Heart failure: not a single organ disease but a multisystem syndrome

Heart failure is not simply a single organ disease; rather it is a complex multi-system clinical syndrome, with impairment of endocrine, haematological, musculoskeletal, renal, respiratory and vascular systems, which influence morbidity and mortality.

Heart failure is defined as 'a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood' (Dickstein et al, 2008). For the purposes of this review, heart failure refers to chronic left ventricular systolic dysfunction – heart failure.

It is well known that heart failure leads to dyspnoea, oedema, fatigue, frequent hospitalizations and premature death. Yet heart failure is not simply a single organ insult but rather a multifaceted syndrome which can result in impairment in 'peripheral vascular function, skeletal muscle physiology, pulmonary dynamics, neurohormonal and reflex autonomic activity, and renal sodium handling' influencing morbidity and mortality (Hunt et al, 2009).

This review discusses the involvement of other body systems within the heart failure syndrome, possible pathophysiological mechanisms, clinical utility and consequences.

Vascular system

Derangement of the vascular endothelium, or endothelial dysfunction, is instigated by risk factors for vascular disease, common in heart failure. This dysfunction refers to an imbalance of the factors regulating vasodilation and vasoconstriction, specifically a reduction in nitric oxide, leading to vasoconstriction, increased peripheral resistance and increased afterload. There are various ways of measuring endothelial function, including non-invasive and invasive, typically before and after a shear stress stimulus is applied, to stimulate the endothelium. Non-invasive measures include flow-mediated dilation, plethysmography, tonometry assessing the change in the calibre of the artery or pulse wave analysis which assesses changes in arterial stiffness. Invasive measures include assessing biomarkers of endothelial function such as selectins or von Willebrand factor.

The exact mechanism for endothelial dysfunction in heart failure is unclear, but it is believed to be the result of a combination of decreased activity of L-arginine–nitric oxide synthetic pathway, increased degradation of nitric oxide by reactive oxygen species, and hypo-responsiveness in vascular smooth muscle (Katz et al, 2005). Nitric oxide-dependent endothelial dysfunction is further impaired during exercise (Katz et al, 1996). This relates to earlier work in terms of reduced nutritive blood flow to skeletal muscle and explains why such patients become breathless on exertion, as tissue demand exceeds supply.

Endothelial dysfunction in heart failure independently predicts morbidity and mortality (Fischer et al, 2005). This is believed to be a consequence of endothelial dysfunction leading to 'increased arterial stiffness and reduced compliance, increase ventricular afterload and left ventricular end-diastolic stress and enhance dilation and failure' (Meyer et al, 2005).

Endothelial function in heart failure can be improved by drugs such as allopurinol, omega-3 polyunsaturated fatty acids and exercise, but studies have examined only an improvement in endothelial function, not effects on morbidity or mortality (Hornig et al, 1996).

Endothelial function is not measured in routine clinical practice, as it requires considerable time, staff and running costs. Until evidence suggests that measurement will alter clinical practice, it will remain of academic interest only.

Musculoskeletal system

Weight loss in heart failure, termed 'cardiac cachexia', has been identified as being an independent risk factor for death (Anker et al, 1997). Similarly, the muscle hypothesis of heart failure (*Figure 1*) proposes that 'exercise performance in heart failure patients is predominantly limited by skeletal muscle and less by the performance of cardiac muscle' (Coats et al, 1994). Indeed, there is a paucity of evidence to suggest that resting measures of left ventricular function have any correlation with functional capacity such as functional class (Senden et al, 2004). Perhaps then,

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it is not weight loss per se that determines heart failure morbidity, but rather heart failure-induced sarcopenia, defined as a reduction of both muscle mass and function.

Specifically, heart failure leads to a reduction in skeletal muscle power, mitochondrial number, surface density of cristae and enzyme activity such as 3-hydroxyacyl-CoA-dehydrogenase, slow twitch type II fibres and aerobic metabolism, all leading to a loss of skeletal muscle performance (Mancini et al, 1992; Mettauer et al, 2001). The degree of metabolic abnormality within skeletal muscle correlates well with the severity of heart failure and it is believed that sarcopenia is a consequence of increased oxidative stress and disuse which leads to skeletal muscle atrophy (Andrews et al, 1997).

Measurement of sarcopenia, by maximal grip strength for example, enables stratification according to functional class, peak oxygen consumption (VO_2) and prognosis. A combined resistance and aerobic exercise programme leads to clinical improvements in physical functioning and quality of life (Gary et al, 2011).

Consideration should be given to measuring sarcopenia in the rehabilitation of patients with heart failure, which along with 6-minute walk distance, will demonstrate tangible gains in physical functioning and rehabilitation success. Prolonged inactivity, bed rest or hospitalization should be avoided when treating patients with heart failure, as these may augment sarcopenia and exacerbate symptoms of breathlessness.

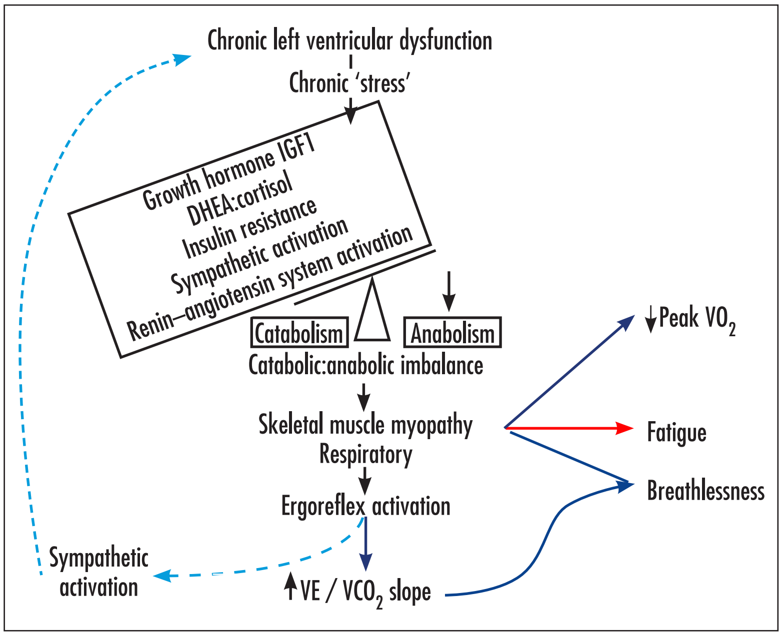


Figure 1. The muscle hypothesis of heart failure symptoms. DHEA = dehydroepiandrosterone; IGF1 = insulin-like growth factor 1; VCO_2 = carbon dioxide production; VE = ventilatory equivalents; VO_2 = oxygen consumption.

Immune system

C-reactive protein

An inflammatory insult leads to the recruitment of the non-specific and innate immune system, known as the acute phase response. At the area local to the insult, cytokines such as interleukins and tumour necrosis factor are released from inflammatory cells, which stimulate the liver to produce acute phase reactants such as fibrinogen, ferritin, serum amyloid A and C-reactive protein. These have wide-ranging effects on coagulation, vascular permeability and the immune system. In particular, C-reactive protein binds to phosphocholine on the cell membrane of necrotic and apoptotic cells, which in turn activates the complement system, facilitating cell opsonisation, lysis, chemotaxis and removal of the dying cells. The normal range of C-reactive protein in healthy adults is <5 mg/ml and of high sensitivity C-reactive protein is <1 mg/ml.

Heart failure is an inflammatory condition leading to elevation of C-reactive protein levels, which is an independent prognostic marker and correlates with the functional class, symptoms and ongoing myocardial injury (Alonso-Martínez et al, 2002; Sánchez-Lázaro et al, 2008; Nakagomi et al, 2010). While the mechanism is unknown, it has been postulated that 'left ventricular dysfunction, hepatic or renal organ damage induced by low cardiac output, hypoperfusion, hypoxia, and venous congestion may all be sources of increased interleukin-6 and hence C-reactive protein production' (Anand et al, 2005).

In patients with heart failure, elevated levels of C-reactive protein improve with cholesterol-lowering agents, e.g. rosuvastatin, and β-blocker therapy, e.g. carvedilol, and by extension it is believed these agents may have an anti-inflammatory action (Nagatomo et al, 2007; McMurray et al, 2009). However, it remains unclear what effect simply lowering C-reactive protein has, over and above the known benefits of β-blockade and plaque stabilization.

At present, there is insufficient evidence of clinical benefit to warrant routine testing in heart failure patients.

Hyperuricaemia

Uric acid is an end product of cellular breakdown in a hypoxic environment. This results in purine bases from deoxyribonucleic acid such as adenosine, being converted into hypoxanthine, xanthine and finally uric acid by xanthine oxidase, which is then excreted in urine. The normal range of serum uric acid in healthy adults is 200–430 umol/litre in men and 140–360 umol/litre in women.

Patients with heart failure are at risk of hyperuricaemia for several reasons; medications such as diuretics reduce its renal excretion, comorbidities including chronic kidney disease, diabetes and hypertension are associated with a higher incidence of hyperuricaemia and as a consequence of chronic inflammation with 'activation of xanthine oxidase, through free radical release, causing leukocyte and endothelial cell activation' (Leyva et al, 1998).

Uric acid impairs nutritive blood flow, and predicts left ventricular filling pressures, haemodynamic compromise, deterioration and death in heart failure (Kittleson et al, 2007; Krishnan, 2009; Amin et al, 2011). Xanthine oxidase inhibitors, which reduce uric acid, improve peripheral blood flow and natriuretic peptides (Doehner et al, 2002).

Measurement of uric acid has been incorporated into the Seattle heart failure model because of its recognized independent power in predicting mortality (Mozaffarian et al, 2007). The model provides an accurate estimate of 1-, 2-, and 3-year survival with the use of easily obtained clinical, pharmacological, device and laboratory characteristics (https://depts.washington.edu/shfm/index.php). While reductions in uric acid have correlated with improvements in biomarkers, there is no evidence that targeting uric acid leads to improved clinical outcomes (Gavin and Struthers, 2005).

By virtue of its inclusion in the Seattle heart failure model (*Figure 2*), the routine measurement of uric acid in clinical practice should be considered to inform decision-making and prognosis in patients with heart failure.

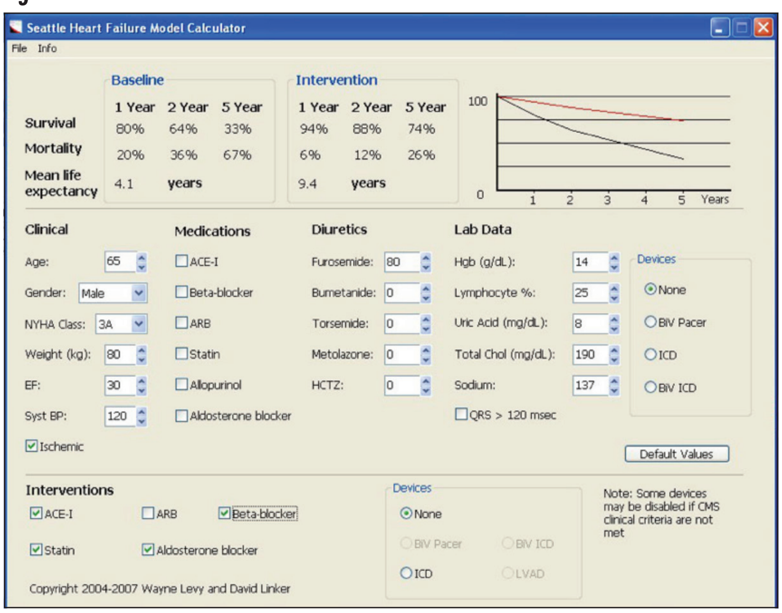
Endocrine system

Hyperparathyroidism

Parathyroid hormone is a polypeptide comprising 84 amino acids, secreted by the chief cells of the parathyroid glands in response to low circulating levels of both calcium and magnesium. Parathyroid hormone indirectly stimulates osteoclasts within bone, increasing bone turnover and raising serum calcium levels, which reduces secretion via negative feedback. It also acts to reduce the resorption of phosphate from the proximal convoluted tubule of the loop of Henle, so reducing calcium retention and lowering serum phosphate levels.

The normal reference range of parathyroid hormone is 15–65 pg/ml and elevated levels are classified into three categories, based on aetiology and calcium level; primary, secondary and tertiary. Of particular interest is secondary hyperparathyroidism, which refers to elevated levels of parathyroid hormone and low or normal calcium levels as a result of a cause originating outwith the parathyroid gland, e.g. kidney disease or heart failure. This is an independent risk factor for hospitalization, worsening morbidity and mortality in heart failure (Hagstrom et al, 2010). The epidemiology of secondary hyperparathyroidism in heart failure is unknown.

Figure 2. The Seattle heart failure model.



Elevated parathyroid hormone levels may 'promote vascular pathology leading to atherosclerosis and ischaemic heart failure but also distinct cardiac pathology, such as myocardial calcification, fibrosis, and hypertrophy, that could lead to non-ischaemic heart failure' and thus augment decline of the failing heart (Hagstrom et al, 2010).

As yet, there are no intervention studies investigating whether reductions in parathyroid hormone levels lead to improvements in clinical outcomes and its utility in routine clinical practice is limited at present.

Vitamin D deficiency

Vitamin D is a fat-soluble essential vitamin and endocrine hormone, obtained from dietary sources such as dairy produce or synthesized from cholesterol during skin exposure to direct sunlight. The form ingested or synthesized is termed cholecalciferol, hydroxylated in the liver into 25-hydroxycholecalciferol (the form of vitamin D measured by blood tests) and in the kidney further hydroxylated to 1,25-dihydroxycholecalciferol (or calcitriol, the biologically active form of vitamin D). This latter form acts to increase uptake of calcium from the gut. Parathyroid hormone increases the activity of 1-α-hydroxylase, an enzyme found in the kidney, which converts 25-hydroxycholecalciferol (calcidiol), released from the liver, to 1,25-dihydroxycholecalciferol (calcitriol).

Vitamin D deficiency, termed hypovitaminosis D (<50 nmol/litre), is common in patients with heart failure with over 90% of patients being deficient in some studies (compared to 15% of the normal population) and is associated with poor functional class, ejection fraction, 6-minute walk distance and mortality (Boxer et al, 2008; Ameri et al, 2010). Vitamin D deficiency in patients with heart failure is likely to have a multi-factorial origin, as a result of aging, inactivity and also chronic disease but the exact mechanism is unknown.

There is limited evidence that vitamin D supplementation improves morbidity in the presence of deficiency in heart failure but in patients without heart failure, such deficiency is associated with reduced exercise capacity and muscle strength (Witham et al, 2010; Stockton et al, 2011).

While measurement of vitamin D is currently en vogue in a whole host of conditions, the evidence suggests that while deficiency is indeed common, routine measurement and treatment in heart failure, with a view to improve morbidity or mortality, is without merit.

Thyroid dysfunction

Thyroid-stimulating hormone or thyrotropin is a glycoprotein produced by the thyrotropin cells in the anterior pituitary, which stimulates the thyroid gland to produce thyroxine (T_4) and tri-iodothyronine (T_3), which govern metabolic rate. The normal range of thyroid-stimulating hormone is 0.4–4.5 mU/litre, free T_4 9.0–25.0 pmol/litre and free T_3 3.5–7.8 pmol/litre.

Serum T_3/T_4 levels are inversely correlated with markers of heart failure such as serum albumin, right atrial pressure and cardiothoracic ratio, despite the absence of autoimmune thyroid disease (Koga et al, 1988). In 58% of patients with heart failure, a low free T_3/inverse T_3 index is a marker of poor prognosis (Hamilton et al, 1990). However, while a low free T_3 level identified an increased risk of death in patients with heart failure, a synthetic hormone analogue was of no benefit (Emdin et al, 2004; Pingitore et al, 2005). The mechanism of the effect of low T_3 on the heart remains unknown.

The effect of heart failure on thyroid function is manifold, but unlike other organ systems, while the influence of the thyroid gland on the heart is well known, the opposite is not true. Thyroid function should be initially checked in all patients referred with a suspected diagnosis of heart failure, but subsequent to this, the routine measurement of thyroid function cannot be recommended unless thyroid dysfunction is suspected.

Renal system

Proteinuria

Urinary microalbumin is a measure of renal dysfunction, specifically the permeability of the glomerular basement membrane to albumin. In health such large molecules are not filtered freely by the kidney and their presence in the urine is pathological. This is termed microalbuminuria if the level of protein is 30–300 mg/24 hours or macroalbuminuria if the level is greater than 300 mg/24 hours. This proteinuria is a marker of endothelial and microvascular dysfunction, leading to nephron loss and nephropathy.

The presence of urinary microalbumin correlates with the prognosis, morbidity and mortality in heart failure independent of renal function, blood pressure or diabetes (Figueiredo et al, 2008; Villacorta et al, 2012). Urinary microalbumin may be reduced and the rate of nephron loss interrupted by angiotensin blockade and urinary microalbumin is present before conventional serum markers of kidney function are deranged (Struthers and Lang, 2007).

In heart failure, urinary microalbumin correlates with the presence of natriuretic peptides and is present in approximately 20–30% of patients, with urinary macroalbumin present in a further 5–10% (Masson et al, 2010; Jackson et al, 2011).

The exact mechanism of urinary microalbumin in heart failure is unclear but it might be a marker of diffuse vascular injury, systemic inflammation, activation of the renin–angiotensin system, altered glomerular haemodynamics or abnormal tubular function (Jackson et al, 2009). Many of these pathophysiological abnormalities also occur in patients with heart failure.

Renal injury

Renal injury is common in patients with heart failure, follows the progression of the disease and carries a worse prognosis. Indeed, over 50% of patients will have creatinine clearance <59 ml/min and there is a 1% increase in mortality for every 1 ml/min decrease (McAlister et al, 2004). The cardio-renal syndrome (*Table 1*) refers to the simultaneous failure of both the heart and the kidney, often where the failure of one precipitates the decline of the other, directly by reduced perfusion, indirectly by neurohormonal mechanisms or iatrogenically following diuretic treatment. There are five sub-types, but type 2 is most relevant: chronic heart failure leading to chronic renal failure (Ronco et al, 2008).

More recently, novel measures of renal injury, such as neutrophil gelatinase-associated lipocalin, have shown promise in predicting mortality in this population, even in the presence of normal renal function (van Deursen et al, 2013). A significant improvement in renal function was found following cardiac resynchronization therapy, suggesting it may offer some renal protection, but urinary microalbumin was not measured (Boerrigter et al, 2008).

It is likely that heart failure leads to type 2 cardio-renal syndrome as a result of hypoperfusion, which leads to urinary microalbumin as a result of nephron loss. Renal function is routinely monitored in all patients with heart failure, and while urinary microalbumin has merit, 24-hour collection can be cumbersome and so neutrophil gelatinase-associated lipocalin may offer a convenient alternative as an early marker of renal injury.

Haematological system

Anaemia in heart failure (defined as <13.0 g/dl in men and <12.0 g/dl in women) is common, affecting one fifth of patients. This is a result of reduced cardiac output, leading to a pro-inflammatory state and renal hypoperfusion, in turn, bone marrow toxicity and reduced erythropoiesis, resulting in reduced red blood cell production. Salt and water retention, combined with chron-

Table 1. Different types of cardio-renal syndromes, causes, consequences and examples

Type	Name	Aetiology	Sequelae	Example
1	Acute cardio-renal syndrome	Acute heart failure	Acute kidney injury	Cardiogenic shock
2	Chronic cardio-renal syndrome	Chronic heart failure	Chronic kidney injury	Dilated cardiomyopathy
3	Acute renal-cardiac syndrome	Acute kidney injury	Acute heart failure	Acute tubular necrosis
4	Chronic renal-cardiac syndrome	Chronic kidney injury	Chronic heart failure	Chronic kidney disease
5	Secondary cardio-renal syndrome	Systemic condition	Combined heart/kidney impairment	Sepsis

ic kidney disease, leads to plasma volume expansion resulting in haemodilution, but not anaemia per se.

In heart failure, there is a linear association between reduced haemoglobin and increased mortality, yet assessment and treatment of anaemia is not discussed in most clinical guidelines. Furthermore, treatments such as synthetic erythropoietin lead to increased mortality, possibly as a result of thrombosis. Functional rather than frank iron deficiency is common in heart failure and, as a consequence, while intravenous iron preparations are tolerated, evidence does not currently support their routine use.

Like the mean corpuscular volume, the red cell distribution width is a measure of the variance in the size of the red blood cell. This is defined as ((standard deviation mean corpuscular volume/mean corpuscular volume) × 100), but the width refers to the distribution, not the cell per se. The distribution width reflects the range of sizes (anisocytosis) and shape (poikilocytosis) of the erythrocyte, approximately 7 um in diameter. The size and shape are altered by haematological pathology such as iron or vitamin B_{12} deficiency, leading to microcytosis or macrocytosis respectively. The red cell distribution width is not routinely reported in clinical practice but the normal range is 10–15%. Elevated red cell distribution width is an independent marker of morbidity and mortality and has similar prognostic power to natriuretic peptides regardless of iron status or haemoglobin level (Felker et al, 2007). There are two hypotheses concerning the elevation of the width in heart failure populations; either it is the result of systemic inflammation found in many chronic diseases or a combination of the typical comorbidities present in this population, such as anaemia, malnutrition, renal failure and hepatic dysfunction.

Anaemia is common in heart failure and is associated with increased mortality but the benefits of common treatments such as erythopoetin and intravenous iron are yet to be realized. No studies have looked specifically at the use of the red cell distribution width as a therapeutic target and furthermore, since not all laboratories report red cell distribution width, its utility is limited.

Respiratory system

The heart and lungs are inextricably linked, but while pulmonary diseases are well recognized in causing right heart failure, the influence of heart failure on the lungs is less well known.

In such patients, at a given workload respiratory effort is increased despite normal blood gases. This is believed to be the result of a combination of increased ratio of dead space/tidal volume and a reduction in the diffusion capacity caused by pulmonary oedema (Johnson, 2000). Both of these lead to ventilatory/perfusion mismatching, but the main determinant of breathlessness in heart failure is reduced peak VO_2. Along with peak VO_2, the gold standard for measuring cardiorespiratory function, the ventilatory efficiency (VE/VCO_2) determined by the slope of VCO_2 against ventilation, is a marker of a poor prognosis (Francis et al, 2000; Kleber et al, 2000). As with skeletal muscle, respiratory muscle endurance and strength are often poor in patients with heart failure. This can be improved with training which leads to improved exercise capacity (Dall'ago et al, 2006).

Finally, obstructive and central sleep apnoea are common in heart failure. While the former can also lead to right heart failure, the latter often arises as a direct consequence of heart failure caused by elevated left ventricular filling pressures. Central sleep apnoea or Cheyne–Stokes respiration refers to the presence of central apnoeas and hypopnoeas alternate with periods of hyperventilation that have a waxing-waning pattern of tidal volume and may be seen in as many as 50% of these patients (Bradley and Floras, 2003). Its presence is an independent prognostic marker of a poor outcome in heart failure and while the evidence for improved outcomes following interventions, e.g. non-invasive ventilation, is mixed (Lanfranchi et al, 1999; Sin et al, 2000) studies such as SERVE-HF are ongoing to answer important questions regarding the use of servo ventilation in heart failure, its cost effectiveness and effect on morbidity and mortality (Cowie et al, 2013).

The cost of screening all patients with heart failure for respiratory dysfunction would be considerable, e.g. peak VO_2, sleep studies and full pulmonary function, and so testing can only be advocated if there is a separate indication, e.g. pre-transplant or severity of dyspnoea not explained by left ventricular function, particularly as the evidence base for treatment of such pathology is mixed.

Gastrointestinal system

Impairment of the gastrointestinal system has been particularly overlooked as a consequence of heart failure. Heart failure leads to mesenteric hypoperfusion and bowel oedema, which triggers an inflammatory response and increased adherent bacteria in the bowel wall (*Figure 3*). Indeed, heart failure results in modification of intestinal morphology, increased permeability and reduced absorption, which exacerbates malnutrition.

At present, the effect of heart failure on the gastrointestinal system remains under researched and the consequences for morbidity and mortality are unclear.

Central nervous system

There is a strong association between heart failure and cognitive impairment, leading to a loss of grey matter, most specifically in areas governing cognitive and emotional processing. The exact mechanisms are unclear but it is believed micro-embolism, chronic and intermittent cerebral hypoperfusion and cerebrovascular endothelial dysfunction leads to cerebral hypoxia and ischaemic brain injury. Specifically, 50% of patients with heart failure have some degree of cognitive impairment.

In heart failure, the cerebral impairment is fluctuant and responds to heart failure treatments, both pharmacological, such as diuretics and renin–aldosterone inhibitors, and non-pharmacological such as physical and cognitive training, but despite this, over time such impairment may lead to dementia. Cognitive impairment in patients with heart failure results in reduced quality of life, increased disability and mortality.

Further research is required to create a robust screening tool for use specifically with heart failure patients, and also specific treatments which can halt neuronal loss and resulting cognitive decline. Doctors should be aware of this association and identify early and treat such patients at risk.

Conclusions

When one considers the far-reaching consequences on the many organ systems as a result of heart failure, the very phrase 'heart failure' seems inadequate. Given that the heart, and in particular the left ventricle, supplies oxygen and nutrients and removes waste and carbon dioxide from all other organ systems, it is perhaps not surprising that when the 'pump' fails, this has systemic effects. Furthermore, as it is the failure of the heart driving such processes, the absence of any clinically meaningful improvement following the attempt to treat such peripheral organ dysfunction is not unsurprising.

Testing for uric acid offers insight into the prognosis of heart failure and will thus help inform decision-making, therapeutic options and end of life care. Measurement of sarcopenia offers insight into the functional capacity of the patient which, if improved, may lead to enhanced quality of life and physical performance.

It is imperative that doctors caring for patients are cognisant of heart failure as a multi-organ syndrome, as abnormalities which are 'normal' for the patient may have a common origin. Otherwise, such incidental findings will lead to further unnecessary testing, referral, follow-up and health anxiety in this already heavily tested patient population. **BJHM**

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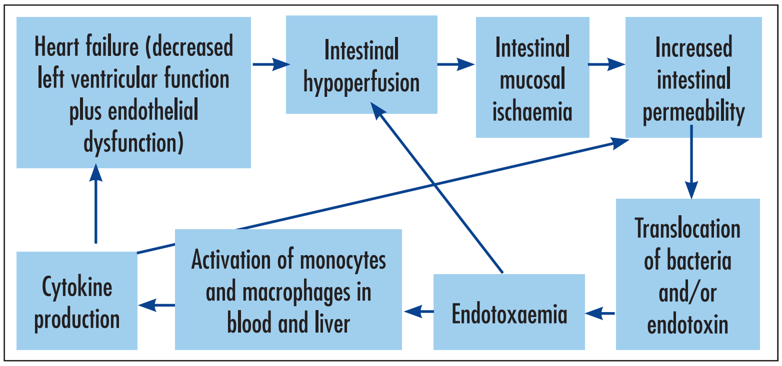

Figure 3. The role of the gut in heart failure.

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KEY POINTS

- Heart failure can lead to multi-organ dysfunction.
- Such dysfunction increases risk of morbidity and mortality in patients with heart failure.
- A paucity of evidence exists that measuring or targeting such downstream pathophysiology, benefits the heart or the patient.
- There is evidence that measuring uric acid and sarcopenia can alter clinical management.

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