

Diastolic Heart Failure: Treatment Based on Mechanisms

The prevalence and clinical challenges of diastolic heart failure cause this condition to be of great concern to the treating physician. This article shows how preventive measures, through the aggressive modification of risk factors, must be the clinician's priority.



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Diastolic heart failure (DHF) is highly prevalent and is associated with significant personal and socioeconomic burden. Patients with DHF show signs and symptoms of HF with a preserved ejection fraction (EF). Recent epidemiological studies have countered the commonly held belief that survival of patients with DHF is better than that of patients with systolic HF (SHF).¹ The high morbidity and mortality associated with DHF highlight the growing need to define new therapeutic targets for this population.

Current DHF therapy

Treatment recommendations from the American College of Cardiology/American Heart Association are based largely on expert opinion and focus on the relief of symptoms.² The guidelines support the following strategies:

- Control of known risk factors such as hypertension
- Control of ventricular rate in patients with atrial fibrillation
- Control of pulmonary congestion and peripheral edema with diuretics
- Coronary revascularization when ischemia is judged to have an adverse effect on cardiac function

Sarah's shortness of breath

Sarah, 76, presents with increasing shortness of breath on exertion for 6 months. Her functional capacity has deteriorated and she is currently only able to walk 1 block or climb 6 steps prior to significant dyspnea.

She has associated two-pillow orthopnea and describes two previous episodes of paroxysmal nocturnal dyspnea. She also has bilateral lower-limb edema. She denies angina, syncope, or palpitations.

Her medical history is significant for long-standing, poorly controlled hypertension. Her only medication is 25 mg of hydrochlorothiazide q.o.d.

A transthoracic ECHO reveals:

- left ventricular hypertrophy,
- preserved systolic function and
- no significant valvular or pericardial disease.

Transmitral inflow and tissue Doppler indices are consistent with abnormal diastolic function. She is treated with diuretics and aggressive control of her hypertension.

Lifestyle interventions including regular exercise and vigilance of fluid and salt intake play an important role in the symptomatic management of patients with DHF.

Many of the therapies proven to be efficacious for SHF, including β -blockers, ACE inhibitors, ARBs and aldosterone blockers have

been suggested to be beneficial for DHF, potentially through different mechanisms. The efficacy of these agents for DHF must be confirmed in large randomized controlled trials prior to their widespread adoption for DHF. Calcium channel blockers have also been suggested to be beneficial for myocardial relaxation and rate control.

DHF is highly prevalent and is associated with significant personal and socioeconomic burden.

Clinical trials

Three large clinical trials have been conducted for existing DHF therapies, although none have demonstrated a mortality benefit. The Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved trial randomized subjects with HF and a preserved EF to candesartan or placebo.³ After a median follow-up of three years, the composite outcome of cardiovascular death or HF hospitalizations reached borderline significance, driven by a slightly lower rate of HF hospitalization in the candesartan group.

The multi-centered Perindopril for Elderly People with Chronic Heart Failure (PEP-CHF) trial focused on an older population and required documented diastolic dysfunction by echocardiography.⁴ After a total mean follow-up time of 26 months, there was no difference between perindopril and placebo groups in the composite outcome of all-cause mortality and HF hospitalizations.

Finally, the ancillary Digitalis Investigation Group (DIG) trial, a sub-study of the original

DIG trial, studied 998 patients with HF and an EF of > 45% who were also in sinus rhythm.⁵ Rates of the primary outcome, a composite of HF mortality and HF hospitalizations, did not differ over the course of the study, although subjects treated with digoxin had slightly better two-year outcomes, driven by decreased rates of HF hospitalization.

FAQ

How do I diagnose diastolic heart failure (DHF)?

The diagnosis of DHF requires the presence of signs and symptoms of HF in the setting of preserved systolic function. Severe valvular or pericardial disease must be ruled out, as well as non-cardiac causes of dyspnea, edema and fatigue. Diastolic function should be assessed by echocardiography.

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Table 1

Steps in management

1. Consider diagnosis in patients with HF and preserved systolic function. Exclude other causes of HF or non-cardiac causes of shortness of breath, edema, or fatigue
2. Control of modifiable risk factors, including systolic and diastolic hypertension
3. Control of ventricular rate
4. Control of pulmonary congestion and peripheral edema with diuretics
5. Coronary revascularization in patients with evidence of ischemia
6. Consider ACE inhibitors, ARBs, or digoxin for a modest reduction in rates of hospitalization

FAQ

What therapies are on the horizon?

Two large clinical trials are currently investigating the effectiveness of an ARB and aldosterone antagonist in the treatment of DHF. Treatments that directly target impaired relaxation and increased stiffness are still under development.

FAQ

How would I treat this condition?

Currently, there are no proven therapies to lower mortality in DHF. Congestive symptoms must be relieved with diuretics, ventricular rate should be controlled and revascularization should be considered in the presence of ischemia. Most importantly, risk factors such as hypertension should be aggressively managed.

Novel therapeutic targets

The primary difference between DHF and traditional SHF is the remodeling response of the ventricle to stress and injury. Epidemiological studies have confirmed the importance of aging, hypertension and diabetes to the DHF phenotype. Each of these risk factors may result in changes in the myocardium as well as in the peripheral vasculature that lead to impaired relaxation or increased myocardial stiffness—the hallmarks of DHF. Calcium homeostasis, myofilament sensitivity to calcium and myocardial energetics mediate the relaxation phase of diastole. Determinants of myocardial stiffness include:

- changes in the extracellular matrix,
- cytoskeletal proteins and
- myofilaments.

Potential novel targets for DHF include those that counter hypertrophy and fibrosis programs. Rho-kinase and phosphodiesterase-5 inhibitors (sildenafil) show promise in promoting the regression of hypertrophy.⁶ Potential antifibrotic agents include:

- inhibitors of the renin-angiotensin-aldosterone pathway,
- transforming-growth-factor- β antagonists,
- matrix metalloproteinase modulators and
- a compound that breaks crosslinks formed by advanced end-glycation products.^{7,8}

Cardiomyocyte distensibility may be improved by modification of titin, increasing the proportion of the more compliant isoform in the myocardium.⁹ Calcium homeostasis is a challenging target, as calcium levels throughout diastole and systole are inexorably linked to one another and difficult to modulate in isolation.¹⁰

Ongoing clinical trials

Two large, multi-centered trials of DHF therapy are currently being conducted. The Irbesartan in heart failure with PRESERVED systolic function (I-PRESERVE) trial is studying irbesartan in an older population with HF and an EF > 45%.¹¹ A large study funded by the National Heart, Lung and Blood Institute, the Treatment Of Preserved Cardiac function heart failure with an Aldosterone antagonist (TOPCAT) trial, is also underway, randomizing patients with DHF to spironolactone or placebo. Both trials will provide answers to the application of proven therapies of SHF to the DHF population.

Table 2

Treatment based on mechanisms


- **Hypertrophy**
 - RAAS antagonists,
 - rho-kinase and phosphodiesterase-5 inhibitors
- **Fibrosis**
 - RAAS antagonists
 - TGF- β antagonists
 - MMP modulators
 - AGE breakers
- **Cardiomyocyte distensibility**
 - Titin modification: activation of protein kinases, isotype switching
- **Improved calcium homeostasis**
 - sarcoplasmic reticulum Ca(2+) ATPase (SERCA2a) gene transfer
 - Increased phospholamban phosphorylation
 - Parvalbumin
 - Ryanodine stabilization
 - Decreased myofilament sensitivity to Ca²⁺
- **Improved energetics**
 - Revascularization

RAAS: Renin-angiotensin-aldosterone system
 TGF- β : Transforming growth factor β
 MMP: Matrix metalloproteinase
 AGE: Advanced glycation end-products

Take-home message

Management of DHF includes prevention of the disease through risk factor modification and treatment based on symptoms and disease mechanism.

Summary

There are few evidence-based recommendations for the treatment of patients with DHF. Evolving insights from epidemiological and fundamental data provide mechanistic targets. Novel therapies must be studied in carefully designed large-scale trials prior to widespread application. In the meantime, preventive measures through aggressive modification of risk factors must be the clinician's priority. 

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