

CHRONIC HEART FAILURE: DIAGNOSIS

Presentation

Presenting symptoms of heart failure such as dyspnea, exercise intolerance and fatigue are non-specific, and mimicked by many other conditions, especially in the elderly (Table 1). Several classification schemes (the most popular being by the New York Heart Association (NYHA), Canadian Cardiovascular Society (CCS), and Killip) have been presented for a semi-quantitative assessment of symptom severity.

Orthopnea, dyspnea that occurs in the recumbent position, is a later manifestation. It may also be seen in patients with chronic obstructive pulmonary disease (COPD) and abdominal obesity or ascites. **Paroxysmal nocturnal dyspnea** refers to acute episodes of dyspnea and coughing that occur at night and awaken the patient. It is relatively specific for heart failure, especially in young patients (<60 years) who also present with increased **JVP pressure** and **hepatomegaly** rather than dyspnea or peripheral oedema and rales.¹ **Pulmonary edema** may develop in acute exacerbations of heart failure. Minor episodes of haemoptysis may represent transient, exercise-induced pulmonary oedema. **Cardiac asthma** refers to wheezing due to bronchospasm or increased pressure in the bronchial arteries. **Cheyne-Stokes respiration** is periodic respiration with apneic phases during which the arterial PO₂ and the PCO₂ rises. It is due to diminished sensitivity of the respiratory center to arterial PCO₂, and occurs with advanced failure. **Syncope** in patients with LVEF<35% (40% arrhythmic) is associated with increased mortality.² Altered **mental status** may reflect hypoperfusion. **Anorexia** or **nausea** and **right upper quadrant pain** and **ascites** reflect bowel and liver congestion. **Cardiac cachexia** may be seen with advanced failure. **Sudden death** characterizes the mode of death in 30–50% of patients with chronic heart failure and a reduced ejection fraction.³ Occasionally, these events have an identifiable pathophysiological trigger, e.g. myocardial infarction, catecholamine surges, or electrolyte imbalances, but in most circumstances, there is no acute precipitating mechanism. Cascading failure in a severely remodelled or fibrotic heart can become manifest electrically as a first-time ventricular tachyarrhythmia that is responsive to the shock delivered by an ICD, or it may present as an acute mechanical failure, which manifest as asystole, bradyarrhythmia, or electromechanical dissociation, or as incessant ventricular fibrillation that persists despite repetitive ICD discharges.³

Presentation of **HF with preserved ejection fraction** may be identical to that of systolic heart failure.⁴ Diabetes usually have a more severely impaired exercise tolerance and worse disease phenotype.⁵ Atrial fibrillation is found in 20-30% of patient.⁶ Obesity seems to be an important factor for developing HFpEF at a young age.⁷ Routine assessments for

metabolic risk factors and kidney function (Cardiovascular-Kidney-Metabolic Syndrome), and metabolic dysfunction–associated steatotic liver disease are recommended among all adults.⁸

Physical Examination

Physical signs are also non-specific (Table 2):

- Sinus tachycardia or AF in 30% of patients with advanced disease.
- Raised jugular venous pulse
- Third heart sound (S₃)
- Basal pulmonary rales
- Peripheral oedema with ankle swelling and hepatomegaly

Pulmonary rales may be absent despite elevated left-sided filling pressures due to chronic lymphatic hypertrophy, which prevents alveolar edema despite elevated interstitial pressures.⁹

Pulmonary oedema may, rarely, be unilateral, involving the right upper lobe (contralateral to the heart) probably due to decreased flow in the left pulmonary artery following compression by the left-sided cardiac enlargement, a severe mitral regurgitation jet that predominantly affects the upper right pulmonary vein, and poorer lymphatic drainage of the right lung.

Ankle oedema may be caused by heart or renal failure and pericardial constriction, particularly with elevated JVP, chronic venous insufficiency, calcium channel blockers, IVC obstruction, prolonged air travel, idiopathic, liver congestion and hypoalbuminemia, and secondary hyperaldosteronism. Anasarca is rare in cardiac failure unless if untreated and there is concomitant hypoalbuminemia. **Unilateral ankle oedema** may be due to venous thrombosis, lymphatic obstruction, saphenous vein harvesting for CABG. Young patients may be not edematous despite intravascular volume overload. In obese patients and elderly patients, edema may reflect peripheral rather than cardiac causes. The Framingham criteria emphasized the importance of jugular venous pressure elevation, an **S₃ gallop**, and a positive hepatojugular reflex in establishing a diagnosis, while minimizing the importance of lower extremity edema. The **Jugular Venous Pressure** is measured as the vertical distance between the venous pulsation and the sternal angle of Louis (where the manubrium meets the sternum) with the patient semi-recumbent at an angle of about 45°. A distance >3 cm (cm of blood or water) is considered abnormal (1.36 cm H₂O = 1 mm Hg). Alternatively, the ability to see venous pulsations above the clavicle in the seated position denotes raised JVP since the clavicle is at least 10 cm above the right atrium.

- **a wave:** atrial contraction, coincident with the P wave of the ECG. Large a wave indicates increased right ventricular end-diastolic pressure (RVEDP)

(PS, pulmonary hypertension) or TS. Cannon a waves are seen in AV dissociation. Absent in AF.

- **c wave:** not visible (TV closure).
- **x' descent:** atrial diastolic suction due to ventricular contraction that pools the TV and RA floor downward.
- **v wave:** atrial filling. Smaller than the a wave; equal in ASD. Accentuated in MR and TR (merges with a wave to produce the s wave).
- **y descent:** reflects fall in right atrial pressure after TV opening. Blunted in TS or tamponade, steep in early diastolic filling as in pericardial constriction (pericardial knock).

The normal JVP should fall by at least 3 mm Hg with inspiration. A rise or failure to decrease with inspiration is a sign of constrictive pericarditis (**Kussmaul sign**), but it can also be seen in restrictive cardiomyopathy, massive pulmonary embolus, and RV failure. The **abdomino-jugular reflex** refers to sustained rise of > 3 cm of JVP for at least 15 sec after release of consistent pressure over the upper abdomen for at least 10 sec.

Diagnostic algorithms for heart failure are presented in Figures 1 and 2.

Physical examination is not helpful in discriminating between systolic and diastolic heart failure. There are symptoms and signs of heart failure, LVEF>50%, and presence of abnormal LV relaxation or diastolic stiffness. The **H2 FPEF** score may be useful for discrimination of HFpEF from noncardiac causes of dyspnoea.¹⁰ The HFA-PEFF scoring system involves pretest assessment of HF, echocardiography and natriuretic peptide score, functional testing including diastolic stress test/right heart catheterization, and special imaging/biopsy/genetic testing to identify cause.¹¹

Investigations

Hematocrit and leukocyte count, blood urea nitrogen and creatinine, glucose and HbA1c, serum electrolytes, liver function tests, lipid profile, and thyroid function tests are taken routinely (Tables 3-5). Close monitoring of serum potassium is necessary, especially after an episode of acute decompensated heart failure.¹² Both renal and liver function may be affected by and cause heart failure.^{13,14} Abnormal liver function tests such as increased γ GT, bilirubin, and alkaline phosphatase are frequently seen in patients with chronic and, especially, acute heart failure, and are associated with adverse prognosis. Transaminases are moderately increased or even remain normal.^{13,15} Typically, elevated transaminases indicate ischemic hepatitis due to diminished cardiac output whereas the concomitant present of cholestasis indicates passive hepatic congestion. Use of both estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR) is

recommended to characterize CKD and guide the use of kidney-protective agents to confer both cardiovascular and kidney benefits.⁸ eGFR 90-15 mL/min/1.73m² and albumin 40-300 mg/g (3-30 mg/mmol) indicate decreased kidney function and worst values kidney failure.⁸ **Natriuretic peptide (BNP)** or its precursor, **N terminal-proBNP**, are sensitive and specific indices for discriminating between causes of dyspnea (Table 5).¹⁶ Low BNP (<100 pg/ml or NT-pro BNP < 400 pg/ml) has very high negative predictive value, making it a useful rule-out test. This peptide is raised with advanced age, female sex, and renal insufficiency and lowered with obesity. A normal BNP in an untreated patient virtually excludes cardiac disease. High values (BNP> 400 pg/ml or NT-proBNP> 2000 pg/ml) suggest that heart failure is likely, whereas diagnosis is uncertain with intermediate values. For patients presenting with acute onset or worsening of symptoms, the optimal exclusion cut-off point is 300 pg/mL for NT-proBNP and 100 pg/mL for BNP. For patients presenting in a non-acute way, the optimum exclusion cut-off point is 125 pg/mL for NT-proBNP and 35 pg/mL for BNP,² but the sensitivity and specificity of BNP and NT-proBNP for the diagnosis of HF are lower in this setting. A meta-analysis has suggested that natriuretic peptide-guided treatment of heart failure can reduce hospitalization and mortality in patients aged <75 years,¹⁷ but recent RCTs have found no such evidence.^{18,19}

Plasma NT-BNP amounts are raised in patients with **heart failure with preserved LVEF** but, in general, to a lesser extent than in systolic heart failure. Natriuretic peptides are, in particular, lower in obese individuals with HFpEF.¹¹ Diagnostic thresholds of 220 pg/mL are usually required for patients with a body mass index ≥ 35 kg/m² and 500 pg/mL for a body mass index <35 kg/m², whereas a value <50 pg/mL rules out HF.²⁰ NT-proBNP provides little value in the presence of AF which is a biomarker of HFpEF.²⁰

Cardiac troponins are detected in most heart failure patients and their values have prognostic significance. High-sensitivity troponin T is a strong and independent predictor of hospitalization and all-cause and cardiovascular mortality.^{21,22}

Other biomarkers In ambulatory chronic heart failure patients, a score derived from multiple biomarkers such as **soluble suppressor of tumorigenicity 2, highly sensitive troponin, galectin-3, midregional proadrenomedullin, cystatin-C, interleukin-6, procalcitonin**, may also improve prediction of adverse events.²³

Screening for **hemochromatosis, sleep-disturbed breathing HIV, rheumatologic diseases, amyloidosis, or pheochromocytoma** is also undertaken when there is a clinical suspicion of these diseases.

ECG Left ventricular hypertrophy, atrial enlargement, previous myocardial infarction, active ischemia, conduction abnormalities, and arrhythmias may be present. An entirely normal ECG makes the diagnosis of systolic dysfunction unlikely (<10%).

Chest radiography may reveal cardiomegaly and/or pulmonary congestion (Kerley B lines

and interstitial edema with upper lobe blood diversion). Pleural effusions may be present with biventricular failure.

Echocardiography, especially three-dimensional echo,²⁴ may provide important information about ventricular dimensions, extent of systolic dysfunction, whether dysfunction is global or segmental, the status of valves, and estimates of pulmonary artery pressure. It is most specific for diagnosis of LV systolic dysfunction. Doppler assessment allows estimation of CVP, atrial and PV pressures, and cardiac output.²⁵

Echocardiographic indices indicative of **diastolic dysfunction** include transmitral and pulmonary venous Doppler filling profiles (E/e') and tissue doppler imaging that provides information on patterns of diastolic relaxation and filling and ventricular dyssynchrony (Table 6, and Figures 3 and 4).²⁶ However, assessment of diastolic dysfunction remains still rather elusive. Combining echocardiographic measures of left atrial volume with diastolic Doppler filling velocity can identify elevated LV filling pressure that is compensatory response to maintain cardiac output in heart failure regardless of LVEF.²⁷ Addition of exercise echocardiographic data ((E/e' ratio>14) offers improved sensitivity but decreased specificity, and it can thus be used to rule out suspected HFpEF.²⁸ RV dysfunction may also be seen. Left ventricular global longitudinal strain offers superior diagnostic and prognostic value compared with ejection fraction, is highly reproducible, and detects subclinical dysfunction before the ejection fraction declines.²⁹ Despite reductions of both longitudinal and circumferential shortening, the EF can be preserved in ventricles with thick walls and/or reduced EDV, and strain rate has been reported to reflect better systolic function in patients with preserved EF.³⁰ A new algorithm for estimating left ventricular filling pressure by echocardiography has been described.³¹ A consensus recommendation from the Heart Failure Association of the ESC for diagnosis of HFpEF has been presented.²⁶

Holter monitoring may be considered in patients who are being investigated for ventricular arrhythmias.

Cardiac magnetic resonance (CMR) provides the most accurate estimate of ventricular structure and function (Table 7, and Figure 5). The use of gadolinium contrast allows detection of inflammation and scarring. MRI-assessed 4D flow is a method for assessment of diastolic dysfunction,³² and CMR bicycle exercise imaging (RT-CMR) is a useful tool for the diagnosis of HFpEF in patients with diastolic dysfunction and dyspnea on exertion.³³ A physiological CMR model consisting of volumetric and functional metrics can accurately predict invasively measured PCWP and improves classification provided by standard TTE models.³⁴

Maximal exercise testing ideally with respiratory gas exchange analysis is useful to differentiate between cardiac or pulmonary limitation to exercise, and to determine functional class in patients who are candidates for cardiac transplantation or in whom the cause of

exercise intolerance is unclear. Peak oxygen uptake (peak VO_2), anaerobic threshold, and VE/VCO_2 slope (ventilatory response to exercise) are useful indicators of the functional capacity of the patient with prognostic significance.³⁵ Cardiopulmonary exercise testing, and invasive exercise testing may also be useful for the diagnosis of HFpEF.²⁶ An excessive rise of pulmonary capillary wedge pressure during exercise despite normal values at rest is associated with increased mortality and may be considered as early HFpEF.³⁶

Selected ion-flow tube mass-spectrometry (SIFT-MS) of exhaled breath samples (collected within 24 h of hospital admission and following an 8-h fast and before the administration of morning pharmacotherapy) has been proposed as a simple test that allows detection of patients with impending decompensation and development of acute HF.³⁷

Polysomnography to detect sleep apnoea should be considered for HFpEF.¹¹

Coronary angiography is indicated when the patient has angina or coronary artery disease is suspected.

Cardiac catheterization may also be needed when echocardiography is insufficient to define the severity of valve disease and/or pulmonary pressures.³⁸ Right heart catheterization allows cardiac output measurement by thermodilution which is more accurate than the oxygen uptake Fick method.³⁹

Myocardial ischemia and viability studies are required in ischemic patients in whom intervention is planned. Imaging modalities with comparable diagnostic accuracy are dobutamine echocardiography, nuclear imaging by SPECT and/or by PET, CMR with dobutamine and/or with contrast agents, CT with contrast agents.

Cardiac biopsy on a routine basis is not recommended in heart failure. It is only needed when specific cause is considered, mainly giant-cell myocarditis.

In NYHA III patients, home transmission of pulmonary artery pressure with an **implanted pressure sensor** has been found useful for guiding therapy and lowering hospital admission rates (CHAMPION trial).⁴⁰ New implantable haemodynamic monitors are also in development.⁴¹

Genetic Screening is indicated in patients in whom a genetic or inherited cardiomyopathy is suspected. In this case a family history should be performed, including at least 3 generations and ideally diagrammed as a family tree pedigree.⁴² Examples of signs and symptoms implicating possible genetic cardiomyopathy are presented in Chapter 36. Familial evaluation and genetic testing (and titin truncating variants) should also be considered in patients presenting with alcoholic cardiomyopathy.⁴³

Investigations for HF of suspected **ischaemic** or **arrhythmic** aetiology are presented in Figures 6 and 7.

Prognosis

Multivariable Risk Scores to Predict Development of Incident HF (such as the Framingham Heart Failure Risk Score, the Health ABC Heart Failure Score, the ARIC Risk Score, and the PCP-HF equations) have been developed.⁴²

Conditions associated with a poor prognosis in heart failure are as age, aetiology, NYHA class, LVEF, key co-morbidities (renal dysfunction, diabetes, anaemia, hyperuricaemia), and plasma natriuretic peptide concentration. Poor loop diuretics response is also associated with a worse prognosis.⁴⁴ Recovery of LV function (LVEF >50%) denotes a better prognosis, but still these patients may experience symptomatology and hospitalizations.⁴⁵ Lower pulse pressure (<53 mmHg) is an independent predictor of mortality in patients with LVEF<30% and systolic BP <140 mm Hg but not necessarily in those with preserved LVEF.⁴⁶ In an analysis of a large dataset has found that the relationship between survival and LVEF assessed by echocardiography in routine clinical practice is u-shaped. Patients with an LVEF of 60–65% have the lowest risk of mortality regardless of age, sex, or other relevant confounders. Patients with LVEF ≥65% had a higher all-cause mortality.⁴⁷

Several risk scores for predicting survival in heart failure, such as MACCIC (www.heartfailure.org), and AHA score (www.mdcalc.com/gwtg-heart-failurerisk-score) have been developed and their use is to estimate subsequent risk of mortality (AHA/ACC 2022 GL on HF, Ila B-NR). Peak VO₂ expressed as percentage of an age-predicted standard strongly predicts mortality and major cardiovascular events in patients with heart failure. Equations have been developed for the purpose of providing reference values for ppVO₂ based on age, sex, body mass, and other factors. The most commonly used are those of Wasserman-Hansen, and the recently derived FRIEND (Fitness Registry and the Importance of Exercise: A National Data Base) equation that is easier to apply and slightly better.⁴⁸

In patients with preserved or mildly reduced LVEF, VT/VF are strongly associated with mortality and appear to be a marker of disease severity rather than risk of sudden death.⁴⁹ The LIFE-Preserved model enables prediction of short-term and lifetime risk of HF hospitalization or CV death in patients with HFpEF.⁵⁰

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