Cardiac failure: an update and the role of the pharmacist

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Abstract

Heart failure (HF) often occurs in patients who have more than one comorbidity, with resultant polypharmacy. Medication errors may occur, along with adverse interactions between medicines. This highlights the importance of the pharmacist as part of the multidisciplinary team in the management of HF. Many advances have been made in the way in which heart failure is classified, diagnosed, managed and treated. The body of knowledge is ever-expanding and hence the need for frequent review of treatment guidelines in light of the data emerging from ongoing research. This article focuses on elucidating some of the currrent strategies to manage and treat this condition. Certain associated pathological conditions and modalities are therefore beyond the scope of this article and the reader is advised to consult the the latest international guidelines for more detailed explanations of advanced treatment strategies, the cardiomyopathies, congenital heart defects, acute cardiac failure, and heart failure within the context of myocardial infarction, cardiac valve replacement surgery, coronary artery revascularisation and other specialised examples.

Keywords: cardiac or heart failure, cardiac output, stroke volume, ejection fraction, systolic dysfunction, LVEF, HF*p*EF, HF*r*EF, brain natriuretic peptide, NT-proBNP, ACE-inhibitor, ARB, ARNI, CCB, β-blocker

Introduction

At its simplest level, heart failure (HF) may be defined as a complex clinical syndrome, which is caused by impaired ventricular filling or contractility, and which typically manifests itself through varying degrees of dyspnoea, fatigue and oedema. Thus, heart failure (*syn.* cardiac failure, or CF) refers to the inability of the heart to meet the metabolic demands and blood flow requirements of the body. (Refer to Figure 1.) Lately, the term 'heart failure' is preferred over the term 'congestive heart failure' (CHF), because not all patients display signs of being oedematous or overloaded with fluid.[1,2]

Based on the left ventricular ejection fraction (EF)—a parameter that has been widely used as a determining factor for patient selection during clinical trials—there are two main categories of heart failure, namely:[1]

- HF with preserved ejection fraction (HF*p*EF), and
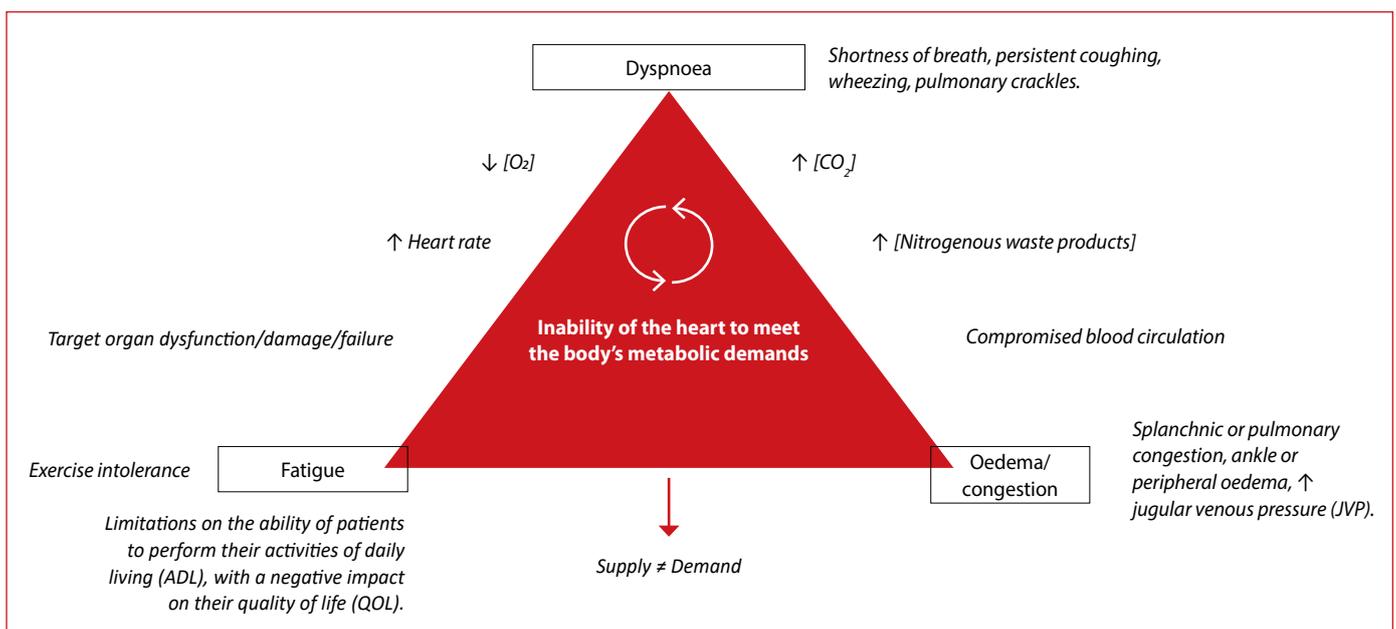- HF with reduced ejection fraction (HF*r*EF).

Figure 1: The heart failure 'triad' of dyspnoea, fatigue and oedema (patients do not always present with all three cardinal features in equal measure)[1,2]

The prognosis of HF remains poor, with more than 8% of adults admitted to hospital because of their deteriorating heart function, dying during their hospitalisation, and a third of those that have been discharged, may be expected to die within the ensuing 12 months. Thus, survival rates remain far from ideal.[3]

Brief epidemiology

The overall prevalence of adult HF in the global population is estimated to be around 1–2%. In the age group of 70 years and older, however, this number increases to around 10%, and roughly one third of the adult population will have a lifetime risk of developing heart failure by the age of 55 years. The condition is also known to affect men in a slightly higher percentage than women. In terms of admissions and complications pertaining to hospital emergency units, HF accounts for around 5% of all such cases.[3]

In addition, the ageing global population and improvements in the management of HF itself, combined with better survival rates following acute myocardial infarction, are expected to result in further increases in the prevalence and disease burden of this condition.[4,5] In terms of the absolute mortality rate, approximately half of all patients with HF will die within five years of being diagnosed.[1]

The pathophysiology of HF

The most prominent and defining feature of heart failure, is the inability of the heart to meet the metabolic demands and blood flow requirements of the body. There are multiple causes and a variety of underlying conditions that may be implicated in the pathophysiological mismatch between metabolic supply and demand, and this often complicates the approach to treatment.[2,3]

Once the heart starts to fail, and a resultant inability to adequately supply in the blood flow and metabolic demands of the body ensues, a number of physiological, compensatory mechanisms are invariably activated. These so-called **neurohormonal compensatory mechanisms** initially limit the harmful effects of the failing heart on the systemic blood circulation, but eventually these mechanisms will result in a downward spiral of worsening cardiac output (CO) and upregulated neurohormonal responses.[3]

Normal cardiac output, and the interplay between stroke volume (SV) and the EF, are explained in Figure 2.

There are three major compensatory mechanisms that become activated when the CO decreases, as well as a number of additional mechanisms that augment these responses. The three major mechanisms are:

- **The sympathetic nervous system (SNS):** Noradrenaline, together with dopamine and adrenaline, are called the catecholamines. They constitute three different products, derived from three different stages of the same enzymatic conversion process, which utilises the amino acid, tyrosine, as its base substrate. Adrenaline, the neurohormone of the sympathetic nervous system, is released into the bloodstream by the secretory cells of the adrenal medulla. The latter should be viewed as an enlarged and specialised sympathetic ganglion. About 10% of the medullary cells produce and secrete noradrenaline. Roughly 80% to 90% of these cells contain the additional enzyme phenylethanolamine N-methyltransferase, which converts noradrenaline to adrenaline and therefore releases adrenaline into the bloodstream during stressful conditions such as anxiety, fear, pain, physical trauma and exertion, a sharp decrease in environmental temperature, or decreased cardiac output. In the context of cardiac failure, SNS stimulation increases the blood pressure via a potent pressor effect on peripheral arterioles, increases HR and the force of myocardial contraction via the cardiac β_1-adrenoceptors, and acts as one of the trigger mechanisms for the activation of the renin-angiotensin-aldosterone system (RAAS).[2]

If a healthy adult male has a HR of 75 bpm and a stroke volume of 70 mℓ, then his cardiac output will be:

(CO = 75 bpm x 70 mℓ) = **5.25 ℓ of blood per minute.**

The heart rate in beats per minute (bpm).

Stroke volume refers to the volume of blood that is ejected by the left ventricle per contraction (~70 mℓ).

CO = HR x SV

Cardiac output refers to the volume of blood that is pumped by the heart (i.e. left ventricle) per minute (~5 ℓ).

EF = end diastolic volume – end systolic volume, expressed as a percentage

If the end-diastolic volume is 110 mℓ, and the SV is 70 mℓ, then the end-systolic volume will be 40 mℓ. Thus, 70 mℓ of the 110 mℓ has been expelled by the left ventricle (or 63.6 % of the end-diastolic volume) and this is the EF.

If the HR remains at 75 bpm, but the stroke volume drops to 45 mℓ, then his cardiac output will decrease to:

(CO = 75 bpm x 45 mℓ) = **3.38 ℓ of blood per minute.**

If the SV remains low, at 45 ml, but the HR increases to 90 bpm, then his cardiac output will increase to:

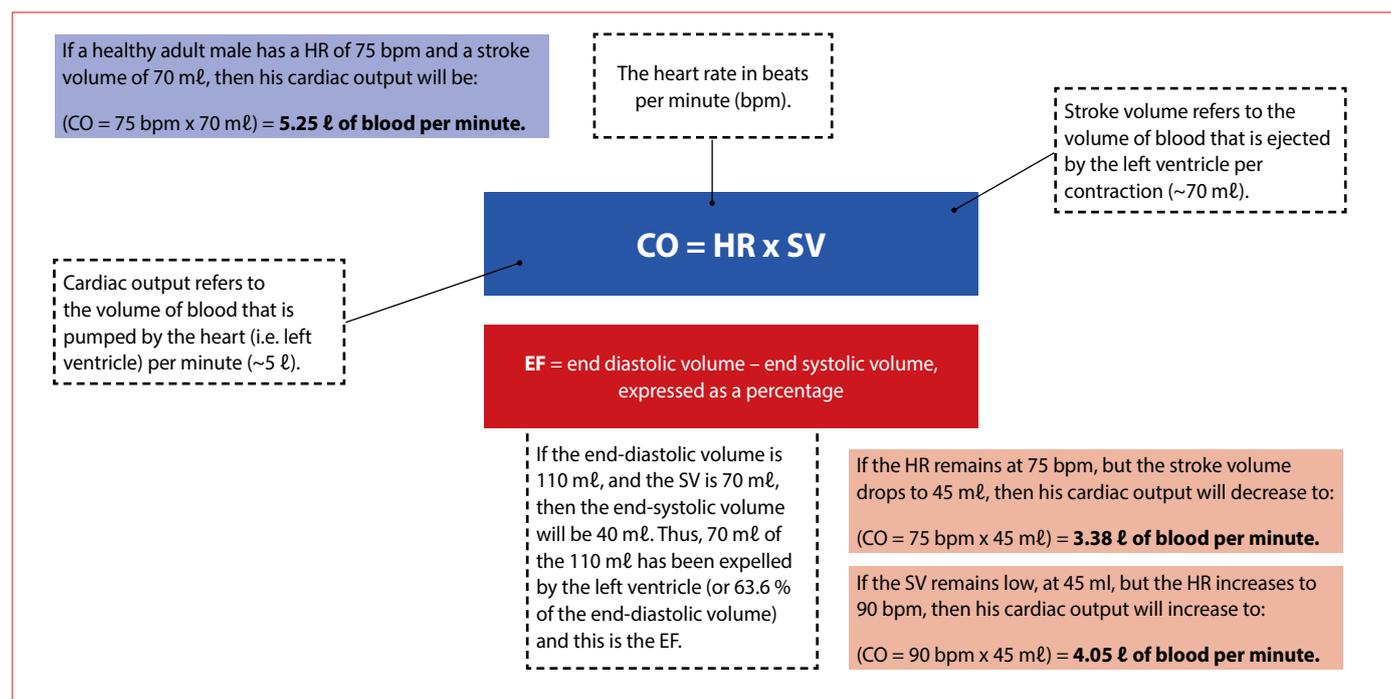(CO = 90 bpm x 45 mℓ) = **4.05 ℓ of blood per minute.**

Figure 2: Cardiac output (CO) and the interplay between stroke volume (SV), heart rate (HR) and ejection fraction (EF)
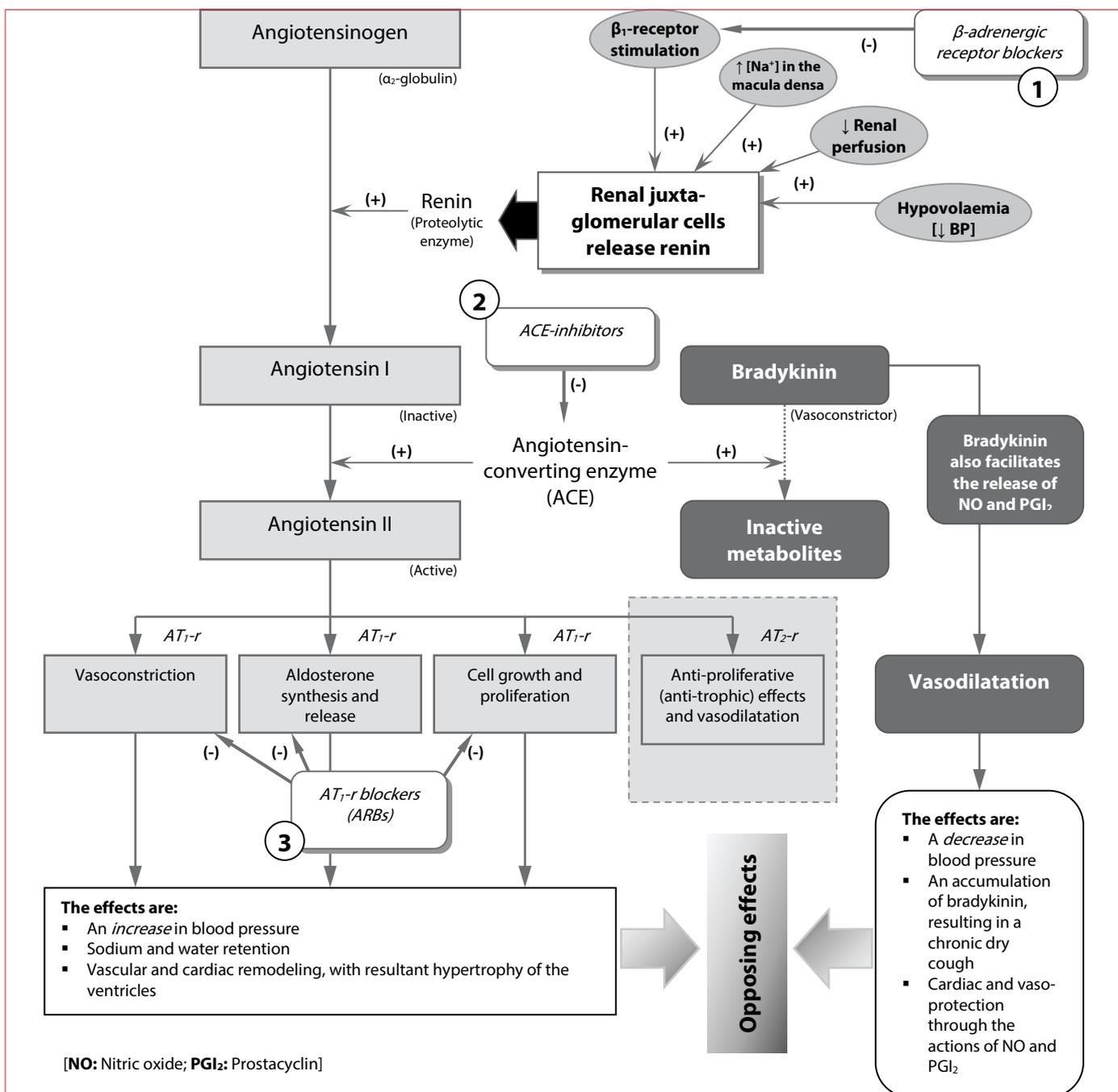
Figure 3: Diagram of the renin-angiotensin-aldosterone system (RAAS) showing the sites of action of (1) the β-adrenergic receptor blockers, (2) the ACE-inhibitors, and (3) the Angiotensin II AT1-receptor blockers (ARBs)[2]

- **The renin-angiotensin-aldosterone system (RAAS):** In patients with heart failure, it is the reduced renal perfusion that results in the activation of this intricate and potent compensatory mechanism. This results in a significant pressor effect, combined with sodium and water retention, and cardiac remodelling. Refer to Figure 3 for more details in this regard.[2,3]

- **The natriuretic peptide system (NPS):** The activation of the NPS actually serves to counteract the pressor effects of the SNS and the RAAS, as well as the accompanying sodium and water retention (via aldosterone release) and cardiac remodelling. The natriuretic peptides are released in response to an increase in ventricular (i.e. myocardial) wall tension.[3,6]

In the case of acute heart failure (AHF), which is the term used to refer to a new-onset or sudden worsening of existing signs and symptoms of heart failure, the characteristic clinical presentation is most often the result of significant congestion and fluid overload. The latter, in turn, is most likely the result of fluid redistribution within the body. AHF frequently requires urgent intervention. Acute congestion may have dire consequences on the normal functioning of multiple organs and organ systems in the body, including the lungs, intestines, liver, kidneys and heart.[7]

Underlying risk factors

According to the ACCF/AHA (American College of Cardiology Foundation/American Heart Association) Guideline for the

Management of Heart Failure, the major risk factors that are associated with the development of heart failure, are:[1]

- **Hypertension:** This is regarded as the *single most important modifiable risk factor* for the development of HF in the United States. Both systolic and diastolic hypertension require effective, long-term management to reduce the likelihood of the patient developing HF in the long run.

- **Diabetes mellitus:** Both obesity and insulin resistance are significant risk factors that will contribute to the development of heart failure.

- **Metabolic syndrome:** This syndrome requires any three of the following to be present in a given patient:
  - hypertension,
  - fasting hyperglycaemia,
  - low levels of HDL (high-density lipoprotein) cholesterol,
  - elevated triglyceride (TG) levels, or
  - abdominal obesity.

Effective management of the high blood pressure levels, dyslipidaemia (typically regarded as elevated total cholesterol, elevated low-density lipoprotein [LDL] cholesterol, elevated TG levels, and low HDL cholesterol levels), diabetes mellitus, and excess body weight, will lower the chances of such a patient developing heart failure.

- **Atherosclerotic disease:** Patients that are known to suffer from existing atherosclerotic disease, are at a much higher risk of developing HF, whether the atherosclerosis affects the peripheral, cerebral and/or coronary blood vessels. Coronary artery disease (CAD) or acute coronary syndrome (ACS) are definite risk factors for the development of heart failure.

Other factors to consider, which may lead to or contribute towards the development of heart failure, include general obesity, tobacco use, and exposure to agents that are known to be cardiotoxic (such as certain chemotherapeutic agents). In addition, uncontrolled heart rate, such as that seen in patients suffering from atrial fibrillation (AF), heavy alcohol use, the abuse of the recreational drugs cocaine and amphetamine, and in some patients, the presence of a genetic predisposition, are further examples of conditions that may lead to HF.[1]

Disease classification and severity

The classification of symptoms is often utilised in an attempt to grade the severity of a patient's condition. The most widely recognised functional classification system, is that of the New York Heart Association (NYHA) and is further illustrated in Figure 4.

In addition to the abovementioned NYHA functional classes, which are independent predictors of mortality,[1] there are a number of other classification systems for HF as well. Examples include the following:

- **The ACCF/AHA stages of HF:** According to this classification system, there are four stages, labelled A to D:[1]
  - **A:** The patient is at high risk, but without any structural heart disease or symptoms of HF.
  - **B:** Structural heart disease, but without signs or symptoms of HF.
  - **C:** Structural heart disease with prior or current symptoms of HF.
  - **D:** Refractory HF requiring specialised interventions.

  The treatment guidelines of the ACCF/AHA are based on these four stages. During stage A, the main aim is to modify the risk factors that are present, during stage B, to treat the structural heart disease, and during stages C and D, to try and reduce the associated morbidity and mortality.[1]

- **Left- and right-sided heart failure:** Irrespective of the ventricle, left or right, which was affected by the primary insult or underlying pathology, it is often inevitable that both ventricles will ultimately fail. This is referred to as biventricular failure.[3]

- **Systolic versus diastolic dysfunction:** The former refers to the existence of a primary dysfunction in the contractility or pumping mechanism of the ventricle, as opposed to a problem
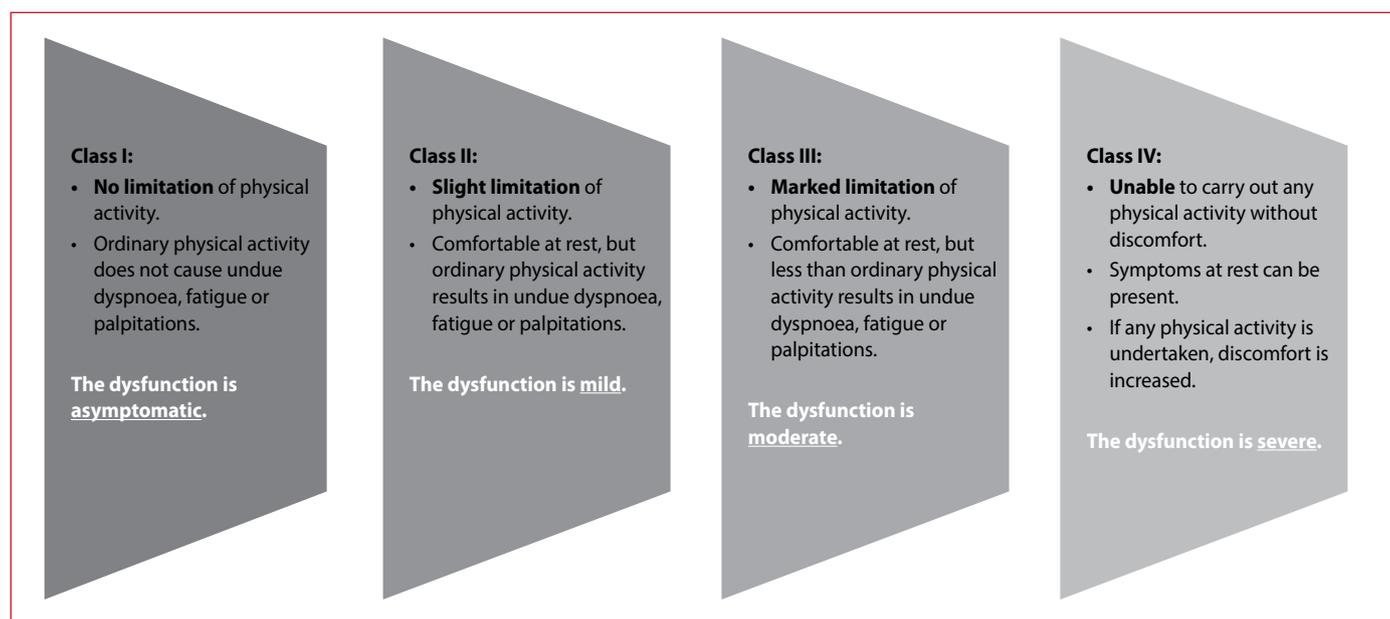
Class I:
- **No limitation** of physical activity.
- Ordinary physical activity does not cause undue dyspnoea, fatigue or palpitations.

The dysfunction is asymptomatic.

Class II:
- **Slight limitation** of physical activity.
- Comfortable at rest, but ordinary physical activity results in undue dyspnoea, fatigue or palpitations.

The dysfunction is mild.

Class III:
- **Marked limitation** of physical activity.
- Comfortable at rest, but less than ordinary physical activity results in undue dyspnoea, fatigue or palpitations.

The dysfunction is moderate.

Class IV:
- **Unable** to carry out any physical activity without discomfort.
- Symptoms at rest can be present.
- If any physical activity is undertaken, discomfort is increased.

The dysfunction is severe.

Figure 4: The stratified, functional classification of heart failure (Class I to IV) according to the New York Heart Association (NYHA)[1,3]

that exists with the relaxation or subsequent filling of the cardiac chamber during diastole.[3] It is also common to find some elements of diastolic dysfunction in patients that have been diagnosed by primary systolic dysfunction.[1]

- **HF with preserved ejection (HF*p*EF) fraction *versus* reduced EF (HF*r*EF):** The ejection fraction may be measured non-invasively through the use of transthoracic echocardiography (ultrasound) and represents the percentage of blood being ejected by the left ventricle during a single cardiac contraction. The normal range is 55–70%. Patients with HF*p*EF usually have an ejection fraction of ≥ 50%; conversely, in HF*r*EF, the EF typically falls below the 40% mark (≤ 40%). Those patients that fall within the 41–49% range, constitute an intermediate or borderline group (HF*p*EF, *borderline*) and would be managed more like HF*r*EF patients than like those with a preserved EF. Lastly, there is a subset of HF*p*EF patients that would have previously had HF*r*EF and that now show an improvement or recovery in their ejection fraction to above the 40% level. These latter patients are classified as being HF*p*EF, *improved*.[1,3]

Recent advances in our understanding of the pathophysiology of HR have refocussed our attention on the diversity of causes that could result in this chronic condition, with the ensuing prospect of multiple subsets of patients, and which points to the fact that not all cases of HF can be or should be treated in the exact same way. HF*p*EF can no longer merely be viewed as a diastolic dysfunction of the heart, and HF*r*EF has progressed from a rapidly fatal disease into a chronic condition that requires long-term treatment strategies and support.[5]

Diagnosing heart failure

Given the fact that HF is a clinical syndrome, certain characteristic signs and symptoms (refer back to Figure 1) allow for a comprehensive medical history, combined with a thorough physical examination of the patient, to be used to arrive at a diagnosis of heart failure based on the clinical judgement of the clinician. This may be augmented by diagnostic tests that are mostly aimed at identifying the underlying cause and quantifying the severity of the condition. Non-invasive echocardiography should form part of the clinical assessment of the patient.[3]

The use of biomarkers in diagnosing HF

There are two specific natriuretic peptides that play an important part in the diagnosis and ongoing monitoring of patients with heart failure, namely:

- B-type natriuretic peptide (BNP), with the 'B' referring to the brain, and
- N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Under normal circumstances, the heart continuously produces small amounts of $proBNP_{108}$, a 108-amino acid precursor peptide, which is subsequently cleaved to release the active hormone, called brain natriuretic peptide (BNP), and an inactive fragment, referred to as N-terminal pro-brain-type natriuretic peptide (NT-proBNP). BNP is secreted from both the atria and the ventricles, as opposed to atrial natriuretic peptide, and is primarily produced in response to increased tension within the myocardial walls. Various factors may, however, result in such an increased wall tension, but especially including heart failure with a reduced left ventricular

ejection fraction (LVEF). Elevated levels of BNP and NT-proBNP in this setting, are associated with poor outcomes. Clinicians should, however, also be aware of the fact that numerous other factors could potentially produce elevated levels of these biomarkers as well.[1,3,6]

A number of other, emerging biomarkers are currently being studied, or are awaiting validation, as well. Note that obesity may be associated with lower concentrations of the natriuretic peptides. In addition, it should also be noted that BNP (but not NT-proBNP, however) acts as a substrate for neprilysin, and this fact will have some significance in HF patients being treated with a neprilysin inhibitor (refer to the pharmacological treatment of heart failure).[8]

The role of the pharmacist in the pharmacological management of heart failure

Pharmacists may have multiple responsibilities in the care of HF, especially in a multidisciplinary team. This may differ from the different practice settings (inpatient vs outpatient) but a few services that may be rendered include medication reconciliation with associated patient medication education. This is important, especially in the geriatric population with polypharmacy. Equally important is providing pharmacotherapeutic recommendations and monitoring (including drug initiation, adjustment, and monitoring); early identification and prevention of adverse drug reactions and interactions; and improving medication adherence.

The two basic methodological approaches, from a pharmacological standpoint, to the management of HF, are to strengthen the force of myocardial contraction, and to decrease the cardiac workload. The latter, in turn, will decrease the myocardial oxygen demand. The increased workload is the result of failing myocardial contractility in the presence of compensatory sympathetic nervous system activity. This in turn results in tachycardia, improved myocardial contractility and increased peripheral resistance, and activation of the renin-angiotensin-aldosterone system (RAAS), which also causes vasoconstriction and an increased peripheral resistance, as well as sodium and water retention.[2]

Drugs that exert positive inotropic effects on the heart will strengthen the force of myocardial contraction to improve signs and symptoms of hypoperfusion, but this mechanism forces the myocardium to work harder and therefore increases its oxygen demand. Conversely, inhibition of the abovementioned neurohormonal pathways has the advantage of counteracting the detrimental effects of the compensatory vasoconstriction, increased peripheral resistance, and sodium and water retention seen in patients with chronic heart failure, without increasing myocardial oxygen demand. The positive inotropic agents are used in **acute settings** to maintain adequate vital organ perfusion.[2]

Drugs that strengthen the force of myocardial contraction

For myocardial contractility to increase (i.e. to produce a positive inotropic effect), the intracellular calcium-ion concentration needs to increase. In cardiac myocytes, cytosolic Ca^{2+} binds to troponin-C (one of the three subunits of troponin; the other two being troponin-I and troponin-T). The conformational change that follows then facilitates actin-myosin interaction, therefore allowing for the cardiac muscle to contract.[2]

DRUGS THAT CAUSE AN INCREASE IN INTRACELLULAR CALCIUM IONS[2]

- The cardiac or digitalis glycosides, such as digoxin, inhibit the Na^+-K^+-ATPase pump. This causes an accumulation of intracellular sodium ions. The sodium ions subsequently facilitate the intracellular movement of calcium ions through the sodium-calcium exchange mechanism.
- Digoxin also causes a heightened vagal nerve tone with subsequent negative chronotropic effects. It also has a direct negative dromotropic effect (i.e. it suppresses the SA-node, and also the conduction velocity through the AV-node). These effects oppose those of the sympathetic nervous system on the heart.
- Digoxin is also used in the management of atrial fibrillation (AF). It has a narrow therapeutic index and requires therapeutic drug monitoring.
- The β_1-receptor agonists, such as dobutamine, facilitate an increase in intracellular cAMP. This also causes the intracellular calcium ion concentration to be increased. Dobutamine and other suitable sympathomimetics are used in the management of acute cardiac failure where target organ perfusion is critically inadequate. Dopamine may also be used, especially in patients with low systolic blood pressure readings and cardiogenic shock. However, these drugs will also increase cardiac oxygen demand and myocardial workload.
- The phosphodiesterase (PDE) inhibitors, such as theophylline, also facilitate an increase in cAMP and subsequently of intracellular calcium ions. Theophylline is a non-selective PDE-inhibitor, as is caffeine. Milrinone (as well as amrinone) is an inhibitor of the PDE-3 isoform of phosphodiesterase. Furthermore, glucagon presents another way of achieving an increase in myocardial contractility through an increase in the synthesis of cAMP, and it is also especially useful in the treatment of a β-blocker overdose.

Drugs that decrease cardiac workload

Decreasing cardiac workload also decreases myocardial oxygen demand. Workload may be decreased through the dilatation of the veins, the arteries, or both. Venous dilatation will decrease central venous pressure, or CVP (i.e. cardiac preload), and dilatation of the arteries will decrease arterial blood pressure and peripheral resistance (i.e. cardiac afterload). However, facilitating selective arterial vasodilatation will elicit reflex tachycardia, due to the fact that the baroreceptors will interpret the drop in arterial blood pressure as hypovolaemia. This would be counterproductive when compared to the goals of the treatment plan.[2]

The most important aspect in the management of cardiac failure, however, is the **inhibition of the neurohormonal compensatory mechanisms** that give rise to the detrimental effects seen in patients with HF, such as fluid overload and oedema, hypoperfusion, and ventricular hypertrophy and cardiac remodelling. Cardio-selective β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and aldosterone antagonists may be employed to achieve an incremental neurohormonal inhibition. In addition, diuretics are used to manage the congestion and fluid overload.[2]

DRUGS THAT DECREASE THE CARDIAC PRELOAD[2]

- Diuretics: Hydrochlorothiazide is suitable for the treatment of chronic cardiac failure because its diuretic effects are not very potent. Furosemide is a powerful loop diuretic that lends itself to the management of acute heart failure, while spironolactone and eplerenone antagonise aldosterone and its effects on the distal convoluted tubule of the nephron. Spironolactone and eplerenone are therefore regarded as potassium-sparing diuretics (and aldosterone antagonists).
- Venous dilators: Morphine, glyceryl trinitrate and other organic nitrates reduce the cardiac preload through direct venous dilatation.

DRUGS THAT DECREASE THE CARDIAC AFTERLOAD[2]

- Hydralazine is a direct-acting arteriolar vasodilator and elicits reflex tachycardia. This makes it unsuited for use in the treatment of cardiac failure, unless it is combined with a nitrate such as isosorbide dinitrate, or a β-blocker.
- Sodium nitroprusside is also direct-acting but dilates both arterioles and veins. Therefore, it does not elicit reflex tachycardia. It has the ability to spontaneously release nitric oxide (NO) from its molecular complex.

DRUGS THAT ANTAGONISE THE NEUROHORMONAL RESPONSE[2,8]

- Through inhibition of the angiotensin-converting enzyme (ACE), the so-called ACE-inhibitors, such as enalapril and perindopril, antagonise the RAAS. This effectively eliminates the vasopressor effects of angiotensin II, and also the sodium and water retention caused by aldosterone. The latter may also be directly antagonised by spironolactone and eplerenone.
- Furthermore, the ACE-inhibitors dilate both the arterial and the venous vascular beds. This effectively prevents a reflex tachycardia as well.
- Always be mindful of the fact that the ACE-inhibitors can cause angioedema, and that they need to be used with caution, and under close supervision, in patients with low systemic blood pressure readings, elevated serum potassium levels, and compromised kidney functioning.
- The angiotensin receptor blockers (ARBs) act as selective antagonists at AT_1-receptors. Examples include losartan, valsartan and candesartan. The ARBs are associated with much lower incidences of angioedema and the bradykinin-induced dry cough that is typically associated with the ACE-inhibitors, but the same cautions apply in terms of the systemic blood pressure, serum potassium levels and renal insufficiency.
- The selective β_1-adrenoceptor antagonists, such as bisoprolol and metoprolol, as well as carvedilol (the non-selective β-blocker and α_1-adrenoceptor antagonist) may be used to counteract the effects of the sympathetic nervous system in patients with cardiac failure.
- Ivabradine is a selective, so-called *funny* current (I_f) inhibitor that acts on the sinoatrial node and produces a selective and effective slowing of the heart rate, both at rest, and during physical exertion—refer to the separate subsection in the body text for more details.
- The newest addition to this group is the co-called ARNI, or angiotensin receptor neprilysin inhibitor, valsartan/sacubitril. This is a fixed-dose combination drug that combines the ARB, valsartan, with the neprilysin inhibitor, sacubitril. The latter inhibits the enzyme, neprilysin, which is responsible for the degradation of the natriuretic peptides, adrenomedullin, bradykinin and other vasoactive peptides. This product should also be used with caution in patients with low systemic blood pressure or renal insufficiency and may also cause angioedema.
- The ARNI should not be used concomitantly with an ACE-inhibitor, or within 36 hours of the last dosage of an ACE-inhibitor that the patient might have received. It is also contraindicated in patients with a history of angioedema.

Treatment according to the ACCF/AHA stages A to D

The following is a brief synopsis of the main treatment recommendations per stage. (A detailed discussion does not fall within the scope of this article).

Stage A

Patients need to be optimally treated for their hypertension, dyslipidaemia, obesity and diabetes mellitus. Relevant and contemporary treatment guidelines need to be followed in this regard. In terms of hypertension, the following agents are known to be effective in helping to prevent HF in this setting: diuretic-based antihypertensive therapy, ACE-inhibitors, ARBs and suitable β-blockers. Patients need to be counselled in terms of other relevant risk factors, such as alcohol consumption, weight loss and the need to quit smoking. In the case of high blood pressure, both

systolic and diastolic hypertension need to be controlled in the long term. The aldosterone antagonists are indicated in patients with refractory hypertension.[1]

Stage B

Generally speaking, all of the abovementioned recommendations for stage A heart failure should be applied to stage B as well. In patients with stage B HF with a reduction in LVEF, the ACE-inhibitors or, if needed, suitable β-blockers, are the agents of choice to improve morbidity and mortality in this setting. Should the ACE-inhibitors not be tolerated, the ARBs may be used as effective substitutes.[1]

Stage C

Patients with symptomatic HF require a sodium-restricted diet. In addition, those suffering from sleep apnoea may benefit from a suitable treatment intervention. Other measures that may warrant more serious consideration and that may have been deemed unnecessary in asymptomatic HF patients, include effective weight management, exercise training or regular physical activity, and the use of a cardiac rehabilitation programme, if indicated.[1]

Wherever appropriate, the pharmacological measures listed for stage A and B patients will also apply to stage C. To reduce morbidity and mortality in these patients, the following options may be utilised to achieve the goal of inhibiting the RAAS:[1,8]

• ACE-inhibitors, or ARBs, or an ARNI (i.e. an angiotensin receptor neprilysin inhibitor), in conjunction with

• an evidence-based β-blocker, and

• in selected patients, the addition of an aldosterone antagonist.

Selected and treatment-resistant patients should be evaluated for the need to add additional drugs to their treatment regimen, such as loop diuretics, digoxin, hydralazine, isosorbide dinitrate, anticoagulants, statins, a suitable second-generation calcium-channel blocker (i.e. amlodipine), etc. It is also recommended that symptomatic HF patients receive an omega-3 polyunsaturated fatty acid (PUFA) supplement, unless otherwise contraindicated.[1]

Another potential treatment option is the I_f channel inhibitor, ivabradine—see further down in the text, as well as the relevant text box, for more details.

Stage D

These are patients with advanced, refractory or end-stage cardiac failure, with a persistently increasing severity of their condition. The management of these severely ill patients does not fall within the scope of this article. Nevertheless, a few important measures or considerations that these patients will require are as follows:[1]

• Fluid restriction in the range of 1.5 to 2 litres per day.

• Inotropic support to preserve the functioning of their vital organs.

• The use of mechanical circulatory support, such as a ventricular assist device (VAD).

• In the case of very carefully selected and eligible patients, a heart transplantation is the ultimate treatment option for end-stage cardiac failure.

Ivabradine and heart failure

Ivabradine offers a different mechanism of action to many of the more traditional treatment approaches to heart failure. Ivabradine is a selective inhibitor of the I_f ion channel found in the cardiac pacemaker cells of the sinoatrial (SA) node. Ivabradine selectively blocks cardiac pacemaker cell I_f or *'funny'* current and exerts significant inhibition thereof at concentrations that do not affect other cardiac ionic currents.[9] Myocardial contractility and atrioventricular conduction are maintained while heart rate, both at rest and during exercise, is reduced.[10]

The I_f current is a mixed Na^+-K^+-inward ionic current, activated by hyperpolarisation, which determines the slope of the diastolic depolarisation, and in turn controls the rate at which the heart beats. It is one of the most important ionic currents for regulating pacemaker activity in the sinoatrial node.[11]

Ivabradine is an effective antianginal and anti-ischaemic drug, not inferior to the β-blocker, atenolol, and the calcium-channel antagonist (CCA), amlodipine.[12] It reduces the frequency of angina attacks and increases the time until the symptoms of angina start to appear during exercise or physical exertion. Ivabradine is not linked to the typical adverse reactions that are associated with the β-blockers or other antianginal drugs, because of its exclusive chronotropic effect (i.e. selectively lowering the heart rate).[12] In addition, it is indicated to reduce the risk of hospitalisation, for worsening heart failure, in patients with stable, symptomatic, chronic heart failure that are in sinus rhythm with an acceptable resting heart rate, and that are either on maximally tolerated dosages of β-blockers as well, or that have a contraindication to β-blocker use.[12,13]

Results from the SHIfT (Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial) trial were published in 2010. SHIfT evaluated heart rate reduction through the direct sinus node inhibition of ivabradine. It was a multinational, randomised, placebo-controlled, parallel-group clinical trial in patients with moderate-to-severe heart failure and left-ventricular systolic dysfunction (with a 35% or lower LVEF, in sinus rhythm and with a heart rate of at least 70 beats per minute).[14] It was the first study conducted to assess whether heart rate reduction by direct sinus node inhibition can decrease cardiovascular outcomes in patients with chronic heart failure and left ventricular systolic dysfunction.[10] It was found that ivabradine substantially reduced the major risks associated with heart failure when combined with guideline-based treatment.[14]

The importance of heart rate in the pathophysiology and clinical course of heart failure was confirmed by the SHIfT study. The beneficial effects of heart rate lowering with ivabradine have therefore been demonstrated by this study.[10,14]

Sacubitril and valsartan combination therapy

Sacubitril is the first in a new class of therapeutic agents to be made available on the local market. It is a neprilysin inhibitor and is currently available in combination with the angiotensin receptor blocker (ARB), valsartan. It is presently indicated as second-line treatment option for symptomatic HF, Class II, III or IV on the NYHA classification system, with systolic dysfunction.[1,8,13]

A previous neprilysin inhibitor, omapatrilat, also acted as an inhibitor of ACE and of aminopeptidase P, but its clinical development was halted due to concerns regarding the high incidence of angioedema associated with this drug. The ARNI is therefore contraindicated in patients with a history of angioedema.[8]

Non-pharmacological interventions

As mentioned in the previous section, a number of non-pharmacological measures form part of the treatment guidelines for heart failure. These include, but are not necessarily limited to:[1]

• Avoiding excessive alcohol consumption and the use of recreational drugs.

• Quitting the smoking habit (and/or other forms of tobacco use).

• Eating a healthy diet (with a firm sodium restriction where needed) and losing excess body weight.

• Sleep disorders are quite frequently observed in patients with heart failure, with more than 60% of adults with chronic HF having been found to suffer from either central or obstructive sleep apnoea. These patients may benefit significantly from the use of a device to provide continuous positive airway pressure, or CPAP, during the night.

• Lastly, a number of invasive cardiac procedures, including coronary revascularisation, as well as mechanical devices, such as the implantable cardioverter-defibrillator (ICD) or the use of cardiac resynchronisation therapy (CRT), may be employed in the management of selected patients with cardiac failure.

Conclusion

HF patients have complex medication regimens that require the expertise of pharmacists and other lifestyle modifications within the multidisciplinary team. The interventions of the pharmacists may include medication reconciliation, educating patients and other healthcare professionals on their medications, which may collectively lead to a reduction in medication errors and drug interactions.

Further to this the article provided a basic overview of the current trends and guidelines in the management of heart failure, including its classification, diagnosis, monitoring and treatment. According to the latest international guidelines, the most important differentiation in the setting of HF, is to determine which patients have HF*p*EF as opposed to HF*r*EF. The basis of HF treatment starts with the correct classification or grading of the severity of the patient's condition, the identification and management of modifiable risk factors, and then, the initiation of appropriate measures that are aimed at counteracting the detrimental effects of the neurohormonal response towards the mismatch in metabolic supply and demand, which is brought about by a failing heart.

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