assessing left ventricular vortex strength in heart failure: a prospective cohort study. Eur Heart J Cardiovasc Imaging. 14:1049–1060
62. Obokata M, Negishi K, Kurosawa K, Arima H, Tateno R, Ui G, Tange S, Arai M, Kurabayashi M (2013) Incremental diagnostic value of la strain with leg lifts in heart failure with preserved ejection fraction. JACC Cardiovasc Imaging. 6(7):749–758
63. Menet A, Greffe L, Ennezat PV, Delelis F, Guyomar Y, Castel AL, Guiot A, Graux P, Tribouilloy C, Marechaux S (2014) Is mechanical dyssynchrony a therapeutic target in heart failure with preserved ejection fraction? Am Heart J. 168:909–916
64. Luo XX, Fang F, Lee AP, Sun JP, Li S, Zhang ZH, Sanderson JE, Kwong JS, Zhang Q, Wang J, Yu CM (2014) What can three-dimensional speckle-tracking echocardiography contribute to evaluate global left ventricular systolic performance in patients with heart failure? Int J Cardiol. 172:132–137
65. Stampehl MR, Mann DL, Nguyen JS, Cota F, Colmenares C, Dokainish H (2015) Speckle strain echocardiography predicts outcome in patients with heart failure with both depressed and preserved left ventricular ejection fraction. Echocardiography. 32:71–78
66. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Anand IS, Liu L, Pitt B, Pfeffer MA, Solomon SD (2015) Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone. Circulation. 132:402–414
67. Kosmala W, Rojek A, Przewlocka-Kosmala M, Mysiak A, Karolko B, Marwick TH (2016) Contributions of nondiastolic factors to exercise intolerance in heart failure with preserved ejection fraction. J Am Coll Cardiol. 67:659–670
68. Morris DA, Krisper M, Nakatani S, Köhncke C, Otsuji Y, Belyavskiy E, Radha Krishnan AK, Kropf M, Osmanoglou E, Boldt LH, Blaschke F, Edelmann F, Haverkamp W, Tschöpe C, Pieske-Kraigher E, Pieske B, Takeuchi M (2017) Normal range and usefulness of right ventricular systolic strain to detect subtle right ventricular systolic abnormalities in patients with heart failure: a multicentre study. Eur Heart J Cardiovasc Imaging. 18:212–223
69. Toufan M, Mohammadzadeh Gharebaghi S, Pourafkari L, Delir Abdolahinia E (2015) Systolic longitudinal function of the left ventricle assessed by speckle tracking in heart failure patients with preserved ejection fraction. J Tehran Heart Cent. 10:194–200
70. Carluccio E, Biagioli P, Zuchi C, Bardelli G, Murrone A, Lauciello R, D'Addario S, Mengoni A, Alunni G, Ambrosio G (2016) Fibrosis assessment by integrated backscatter and its relationship with longitudinal deformation and diastolic function in heart failure with preserved ejection fraction. Int J Cardiovasc Imaging. 32:1071–1080
71. Iwano H, Kamimura D, Fox ER, Hall ME, Vlachos P, Little WC (2016) Presence and implication of temporal nonuniformity of early diastolic left ventricular wall expansion in patients with heart failure. J Card Fail. 22:945–953
72. Hung CL, Yun CH, Lai YH, Sung KT, Bezerra HG, Kuo JY, Hou CJ, Chao TF, Bulwer BE, Yeh HI, Shih SC, Lin SJ, Cury RC (2016) An observational study of the association among interatrial adiposity by computed tomography measure, insulin resistance, and left atrial electromechanical disturbances in heart failure. Medicine (Baltimore) 95:e3912
73. Donal E, Lund LH, Oger E, Bosseau C, Reynaud A, Hage C, Drouet E, Daubert JC, Linde C, on behalf of the KaRen Investigators (2017) Importance of combined left atrial size and estimated pulmonary pressure for clinical outcome in patients presenting with heart failure with preserved ejection fraction. Eur Heart J Cardiovasc Imaging 18:629–635
74. Kosmala W, Przewlocka-Kosmala M, Sharman JE, Schultz MG, Marwick TH (2017) Stability of left ventricular longitudinal and circumferential deformation over time and standard loading conditions. Eur Heart J Cardiovasc Imaging. 18:1001–1007
75. Pellicori P, Kallvikbacka-Bennett A, Khaleva O, Carubelli V, Costanzo P, Castiello T, Wong K, Zhang J, Cleland JG, Clark AL (2014) Global longitudinal strain in patients with suspected heart failure and a normal ejection fraction: does it improve diagnosis and risk stratification? Int J Cardiovasc Imaging. 30:69–79
76. Freed BH, Daruwalla V, Cheng JY, Aguilar FG, Beussink L, Choi A, Klein DA, Dixon D, Baldridge A, Rasmussen-Torvik LJ, Maganti K, Shah SJ (2016) Prognostic utility and clinical significance of cardiac mechanics in heart failure with preserved ejection fraction: importance of left atrial strain. Circ Cardiovasc Imaging 9(3):e003754
77. Obokata M, Takeuchi M, Negishi K, Ohte N, Izumo M, Yamashita E, Ebato M, Yuda S, Kurabayashi M, Nakatani S (2016) Relation between echocardiogram-based cardiac parameters and outcome in heart failure with preserved and reduced ejection fraction. Am J Cardiol. 118:1356–1362
78. Buggey J, Alenezi F, Yoon HJ, Phelan M, DeVore AD, Khouri MG, Schulte PJ, Velazquez EJ (2017) Left ventricular global longitudinal strain in patients with heart failure with preserved ejection fraction: outcomes following an acute heart failure hospitalization. ESC Heart Fail. 4:432–439
79. Donal E, Lund LH, Oger E, Hage C, Persson H, Reynaud A, Ennezat PV, Bauer F, Drouet E, Linde C, Daubert C, KaRen investigators (2015) New echocardiographic predictors of clinical outcome in patients presenting with heart failure and a preserved left ventricular ejection fraction: a subanalysis of the Ka (Karolinska) Ren (Rennes) Study. Eur J Heart Fail 17:680–688
80. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A, I-PRESERVE Investigators (2008) Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 359:2456–2467
81. Oghlakian GO, Sipahi I, Fang JC (2011) Treatment of heart failure with preserved ejection fraction: have we been pursuing the wrong paradigm? Mayo Clin Proc. 86:531–539
82. Shah RV, Desai AS, Givertz MM (2010) The effect of renin-angiotensin system inhibitors on mortality and heart failure hospitalization in patients with heart failure and preserved ejection fraction: a systematic review and meta-analysis. J Card Fail. 16:260–267
83. Kitzman DW, Hundley WG, Brubaker PH, Morgan TM, Moore JB, Stewart KP, Little WC (2010) A randomized double-blind trial of enalapril in older patients with heart failure and preserved ejection fraction: effects on exercise tolerance and arterial distensibility. Circ Heart Fail. 3:477–485
84. Tehrani F, Phan A, Chien CV, Morrissey RP, Rafique AM, Schwarz ER (2009) Value of medical therapy in patients >80 years of age with heart failure and preserved ejection fraction. Am J Cardiol. 103:829–833

85. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J (2006) The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 27:2338–2345
86. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, CHARM Investigators and Committees (2003) Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 362:777–781
87. Paulus WJ, Tschöpe C (2013) 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. 62:263–271. https://doi.org/10.1016/j.jacc.2013.02.092

Heart Failure Reviews
https://doi.org/10.1007/s10741-019-09836-8

Heart failure with preserved ejection fraction: the missing pieces in diagnostic imaging

Sadi Loai [1,2] · Hai-Ling Margaret Cheng [1,2,3,4,5]

Abstract
Heart failure with preserved ejection fraction (HFpEF) is an increasingly prevalent phenotype affecting over half of today's heart failure patients. With no proven therapy and no universally accepted diagnostic guideline, many HFpEF patients continue to be misdiagnosed or underdiagnosed at the early stages until the disease has progressed much further along. It is extremely difficult to diagnose the HFpEF patient, because they have a normal ejection fraction and present with non-specific symptoms such as dyspnea or exercise intolerance. To provide greater specificity, the current diagnostic criteria mandate the presence of diastolic dysfunction, where myocardial relaxation is impaired and ventricular filling pressure is elevated as a result of a hypertrophic and stiff heart. Unfortunately, diastolic dysfunction reflects late-stage structural and functional changes and offers a very narrow window, if at all, for successful intervention. In this article, we review the imaging modalities used in the current diagnostic workflow for assessing HFpEF. We also describe the most up-to-date insight into its pathophysiological basis, which attributes systemic inflammation driven by comorbidities as the initiator of disease. With this extramyocardial perspective, we provide our recommendation on new imaging targets that extend beyond the heart to enable early, accurate diagnosis of HFpEF and allow an opportunity for treating this fatal condition.

Keywords Heart failure · Preserved ejection fraction · Diastolic dysfunction · Cardiac magnetic resonance imaging · Echocardiography

Introduction

Heart failure (HF) is a clinical syndrome characterized by structural and/or functional abnormalities that impair ventricular filling and/or ejection of blood in accordance with the metabolic demands of the body [1]. Our understanding of the pathophysiology of HF continues to evolve, with the current definition recognizing two distinct HF phenotypes: "HF with reduced ejection fraction" (HFrEF) and "HF with preserved ejection fraction" (HFpEF). The latter nomenclature nods to the fact that over the past 30 years, the incidence of HF patients with a near normal, or preserved, left ventricular (LV) ejection fraction (LVEF ≥ 50%) has increased to a staggering ≥ 50% of all HF cases [2]. Continuing to rise in prevalence at 1% a year, HFpEF is projected to be the dominant HF phenotype in a decade [3]. The mortality rate is similar to that of HFrEF, as are signs and symptoms (e.g., dyspnea, exercise intolerance, congestion) [4]. Nonetheless, HFpEF is a distinct disease and has a heterogeneous etiology that remains poorly understood [5]. Treatments that have proven effective in HFrEF fail to provide a survival benefit for HFpEF patients [6]. Our incomplete understanding of the disease presents a barrier not only to treatment but also to accurate and early diagnosis. To date, there is still no universal consensus on a clear diagnostic guideline [7, 8, 5]. In fact, a third category, HFmEF (mid-range ejection fraction 41–49%), was introduced in 2017 in heart failure management guidelines [9]. The physiological significance of HFmEF and

✉ Hai-Ling Margaret Cheng
hailing.cheng@utoronto.ca

1 Institute of Biomaterials & Biomedical Engineering, University of Toronto, 164 College Street, RS407, Toronto, Ontario M5S 3G9, Canada

2 Translational Biology & Engineering Program, Ted Rogers Centre for Heart Research, 661 University Avenue, Room 1433, Toronto, Ontario M5G 1M1, Canada

3 The Edward S. Rogers Sr. Department of Electrical and Computer Engineering, University of Toronto, 10 King's College Road, Room SFB540, Toronto, Ontario M5S 3G4, Canada

4 Heart & Stroke/Richard Lewar Centre of Excellence for Cardiovascular Research, 6 Queens Park Crescent West, Room 202, Toronto, Ontario M5S 3H2, Canada

5 Ontario Institute for Regenerative Medicine, 661 University Avenue, Suite 510, Toronto, Ontario M5G 0A3, Canada

whether it should be classified as part of the HFrEF or HFpEF spectrum remain to be determined. Despite all this, what is clear is that patients of the HFpEF phenotype are often misdiagnosed and the severity of disease underestimated [7].

The current diagnosis of HFpEF requires three levels of evidence: (i) clinical symptoms of HF (e.g., dyspnea on exertion, fatigue, exercise intolerance), (ii) LVEF ≥ 50% with normal LV dimensions, and (iii) diastolic dysfunction, defined as impaired myocardial relaxation and passive stiffness (i.e., decreased LV compliance) [10]. It should be noted that the third criterion, diastolic dysfunction, once believed to be the main driver of HFpEF [11], is actually not unique to HFpEF [12] and that extramyocardial factors from comorbidities—hypertension, obesity, diabetes, and kidney disease—have since been uncovered as contributors to the syndrome independent of diastolic dysfunction [4]. According to a 2016 recommendation from the European Society of Cardiology, the current diagnostic criteria need to be reappraised to incorporate new pathophysiological insights in order to diagnose HFpEF patients correctly [13]. At present, HFpEF is commonly missed in the early stages, with the majority of patients diagnosed initially not for HF but for hypertension or type II diabetes [14]. In this review article, we frame our current understanding of the pathophysiology of HFpEF as a backdrop for appreciating what diagnostics are currently used and why, and for evaluating what new diagnostics are needed to diagnose HFpEF patients early and accurately. We focus on non-invasive imaging diagnostics and recommend new applications of advanced imaging techniques to improve the diagnosis of an increasingly prevalent form of HF.

Comorbidities

To shed light on the pathophysiology of HFpEF, it is worth noting that HFpEF patients tend to be older (~ 75 years), female (55–73%), and have multiple comorbidities such as hypertension (~ 75%), obesity/overweight (> 80%), diabetes (~ 40%), and renal disease (25–50%) [15–17, 8, 14]. These comorbidities are major risk factors for HFpEF [18, 19]. It is important also to emphasize that they all share a common link—systemic inflammation—which has been hypothesized to introduce an extramyocardial origin in the progression of HFpEF that does not exist in HFrEF [20]. With this hypothesis, inflammation is believed to damage the myocardium by inducing structural and functional abnormalities, including hypertrophy, interstitial fibrosis, impaired myocardial relaxation, and coronary microvascular dysfunction [20, 21]. The insult from systemic inflammation extends beyond the heart, which would explain the symptoms, such as exertional dyspnea and exercise intolerance, with which many HFpEF patients present. Figure 1 illustrates these pathophysiological changes together with HFpEF comorbidities and symptoms.

Despite the known associations with HFpEF, patients with the aforementioned comorbid conditions are not screened for heart disease until overt symptoms manifest, which is often too late in disease progression. Diabetic patients, for example, have a 10-fold increase in mortality and a 5-year survival of 15.5% by the time they exhibit HF symptoms [22–24]. Obesity is another common comorbidity, and again, patients are not screened for heart disease until HF symptoms appear. The association between obesity and HFpEF is not as well understood, but it is known that in and of itself, obesity can increase aortic stiffness and myocardial load that leads to the hypertrophy seen in HFpEF. A recent clinical trial assessed the outcome of HFpEF patients with abdominal obesity and concluded that the risk of all-cause mortality was significantly higher for obese patients compared to the non-obese cohort [25].

Pathophysiology

The current diagnostic guidelines for HFpEF were developed over a decade ago, when our understanding of the phenotype lagged far behind what we know today. In fact, as recently as the turn of the millennium, the term HFpEF did not exist and the condition was called “diastolic HF” to distinguish it from “systolic HF,” or what we currently refer to as HFrEF [26]. Today, however, we know that depressed systolic function is common in HFpEF. Similarly, HFrEF involves not only systolic dysfunction but, in many patients, diastolic dysfunction also. Given the significant overlap in diastolic and systolic dysfunction between the two HF phenotypes, the more accurate terminology of HFpEF versus HFrEF emerged.

At the macroscopic level, HFpEF is distinguished from HFrEF by virtue of concentric LV remodeling, where there is an increase in LV wall thickness and in LV mass, leading to hypertrophy [27]. This is in stark contrast to the eccentric remodeling and diminished LV wall thickness seen in HFrEF. The increased wall thickness and mass are supported by observations at the tissue level, where fat cardiomyocytes with a higher resting tension have replaced normally long and narrow cardiac muscle cells [15]. What ensues is the defining pathophysiological hallmark of HFpEF: increased LV tissue stiffness. As a result of a stiff ventricle, LV relaxation becomes impaired and LV filling pressure is elevated both overall and at end-diastole [28]. In order to maintain stroke volume and mechanical efficiency, systolic performance increases, thus maintaining the LVEF [29]. Mechanically, the manner in which the LV fills with blood during diastole also changes. In the healthy heart, as the LV untwists during early diastole, a negative pressure is created in the LV, sucking blood from the left atrium (LA). This accounts for 70–80% of the LV filling, while the remaining 20–30% occurs under subsequent LA contraction. With progressive worsening of diastolic dysfunction, LV filling during early diastole is reduced and pressure

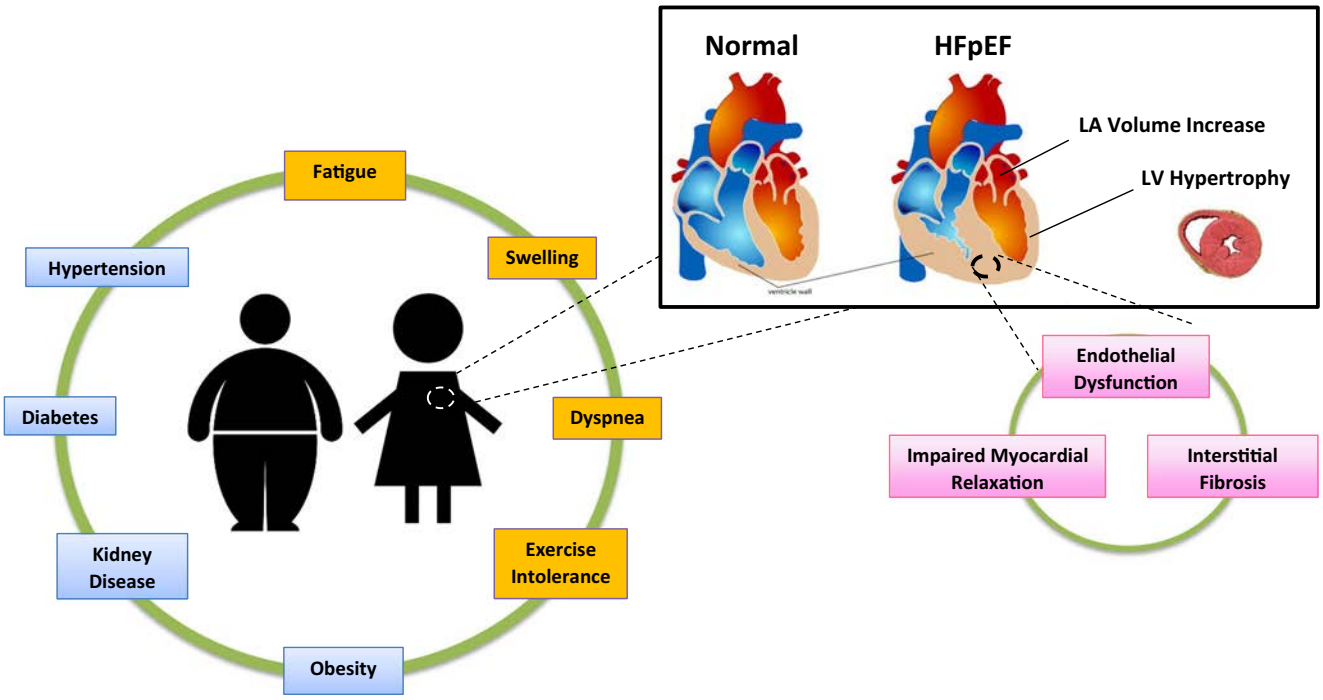


Fig. 1 Common symptoms (orange boxes) and comorbidities (blue boxes) associated with the HFpEF heart, which is characterized by LV hypertrophy and LA volume increase. At the tissue level are various physical and functional changes, including coronary endothelial dysfunction, interstitial fibrosis, and impaired myocardial relaxation. LV hypertrophy cross-section adapted from Patrick J. Lynch, medical illustrator; C. Carl Jaffe, MD, cardiologist. https://creativecommons.org/licenses/by/2.5/

increases within the LA. The result is an enlarged LA and entry of blood into the LV by positive rather than negative pressure.

The structural and functional changes described above take many years to develop, and when a patient is diagnosed with HFpEF based on these changes, he/she is no longer in the early stages of disease progression. Unfortunately, current diagnostic guidelines and the associated technologies are focused on these late-stage cardiac changes, and these guidelines have remained fairly static over the years. Meanwhile, our mechanistic understanding of HFpEF has improved immensely. As discussed in the section "Comorbidities," the current HFpEF paradigm supports the role of systemic inflammation driven by comorbidities as a key initiator of disease [20]. This paradigm begins with inflammation of the endothelium, which reduces the bioavailability of nitric oxide (NO), a key regulator of vasodilation and smooth muscle relaxation [20]. The action of NO is mediated through the NO-soluble guanyl cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signaling pathway, which is increasingly recognized as a key regulator of cardiac function, exerting inotropic, lusitropic, and chronotropic effects [30]. In heart failure, low NO levels reduce intracellular cGMP and protein kinase G (PKG) activity, promoting cardiomyocyte hypertrophy and delaying myocardial relaxation. This direct impact on cardiac function is further aggravated by NO-mediated effects on the systemic circulation that alters preload and afterload conditions [31]. Another consequence of dysfunction in the systemic circulation is seen in skeletal muscle, where endothelial dysfunction translates to the exercise intolerance frequently seen in HFpEF patients [32, 33]. The coronary microvasculature is also affected by endothelial inflammation, which has been verified in myocardial biopsy samples, and explains the chest pain that results from reduced coronary perfusion and microvascular rarefaction [20]. Beyond these changes, cardiac inflammation will also initiate fibrosis, which has been observed in myocardial specimens from HFpEF patients [34]. In summary, HFpEF is increasingly recognized as a systemic syndrome rather than an isolated cardiac disease [35], a consideration that is pivotal for designing future diagnostic and therapeutic approaches.

Current diagnostics for HFpEF

The current guidelines recommended by the European Society of Cardiology focus on patients at more advanced stages and retain the diagnostic criteria described earlier: clinical symptoms of HF, normal LVEF, and diastolic dysfunction assessed invasively or non-invasively. The first criterion is easily assessed from patient reports of breathlessness, fatigue, and exercise intolerance and from signs such as swelling in the extremities. Many of these symptoms are not specific to HFpEF, however, and are often misdiagnosed and attributed to non-cardiac causes, such as chronic lung disease and

anemia [36]. The second criterion is also easily determined, but accuracy depends highly on the imaging approach. Echocardiography, the undisputed workhorse of cardiac examinations, can measure the LVEF and LV end-diastolic volume index, with nominal cut-off values of ≥ 50% and < 97 ml/m^2, respectively, as thresholds for normal systolic function and normal ventricular volume [10]. Because these numbers are averages only, sex- and age-dependent cut-off values are recommended instead—for example, the normal LVEF range for men (52–72%) differs from that for women (54–74%); see the American Society of Echocardiography 2015 quantitative guidelines for sex- and age-related changes in LV size and function [37]. Traditional two-dimensional (2D) echocardiography provides the easiest access to LVEF and LV volume estimation, but there can be substantial variability due to dependence on clear endocardial definition, which is absent in one third of cases [38]. To address this hurdle, ultrasound contrast agents can be administered to enhance the endocardial border for more accurate estimates of LV function and size [39]. Three-dimensional (3D) echocardiography has the potential for higher accuracy and reproducibility approaching that of cardiac MRI; the challenge with 3D echocardiography, however, is even greater susceptibility to operator expertise compared to 2D imaging, and both 3D ultrasound and MRI require breath-holding, which is a challenge for patients dyspneic at rest [40]. Accuracy and reproducibility are crucial, because diagnosing HFpEF is premised on correctly establishing a normal LVEF.

The most discriminatory piece of information comes from the third criterion of diastolic dysfunction, which of all three criteria is the most difficult to establish. It should be noted that diastolic dysfunction is a pathophysiological condition and can present in the absence of HF [41, 13, 11]. Only when diastolic dysfunction is present with the other two criteria is a diagnosis of HFpEF confirmed. To diagnose diastolic dysfunction definitively, there must be evidence of elevated LV filling pressures. Invasive catheterization of the LV remains the gold standard technique and involves measuring the LV end-diastolic pressure (> 16 mmHg), the time constant of LV relaxation (> 48 ms), and the pulmonary capillary wedge pressure (> 12 mmHg) [10]. However, since invasive techniques are not viable in most patients, non-invasive imaging based on echocardiography is used instead.

On a 2D echocardiogram, the HFpEF heart rarely appears normal in the late stages: the LV wall is usually thickened and the left atrial volume increased. These structural indices are suggestive of diastolic failure but are not surrogate measures of filling pressures, however. Functional indices based on Doppler echocardiography of mitral flow and tissue Doppler are used to determine if LV filling pressures are elevated, which is recommended as the first step to diagnosing diastolic dysfunction [42, 43]. In brief, tissue Doppler is used to measure the LV basal, longitudinal cardiac shortening, and/or lengthening velocity; measurements are taken at the position of the mitral annulus, and several velocities are taken, including early diastolic mitral annular velocity (e′) and late (atrial) diastolic mitral annular velocity (a′). Flow Doppler is used to measure the peak blood flow velocity through the mitral valve at early filling (E) and at late filling (A) due to atrial contraction. The ratio E/e′ is then calculated, and this index has been shown to be highly specific for increased LV filling pressures [44]. The ratio E/e′ < 8 in the normal heart but increases in diastolic dysfunction due to a lower e′, or less blood entering the LV during early filling, from impaired relaxation. The likelihood of increased filling pressures is much higher if the lateral E/e′ > 12 (or septal E/e′ > 15) *and* there is no mitral annual calcification, mitral regurgitation or valve prosthesis, tachycardia, atrioventricular block, atrial fibrillation, constrictive physiology, ventricular dyssynchrony, or focal wall motion abnormalities [45]. An alternative means to measure filling pressure (e.g., invasive hemodynamic testing) is required when these aforementioned conditions exist [45]. In addition to E/e′, it is currently recommended for improved specificity that the annular e′ velocity (septal e′ < 7 cm/s, lateral e′ < 10 cm/s), peak tricuspid regurgitation velocity (> 2.8 m/s), and left atrial volume index (> 34 mL/m^2) also be considered. Taking all four parameters together decreases the likelihood of false positive findings; with this approach, diastolic dysfunction is diagnosed only when over half of these parameters meet respective abnormal cut-off values [43]. Once diastolic dysfunction is determined, disease grading is performed by calculating the mitral valve flow velocity ratio (E/A), which is typically ≥ 1.5 in the normal heart. In healthy individuals, the E-wave prevails due to efficient LV filling in early and mid-diastole, whereas in older individuals or in mild diastolic dysfunction, early LV filling decreases and the A-wave dominates (E/A < 0.8). With worsening diastolic dysfunction, the E/A ratio increases above 0.8 back into the normal range as left atrial pressure increases; the Valsalva maneuver is helpful in this scenario for distinguishing normal diastolic function from dysfunction [45]. Full details on the diagnostic tree are found in the 2016 guidelines from the American Society of Echocardiography and the European Association of Cardiovascular Imaging [43]. Finally, plasma levels of brain natriuretic peptide (BNP) and N-terminal pro brain natriuretic peptide (NT-proBNP) should be tested to make a diagnosis for HFpEF, since the production of biomarkers is minimal in healthy individuals but becomes elevated (BNP > 200 pg/mL or NT-proBNP > 220 pg/mL) in both HFpEF and HFrEF [46, 47]. However, caution must be exercised with the use of these biomarkers, since BNP levels tend to be lower in HFpEF and even normal in some HFpEF patients [48, 49]. Figure 2 illustrates various echocardiographic techniques [37, 45, 39, 50].

Cardiac magnetic resonance imaging (MRI) is seldom used in routine clinical practice and is not part of the

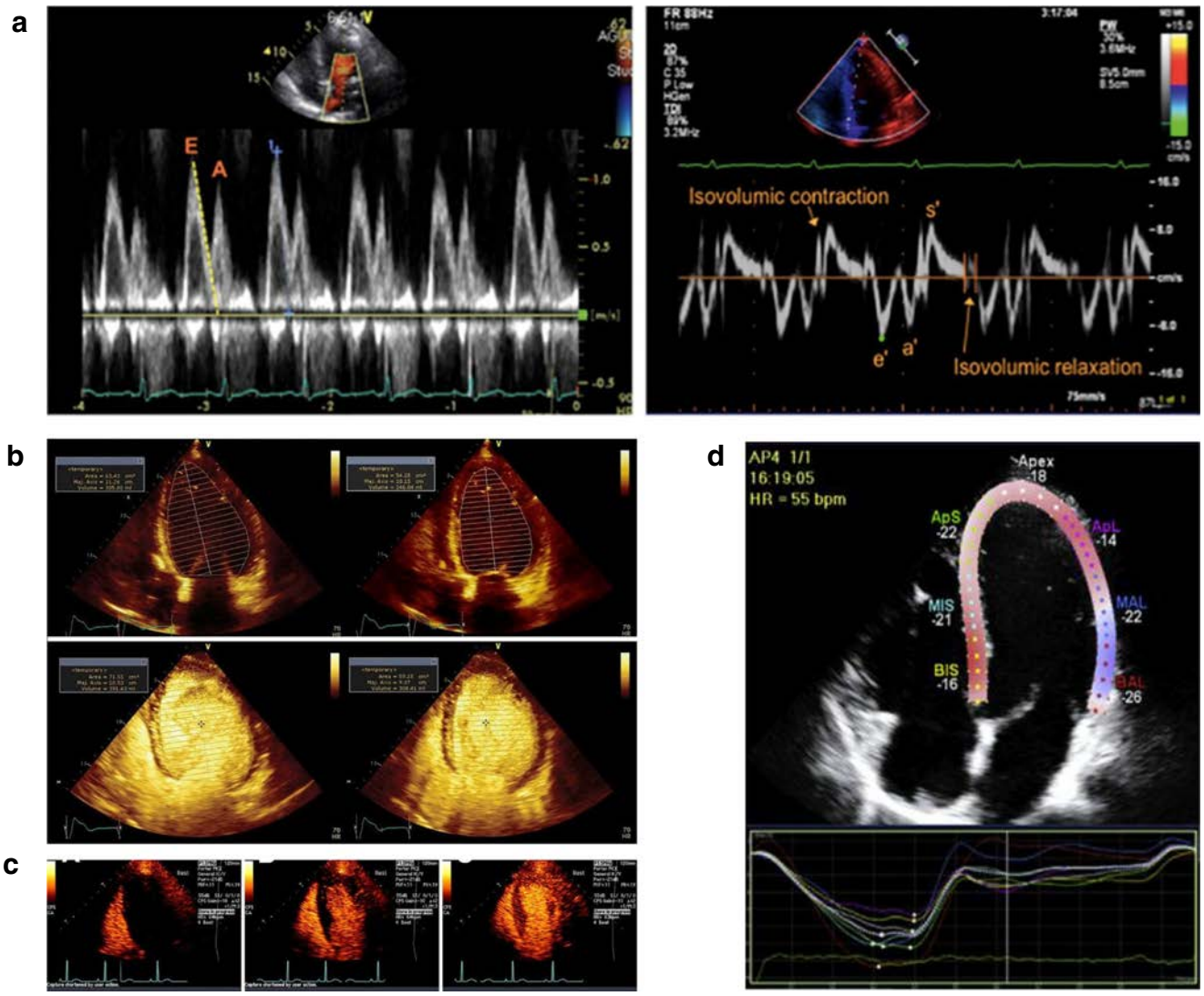


Fig. 2 Echocardiography of LV diastolic function. **a** Doppler transmitral flow demonstrating early (E) and late/atrial (A) waves on pulsed-wave Doppler at the mitral leaflet tips in the apical 4-chamber view (left). Pulsed-wave tissue Doppler velocities at the lateral mitral annulus (e′ = early diastolic, a′ = late/atrial diastolic, and s′ = systolic tissue velocities) (right). (Reprinted from Mitter et al. [45]). **b** Differences in end-diastolic/systolic volumes observed without contrast (top) and with contrast and low-mechanical index imaging (bottom). A marked increase in volume size is noted post-contrast. (Reprinted from Porter et al. [39]). **c** Myocardial perfusion via contrast. (Reprinted from Porter and Xie [50]). **d** Measurement of global longitudinal strain via speckle tracking. (Reprinted from Lang et al. [37])

current diagnostic flowcharts for HFpEF due to high costs and limited availability. For patients who have poor quality echocardiographic findings, however, cardiac MRI is the only other alternative able to measure cardiac structure and function. Its inherent superior soft-tissue contrast and high spatial resolution make cardiac MRI the gold-standard modality for measuring LA volume, LV volume, and LV mass [51]. In fact, cardiac MRI is preferred over echocardiography for its reproducibility and for monitoring small changes in LV mass or LV volume during disease progression. Dynamic CINE acquisitions of the whole heart allow us to measure LVEF much more reproducibly than from echocardiography [52] in addition to a wide range of LV filling parameters identical to those from echocardiography [10]. Myocardial perfusion and viability can also be assessed with the aid of an intravascular injection of gadolinium-based MR contrast agent [53, 54]. Perhaps the most important capability of cardiac MRI, one for which there is no echocardiographic analog, is myocardial tissue characterization—only cardiac MRI can identify and delineate ischemic tissue, inflammation, and infiltrative diseases [55]. Quantitative MRI methods such as parametric cardiac T1, T2, and T2* mapping reflect intrinsic tissue magnetic properties and are increasingly accessible on clinical MR scanners [56]. If implemented robustly, quantitative mapping can provide information on fibrosis (T1) [57, 58], edema and inflammation (T2) [59, 60], and iron overload and hemorrhage (T2*)

[61, 62]. The first multicenter randomized, controlled clinical trial to evaluate the role of cardiac MRI in non-ischemic heart failure or HFpEF (IMAGE-HF project 1-B) is underway to investigate if routine cardiac MRI can identify more specific heart failure etiologies compared to echocardiography alone [63]. Depending on the results of the trial, the inclusion of cardiac MRI in future strategies for HFpEF diagnosis may be recommended. Figure 3 demonstrates the capabilities of cardiac MRI [64–68].

The structural and functional metrics described above for both echocardiography and cardiac MRI reflect the status of the heart at rest. However, a stress echocardiogram or a stress MRI may be performed to assess cardiac performance under stress. The stress could be triggered either by exercise on a treadmill or by dobutamine, which is injected intravenously to raise heart rates in patients who cannot exercise. Using stress echocardiography, myocardial viability is then assessed via measurement of contractile reserve and biphasic response.

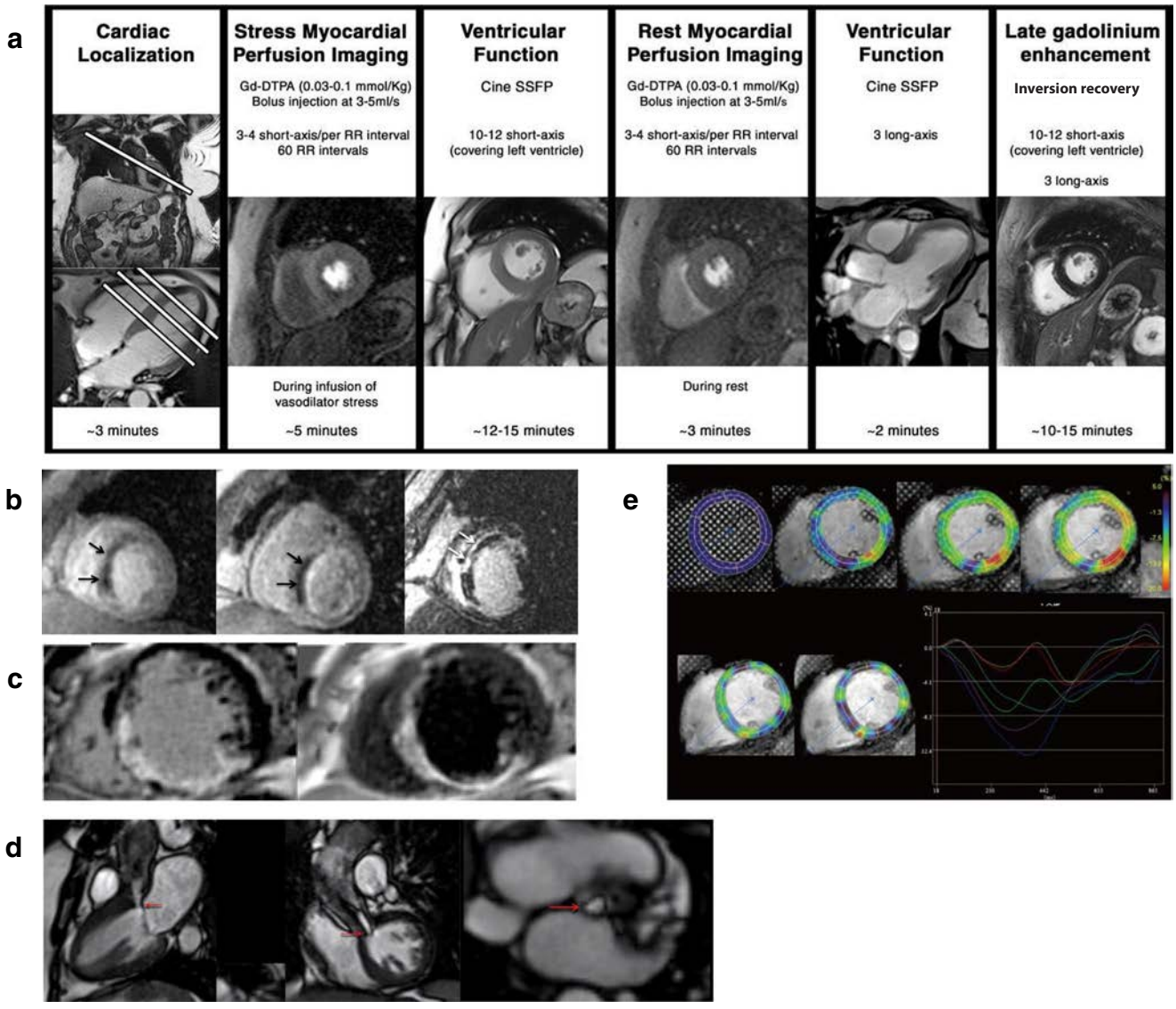


Fig. 3 Cardiac MRI. **a** Acquisition protocol includes assessment at rest and during vasodilator stress. (Reproduced from Coelho-Filho et al. [64]). **b** Short-axis perfusion MRI showing mid-anteroseptal and anterior wall motion abnormality, rest (left) and stress (middle) perfusion abnormality (black arrows), and myocardial delayed enhancement (right, white arrows) consistent with infarct. (Adapted from Jenson et al. [65]). **c** Bright-blood and dark-blood late gadolinium enhancement reveals contrast between the subendocardial scar and adjacent blood pool. (Adapted from Francis et al. [66]). **d** Subvalvular obstruction (red arrows) secondary to subaortic membrane seen on 3-chamber (left) and coronal (right) views. (Reprinted from Cavalcante et al. [67]). **e** Color-coded strain map of tagged MRI shows heterogeneous strain values in the left ventricle throughout one cardiac cycle (left upper: first frame at end-diastole; right upper: end-systole; lower row: diastole). The time-strain curves of six myocardial segments show variations in the peak time of each strain curve; left ventricular dyssynchrony is identified (right lower). (Figure reproduced from Nagao and Yamasaki [68])

Using cardiac MRI, myocardial viability is assessed via spatial distribution of intravenously injected contrast agents. The same injection also provides information on the perfusion status of heart muscle. Table 1 summarizes the role of various imaging modalities in the diagnosis of HFpEF. Table 2 highlights imaging modalities that are useful for assessing various physical or functional parameters relevant to HFpEF.

Challenges of diagnosing HFpEF and future directions

One of the major limitations of existing diagnostic workup is lack of information on heart function when the patient is under stress (e.g., from exercise). Some patients are asymptomatic at rest and do not exhibit cardiac structural or functional abnormalities, particularly those at the early stages of disease progression [69, 5]. These patients in the early stages may report dyspnea and/or fatigue on exertion but otherwise have negative findings on routine physical and radiological examination. Hemodynamic assessment during exercise then becomes the only approach to determine the existence of HFpEF [4]. For example, since elevated LV filling pressure is critical to the current diagnosis of HFpEF, if echocardiography and invasive hemodynamic measurements all yield inconclusive results, then one should resort to exercise stress testing and/or manoeuvers such as leg raises and fluid challenge [11]. There is evidence that many patients who have normal echocardiography findings at rest have significantly altered hemodynamics during exercise; increases in the E/e′ ratio and impaired ventricular-arterial coupling have all been reported [70, 71]. Chronotropic incompetence and abnormalities outside the heart, such as impaired vascular reserve, can also help uncover the presence of HFpEF during exercise [70].

It is also important to recall that diastolic dysfunction is not present in all HFpEF patients and that a diagnosis of diastolic dysfunction alone does not constitute a diagnosis of HFpEF [11]. In other words, heart failure with diastolic dysfunction is only a subset of HFpEF. This distinction between a pathophysiological state (diastolic dysfunction) and a clinical syndrome (HFpEF) highlights the importance of thinking broadly about the complex etiologies of HFpEF when advancing new technologies and approaches for earlier, more sensitive, and more specific diagnosis. Furthermore, we must remember that many of the current indices recommended for diagnosis (e.g., elevated E/e′ ratio, LV hypertrophy, left atrial enlargement) are indirect measures of LV stiffness, the hallmark of HFpEF and the parameter that provides the most direct evidence of disease if it can be measured accurately [72]. In the following, we discuss new targets and imaging-based tools for improving diagnostic accuracy.

Myocardial stiffness

Although the E/e′ ratio is regarded as the echocardiographic gold standard for measuring LV diastolic function, recent studies have shown inaccuracies in its measurement when regional wall motion is abnormal. This is problematic, as several studies have shown that abnormalities in regional contractility are common in HFpEF patients [32]. To address this dilemma, newer echocardiographic methods have been applied to quantify regional cardiac stiffness *directly* through

Table 1 Imaging modalities for diagnosing heart failure

	Advantages	Disadvantages
X-ray angiography	Establishes coronary artery disease	Invasive Not suitable for all patients
Echocardiography	True real-time cardiac imaging Accessible to all patients Measures systolic function Ideal for measuring diastolic function Assesses anatomy (chamber size, wall thickness, valves) Assesses function (ventricular filling pressure, Doppler flow) Measures myocardial perfusion Widely available; low cost	Reproducibility of ejection fraction estimation is operator dependent Lower reproducibility in anatomical measurements compared to MRI Poor tissue characterization
Cardiac MRI	Superb tissue/border delineation Excellent tissue characterization (viable myocardium, infarct, scar) Measures systolic function High reproducibility in anatomical and functional measurements (ejection fraction, atrial volume, ventricular volume/mass, wall thickness) Measures myocardial perfusion	Currently not recommended for clinical assessment of HFpEF Contraindicated for patients with MRI-incompatible pacemakers Non-real-time cardiac imaging Lengthy scan times Not widely available; high cost
PET-CT	Gold standard for myocardial perfusion Gold standard for myocardial viability	Exposure to ionizing radiation and radioactive tracers Low availability; very high cost

Table 2 Pathological features in HFpEF and diagnostic modalities for assessment

	Diagnostic modality					
	Chest X-ray	Echocardiography	Cardiac MRI	PET-CT	X-ray angiography	ECG
Hypertrophy	✓	✓	✓			
Atrial fibrillation		✓	✓			✓
Coronary artery disease		✓	✓		✓	✓
LA/LV volume, wall thickness		✓	✓			
LV ejection fraction		✓	✓			
LV filling pressure		✓	✓			
LV relaxation and filling		✓	✓			
Myocardial perfusion[a]		✓	✓	✓		
Myocardial viability		✓	✓	✓		
LV stiffness		✓	✓			
Diffuse fibrosis			✓			
Endothelial dysfunction			✓			
Inflammation			✓	✓		
Stress testing		✓	✓	✓		

ECG electrocardiogram

[a] Perfusion imaging is performed with intravenous injection of modality-specific tracers

an assessment of myocardial deformation [73]. This technique, known as speckle-tracking echocardiography [74], uses frame-by-frame tracking of small myocardial regions-of-interest, each with a unique speckle pattern, and calculates cardiac strain (i.e., tissue deformation) from temporal changes in the segment length. The calculated strain, together with its temporal derivative, the strain rate, can be measured on a regional basis or can be averaged to yield a global strain score, longitudinally, radially, and circumferentially [75, 76]. A strong linear association between the global strain score and functional capacity has been reported in HFpEF patients [77]. Recent insights from the RELAX trial of sildenafil in HFpEF patients showed that the LV global longitudinal strain as determined by speckle-tracking was significantly impaired in HFpEF and was associated with collagen synthesis and diastolic dysfunction [78]. However, impaired LV global longitudinal strain was not associated with quality of life or exercise tolerance, indicating that other factors, intra- or extramyocardial, are at play. Another difficulty is the low reproducibility of strain value, particularly circumferential and radian strain, due to variability in software algorithms for analysis [79]. Clearly, more work lies ahead to determine the prognostic value of strain measurements.

Cardiac MRI is also capable of providing information on regional myocardial strain by using a method to "tag" myocardial tissue with a "grid" and track movement during systole [80]. In applying the method to diastole, however, a major limitation is fading of grid lines over the cardiac cycle interval. The consequence is that while the early diastolic strain rate can be measured in 80% of segments analyzed, atrial-induced strain could be measured in only 32% of patients [81]. More recently, a method known as feature tracking using CINE balanced steady-state free precession acquisitions was introduced as a robust and rapid method for measuring myocardial strain and diastolic strain rate [82]. This technique requires considerably less data processing time than tissue tagging and has even been applied to both obese and diabetic patients to assess LA strain for early detection of diastolic dysfunction [83] and to echocardiography-confirmed HFpEF patients without co-morbidities to assess LV diastolic strain rate [84]. To advance this promising cardiac MRI technique into widespread clinical implementation, more rapid image acquisition solutions are needed.

Ventricular-arterial coupling

Hypertension is a well-known antecedent to the development of HF. In the HFpEF population, approximately 75% of patients are hypertensive, and in these patients, there is evidence of stiffening in the LV and arteries [4, 85]. One school of thought has proposed arterial-ventricular stiffening as a main contributor to increases in blood pressure, which then impairs diastolic LV relaxation [86]. The result of this stiffening and non-compliance in both the ventricular and arterial compartments negatively alters ventricular-arterial coupling, which is defined by the ratio of arterial elastance (afterload Ea) and end-systolic ventricular elastance (end-systole elastance Ees) [7]. In HFpEF patients, the coupling ratio (Ea/Ees) is decreased relative to control hypertensive subjects without HF [87]. This decrease stems from a proportionally higher change

in ventricular stiffening, or Ees. Alterations in ventricular-arterial coupling have an especially pronounced impact on cardiac function during exercise and variations of volume load, and its measurement may provide valuable information for managing patients. In a recent study of patients who had negative results on stress echocardiography, higher rates of mortality and hospitalization were predicted by altered ventricular-arterial coupling [88].

Although measuring ventricular-arterial coupling remains challenging, both echocardiography and cardiac MRI have demonstrated the potential for non-invasive assessment. The arterial elastance, Ea, is calculated as the ratio of end-systolic pressure to stroke volume. The end-systolic ventricular elastance, Ees, is calculated as the change in pressure for a given change in chamber volume. From these two numbers, the ventricular-arterial coupling (Ea/Ees) is computed. Echocardiography provides continuous temporal monitoring and measures ventricular-arterial coupling using a single-beat method developed by Chen et al. [89]. This method involves complex mathematical formulae that require computer algorithms for easy calculation of the ratio Ea/Ees in the clinical setting. More recent application of 3D echocardiography has demonstrated higher reproducibility and sensitivity over 2D methods [90]. In contrast, cardiac MRI does not have sufficient temporal resolution to capture the beat-to-beat changes in the LV pressure-volume relationship required to measure Ees. Using conventional CINE acquisitions, Ees is approximated as the ratio of end-systolic pressure to end-systolic volume [91]. Improved estimation of Ees using MRI is possible using real-time acquisition approaches to allow essentially continuous measurement of LV volume changes [92]; however, these custom sequences are not widely accessible. Irrespective of the relative advantage of echocardiography over cardiac MRI in this setting, determination of ventricular-arterial coupling is simply not in the current diagnostic workflow due to complexity of measurement. Prognostic clinical trials are needed to determine its predictive value on the outcomes of cardiovascular disease.

Myocardial fibrosis

The diffuse myocardial fibrosis observed in the hypertrophic HFpEF heart is a result of chronic inflammation. Activated fibroblasts (myofibroblasts), in their role of inflammatory supporter cells, deposit collagen and release cytokines that drive a vicious circle triggering further inflammation and fibrosis [93]. Although diffuse fibrosis has not traditionally been considered as an early marker of HFpEF [94], there is recent evidence that suggests otherwise: patients at risk for HFpEF (elevated BNP levels) exhibited the same degree of fibrosis as those with a confirmed HFpEF diagnosis [95]. The temporal relationship between myocardial fibrosis and the progression of HFpEF is not well characterized due to the scarcity of methods able to assess fibrosis non-invasively. Consequently, the evaluation of myocardial fibrosis should be considered in future investigations and explorations of early biomarkers.

To date, most attempts to detect diffuse cardiac fibrosis have been achieved using cardiac MRI because of its exquisite spatial delineation [96, 97]. However, the gadolinium-contrast-enhanced MRI method employed is sensitive to the extracellular volume fraction and, therefore, is not specific to fibrosis. Ambiguity is a problem, as other pathologies, including cell death and edema, can give rise to a higher extracellular volume fraction. In order to detect fibrosis with certainty, molecular probes with an affinity for collagen are required. Currently, there is very little effort in the development of targeted probes for imaging fibrosis, although there are a few reports in animals in various anatomical regions of the body [98–100]. An important future emphasis is to translate these molecular probes into human patients.

Endothelial dysfunction

A potentially very powerful diagnostic approach is to look also for extramyocardial evidence of disease, in contrast to focusing exclusively on the heart. As described earlier, the current paradigm on the etiology of HFpEF attributes coronary microvascular dysfunction and impaired vascular reserve, amongst other, to endothelial dysfunction, which is a deleterious outcome of inflammation. Given that the most common comorbidities of HFpEF all involve inflammation, it is reasonable, even logical, to place the occurrence of endothelial dysfunction at the same time as, if not earlier than, the earliest development of abnormalities in the heart. If our ultimate goal is to achieve *early* detection of HFpEF, it may very well be that waiting until overt indications of diagnostic dysfunction appear is already too late. With this philosophy, we would need to detect and diagnose endothelial dysfunction directly. It is important to note that the complications of endothelial dysfunction—such as impaired vasodilation, microvessel rarefaction, and a reduced systemic vasodilatory response [101]—are all consistent with HFpEF symptoms (dyspnea on exertion, exercise intolerance) that have been observed in the *absence* of diastolic dysfunction [32]. While it is true that endothelial dysfunction and inflammation may not necessarily lead to HFpEF, they do put patients at risk for heart disease and represent the earliest known biomarker than can be assessed on diagnostic imaging.

The gold standard for measuring endothelial function is angiography under injection of acetylcholine, a vasodilator [102]. This method, however, is invasive and limited to large blood vessels such as the coronary artery. Another large-vessel but non-invasive method is ultrasound-measured flow-mediated dilation of the brachial artery. Laser Doppler allows non-invasive assessment of microvessel flow, but it can only be

applied to superficial tissue [103]. PET imaging involving radioactive tracers allows deep-tissue assessment of myocardial perfusion [104] and sympathetic nerve activity [105, 106]. Importantly, HFpEF patients with compromised coronary flow reserve as identified on PET stress/rest perfusion have been shown in separate studies to have markedly greater risk of HFpEF events [107, 108], but this capability must be balanced against the risk of exposing patients to radioactive tracers. A completely non-invasive alternative is MRI, which offers superior spatial resolution to PET imaging. To probe endothelial dysfunction, blood oxygenation level-dependent (BOLD) MRI methods developed from neuroimaging has been applied to the heart, but this method is inappropriate due to inherent sensitivity to many factors unrelated to microvascular tone [109]. The only MRI technique that has been reported in the literature to date for the direct assessment of endothelial function and dysfunction is specifically sensitized to microvascular volume [110]. This approach was developed for high- and low-flow organs and has been applied to ischemic muscle tissue to elucidate compromised microvessel dilation [111]. The translation of this method to humans is underway and should be considered in future investigations on the prognostic and early diagnostic value of assessing endothelial dysfunction both intra- and extramyocardially.

Inflammation

In our discussion of future perspectives for earlier and more accurate HFpEF diagnosis, we have highlighted entities (stress testing, myocardial stiffness, ventricular-arterial coupling, fibrosis, and endothelial dysfunction) that have the potential to be included in a new imaging diagnostic workflow. Of these, endothelial dysfunction is one of the earliest changes that manifest, possibly first extramyocardially before the heart is even affected. Another pathophysiology that likely forebodes cardiac changes is inflammation. Using radiotracer probes on nuclear medicine imaging, immune cell migration to the myocardium may be visualized [112] and acute and post-inflammatory reaction may be distinguished [113]. MRI is less useful for this purpose, because inflammation is identified indirectly through increased extravasation of intravenously injected contrast agents. Since the current HFpEF paradigm places inflammation as the initiator of disease, it would be worthwhile to consider the value of imaging systemic inflammation in the prognosis of HFpEF.

Conclusions

HFpEF is a heterogeneous disease whose pathophysiological basis is still being uncovered. There is no uniformly accepted set of validated diagnostic guidelines and no proven therapy. What is certain, however, is that HFpEF patients are often misdiagnosed at the early stages but then are far along in disease progression when a HFpEF diagnosis is eventually confirmed. This review article summarized our current understanding of the etiology of the syndrome and proposed new approaches to diagnosis that take a systemic perspective to enable earlier, more accurate diagnosis of a prevalent and equally fatal phenotype of HF. We also reviewed the mainstay of cardiac diagnostics, namely, echocardiography, cardiac MRI, and cardiac PET. Each modality provides complementary information, but a different modality may assume a more dominant role in diagnosis depending on the stage of disease. In the early stages of HFpEF development, where tissue-level changes—such as microstructural alterations, reactive fibrosis, and vascular changes—manifest in the absence of overt functional and structural alterations, cardiac MRI may be arguably the best modality for early detection of disease. As disease progresses and the increasingly stiffer myocardium begins to impair mechanics, both echocardiography and cardiac MRI can inform on the severity of disease. One distinct advantage that echocardiography has over the other modalities, however, is its unique real-time acquisition ability, which provides specific information on diastolic function and dysfunction. Ultimately, the relative diagnostic value of each modality at different stages of HFpEF progression can only be determined with improved understanding of the etiology and development of HFpEF.

Funding sources This work was supported in part by grants from the Natural Sciences and Engineering Research Council of Canada (#355795) and the Ted Rogers Centre for Heart Research. S. L. is funded by a Heart & Stroke Richard Lewar Centre of Excellence Studentship.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Garg A, Virmani D, Agrawal S, Agarwal C, Sharma A, Stefanini G, Kostis JB (2017) Clinical application of biomarkers in heart failure with a preserved ejection fraction: a review. Cardiology 136(3):192–203. https://doi.org/10.1159/000450573
2. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM (2006) Trends in prevalence and outcome of heart failure with preserved ejection fraction. New England Journal of Medicine 355:251–259
3. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, Hernandez AF, Fonarow GC (2012) Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation 126(1):65–75
4. Borlaug BA, Paulus WJ (2011) Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. Eur Heart J 32(6):670–679. https://doi.org/10.1093/eurheartj/ehq426

5. Tschöpe C, Lam CSP (2012) Diastolic heart failure: what we still don't know. Looking for new concepts, diagnostic approaches, and the role of comorbidities. Herz 37(8):875–879. https://doi.org/10.1007/s00059-012-3719-5
6. Ho JE, Enserro D, Brouwers FP, Kizer JR, Shah SJ, Psaty BM, Bartz TM, Santhanakrishnan R, Lee DS, Chan C, Liu K, Blaha MJ, Hillege HL, van der Harst P, van Gilst WH, Kop WJ, Gansevoort RT, Vasan RS, Gardin JM, Levy D, Gottdiener JS, de Boer RA, Larson MG (2016) Predicting heart failure with preserved and reduced ejection fraction: The International Collaboration on Heart Failure Subtypes. Circ Heart Fail 9(6). https://doi.org/10.1161/circheartfailure.115.003116
7. Becher PM, Lindner D, Fluschnik N, Blankenberg S, Westermann D (2013) Diagnosing heart failure with preserved ejection fraction. Expert Opinion on Medical Diagnostics 7(5):463–474. https://doi.org/10.1517/17530059.2013.825246
8. Campbell RT, McMurray JJV (2014) Comorbidities and differential diagnosis in heart failure with preserved ejection fraction. Heart Fail Clin 10(3):481–501. https://doi.org/10.1016/j.hfc.2014.04.009
9. Ezekowitz JA, O'Meara E, McDonald MA, Abrams H, Chan M, Ducharme A, Giannetti N, Grzeslo A, Hamilton PG, Heckman GA, Howlett JG, Koshman SL, Lepage S, McKelvie RS, Moe GW, Rajda M, Swiggum E, Virani SA, Zieroth S, Al-Hesayen A, Cohen-Solal A, D'Astous M, De S, Estrella-Holder E, Fremes S, Green L, Haddad H, Harkness K, Hernandez AF, Kouz S, MH L, Fa M, Rose HJ, Roussin A, Sussex B (2017) 2017 Comprehensive update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Canadian Journal of Cardiology 33(11):1342–1433
10. Paulus WJ, Tschöpe C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbély A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL (2007) How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. Eur Heart J 28(20):2539–2550. https://doi.org/10.1093/eurheartj/ehm037
11. Oktay AA, Shah SJ (2015) Diagnosis and management of heart failure with preserved ejection fraction: 10 key lessons. Curr Cardiol Rev 11(1):42–52
12. Hadano Y, Murata K, Yamamoto T, Kunichika H, Matsumoto T, Akagawa E, Sato T, Tanaka T, Nose Y, Tanaka N, Matsuzaki M (2006) Usefulness of mitral annular velocity in predicting exercise intolerance in patients with impaired left ventricular systolic function. American Journal of Cardiology 97:1025–1028
13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Group ESCSD (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 37(27):2129–2200. https://doi.org/10.1093/eurheartj/ehw128
14. Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, Paulus WJ (2016) Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. Circulation 134(1):73–90. https://doi.org/10.1161/circulationaha.116.021884
15. Borlaug BA, Redfield MM (2011) Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation 123(18):2006–2013; discussion 2014. https://doi.org/10.1161/circulationaha.110.954388
16. Altara R, Giordano M, Nordén ES, Cataliotti A, Kurdi M, Bajestani SN, Booz GW (2017) Targeting obesity and diabetes to treat heart failure with preserved ejection fraction. Front Endocrinol (Lausanne) 8:160. https://doi.org/10.3389/fendo.2017.00160
17. Beale AL, Meyer P, Marwick TH, Lam CSP, Kaye DM (2018) Sex differences in cardiovascular pathophysiology: why women are overrepresented in heart failure with preserved ejection fraction. Circulation 138(2):198–205. https://doi.org/10.1161/circulationaha.118.034271
18. Afsar B, Rossignol P, van Heerebeek L, Paulus WJ, Damman K, Heymans S, van Empel V, Sag A, Maisel A, Kanbay M (2017) Heart failure with preserved ejection fraction: a nephrologist-directed primer. Heart Fail Rev. https://doi.org/10.1007/s10741-017-9619-2
19. Haass M, Kitzman DW, Anand IS, Miller A, Zile MR, Massie BM, Carson PE (2011) Body mass index and adverse cardiovascular outcomes in heart failure patients with preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Circ Heart Fail 4(3):324–331. https://doi.org/10.1161/CIRCHEARTFAILURE.110.959890
20. Paulus WJ, Tschöpe C (2013) 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 62(4):263–271. https://doi.org/10.1016/j.jacc.2013.02.092
21. O'Meara E, de Denus S, Rouleau J-L, Desai A (2013) Circulating biomarkers in patients with heart failure and preserved ejection fraction. Curr Heart Fail Rep 10(4):350–358. https://doi.org/10.1007/s11897-013-0160-x
22. Hippisley-Cox J, Coupland C (2016) Diabetes treatments and risk of heart failure, cardiovascular disease, and all cause mortality: cohort study in primary care. BMJ 354:i3477. https://doi.org/10.1136/bmj.i3477
23. Sandesara PB, O'Neal WT, Kelli HM, Samman-Tahhan A, Hammadah M, Quyyumi AA, Sperling LS (2018) The prognostic significance of diabetes and microvascular complications in patients with heart failure with preserved ejection fraction. Diabetes Care 41(1):150–155. https://doi.org/10.2337/dc17-0755
24. Boonman-de Winter LJM, Cramer MJ, Hoes AW, Rutten FH (2016) Uncovering heart failure with preserved ejection fraction in patients with type 2 diabetes in primary care: time for a change. Neth Heart J 24(4):237–243. https://doi.org/10.1007/s12471-016-0809-7
25. Tsujimoto T, Kajio H (2017) Abdominal obesity is associated with an increased risk of all-cause mortality in patients with HFpEF. J Am Coll Cardiol 70(22):2739–2749. https://doi.org/10.1016/j.jacc.2017.09.1111
26. How to diagnose diastolic heart failure European study group on diastolic heart failure (1998). Eur Heart J 19(7):990–1003
27. Mohammed SF, Borlaug BA, Roger VL, Mirzoyev SA, Rodeheffer RJ, Chirinos JA, Redfield MM (2012) Comorbidity and ventricular and vascular structure and function in heart failure with preserved ejection fraction: a community-based study. Circ Heart Fail 5(6):710–719. https://doi.org/10.1161/circheartfailure.112.968594
28. Hay I, Rich J, Ferber P, Burkhoff D, Maurer MS (2005) Role of impaired myocardial relaxation in the production of elevated left ventricular filling pressure. Am J Physiol Heart Circ Physiol 288(3):H1203–H1208. https://doi.org/10.1152/ajpheart.00681.2004

29. Gladden JD, Linke WA, Redfield MM (2014) Heart failure with preserved ejection fraction. Pflugers Arch 466(6):1037–1053. https://doi.org/10.1007/s00424-014-1480-8
30. Lim SL, Lam CS, Segers VF, Brutsaert DL, De Keulenaer GW (2015) Cardiac endothelium-myocyte interaction: clinical opportunities for new heart failure therapies regardless of ejection fraction. Eur Heart J 36(31):2050–2060. https://doi.org/10.1093/eurheartj/ehv132
31. van Heerebeek L, Hamdani N, Falcao-Pires I, Leite-Moreira AF, Begieneman MP, Bronzwaer JG, van der Velden J, Stienen GJ, Laarman GJ, Somsen A, Verheugt FW, Niessen HW, Paulus WJ (2012) Low myocardial protein kinase G activity in heart failure with preserved ejection fraction. Circulation 126(7):830–839. https://doi.org/10.1161/CIRCULATIONAHA.111.076075
32. Borlaug BA, Olson TP, Lam CSP, Flood KS, Lerman A, Johnson BD, Redfield MM (2010) Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol 56(11):845–854. https://doi.org/10.1016/j.jacc.2010.03.077
33. Akiyama E, Sugiyama S, Matsuzawa Y, Konishi M, Suzuki H, Nozaki T, Ohba K, Matsubara J, Maeda H, Horibata Y, Sakamoto K, Sugamura K, Yamamuro M, Sumida H, Kaikita K, Iwashita S, Matsui K, Kimura K, Umemura S, Ogawa H (2012) Incremental prognostic significance of peripheral endothelial dysfunction in patients with heart failure with normal left ventricular ejection fraction. J Am Coll Cardiol 60(18):1778–1786. https://doi.org/10.1016/j.jacc.2012.07.036
34. Westermann D, Lindner D, Kasner M, Zietsch C, Savvatis K, Escher F, von Schlippenbach J, Skurk C, Steendijk P, Riad A, Poller W, Schultheiss H-P, Tschöpe C (2011) Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction. Circ Heart Fail 4(1):44–52. https://doi.org/10.1161/circheartfailure.109.931451
35. Lam CS, Lyass A, Kraigher-Krainer E, Massaro JM, Lee DS, Ho JE, Levy D, Redfield MM, Pieske BM, Benjamin EJ, Vasan RS (2011) Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. Circulation 124(1):24–30
36. Bell DSH (2003) Heart failure: the frequent, forgotten, and often fatal complication of diabetes. Diabetes Care 26(8):2433–2441
37. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European heart journal cardiovascular imaging 16(3):233–270
38. Hare JL, Brown JK, Marwick TH (2008) Performance of convetional echocardiographic parameters and myocardial measurements in the sequential evaluation of left ventricular function. American Journal of Cardiology 101:706–711
39. Porter TR, Mulvagh SL, Abdelmoneim SS, Becher H, Belcik JT, Bierig M, Choy J, Gaibazzi N, Gillam LD, Janardhanan R, Kutty S, Leong-Poi H, Lindner JR, Main ML, Mathias WJ, Park MM, Senior R, Villanueva F (2018) Clinical applications of ultrasonic enhancing agents in echocardiography: 2018 American Society of Echocardiography Guidelines Update. Journal of the American Society of Echocardiography 31(3):241–274
40. Soliman OI, Kirschbaum SW, van Dalen BM, van der Zwaan HB, Mahdavian Delavary B, Vletter WB, van Geuns RJ, Ten Cate FJ, Geleijnse ML (2008) Accuracy and reproducibility of quantitation of left ventricular function by real-time three-dimensional echocardiography versus cardiac magnetic resonance. American Journal of Cardiology 102(6):778–783
41. Butrous H, Pai RG (2013) Heart failure with normal ejection fraction: current diagnostic and management strategies. Expert Rev Cardiovasc Ther 11(9):1179–1193. https://doi.org/10.1586/14779072.2013.827468
42. Gillebert TC, De Pauw M, Timmermans F (2013) Echo-doppler assessment of diastole: flow, function and haemodynamics. Heart 99:55–64
43. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD (2016) Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European Heart Journal Cardiovascular Imaging 17(12):1321–1360
44. Kasner M, Westermann D, Steendijk P, Gaub R, Wilkenshoff U, Weitmann K, Hoffmann W, Poller W, Schultheiss HP, Pauschinger M, Tschöpe C (2007) Utility of Doppler echocardiography and tissue Doppler imaging in the estimation of diastolic function in heart failure with normal ejection fraction: a comparative Doppler-conductance catheterization study. Circulation 116(6):637–647
45. Mitter SS, Shah SJ, Thomas JD (2017) A test in context: E/A and E/e' to assess diastolic dysfunction and LV filling pressure. J Am Coll Cardiol 69(11):1451–1464. https://doi.org/10.1016/j.jacc.2016.12.037
46. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW (2009) 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 53(15):e1–e90
47. Hunt PJ, Richards AM, Nicholls MG, Yandle TG, Doughty RN, Espiner EA (1997) Immunoreactive amino-terminal pro-brain natriuretic peptide (NT-PROBNP): a new marker of cardiac. Clinical endocrinology 47(3):287–296
48. Anjan VY, Loftus TM, Burke MA, Akhter N, Fonarow GC, Gheorghiade M, Shah SJ (2012) Prevalence, clinical phenotype, and outcomes associated with normal B-type natriuretic peptide levels in heart failure with preserved ejection fraction. American Journal of Cardiology 110(6):870–876
49. Mehra MR, Uber PA, Park MH, Scott RL, Ventura HO, Harris BC, Frohlich ED (2004) Obesity and suppressed B-type natriuretic peptide levels in heart failure. American Journal of Cardiology 43(9):1590–1595
50. Porter TR, Xie F (2010) Myocardial perfusion imaging with contrast ultrasound. JACC Cardiovasc Imaging 3(2):176–187. https://doi.org/10.1016/j.jcmg.2009.09.024
51. Rademakers FE (2003) Magnetic resonance imaging in cardiology. Lancet 361(9355):359–360
52. Mertens LL, Friedberg MK (2010) Imaging the right ventricle – current state of the art. Nat Rev Cardiol 7(10):551–563
53. Hendel RC, Friedrich MG, Schulz-Menger J, Zemmrich C, Bengel F, Berman DS, Camici PG, Flamm SD, Le Guludec D, Kim R, Lombardi M, Mahmarian J, Sechtem U, Nagel E (2016) CMR first-pass perfusion for suspected inducible myocardial ischemia. JACC Cardiovascular Imaging 9(11):1338–1348
54. Shehata ML, Basha TA, Hayeri MR, Hartung D, Teytelboym OM, Vogel-Claussen J (2014) MR myocardial perfusion imaging: insights on techniques, analysis, interpretation, and findings. Radiographics 34(6):1636–1657
55. Kanagala P, Cheng ASH, Singh A, McAdam J, Marsh A-M, Arnold JR, Squire IB, Ng LL, McCann GP (2018) Diagnostic

and prognostic utility of cardiovascular magnetic resonance imaging in heart failure with preserved ejection fraction - implications for clinical trials. Journal of Cardiovascular Magnetic Resonance 20(1):4. https://doi.org/10.1186/s12968-017-0424-9

56. Salerno M, Kramer CM (2013) Advances in parametric mapping with CMR imaging. JACC Cardiovascular Imaging 6(7):806–822
57. Reiter G, Reiter C, Krauter C, Fuschsjager M, Reiter U (2018) Cardiac magnetic resonance T1 mapping. Part 1: aspects of acquisition and evaluation. European journal of radiology 109:223–234
58. Zhuang B, Sirajuddin A, Wang S, Arai A, Zhao S, Lu M (2018) Prognostic value of T1 mapping and extracellular volume fraction in cardiovascular disease: a systematic review and meta-analysis. Heart Fail Rev 23(5):723–731
59. Bohnen S, Radunski UK, Lund GK, Ojeda F, Looft Y, Senel M, Radziwolek L, Avanesov M, Tahir E, Stehning C, Schnackenburg B, Adam G, Blankenberg S, Muellerleile K (2017) Tissue characterization by T1 and T2 mapping cardiovascular magnetic resonance imaging to monitor myocardial inflammation in healing myocarditis. Eur Heart J Cardiovasc Imaging 18(7):744–751
60. Hartung D, Hueper K, Chen R, Gutberlet M, Wacker F, Meier M, Rong S, Jang MS, Bräsen JH, Gueler F (2018) T2 mapping for noninvasive assessment of interstitial edema in acute cardiac allograft rejection in a mouse model of heterotopic heart transplantation. Investigative Radiology 53(5):271–277
61. Krittayaphong R, Zhang S, Saiviroonporn P, Viprakasit V, Tanapibunpon P, Rerkudom B, Yindeengam A, Wood JC (2019) Assessment of cardiac iron overload in thalassemia with MRI on 3.0-T: high-field T1, T2, and T2* quantitative parametric mapping in comparison to T2* on 1.5-T. JACC Cardiovascular Imaging 12(4):752–754
62. Ghugre NR, Ramanan V, Pop M, Yang Y, Barry J, Qiang B, Connelly KA, Dick AJ, Wright GA (2011) Quantitative tracking of edema, hemorrhage, and microvascular obstruction in subacute myocardial infarction in a porcine model by MRI. Magn Reson Med 66(4):1129–1141
63. Paterson I, Wells GA, Ezekowitz JA, White JA, Friedrich MG, Mielniczuk LM, O'Meara E, Chow BS, DeKemp RA, Klein R, Dennie C, Dick A, Coyle D, Dwivedi G, Rajda M, Wright GA, Laine M, Hanninen H, Larose E, Connelly KA, Leong-Poi H, Howarth AG, Davies RA, Duchesne L, Yla-Herttuala S, Saraste A, Farand P, Garrard L, Tardif JC, Arnold M, Knuuti J, Beanlands R, Chan KL (2013) Routine versus selective cardiac magnetic resonance in non-ischemic heart failure - OUTSMART-HF: study protocol for a randomized controlled trial (IMAGE-HF (heart failure) project 1-B). Trials 14:332
64. Coelho-Filho OR, Rickers C, Kwong RY, Jerosch-Herold M (2013) MR myocardial perfusion imaging. Radiology 266(3): 701–715. https://doi.org/10.1148/radiol.12110918
65. Jenson S, Craig S, York G, Steel K (2013) Review of cardiac MR perfusion imaging. Journal of the American Osteopathic College of Radiology 2(2):1–7
66. Francis R, Kellman P, Kotecha T, Baggiano A, Norrington K, Martinez-Naharro A, Nordin S, Knight DS, Rakhit RD, Lockie T, Hawkins PN, Moon JC, Hausenloy DJ, Xue H, Hansen MS, Fontana M (2017) Prospective comparison of novel dark blood late gadolinium enhancement with conventional bright blood imaging for the detection of scar. J Cardiovasc Magn Reson 19(1): 91. https://doi.org/10.1186/s12968-017-0407-x
67. Cavalcante JL, Lalude OO, Schoenhagen P, Lerakis S (2016) Cardiovascular magnetic resonance imaging for structural and valvular heart disease interventions. JACC Cardiovasc Interv 9(5):399–425. https://doi.org/10.1016/j.jcin.2015.11.031
68. Nagao M, Yamasaki Y (2018) Cardiac strain analysis using cine magnetic resonance imaging and computed tomography. Cardiovascular Imaging Asia 2:76–84
69. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM (2010) Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circulation Heart failure 3(5):588–595
70. Borlaug BA, Melenovsky V, Russell SD, Kessler K, Pacak K, Becker LC, Kass DA (2006) Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. Circulation 114(20):2138–2147
71. Donal E, Thebault C, Lund LH, Kervio G, Reynaud A, Simon T, Drouet E, Nonotte E, Linde C, Daubert JC (2012) Heart failure with a preserved ejection fraction additive value of an exercise stress echocardiography. European Heart Journal Cardiovascular Imaging 13(8):656–665
72. Oren O, Goldberg S (2017) Heart failure with preserved ejection fraction: diagnosis and management. Am J Med 130(5):510–516. https://doi.org/10.1016/j.amjmed.2016.12.031
73. Ohtani T, Mohammed SF, Yamamoto K, Dunlay SM, Weston SA, Sakata Y, Rodeheffer RJ, Roger VL, Redfield MM (2012) Diastolic stiffness as assessed by diastolic wall strain is associated with adverse remodelling and poor outcomes in heart failure with preserved ejection fraction. Eur Heart J 33(14):1742–1749
74. Kaluzynski K, Chen X, Emelianov SY, Skovoroda AR, O'Donnell M (2001) Strain rate imaging using two-dimensional speckle tracking. IEEE transactions on ultrasonics, ferroelectrics, and frequency control 48(4):1111–1123
75. Korinek J, Wang J, Sengupta PP, Miyazaki C, Kjaergaard J, McMahon E, Abraham TP, Belohlavek M (2005) Two-dimensional strain–a Doppler-independent ultrasound method for quantitation of regional deformation: validation in vitro and in vivo. Journal of the American Society of Echocardiography 18(12):1247–1253
76. Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, Støylen A, Ihlen H, Lima JA, Smiseth OA, Slørdahl SA (2006) Noninvasive myocardial strain measurement by speckle tracking echocardiography. validation against sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 47(4):789–798
77. Petersen JW, Nazir TF, Lee L, Garvan CS, Karimi A (2013) Speckle tracking echocardiography-determined measures of global and regional left ventricular function correlate with functional capacity in patients with and without preserved ejection fraction. Cardiovascular ultrasound 11:20
78. DeVore AD, McNulty S, Alenezi F, Ersboll M, Vader JM, Oh JK, Lin G, Redfield MM, Lewis G, Semigran MJ, Anstrom KJ, Hernandez AF, Velazquez EJ (2017) Impaired left ventricular global longitudinal strain in patients with heart failure with preserved ejection fraction: insights from the RELAX trial. Eur J Heart Fail 19(7):893–900
79. Risum N, Ali S, Olsen NT, Jons C, Khouri MG, Lauridsen TK, Samad Z, Velazquez EJ, Sogaard P, Kisslo J (2012) Variability of global left ventricular deformation analysis using vendor dependent and independent two-dimensional speckle-tracking software in adults. Journal of the American Society of Echocardiography 25(11):1195–1203
80. McVeigh ER, Zerhouni EA (1991) Noninvasive measurement of transmural gradients in myocardial strain with MR imaging. Radiology 180(3):677–683
81. Edvardsen T, Rosen BD, Pan L, Jerosch-Herold M, Lai S, Hundley WG, Sinha S, Kronmal RA, Bluemke DA, Lima JA (2006) Regional diastolic dysfunction in individuals with left ventricular hypertrophy measured by tagged magnetic resonance imaging–the Multi-Ethnic Study of Atherosclerosis (MESA). Am Heart J 151(1):109–114
82. Hor KN, Baumann R, Pedrizzetti G, Tonti G, Gottliebson WM, Taylor M, Benson DW, Mazur W (2011) Magnetic resonance

derived myocardial strain assessment using feature tracking. Journal of Visualized Experiments: JoVE 48:2356
83. Evin M, Broadhouse KM, Callaghan FM, McGrath RT, Glastras S, Kozor R, Hocking SL, Lamy J, Redheuil A, Kachenoura N, Fulcher GR, Figtree GA, Grieve SM (2016) Impact of obesity and epicardial fat on early left atrial dysfunction assessed by cardiac MRI strain analysis. Cardiovascular Diabetology 15(1):164
84. Mahmod M, Pal N, Rayner J, Holloway C, Raman B, Dass S, Levelt E, Ariga R, Ferreira V, Banerjee R, Schneider JE, Rodgers C, Francis JM, Karamitsos TD, Frenneaux M, Ashrafian H, Neubauer S, Rider O (2018) The interplay between metabolic alterations, diastolic strain rate and exercise capacity in mild heart failure with preserved ejection fraction: a cardiovascular magnetic resonance study. Journal of Cardiovascular Magnetic Resonance 20(1):88
85. Borlaug BA, Kass DA (2011) Ventricular-vascular interaction in heart failure. Cardiology clinics 29(3):447–459
86. Borlaug BA, Jaber WA, Ommen SR, Lam CS, Redfield MM, Nishimura RA (2011) Diastolic relaxation and compliance reserve during dynamic exercise in heart failure with preserved ejection fraction. Heart 97(12):964–969
87. Gillebert TC, Leite-Moreira AF, De Hert SG (2000) Load dependent diastolic dysfunction in heart failure. Heart Fail Rev 5:345–355
88. Bombardini T, Costantino MF, Sicari R, Ciampi Q, Pratali L, Picano E (2013) End-systolic elastance and ventricular-arterial coupling reserve predict cardiac events in patients with negative stress echocardiography. Biomed Res Int 2013:235194
89. Chen CH, Fetics B, Nevo E, Rochitte CE, Chiou KR, Ding PA, Kawaguchi M, Kass DA (2001) Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol 38(7):2028–2034
90. Gayat E, Mor-Avi V, Weinert L, Yodwut C, Lang RM (2011) Noninvasive quantification of left ventricular elastance and ventricular-arterial coupling using three-dimensional echocardiography and arterial tonometry. Am J Physiol Heart Circ Physiol 301(5):H916–H923
91. Wong RC, Dumont CA, Austin BA, Kwon DH, Flamm SD, Thomas JD, Starling RC, Desai MY (2010) Relation of ventricular-vascular coupling to exercise capacity in ischemic cardiomyopathy: a cardiac multi-modality imaging study. The International Journal of Cardiovascular Imaging 26(2):151–159
92. Witschey WR, Contijoch F, McGarvey JR, Ferrari VA, Hansen MS, Lee ME, Takebayashi S, Aoki C, Chirinos JA, Yushkevich PA, Gorman JH, Pilla JJ, Gorman RC (2014) Real-time magnetic resonance imaging technique for determining left ventricle pressure-volume loops. The annals of thoracic surgery 97(5):1597–1603
93. Westermann D, Lindner D, Kasner M, Zietsch C, Savvatis K, Escher F, von Schlippenbach J, Skurk C, Steendijk P, Riad A, Poller W, Schultheiss HP, Tschöpe C (2011) Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction. Circ Heart Fail 4(1):44–52
94. Desai S, Haines P, Zamani P, Konda P, Shiva-Kumar P, Peddireddy S, Shekhar RC, Jain S, Kers S, Ferrari V, Chirinos J (2018) Diffuse myocardial fibrosis is greatly elevated in males with heart failure with reduced ejection fraction, but not heart failure with preserved ejection fraction. J Am Coll Cardiol 63(12 Supplement):A967. https://doi.org/10.1016/s0735-1097(14)60967-0
95. Schelbert EB, Fridman Y, Wong TC, Abu Daya H, Piehler KM, Kadakkal A, Miller CA, Ugander M, Maanja M, Kellman P, Shah DJ, Abebe KZ, Simon MA, Quarta G, Senni M, Butler J, Diez J, Redfield MM, Gheorghiade M (2017) Temporal relation between myocardial fibrosis and heart failure with preserved ejection fraction: association with baseline disease severity and subsequent outcome. JAMA cardiology 2(9):995–1006
96. Su MY, Lin LY, Tseng YH, Chang CC, Wu CK, Lin JL, Tseng WY (2014) CMR-verified diffuse myocardial fibrosis is associated with diastolic dysfunction in HFpEF. JACC Cardiovascular imaging 7(10):991–997
97. Duca F, Kammerlander AA, Zotter-Tufaro C, Aschauer S, Schwaiger ML, Marzluf BA, Bonderman D, Mascherbauer J (2016) Interstitial fibrosis, functional status, and outcomes in heart failure with preserved ejection fraction: insights from a prospective cardiac magnetic resonance imaging study. Circulation, cardiovascular imaging 9(12):e005277
98. Helm PA, Caravan P, French BA, Jacques V, Shen L, Xu Y, Beyers RJ, Roy RJ, Kramer CM, Epstein FH (2008) Postinfarction myocardial scarring in mice: molecular MR imaging with use of a collagen-targeting contrast agent. Radiology 247(3):788–796
99. Tassali N, Bianchi A, Lux F, Raffard G, Sanchez S, Tillement O, Crémillieux Y (2016) MR imaging, targeting and characterization of pulmonary fibrosis using intra-tracheal administration of gadolinium-based nanoparticles. Contrast media and molecular imaging 11(5):396–404
100. Caravan P, Das B, Dumas S, Epstein FH, Helm PA, Jacques V, Koerner S, Kolodziej A, Shen L, Sun WC, Zhang Z (2007) Collagen-targeted MRI contrast agent for molecular imaging of fibrosis. Angewandte chemie 46(43):8171–8173
101. Deanfield J, Donald A, Ferri C, Giannattasio C, Halcox J, Halligan S, Lerman A, Mancia G, Oliver JJ, Pessina AC, Rizzoni D, Rossi GP, Salvetti A, Schiffrin EL, Taddei S, Webb DJ (2005) Endothelial function and dysfunction. Part I: Methodological issues for assessment in the different vascular beds. a statement by the Working Group on Endothelin and Endothelial Factors of the European Society of Hypertension. J Hypertens 23(1):7–17
102. Ludmer PL, Selwyn AP, Shook TL, Wayne RR, Mudge GH, Alexander RW, Ganz P (1986) Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. N Engl J Med 315(17):1046–1051. https://doi.org/10.1056/NEJM198610233151702
103. Felmeden DC, Lip GY (2005) Endothelial function and its assessment. Expert Opin Investig Drugs 14(11):1319–1336. https://doi.org/10.1517/13543784.14.11.1319
104. Berman DS, Kiat H, Van Train KF, Friedman J, Garcia EV, Maddahi J (1990) Comparison of SPECT using technetium-99m agents and thallium-201 and PET for the assessment of myocardial perfusion and viability. American Journal of Cardiology 66(13):72E–79E
105. Thackeray JT, Radziuk J, Harper ME, Suuronen EJ, Ascah KJ, Beanlands RS, Dasilva JN (2011) Thackeray JT, Radziuk J, Harper ME, Suuronen EJ, Ascah KJ, Beanlands RS, Dasilva JN. Cardiovascular Diabetology 10:75
106. Schwaiger M, Kalff V, Rosenspire K, Haka MS, Molina E, Hutchins GD, Deeb M, Wolfe EJ, Wieland DM (1990) Noninvasive evaluation of sympathetic nervous system in human heart by positron emission tomography. Circulation 82(2):457–464
107. Taqueti VR, Solomon SD, Shah AM, Desai AS, Groarke JD, Osborne MT, Hainer J, Bibbo CF, Dorbala S, Blankstein R, Di Carli MF (2018) Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. Eur Heart J 39(10):840–849
108. Srivaratharajah K, Coutinho T, deKemp R, Liu P, Haddad H, Stadnick E, Davies RA, Chih S, Dwivedi G, Guo A, Wells GA, Bernick J, Beanlands R, Mielniczuk LM (2016) Reduced myocardial flow in heart failure patients with preserved ejection fraction. Circ Heart Fail 9(7):e002562
109. Gillies RJ, Bhujwalla ZM, Evelhoch J, Garwood M, Neeman M, Robinson SP, Sotak CH, Van Der Sanden B (2000) Applications

of magnetic resonance in model systems: tumor biology and physiology. Neoplasia 2(1–2):139–151
110. Ganesh T, Estrada M, Yeger H, Duffin J, Margaret Cheng H-L (2017) A non-invasive magnetic resonance imaging approach for assessment of real-time microcirculation dynamics. Sci Rep 7(1): 7468. https://doi.org/10.1038/s41598-017-06983-6
111. Ganesh T, Zakher E, Estrada M, Cheng HL (2018) Assessment of microvascular dysfunction in acute limb ischemia-reperfusion injury. Journal of magnetic resonance imaging 49(4):1174–1185
112. Rischpler C, Dirschinger RJ, Nekolla SG, Kossmann H, Nicolosi S, Hanus F, van Marwick S, Kunze KP, Meinicke A, Götze K, Kastrati A, Langwieser N, Ibrahim T, Nahrendorf M, Schwaiger M, Laugwitz K-L (2016) Prospective evaluation of 18F-fluorodeoxyglucose uptake in postischemic myocardium by simultaneous positron emission tomography/magnetic resonance imaging as a prognostic marker of functional outcome. Circulation: Cardiovascular Imaging 9(4):1–13
113. Werner RA, Wakabayashi H, Bauer J, Schütz C, Zechmeister C, Hayakawa N, Javadi MS, Lapa C, Jahns R, Ergün S, Jahns V, Higuchi T (2018) Longitudinal 18F-FDG PET imaging in a rat model of autoimmune myocarditis. Eur Heart J Cardiovasc Imaging 20(4):467–474

Heart Failure Reviews
https://doi.org/10.1007/s10741-019-09830-0

Current challenges in sudden cardiac death prevention

Domenico Corrado[1] · Alessandro Zorzi[1] · Emilio Vanoli[2,3] · Edoardo Gronda[3]

Abstract
Ischemic heart disease and non-ischemic dilated cardiomyopathy are the most common causes of arrhythmic sudden cardiac death (SCD). Implantable cardioverter defibrillator (ICD) therapy is the only strategy that proved to be effective in preventing SCD in high-risk individuals while the role of antiarrhythmic drugs is limited to symptoms relief. Current guidelines recommend selecting candidates to ICD implantation based on etiology, symptoms of heart failure (NYHA class), and severely depressed left ventricular ejection fraction, but these parameters are neither sensitive nor specific. The review addresses the mechanisms of SCD in patients with heart failure of either ischemic or non-ischemic etiology, risk stratification, and strategies for prevention of SCD in the clinical practice (including optimization of heart failure therapy, avoidance of triggering factors, antiarrhythmic drugs, ICD therapy, early resuscitation, and public access defibrillators).

Keywords Antiarrhythmic drugs · Heart failure · Implantable cardioverter defibrillator · Resuscitation · Ventricular arrhythmias

Introduction

Sudden cardiac death (SCD) is defined as unexpected death from cardiovascular causes which occurs within one hour of the beginning of symptoms in an apparently healthy subject or in one affected by a disease not severe enough to predict such an abrupt outcome [1]. Sudden cardiac death is an important clinical challenge of modern cardiology considering that it has an estimated incidence of 350,000 to 400,000 cases/year in the adult population in the USA and that most of these individuals have pre-existing heart disease [2].

The risk of SCD generally increases with age and is greater in men. In the general population of middle-aged and elderly, the estimated rate of SCD ranges from 1/1000 to 2/1000 per year; in comparison, a significantly lower incidence of fatal events has been reported in young people (1/100,000/year) [2]. The most common mechanism of a cardiac arrest leading to SCD is abrupt sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) as a consequence of an underlying cardiovascular disease, which provides a substrate for the electrical instability of the heart [3]. While a broad spectrum of cardiovascular substrates (including congenital and inherited heart disorders) may underlie SCD in young people, ischemic heart disease (IHD), either acute coronary syndromes or chronic IHD, and non-ischemic dilated cardiomyopathy (NIDC) are the most common causes of SCD in adults and elderly subjects [4].

✉ Domenico Corrado
domenico.corrado@unipd.it

[1] Department of Cardiac Thoracic, Vascular Sciences and Public Health, University of Padova, Via N. Giustiniani 2, 35121 Padova, Italy

[2] Molecular Medicine Department, Università degli Studi di Pavia, Pavia, Italy

[3] Cardiovascular Department, IRCCS MultiMedica, Sesto San Giovanni, Milan, Italy

Mechanisms of sudden cardiac death

Ischemic heart disease

Sudden cardiac death in the setting of IHD is almost invariably arrhythmic and may be the result of either ischemia-induced or scar-related malignant ventricular arrhythmias [3]. Cardiac arrest may be the earliest manifestation of acute coronary syndromes. Many patients who are resuscitated after a cardiac arrest develop overt signs of myocardial infarction such as ST-T abnormalities and serum enzyme elevations, and at coronary angiography, an acute coronary thrombosis is often evident [5]. Most deaths related to acute myocardial infarction occur within the first hour of symptoms onset out of hospital and are the consequence of ischemia-induced electrical instability. In this setting, VF may occur even before the

myocardial infarction lesion develops. Sudden cardiac death may be also caused by transient myocardial ischemia in the setting of unstable angina or coronary spasm, which may trigger fatal arrhythmias in the absence of overt myocardial damage [6]. The postulated arrhythmogenic mechanism consists of ischemia-induced raise in extracellular K+, due to the depression of the Na/K pumping system and fall in pH because of lactic acid that accumulates within cells and diffuses into the intercellular spaces. These modifications cause a transmural heterogeneity of myocyte repolarization predisposing to phase 2 reentry ("R on T" phenomenon) and VF [7].

In patients with a history of myocardial infarction, SCD may occur late after the acute event in relation to the development of a myocardial scar that acts as the structural arrhythmogenic substrate. In this context, VT may be induced by slowing and fragmentation of the ventricular myocardium depolarization wavefront that, in turn, predisposes to a macroreentry mechanism at the border between normal myocardium and scar and within the fibrotic area. Adrenergic stimulation such that occurring during sports activity may have a triggering role. Ventricular tachycardia may degenerate into VF and cause SCD, mostly in patients with severely depressed left ventricular (LV) systolic function and particularly during episodes of acute decompensated heart failure [8].

Non-ischemic dilated cardiomyopathy

Non-ischemic dilated cardiomyopathy is a common heart muscle disorder that is responsible for approximately one-third of heart failures and is the second leading cause of SCD. Although heart failure is the cardinal clinical manifestation of NIDC and the majority of these patients die for cardiogenic shock, SCD accounts for approximately 30% of all fatalities [9]. A variety of mechanisms may be involved in the development of life-threatening ventricular tachyarrhythmias, which include scar-related reentry, anisotropic interventricular conduction, spatial dispersion of ventricular repolarization, or functional bundle branch/interfascicular macro reentry.

Risk stratification for SCD

Implantable cardioverter defibrillator (ICD) therapy significantly reduces mortality in both IDCM and NIDC. Since the ICD was first introduced in the clinical practice in the 1980s, several trials have demonstrated that it is effective in preventing SCD not only among survivors of sudden cardiac arrest (secondary prevention) but also among high-risk patients with IHD or NIDC (primary prevention) [10–14]. In addition, the association between ICD and cardiac resynchronization therapy (CRT) was demonstrated to further improve survival rates and quality of life in patients with heart failure [15–17].

An important challenge is the identification of patients with heart failure, of either ischemic or non-ischemic origin, who most benefit from ICD implantation for primary prevention based on an individual risk assessment. Unfortunately, the majority of SCD victims were unaware of their underlying disease or classified at low risk according to the current risk stratification criteria [5, 9]. In particular, myocardial ischemia-induced SCD is an unpredictable event that most often occurs in the absence of a recognized IHD. According to available estimates, about one-third of SCD occur in previously asymptomatic individuals [5].

Randomized trials demonstrated that ICD therapy improves survival in patients with LV ejection fraction (EF) < 35% and NYHA class II–III and, as a consequence, current guidelines recommend that these patients should receive an ICD for primary prevention provided that the expected survival is at least 1 year [18, 19]. However, risk assessment based on LV EF alone is not accurate enough given that the majority of heart failure patients with an ICD never experience appropriate therapy while, on the other hand, a sizeable proportion of SCD victims with IHD or NIDC did not receive an ICD because the LV EF was ≥ 35% [5, 20]. A plausible explanation is that EF represents a global assessment of LV systolic function and does not necessarily correlate with myocardial lesions and electrophysiological abnormalities underlying ventricular electrical instability. This limitation of LV EF underscores the need to use other parameters for SCD risk stratification. A more accurate arrhythmic risk assessment offers the potential to improve both outcomes and cost-effectiveness of ICD therapy.

Although several noninvasive risk markers other than LV EF have been proposed, their predictive value has not been validated by randomized studies (Table 1). One of the most promising is the identification and quantification of myocardial fibrosis by cardiac magnetic resonance (CMR). Unlike traditional imaging techniques such as echocardiography which discloses LV mechanical dysfunction (either regional or global), CMR allows the demonstration of myocardial fibrosis using dedicated T1 sequences some minutes after the injection of a gadolinium-based contrast medium that distributes principally in the extracellular interstitial space (late gadolinium enhancement, LGE). Myocardial fibrosis acts as a substrate for life-threatening ventricular tachyarrhythmias and this explains why the presence of LGE has been found to be a stronger predictor of arrhythmic events than LV EF [28]. Several studies demonstrated that the detection and quantification of myocardial LGE by CE-CMR in patients with NIDC are independently associated with an adverse arrhythmic prognosis [20, 28, 30–32]. Risk stratification based on the myocardial scar burden has the potential to better identify patients at risk of SCD and guide ICD implantation. Particularly, patients not currently fulfilling the criteria for ICD implantation because of a mild to moderate LV dysfunction, but with large myocardial scars demonstrated by CMR,

Table 1 Main adjunctive arrhythmic risk stratification parameters in patients with reduced left ventricular ejection fraction

	Definition	Reference
Genetic variants	Detection of mutations in genes encoding for proteins associated with an increased risk of ventricular arrhythmias such as lamin A/C (apply to non-ischemic dilated cardiomyopathy only).	[21]
Markers of autonomic dysfunction		
Baroreflex sensitivity	Changes in heart rate in response to changes in blood pressure (spontaneous or after phenylephrine administration).	[22]
Heart rate turbulence	Reaction of heart rate in response to premature ventricular beats (turbulence onset, reflecting the initial acceleration of heart rate following premature beat, and turbulence slope, describing subsequent deceleration of heart rate).	[23]
Heart rate variability	Beat-to-beat variation of the RR-interval obtained during a short time period or from 24-h Holter recordings and analyzed in the time domain and frequency domain, or by non-linear methods.	[24]
ECG parameters		
QRS duration	Duration of the QRS complex or presence of left bundle branch block.	[25]
Fragmented QRS complex	Presence of an R' wave (excluding V1) or spikes in the QRS complex.	
T-peak–T-end interval	Interval from the peak to the end of the T-wave, in absolute values or relative to the QT-interval duration.	
QT dispersion	Maximum difference between QT intervals in two leads of the 12-lead ECG.	
Microvolt T-wave alternans	Beat-to-beat fluctuation of T-wave amplitude and morphology at the microvolt level.	[26]
Prolonged ECG monitoring		
Non-sustained ventricular tachycardia	≥ 3 (or ≥ 5) consecutive premature ventricular beats.	[27]
Cardiac magnetic resonance		
Presence/extent of myocardial fibrosis	Presence or extent (% of the myocardium) of late gadolinium enhancement on post-contrast T1 sequences.	[28]
Programmed ventricular stimulation		
Induced sustained ventricular tachycardia	Induction of sustained ventricular tachycardia (> 30 s or causing hemodynamic impairment) by programmed ventricular stimulation. Induction of non-sustained ventricular tachycardia or ventricular fibrillation is less specific.	[29]

may be classified as at high risk of SCD and warrant prophylactic ICD.

Strategies to prevent sudden death in the clinical practice

Optimization of heart failure therapy

Acute decompensated heart failure is a well-recognized trigger of sustained VT and VF in patients with dilated cardiomyopathy [33] (Fig. 1). In a study on 10,741 consecutive patients admitted to the cardiology department of the University of Padova in 2009–2014, acutely ill patients with LV systolic dysfunction showed the highest rate of in-hospital life-threatening ventricular arrhythmias, regardless of the underlying cardiac disease (ischemic or non-ischemic). Clinical signs of acute heart failure preceding the event were present in 62% of patients suffering major ventricular arrhythmias [34].

Medical therapy optimization not only reduces hospitalizations for acute heart failure and prolongs survival but also improves the arrhythmic prognosis. Beta-blockers have various beneficial effects on arrhythmogenic mechanisms and randomized controlled trials have consistently demonstrated

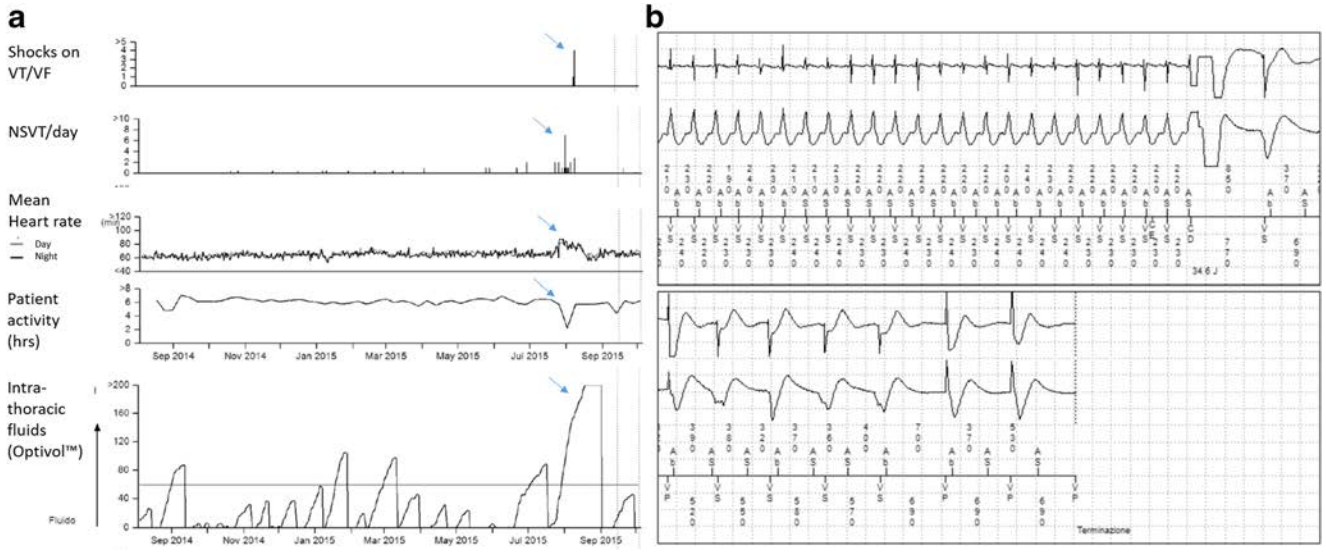


Fig. 1 Representative example of a patient suffering from arrhythmic storm in the context of acute decompensated heart failure. A 68-year-old male patient with ischemic cardiomyopathy and severely reduced ejection fraction received an implantable cardioverter defibrillator (ICD) for primary prevention with remote monitoring in 2010. In august 2015, at the age of 73, he suffered his first episode of acute decompensated heart failure. As indicated by the arrows, the data stored in the ICD memory and displayed on graphs showing trends over time (panel A) revealed an increase in mean heart rate, decrease in patient physical activity, and increase in intra-thoracic fluids days before the heart failure became clinically evident. At the same time, the burden of non-sustained ventricular tachycardia worsened. Few days after, he experienced a storm of sustained ventricular tachycardia that required four ICD shocks on the same day (**a**, 1st graph). The intracardiac recording of an episode of sustained ventricular tachycardia interrupted by an ICD shock is shown on **b**. The patient was hospitalized and potassium level at admission was 3.1 mmol/mol. He was treated for the acute heart failure and discharged 9 days after. No other episodes of acute decompensated heart failure or appropriate ICD interventions were observed until the last follow-up evaluation (March 2019)

that they reduce the risk of SCD by ≈30% in heart failure patients [35]. Angiotensin-converting enzyme inhibitors and mineralocorticoid-receptor antagonists have also shown to reduce both all-cause mortality and SCD [19]. A recent study on ICD carriers with symptomatic LV EF ≤40% demonstrated that the rate of sustained VT and appropriate ICD shocks over a 9-month period decreased from 6.7 to 0.8% ($p < 0.02$) following the replacement of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers with the recently developed sacubitril/valsartan association [36].

Cardiac resynchronization therapy improves the prognosis of symptomatic heart failure patients with a left bundle branch block. Several randomized trials demonstrated that cardiac resynchronization therapy alone (CRT-P) reduces the risk of SCD by inducing reverse LV remodelling [15–17]. The magnitude of the effect is so high that the incremental value of CRT-D (i.e., CRT-P plus ICD) over CRT-P has been questioned, particularly for patients with NIDC [37, 38].

Avoidance of triggering factors

The propensity to electrical instability of patients with heart failure is mostly related to the underlying myocardial substrate. However, apart from acute decompensated heart failure, several other potentially avoidable factors may favor ventricular arrhythmias.

Serum potassium disturbances (both hypokalemia and iperkalemia) resulting from kidney failure, diuretics therapy, or viral gastroenteritis with vomiting and diarrhea triple the arrhythmic risk of patients with chronic heart failure [39]. Hypomagnesemia is also a well-known triggering factor of malignant arrhythmias [40].

Infective diseases are another potential cause of worsening heart failure and ventricular arrhythmias. In particular, respiratory infections such as community-acquired pneumonia and influenza can precipitate cardiovascular events including SCD [41]. Of note, both pneumococcal pneumonia and influenza may be prevented by vaccination that should be offered to patients with heart failure [42].

Drugs may have pro-arrhythmic side effects. A well-known example is digoxin, which is largely used for rate control in patients with heart failure and atrial fibrillation. A recent subanalysis focused on the effect of digoxin in patients enrolled in the ENGAGE AF-TIMI 48 trial, which compared the anticoagulant edoxaban with warfarin for the prevention of systemic embolism in patients with atrial fibrillation. Among the 12,124 patients with heart failure, one-third was treated with digoxin. In this group, there was an adjusted 45% increase in the rate of SCD [43]. Other noncardiovascular drugs that are commonly used in heart failure patients, such as antidepressants, are known to increase the arrhythmic risk because of their secondary effects on the myocardial ion currents causing QRS complex or QT-interval prolongation [44].

Finally, although moderate-intensity physical activity is a well-established therapy for heart failure, high-intensity competitive sports may increase the risk of ventricular arrhythmias because of the high adrenergic stimulation and increased myocardial workload [45]. For this reason, the recent European Society of Cardiology recommendations discourage competitive sports activity in patients with dilated cardiomyopathy who are symptomatic, have a LV EF < 40%, show an extensive myocardial scar on CMR, and/or have frequent/complex ventricular arrhythmias on ambulatory ECG monitoring or exercise testing [46]. Similarly, the American Heart Association guidelines agree that symptomatic dilated cardiomyopathy patients should not engage in competitive sports activity [47].

Antiarrhythmic drug therapy

Antiarrhythmic drugs play a neutral or negative role in preventing SCD because of their potential pro-arrhythmic effects [48]. The Cardiac Arrhythmia Suppression Trial (CAST) tested the hypothesis that in patients with previous myocardial infarction and premature ventricular beats suppressed by encainide (a class I antiarrhythmic drug), long-term treatment with flecainide (another class I drug) would prevent SCD. However, the study was ended early because of an excess of deaths due to arrhythmias and cardiogenic shock after acute recurrent myocardial infarction [49]. The CAST II trial investigated the effects of the treatment with another class I antiarrhythmic drug (moracizine) and was again terminated early for increased mortality [50]. The Survival With Oral d-Sotalol (SWORD) trial verified whether the class III antiarrhythmic drug reduced all-cause mortality in patients with previous myocardial infarction and LV dysfunction. The trial was stopped early because of increased mortality in the treatment arm due to presumed arrhythmic deaths [51]. The Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) study tested whether Dronedarone may improve the outcome of NYHA class III and IV heart failure patients by preventing both atrial and ventricular arrhythmias [52]. The trial was prematurely terminated for excess mortality that was predominantly due to worsening heart failure [11]. Amiodarone showed a neutral effect on total mortality in the SCD-HeFT trial comparing amiodarone with placebo. A meta-analysis including 8522 patients post-myocardial infarction or with systolic heart failure randomized to placebo or amiodarone demonstrated a 28% reduction in SCD, again with a neutral effect on overall mortality because of its extracardiac toxicity [53]. In summary, available evidence suggests that the role of antiarrhythmic drugs should be limited to symptomatic treatment of patients with recurrent ventricular arrhythmias [48].

Atrial fibrillation can worsen heart failure throughout different mechanisms, including decreased cardiac output, worsening the neurohormonal response, functional mitral annular enlargement with resultant mitral regurgitation, and tachycardia-induced cardiomyopathy [54]. Two trials which compared a rhythm control strategy with antiarrhythmic drugs with rate control only in heart failure did not show differences in the mortality according to the therapeutic strategy, because the benefits of sinus rhythm maintenance were counterbalanced by the drugs side effects [55, 56]. However, recent randomized studies demonstrated that catheter ablation of atrial fibrillation was associated with a significant reduction in mortality and heart failure–related hospitalizations as well as an improvement in systolic function and quality of life in patients with reduced EF [57].

Implantable cardioverter defibrillator

Implantable cardioverter defibrillation therapy is the most effective treatment for the prevention of SCD in high-risk patients with dilated cardiomyopathy. Patients with a history of arrhythmic cardiac arrest, sustained ventricular tachycardia, or arrhythmic syncope have the strongest indications to ICD implantation (secondary prevention). The European Society of Cardiology guidelines recommend ICD implantation for primary prevention in symptomatic heart failure patients (NYHA class II or III) with LV EF ≤ 35% despite optimal medical therapy who are expected to survive substantially longer than 1 year with good functional status, irrespective of etiology (class I recommendation) [18]. The American Heart Association guidelines confirmed and expanded these recommendations by suggesting ICD implantation for primary prevention of SCD also in NYHA I patients with severe LV dysfunction (class I for patients with IHD) [19]. The utility of ICD implantation in NIDC has been recently questioned by the DANISH trial [58]. The study randomized 1116 patients with LV EF < 35% and NYHA class ≥ II to an ICD or no. Although ICD therapy halved the rate of SCD, it did not improve survival. Subsequent analysis demonstrated that the benefit of ICD therapy was age-dependent: in patients ≤ 70 years but not in those > 70 years, ICD demonstrated to reduce all-cause mortality [59].

The etiology of the disease (ischemic versus non-ischemic), the presence of symptoms, and the LV EF still remain the only determinants of indications to ICD implantation according to current guidelines, reflecting the enrollment criteria of main ICD trials [10–14]. However, as previously discussed, recent evidence indicates that other parameters may be useful to refine the arrhythmic risk, particularly in patients with NIDC (Table 1), although their use is not guideline-recommended. Among them, the presence and extent of myocardial fibrosis at CMR have been consistently demonstrated to

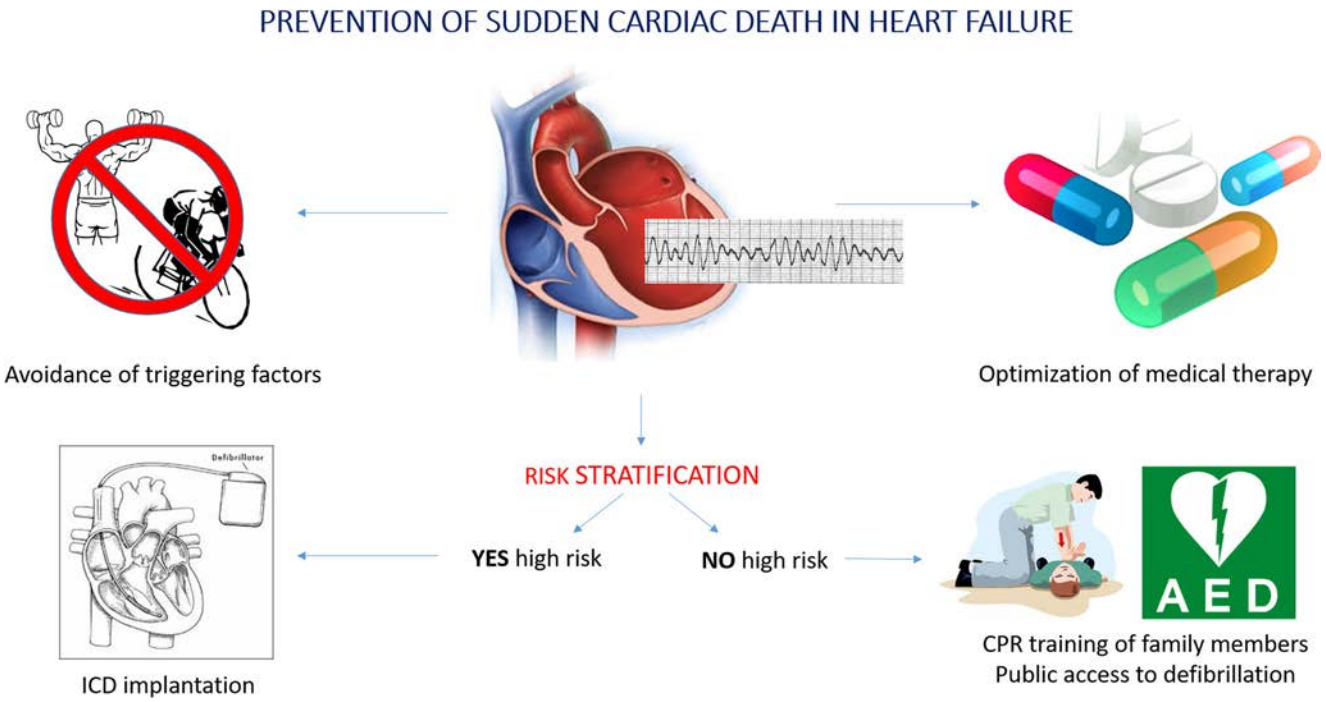


Fig. 2 Strategies to prevent sudden cardiac death in patients with dilated cardiomyopathy

identify subgroups of patients at a higher risk of SCD [28]. A clinical trial (CMR GUIDE, Clinical trials.gov identifier NCT01918215) is randomizing patients with mild to moderate LV EF reduction and LGE on CMR to an ICD or loop recorder and will test the superiority of a CMR-guided risk stratification approach in patients with heart failure who do not fulfill current ICD indications. Results are expected in 2023 [60].

Early resuscitation and public access defibrillators

As previously discussed, many patients with heart failure do not qualify for ICD therapy but may still be at risk for SCD. Ventricular fibrillation can also occur in subjects who are unaware of their disease or in the context of an acute event such as acute myocardial infarction. In these cases, survival depends on early cardiopulmonary resuscitation and defibrillation. Several studies demonstrated that the outcome is very poor (survival < 10%) if resuscitation efforts are started only after the arrival of the emergency medical system while chest compression by a bystander and early use of a publicly available automated external defibrillation (AED) each increases survival rates by 2–3 times [61]. Although AEDs are particularly useful for out-of-hospital cardiac arrests occurring in public places, 60–80% of these events take place at home [61]. This suggests that training family members of at-risk cardiac patients could have a significant impact on survival from sudden cardiac arrest. In particular, hands-only resuscitation (i.e., chest compressions with no rescue breaths) is as effective as conventional resuscitation and can be learned by simply watching a short video (Fig. 2) [62, 63].

References

1. Zipes DP, Wellens HJ (1998) Sudden cardiac death. Circulation. 98: 2334–2351
2. Deo R, Albert CM (2012) Epidemiology and genetics of sudden cardiac death. Circulation. 125:620–637
3. Zipes DP (2005) Epidemiology and mechanisms of sudden cardiac death. Can J Cardiol 21(Suppl A):37A–40A
4. Thiene G (2014) Sudden cardiac death and cardiovascular pathology: from anatomic theater to double helix. Am J Cardiol 114: 1930–1936
5. Myerburg RJ, Junttila MJ (2012) Sudden cardiac death caused by coronary heart disease. Circulation. 125:1043–1052
6. Thomas DE, Jex N, Thornley AR (2017) Ventricular arrhythmias in acute coronary syndromes—mechanisms and management. Contin Cardiol Educ 3:22–29
7. Di Diego JM, Antzelevitch C (2011) Ischemic ventricular arrhythmias: experimental models and their clinical relevance. Heart Rhythm 8:1963–1968
8. Lo R, Chia KK, Hsia HH (2017) Ventricular tachycardia in ischemic heart disease. Card Electrophysiol Clin 9:25–46
9. Banna M, Indik JH (2011) Risk stratification and prevention of sudden death in patients with heart failure. Curr Treat Options Cardiovasc Med 13:517–527
10. Moss AJ (2003) MADIT-I and MADIT-II. J Cardiovasc Electrophysiol 14:S96–S98

11. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH (2005) Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 352:225–237
12. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G (1999) A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter unsustained tachycardia trial investigators. N Engl J Med 341: 1882–1890
13. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, Calkins H, Hoch D, Goldberger J, Shalaby A, Sanders WE, Schaechter A, Levine JH, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators (2004) Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 350:2151–2158
14. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med. 1997;337:1576–83
15. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L et al (2006) Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. Eur Heart J 27:1928–1932
16. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L, Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators (2005) The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 352:1539–1549
17. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T et al (2004) Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 350:2140–2150
18. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Document Group (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 37:2129–2200
19. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB et al (2018) 2017 AHA/ACC/HRS Guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Circulation 138:e272–e391
20. Disertori M, Gulizia MM, Casolo G, Delise P, Di Lenarda A, Di Tano G, Lunati M, Mestroni L, Salerno-Uriarte J, Tavazzi L. Improving the appropriateness of sudden arrhythmic death primary prevention by implantable cardioverter-defibrillator therapy in patients with low left ventricular ejection fraction. J Cardiovasc Med (Hagerstown). 2016;17(4):245-55.
21. Rai V, Agrawal DK (2017) Role of risk stratification and genetics in sudden cardiac death. Can J Physiol Pharmacol 95:225–238
22. La Rovere MT, Pinna GD, Maestri R, Sleight P (2013) Clinical value of baroreflex sensitivity. Neth Hear J 21:61–63
23. Disertori M, Mase M, Rigoni M, Nollo G, Ravelli F (2016) Heart rate turbulence is a powerful predictor of cardiac death and ventricular arrhythmias in postmyocardial infarction and heart failure patients: a systematic review and meta-analysis. Circ Arrhythm Electrophysiol 9; pii: e004610
24. Wu L, Jiang Z, Li C, Shu M (2014) Prediction of heart rate variability on cardiac sudden death in heart failure patients: a systematic review. Int J Cardiol 174:857–860
25. Tse G, Yan BP (2017) Traditional and novel electrocardiographic conduction and repolarization markers of sudden cardiac death. Europace 19:712–721
26. Aro AL, Kentta TV, Huikuri HV (2016) Microvolt T-wave alternans: where are we now? Arrhythmia Electrophysiol Rev 5: 37–40
27. Katritsis DG, Zareba W, Camm AJ (2012) Nonsustained ventricular tachycardia. J Am Coll Cardiol 60:1993–2004
28. Becker MAJ, Cornel JH, van de Ven PM, van Rossum AC, Allaart CP, Germans T (2018) The prognostic value of late gadolinium-enhanced cardiac magnetic resonance imaging in nonischemic dilated cardiomyopathy: a review and meta-analysis. JACC Cardiovasc Imaging 11:1274–1284
29. Gatzoulis KA, Tsiachris D, Arsenos P, Tousoulis D (2016) Electrophysiologic testing guided risk stratification approach for sudden cardiac death beyond the left ventricular ejection fraction. World J Cardiol 8:112–113
30. Gulati A, Jabbour A, Ismail TF, Guha K, Khwaja J, Raza S, Morarji K, Brown TDH, Ismail NA, Dweck MR, di Pietro E, Roughton M, Wage R, Daryani Y, O'Hanlon R, Sheppard MN, Alpendurada F, Lyon AR, Cook SA, Cowie MR, Assomull RG, Pennell DJ, Prasad SK (2013) Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. JAMA. 309:896–908
31. Perazzolo Marra M, De Lazzari M, Zorzi A, Migliore F, Zilio F, Calore C et al (2014) Impact of the presence and amount of myocardial fibrosis by cardiac magnetic resonance on arrhythmic outcome and sudden cardiac death in nonischemic dilated cardiomyopathy. Heart Rhythm 11:856–863
32. Halliday BP, Cleland JGF, Goldberger JJ, Prasad SK (2017) Personalizing risk stratification for sudden death in dilated cardiomyopathy: the past, present, and future. Circulation. 136:215–231
33. Singh JP, Hall WJ, McNitt S, Wang H, Daubert JP, Zareba W, Ruskin JN, Moss AJ (2005) Factors influencing appropriate firing of the implanted defibrillator for ventricular tachycardia/fibrillation: findings from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II). J Am Coll Cardiol 46:1712–1720
34. Zorzi A, Peruzza F, Stella F, Del Monte A, Migliore F, Gasparetto N et al (2016) Life-threatening ventricular tachyarrhythmias in the cardiology department: implications for appropriate prescription of telemetry monitoring. Resuscitation. 101:6–11
35. Al-Gobari M, El Khatib C, Pillon F (2013) Gueyffier F beta-blockers for the prevention of sudden cardiac death in heart failure patients: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord 13:52
36. de Diego C, Gonzalez-Torres L, Nunez JM, Centurion Inda R, Martin-Langerwerf DA, Sangio AD et al (2018) Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices. Heart Rhythm 15:395–402
37. Kutyifa V, Geller L, Bogyi P, Zima E, Aktas MK, Ozcan EE, Becker D, Nagy VK, Kosztin A, Szilagyi S, Merkely B (2014) Effect of cardiac resynchronization therapy with implantable cardioverter defibrillator versus cardiac resynchronization therapy with pacemaker on mortality in heart failure patients: results of a high-volume, single-centre experience. Eur J Heart Fail 16:1323–1330
38. Barra S, Boveda S, Providencia R, Sadoul N, Duehmke R, Reitan C et al (2017) Adding defibrillation therapy to cardiac resynchronization on the basis of the myocardial substrate. J Am Coll Cardiol 69:1669–1678
39. Aldahl M, Jensen AC, Davidsen L, Eriksen MA, Moller Hansen S, Nielsen BJ et al (2017) Associations of serum potassium levels with mortality in chronic heart failure patients. Eur Heart J 38:2890–2896
40. Tangvoraphonkchai K, Davenport A (2018) Magnesium and cardiovascular disease. Adv Chronic Kidney Dis 25:251–260

41. Feldman C, Normark S, Henriques-Normark B, Anderson R (2018) Pathogenesis and prevention of risk of cardiovascular events in patients with pneumococcal community-acquired pneumonia. J Intern Med 285:635-652
42. Bhatt AS, DeVore AD, Hernandez AF, Mentz RJ (2017) Can vaccinations improve heart failure outcomes?: contemporary data and future directions. JACC Heart Fail 5:194–203
43. Eisen A, Ruff CT, Braunwald E, Hamershock RA, Lewis BS, Hassager C, Chao TF, le Heuzey JY, Mercuri M, Rutman H, Antman EM, Giugliano RP (2017) Digoxin use and subsequent clinical outcomes in patients with atrial fibrillation with or without heart failure in the ENGAGE AF-TIMI 48 trial. J Am Heart Assoc 6; pii:e006035
44. Teply RM, Packard KA, White ND, Hilleman DE, DiNicolantonio JJ (2016) Treatment of depression in patients with concomitant cardiac disease. Prog Cardiovasc Dis 58:514–528
45. Zorzi A, Pelliccia A, Corrado D (2018) Inherited cardiomyopathies and sports participation. Neth Hear J 26:154–165
46. Pelliccia A, Solberg EE, Papadakis M, Adami PE, Biffi A, Caselli S, la Gerche A, Niebauer J, Pressler A, Schmied CM, Serratosa L, Halle M, van Buuren F, Borjesson M, Carrè F, Panhuyzen-Goedkoop NM, Heidbuchel H, Olivotto I, Corrado D, Sinagra G, Sharma S (2019) Recommendations for participation in competitive and leisure time sport in athletes with cardiomyopathies, myocarditis, and pericarditis: position statement of the Sport Cardiology Section of the European Association of Preventive Cardiology (EAPC). Eur Heart J 40:19–33
47. Maron BJ, Udelson JE, Bonow RO, Nishimura RA, Ackerman MJ, Estes NA 3rd et al (2015) Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task force 3: hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and other cardiomyopathies, and myocarditis: a scientific statement from the American Heart Association and American College of Cardiology. J Am Coll Cardiol 66:2362–2371
48. Erath JW, Hohnloser SH (2017) Drugs to prevent sudden cardiac death. Int J Cardiol 237:22–24
49. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, Arensberg D, Baker A, Friedman L, Greene HL, Huther ML, Richardson DW (1991) Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The cardiac arrhythmia suppression trial. N Engl J Med 324:781–788
50. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. N Engl J Med. 1992;327:227–33
51. Waldo AL, Camm AJ, deRuyter H, Friedman PL, MacNeil DJ, Pauls JF, et al. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral d-Sotalol. Lancet. 1996;348:7–12
52. Kober L, Torp-Pedersen C, McMurray JJ, Gotzsche O, Levy S, Crijns H et al (2008) Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 358:2678–2687
53. Piccini JP, Berger JS, O'Connor CM (2009) Amiodarone for the prevention of sudden cardiac death: a meta-analysis of randomized controlled trials. Eur Heart J 30:1245–1253
54. Skanes AC, Tang ASL (2018) Atrial fibrillation and heart failure: untangling a modern Gordian knot. Can J Cardiol 34:1437–1448
55. Pedersen OD, Bagger H, Keller N, Marchant B, Kober L, Torp-Pedersen C (2001) Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: a Danish investigations of arrhythmia and mortality on dofetilide (diamond) substudy. Circulation. 104:292–296
56. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JMO, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, le Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL (2008) Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 358:2667–2677
57. AlTurki A, Proietti R, Dawas A, Alturki H, Huynh T, Essebag V (2019) Catheter ablation for atrial fibrillation in heart failure with reduced ejection fraction: a systematic review and meta-analysis of randomized controlled trials. BMC Cardiovasc Disord 19:18
58. Kober L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E et al (2016) Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 375:1221–1230
59. Elming MB, Nielsen JC, Haarbo J, Videbaek L, Korup E, Signorovitch J et al (2017) Age and outcomes of primary prevention implantable cardioverter-defibrillators in patients with nonischemic systolic heart failure. Circulation 136:1772–1780
60. Selvanayagam JB, Hartshorne T, Billot L, Grover S, Hillis GS, Jung W, Krum H, Prasad S, McGavigan AD (2017) Cardiovascular magnetic resonance-GUIDEd management of mild to moderate left ventricular systolic dysfunction (CMR GUIDE): study protocol for a randomized controlled trial. Ann Noninvasive Electrocardiol 22; doi:10.1111/anec.12420
61. Zorzi A, Gasparetto N, Stella F, Bortoluzzi A, Cacciavillani L, Basso C (2014) Surviving out-of-hospital cardiac arrest: just a matter of defibrillators? J Cardiovasc Med (Hagerstown) 15:616–623
62. Blewer AL, Putt ME, Becker LB, Riegel BJ, Li J, Leary M, Shea JA, Kirkpatrick JN, Berg RA, Nadkarni VM, Groeneveld PW, Abella BS, CHIP Study Group* (2016) Video-only cardiopulmonary resuscitation education for high-risk families before hospital discharge: a multicenter pragmatic trial. Circ Cardiovasc Qual Outcomes 9:740–748
63. Panchal AR, Meziab O, Stolz U, Anderson W, Bartlett M, Spaite DW, J. Bobrow B, Kern KB (2014) The impact of ultra-brief chest compression-only CPR video training on responsiveness, compression rate, and hands-off time interval among bystanders in a shopping mall. Resuscitation. 85:1287–1290

Clinical Research in Cardiology (2019) 108:225–233
https://doi.org/10.1007/s00392-018-1340-1

REVIEW

Subclinical hypothyroidism and the development of heart failure: an overview of risk and effects on cardiac function

Agata Bielecka-Dabrowa[1,4] · Breno Godoy[2] · Tsuyoshi Suzuki[2,3] · Maciej Banach[1] · Stephan von Haehling[2]

Received: 20 December 2017 / Accepted: 18 July 2018 / Published online: 8 August 2018

Abstract
The prevalence of subclinical hypothyroidism (SCH) ranges from 5 to 15% of the general population. However, it remains controversial if SCH warrants life-long thyroxine replacement therapy. Patients with a thyroid-stimulating hormone (TSH) level > 10 mIU/L have a higher risk of developing heart failure with reduced ejection fraction as compared to subjects with normal thyroid function. However, abnormally high TSH levels could also be connected with an overall lower metabolic rate and better survival in elderly subjects. The potential mechanisms responsible for diastolic dysfunction of the left ventricle (LV) in SCH are connected with endothelial dysfunction and arterial stiffness, inflammatory state and are driven by TSH apoptosis-derived microparticles. The impact of SCH on LV systolic function is more controversial, and it is connected not only with cardiac remodelling but also with predisposition of patients with SCH to the conditions leading to heart failure. This review presents an overview of processes in the context of potential benefits of thyroxine supplementation therapy.

Keywords Subclinical hypothyroidism · Heart failure · Heart failure with preserved ejection fraction · L-thyroxine · Diastolic dysfunction

The scale and significance of subclinical hypothyroidism in the context of heart failure events and mortality

Subclinical hypothyroidism (SCH) can be identified by the detection of elevated thyroid-stimulating hormone (TSH) levels in serum in the presence of free thyroxine (T_4) and triiodothyronine (T_3) levels within the normal reference range. It is usually discovered on biochemical testing [1–3].

✉ Stephan von Haehling
stephan.von.haehling@web.de

1 Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz (UMED), Lodz, Poland

2 Department of Cardiology and Pneumology, University Medical Centre Goettingen (UMG), Georg-August-University, Robert-Koch-Strasse 40, 37075 Goettingen, Germany

3 Department of Cardiology, Tokyo Women's Medical University, Tokyo, Japan

4 Department of Cardiology and Congenital Diseases of Adults, Polish Mother's Memorial Hospital Research Institute (ICZMP), Lodz, Poland

The presence of SCH is usually associated with few or no definitive clinical signs or symptoms of thyroid dysfunction [1]. Autoimmunity is the commonest cause of SCH. About 2–5% of patients with SCH progress to clinically overt hypothyroidism each year; the rate of progression is higher in patients with thyroid autoantibodies and higher TSH levels [1, 2]. Although the prevalence of SCH may range from 5 to 15% in the general population [3], it remains controversial whether this condition warrants lifelong replacement T_4 therapy. In younger adults < 65 years, SCH is associated with an increased risk of coronary heart disease (CHD), heart failure (HF), and cerebrovascular disease [3, 4].

Subclinical hypothyroidism and incidence of heart failure

Several studies have addressed the effects of SCH on cardiovascular (CV) morbidity and mortality, however, a full understanding is still lacking. For example, the Healthy Aging and Body Composition study, a population-based analysis of 2730 men and women aged 70–79 years old, followed patients over 4 years investigating TSH levels and harmful CV effects. SCH was present in 12.4% of the subjects. Based on multivariate analyses, the study concluded

that patients with TSH from 7.0 to 9.9 mIU/L {hazard ratio (HR) 2.58 [95% confidence interval (95% CI) 1.19–5.6]} and TSH ≥ 10 mIU/L (HR 3.26, 95% CI 1.37–7.77) had up to a 3.26-fold higher risk for developing HF [5]. Similarly, the Cardiovascular Health Study performed echocardiography routinely for 6 years in a cohort of subjects to determine patients at risk for developing HF. It was found that patients with TSH > 10 mIU/L had higher risk of HF with reduced ejection fraction (HFrEF) as compared to the population with normal thyroid function [6]. Another study conducted by Rodondi et al. in over 55,000 individuals aged 18–100 years—3450 of whom had SCH (6.2%)—demonstrated a positive correlation between the degree of TSH elevations, CV event rates and mortality [7].

Gencer et al. [8] performed a pooled analysis of individual participant data using all available prospective cohorts with thyroid function tests and subsequent follow-up of HF events in 25,390 participants with 216,248 person-years of follow-up in the United States and Europe. A total of 2068 participants (8.1%) were found to have SCH. Risks of HF events were increased with higher TSH levels, particularly for TSH ≥ 10 mIU/L (Fig. 1) [8–11].

Definitions of selected parameters of cardiac function used in the text are presented in Table 1

Thyroid dysfunction in patients with HF

The circumstances in patients with established HF is altogether different than that from those in patients at risk of developing HF. Chen et al. performed a prospective follow-up study on the relationship between TSH levels and outcomes in patients with HF. A total of 5599 patients were followed at a health maintenance organisation and were assessed for cardiac-related hospitalisations and mortality. The median follow-up period was slightly over 14 months. From their results it became apparent that both a high TSH level and a low TSH level were associated with an increased mortality rate. Patients were divided into quartiles of TSH level, and the mortality in the highest quartile was 36% higher than that in the second quartile. Subjects with TSH > 10 mIU/L had a more than twofold increase in mortality [12]. Finally, a recent meta-analysis of prospective cohort studies has shown that SCH is associated with an increased risk of CHD-related events, CHD mortality and HF events, especially in individuals with TSH levels ≥ 10.0 mIU/L [13, 14].

In contrast to the aforementioned findings, investigators from the Leiden 85-plus study reported data from a prospective, observational population-based study in 599 individuals aged 85 through 89 years who were followed for a mean of

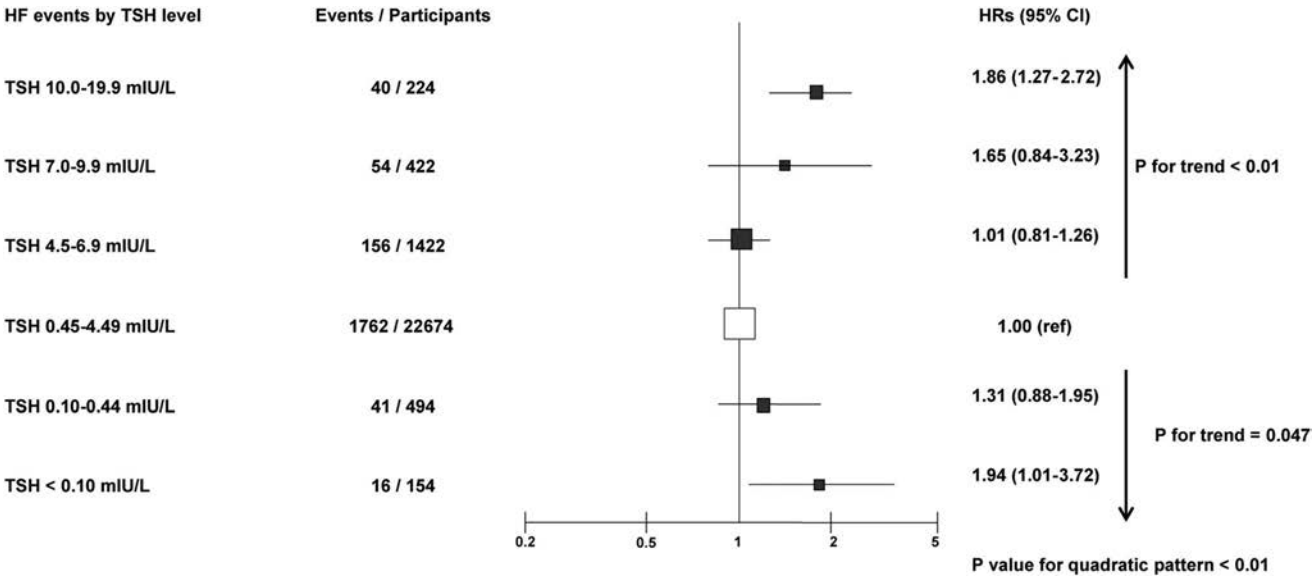


Fig. 1 Forest plots of Heart Failure (HF) events in Subclinical Hypothyroidism vs. Euthyroidism adapted from Gencer B, Collet TH, Virgini V, et al. Thyroid Studies C. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. Circulation 2012;126:1040–1049 [8]. *CI* confidence interval, *HR* hazard ratio age- and gender-adjusted HRs and their 95% CI are represented by squares. Squares to the right of the solid lines indicate increased risk of HF events

Table 1 Definitions of selected parameters of cardiac function used in text

Parameter of cardiac function	Definition	Relevant references
Augmentation index (AI)	It is determined from either a directly measured or a derived central arterial pressure waveform proposed as a measure of aortic stiffness and wave reflection, AI is the percentage of central pulse pressure attributable to the secondary systolic pressure rise produced by the overlap of the forward and reflected pressure waves	[32, 36]
Pulse wave velocity (PWV)	It is the velocity at which the arterial pulse propagates through the circulatory system. PWV is used clinically as a measure of arterial stiffness. It is easy to measure invasively and non-invasively in humans, it is highly reproducible and has a strong correlation with cardiovascular events and all-cause mortality	[32, 34]
Isovolumetric relaxation time (IVRT)	It is an interval in the cardiac cycle, from the aortic component of the second heart sound, that is, closure of the aortic valve, to the onset of filling by opening of the mitral valve	[20, 21, 28, 29]
Pulsed wave tissue Doppler imaging (PWTDI)	This technique uses the Doppler principle to assess the ventricular wall motion velocity by positioning the sample volume within the myocardium	[20, 21]
E/*A* ratio	The *E*/*A* ratio represents the ratio of peak velocity blood flow in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave) assessed by PW Doppler	[17]
e' a'	The *e*′ (*e* prime) represents the early diastolic filling velocity and the *a*′ (*a* prime) the late diastolic filling velocity using tissue Doppler of the mitral annulus	[17, 35]
Myocardial precontraction time (PCTm)	It is the time from the onset of ECG QRS complex to the beginning of the mitral annular peak systolic velocity	[20]
Myocardial contraction time (CTm)	It is the time from the beginning to the end of the mitral annular peak systolic velocity	[20]
Preejectional period (PEP)	It is a delay from the Q wave of the QRS complex to the aortic valve opening; PEP is the interval from the onset of ventricular depolarisation to the beginning of aortic ejection	[20, 55]
Left ventricular ejection time (LVET)	It represents the interval from beginning to termination of aortic flow	[20]
Myocardial performance index (Tei index)	It is an index that incorporates both systolic and diastolic time intervals in expressing global systolic and diastolic ventricular function. Systolic dysfunction prolongs preejection (isovolumetric contraction time) and shortens the LVET. Both systolic and diastolic dysfunction result in abnormality in myocardial relaxation which prolongs the IVRT	[54, 55, 58]
Cardio-ankle vascular index (CAVI)	CAVI reflects the stiffness of the aorta, femoral artery, tibial artery and involves measurement of brachial, ankle PWV and blood pressure. It is obtained by recording the distance from the level of the aortic valve to the measuring point (for example the ankle) and the time delay between the closing of the aortic valve to the detected change in arterial pressure wave at the set point	[35]

3.7 years. Controversially, increasing levels of TSH were associated with a lower mortality rate that remained after adjustments were made for baseline disability and health status. The abnormally high TSH levels could be linked to a lower metabolic rate and perhaps to caloric restriction as a result of this state [15]. However, such observational results should be interpreted with caution as other alterations in the oldest age group are also—and counterintuitively—associated with better survival, such as high blood pressure and high cholesterol.

In patients admitted for acute HF, Hayashi et al. [14] have recently shown that SCH is an independent predictor of adverse CV outcomes, suggesting a possible interaction between thyroid dysfunction and the pathophysiology of this state [14]. In light of the foregoing findings, it is somewhat disappointing to learn that the 2016 European Society of Cardiology (ESC) guidelines for the management of HF mention only that both hypothyroidism and hyperthyroidism may precipitate acute HF. Accordingly, TSH should be assessed in all newly diagnosed patients with acute HF. The impact of different TSH levels is not discussed in the HF guideline [16].

Subclinical hypothyroidism and diastolic dysfunction

Previous studies have documented the role of diastolic dysfunction in the development and progression of HF with preserved ejection fraction (HFpEF) [17–19]. Although there is no clear evidence that SCH causes clinical heart disease [16], changes in thyroid status in SCH are associated with changes in several cardiac parameters manifested by left ventricular dysfunction at rest and systolic dysfunction on effort. Vitale et al. [20] conducted a study with 40 women: 20 healthy and 20 with established SCH (mean TSH > 10 mIU/L over 6 months). They underwent standard Doppler and pulsed wave tissue Doppler imaging (PWTDI). Standard Doppler showed an increase in LV preejection period (PEP), preejection period/LV ejection time ratio (PEP/LVET) and isovolumetric relaxation time (IVRT) in SCH ($r = 0.35$; $p < 0.05$; Table 1). By PWTDI analysis, the adjusted myocardial precontraction time/myocardial contraction time ratio (PCTm/CTm) was positively associated with TSH ($r = 0.32$; $p < 0.05$), as well as the adjusted myocardial relaxation time (RTm) at the level of the posterior septum ($r = 0.40$; $p < 0.01$). In the whole population, IVRT, PCTm, and RTm were negatively related to FT4 (Table 1) [20]. Similarly Zoncu et al. demonstrated in a study with 32 subjects with classical Hashimoto's thyroiditis (69% with TSH > 3 mU/mL) that PWTDI indices were delayed in diastolic relaxation and decreased in the compliance to the ventricular filling [21].

Case–control studies found patients with SCH to have prolonged IVRT, increased peak atrial filling velocity (A wave), and a diminished ratio of peak velocity flow in early diastole (E wave) to peak velocity flow in late diastole caused by atrial contraction (E/A ratio) [17]. In the aforementioned Cardiovascular Health Study [6] 3044 adults with ≥ 65 years underwent a mean 12-year-follow-up and changes in the cardiac function over 5 years. Participants with TSH ≥ 10.0–19.9 mIU/L who were untreated by thyroxine replacement had a greater incidence of HF events compared to euthyroid participants (41.7 vs. 22.9/1000 person-years, $p = 0.01$), but rates were similar for those with TSH between 4.5 and 9.9 mIU/L. Echocardiography was obtained on 70.6% of participants after 5 years; In the more pronounced SCH subgroup (TSH ≥ 10 mIU/L) there was a larger increase in LV mass (+ 21 vs. +4 g, $p = 0.04$). Peak E velocity decreased more than in euthyroid participants (− 0.10 vs. −0.01 m/s, $p = 0.005$), which might be related to the gain in LV mass over time and progressive impairment of LV relaxation [22, 23]. The higher early diastolic filling velocity reflects increased left atrial pressure (LAP) and diastolic dysfunction. Nonetheless CV abnormalities have been shown to regress with L-thyroxine therapy [24–26]. Other studies have controversially shown that cardiac structure and function remain overall normal in SCH [26].

Pathogenical mechanisms linking subclinical hypothyroidism to diastolic dysfunction

Endothelial dysfunction and arterial stiffness

Central aortic stiffness is augmented in many patients with HF and some researchers have assumed a relationship of arterial stiffness and early diastolic dysfunction in middle-aged and elderly populations [27, 28]. Differences in central aortic stiffness are also present in HFpEF patients in the absence of other parameters of diastolic function, as assessed by PWTDI, and correlate with LV mass and B-type natriuretic (BNP) levels, highlighting the potential contribution of abnormal pulsatile load and arterio-ventricular coupling (interaction of arterial stiffness, systolic and diastolic function) to the development of HF. However, this mechanism is not yet completely understood [28, 29]. Increased arterial stiffness is involved in the development of diastolic dysfunction via impairment of coronary blood supply as a consequence of a reduced diastolic blood pressure, induction of cardiac hypertrophy or, incremented cardiac stiffening [29]. Moreover, aortic stiffness leads to an increase in afterload, which itself strengthens the pulse pressure, resulting in higher oxygen consumption. A reduction in diastolic blood pressure leads as well to diminished myocardial perfusion. In summary, diastolic relaxation is deranged in case of elevated afterload [30, 31].

The decline in global endothelial function is associated with parameters of arterial stiffness—increased aortic stiffness assessed via pulsed wave velocity (PWV) and augmentation index (AI) (Table 1) [32]. Stiffness of large arteries and central haemodynamics, on the other hand, are influenced by endothelial function and support findings describing the importance of nitric oxide (NO) in the regulation of large artery stiffness in vivo [32]. SCH may be directly associated with endothelial dysfunction and impaired coronary flow reserve through specific molecular pathways in endothelial cells, by affecting NO production and by facilitating increased degradation of vasodepressor intermediates [33]. Several studies have demonstrated cellular, subcellular and intercellular transformation in patients with HFpEF, for instance, cytokine-mediated dysfunction of myocyte strain and defects of myofibroblasts with resulting left ventricular fibrosis. However, the disturbed arterio-ventricular coupling is one of the main factors for developing left ventricular failure in patients with HFpEF [31]. In addition, reduced cardiac preload has been shown via cardiac magnetic resonance imaging (MRI) in patients with SCH together with increased

afterload [2]. After a period of T_4 therapy in these patients, the haemodynamic alterations were well reversible.

Another parameter for the assessment of arterial stiffening and a predictor for the presence of CHD is brachial-ankle PWV. Significantly elevated values of brachial-ankle PWV have interestingly been reported in patients with SCH [34]. Masaki et al. conducted a cross-sectional study of 83 patients with untreated SCH and compared them with 83 randomly selected controls from health check-ups to assess the relationship of thyroid hormone level to cardio-ankle vascular index (CAVI) (Table 1) and left ventricular diastolic function. When compared with the control group, patients with SCH had significantly higher values of N-terminal pro-BNP (NT-proBNP), C-reactive protein (CRP), and CAVI as well as lower *e′* values. In the SCH group, CAVI was significantly associated with NT-proBNP, CRP and *e′*. These findings suggest that SCH may be a risk factor for CV events related to arterial stiffening and left ventricular diastolic dysfunction [35]. Owen et al. revealed that arterial stiffness is increased in SCH and improves with L-thyroxine therapy, which may be beneficial, whereas myocardial functional reserve was similar to controls and remained unaltered after treatment (Fig. 2) [36].

Apoptotic-derived extracellular microparticles

The pathogenesis of diastolic dysfunction might be influenced by TSH stimuli for apoptotic-derived microparticles. In this context, it is important to understand extracellular microparticles (EMPs). EMPs are microvesicles with sizes ranging between 50 and 1000 nm released from plasma membranes of different cell types, such as endothelial cells, mononuclear cells or platelets. Such EMPs are released upon specific (e.g. cytokine stimulation, apoptotic agents, mononuclear cooperation, coagulation) and non-specific (shear stress) stimuli [39]. EMPs transport microribonucleic acid (miRNA), active molecules, hormones, peptides, regulator proteins and other substances, thereby mediating cell-to-cell cross-talk [37]. Their role is not entirely clear, but they seem to take part in endothelial reparation, tissue injury, and vascular remodelling [38]. The different patterns of circulating EMPs in CV diseases including HF suggest that impaired EMP phenotypes are potentially available for risk stratification in patients with CV and metabolic disease [39, 40]. In this context, circulating EMPs may function as novel biological markers for endothelial injury, vascular tone disorders, and vascular aging, which may demonstrate the impact of SCH in CV disease progression. However, it remains controversial whether or not a causal role of EMP patterns in patients with HF with SCH exists [41]. An example of this controversy is that it is still unknown if circulating EMPs found in peripheral blood cause injury to the endothelium and worsening HF and whether they are the result of disease progression in response to endothelial dysfunction and vascular disintegrity [42]. The results of the study of Berezin et al. suggest that SCH in patients with HF might be associated with an impaired release pattern of circulating EMPs with a predominantly increased number of apoptotic-derived microparticles [43]. In cohort of 388 patients with HF, 53 of whom had SCH, the presence of SCH was associated with an impaired pattern of circulating EMPs with predominantly increased number of apoptotic-derived microparticles [44].

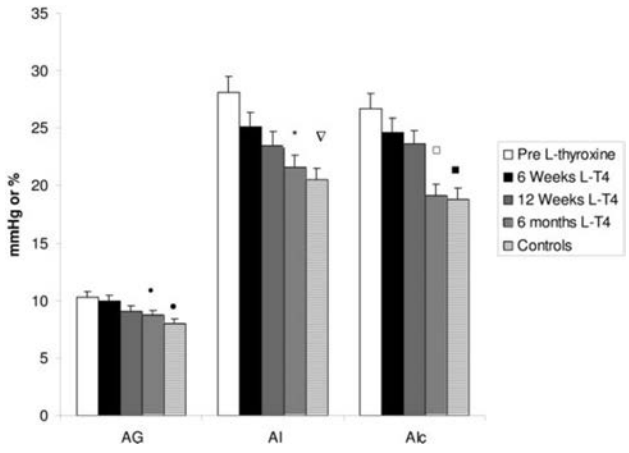


Fig. 2 Indices of central arterial stiffness in SCH patients before and after 6 months of L-thyroxine [36]. *AG* augmentation gradient (mm Hg), *AI* augmentation index (percent), *AIc* corrected augmentation index (percent). Significance levels: $*p < 0.0001$, before treatment, compared with post treatment for AI; $\bullet p < 0.05$, pre-treatment, compared with post treatment for AG; $\Lambda p < 0.001$, pre-treatment, compared with controls, for AI; $\square p < 0.001$, pre-treatment, compared with post treatment for AIc; $\blacksquare p < 0.002$, pre-treatment, compared with controls for AIc

Systemic inflammation

Apart from EMPs, some evidence points towards a strong involvement of systemic inflammation associated with diastolic dysfunction, which may also impact the remodelling process [45, 46]. Gupta et al. found TSH levels to be positively correlated with inflammatory markers such as CRP, interleukin-6 (IL-6), and erythrocyte sedimentation rate (ESR) in patients with SCH. They were significantly higher in SCH, subsequently increasing with disease progression and in the absence of treatment [47]. These findings (elevated levels of CRP and IL-6) are in line with those reported by Vaya et al. and Taddai et al. [48, 49]. The interaction between SCH and LV diastolic dysfunction are presented in Fig. 3.

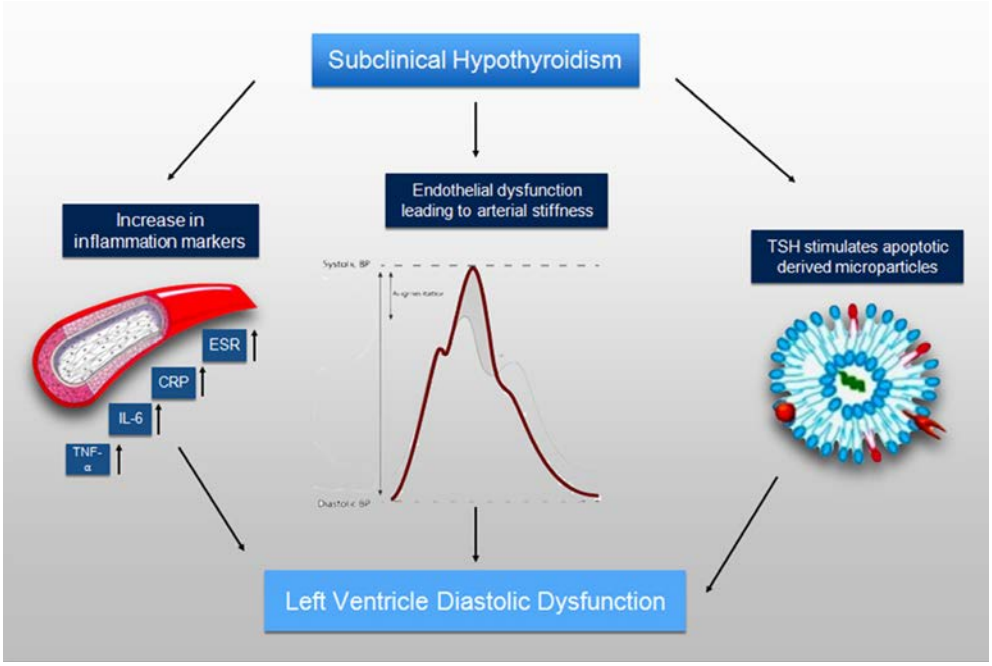


Fig. 3 The interaction between subclinical hypothyroidism and left ventricular diastolic dysfunction. *TNF-α* tumour necrosis factor α, *IL-6* interleukin 6, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

The impact of subclinical hypothyroidism on systolic function

The impact of SCH on left ventricular systolic function is more contentious than that on diastolic function. As discussed earlier, SCH can represent a risk factor for the progression of chronic HF. SCH may induce cardiac remodelling by influencing the expression of genes involved in calcium handling and contractile properties of myocardiocytes [50] but also through tissue changes (e.g. collagen alteration, dehydration, myocardial fibre orientation or capillary distribution) [25, 51].

SCH may also favour the blossoming of substrate conditions, such as dyslipidaemia and atherogenesis, which implicate in the progression of chronic HF. Examining the prevalence of CHD in subjects with and without SCH, Walsh et al. found a higher risk of CHD in patients with SCH. This ratio prevailed even after adjustment for standard CV risk factors, sex and age. Since CHD is arguably one of the most common causes of HF, the potential contribution of thyroid abnormality to the development of HF is evident [52]. Pesic et al. examined 120 patient, 60 with SCH and 60 healthy individuals to assess the metabolic syndrome components. The following indices were statistically significantly higher in SCH subjects: body mass index, diastolic blood pressure, total cholesterol, triglycerides and basal insulin level [53].

Few studies have investigated the effects of SCH on left ventricular systolic function. Ilic et al. reported that the LV mass index of patients with SCH was elevated before and also after replacement therapy as compared to controls. Besides, global LV function estimated by the myocardial performance index (Tei index) (Table 1) was impaired and the LV systolic function was lessened in SCH patients as compared to controls. Additionally, SCH participants had enlarged right ventricular (RV) wall thickness and impaired RV diastolic and global function [54]. Some researchers presented results indicating that LV ejection fraction was unchanged among SCH patients [55–58].

Impaired LV diastolic function at rest may be an important cause of systolic dysfunction on effort in patients with SCH. The increase in heart rate in response to exercise reduces LV diastolic filling time [59]. Under physiologic conditions, this effect is counterbalanced by an improvement in diastolic function. In this context, a slowed rate of LV relaxation in patients with SCH could critically undermine ventricular filling during exercise and together with altered vascular reactivity yield LV systolic dysfunction [59]. The first assessment of cardiac function on effort in patients with SCH has been performed by Bell et al. using radionuclide ventriculography. They demonstrated that the restoration of euthyroidism by L-thyroxine administration—compared to pre-treatment values—induced a small but significant rise in the peak exercise LV ejection fraction, although there was no change at rest or during moderate effort [60]. Kahaly et al. revealed that the oxygen pulse (oxygen uptake per heart beat), an index assumed to represent LV stroke volume, was also reduced both at the anaerobic threshold and at maximal exercise, and the work rate was diminished at the anaerobic threshold in untreated patients [61].

Subclinical hypothyroidism as a therapeutic target

As discussed above, thyroid hormone dysfunction can result in altered ventricular contractility and relaxation dynamics as well as compromised cardiac function. These considerations have important clinical implications in that thyroid dysfunction represents one of the few potentially reversible causes of HF [55, 62]. Unfortunately, there is a paucity of evidence on the beneficial effects of thyroxine hormone replacement on CV mortality outcomes in patients with SCH [63]. Also, the clinical relevance of measuring and treating supra-normal TSH levels in newly diagnosed patients with HFpEF requires further study [41].

The available evidence suggests that several cardiac function parameters are normalised in patients treated for SCH. L-thyroxine in SCH decreased the ratio between PEP and LV ejection time in 46 adults [55] and improved cardiac preload and contractility in 30 women [2]. Nevertheless, these studies are limited by their small sample size, short duration, non-standardised definitions of SCH or echo measurements [11]. The effects of thyroid hormone supplementation was further prospectively evaluated in a double-blind, randomised, placebo-controlled, parallel-group trial in 737 subjects who were at least 65 years of age with SCH in the TRUST trial (Thyroid Hormone Replacement for Subclinical Hypo-Thyroidism) [64]. In this study, SCH was defined as having TSH levels between 4.5 and 20 mIU/L, with free T_4 levels still within the normal range. A total of 368 patients were assigned to receive L-thyroxine and 369 patients to receive placebo. The authors found no difference in the mean change at 1 year in the Hypothyroid Symptoms score and the Tiredness score between the L-thyroxine and the control group. The incidence of serious adverse events of special interest (atrial fibrillation, HF, fracture, or new diagnosis of osteoporosis) was similar in the two groups. L-thyroxine provided no apparent benefit in older persons with SCH. It is worth to notice that observational studies show that TSH tends to increase with age, which seems to be a physiological process and a marker of advancing age rather than a pathological development [64, 65]. There might be a danger of SCH overdiagnosis, especially in the elderly, but age-based cut-off points have not yet been standardised. In the context of the TRUST trial it is worth to see the potential outcomes of the use of thyroxine to treat SCH in younger population [65–67]. For that matter a large observational study of the UK General Practice Research Database has corroborated that L-thyroxine may minimise the risk of CHD in younger patients (< 70 years) [3].

Conclusion

Patients with SCH are presently often classified into 2 groups: those with mild SCH in whom TSH is mildly increased (TSH 4.5–9.9 mIU/L) and those with a more severe dysfunction when TSH is ≥ 10 mIU/L. A slightly increased serum TSH might not always reflect mild thyroid hormone deficiency but rather different reference values at different ages [68]. Thus, cut-off limits for age and age-adjusted serum TSH levels should be accounted for during L-thyroxine replacement therapy [69].

In 2005, a consensus panel from the American Association of Clinical Endocrinologists, the American Thyroid Association and the Endocrine Society recommended against replacing thyroid hormones if TSH is < 10 mIU/L but that treatment was reasonable if TSH is > 10 mIU/L [70]. Cooper and Biondi recommend on the other hand to treat patients with mild SCH, but only in those < 75 years [71]. Otherwise treatment should be individualised [72]. It has also not been determined which patients are likely to progress to overt hypothyroidism.

Thyroid dysfunction emerges as a comorbidity of HF. It is noteworthy that the current recommendations stem from endocrinological, yet not cardiological guidelines. We encourage that a subset of SCH patients, in which the treatment may warrant overall benefit, should be contemplated, foremost those with hypertension, hyperlipidaemia, atherosclerosis, arterial stiffness, CHD and early or established diastolic dysfunction.

Compliance with ethical standards

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

References

1. Surks MI, Ortiz E, Daniels GH et al (2004) Subclinical thyroid disease. JAMA 291:228–243
2. Ripoli A, Pingitore A, Favilli B et al (2005) Does subclinical hypothyroidism affect cardiac pump performance? Evidence from a magnetic resonance imaging study. J Am Coll Cardiol 45:439–445
3. Redford C, Vaidya B (2017) Subclinical hypothyroidism: should we treat? Post Reprod Health 23:55–62
4. Störk S, Handrock R, Jacob J et al (2017) Epidemiology of heart failure in Germany: a retrospective database study. Clin Res Cardiol 106(11):913–922
5. Rodondi N, Newman AB, Vittinghoff E et al (2005) Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. Arch Intern Med 165:2460–2466
6. Biondi B (2012) Mechanisms in endocrinology: Heart failure and thyroid dysfunction. Eur J Endocrinol 167(5):609–618

7. Rodondi N, den Elzen WP, Bauer DC et al (2010) Subclinical hypothyroidism the risk of coronary heart disease mortality. JAMA 304(12):1365–1374
8. Gencer B, Collet TH, Virgini V et al (2012) Thyroid Studies C. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. Circulation 126:1040–1049
9. Chaker L, Bianco AC, Jonklaas J, Peeters RP (2017) Hypothyroidism. Lancet 390:1550–1562
10. Parretti H, Okosieme O, Vanderpump M (2016) Current recommendations in the management of hypothyroidism: developed from a statement by the British Thyroid Association Executive. Br J Gen Pract 66:538–540
11. Floriani C, Gencer B, Collet TH, Rodondi N (2018) Subclinical thyroid dysfunction and cardiovascular diseases: 2016 update. Eur Heart J 14(7):503–507 39(
12. Chen S, Shauer A, Zwas DA, Lotan C, Keren A, Gotsman I (2014) The effect of thyroid function on clinical outcome in patients with heart failure. Eur J Heart Fail 16(2):217–226
13. Gencer B, Collet TH, Virgini V, Auer R, Rodondi N (2013) Subclinical thyroid dysfunction and cardiovascular outcomes among prospective cohort studies. Endocr Metab Immune Disord Drug Targets 13:4–12
14. Hayashi T, Hasegawa T, Kanzaki H et al (2016) Subclinical hypothyroidism is an independent predictor of adverse cardiovascular outcomes in patients with acute decompensated heart failure. ESC Heart Fail 3:168–176
15. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG (2004) Thyroid status, disability and cognitive function, and survival in old age. JAMA 292:2591–2599
16. Ponikowski P, Voors AA, Anker SD et al (2016) 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Rev Esp Cardiol (Engl Ed 69:1167
17. Lam CS, Lyass A, Kraigher-Krainer E et al (2011) Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. Circulation 124:24–30
18. Hammoudi N, Laveau F, Helft G et al (2017) Low level exercise echocardiography helps diagnose early stage heart failure with preserved ejection fraction: a study of echocardiography versus catheterization. Clin Res Cardiol 106(3):192–201
19. Morbach C, Buck T, Rost C et al (2018 Feb) Point-of-care B-type natriuretic peptide and portable echocardiography for assessment of patients with suspected heart failure in primary care: rationale and design of the three-part Handheld-BNP program and results of the training study. Clin Res Cardiol 107(2):95–107
20. Vitale G, Maurizio G, Gelsy AL et al (2002) Left ventricular myocardial impairment in subclinical hypothyroidism assessed by a new ultrasound tool: pulsed tissue Doppler. J Clin Endocrinol Metab 87:4350–4355
21. Zoncu S, Pigliaru F, Putzu C et al (2005) Cardiac function in borderline hypothyroidism: a study by pulsed wave tissue doppler imaging. Eur J Endocrinol 152:527–533
22. Biondi B, Fazio S, Palmieri EA et al (1999) Left ventricular diastolic dysfunction in patients with subclinical hypothyroidism. J Clin Endocrinol Metab 84:2064–2067
23. Rodondi N, Bauer DC, Cappola AR et al (2008) Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure. The Cardiovascular Health study. J Am Coll Cardiol 52:1152–1159
24. Biondi B, Palmieri EA, Lombardi G, Fazio S (2002) Effects of subclinical thyroid dysfunction on the heart. Ann Intern Med 137:904–914
25. Biondi B, Palmieri EA, Lombardi G, Fazio S (2002) Subclinical hypothyroidism and cardiac function. Thyroid 12:505–510
26. Arem R, Rokey R, Kiefe C, Escalante DA, Rodriguez A (1996) Cardiac systolic and diastolic function at rest and exercise in subclinical hypothyroidism: effect of thyroid hormone therapy. Thyroid 6:397–402
27. Weber T, O'Rourke MF, Ammer M, Kvas E, Punzengruber C, Eber B (2008) Arterial stiffness and arterial wave reflections are associated with systolic and diastolic function in patients with normal ejection fraction. Am J Hypertens 21:1194–1202
28. Desai AS, Mitchell GF, Fang JC, Creager MA (2009) Central aortic stiffness is increased in patients with heart failure and preserved ejection fraction. J Card Fail 15:658–664
29. Kang S, Fan HM, Li J et al (2010) Relationship of arterial stiffness and early mild diastolic heart failure in general middle and aged population. Eur Heart J 31:2799–2807
30. Paglia A, Sasso L, Pirozzi F et al (2014) Arterial wave reflections and ventricular–vascular interaction in patients with left ventricular systolic dysfunction. Int Heart J 55:526–532
31. Lüers C, Trippel TD, Seeländer S et al (2017) 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 11(5):303–313
32. McEniery CM, Wallace S, Mackenzie IS et al (2006) Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans. Hypertension 48:602–608
33. Lee SW, Cho KI, Kim HS, Heo JH, Cha TJ (2015) The impact of subclinical hypothyroidism or thyroid autoimmunity on coronary vasospasm in patients without associated cardiovascular risk factors. Korean Circ J 45(2):125. https://doi.org/10.4070/kcj.2015.45.2.125
34. Nagasaki T, Inaba M, KumedaY et al (2005) Increased pulse wave velocity in subclinical hypothyroidism. J Clin Endocrinol Metab 91:154–158
35. Masaki M, Komamura K, Goda A et al (2014) Elevated arterial stiffness and diastolic dysfunction in subclinical hypothyroidism. Circ J 78(6):1494–1500
36. Owen PJ, Rajiv C, Vinereanu D, Mathew T, Fraser AG, Lazarus JH (2006) Subclinical hypothyroidism, arterial stiffness, and myocardial reserve. J Clin Endocrinol Metab 91(6):2126–2132
37. Mause SF, Weber C (2010) Microparticles: protagonists of a novel communication network for intercellular information exchange. Circ Res 107(9):1047–1057
38. Distler JH, Huber LC, Gay S, Distler O, Pisetsky DS (2006) Microparticles as mediators of cellular cross-talk in inflammatory disease. Autoimmunity 39(8):683–690
39. Nozaki T, Sugiyama S, Sugamura K et al (2010) Prognostic value of endothelial microparticles in patients with heart failure. Eur J Heart Fail 12(11):1223–1228
40. Yong PJ, Koh CH, Shim WS (2013) Endothelial microparticles: missing link in endothelial dysfunction? Eur J Prev Cardiol 20(3):496–512
41. Berezin AE, Kremzer AA, Martovitskaya YV, Samura TA, Berezina TA (2015) The association of subclinical hypothyroidism and pattern of circulating endothelial-derived microparticles among chronic heart failure patients. Res Cardiovasc Med 4(4):e29094
42. Berezin AE, Kremzer AA, Martovitskaya YV et al (2015) The predictive role of circulating microparticles in patients with chronic heart failure. BBA Clin 3:18–24
43. Berezin AE, Kremzer A, Berezina T, Martovitskaya Y (2016) The signature of circulating microparticles in heart failure patients with metabolic syndrome. J Circ Biomark 5:1849454416663659
44. Berezin AE, Kremzer AA, Martovitskaya YV, Samura TA, Berezina TA (2016) Pattern of circulating endothelial-derived microparticles among chronic heart failure patients with

dysmetabolic comorbidities: the impact of subclinical hypothyroidism. Diabetes Metab Syndr 10(1):29–36
45. Paulus WJ, Tschope C (2013) 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 62:263–271
46. Maaten JM, Damman K, Verhaar MC et al (2016) Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation. Eur J Heart Fail 18:588–598
47. Gupta G, Sharma P, Kumar P, Itagappa M (2015) Study on subclinical hypothyroidism and its association with various inflammatory markers. J Clin Diagn Res 9(11):BC04–B6
48. Vaya A, Gimenez C, Sarnago A et al (2014) Subclinical hypothyroidism and cardiovascular risk. Clin Hemorheol Microcirc 58:1–7
49. Taddei S, Caraccio N, Virdis A et al (2006) Low grade systemic inflammation causes endothelial dysfunction in patients with hashimato's thyroiditis. J Clin Endocrinol Metab 91:5076–5082
50. Dillmann WH (1990) Biochemical basis of thyroid hormone action in the heart. Am J Med 88:626–632
51. Türemen EE, Çetinarslan B, Sahin T, Cantürk Z, Tarkun I (2011) Endothelial dysfunction and low grade chronic inflammation in subclinical hypothyroidism due to autoimmune thyroiditis. Endocr J 58:349–354
52. Walsh JP, Bremner AP, Bulsara MK et al (2005) Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. Arch Intern Med 165:2467–2472
53. Pesic MM, Radojkovic D, Antic S, Kocic R, Stankovic-Djordjevic D (2015) Subclinical hypothyroidism: association with cardiovascular risk factors and components of metabolic syndrome. Biotechnol Biotechnol Equip 29:157–163
54. Ilic S, Tadic M, Ivanovic B, Caparevic Z, Trbojevic B, Celic V (2013) Left and right ventricular structure and function in subclinical hypothyroidism: the effects of one-year levothyroxine treatment. Med Sci Monit 10:19:960–968
55. Monzani F, Di Bello V, Caraccio N et al (2001) Effect of levothyroxine on cardiac function and structure in subclinical hypothyroidism: a double blind, placebo-controlled study. J Clin Endocrinol Metab 86(3):1110–1115
56. Mishra TK, Routray SN, Das S, Behera M (2005) Left ventricular dysfunction in patients with subclinical hypothyroidism and its reversibility after hormone therapy. J Assoc Physicians India 53:943–946
57. Aghini-Lombardi F, Di Bello V, Talini E et al (2006) Early textural and functional alterations of left ventricular myocardium in mild hypothyroidism. Eur J Endocrinol 155:3–9
58. Iqbal A, Schirmer H, Lunde P et al (2007) Thyroid stimulating hormone and left ventricular function. J Clin Endocrinol Metab 92:3504–3510
59. McDermott MM, Feinglass J, Sy J, Gheorghiade M (1995) Hospitalized congestive heart failure patients with preserved versus abnormal left ventricular systolic function: Clinical characteristics and drug therapy. Am J Med 99:629–635
60. Bell GM, Todd WT, Forfar JC et al. End-organ responses to thyroxine therapy in subclinical hypothyroidism. Clin Endocrinol (Oxf) 22:83–89
61. Kahaly GJ (2000 Aug) Cardiovascular and atherogenic aspects of subclinical hypothyroidism. Thyroid 10(8):665–679
62. Kirchhof G, Lindner JF, Achenbach S et al (2018 Mar) Stratified prevention: opportunities and limitations. Report on the 1st interdisciplinary cardiovascular workshop in Augsburg. Clin Res Cardiol 107(3):193–200
63. Störk S, Handrock R, Jacob J et al (2017) Treatment of chronic heart failure in Germany: a retrospective database study. Clin Res Cardiol 106(11):923–932
64. Stott DJ, Rodondi N, Kearney PM, TRUST Study Group (2017) Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. N Engl J Med 376:2534–2544
65. Vadiveloo T, Donnan PT, Murphy MJ, Leese GP (2013) Age- and gender-specific TSH reference intervals in people with no obvious thyroid disease in Tayside, Scotland: the Thyroid Epidemiology, Audit, and Research Study (TEARS). J Clin Endocrinol Metab 98:1147–1153
66. Waring AC, Arnold AM, Newman AB, Buzkova P, Hirsch C, Cappola AR (2012) Longitudinal changes in thyroid function in the oldest old and survival: the cardiovascular health study all-stars study. J Clin Endocrinol Metab 97:3944–3950
67. Surks MI, Boucai L (2010) Age- and race-based serum thyrotropin reference limits. J Clin Endocrinol Metab 95:496–502
68. Surks MI, Hollowell JG (2007) Age-specific distribution of serum thyrotropin and antithyroid antibodies in the U.S. population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab 92:4575–4582
69. Biondi B, Wartofsky L (2014) Treatment with thyroid hormone. Endocr Rev 35:433–512
70. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT (2005) Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. J Clin Endocrinol Metab 90:581–585
71. Cooper DS, Biondi B (2012) Subclinical thyroid disease. Lancet 379:1142–1154
72. Rhee SS, Pearce EN (2011) Update: Systemic Diseases and the Cardiovascular System (II). The endocrine system and the heart: a review. Rev Esp Cardiol 64:220–231

Current Heart Failure Reports
https://doi.org/10.1007/s11897-019-00431-4

UPDATES IN ADVANCED HEART FAILURE (E. RAME AND M. ST. JOHN SUTTON, SECTION EDITORS)

Pulmonary Hypertension in Advanced Heart Failure: Assessment and Management of the Failing RV and LV

Sriram D. Rao[1] · Jonathan N. Menachem[2] · Edo Y. Birati[1] · Jeremy A. Mazurek[1,3]

Abstract

Purpose of Review In patients with heart failure with reduced ejection fraction, the presence of pulmonary hypertension (PH-LHD) has a significant impact on their prognosis. The purpose of this review is to explain the methods of diagnosing PH-LHD and then discuss the available therapeutic options.

Recent Findings We begin by examining the methods of assessment of PH-LHD—echocardiography, cardiopulmonary exercise testing, and right heart catheterization—with a particular focus on the importance of accurate measurement to ensure the proper determination of PH-LHD. We then focus primarily on management of PH-LHD, with an examination of trials of therapeutic options, use of mechanical circulatory support, and transplantation.

Summary This review highlights the complexities in diagnosis and management of PH-LHD. We outline a number of useful ways to maximize the yield of diagnostic testing, as well as give suggestions on the use of medical therapies, the role of both temporary mechanical support and left ventricular assist device, and finally the ways to best bridge these patients to transplantation.

Keywords Pulmonary hypertension · Heart failure · Post capillary · Ventricular dysfunction, left · Ventricular dysfunction, right

Introduction

Heart failure (HF) is a growing problem, with associated morbidity and mortality placing an enormous burden on the healthcare system. Within the overall HF population due to left heart disease, the subset of patients who develop pulmonary hypertension (PH-LHD) is increasingly recognized and at higher risk for poor outcome [1]. Unfortunately, not only are limited treatment options available for this cohort, but the presence of PH-LHD often complicates standard treatment approaches for advanced HF. HF itself is a broad diagnosis, encompassing patients with left ventricular ejection fraction (LVEF) < 40% (heart failure with reduced ejection fraction (HFrEF)), patients with LVEF > 50% (heart failure with preserved ejection fraction (HFpEF)), and patients with isolated valvular lesions. This review will specifically focus on PH in the HFrEF population, outlining the complexity in achieving a diagnosis and the evolving management options.

This article is part of the Topical Collection on *Updates in Advanced Heart Failure*

✉ Jeremy A. Mazurek
jeremy.mazurek@pennmedicine.upenn.edu

[1] Advanced Heart Failure/Transplantation Program, Division of Cardiovascular Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

[2] Advanced Heart Failure and Cardiac Transplant Program, Advanced Congenital Cardiac Therapies, Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

[3] Pulmonary Hypertension Program, Division of Cardiovascular Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Definition, Prevalence, and Prognosis

The World Health Organization (WHO) previously defined PH as a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg, with PH-LHD, also known as WHO Group II PH, defined as a mPAP ≥ 25 mmHg in the setting of a pulmonary artery wedge pressure (PAWP) > 15 mmHg [2]. More recently, the threshold to define PH has decreased from ≥ 25 mmHg to > 20 mmHg [3]. PH-LHD is remarkably common, accounting for 65–80% of all PH

patients [4] and with the prevalence of PH in the HFrEF population estimated at 40–75% [5–7]. PH is a poor prognostic indicator in all HF patients, with PASP > 45 mmHg on echo being associated with increased 5-year mortality, independent of the severity of HF and other comorbidities [8, 9]. Specifically, in the HFrEF population, those with evidence of PH on RHC had the worst prognosis [5].

Since the initial definition was proposed, advances in our understanding of the pathophysiology have led to a recognition that there is likely a continuum of disease comprising PH-LHD—from elevated left-sided filling pressures causing a direct elevation in pulmonary pressures to long-term elevations in pulmonary pressures leading to secondary pulmonary vascular remodeling [10].

In order to differentiate between these two sub-groups, further hemodynamic variables have been incorporated into the definition of PH-LHD, namely the diastolic pressure gradient (DPG) which is defined as the difference between the diastolic pulmonary artery pressure and the PAWP, and more recently the pulmonary vascular resistance (PVR) defined as the transpulmonary gradient (mPAP-PAWP) divided by the cardiac output.

Isolated post-capillary PH (Ipc-PH), defined as PH-LHD with PVR < 3, represents the majority of PH-LHD, with the predominant causative factor being elevation in left-sided pressures. By comparison, combined post- and pre-capillary PH (Cpc-PH), the group previously referred to as "out-of-proportion" or "reactive" PH-LHD, is defined as PH-LHD with PVR ≥ 3 and occurs in 12–38% of all HF patients [4]. This subdivision has implications across PH-LHD, as the presence of Cpc-PH is associated with increased morbidity and mortality, with potential limitations of and complications with therapeutic options [4] including heart transplantation and left ventricular assist device (LVAD) [11], as we will discuss in detail below.

Diagnosis

Noninvasive Testing

Echocardiography

Echocardiography is one of the mainstays of investigation in LHD in general and in HFrEF specifically. Furthermore, efforts have been made to identify features to diagnose and monitor PH-LHD using routinely acquired echo-Doppler images [12–14]. Direct estimation of pulmonary artery systolic pressure is able to be calculated by adding estimates of right ventricular systolic pressure (calculated by applying the Bernoulli equation to the peak tricuspid regurgitation velocity) and estimates of right atrial pressure (based on a number of factors including inferior vena cava size, tricuspid inflow filling pattern, tricuspid e/e', right atrial volume) [15–19]. Studies have shown a good correlation with invasive hemodynamic measurements [20], with the caveat of high-quality images and Doppler signals. In day-to-day practice, this becomes less accurate as estimates are effected by numerous factors—the technical ability to acquire quality images; tricuspid regurgitation velocity is low, absent, or of poor quality; and when right atrial volume is unable to be assessed or is inaccurately estimated. Furthermore, the presence of an elevated PASP does not inform as to the underlying hemodynamic state, specifically the presence of elevated RV afterload [12].

Given these inherent limitations, many have sought to identify other measures on echo that are more easily reproducible, less prone to measurement error, and more informative as to the state of RV-PA interaction. Parameters including degree of septal flattening, particularly in systole, RV dilatation, and RV to LV ratio, RV apex angle, and RV dysfunction by RV fractional area change or tricuspid annular plane systolic excursion (TAPSE) are routinely available on clinical echocardiography [12]. Furthermore, parameters assessing the pulse-wave Doppler profile in the right ventricular outflow tract (RVOT), including acceleration time, velocity time integral (VTI), and notching profile have been seen as a marker of elevated PVR across the spectrum of PH [12, 21] and correlated with worse prognosis in patients with PAH [22]. More recently, the ratio of TAPSE/PASP has been described as an index of right ventriculo-arterial coupling (independent of LV dysfunction) and shown to be associated with functional capacity and prognosis in HFrEF [23, 24]. Recently, we described the RVOT-VTI/PASP relationship as a noninvasive estimate of PA compliance which stratified patients across the PH spectrum (from Ipc-PH to Cpc-PH to PAH) and was correlated with 6-min walk distance [25].

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET), primarily with standardized exercise minute oxygen consumption (VO_2 max) protocols, is routinely used to prognosticate progression and severity of HFrEF [26, 27]. A study of 320 HFrEF patients showed that PH-LHD was associated with reduced exercise tolerance, with a direct correlation with severity of PH-LHD and degree of exercise impairment [28]. Furthermore, other parameters including ventilatory inefficiency, as expressed by increased minute ventilation to carbon dioxide production (VE/VCO_2), are associated with increased morbidity and mortality in patients with HFrEF and have been linked with severity of RV dysfunction and PH [29, 30].

Based on the above information, we recommend routine transthoracic echocardiography with serial assessment of biventricular structure and function, parameters of RV afterload, and the use of CPET to describe disease pathophysiology, severity, and prognosis in this population.

Invasive Testing

Guidelines indicate that a right heart catheterization (RHC) is needed to definitively make a diagnosis of PH, and in the case of PH-LHD, it is vital in determining not only the diagnosis, but to differentiate between Ipc-PH and Cpc-PH. Although invasive, this procedure is relatively safe and is now routine practice in most centers. The predicament is that the crucial recording—the PAWP—also happens to be the one that is most prone to error in measurement during the procedure. We recommend that extra time and care be taken while documenting the PAWP. We have identified the following three strategies for ensuring an accurate PAWP measurement:

1. Ensuring that the reference level is appropriately set at the mid thoracic position, and that it has been zeroed prior to measurement [31]
2. Confirm catheter tip position with either fluoroscopy or with aspiration and assessment of PAWP blood (ensuing appropriately high oxygenation as representative of PAWP blood)
3. Minimize the effect of respirophasic changes in intrathoracic pressure by measuring the PAWP at the end of the expiratory phase during normal respiration [32]

In addition to standard measurements, PH-LHD is a common situation where additional procedural techniques are performed. There are no standardized protocols though a growing consensus is forming that this testing will assist in both clarifying diagnosis and may aid with tailoring appropriate therapy. The commonly used additional testing maneuvers include:

- *Fluid challenge*: Patients are often on diuretic therapy, which, when combined with peri-procedural fasting, can lead to significantly lower PAWP measurements than are normal for the patient. If this occurs, a small (no more than 500 mL) intravenous fluid challenge can be performed and then hemodynamic measurements reassessed, with specific focus on increases in PAWP and TPG [33]. This can be very helpful in PH-HFpEF and may have less of a pivotal role in PH-HFrEF.
- *Exercise*: Invasive hemodynamic testing during exercise can help illicit if there is exercise-induced PH, the presence of exercise-induced diastolic dysfunction, worsening mitral regurgitation, and relative imbalances in changes in PVR and/or SVR with exercise. The definitive method is to perform an invasive cardiopulmonary exercise test (iCPET), during which the invasive measurement of cardiac output and peripheral oxygen consumption can be correlated with CPET measures to assess if there is truly exercise-induced PH in addition to the resting HFrEF [34].
- *Vasodilator testing*: As will be discussed below, the reversibility of PH-LHD has most traditionally been used in assessing patients for orthotropic heart transplantation (OHT), where a response to vasodilator challenge, defined by a reduction in PA pressures and increase in CO with resultant decrease in PVR, would suggest safety and success of OHT alone. We recommend using intravenous sodium nitroprusside (dose 0.5–1.5 μg/kg/min, titrated in 25–50 μg/min increments) [35] or inhaled nitric oxide (dose 20 to 80 ppm) [36] due to their relatively short half-life and ease of use. We would advise caution with using inhaled nitric oxide, specifically if PAWP is elevated. Alternatives described include intravenous milrinone (dose 50 μg/kg bolus) [37] and intravenous prostaglandin E1 (dose 0.02–0.4 μg/kg/min, titrated upwards in doubling doses) [38].

Management

Optimizing HFrEF Treatment

In our opinion, the main tenet of management in this population is optimization of HFrEF management, with optimization of hemodynamics including reduction in PAWP and LV unloading to allow for improved systemic output. Only in the situations where this fails, and in the context of parameters from the above-described testing, do we consider further interventions (both medical and surgical). Therefore, adequate diuretic therapy, an often under emphasized avenue of therapy, is vital to symptom control. Recently, the CHAMPION trial [39] showed that invasive monitoring of left-sided filling pressures using the pulmonary artery diastolic pressure (as a surrogate marker of PAWP) to guide diuretic therapy reduces heart failure hospitalizations in a homogenous heart failure population. This study has led to much excitement for the potential role of this form on monitor-guided diuretic therapy in PH-LHD, and upcoming studies using the CardioMEMS device may provide more evidence for its future use [40]. In addition to diuretics, the role of optimizing medical therapy, utilizing device therapy, and addressing mitral regurgitation should remain a major focus for both symptomatic and prognostic improvements. We believe that this should include the consideration of long-term inotropic support ("vasodilator conditioning"), which has been shown to significantly reduce PH [41], and may be especially useful in those for consideration of OHT.

Pulmonary Hypertension-Specific Therapy

The use of PH-specific therapy in PH-LHD has always seemed mechanistically viable, considering many similar changes in vasoactive mediators occur in patients with PAH and PH-LHD [42]. This has led to a number of trials being performed to test this treatment avenue, and we have summarized these in Table 1.

Table 1 Summary of Clinical Trials of Pulmonary Hypertension Specific Therapy in Heart Failure

Study name	Year	Drug studied	Patient population	Number of subjects	Primary outcome	Result
FIRST [41]	1996	IV epoprostenol	NYHA class IIIB/IV, no specific requirement for PH	471	Mortality	Terminated early due to mortality
HEAT [42]	2002	Darusentan	NYHA class III, no specific requirement for PH	179	Change in invasive hemodynamics	Improvement in cardiac output with no change in PA pressures
EARTH [43]	2004	Darusentan	NYHA class IIIB/IV, no specific requirement for PH	642	Change in LV size	No benefit
REACH-1 [44]	2005	Bosentan (500 mg twice a day)	NYHA class III/IV, no specific requirement for PH	174	Improvement in HF symptoms	Early termination, although trend to benefit in those that completed study
Guazzi [45]	2007	Sildenafil	NYHA class II/III, no specific requirement for PH	46	Peak VO_2	Improved exercise capacity
Guazzi [46]	2011	Sildenafil	NYHA class II/III, no specific requirement for PH	45	Diastolic function, cardiac geometry, exercise capacity	Improvement in all parameters
LEPHT [47]	2013	Riociguat	LV ejection fraction $\leq 40\%$, mPAP ≥ 25 mmHg by right heart catheterization	201	Change in mPAP	No benefit
PITCH-HF [48]	2014	Tadalafil	NYHA class II/III, documented PH within 6 months	23	Mortality and HF hospitalizations	Terminated due to poor enrolment
SIL-HF [49]	2014	Sildenafil	NYHA class II/III, SPAP > 40 mmHg on TTE	75	Patient-reported symptoms, 6 min walk test	Enrolment complete, results pending
ENABLE [50]	2017	Bosentan (125 mg twice a day)	NYHA class IIIB/IV, no specific requirement for PH	1613	Mortality	No benefit
MELODY-1 [51]	2018	Macitentan	HFrEF, NYHA class II/III, Cpc-PH by right heart catheterization	63	Safety (fluid retention or worsening NYHA class)	Increased fluid retention in study arm

Initial clinical trials using intravenous prostacyclins [43]; darusentan, a selective endothelin A antagonist [44, 50]; and bosentan, a dual endothelin A and B antagonist [52, 53], were negative, although it is important to note these studies included all HFrEF patients, failed to focus specifically on the PH-LHD population, and often studied dosing several times higher than those used in PAH.

Further studies have been performed to assess the use of sildenafil, a PDE5 inhibitor, in this population. This was based on initial data showing that sildenafil acutely reduces mPAP and PVR when co-administered with inhaled nitric oxide [45]. In a single-arm, open-label study of 13 patients with HFrEF, Lewis et al. showed a significant improvement in hemodynamics and CPET parameters including VO_2 and VE/VCO_2 after 50 mg of sildenafil [46]. Guazzi et al. prospectively studied the role of sildenafil in HFrEF in a single-center, randomized trial and showed improvements in hemodynamics, echocardiographic markers of left ventricular diastolic function, and cardiac geometry, as well as functional status (by CPET) and quality of life [48, 49]. Larger randomized, double-blind placebo-controlled trials with PDE5 inhibitors were then begun, but have been plagued by poor recruitment and funding. PITCH-HF [47], evaluating tadalafil, was terminated due to enrollment difficulties, while SIL-HF [51], a small multicenter trial of 78 patients, assessing sildenafil, has just finished recruitment.

Finally, two studies using other PH-specific therapy have recently been published. LEPHT [54], a study using riociguat, a nitric oxide pathway soluble guanylate cyclase stimulator, was performed which also failed to show any significant reduction in PAP or PVR after 16 weeks of treatment. MELODY-1 [55], which was a phase II exploratory study in the Cpc-PH population using macitentan, a dual endothelin A and B antagonist, showed increased fluid retention in the treatment arm within 4 weeks of starting therapy. Thus, at this time, large multicenter data are lacking supporting the use of PH-specific therapy in HFrEF.

Mechanical Circulatory Support

Temporary Mechanical Circulatory Support

There have been recent advances in technology in the development of devices for temporary mechanical circulatory support (MCS), but the majority are focused at LV support which is insufficient in patients with PH-LHD who will often require simultaneous support for both the LV and the RV. There are two percutaneous devices that are approved for percutaneous temporary RV support—the Impella RP (Abiomed Inc., Danvers, MA) and the Tandem Heart RVAD/Protek Duo (TandemLife, Pittsburgh, PA)—which have both being used in conjunction with percutaneous LV support. Both of these devices are configured to bypass the RV, mechanically moving blood from the RA to PA, which has the net effect of increasing the mPAP [56] and therefore may introduce difficulty in managing patients with PH-LHD.

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is configured to bypass the whole heart and mechanically moves blood from the RA to the femoral artery. This configuration has no direct effect on the mPAP, but has been well described to have an increase in LV afterload resulting in increased PAWP, which in turn can cause increased mPAP. As such, we recommend approaching the use of temporary MCS in PH-LHD with caution, and if faced with this situation, our strategy is to use VA-ECMO as our primary temporary MCS platform with careful monitoring of PA pressures and a low threshold for the addition of a second device (such as Intra-aortic Balloon Pump [57], Impella LV device [58], transeptal puncture [59], or direct LV drainage [60]) to decompress the left ventricle.

Durable Mechanical Support

Left ventricular assist device (LVAD) therapy has become a mainstay in the treatment of end-stage HFrEF, with multiple devices now FDA approved for both bridge-to-transplant (BTT) and destination therapy (DT) indications [61]. Pre-implant PH-LHD has been identified as a risk factor for both 30-day mortality [62] and risk of early right heart failure post-LVAD implant [63]. Several markers of RV-PA uncoupling pre-LVAD implantation have been described as predictive of RV failure post-LVAD including right atrial pressure (RAP), RAP/PAWP ratio, PA pulsatility index (PAPi; PA pulse pressure/RAP), and indexed PA compliance [64]. Despite much study, RV failure post-LVAD, both early and late, remain an Achilles heel of isolated LVAD technology, with poorly performing predictive models when applied to external validation cohorts [65].

Many studies over the years have shown reversal of PH-LHD with LVAD support thought to impact both acute mechanical unloading of the left ventricle and the persistent reduction in filling pressures postulated to lead to reverse remodeling of the pulmonary vasculature as seen in Cpc-PH. This has been shown in a number of single-center observational studies in the pre-transplant population [66–68] and in a more recent study which showed significant reduction in PH when compared to medical therapy in a similar population [69].

In a recent study, Tsukashita et al. [70] compared outcomes of patients who underwent BTT LVAD support and dichotomized them by pre-LVAD PVR (low and high; $<$ and ≥ 5 Wood units [WU], respectively). While LVAD placement led to a reduction of PVR in the high PVR group to a level similar to that of the low PVR group (<3 WU), there was an increase in 30-day post-OHT mortality in the pre-LVAD high PVR group, with a pre-LVAD PVR ≥ 5 WU strongly associated

with early mortality (odds ratio, 5.99; 95% confidence interval, 1.25–28.9; $P < .05$). More recently, Imamura et al. [71, 72] highlighted the prognostic importance of a sustained or de novo DPG elevation after LVAD placement and with ramp study. This underscores the notion that LVAD therapy does not uniformly address the underlying pulmonary vascular abnormalities, requiring us to better hone our understanding and abilities in the assessment and management of these patients.

In an effort to address this, both inhaled milrinone [73] and inhaled NO [74] have been used in the early post-LVAD period to successfully reduce mPAP. Despite the clear hemodynamic effects, Potapov et al. [75] showed that inhaled NO did not show any benefit in preventing right ventricular dysfunction, duration of mechanical ventilation, length of stay, or the need for mechanical right ventricular support after LVAD implantation.

In the group that are successfully supported through the early post-operative period, the majority of patients appear to reduce the degree of PH-LHD over time with LVAD support. However, there is a subgroup that do not seem to achieve this benefit, and there is still no consensus as to the ideal treatment modality for this group. There have been several small, mostly single-center trials evaluating the role of sildenafil after LVAD placement. For example, Tedford et al. [76] performed a single-center study where they identified patients who did not normalize their PVR within 1 month of implant who received sildenafil as compared to those who did not. In this small, non-randomized study, sildenafil treatment ($n = 26$) led to a significant reduction mPAP, improved CO, and reduction in PVR. This and other similar data led to the International Society for Heart and Lung Transplantation (ISHLT) recommending the use of PDE-5 inhibitors in patients with RV dysfunction and PH post-LVAD (Class IIb, Level of Evidence C) [77]. Additionally, there has been interest in the role of other agents including bosentan for the treatment of PH after LVAD implantation [78] and the ongoing SOPRANO trial (Clinical Study to Assess the Efficacy and Safety of Macitentan in Patients with Pulmonary Hypertension After Left Ventricular Assist Device Implantation) [79] which aims to assess the efficacy of the macitentan in those with persistent Cpc-PH after LVAD implantation.

Thus, while the data suggest that LVAD therapy is associated with improvements in cardiopulmonary hemodynamics both acutely and over time, there are patients who have persistent PH and/or RV failure (early or late) after LVAD implantation. While several smaller trials suggest hemodynamic benefit from the use of PH-specific therapy, and we use such therapy in isolated cases, there is currently a lack of large, randomized data to support its use more broadly across this population. Finally, in patients with severe biventricular failure precluding LVAD alone and/or RV failure post-LVAD, the use of durable mechanical RV support (i.e., Heartware HVAD (Medtronic, Minneapolis, MN) [80, 81] and Heartmate 3 (Abbott, Abbott Park, IL) [82] in the right-sided position) is becoming more widespread. As these pumps are not designed for the RV, questions remain about optimal placement (RA vs RV cannulation), impact of RV trabeculations, avoidance of pulmonary overflow, and potential for suction events in the lower pressure and more compliant right ventricle, with relatively poor outcomes in this population [56]. Prior use of the Syncardia Total Artificial Heart (SynCardia Systems, Tucson, AZ) has been limited by its large size, mechanical failure, diminished quality of life compared with continuous flow pumps, and lack of temporary use as it requires ventricular excision, among other issues.

Transplantation

Despite advances in LVAD technology and outcomes, OHT is still considered the definitive treatment for end-stage HFrEF. Unfortunately, patients with PH-LHD have significantly worse outcomes post transplantation, with RV failure accounting for nearly 20% of early deaths after OHT [83]. In the early 1990s, the Stanford program identified key hemodynamic markers associated with improved survival despite the presence of PH pre-OHT [35]. Specifically, they assessed the role of nitroprusside challenge on those with PVR > 2.5 WU and found that those with reversibility of their PVR to < 2.5 WU while maintaining a systolic blood pressure > 85 mmHg had similar survival to those without PH. Conversely, those who did not reverse their PVR < 2.5 WU or did so with a concomitant decrease in systemic blood pressure to < 85 mmHg had significantly higher risk of mortality due to RV failure at 3 months (33%; 14% related to RV failure vs 6%). As we discussed earlier, agents such as inhaled NO and prostacyclins are commonly used to assess response of PVR prior to OHT. The ISHLT guidelines also suggest the use of intra-aortic balloon pump to augment output and reduce PVR [84], although there are no studies that show a sustained reduction in PVR and many centers not prefer to progress directly to LVAD implantation.

An analysis of the United Network for Organ Sharing (UNOS) registry in 2012 [85] showed that pre-transplant PVR of > 2.5 WU was an independent predictor of mortality, although interestingly the degree of elevation of PVR above this threshold did appear not increase mortality in a linear fashion. More recently, Tedford et al. evaluated the prognostic role of the DPG to predict post-OHT survival. In this UNOS analysis, they found that an elevated DPG at various cut points, nor TPG or PVR predicted survival post-OHT. Of note, as this was a UNOS analysis, it evaluated these parameters in patients who were "cleared" for and had undergone transplant, thus a selected population that presumably had shown encouraging hemodynamic responses to reversibility testing previously. Taken together, these studies and the approach of the guidelines underscore the fact that evaluation of PH-LHD in the context of OHT must be dynamic,

provocative, and serial, such that reliance on one specific parameter to characterize the degree/type of PH prior to OHT is inadequate. The most recent ISHLT guidelines have suggested a stepwise approach to the transplant candidate with an elevated PVR, which we have summarized in Fig. 1.

Our practice is to carefully and serially assess patients with PH-LHD who are being considered for OHT. In addition to nitroprusside challenge, we will often tailor medical therapy with the help of an indwelling PA catheter. This entails the use of inodilator support (milrinone), standard vasodilators used in HFrEF along with selected use of sildenafil to ensure that the PVR remains < 3 WU, which is based on a number of single-center studies that have used this in the pre-OHT population [86, 87]. In those patients who have ongoing elevated PVR, we will then consider the appropriateness of long-term mechanical support and implant an LVAD with intent to list for transplant after normalization of the PVR. In those patients who undergo OHT despite the presence of PH-LHD (deemed reversible with PVR < 3 WU), we have a detailed perioperative management protocol that involves the use of inhaled NO or inhaled Flolan with a slow wean, while optimizing ventilator support for longer than typical post-OHT to prevent hypoxic vasoconstriction. We also carefully monitor hemodynamics while titrating vasoactive support, diuresis, and often reinitiation of sildenafil should there be signs of RAP elevation, RV dysfunction, CO reduction, and/or PVR elevation. If there is early graft dysfunction (whether LV, RV, or both), careful consideration is given to mechanical unloading with intra-aortic balloon pump or EMCO support. These measures are in place to ensure optimization of RV preload, afterload, coronary perfusion, and pulmonary mechanics [88].

Finally, in those patients whom the PVR remains elevated, and without a viable mechanical support option as may be the case in the congenital population, selected patients may be eligible for combined heart-lung transplantation. This option, however, is not without significant pitfalls, as this procedure is performed at only a select number of centers and has a high post-operative morbidity and mortality when compared to

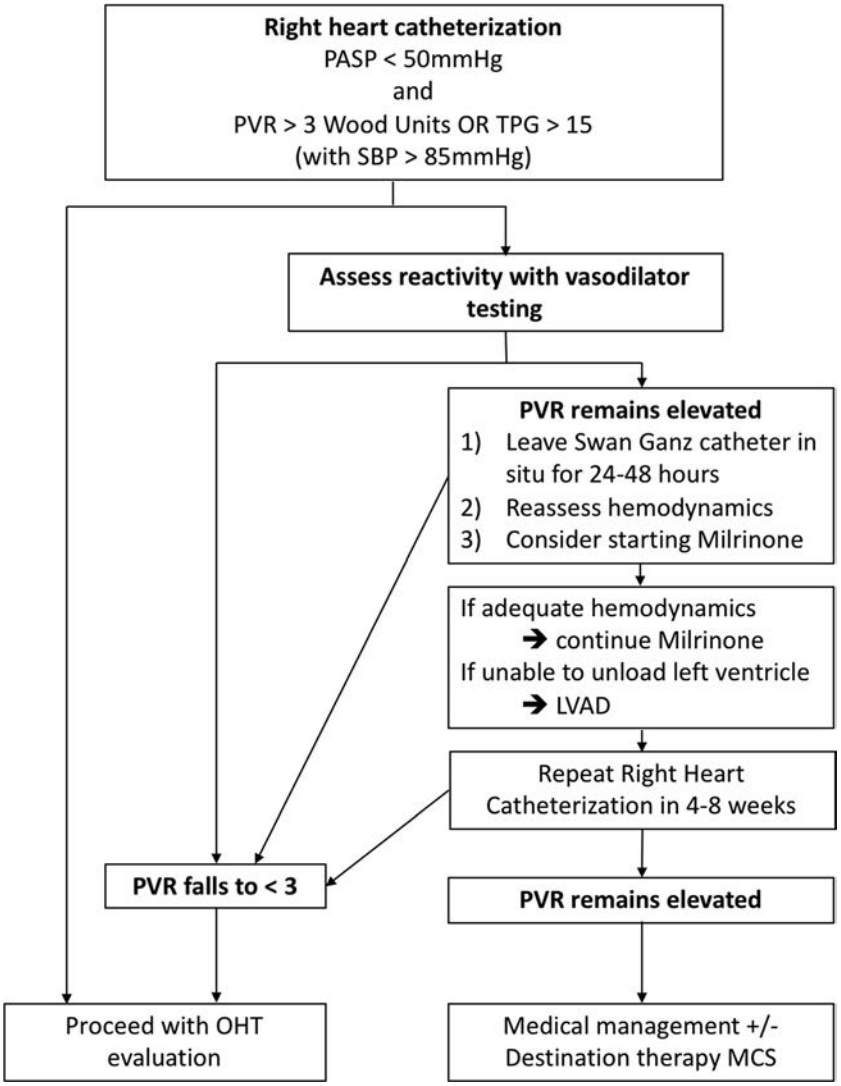


Fig. 1 Proposed investigation and management algorithm for patients with PH-LHD being assessed for advanced therapies

OHT. In fact, in a recent ISHLT report [89], only 58 procedures were reported in 2016. Interestingly, while the majority of patients undergoing this procedure are young, nearly 1/3 of recipients in North America between 2004 and 2017 were over the age of 50. The median survival for heart-lung transplant recipients has improved over the last 30 years, currently 5.8 years for those transplanted between 2004 and June 2016—a figure significantly less than that of OHT alone. Therefore, we believe it should be reserved for those in which all other options have been exhausted, and in particular those who are unable to undergo LVAD implantation due to technical/anatomical reasons.

Conclusion and Future Directions

As the above review has shown, PH-LHD remains a significant issue in the context of advanced HFrEF and one that complicates many treatment options in this population. Further studies, including the SIL-HF trial which has completed recruitment but has yet to report, along with the recently opened SILHF-US study [90] and ongoing SOPRANO trial [79], may help grow our knowledge in the field. Finally, the recent launch of the PVDOMICS (Redefining Pulmonary Hypertension through Pulmonary Vascular Disease Phenomics) [91] initiative will hopefully allow us to gain further insight into the "omics" (including genomics, transcriptomics, proteomics, metabolomics, coagulomics, and cell biomics) across the spectrum of pulmonary vascular disease to one day actualize the promise of personalized medicine for our patients with advanced cardiopulmonary disease.

Compliance with Ethical Standards

Conflict of Interest Sriram D. Rao and Jonathan N. Menachem declare no conflict of interest. Dr. Birati reports personal fees from Luitpold Pharmaceuticals, Inc. Dr. Mazurek reports personal fees from Actelion Pharmaceuticals.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. Circulation. 2012;126(8):975–90. https://doi.org/10.1161/CIRCULATIONAHA.111.085761.

2.•• Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37(1):67–119. https://doi.org/10.1093/eurheartj/ehv317. **An excellent summary of pulmonary hypertension with recent guideline recommendations**.

3. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53.

4. Rosenkranz S, Gibbs JSR, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiéry J-L. Left ventricular heart failure and pulmonary hypertension. Eur Heart J. 2016;37(12):942–54. https://doi.org/10.1093/eurheartj/ehv512.

5. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol. 2001;37(1):183–8. https://doi.org/10.1016/S0735-1097(00)01102-5.

6. Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: Pulmonary Hypertension and Heart Failure. JACC Heart Fail. 2013;1(4):290–9. https://doi.org/10.1016/j.jchf.2013.05.001.

7. Tampakakis E, Leary PJ, Selby VN, de Marco T, Cappola TP, Felker GM, et al. The diastolic pulmonary gradient does not predict survival in patients with pulmonary hypertension due to left heart disease. JACC Heart Fail. 2015;3(1):9–16. https://doi.org/10.1016/j.jchf.2014.07.010.

8. Miller WL, Mahoney DW, Enriquez-Sarano M. Quantitative Doppler-echocardiographic imaging and clinical outcomes with left ventricular systolic dysfunction. Circ Cardiovasc Imaging. 2014;7(2):330–6. https://doi.org/10.1161/CIRCIMAGING.113.001184.

9. Salamon JN, Kelesidis I, Msaouel P, Mazurek JA, Mannem S, Adzic A, et al. Outcomes in World Health Organization group II pulmonary hypertension: mortality and readmission trends with systolic and preserved ejection fraction–induced pulmonary hypertension. J Card Fail. 2014;20(7):467–75. https://doi.org/10.1016/j.cardfail.2014.05.003.

10. Adusumalli S, Mazurek JA. Pulmonary hypertension due to left ventricular cardiomyopathy: is it the result or cause of disease progression? Curr Heart Fail Rep. 2017;14(6):507–13. https://doi.org/10.1007/s11897-017-0368-2.

11. Sparrow CT, LaRue SJ, Schilling JD. Intersection of pulmonary hypertension and right ventricular dysfunction in patients on left ventricular assist device support: is there a role for pulmonary vasodilators? Circ Heart Fail. 2018;11(1):e004255. https://doi.org/10.1161/CIRCHEARTFAILURE.117.004255.

12. Opotowsky AR, Clair M, Afilalo J, Landzberg MJ, Waxman AB, Moko L, et al. A simple echocardiographic method to estimate pulmonary vascular resistance. Am J Cardiol. 2013;112(6):873–82. https://doi.org/10.1016/j.amjcard.2013.05.016.

13. Forfia PR, Vachiéry J-L. Echocardiography in pulmonary arterial hypertension. Am J Cardiol. 2012;110(6, Supplement):S16–24. https://doi.org/10.1016/j.amjcard.2012.06.012.

14. Mazurek JA, Forfia PR. Enhancing the accuracy of echocardiography in the diagnosis of pulmonary arterial hypertension: looking at the heart to learn about the lungs. Curr Opin Pulm Med. 2013;19(5):437–45. https://doi.org/10.1097/MCP.0b013e3283645966.

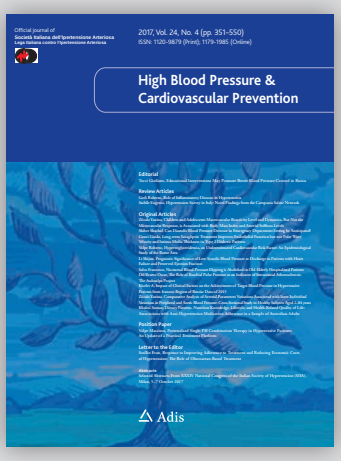
15. Brennan JM, Blair JE, Goonewardena S, Ronan A, Shah D, Vasaiwala S, et al. Reappraisal of the use of inferior vena cava for estimating right atrial pressure. J Am Soc Echocardiogr. 2007;20(7):857–61. https://doi.org/10.1016/j.echo.2007.01.005.
16. Beigel R, Cercek B, Luo H, Siegel RJ. Noninvasive evaluation of right atrial pressure. J Am Soc Echocardiogr. 2013;26(9):1033–42. https://doi.org/10.1016/j.echo.2013.06.004.
17. Do DH, Therrien J, Marelli A, Martucci G, Afilalo J, Sebag IA. Right atrial size relates to right ventricular end-diastolic pressure in an adult population with congenital heart disease. Echocardiography. 2011;28(1):109–16. https://doi.org/10.1111/j.1540-8175.2010.01277.x.
18. Sundereswaran L, Nagueh SF, Vardan S, Middleton KJ, Zoghbi WA, Quiñones MA, et al. Estimation of left and right ventricular filling pressures after heart transplantation by tissue Doppler imaging. Am J Cardiol. 1998;82(3):352–7.
19. Sade LE, Gulmez O, Eroglu S, Sezgin A, Muderrisoglu H. Noninvasive estimation of right ventricular filling pressure by ratio of early tricuspid inflow to annular diastolic velocity in patients with and without recent cardiac surgery. J Am Soc Echocardiogr. 2007;20(8):982–8. https://doi.org/10.1016/j.echo.2007.01.012.
20. Amsallem M, Sternbach JM, Adigopula S, Kobayashi Y, Vu TA, Zamanian R, et al. Addressing the controversy of estimating pulmonary arterial pressure by echocardiography. J Am Soc Echocardiogr. 2016;29(2):93–102. https://doi.org/10.1016/j.echo.2015.11.001.
21. Arkles JS, Opotowsky AR, Ojeda J, Rogers F, Liu T, Prassana V, et al. Shape of the right ventricular Doppler envelope predicts hemodynamics and right heart function in pulmonary hypertension. Am J Respir Crit Care Med. 2011;183(2):268–76. https://doi.org/10.1164/rccm.201004-0601OC.
22. Takahama H, McCully RB, Frantz RP, Kane GC. Unraveling the RV ejection Doppler envelope: insight into pulmonary artery hemodynamics and disease severity. JACC Cardiovasc Imaging. 2017;10(10, Part B):1268–77. https://doi.org/10.1016/j.jcmg.2016.12.021.
23. Guazzi M, Naeije R, Arena R, Corrà U, Ghio S, Forfia P, et al. Echocardiography of right ventriculoarterial coupling combined with cardiopulmonary exercise testing to predict outcome in heart failure. Chest. 2015;148(1):226–34. https://doi.org/10.1378/chest.14-2065.
24. Guazzi M, Bandera F, Pelissero G, Castelvecchio S, Menicanti L, Ghio S, et al. Tricuspid annular plane systolic excursion and pulmonary arterial systolic pressure relationship in heart failure: an index of right ventricular contractile function and prognosis. Am J Physiol Heart Circ Physiol. 2013;305(9):H1373–81. https://doi.org/10.1152/ajpheart.00157.2013.
25. Bhattacharya PT, Troutman GS, Mao F, Fox AL, Tanna MS, Zamani P, Grandin EW, Menachem JN, Birati EY, Chirinos JA, Mazimba S, Smith KA, Kawut SM, Forfia PR, Vaidya A, Mazurek JA. Right ventricular outflow tract velocity time integral-to-pulmonary artery systolic pressure ratio: a non-invasive metric of pulmonary arterial compliance differs across the spectrum of pulmonary hypertension. Pulm Circ. 2019 Apr-Jun;9(2):2045894019841978.
26. Guazzi M, Adams V, Conraads V, Halle M, Mezzani A, Vanhees L, et al. EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation. 2012;126(18):2261–74. https://doi.org/10.1161/CIR.0b013e31826fb946.
27. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation. 2002;106(14):1883–92.
28. Butler J, Chomsky DB, Wilson JR. Pulmonary hypertension and exercise intolerance in patients with heart failure. J Am Coll Cardiol. 1999;34(6):1802–6. https://doi.org/10.1016/S0735-1097(99)00408-8.
29. Arena R, Lavie CJ, Milani RV, Myers J, Guazzi M. Cardiopulmonary exercise testing in patients with pulmonary arterial hypertension: an evidence-based review. J Heart Lung Transplant. 2010;29(2):159–73. https://doi.org/10.1016/j.healun.2009.09.003.
30. Methvin AB, Owens AT, Emmi AG, Allen M, Wiegers SE, Dries DL, et al. Ventilatory inefficiency reflects right ventricular dysfunction in systolic heart failure. Chest. 2011;139(3):617–25. https://doi.org/10.1378/chest.10-0318.
31. 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(3):252–7. https://doi.org/10.1164/rccm.201402-0269PP.
32. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D42–50. https://doi.org/10.1016/j.jacc.2013.10.032.
33. Robbins IM, Hemnes AR, Pugh ME, Brittain EL, Zhao DX, Piana RN, et al. High prevalence of occult pulmonary venous hypertension revealed by fluid challenge in pulmonary hypertension. Circ Heart Fail. 2014;7(1):116–22. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000468.
34. Maron BA, Cockrill BA, Waxman AB, Systrom DM. The invasive cardiopulmonary exercise test. Circulation. 2013;127(10):1157–64. https://doi.org/10.1161/CIRCULATIONAHA.112.104463.
35. Costard-Jäckle A, Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. J Am Coll Cardiol. 1992;19(1):48–54. https://doi.org/10.1016/0735-1097(92)90050-W.
36. Ichinose F, Roberts JD, Zapol WM. Inhaled nitric oxide: a selective pulmonary vasodilator: current uses and therapeutic potential. Circulation. 2004;109(25):3106–11. https://doi.org/10.1161/01.CIR.0000134595.80170.62.
37. Givertz MM, Hare JM, Loh E, Gauthier DF, Colucci WS. Effect of bolus milrinone on hemodynamic variables and pulmonary vascular resistance in patients with severe left ventricular dysfunction: a rapid test for reversibility of pulmonary hypertension. J Am Coll Cardiol. 1996;28(7):1775–80. https://doi.org/10.1016/S0735-1097(96)00399-3.
38. Murali S, Uretsky BF, Armitage JM, et al. Utility of prostaglandin E1 in the pretransplantation evaluation of heart failure patients with significant pulmonary hypertension. J Heart Lung Transplant. 1992;11(4 Pt 1):716–23.
39. 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. 2011;377(9766):658–66. https://doi.org/10.1016/S0140-6736(11)60101-3.
40. Hemodynamic-GUIDEd Management of Heart Failure—full-text view—ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03387813. Accessed 29 Nov 2018.
41. Botha P, Parry G, Dark JH, MacGowan GA. Acute hemodynamic effects of intravenous sildenafil citrate in congestive heart failure: comparison of phosphodiesterase type-3 and -5 inhibition. J Heart Lung Transplant. 2009;28(7):676–82. https://doi.org/10.1016/j.healun.2009.04.013.
42. Farber HW, Loscalzo J. Pulmonary arterial hypertension. N Engl J Med. 2004;351(16):1655–65. https://doi.org/10.1056/NEJMra035488.

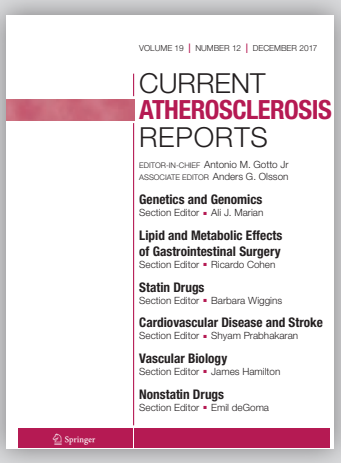
43. Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). Am Heart J. 1997;134(1):44–54.
44. Anand I, McMurray J, Cohn JN, Konstam MA, Notter T, Quitzau K, et al. Long-term effects of darusentan on left-ventricular remodelling and clinical outcomes in the EndothelinA Receptor Antagonist Trial in Heart Failure (EARTH): randomised, double-blind, placebo-controlled trial. Lancet. 2004;364(9431):347–54. https://doi.org/10.1016/S0140-6736(04)16723-8.
45. Bursi F, McNallan SM, Redfield MM, et al. Pulmonary pressures and death in heart failure: a community study. J Am Coll Cardiol. 2012;59(3):222–31. https://doi.org/10.1016/j.jacc.2011.06.076.
46. Lewis GD, Lachmann J, Camuso J, Lepore JJ, Shin J, Martinovic ME, et al. Sildenafil improves exercise hemodynamics and oxygen uptake in patients with systolic heart failure. Circulation. 2007;115(1):59–66. https://doi.org/10.1161/CIRCULATIONAHA.106.626226.
47. Phosphodiesterase type 5 inhibition with tadalafil changes outcomes in heart failure—full-text view—ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01910389. Accessed 29 Nov 2018.
48. Guazzi M, Samaja M, Arena R, Vicenzi M, Guazzi MD. Long-term use of sildenafil in the therapeutic management of heart failure. J Am Coll Cardiol. 2007;50(22):2136–44. https://doi.org/10.1016/j.jacc.2007.07.078.
49. Guazzi M, Vicenzi M, Arena R, Guazzi MD. PDE5 inhibition with sildenafil improves left ventricular diastolic function, cardiac geometry, and clinical status in patients with stable systolic heart failure: results of a 1-year, prospective, randomized, placebo-controlled study. Circ Heart Fail. 2011;4(1):8–17. https://doi.org/10.1161/CIRCHEARTFAILURE.110.944694.
50. Lüscher TF, Enseleit F, Pacher R, et al. Hemodynamic and neurohumoral effects of selective endothelin A (ET(A)) receptor blockade in chronic heart failure: the Heart Failure ET(A) Receptor Blockade Trial (HEAT). Circulation. 2002;106(21):2666–72.
51. Sildenafil versus placebo in chronic heart failure—full-text view—ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01616381. Accessed 29 Nov 2018.
52. Packer M, McMurray JJV, Krum H, et al. Long-term effect of endothelin receptor antagonism with bosentan on the morbidity and mortality of patients with severe chronic heart failure: Primary Results of the ENABLE Trials. JACC Heart Fail. 2017;5(5):317–26. https://doi.org/10.1016/j.jchf.2017.02.021.
53. Packer M, McMurray J, Massie BM, Caspi A, Charlon V, Cohen-Solal A, et al. Clinical effects of endothelin receptor antagonism with bosentan in patients with severe chronic heart failure: results of a pilot study. J Card Fail. 2005;11(1):12–20.
54. Bonderman D, Ghio S, Felix Stephan B, et al. Riociguat for patients with pulmonary hypertension caused by systolic left ventricular dysfunction. Circulation. 2013;128(5):502–11. https://doi.org/10.1161/CIRCULATIONAHA.113.001458.
55. Vachiéry J-L, Delcroix M, Al-Hiti H, et al. Macitentan in pulmonary hypertension due to left ventricular dysfunction. Eur Respir J. 2018;51(2):1701886. https://doi.org/10.1183/13993003.01886-2017.
56. • Kapur Navin K, Esposito Michele L, Yousef B, et al. Mechanical circulatory support devices for acute right ventricular failure. Circulation. 2017;136(3):314–26. https://doi.org/10.1161/CIRCULATIONAHA.116.025290. **A concise and recently published in-depth review on mechanical support options for right ventricular failure in general.**
57. Ro SK, Kim JB, Jung SH, Choo SJ, Chung CH, Lee JW. Extracorporeal life support for cardiogenic shock: influence of concomitant intra-aortic balloon counterpulsation. Eur J Cardiothorac Surg. 2014;46(2):186–92; discussion 192. https://doi.org/10.1093/ejcts/ezu005.
58. Koeckert MS, Jorde UP, Naka Y, Moses JW, Takayama H. Impella LP 2.5 for left ventricular unloading during venoarterial extracorporeal membrane oxygenation support. J Card Surg. 2011;26(6):666–8. https://doi.org/10.1111/j.1540-8191.2011.01338.x.
59. Kang M-H, Hahn J-Y, Gwon H-C, Song YB, Choi JO, Choi JH, et al. Percutaneous transseptal left atrial drainage for decompression of the left heart in an adult patient during percutaneous cardiopulmonary support. Korean Circ J. 2011;41(7):402–4. https://doi.org/10.4070/kcj.2011.41.7.402.
60. Fumagalli R, Bombino M, Borelli M, Rossi F, Colombo V, Osculati G, et al. Percutaneous bridge to heart transplantation by venoarterial ECMO and transaortic left ventricular venting. Int J Artif Organs. 2004;27(5):410–3.
61. Miller LW, Rogers JG. Evolution of left ventricular assist device therapy for advanced heart failure: a review. JAMA Cardiol. 2018;3(7):650–8. https://doi.org/10.1001/jamacardio.2018.0522.
62. Selby VN, Teuteberg JJ, Allen IE, Tedford RJ, Kormos RL, Marco TD. Characterization and impact of pulmonary hypertension on outcomes after left ventricular assist device implantation. J Heart Lung Transplant. 2015;34(4):S142. https://doi.org/10.1016/j.healun.2015.01.384.
63. Houston BA, Kalathiya RJ, Hsu S, Loungani R, Davis ME, Coffin ST, et al. Right ventricular afterload sensitivity dramatically increases after left ventricular assist device implantation: a multicenter hemodynamic analysis. J Heart Lung Transplant. 2016;35(7):868–76. https://doi.org/10.1016/j.healun.2016.01.1225.
64. Grandin EW, Zamani P, Mazurek JA, Troutman GS, Birati EY, Vorovich E, et al. Right ventricular response to pulsatile load is associated with early right heart failure and mortality after left ventricular assist device. J Heart Lung Transplant. 2017;36(1):97–105. https://doi.org/10.1016/j.healun.2016.06.015.
65. Kalogeropoulos AP, Kelkar A, Weinberger JF, Morris AA, Georgiopoulou VV, Markham DW, et al. Validation of clinical scores for right ventricular failure prediction after implantation of continuous-flow left ventricular assist devices. J Heart Lung Transplant. 2015;34(12):1595–603. https://doi.org/10.1016/j.healun.2015.05.005.
66. Torre-Amione G, Southard RE, Loebe MM, Youker KA, Bruckner B, Estep JD, et al. Reversal of secondary pulmonary hypertension by axial and pulsatile mechanical circulatory support. J Heart Lung Transplant. 2010;29(2):195–200. https://doi.org/10.1016/j.healun.2009.05.030.
67. Mikus E, Stepanenko A, Krabatsch T, Loforte A, Dandel M, Lehmkuhl HB, et al. Reversibility of fixed pulmonary hypertension in left ventricular assist device support recipients. Eur J Cardiothorac Surg. 2011;40(4):971–7. https://doi.org/10.1016/j.ejcts.2011.01.019.
68. Beyersdorf F, Schlensak C, Berchtold-Herz M, Trummer G. Regression of "fixed" pulmonary vascular resistance in heart transplant candidates after unloading with ventricular assist devices. J Thorac Cardiovasc Surg. 2010;140(4):747–9. https://doi.org/10.1016/j.jtcvs.2010.05.042.
69. Kumarasinghe G, Jain P, Jabbour A, Lai J, Keogh AM, Kotlyar E, et al. Comparison of continuous-flow ventricular assist device therapy with intensive medical therapy in fixed pulmonary hypertension secondary to advanced left heart failure. ESC Heart Fail. 2018;5(4):695–702. https://doi.org/10.1002/ehf2.12284.
70. Tsukashita M, Takayama H, Takeda K, Han J, Colombo PC, Yuzefpolskaya M, et al. Effect of pulmonary vascular resistance before left ventricular assist device implantation on short- and long-term post-transplant survival. J Thorac Cardiovasc Surg. 2015;150(5):1352–60, 1361.e1-2. https://doi.org/10.1016/j.jtcvs.2015.07.012.
71. Imamura T, Chung B, Nguyen A, Rodgers D, Sayer G, Adatya S, et al. Decoupling between diastolic pulmonary artery pressure and

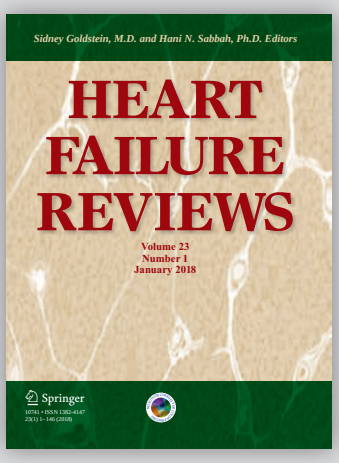
pulmonary capillary wedge pressure as a prognostic factor after continuous flow ventricular assist device implantation. Circ Heart Fail. 2017;10(9). https://doi.org/10.1161/CIRCHEARTFAILURE.117.003882.

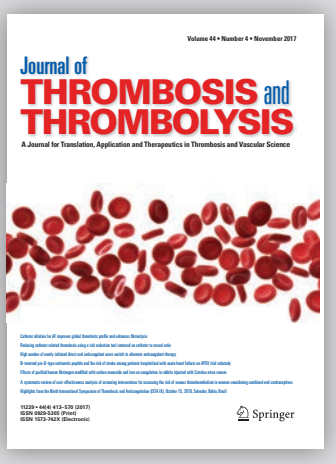
72. Imamura T, Kim G, Raikhelkar J, Sarswat N, Kalantari S, Smith B, et al. Decoupling between diastolic pulmonary arterial pressure and pulmonary arterial wedge pressure at incremental left ventricular assist device (LVAD) speeds is associated with worse prognosis after LVAD implantation. J Card Fail. 2018;24(9):575–82. https://doi.org/10.1016/j.cardfail.2018.08.003.
73. Haglund NA, Burdorf A, Jones T, Shostrom V, Um J, Ryan T, et al. Inhaled milrinone after left ventricular assist device implantation. J Card Fail. 2015;21(10):792–7. https://doi.org/10.1016/j.cardfail.2015.04.011.
74. Argenziano M, Choudhri AF, Moazami N, et al. Randomized, double-blind trial of inhaled nitric oxide in LVAD recipients with pulmonary hypertension. Ann Thorac Surg. 1998;65(2):340–5.
75. Potapov E, Meyer D, Swaminathan M, Ramsay M, el Banayosy A, Diehl C, et al. Inhaled nitric oxide after left ventricular assist device implantation: a prospective, randomized, double-blind, multicenter, placebo-controlled trial. J Heart Lung Transplant. 2011;30(8):870–8. https://doi.org/10.1016/j.healun.2011.03.005.
76. Tedford RJ, Hemnes AR, Russell SD, Wittstein IS, Mahmud M, Zaiman AL, et al. PDE5A inhibitor treatment of persistent pulmonary hypertension after mechanical circulatory support. Circ Heart Fail. 2008;1(4):213–9. https://doi.org/10.1161/CIRCHEARTFAILURE.108.796789.
77. Feldman D, Pamboukian SV, Teuteberg JJ, Birks E, Lietz K, Moore SA, et al. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. J Heart Lung Transplant. 2013;32(2):157–87. https://doi.org/10.1016/j.healun.2012.09.013.
78. LaRue SJ, Garcia-Cortes R, Nassif ME, et al. Treatment of secondary pulmonary hypertension with bosentan after left ventricular assist device implantation. Cardiovasc Ther. 2015;33(2):50–5. https://doi.org/10.1111/1755-5922.12111.
79. Clinical study to assess the efficacy and safety of macitentan in patients with pulmonary hypertension after left ventricular assist device implantation—full-text view—ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02554903. Accessed 29 Nov 2018.
80. Shehab S, Macdonald PS, Keogh AM, Kotlyar E, Jabbour A, Robson D, et al. Long-term biventricular HeartWare ventricular assist device support—case series of right atrial and right ventricular implantation outcomes. J Heart Lung Transplant. 2016;35(4):466–73. https://doi.org/10.1016/j.healun.2015.12.001.
81. Tran HA, Pollema TL, Silva Enciso J, Greenberg BH, Barnard DD, Adler ED, et al. Durable biventricular support using right atrial placement of the HeartWare HVAD. ASAIO J. 2018;64(3):323–7. https://doi.org/10.1097/MAT.0000000000000645.
82. Lavee J, Mulzer J, Krabatsch T, Marasco S, McGiffin D, Garbade J, et al. An international multicenter experience of biventricular support with HeartMate 3 ventricular assist systems. J Heart Lung Transplant. 2018;37(12):1399–402. https://doi.org/10.1016/j.healun.2018.08.008.
83. Kobashigawa J, Zuckermann A, Macdonald P, Leprince P, Esmailian F, Luu M, et al. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. J Heart Lung Transplant. 2014;33(4):327–40. https://doi.org/10.1016/j.healun.2014.02.027.
84. Jessup M, Banner N, Brozena S, Campana C, Costard-Jäckle A, Dengler T, et al. Optimal pharmacologic and non-pharmacologic management of cardiac transplant candidates: approaches to be considered prior to transplant evaluation: International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates—2006. J Heart Lung Transplant. 2006;25(9):1003–23. https://doi.org/10.1016/j.healun.2006.06.007.
85. Vakil K, Duval S, Sharma A, Adabag S, Abidi KS, Taimeh Z, et al. Impact of pre-transplant pulmonary hypertension on survival after heart transplantation: a UNOS registry analysis. Int J Cardiol. 2014;176(3):595–9. https://doi.org/10.1016/j.ijcard.2014.08.072.
86. De Santo LS, Buonocore M, Agrusta F, et al. Pattern of resolution of pulmonary hypertension, long-term allograft right ventricular function, and exercise capacity in high-risk heart transplant recipients listed under oral sildenafil. Clin Transpl. 2014;28(7):837–43. https://doi.org/10.1111/ctr.12387.
87. Pons J, Leblanc M-H, Bernier M, Cantin B, Bourgault C, Bergeron S, et al. Effects of chronic sildenafil use on pulmonary hemodynamics and clinical outcomes in heart transplantation. J Heart Lung Transplant. 2012;31(12):1281–7. https://doi.org/10.1016/j.healun.2012.09.009.
88. Stobierska-Dzierzek B, Awad H, Michler RE. The evolving management of acute right-sided heart failure in cardiac transplant recipients. J Am Coll Cardiol. 2001;38(4):923–31. https://doi.org/10.1016/S0735-1097(01)01486-3.
89. Chambers DC, Cherikh WS, Goldfarb SB, Hayes D Jr, Kucheryavaya AY, Toll AE, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-fifth adult lung and heart-lung transplant report—2018; focus theme: multiorgan transplantation. J Heart Lung Transplant. 2018;37(10):1169–83. https://doi.org/10.1016/j.healun.2018.07.020.
90. Sildenafil in US heart failure patients (SilHF-US)—full-text view—ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03460470. Accessed 6 Dec 2018.
91. Pulmonary vascular disease phenomics program PVDOMICS—full-text view—ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02980887. Accessed 6 Dec 2018.

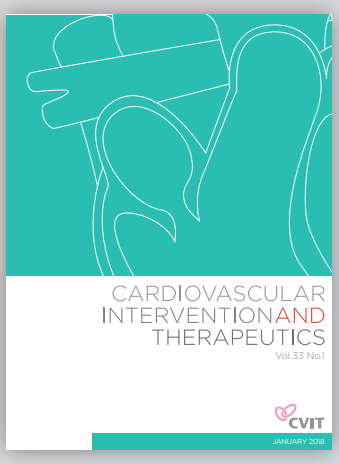
Springer Nature Cardiology Journals

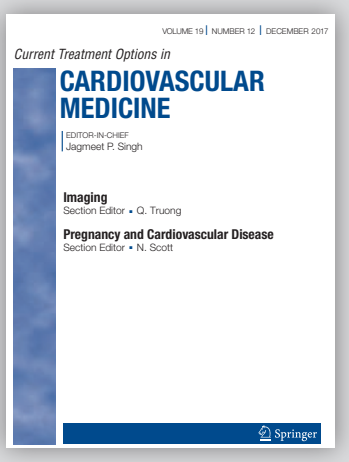












Vasodilating β blocker that

Understands the heart better

cardivas

(Carvedilol Tablets 3.125/6.25/12.5/25 mg)

THE RIGHT CHOICE for Improved Survival

In Heart Failure

Inapure

Ivabradine Tablets 5 mg

Control Heart Rate In a Pure Way

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

8346544 / L21346A79