Chronic Heart Failure

8

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8.1 Case Report

A 67-year-old man came to the emergency room of our hospital for worsened exertional dyspnea, orthopnea, increased fatigue during ordinary activities, swollen ankles and reduced urine output. He was affected by chronic nonischemic dilated cardiomyopathy. He reported on a progressively worsening of symptoms in the previous 15 days and a weight gain of about 6 kg.

Medical History and Cardiovascular Risk Factors

- In 2007 the patient underwent to the first hospitalization for heart failure with a diagnosis of nonischemic hypokinetic dilated cardiomyopathy (confirmed by a coronary catheterization). Since then he started a therapy with loop diuretic, beta-blocker, ACE inhibitor, and aldosterone antagonist.
- Since 2007 nowdays he underwent to several hospital admissions for acute exacerbation of heart failure.
- In 2013 a CRT-D has been implanted because of low ejection fraction (EF 25 %), LBBB (left bundle branch block), and persistent symptoms in NYHA functional class III despite optimized medical therapy. The ambulatory device follow-up highlighted some episodes of sustained ventricular tachycardia treated with overdrive or shock and episodes of atrial fibrillation. For these reasons he started a therapy with amiodarone and VKA (vitamin K antagonist: warfarin) therapies.
- Chronic renal failure.
- Hypertension.
- Benign prostatic hypertrophy.

Medications

Furosemide 50 mg at 8:00 am, metolazone 5 mg at 6:00 pm on alternate days, spironolactone 25 mg at 8:00 pm, metoprolol 25 mg at 8:00 am and 25 mg at 8:00 pm, warfarin according to INR, amiodarone 200 mg at 1:00 pm, dutasteride 0.5 mg at 8:00 am, and tamsulosin 0.4 mg at 8:00 pm. Allopurinol 150 mg ore at 8:00 pm and pantoprazole 20 mg ore at 7:00 am

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Vital Signs

- Temperature: 36.4 °C
- Heart rate: 70 bpm
- Blood pressure: 110/60 mmHg
- Respiratory rate: 20 breaths per minute (mild tachypnea)
- Oxygen saturation while breathing ambient air: 93 %

Physical Examination

- General: fatigued, short of breath, alert, awake, and oriented; well developed and well nourished
- Head, eyes, ears, nose, and throat: normocephalic, atraumatic, mucous membranes moist, extraocular muscles intact, pupils equally round and reactive to light and accommodation bilaterally, bilateral tympanic membrane intact, bilateral sclera anicteric, and no conjunctival injection
- Neck: supple, no jugular venous distention, no lymphadenopathy, and no carotid bruit
- Cardiovascular: regular rate and rhythm, laterally and down displaced apical impulse, S1 and S2 normal, S3 present (gallop rhythm), 3/6 systolic murmur at the cardiac apex and mesocardium, and no hepatojugular reflux
- Lungs: rales at auscultation at the bases bilaterally, mild wheezing, no rhonchi, no alterations in tactile fremitus, and normal percussion
- Abdomen: mild overweight, no pulsatile masses, normal bowel sounds in all four quadrants, no high-pitched or tinkling sounds, resonant to percussion, soft, non-distended/non-tender, no rebound or guarding, and no hepatosplenomegaly
- Extremities: no cyanosis or clubbing; mild peripheral edema of the ankles
- Neurologic: cranial nerves II through XII intact and, no focal deficit
- Psychiatric: normal affect, no hallucinations, normal speech, and no dysarthria
- Skin: intact, no rashes, no lesions, and no erythema

Which Are the Possible Precipitants for Heart Failure Decompensation?

- Inadequate dose/adherence to prescribed therapies
- Noncompliance with dietary restrictions (sodium and/or liquids, etc.)
- Acute myocardial ischemia
- Worsened valvular heart disease
- Arrhythmias (bradyarrhythmias or tachyarrhythmias)
- Exacerbation of chronic obstructive pulmonary disease with or without pneumonia
- Infections (pneumonia, influenza, etc.)
- Renal dysfunction
- Endocrine disorders (diabetes mellitus, hypo-/hyperthyroidism)
- Anemia
- Medications (nonsteroidal anti-inflammatory drugs, drugs with negative inotropic effect such as calcium channel blockers)

EKG

A routine EKG at rest was performed (Fig. 8.1).

Report: sinus rhythm, heart rate 72 bpm with atrium-driven biventricular pacing, QRS duration 160 msec.

Despite correct biventricular pacing (axis directed upper right), the QRS complex is wide. Several lead configurations have been tried assessing EKG and echocardiographic findings in order to find the best stimulation without success.

Routine Laboratory Tests

- Complete blood count: normal
- Cholesterol (total, HDL, LDL) and TG: normal
- Hepatic function (GOT, GPT, γ-GT, ALP, bilirubin): slight increase in transaminases

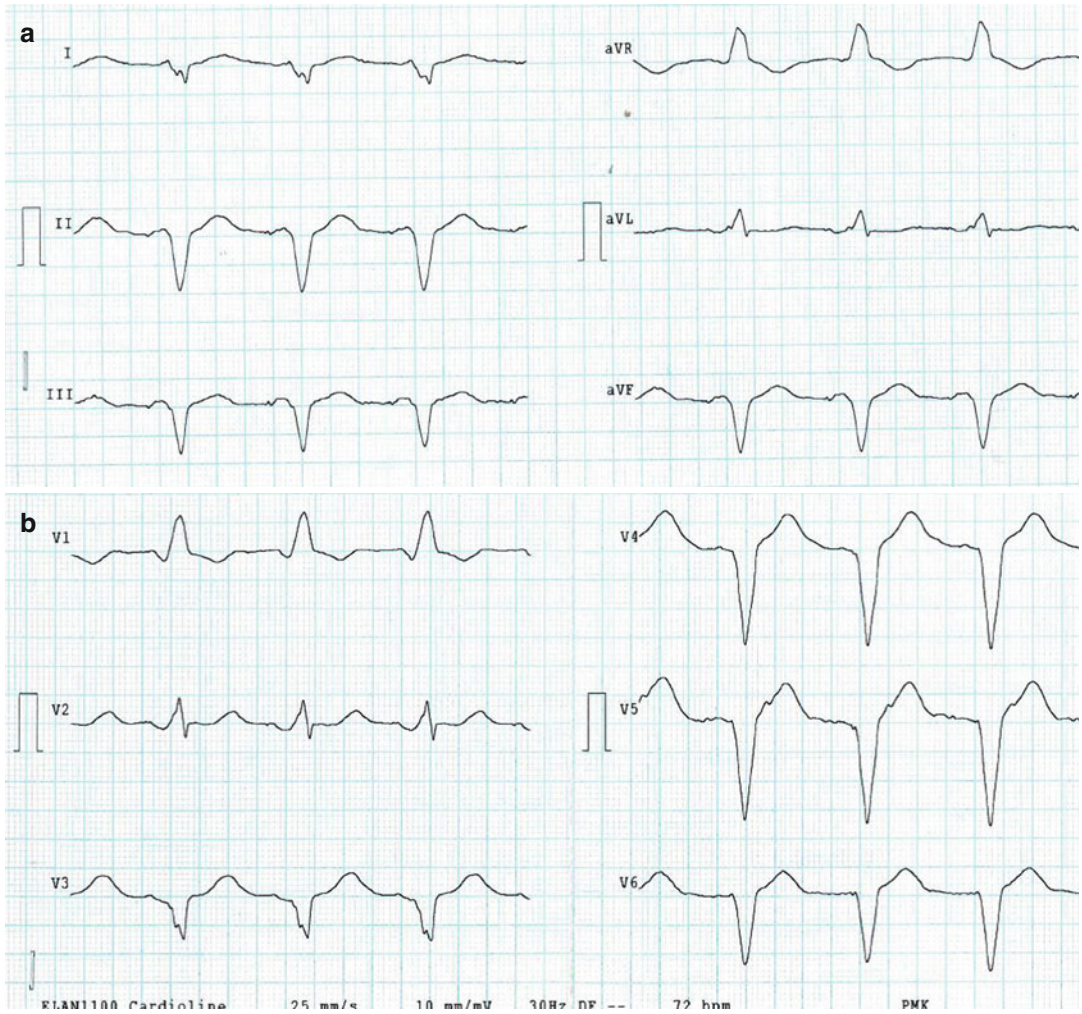

Fig. 8.1 (**a**, **b**) Routine EKG at rest. Despite correct biventricular pacing (axis directed upper right), the QRS complex is wide. Several lead configurations have been tried assessing EKG and echocardiographic findings in order to find the best stimulation without success

- Thyroid function (TSH, FT3, FT4): normal
- Renal function: creatinine 1.7 mg/dl (estimated glomerular filtration rate with the Cockcroft–Gault equation (GFR-CG) = 50 ml/min → moderate chronic kidney disease), BUN 55 mg/dl
- Electrolytes: mild hyponatremia 134 mEq/l and hypokalemia 2.1 mEq/l
- Fasting blood glucose: 194 m/dl (10.78 mmol/L)
- HbA1c: 6.8 % (50.8 mmol/mol)
- TnI-hs and CK-MB: normal
- BNP: 1,100 pg/ml

Chest X-Ray

A chest X-ray was performed too (Fig. 8.2). Cardiac shadow was slightly enlarged for an increase of cardiac transverse diameter. A left-sided pleural effusion was seen obliterating the costophrenic recess associated with a bilateral hilar enlargement with widespread bronchovascular marking and interstitial pulmonary congestion was presence of right ventricular and atrial leads and coronary sinus lead.

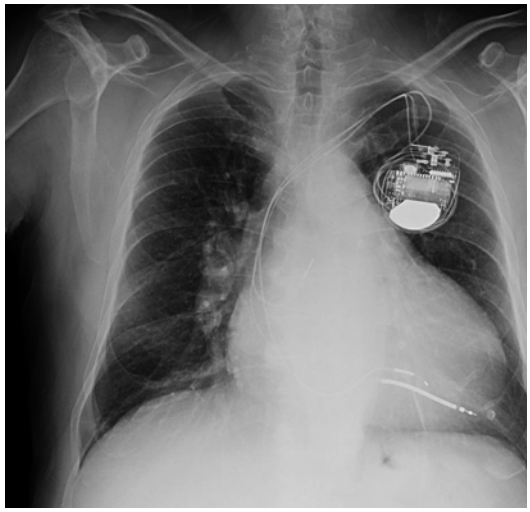

Fig. 8.2 Chest X-ray. The cardiac shadow is slightly enlarged due to an increase of cardiac transverse diameter. A left-sided pleural effusion obliterates the costophrenic recess and is associated with a bilateral hilar enlargement with widespread bronchovascular marking and interstitial pulmonary congestion. The presence of right ventricular and atrial leads and coronary sinus lead

Echocardiography

In order to complete the diagnostic process at admission, an echocardiography was performed.

- The left ventricle was severely dilated (indexed left ventricular end-diastolic volume (iLVEDV) 167 ml/m^2) with severe reduction of systolic function (ejection fraction measured with Simpson's biplane method = 25 %; stroke volume = 29.4 cc; cardiac output = 2.1 l/min; cardiac index = 1 l/m^2) and restrictive diastolic pattern. Moreover, filling pressures were increased (*E*/*E*' = 16).
- Right ventricle was slightly dilated and hypokinetic (basal diameter "RVD1" = 42 mm; tricuspid ring excursion "TAPSE" = 14 mm).
- Severe dilatation of both atria (LA diameter M-mode = 53.5 cm; RA area A4C = 34 cm^2).
- No pericardial effusion.
- The inferior vena cava was dilated without inspiratory collapse.
- The aortic valve was trileaflet and sclerotic.
- The mitral ring was dilated with moderate valvular regurgitation.
- There was evidence of massive tricuspid regurgitation with pulmonary hypertension (estimated PAPs of about 60 mmHg).

Clinical Course and Medical Therapy

- Furosemide: 40 mg t.i.d. (three times a day) intravenous boluses
- Slow-release potassium chloride: 1,200 mg b.i.d. (bis in die) per os
- Canrenoate potassium: 100 mg o.d. (once daily) intravenous boluses
- Saline 0.9 % continuous infusion 40 cc/h + KCl 40 mEq
- Dobutamine (250 mg/50 ml): 2 μg/kg/min continuous infusion
- Dopamine (200 mg/50 ml): 2 μg/kg/min continuous infusion
- Metoprolol: 25 mg b.i.d. per os
- Ivabradine: 5 mg b.i.d. per os
- Amiodarone: 200 mg o.d. per os
- Warfarin: according to INR
- Tamsulosin: 0.4 mg o.d. per os
- Dutasteride: 0.5 mg o.d. per os
- Pantoprazole: 20 mg o.d. per os

C-PAP therapy was administered (PEEP 7.5 mmHg, FiO2 0.5) with intermittent cycles of about 2 h.

After 48–72 h there was a significant loss of fluids supported by good diuresis. The patient reported improvement in dyspnea, and we observed a consistent reduction of ankle edema. The inotropic support was gradually discontinued. The laboratory tests showed a progressive increase of potassium values and reduced levels of BNP. The chest X-ray showed a reduced degree of pulmonary congestion, and the echocardiogram showed stable EF (0.25) associated with a small increase in cardiac index (1.3 ml/min/m^2) and a slight reduction of the PAPs (50 mmHg).

Once the patient reached an acceptable grade of compensation, he was proposed for the implantation of a left ventricular assist device as

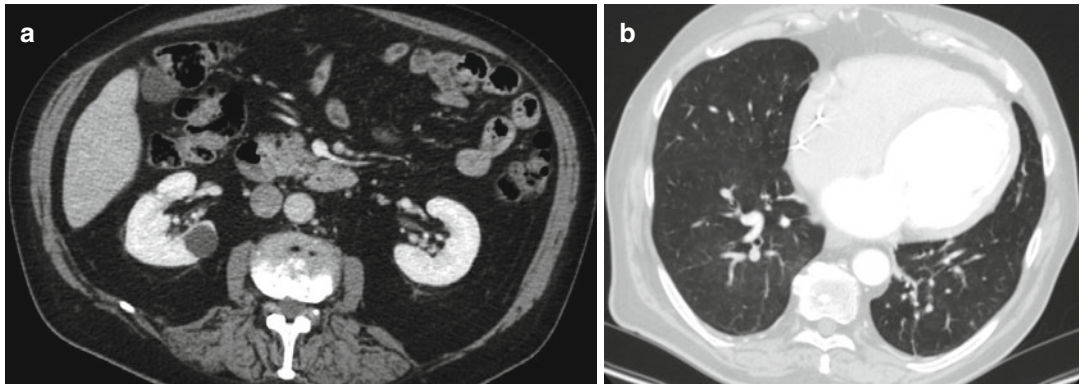

Fig. 8.3 (**a**, **b**) Chest–abdomen CT with contrast, with completely normal appearance

destination therapy. For this purpose the patient underwent to a new coronary angiography and chest–abdomen CT with contrast which were completely normal (Fig. 8.3a, b).

In order to perform a complete evaluation before the left ventricular assist device implant, we performed a right heart catheterization which showed:

- Normal pressures in the right atrium, right ventricle, pulmonary artery, and wedge
- Slight increase in total pulmonary resistance
- Arteriolar resistance at the upper limit of normal

By the investigations carried out during the hospitalization, the patient has been judged suitable for LVAD as a destination therapy and added to the waiting list at a referral center for the implant.

Until the LVAD implant, on top therapy to chronic heart failure including loop diuretic, aldosterone antagonist, ACE inhibitor, and beta-blocker, the patient underwent cyclic intravenous inotropic therapy.

8.2 Heart Failure

Definition

Heart failure (HF) can be clinically defined as a syndrome in which patients have typical symptoms (e.g., breathlessness, ankle swelling) and signs (e.g., elevated jugular venous pressure, pulmonary crackles) resulting from an abnormality of cardiac structure or function [1].

Chronic heart failure (CHF) can be caused by several types of cardiac dysfunction and is most commonly due to left ventricular dysfunction. An isolated right ventricular (RV) dysfunction is very rare, and generally RV involvement is secondary to left ventricular (LV) dysfunction.

Demonstration of an underlying cardiac cause is essential to diagnose HF as the precise pathology determines the specific treatment used. More recently, CHF has been classified into two categories: HF due to LV dysfunction even called HF with reduced ejection fraction (HF-REF or systolic heart failure) and HF where only a diastolic dysfunction is detectable called HF with preserved ejection fraction (HF-PEF or diastolic heart failure). 1 HF-REF is the best understood type of HF in terms of pathophysiology and treatment and is the focus of this chapter.

Furthermore, HF can present either as a chronic condition or acutely, occurring de novo, or as a decompensation of CHF. The purpose of this chapter is to cover CHF, while acute heart failure is discussed in another section of this book.

Epidemiology

CHF prevalence is 1–2 % of the population, and the prevalence increases to approximately 15 %

in the elderly [2]. At least half of patients with HF have a low EF, and approximately 50 % of patients with significant LV systolic dysfunction have no symptoms or signs of heart failure. HF occurs more frequently in male rather than female sex.

Etiology

The causes of CHF are listed in Table 8.1. There is a geographical variation regarding the etiology of CHF. In Western countries two-thirds are secondary to ischemic disease, and other important contributors are hypertension, valve disease, and alcohol. Rheumatic disease still remains the most common cause of CHF in the developing countries, while Chagas disease is frequent in South America.

Pathophysiology

Left ventricular dysfunction is associated with hemodynamic, autonomic, neurohumoral, and immunological changes.

The term "systolic dysfunction" refers to a decrease in myocardial contractility and consequently a decrease in cardiac output. Signs and symptoms of HF are due in part to compensatory mechanisms utilized by the body in an attempt to adjust for a primary deficit in cardiac output. Many of the processes involved in sustaining HF are maladaptive which means that they were originally designed to maintain blood pressure and vital organ perfusion.

Table 8.1 Causes of chronic heart failure

Coronary artery disease
Hypertension
Valve disease
Congenital heart disease
Infective: viral myocarditis, Chagas, HIV, Lyme disease
Alcohol
Toxins: anthracyclines or trastuzumab
Deficiencies: beriberi, thiamine
Hemochromatosis
Idiopathic
Familiar
Peripartum
Tachycardia induced
Infiltrative states: amyloid, sarcoid, endomyocardial fibrosis, hypereosinophilic syndrome
High output: AV fistulae, Paget's disease

Changes in Hemodynamics

Decrease of cardiac output leads to an increase of:

- Left ventricular end-diastolic pressure
- Pulmonary capillary wedge pressure

Based on the Frank–Starling law, the initial increase of left ventricular end-diastolic pressure is initially compensated by an increase of contractility, but as the increase persists, the myocardium fails and cardiac output drops.

Neurohumoral Changes

Neurohumoral adaptations, such as activation of the renin–angiotensin–aldosterone and sympathetic nervous systems by the low-output state, can contribute to maintenance of perfusion of vital organs in two ways:

- Maintenance of systemic pressure by vasoconstriction, resulting in redistribution of blood flow to vital organs
- Restoration of cardiac output by increasing myocardial contractility and heart rate and by expansion of the extracellular fluid volume

The principal neurohumoral systems involved in the response to HF are the sympathetic nervous system, the renin–angiotensin–aldosterone system (RAAS), and antidiuretic hormone [3, 4, 5]. One of the first responses to a decrease in cardiac output is activation of the sympathetic nervous system, resulting in both increased release and decreased uptake of norepinephrine at adrenergic nerve endings. The effects of high circulating concentrations of epinephrine and norepinephrine include:

- Increase in heart rate, blood pressure, and myocardial oxygen demand
- A toxic damage on the myocardium leading to cell apoptosis
- A downregulation of beta-1 receptors in the heart

The decrease of cardiac output leads to a reduction of renal afferent arteriolar blood flow causing secretion of renin and, subsequently, production of angiotensinogen and angiotensin I. The angiotensin I is then converted by the ACE present in the lung to angiotensin II. There is also evidence that angiotensin II can be synthesized locally at a variety of tissue sites including the kidney, blood vessels, adrenal gland, and brain [6].

Angiotensin II increases aldosterone release, inducing systemic and renal vasoconstriction. Furthermore, angiotensin II can act directly on myocytes and in the myocardium to promote pathologic remodeling as myocyte hypertrophy, re-expression of fetal protein isoforms, myocyte apoptosis, and alterations in the interstitial matrix. Aldosterone-mediated effects are sodium and water retention and hypokalemia resulting in pulmonary and peripheral edema and increased afterload. Activation of the carotid sinus and aortic arch baroreceptors by the low cardiac output in heart failure leads to enhanced release of antidiuretic hormone and stimulation of thirst. Elevated levels of ADH may contribute to the increase in systemic vascular resistance in HF via stimulation of the V1A receptor, which is found on vascular smooth muscle cells, and also promote water retention via the V2 receptor by enhancing water reabsorption in the collecting tubules. The combination of decreased water excretion and increased water intake via thirst often leads to a fall in the plasma sodium concentration. The degree of hyponatremia is an important predictor of survival in these patients.

The Natriuretic Peptide System

The increased LV and left atrium wall stretch due to raised left ventricular end-diastolic pressure leads to secretion of the natriuretic peptide hormones. The types of natriuretic peptide hormones which circulate in high concentration in HF are:

Brain natriuretic peptides

- BNP, the active peptide
- NT-proBNP, the inactive N-terminal fragment

Atrial natriuretic peptides (ANP and NT-ANP)
These peptides cause:

- Natriuresis
- Vasodilatation
- Offset in the activation of RAAS

Plasma ANP levels rise early in the course of the disease and have been used as a marker for the diagnosis of asymptomatic left ventricular dysfunction.

All these processes are responsible for sodium and water retention and a progressive depression of myocardial function. The last step of this fall is an adverse remodeling of the left ventricle involving myocyte hypertrophy, death, and fibrosis.

Diagnosis

Clinical Symptoms and Signs

The three most common symptoms and signs of HF are:

- Breathlessness
- Fatigue
- Peripheral edema

Breathlessness is induced by exercise, and only in case of advanced heart failure, it appears at rest. Symptoms that are more specific (i.e., orthopnea and paroxysmal nocturnal dyspnea) are less common, especially in patients with milder form of HF and who are, therefore, insensitive [7, 8].

Many of the symptoms of HF are nonspecific and do not, therefore, help discriminate between HF and other problems.

Symptoms are used to assign NYHA class to patients as listed in Table 8.2.

Table 8.2 Since many of the symptoms of HF are non-specific and do not, therefore, help discriminate between heart failure and other problems, patients are usually assigned an NYHA class

New York Heart Association functional classification based on the severity of symptoms and physical activity	
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations
Class VI	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased

Physical signs can be related to the presence of either fluid retention or poor cardiac output. They usually include:

- Elevated jugular venous pressure
- Orthopnea
- Hepatojugular reflux
- Third heart sound (gallop rhythm)
- Laterally displaced apical impulse
- Cardiac murmur
- Peripheral edema (ankle, sacral, scrotal)
- Wheezing, pulmonary crepitations
- Weight gain (>2 kg/week)
- Reduced air entry and dullness to percussion at lung bases (pleural effusion)
- Tachycardia
- Bloated feeling, irregular pulse
- Tachypnea (>16 breaths/min)
- Hepatomegaly
- Ascites
- Palpitations
- Tissue wasting (cachexia)

To diagnose HF both of the following criteria should be present:

- Symptoms and/or signs of heart failure
- Cardiac dysfunction at rest

The presence of cardiac dysfunction must be proved to make the diagnosis of heart failure.

As stated in the current guidelines 1, investigations that should be considered in *all patients* are:

- A 12-lead ECG, to determine heart rhythm, heart rate, QRS morphology, and QRS duration and to detect other relevant abnormalities. HF is rare in the presence of a normal ECG. The predictive value of the ECG is >90 %.
- Measurement of natriuretic peptide (BNP, NT-proBNP) to exclude alternative causes of dyspnea. If the value is within a normal range, HF is very unlikely. Natriuretic peptide measurement has an extremely high negative predictive value (>98 %).
- A chest radiograph (X-ray), to detect/exclude certain types of lung disease (e.g., cancer, asthma/COPD). It may allow also to identify pulmonary congestion/edema. A normal X-ray does not exclude a diagnosis of heart failure.
- Transthoracic echocardiography is the key exam in the diagnostic process of HF. It allows to evaluate cardiac structure and function, to measure LV ejection fraction, and to understand the cause of cardiac dysfunction.
- Measurement of blood chemistry (including sodium, potassium, calcium, urea/blood urea nitrogen, creatinine/estimated glomerular filtration rate, liver enzymes and bilirubin, ferritin/total iron blood capacity) and thyroid.
- A complete blood count to detect anemia, which may be a cause or effect of CHF.

Furthermore, only in case of clinical suspicions, the following investigations can be considered 1:

- Coronary angiography in patients with angina pectoris to evaluate the coronary anatomy
- Myocardial perfusion/ischemia imaging (echocardiography, CMR, SPECT, or PET) in patients thought to have CAD and who are considered suitable for coronary revascularization, to determine whether there is reversible myocardial ischemia or viable myocardium
- Exercise testing to detect reversible myocardial ischemia or as part of the evaluation of patients for heart transplantation and mechanical circulatory support, to aid in the prescription of exercise training, and to obtain prognostic information
- CMR imaging: recommended to evaluate cardiac structure and function, to measure LVEF, and to characterize cardiac tissue, especially in subjects with inadequate echocardiographic images or where the echocardiographic findings are inconclusive
- Left and right heart catheterization as part of evaluation process for heart transplantation or mechanical circulatory support, to estimate right and left heart function and pulmonary arterial resistance

Management

The goals of HF therapy are clinical relief of symptoms and a reduction in the risk of morbidity (including the rate of hospitalization) and mortality.

Management of HF begins with an accurate assessment of the underlying etiology, contributing factors, and severity of the syndrome. This is followed by a therapeutic regimen aimed at the following factors as well as addressing underlying and concurrent cardiovascular disease.

Treatment should address systemic contributing factors (e.g., thyroid dysfunction, infection, uncontrolled diabetes), as well as comorbidities such as chronic obstructive pulmonary disease and sleep apnea.

Recommendations for lifestyle modification are:

- Cessation of smoking
- Restriction of alcohol consumption
- Salt restriction (<2 g/day in patients with symptomatic HF)
- Fluid restriction (1.5–2 L/day) in patients with refractory HF, particularly those with hyponatremia
- Weight reduction in obese subjects
- Daily weight monitoring recommended to detect fluid accumulation
- Appropriate preventative care including pneumococcal vaccination and annual influenza vaccination

Review of Drugs

The drugs that now form the cornerstones in the management of HF are:

- Diuretics
- Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor antagonists (ARBs)
- Beta-adrenoceptor antagonists
- Mineralocorticoid receptor antagonist (MRA)
- Nitrate plus hydralazine
- Digoxin

Loop Diuretics

Loop diuretics are generally introduced first for fluid control in patients in overt HF. The goal is relief of signs or symptoms of volume overload, such as dyspnea and peripheral edema. In general loop diuretic therapy is based on furosemide, bumetanide, or torasemide. The aim is to use the

minimum dose necessary to render the patient euvolemic. The most common side effects are renal dysfunction, hypokalemia, hyponatremia, hyperglycemia, and gout.

The usual starting dose in outpatients with HF is 20–40 mg of furosemide or its equivalent. Subsequent dosing is determined by the diuretic response. In patients who are volume overloaded, a reasonable goal is weight reduction of 1.0 kg/day. If a patient does not respond, the diuretic dose should initially be increased to find the single effective dose, rather than giving the same dose twice a day.

Intravenous diuretics (either as a bolus or a continuous infusion) are more potent than their equivalent oral doses and may be required for unstable or severe disease.

Some patients can develop a "loop diuretic" resistance if they are treated for a long time. In this category of patients, it is useful to add a thiazide diuretic (i.e., metolazone 2.5–5 mg/day) instead of increasing the dose of loop diuretics (i.e., >80 mg b.i.d. furosemide) to block differing sites in the nephron and overcome the resistance.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Antagonists

ACE inhibitors or, if not tolerated, ARBs are typically initiated during or after the optimization of diuretic therapy. ACEi and ARBs were first used because of their vasodilatory effect in the treatment of HF. It was subsequently understood that their beneficial effects arise above all from the antagonism of the rennin–angiotensin system.

These drugs are now first-line agents for all patients with HF, and unless there are contraindications, their use should be considered mandatory in all patients. It has been proved that they reduce both mortality and morbidity in large randomized clinical trials with a relative risk reduction of 20–25 %.

ACEi and ARB must be used with caution in patients with significant renal dysfunction; moreover, ACEi can induce cough (5–10 %) and angioedema. ARB can be used in case of ACEi intolerance.

These drugs are usually started at low doses and then titrated. ACEi and ARBs with proven clinical efficacy in HF based on randomized clinical trials with their suggested dosing are listed in Table 8.3.

Table 8.3 Suggested dosage for ACEi and ARBs with proved clinical efficacy for HF based on randomized clinical trials

ACE inhibitors	**Starting dose (mg)**	**Target dose (mg)**
Captopril	6.25 t.i.d.	50 t.i.d
Enalapril	2.5 b.i.d.	10–20 b.i.d.
Lisinopril	2.5–5.0 o.d.	20–35 o.d.
Ramipril	2.5 o.d.	5 b.i.d.
Trandolapril	0.5 o.d.	4 o.d.
ARB	**Starting dose (mg)**	**Target dose (mg)**
Candesartan	4 or 8 o.d.	32 o.d.
Valsartan	40 b.i.d.	160 b.i.d.
Losartan	50 o.d.	150 o.d.

Beta-Adrenoceptor Antagonists

Beta-adrenoceptor antagonists are also mandatory in patients with HF. Beta-blockers are initiated after the patient is stable on ACE inhibitors, again beginning at low doses with titration to trial goals as tolerated. The beta-blocker trials in HF were carried out in patients receiving therapy with an ACE inhibitor; thus, the improvement in survival is additive to that induced by ACE inhibitors [9, 10]. They unequivocally reduce both mortality and morbidity in clinical trials with a 35 % relative risk reduction on average. They can be used in patients with COPD but are contraindicated in patients with significant reversible airway obstruction. Furthermore, they should be used with caution in patients with peripheral vascular disease even if there is not an absolute contraindication.

Drugs with proven efficacy in clinical trials and the approved doses are listed in Table 8.4.

Table 8.4 Beta-blockers with proven efficacy in clinical trials and approved dosages

Beta-blocker	Starting dose (mg)	Target dose (mg)
Bisoprolol	1.25 o.d.	10 o.d.
Carvedilol	3.125 b.i.d.	25–50 b.i.d.
Nebivolol	1.25 o.d.	10 o.d.
Metoprolol succinate (CR/XL)	12.5/25 o.d.	200 o.d.

Mineralocorticoid Receptor Antagonist (MRA)

Spironolactone and eplerenone, which compete with aldosterone for the mineralocorticoid receptor, prolong survival in selected patients with HF as demonstrated in randomized controlled trials [11].

MRAs are recommended to treat HF in patients who have NYHA functional class II and a left ventricular ejection fraction (LVEF) ≤30 % or NYHA functional classes III to IV and an LVEF <35 %, who can be carefully monitored for serum potassium and renal function. MRAs are also recommended for patients post ST elevation myocardial infarction who are already receiving therapeutic doses of ACE inhibitor, have an LVEF ≤40 %, and have either symptomatic HF or diabetes mellitus and who can be carefully monitored for serum potassium and renal function. The serum potassium should be <5.0 mEq/L and estimated glomerular filtration rate should be ≥30 mL/min per 1.73 m. The endocrine side effects of spironolactone result from nonselective binding to androgen and progesterone receptors; eplerenone has greater specificity for the mineralocorticoid receptor and therefore has a lower incidence of endocrine side effects (1 versus 10 % in clinical trials). Although eplerenone is associated with fewer endocrine side effects than spironolactone (i.e., painful gynecomastia), this advantage must be weighed against the marked difference in cost between the two drugs. It may be reasonable to begin with spironolactone (25–50 mg/day) and switch to eplerenone (25 and after 4 weeks 50 mg/day) if endocrine side effects occur. It is essential that serum potassium and creatinine be checked 1–2 weeks after starting spironolactone or eplerenone and periodically thereafter. Patients with poor renal function are particularly at risk for hyperkalemia. For these reasons they should be used with caution in elderly.

Table 8.5 Approved dosages for mineralocorticoid receptor antagonists

MRA	Starting dose	Target dose
Eplerenone	25 o.d.	50 o.d.
Spironolactone	25 o.d.	25–50 o.d.

The approved doses are listed in Table 8.5.

Other Drug Options

Ivabradine

It should be considered for patients in NYHA II–IV heart failure with a heart rate ≥70/min in sinus rhythm and LVEF ≤35 % despite treatment with evidence-based doses of:

- ACEi (or ARB)
- Beta-blocker
- MRA

It may be also considered for patients in NYHA II–IV heart failure with a heart rate ≥70/min in sinus rhythm and LVEF ≤35 % who are unable to tolerate beta-blockers (true asthmatics).

Hydralazine Plus Nitrates

In African-American population the addition of hydralazine plus oral nitrate therapy is recommended for patients with persistent NYHA classes III–IV and LVEF <40 % despite optimal therapy including a beta-blocker, ACEi (or ARB), MRA (if indicated), and diuretics. Although the evidence of benefit is stronger in blacks, the addition of hydralazine plus oral nitrate may be considered in non-blacks who have persistent NYHA class II or IV despite optimal conventional therapy.

Digoxin

Digoxin is given to patients with HF and systolic dysfunction to control symptoms (such as fatigue, dyspnea, and exercise intolerance) and to patients with atrial fibrillation to control the ventricular rate. As demonstrated in the DIG trial, 12 digoxin therapy was associated with a significant reduction in hospitalization for HF but no benefit in terms of overall mortality. Digoxin is indicated in patients with left ventricular systolic dysfunction (LVEF <40 %) who continue to have NYHA functional class II, III, and IV symptoms despite appropriate therapy including an ACE inhibitor, a beta-blocker, an aldosterone antagonist if indicated, and an additional diuretic if necessary for fluid control. The usual daily dose of digoxin is 0.125 mg or less, based upon renal function. Based upon the data from the DIG trial, the recommended serum digoxin concentration is maintained between 0.5 and 0.8 ng/mL.

It is a useful drug in patients with atrial fibrillation to reach an adequate rate control. It should be avoided in patients with ventricular arrhythmias.

Device Therapy

Device therapy in heart failure addresses two potential consequences of left ventricular dysfunction:

- Malignant arrhythmias that can lead to sudden death
- Ventricular dyssynchrony

Prevention of sudden death is an important goal in HF because heart failure is a pro-arrhythmogenic condition arising from combination of structural heart disease and electrolyte imbalance. Ventricular arrhythmias, from premature ventricular beats to ventricular fibrillation, occur in 80 % of patients with heart failure and cardiomyopathy. Up to 50 % of heart failure deaths are sudden cardiac death, usually arrhythmic.

Implantable Cardiac Defibrillators

Implantable cardiac defibrillators (ICDs) have revolutionized the management of heart failure. An ICD is an advanced form of pacemaker that can detect and treat arrhythmias. Several types of ICDs can be implanted: a single bipolar lead placed in the right ventricular apex or a dual-chamber device with a further atrial lead to improve detection of atrial from ventricular arrhythmias. ICDs use the following criteria to distinguish ventricular tachycardia or fibrillation:

- Rate detection zone.
- Rate stability based on the principle that ventricular tachycardia is a stable rhythm without a significant inter-beat variation.
- Sudden onset: ventricular arrhythmias usually have a sudden onset.

According to the current guidelines 1, recommendations for the use of ICDs in patients with HF are resumed in Table 8.6.

Resynchronization Therapy

Resynchronization therapy aims to address the problem of ventricular dyssynchrony in HF. Dyssynchrony is a complex phenomenon which occurs at three different levels:

- Electrical dyssynchrony considered as an intra- or interventricular conduction delay usually manifested as a left ventricular bundle branch block.
- Structural dyssynchrony results from disruption of the myocardial collagen matrix impairing and electrical conduction and mechanical efficiency.
- Mechanical dyssynchrony manifests as regional wall motion abnormalities leading to increased workload and stress, paradoxical septal wall motion, presystolic mitral regurgitation, and reduced diastolic filling times.

Cardiac resynchronization (CRT) typically uses leads in the right atrium, right ventricular

Table 8.6 Current guideline recommendations for the use of ICDs in patients with HF [1]

Recommendations	Recommendation class	Recommendation level
Secondary prevention An ICD is recommended in a patient with a ventricular arrhythmia causing hemodynamic instability, who is expected to survive for >1 year with good functional status, to reduce the risk of sudden death	IA	A
Primary prevention An ICD is recommended in a patient with symptomatic HF (NYHA classes II–III) and an EF ≤35 % despite ≥3 months of treatment with optimal pharmacological therapy, who is expected to survive for >1 year with good functional status, to reduce the risk of sudden death	IA	A
(i) Ischemic etiology and >40 days after acute myocardial infarction	IA	
(ii) Nonischemic etiology	IB	B

apex, and coronary sinus. CRT functioning will be discussed more in detail in a separate section of this book.

Based on the current guidelines 1, the current indications for CRT implant are listed in Table 8.7.

8.3 Management of Refractory HF

Although the majority of patients with heart failure due to systolic dysfunction respond to optimal medical therapy, some patients do not improve and usually experience rapid recurrence of symptoms. These patients have symptoms at rest and often require repeated prolonged hospitalizations. Specialized strategies are generally considered for these patients, including:

- Continuous or cyclic intravenous positive inotropic therapy with dobutamine or levosimendan
- Mechanical circulatory support
- Cardiac transplantation

Mechanical Circulatory Support

Mechanical circulatory support is a collection of technologies that can be used to offer short-or long-term ventricular assistance for patients with heart failure. They can be classified as follows:

Extracorporeal ventricular support (useful for a short-term time support)

- Intra-aortic balloon pump
- Pulsatile ventricular assist device (VAD)
- Non-pulsatile VAD

Extracorporeal membrane oxygenation (ECMO) → useful for a short-term time support

Intracorporeal ventricular assist devices → useful for a long-term time support

- Pulsatile VAD
- Non-pulsatile VAD
- Total artificial heart

The intentions to use these devices are resumed in Table 8.8.

Short-term devices are used in general in patients with acute heart failure or cardiogenic shock as BTD, BTR, or BTT, while long-term devices are generally reserved as BTT, or in some countries, as Italy, they are approved as DT. Continuous-flow VADs are by far the most commonly used long-term devices.

Cardiac Transplantation

Cardiac transplantation is the final intervention for patients who remain symptomatic despite optimal medical and device therapy. The patient selection

Table 8.7 Current indications for CRT implant

Recommendations for the use of CRT where the evidence is strong—patients in sinus rhythm with NYHA functional class III and ambulatory class IV heart failure and a persistently reduced ejection fraction, despite optimal pharmacological therapy		
LBBB QRS morphology CRT-P/CRT-D is recommended in patients in sinus rhythm with a QRS duration of 120 ms, LBBB QRS morphology, and an EF 35 %, who are expected to survive with good functional status for >1 year, to reduce the risk of HF hospitalization and the risk of premature death	I	A
Non-LBBB QRS morphology CRT-P/CRT-D should be considered in patients in sinus rhythm with a QRS duration of 150 ms, irrespective of QRS morphology, and an EF ≤35 %, who are expected to survive with good functional status for >1 year, to reduce the risk of HF hospitalization and the risk of premature death	II	A
Recommendations for the use of CRT where the evidence is strong—patients in sinus rhythm with NYHA functional class II heart failure and a persistently reduced ejection fraction, despite optimal pharmacological therapy		
LBBB QRS morphology CRT, preferably CRT-D, is recommended in patients in sinus rhythm with a QRS duration of ≥130 ms, LBBB QRS morphology, and an EF ≤30 %, who are expected to survive for >1 year with good functional status, to reduce the risk of HF hospitalization and the risk of premature death	I	A
Non-LBBB QRS morphology CRT, preferably CRT-D, should be considered in patients in sinus rhythm with a QRS duration of 150 ms, irrespective of QRS morphology, and an EF 30 %, who are expected to survive for >1 year with good functional status, to reduce the risk of HF hospitalization and the risk of premature death	II	A

Table 8.8 Terms describing various uses of mechanical circulatory support (MCS)

Bridge to decision (BTD)	Use of MCS in patients with drug-refractory acute circulatory collapse and at immediate risk of death to sustain life until a full clinical evaluation can be completed and additional therapeutic options can be evaluated
Bridge to candidacy (BTC)	Use of MCS to improve end-organ function in order to make an ineligible patient eligible for transplantation
Bridge to transplantation (BTT)	Use of MCS to keep a patient at high risk of death before transplantation alive until a donor organ becomes available
Bridge to recovery (BTR)	Use of MCS to keep patient alive until intrinsic cardiac function recovers sufficiently to remove MCS
Destination therapy (DT)	Long-term use of MCS as an alternative to transplantation in patients with end-stage heart failure ineligible for transplantation

for transplantation is very restrictive; indeed patients have to be able to face the major cardiac surgery and the massive immunosuppressive regime. Cardiac transplantation "is not a cure" but is "the last chance" even because 1 year mortality is approximately 17 % with a median survival of 10.9 years.

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