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REVIEW

Reciprocal organ interactions during heart failure: a position paper from the ESC Working Group on Myocardial Function

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Abstract

Heart failure—either with reduced or preserved ejection fraction (HFrEF/HFpEF)—is a clinical syndrome of multifactorial and gender-dependent aetiology, indicating the insufficiency of the heart to pump blood adequately to maintain blood flow to meet the body's needs. Typical symptoms commonly include shortness of breath, excessive fatigue with impaired exercise capacity, and peripheral oedema, thereby alluding to the fact that heart failure is a syndrome that affects multiple organ systems. Patients suffering from progressed heart failure have a very limited life expectancy, lower than that of numerous cancer types. In this position paper, we provide an overview regarding interactions between the heart and other organ systems, the clinical evidence, underlying mechanisms, potential available or yet-to-establish animal models to study such interactions and finally discuss potential new drug interventions to be developed in the future. Our working group suggests that more experimental research is required to understand the individual molecular mechanisms underlying heart failure and reinforces the urgency for tailored therapeutic interventions that target not only the heart but also other related affected organ systems to effectively treat heart failure as a clinical syndrome that affects and involves multiple organs.

Keywords Heart failure • Multi-organ clinical syndrome • Lung • Intestine • Kidney • Brain • Adipose tissue • Liver • Non-coding RNAs

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1. Introduction

The concept that heart failure is a clinical syndrome involving numerous organ systems is not new. However, how organ crosstalk during heart failure mechanistically develops and may represent an opportunity to create new treatment paradigms remains a fascinating future area to be explored. The complex feedback between different organs or even cells is mediated via mechanical, soluble, and cellular mechanisms.[1–3] On the one hand, there is a need for organ crosstalk to maintain body homeostasis; however, once a pathological state develops in one organ system, this can lead to functional and structural dysfunction in other organs. The same organ-interaction concept can also be adopted to the cellular level, where disease phenotypes within a given cell type can detrimentally affect other cell types, thereby leading to a detrimental vicious cycle that finally leads to organ dysfunction.[4]

In this position paper, we provide an overview of interactions between the heart and several main organs and tissues with a focus on the kidney, brain, lung, skeletal muscle, intestine, liver, adipose tissue, and finally innate immunity (*Figure 1*). Additional interactions between the heart and other organs systems exist but are beyond the scope of this review.

We highlight new experimental evidence that heart failure must be viewed as a multi-organ clinical syndrome with numerous subtypes, which are based on other organs involved. We also discuss consequences on new diagnostic, prognostic, and therapeutic strategies. Such strategies must be further developed with the aim of optimizing a root cause analysis of individual HF patients. This also implies the need for the development and/or use of new model systems that aim to study the mechanistic details of such organ interactions during heart failure. Future treatment strategies of novel yet to be discovered mechanisms either directly in the heart of affected HF patients or indirectly in organs supporting HF development need to be developed.

2. The use of HF terminology

The authors of this position paper agree that a certain form of HF subtype definitions, such as 'HFrEF', 'HFmrEF', or 'HFpEF', is required. However, we also agree that such an approach fails to explain the clinical diversity of HF patients, particularly those that have comorbidities that contribute to HF. However, in this position paper, we continue to use

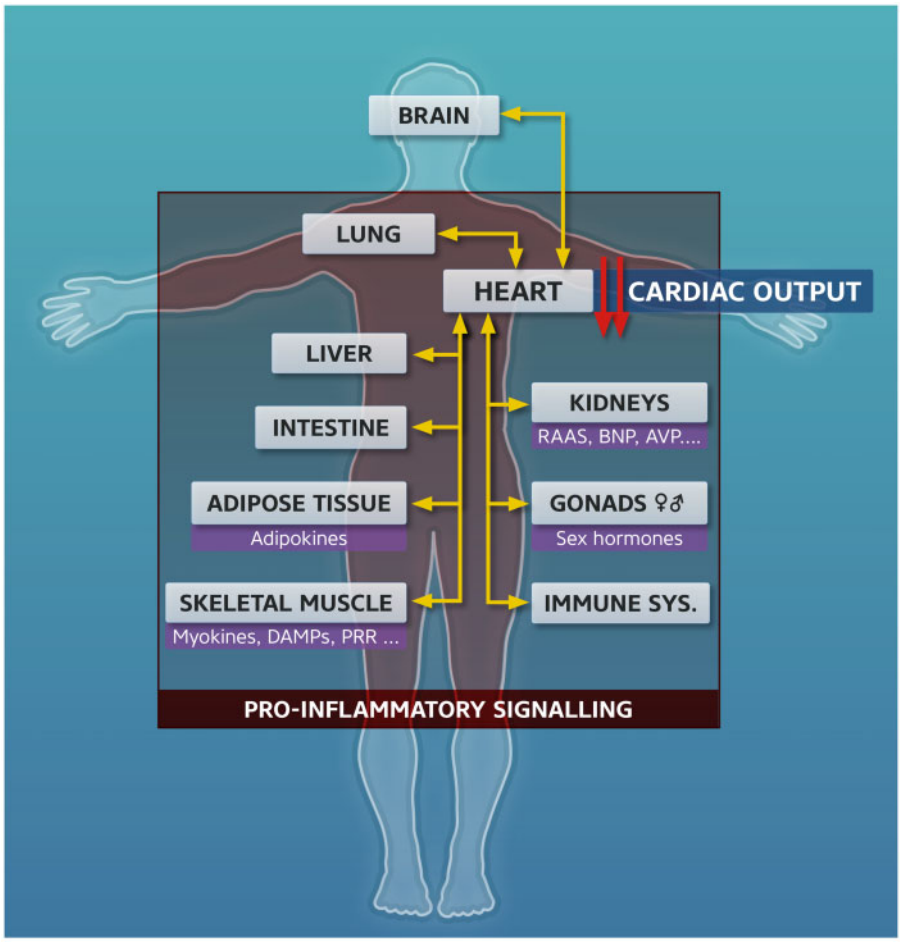

Figure 1 Diagram of postulated organ crosstalk in heart disease—namely between the heart, kidneys, brain, lung, skeletal muscle, intestine, liver, adipose tissue, gonads, and the immune system. Details are elaborated in the respective subsections. RAAS, renin–angiotensin–aldosterone system; BNP, natriuretic brain peptide; AVP, argininge vasopressin; DAMP, danger associated molecular patterns; PRR, pattern recognition receptors.

such a terminology, while continually bearing in mind the clinical diversity.

3. Heart and kidney

Interactions between the heart and the kidney are amongst the best characterized organ interactions in the human body thus far. Indeed, cardiac and renal functions are tightly and reciprocally regulated through several bidirectional pathways, including hemodynamic, neurohormonal, endocrine, inflammatory, and epigenetic mechanisms.[5] Dysregulation of this complex network leads to the well-described cardiorenal syndrome (CRS), which includes a series of different clinical phenotypes that underline the reciprocal influence of the heart and kidney in pathological conditions.[6] Therefore, the identification of cardiac–renal network-activated signalling through various pathological conditions has an essential therapeutic and prognostic value.

The current knowledge regarding CRS mechanisms derive from both pre-clinical and clinical studies. In the animal model, the clinical cardiorenal phenotype can be reproduced by inducing a primary cardiac injury, primary renal disease, or a simultaneous renocardio/cardiorenal dysfunction.[7] However, murine models do not always recapitulate CRS, thereby indicating—in particular—limits related to the timeframe required between the development of HF and the onset of renal failure.

In the pathophysiological context, cardiac output represents the primary regulator of renal function, as measured by the estimated glomerular filtration rate (eGFR). As described below in other subchapters, this also holds true for other organ systems such as the liver, the gut, and the brain. Indeed, impaired systolic function as observed in congestive heart failure, particularly in heart failure with reduced ejection fraction (HFrEF), affects renal function via activation of neurohormonal mechanisms—such as the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system—aimed to maintain adequate organ perfusion, including the kidney.[8] In addition to reduced systolic function, pathophysiological studies evidenced that other variables, such as resting heart rate and arterial stiffness, can influence the cardio-renal network, which may explain the deterioration of renal function in the presence of preserved or mildly reduced systolic function (HFpEF and HFmrEF). For example, adequate rhythm control in patients with atrial fibrillation (AF) improves and preserves eGFR.[9] In addition, elevated resting heart rate appears associated with the deterioration of renal function in the presence of increased arterial stiffness. This may potentiate the increased pulsatile flow wave caused by elevated heart rate, thereby leading to accelerating kidney injury.[10] The role of neurohormonal mechanisms in the cardio-renal network is manifold. The effects of RAAS in the control of volume load is well-known, as are the long-term effects on cardiac and vasculature remodelling that lead to chronic heart failure. The natriuretic peptide system accounts for the endocrine function of the heart and enables it to directly modify renal function. Natriuretic Brain Peptide (BNP), beyond its natriuretic and vasorelaxant effects, can inhibit renin production and reduce aldosterone synthase (CYP11B2) mRNA expression with attenuation of cardiac hypertrophy and fibrosis.[11] The contribution of arginine vasopressin (AVP) to the development of the CRS is also relevant. AVP levels are increased in heart failure, thereby leading to fluid retention and vasoconstriction.[12] Moreover, AVP is part of a vicious cycle in HF, where renal ischemia secondary to reduced blood perfusion induces RAAS activation, which stimulates the release of AVP. of the activation of V1a receptors by AVP causes peripheral vasoconstriction, contributing to worsening of renal function.[13,14] According to recent work, the multifactorial mechanisms causing the clinical picture do not only include hemodynamic parameters (such as extracellular fluid volume, cardiac output, and arterial pressure) but also endothelial injury, imbalance of immunological processes, cell death and apoptosis, oxidative stress, leucocyte trafficking, and release of extracellular vesicles.[15,16]

The communication between heart and kidney also follows other routes involving, for example, immune-mediated mechanisms. Acute heart damage may release pro-inflammatory factors that extend the damage to the kidney. While still lacking a model that associates dysregulation of the immune system and alteration of the cardiac–renal network, the vascular endothelium appears primarily involved in activation of the innate immunity and inflammatory responses.[17]

Epigenetics represents another fascinating field to further understand cardio-renal interaction. The uremic milieu fosters epigenetic gene regulation and promotes arteriosclerosis and cardiovascular disease.[18–20] In particular, non-coding RNA (ncRNA) can facilitate communication between organs and, thus, participate in the cardio-renal network. Several miRNAs are also expressed in both and can mediate cardiac and renal diseases.[21] For example, cardiac miR-21 and miR-29b appear oppositely regulated after lowering uremic toxin levels in a rat model of CRS.[22] Further, miR-21 regulates the proliferation of tubular epithelial cells[23] and promotes the development of renal fibrosis.[24,25] Similarly, antagomir-21 counteracts atrial fibrosis in experimental postinfarction HF.[26,27] Strikingly, inhibition of miR-21 has been shown to have anti-fibrotic and protective effects in both kidney as well as cardiac disease.[28,29] Effects of other ncRNAs in both kidney and cardiac diseases have been recently summarized.[21]

Collectively, the cardiac–renal network consists of multiple intricated regulatory systems that are essential for maintenance of cardiac function and perfusion of organs. Perturbations in these systems are responsible for the deterioration of both cardiac and renal functions, but also indicate that novel therapeutic strategies targeting common pathways may improve the functioning of both organs. The anti-fibrotic effects of a miR-21 inhibitor are currently being tested in a phase II study in patients with kidney fibrosis (www.clinicaltrial.gov, NCT02855268); however, the potential benefit of selective kidney targeting of microRNA-21 in patients with heart failure or other cardiovascular disease remains unaddressed.

Canagliflozin, a sodium-glucose transport protein 2 inhibitor, has demonstrated the ability to reduce major cardiovascular events and kidney failure in patients with type 2 diabetes mellitus and chronic kidney disease.[30] A recent co-culture study on the interaction between endothelial cells and cardiomyocytes indicated a positive effect of empagliflozin. In the latter experimental study, co-culturing of endothelial cells with cardiomyocytes enhanced cardiomyocyte contractility. The positive effect of endothelial cells on cardiomyocyte function was blunted by exposure of endothelial cells to tumour necrosis factor-α (TNF-α), and was restored in the presence of empagliflozin. In addition to recent studies that indicate direct positive effects of empagliflozin on the heart, this illustrates the potential of a sodium-glucose transport protein 2 inhibitor to target different cell types and organs.[31–33]

In summary, it has become necessary to develop a specific model to deepen the molecular and pathophysiological mechanisms of CRS and design clinical trials to assess the efficacy of a novel pharmacological strategy aimed to preserve cardiac and renal functions and improve patient outcome.

4. Heart and brain

Several animal models were employed to study the basic mechanisms that address the link between heart failure (HF) and brain dysfunction. The most frequently used animal models for studying the effect of HF on the brain are the transverse aortic constriction (TAC) and the myocardial infarction (MI) model,[34,35] which mimic pressure-overload and ischemic cardiac disease. Multiple studies were conducted to define cardiac pathomechanisms in TAC and MI mice, although only a few addressed brain functioning.

In the TAC mouse model, the aortic arch is partially obstructed in order to induce pressure overload on the heart. This surgical intervention decreases cerebral blood velocity, increases blood–brain barrier permeability, inflammation, and cognitive dysfunction (reviewed in Ref. 35). A recent systematic review and meta-analysis highlighted the heterogeneity between the different functional outcome measurements of the TAC model,[36] thereby emphasizing the need for more robust studies regarding the functional outcome measurements for TAC, which also must be conducted in relation to the brain.

In the MI model, the left anterior descending coronary artery is permanently ligated to induced ischemia and cardiac dysfunction. This resulted in reduced cerebral blood flow; however, MI did not reveal neuronal damage six weeks after the intervention, while reduction in cerebral blood flow was reduced by 4–6 weeks.[35,37,38] Vascular inflammation—more specifically, TNFα—was found to increase in cerebral vascular smooth muscle cells of the MI mice six weeks after intervention. Interrupting the TNFα signalling pathway could reverse the decrease in cerebral blood flow by reversing cerebral artery vasoconstriction.[37] Further, Angiotensin-(1-7) attenuated MI-induced cognitive impairment after four weeks of treatment.[39] These studies emphasize the therapeutic importance of studying these mice models in relation to the brain; however, these studies are currently rather sparse.

The most prominent feature of HF on the brain is cerebral hypoperfusion. In order to more specifically study the underlying consequences of cerebral hypoperfusion, the bilateral common carotid artery stenosis mouse model, which mimics chronic cerebral hypoperfusion, is employed as the most promising model.[40] In this model, cerebral hypoperfusion leads to, among other things, increased blood–brain–barrier permeability, increased inflammation, white matter lesions and decreased cognition; however, underlying mechanisms are currently unknown. Rats and non-human primates are used as animal models for cerebral hypoperfusion after an ischemic event as well.[41] However, while hypoperfusion animal models mimic a broad spectrum of human brain dysfunction after HF, not all pathological and cognitive aspects can be translated from animals. Moreover, cognitive features, as one of the most important aspects of brain functioning, is not the same between animals and humans. Nevertheless, including animal cognitive and pathophysiological measurements and in-depth molecular pathway analysis in a robust and comprehensive manner in more HF or HF-related animal studies is necessary to gain more insight into the basic mechanisms of HF and brain interaction. Further, thus far, studies have been mainly performed in young animals, while brain disorder in humans is highly age-related. Therefore, more comprehensive studies in aging mice must be included.

Both chronic HF and cognitive impairment are common conditions in the general population and also tend to co-occur. The process of normal aging is associated with a decline in cognitive abilities. A large proportion of the elderly experience at least mild to moderate decline in memory function and mental speed. A large proportion of these patients do not fulfil the diagnostic criteria for dementia. The symptomatic stage preceding dementia is called 'mild cognitive impairment' (MCI) and describes the presence of cognitive impairment without interference in daily living. MCI can be a first sign of dementia, but a proportion of the patients have cognitive impairment due to causes other than neurodegenerative disease, such as depression, medication, or other (treatable) conditions. The term vascular cognitive impairment (VCI) has been introduced to describe the complete spectrum of cognitive impairment, from MCI to dementia, related to vascular brain injury.[42] Patients with heart failure and other cardiovascular diseases have an increased risk for VCI. Cognitive impairment in patients with HF has been associated with adverse health outcomes, including poor survival, high mortality, and poor engagement in self-care.[43–45] Moreover, the complex (pharmacological) management of HF may interfere with cognitive impairment. This underlines the importance of detecting the extent and nature of cognitive impairment in HF. Thus far, studies have shown that 14%–70% of patients with heart failure have cognitive impairment to a certain extent.[46–49] In the Heart-Brain Connection study,[50] a Dutch multi-centre observation study in patients with cardiovascular disease, we found that 18% of patients with HF had cognitive impairment, in particular in the domains of memory and attention-psychomotor speed.[51] The prevalence of cognitive impairment varies due to differences in neuropsychological tests, the cut-off scores used to indicate cognitive impairment, and the characteristics and demographics of the population with HF. In most studies, only a short cognitive screening, such as the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA), was used. These tests are helpful in the identification of patients who are at risk for cognitive impairment. However, a comprehensive neuropsychological assessment, performed by a neuropsychologist, can determine the nature and severity of cognitive impairment.

In patients with HF, global and regional atrophy and vascular brain injury [e.g. white matter hyperintensities (WMH) and (lacunar) infarcts, microbleeds] are frequently detected on brain MR, which may cause cognitive impairment.[47,52–55] In addition, patients with HF are found to have an increased risk of symptomatic stroke; however, clinically 'silent' lesions are also prevalent. A recent study indicated that cerebral cortical microinfarcts, a novel marker of vascular brain injury, were found in 17% of patients with HF and were related to vascular risk factor profile and severity of cardiac dysfunction.[56]

Further, chronic cerebral hypoperfusion, primarily related to low cardiac output, is thought to be the main cause of brain changes in patients with HF. There is ample evidence that an adequate cerebral blood flow (CBF) is a prerequisite for optimal cognitive functioning. Reduced CBF is associated with worse cognitive functioning.[57,58] However, a recent study showed no relation between cerebral blood flow, measured with arterial spin labelling MRI, and cognitive functioning in patients with HF and vascular brain injury.[59] In two studies comparing patients with HF to controls, medial temporal lobe atrophy (MTA) was related to cognitive functioning in patients with HF.[47,60] MTA is an early feature of Alzheimer's disease (AD) and is associated with an increased risk of progression to dementia. A probable explanation for this finding could be that patients with HF are more susceptible to the development of concomitant AD. Other potential underlying mechanisms beyond the role of cardiovascular disease and brain changes, including oxidative stress and inflammatory factors, are now receiving increasing attention.[61] We need more evidence to understand the interplay between cardiovascular disease, the development of AD, and brain changes leading to cognitive decline.

With regard to therapeutic options, studies on cognitive functioning in patients with HF are increasingly available, but there is a need for more prospective longitudinal studies, with longitudinal brain MRI and neuropsychological assessment. The implementation of 'heart-brain clinics' in clinical care—with a multidisciplinary team of cardiologists, internist-geriatricians, neuropsychologists, and neurologists—results in a systemic focus on both heart and brain instead of focusing only on one specific organ. The heart–brain clinic can enable the early detection of patients at risk for cognitive impairment. This approach could lead to better risk stratification for cognitive impairment, tailored disease management, and medical decision-making in patients with HF. Similarly, animal studies on HF must be performed in older mice over a time span of several months, as the ageing brain is most likely more sensitive to HF-induced hypoperfusion.

5. Heart and lung

The cardio-pulmonary continuum has been proposed as a more comprehensive therapeutic target due to shared risk factors and the overlap of pathogenic mechanisms seen in common cardiac and pulmonary diseases.[62,63] For example, the observation that heart failure and chronic obstructive pulmonary disease (COPD) co-exist more frequently than expected from their inferred prevalence in large populations strongly supports this concept.[64,65] 14 million Americans have COPD and 5 million have chronic HF.[66,67] *Unrecognized* heart failure has been reported in up to 46% of COPD patients in the United Kingdom (UK).[68,69] Recent evidence reveals that this continuum may be present in other diseases with more subtle clinical phenotypes than overt, end-stage heart failure or COPD: for example, patients with a prior episode of takotsubo cardiomyopathy have both a heart failure phenotype (albeit with preserved or mid-range ejection fraction) and alterations in their lung function tests reduced forced expiratory volume (FEV1) that cannot be explained by any pre-existent or concurrent pulmonary condition.[70] However, the precise mechanism by which COPD induces cardiovascular events remains obscure. COPD is characterized by persistent lung and systemic inflammation, which intensifies during acute exacerbations.[71,72] After such exacerbation, triggered by viral or bacterial infection, COPD patients have the highest risk of myocardial infarction and stroke within a period of the first five days compared to later periods.[73]

On the other hand, acute and chronic lung inflammation is frequently underrecognized as a risk factor for cardiovascular diseases, while ample evidence from epidemiological data demonstrates the strong relationship between airway exposures to cigarette smoke, air pollution particles, or pathogens and cardiovascular morbidity and mortality.[74–76] COPD patients indicated a high prevalence of LV systolic dysfunction, which could be due to the low-grade systemic inflammation that accelerates progression of coronary atherosclerosis as well as microvascular dysfunction, which eventually results in ischemic cardiomyopathy. This fits perfectly with the high incidence of LV wall motion abnormalities seen clinically in patients with COPD and LV dysfunction.[77] In addition, patients with pulmonary hypertension and pulmonary heart disease may have not a normal left atrial pressure, which is particularly true for the elderly, those with obesity, and those with sleep-disordered breathing, all of whom are characterized with hypertensive left atrial enlargement. This could even be the predominant cause of pulmonary hypertension.[78,79] The pulmonary venous congestion component in these patients brings an additional deleterious effect on already compromised lung mechanics. In numerous clinical scenarios, treatment of both left heart congestion and COPD exacerbation is the practical option that is frequently selected by many in order to achieve any clinical improvement. These pathophysiological mechanisms rely on common pro-inflammatory mediators including C-reactive protein, Interleukins (IL1β, IL-6, IL-8, IL-12), chemokines, and TNF-α. This inflammation may result from multiple causes; however, infections are likely to initiate or perpetuate such inflammation. Whilst these concepts are only just emerging, there is little achieved in terms of therapy that is beneficial in tackling pro-inflammatory pathways in chronic diseases: a recent example of a monoclonal antibody targeting IL1β showed promising effects in post-ischemic heart failure;[80] however, the medical community has not yet assessed such therapies by examining multi-organ benefit in clinical trials.

The pathological interplay between the heart and the lungs is complex, bidirectional, poorly defined, and currently orphaned of any therapy. Studies in animal models and human cardiac samples from PAH-induced right heart failure provided evidence for diastolic dysfunction due to increased fibrosis, which may be caused by systemic inflammation.[81,82] Potential pathways that could link lung and heart disease are, for example, systemic infections that may stimulate inflammation and immune activation and thereby worsen lung and heart disease. Microbial translocation of bacteria or other organisms from the gastrointestinal tract or other sites could move to the lung or the vasculature and infect tissues, which in turn may stimulate local and systemic inflammation, thereby resulting in tissue damage.[83] One possibility of how to study this, one may believe that the distribution of E. coli or other bacteria of interest can be tracked with Green Fluorescence Protein (GFP) in different organs. Thus, staining the organs and evaluating the localization provides information regarding the severity of the infection. This can be paired with well-established protocols for assessing inflammatory cytokines—such as ILs, VCAM, ICAM, and TNFα—for obtaining insight into local inflammatory status. For systemic inflammation, C-reactive protein can be used in the blood, as it is one of the best inflammation markers available. Therefore, understanding the mechanistic pathways is mandatory, and building on robust, complex clinical trials of anti-inflammatory therapy requires collaboration between cardiologists and chest physicians as well as significant financial support from research councils and charities. If we are to understand and treat multi-morbidity this translational approach, this is the only way forward.

The identification of individual susceptibility of patients is more likely to develop pathology straddles the cardio-pulmonary continuum in favour of each single organ, in particular, has been elusive thus far, as only a few potential candidate genes[84] have ever been examined.

In a clinical setting, it is often difficult to differentiate between cardiac and lung pathologies. There is significant overlapping in the symptom burden—such as dyspnoea, fatigue, cough, reduced exercise capacity, muscle weakness, poor sleep, added anxiety, and depression. The investigations performed in one direction often identify one cause (either pulmonary or cardiac) and settle the clinical diagnosis with a narrow focus, occasionally misguiding therapy. A significant example of treatment equipoise is the case of beta-blockers therapy, which has indisputable survival benefits in heart failure[85,86] but have traditionally been avoided in patients with pulmonary disease. For example, bisoprolol provided benefit in an experimental rat model of pulmonary hypertension-induced right heart failure.[87] In addition, more recent registry and meta-analysis data have poignantly noted that beta-blockers appear to reduce the number of exacerbations on COPD patients.[88,89] However, no benefit was observed from bisoprolol treatment in a single-centre study in patients with idiopathic pulmonary arterial hypertension (PAH).[90] In addition, a randomized controlled study did not support a positive effect of

beta-blocker therapy.[80] The ongoing larger study of bisoprolol in COPD will bring further evidence either in support or to refute the matter of beta-blockers as the first therapy to be put into trial in the cardiopulmonary continuum, as it will emerge from its mechanistic, cardiac sub-study (http://www.isrctn.com/ISRCTN10497306; EudraCT No. 2017-002779-24).

6. Heart and skeletal muscle

Past clinical studies have already indicated that major structural and functional changes occur in the skeletal muscle of patients with either HFrEF or HFpEF. These changes include (i) decreased number of type I fibres; (ii) reduced mitochondrial density, oxidative capacity, and cross-sectional area of type II fibres; and (iii) increased glycolysis.[91,92] These result in muscle atrophy and reduced strength, a condition termed sarcopenia and largely responsible for exercise intolerance and poor prognosis.[93,94] Breathlessness, muscle weakness, and exercise intolerance are features typically observed in the majority of HF patients, while cachexia, namely the loss of over 5% of body weight over 12 months, occurs in 5%–15% of end-stage HF patients. Patients who develop cardiac cachexia have a devastating prognosis, independently of their cardiac function.[95]

While a reduced cardiac output and increased venous pressure have been traditionally considered as major determinants of skeletal muscle dysfunction, at least in HFrEF, intrinsic abnormalities of the muscle fibres are emerging as causative in HF-associated sarcopenia. A recent paradigm attributes a major role to impaired oxygen diffusion from capillaries to mitochondria in patients with HF,[96] although certain concerns have been raised on the methodology used to measure oxygen diffusion in these studies.[97]

Skeletal muscle alterations are not entirely shared between HFrEF and HFpEF. Most knowledge is available regarding the pathological features of skeletal muscle myopathy associated with HFrEF, which includes fibre atrophy, isoform shift, and increased levels of pro-inflammatory cells and cytokines, such as TNFα, IL-1β, IL-6, IL-2, and sphingosine.[98,99] These have multiple negative effects on muscle mass and function. For example, IL6 signalling via STAT3 activates myostatin, an important mediator of skeletal muscle catabolism.[100] TNF family members—including TNFα and TWEAK (TNF-like weak inducer of apoptosis)—activate NF-kB in the muscle, which in turn determines severe muscle wasting, which is mediated by the ubiquitin ligase MuRF1 and the suppression of insulin-like growth factor 1 (IGF1) signaling.[101–103]

HFrEF is also characterized by a systemic mitochondrial deficit, as indicated by reduced mitochondrial energy production in both skeletal and cardiac muscles. Sex-specific mitochondrial phenotypes in skeletal muscle that predispose an individual towards exercise intolerance have been reported, as indicated by more prominent alterations in mitochondrial 'quantity' in female and mitochondrial 'quality' in male patients.[104] Mitochondrial deficits are largely consequent to neurohormonal activation, which represents an adaptive reaction to HFrEF and is defined as exaggerated sympathetic tone and increased systemic epinephrine, norepinephrine, and angiotensin II levels.[105] Chronic epinephrine and norepinephrine exposure results in reduced β2-adrenergic receptor signalling and persistent β1-adrenergic receptor stimulation, which in turns activates mitochondrial cAMP/PKA signalling and phosphorylation of electron transport chain (ETC) complexes. cAMP-dependent phosphorylation of specific ETC subunits limits their incorporation into functional super-complexes, thereby reducing overall mitochondrial function and promoting oxidative stress in skeletal muscle.[106–108] Increased Angiotensin II levels also trigger the generation of damaging reactive oxygen species through direct stimulation of NADPH oxidase,[109,110] activate NF-κB dependent pro-inflammatory gene expression, and suppress the anti-inflammatory signalling of IGF1 in skeletal muscle myocytes.[111,112]

Less information is available on the mechanisms responsible for skeletal muscle alterations during HFpEF.[113] A single study compared the modifications in limb and respiratory skeletal muscle upon either ligation of the left anterior descendent (LAD) coronary artery (as a model of HFrEF) or high-salt diet (as a model of HFpEF) in rats and detected more pronounced oxidative stress and mitochondrial dysfunction in the former group.[114] The exacerbated muscle damage in HFrEF was associated with a different profile of circulating inflammatory cytokines, as TNFα was higher in HFrEF while IL-1β and IL-12 were particularly elevated in HFpEF.[114] Houstis *et al.* found that the majority of HFpEF patients (97%) displayed limitations in multiple components of the O_2 pathway during cardiopulmonary exercise testing, undermining their exercise intolerance and favouring to treat multiple defects simultaneously, as with exercise training. This study also suggests that an important source of disease heterogeneity stemmed from variation in each patient's clinical features.[96] On the other hand, vascular impairment and endothelial dysfunction may be more relevant in HFpEF, resulting in reduced oxygen transport and vasodilation, particularly during exercise.[115–118]

While these mechanisms describe the effect of a failing heart on skeletal muscle structure and function, the skeletal muscle also possesses an endocrine function and secretes a variety of small proteins, cytokines, and peptides, all of which are commonly referred to as myokines. The prototype myokine, IL-6, is highly expressed and released by both muscle fibre types in response to exercise. Locally, it binds gp130Rβ/IL-6Rα, thereby determining the stimulation of 5' adenosine monophosphate-activated protein kinase (AMPK) and/or PI3-kinase to enhance glucose uptake and fat oxidation, while in the liver and adipose tissue it increases hepatic glucose synthesis and lipolysis, respectively.[119] Plasmatic IL-6 levels are particularly high in patients with unstable angina and have been proposed as markers of cardiovascular disease outcome and risk.[120,121] Other potentially relevant myokines are irisin and follistatin-like protein 1 (FLST-1), which play an essential role in glucose homeostasis and heart metabolism.[122] The possibility that reduced levels of cardioprotective myokines, as a consequence of HF-induced sarcopenia, might contribute to worsening the prognosis of HF patients is a plausible but unproven hypothesis that will require further investigation.

In addition to endocrine signalling, during the progression of HF-induced cachexia, dying myocytes release danger-associated molecular patterns (DAMPs), including alarmins, nucleotides, bioactive lipids, extracellular matrix fragments, and lectins. These are recognized by pattern recognition receptors (PRRs), which are abundantly expressed by leucocytes, endothelial cells, and fibroblasts in most organs, including skeletal muscle and the heart.[123] Whether DAMPs derived from skeletal muscle contribute to the progression of heart failure remains unclear.

Various genetic, pharmacological, and surgical models have been used to study the cross-talk between the failing heart and skeletal muscle. These are instrumental to both understanding the molecular players involved in this cross-talk and assessing the efficacy of therapeutic interventions.

The most commonly used genetic models include calsequestrin (CSQ)-overexpressing mice and Dahl salt-sensitive rats. Transgenic mice overexpressing the cardiac isoform of CSQ under the control of the α-myosin heavy chain (MyHC) promoter were found to develop severe

cardiac hypertrophy beginning at eight weeks of age and leading to progressive HF and death by weeks 10–16.[124,125] In these mice, a significant reduction in body weight and exercise tolerance was already detectable at eight weeks, exclusively in males.[126] The Dahl salt-sensitive rats belong to a particular strain characterized by a marked genetic susceptibility to develop hypertension following excessive salt ingestion.[127] When fed a high-salt (8% NaCl) diet, they develop hypertension and congestive HF, which usually become apparent at 17–19 weeks of age. These animals present elevated levels of pro-inflammatory cytokines, such as TNF-α and IL-1β, and abnormal expression of genes related to mitochondria function in both cardiac and skeletal muscles.[128,129] More recently, muscle alterations have been detected in genetic models of familial cardiomyopathies (i.e. cardiac myosin binding protein-C null mice[130]), which is consistent with the appearance of marked muscle wasting in young patients with symptomatic dilated and hypertrophic cardiomyopathy.[131,132]

Pharmacological interventions leading to HF that are used to unveil the consequences of this condition on muscle structure and function are based on the administration of compounds eliciting either systemic or pulmonary hypertension. An infusion of 500 ng/kg/min angiotensin II for up to 14 days is well known to increase blood pressure, thereby leading to progressive HF and subsequent muscle atrophy in both rats and mice.[111,133–135] With similar mechanisms, monocrotaline administration at a dose of 60 mg/kg is known to cause pulmonary hypertension, followed by the rapid onset of progressive right ventricular failure and cachexia.[136] Rats are more sensitive to monocrotaline than mice, but they become severely anorexic. In contrast, mice progressively lose muscle mass in the absence of anorexia and, therefore, are the preferred model to study the mechanisms of muscular dysfunction in pulmonary hypertension-induced HF without the confounding effect of anorexia.[137]

The most common and reliable animal models are based on surgical interventions, inducing either acute myocardial infarction (MI) by LAD ligation or decreased left ventricular output through aortic constriction. LAD ligation is commonly performed in adult mice and rats and leads to a progressive decline in cardiac function, beginning with a thinning of left ventricular walls evident after two days and resulting in massive collagen deposition and scar formation at one week. While in mice, HF is usually evident at one month, rats take longer to develop cardiac dysfunction. In both species, hindlimb and diaphragm muscle weakening becomes evident a few months after the onset of HF.[110,138]

The other approach, commonly used to study the consequence of HF on the skeletal muscle, is obtained by constriction of either the ascending aorta or the aortic arch. Both interventions provide extreme load on the left ventricle and HF. Depending on the site and degree of the constriction as well as on the species, age, gender, and weight of the animals, the disease progresses with variable speed, but almost invariably leads to a significant loss of body weight and muscle mass.[139–141]

A few studies have investigated the cross-talk between the failing heart and the skeletal muscle in large animals. Either rapid ventricular pacing[142] or intracoronary microembolization[143] in dogs causes congestive HF with skeletal muscle alterations that mimic the human condition. These models have been instrumental in unveiling the negative effect of HF on muscle integrity and performance. The other direction of this cross-talk—namely, the extent to which the muscle can influence the progression of HF—is much less explored due to the lack of reliable *in vivo* models. The implementation of animal models with contextual cardiac and muscle diseases (i.e. HF and cancer-induced cachexia, HF and traumatic muscle loss) will be necessary and warranted to define the bi-directional cross-talk between the failing heart and the skeletal muscle in greater detail.

7. Heart and intestine

Heart failure (HF) has long been shown to be linked to impaired gut function.[144,145] Impaired systolic function in HF leads to gut ischaemia with congestion of the splanchnic circulation. This leads to intestinal wall oedema and damaged activity of the gut barrier (*Figure 2*). This condition can increase the overall inflammatory state as well as oxidative stress due to HF-produced ischaemia and congestion within the gut via enhanced bacterial translocation and the presence of bacterial products in the systemic bloodstream. It has been hypothesized that the leakiness of the gut barrier may modify the gut environment and affect its resident microbial population and, consequently, the metabolites generated from such bacteria.[146] The metabolic pathways involve the fermentation of non-digestible fibres to short-chain fatty acids that confer protective properties, such as lowering inflammatory processes and oxidative stress[147,148] and ameliorating vessel tone. Dietary sources that include choline, phosphatidylcholine, l-carnitine, and other methylamine-containing nutrients provide substrates for microbiota-mediated generation of trimethylamine (TMA). TMA then accesses the portal circulation and is transformed into trimethylamine *N*-oxide (TMAO) by the hepatic flavin-containing monooxygenase (FMO) family of enzymes. TMAO is able to trigger atherosclerosis, thrombosis, kidney failure, and HF. Interestingly, it has been shown that elevated levels of TMAO may predict mortality and CV mortality in HFrEF but not HFpEF patients, and TMAO has predictive value in HFrEF patients above and beyond NT-proBNP.[149] In addition, the bacterial transformation of bile acids can lead to altered bile acid profiles, which in turn can impact systemic inflammation and fibrosis. All these processes are able to affect the personal susceptibility to, and severity of, HF.[146]

These data suggest that intestinal microbiota may function as an endocrine organ by producing bioactive metabolites that can directly or indirectly influence host homeostasis. A series of products generated by intestinal bacteria from dietary metabolism have been associated with conditions such as atherosclerosis, hypertension, HF, chronic kidney disease, obesity, and type 2 diabetes mellitus. In particular, short-chain fatty acids (SCFAs) produced by the gut microbiome may impact the cardiocirculatory system by indirectly ameliorating the activity of the gut barrier by stimulating mucus production; activating olfactory receptor 51E2 (OR51E2; also known as OLFR78) in the renal juxtaglomerular apparatus (JGA) and peripheral vasculature, which in turn leads to enhanced renin generation and increased blood pressure, hence counterbalancing hypotensive responses mediated by free fatty acid receptor 3 (FFAR3; also known as GPR41); and stimulating histone acetyltransferases (HATs) while suppressing histone deacetylases (HDACs), with a consequent decrease in inflammatory processes, balancing gene modulation (epigenome), and regulating inflammatory cell activation.[146–148,150–156]

In addition, bacterial transformation of bile acids leads to altered bile acid profiles, which in turn can affect systemic inflammatory and fibrotic processes.[146] Microbiota-derived peptide mimics may also trigger HF by promoting lethal inflammatory cardiomyopathy. Cardiac myosin-specific TH17 cells are being imprinted in the intestine by a commensal Bacteroides species peptide mimic. These cells induce heart inflammation and dysfunction in genetically susceptible individuals.[157]

Importantly, patients with HF exhibit modifications in the composition and diversity of the intestinal microbiome.[146] Indeed, the composition of

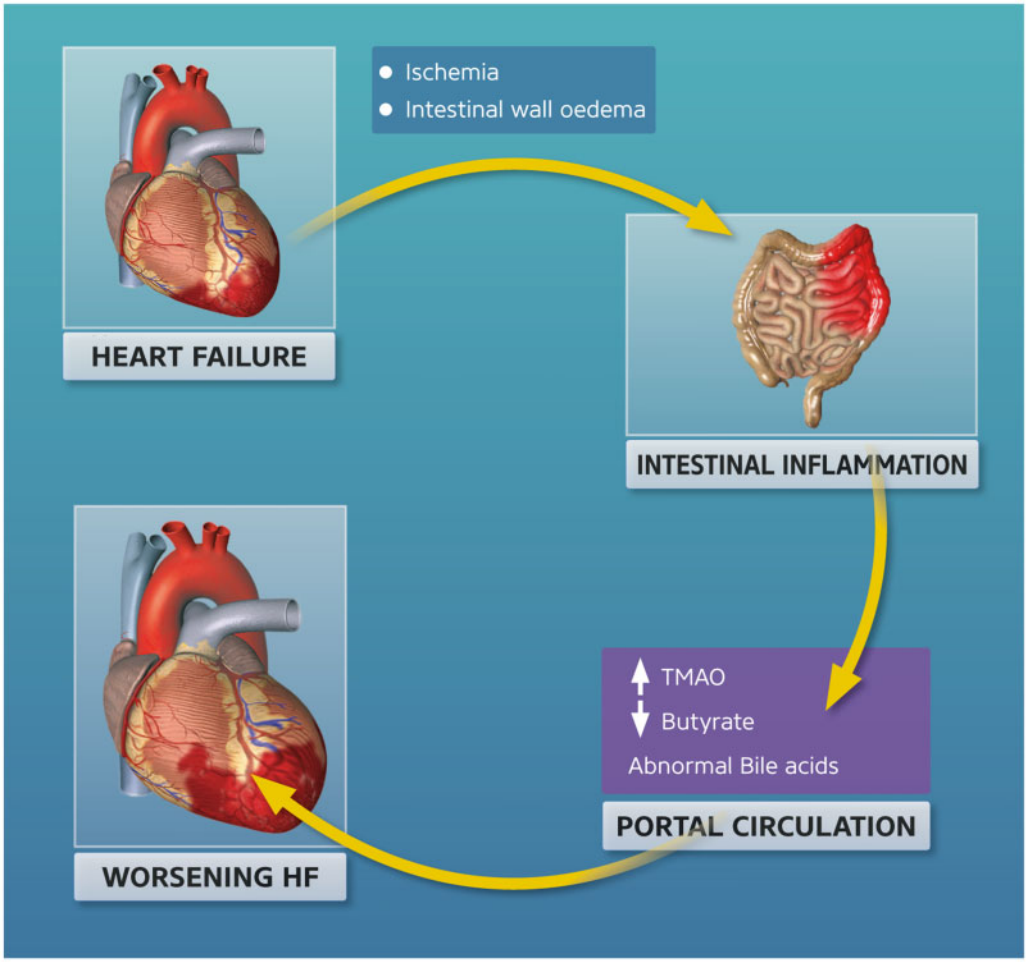

Figure 2 Display of the hypothesized interaction between the failing heart and the intestine. TMAO, trimethylamine N-oxide.

the intestinal microbiota can be affected by various conditions including individual genetic variability, lifestyle, colonization and delivery at birth,[158–160] changes in diet, presence of diseases and relative treatments, all of which may hamper reproducibility and translation of results in basic research in this field.[161]

Advancements in our understanding of how the intestinal microbiome affects humans in health and diseases have increased our knowledge of how microbial composition and function plays a role in the regulation of the homeostasis of the human host. New therapeutic approaches regarding gut microbial metabolic pathways and/or metabolites as well as modifying the composition of the intestinal microbiota may be able to regulate HF susceptibility and halt its progression.

8. Heart and liver

An interaction between heart and liver during diseases has been known since the mid-nineteenth century.[162] However, and surprisingly, data regarding the reasons and consequences of heart failure on liver function and *vice versa* are sparse. One of the first observations of pathohistological liver abnormalities during heart failure has been correlated to hepatic congestion and/or impaired arterial perfusion.[163] In terms of lab chemistry changes, an elevation of transaminases and cholestatic enzymes was reported in various forms of heart failure.[164–167] In addition to diagnostic differences, prognostic information can also be achieved by liver lab chemistry data; indeed, transaminases, total bilirubin (T-Bil), and γ-glutamyltransferase (GGT) have been associated with poor outcome in heart failure.[168,169] In a study involving 1032 consecutive ambulatory patients with chronic heart failure, cholestatic enzymes, but not transaminases, were significantly associated with the severity of heart failure syndrome and backward failure. T-Bil, γ-glutamyltransferase (GGT), and alkaline phosphatase (ALP) were associated with adverse outcome in bivariate models.[169] Thus, liver dysfunction is frequent in chronic heart failure and is characterized by a predominantly cholestatic enzyme profile that is associated with disease severity and prognosis. Hepatic cardiomyopathy has been characterized by latent cardiac contractile and diastolic dysfunction coupled with hyperdynamic circulation.[170] This hyperdynamic circulation begins in the portal venous bed and is a simple consequence of portal hypertension. The dilatation of the portal vein is then linked to increased blood flow and is, thus, a 'hyperdynamic circulation'.[171] Moreover, an altered diastolic relaxation detected by reduced E: A ratio is of prognostic value in patients with cirrhotic cardiomyopathy.[172]

Although a few basic mechanisms of organ interaction have been discovered, a large number of interactions are less clear and only little

experimental research has been performed until now. Recently, a more reliable model of hepatic cardiomyopathy in mice was developed.[173] In this model, the detailed haemodynamics of mice with bile-duct ligation (BDL)-induced liver fibrosis were investigated by monitoring echocardiography and intracardiac pressure–volume (PV) relationships as well as myocardial structural alterations. BDL induced a massive inflammation, oxidative stress, microvascular dysfunction, and fibrosis in the liver of mice. These liver changes were strongly correlated with impaired cardiac diastolic, systolic, and macrovascular dysfunction; cardiac inflammation; and oxidative stress. An intervention with a selective cannabinoid-2 receptor (CB_2-R) agonist, known to attenuate inflammation and fibrosis, improved cardiac dysfunction, myocardial inflammation, and oxidative stress emphasizing the importance of inflammatory mediators in the pathology of hepatic cardiomyopathy.[173] Since no specific therapy is currently available for hepatic cardiomyopathy, there is an unmet need for novel pharmacological interventions for the treatment of liver failure-associated cardiac and vascular complications. Currently, liver transplantation is the only proven treatment with a specific effect on cirrhotic cardiomyopathy.[174]

As shown recently by experimental CB_2-R agonist treatment, anti-inflammatory and anti-fibrotic interventions may be used to attenuate hepatic cardiomyopathies. In addition to small-molecule modulators, ncRNAs-based intervention could also be used to achieve anti-fibrotic or anti-inflammatory effects.[29,175,176] Interestingly, the liver-specific microRNA miR-122 is predicting all-cause and cardiovascular mortality and improved risk stratification of HFrEF patients and, thus, might be a new biomarker for risk assessment in HFrEF.[177,178] However, its value in stratifying patients with different forms of heart failure appears limited.[179]

There are numerous bi-directional effects of the heart and the liver and both heart failure and liver failure are closely connected. In addition to circulating cytokines and non-coding RNAs, which may also have interorgan effects, there is only limited information regarding mechanistic interactions in these two diseases. Thus, we suggest the employment of novel experimental models (e.g. see Ref. 173) and focus more closely on hepatic-driven cardiomyopathy as a distinct disease. This would allow the unravelling of new molecular targets for more tailored and specific therapeutic approaches.

9. Heart and adipose tissue

In previous decades, the prevalence of metabolic syndrome, obesity, and its associated risk factors has become a worldwide epidemic that will seriously increase the risk of heart failure (HF). Studies reveal that 32%–49% of patients suffering from HF are obese and 31%–40% are overweight.[180] This link has been ascribed mostly to the obesity-induced pro-inflammatory state and results in the so-called 'obesity cardiomyopathy'. Apart from inflammation, obesity cardiomyopathy includes features such as insulin resistance, cardiac hypertrophy, and diastolic dysfunction. Adipose tissue (AT) is the main 'organ' mediating this inflammatory state and, currently, strong evidence supports the cross-talk between AT (in particular visceral and epicardial), body metabolism, and the heart. AT expansion during excessive energy intake is associated with an increase in adipocyte numbers (hyperplasia) and/or size (hypertrophy), adipocyte dysfunction with a pro-inflammatory secretory profile, and insulin resistance that elicit impaired metabolic status and increased the risk of HF, particularly HFpEF.[180–183]

The biology of AT and its pathophysiological role in obesity-related complications, such as obesity cardiomyopathy and HF, have been extensively studied in the previous decade. Indeed, there is increasing evidence of a cross-talk between AT, body metabolism, and the heart; however, mechanisms remain to be clarified. Strong evidence of this cross-talk is the so-called 'obesity paradox', in which moderately obese patients with heart failure have a more favourable outcome than lean counterparts, thereby indicating that 'AT quality' rather than its 'quantity' differentially impacts cardiac tissue. Several hypotheses have been proposed to explain the beneficial effects of AT in heart failure, most of which are related to higher metabolic reserves to deal with the catabolic state and the cardioprotective profile of adipocytokines released by AT.[180]

The classic perspective of AT as inert lipid storage has evolved into perceiving it as a metabolically dynamic endocrine organ capable of remotely signalling other tissues to alter their metabolism.[182] Moreover, it comprises multiple cell types, including adipocytes, monocytes/macrophages, pericytes, endothelial cells, and various stem cells, which are responsible for carrying out a diversity of biological functions.[183] Apart from metabolic regulation, other actions of AT on the heart identified thus far include regulation of inflammation and oxidative stress as well as cell proliferation, migration, and hypertrophy. Under normal conditions, AT produces and secretes a variety of bioactive polypeptides,[184] including adipocytokines,[185] that regulate cell metabolism endocrinally or paracrinally.[186] In a pathophysiological context, AT dysregulation switches the expression pattern of adipocytokines towards a more pro-inflammatory profile.[187] Thus, not surprisingly, dysfunctional AT can directly affect the heart or indirectly—via its metabolic, pulmonary, renal, and vascular actions—as it is responsible for precipitating multiple age-related diseases and leading to premature death from diabetes or HF.[180] *Figure 3* depicts the cardiovascular impact of dysfunctional AT.

AT can be classified into white or brown AT and, accordingly, into its distribution (visceral, subcutaneous, epicardial, intramyocardial, and perivascular, among others).[188] Apart from its endocrine function, numerous fat depots serve specialized functions related to their neighbouring tissues.

Visceral adipose tissue represents approximately 20% of total body AT. It secretes adipocytokines into the portal vein, which rapidly contribute to insulin resistance in the liver and subsequently in the peripheral organs.[189,190] This feature, along with its elevated metabolic activity, associates this fat pad with higher deleterious metabolic consequences when compared with other fat depots[191] (*Figure 3*).

The subcutaneous adipose tissue (SAT) is the most represented type of AT that corresponds to approximately 80% of all the fat in the body.[189] Nevertheless, it is clinically less important compared with the visceral adipose tissue. The different physiological processes triggered and secretory pattern presented by SAT is the underlying cause of its almost insignificant role in the development of metabolic disorders and CVD. However, recent categorization of this SAT into subcutaneous or deep SAT has pointed towards distinct roles of these two subtypes.

The epicardial adipose tissue (EAT) is located between the visceral pericardium and the myocardium, accounting for 20% of total heart weight.[192,193] There is no fascia separating EAT from the myocardium or coronary arteries.[187,188,194–196] Thus, several pieces of evidence suggest that this proximity provides conditions for direct crosstalk between the epicardial AT, the coronary arteries, and the myocardium through proinflammatory and profibrotic adipocytokines that can modulate, locally, the endothelial cells and the cardiomyocytes independently of the traditional risk factors and the other visceral fat depot.

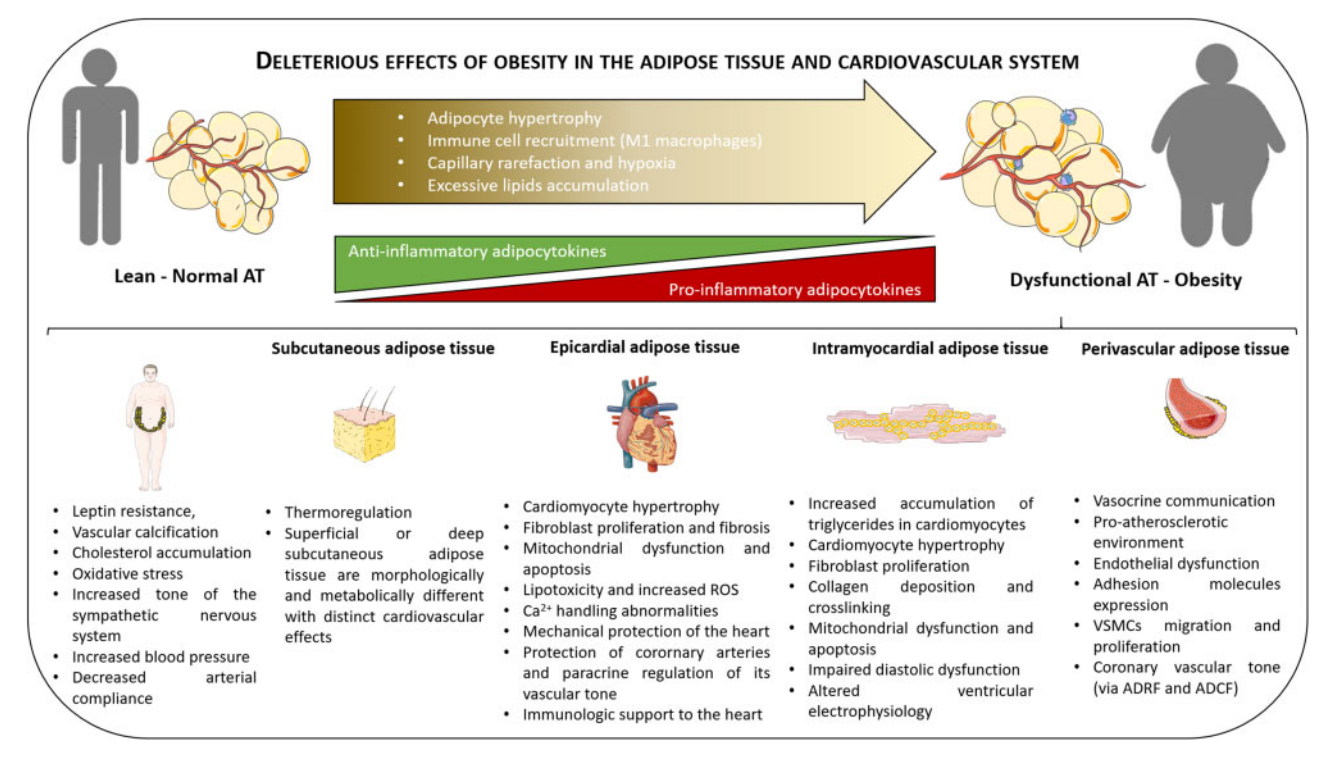

Figure 3 Obesity-induces adipose tissue dysfunction (upper panel). The cardiac consequences of dysfunctional visceral, subcutaneous, epicardial, intramyocardial, and perivascular adipose tissue are depicted in the lower panel. Of note, certain cardiovascular actions are shared by distinct fat pads. ADRF, adipocyte-derived relaxing factors; ADCF, adipocyte-derived contracting factors.

Perivascular adipose tissue (PVAT) is defined as the AT located around blood vessels[197,198] with a rather active role in paracrinally regulating vascular tone.[199] This regulation has been ascribed to the release of adipocyte-derived relaxing factors (ADRFs) that diminish the contractile actions of vasoconstrictors or adipocyte-derived contracting factors (ADCFs)[200] that are increasingly formed under disease conditions such as obesity and diabetes.[201] The PVAT secretory profile contains bioactive substances which are crucial for regulating vascular tone, remodelling, and endothelial function and, thus, arterial pressure and blood flow.[202] These bioactive factors establish an important link between body fat and the cardiovascular system and include adipocytokines, chemokines, gaseous molecules, prostacyclin, and ROS, among others.[203,204]

Finally, intramyocardial adipose (IMAT) tissue is represented by intramyocellular triglyceride accumulation and closely correlates to insulin-resistance. IMAT has been shown to contribute to electrophysiological dysfunction and ventricular tachycardia in large animal models of myocardial infarction, which is consistent with its colocalization with areas of fibrosis.[205,206]

Obese animal models for studying AT-myocardial interaction are often obtained by selectively crossing rats with one out of the two most significant mutations in leptin receptor, *fa* (on the *fatty* gene group) and *cp* (*corpulent* gene mutation). This is true for the Zucker fatty rats that present an *fa* mutation[194] or JCR: La-cp rats that carry the *cp* mutation. Numerous crossings have been made between these two 'families', thereby resulting in the SHROB, the obese spontaneous hypertensive heart failure rat (SHHF/Mcc-fa^{cp} rats),[195] the obese Zucker diabetic fatty (ZDF), and the obese ZSF1. From a different lineage, the Otsuka Long-Evans Tokushima Fatty (OLETF) rat presents with obesity, hyperglycaemia, hyperinsulinemia, and chronic diabetes. The cardiac changes and subtype of HF these rats develop are strain-dependent: (i) the Zucker fatty or Zucker obese rat exhibits hypertrophy, impaired left ventricular (LV) shortening, and early diastolic dysfunction (prolonged IVRT);[207,208] (ii) the SHROB develop hypertension, cardiac hypertrophy, and decreased fractional shortening;[209] (iii) the obese SHHF indicate a progressive decrease of ejection fraction, fibrosis, and increased LV volume progressing towards a dilated hypertrophy, which mostly resembles a phenotype of HFrEF;[210] (iv) the obese ZDF rats exhibit moderate hypertension, impaired LV shortening, and relaxation (decreased E/A) with increased arterial stiffness. Moreover, LV wall thickness is lower and LV end-systolic wall stress is higher than that in the controls;[31,140,208,211] (v) the obese ZSF1 presents impaired relaxation and increased stiffness around 20 weeks of age while preserving the ejection fraction. Moreover, it shows effort intolerance and lung congestion and is, therefore, considered a robust animal model of HFpEF,[212] and (vi) OLEFT develops diastolic dysfunction from 20 weeks of age as observed by deceleration time of the E-wave and decreased E/A.[211] Mice strains with leptin deficiency (*ob/ob* mice[213]) or with a mutation in the leptin receptor (*db/db* mice[214]) are the most used models of obesity. The advantageous features as models of obesity and metabolic syndrome are hyperglycaemia and hyperlipidaemia without hypertension. Both models develop diastolic and systolic dysfunction at different time points of the progression of the disease.

In addition to the transgenic strains, a large number of animal models of obesity can be induced by the intake of modified diets, such as high-fat

Table 1 Available animal models to test inter-organ effects during heart failure

Species	Model	Ref
Surgical/interventional models		
Mouse/rat	Surgical models: • LAD → AMI • AC → decreased left ventricular output • constriction of either the ascending aorta or the aortic arch → extreme load of the left ventricle; HF	138–141
Mouse	Models of VCI: • bilateral common carotid artery stenosis • middle cerebral artery occlusion • asymmetric common carotid artery surgery • TAC, MI, mixed models	41,34,35
Mouse	Model of hepatic cardiomyopathy: mice with bile-duct ligation (BDL)-induced liver fibrosis	173
Rat	experimental renal failure (by 5/6 nephrectomy) causing cardiac dysfunction	217,218
Rat	Double-hit model of CRS: subtotal nephrectomy followed by NO depletion or surgically induced MI	219,220
Rat	Model of VCI: • Bilateral common carotid artery occlusion	34
Rat	Model of pulmonary hypertension: • By pulmonary artery banding for 7 weeks, different diameters causing mild vs. severe RV dysfunction	81
Dog	Model of congestive HF with skeletal muscle alterations achieved by • rapid ventricular pacing • sequential intracoronary microembolization	142 143
Sheep	Model of VCI: • Middle cerebral artery occlusion	41
Baboon	Model of VCI: • Three-vessel occlusion (both the internal carotid arteries and the left vertebral artery)	34
Pharmacological and diet-based models		
Mouse	Doxorubicin-induced cardiomyopathy	140
Mouse	Model of pulmonary hypertension, induced by infusion of AT II over 2 weeks (500 ng/kg/min)	134,135
Mouse	Diet-based models of obesity: • C57BL/6 mouse fed with a high-fat diet • High-carbohydrate diet protocols	221
Rat	Genetic/diet-based model of cardiac hypertrophy, the Dahl salt-sensitive rats: a particular strain characterized by a marked genetic susceptibility to develop hypertension and congestive HF following ingestion of high-salt diet	127–129
Rat	Model of pulmonary hypertension induced by: • single injection of monocrotaline (60 mg/kg) • infusion of AT II over 2 weeks (500 ng/kg/min)	81,111,136
Genetic models		
Mouse	Genetic model of cardiac hypertrophy: transgenic mice overexpressing the cardiac isoform of calsequestrin under the control of the α-myosin heavy chain promoter	124–126
Mouse	Genetic model of familial cardiomyopathy: cardiac myosin binding protein-C null mice	130
Mouse	Genetic models of obesity and metabolic syndrome based on the leptin receptor: • *ob/ob* mice • *db/db* mice	213,214,222
Rat	Genetic models for studying AT-myocardial interaction in obese animals: • obese spontaneous hypertensive heart failure SHHF/Mcc-facp rat • Otsuka Long-Evans Tokushima Fatty (OLETF) rat	140,194–196,210,223,224

AC, aortic constriction; AMI, acute myocardial infarction; AT, adipose tissue; AT II, angiotensin II; BDL, bile-duct ligation; CRS, cardio-renal syndrome; HF, heart failure; LAD, left anterior descending artery; MI, myocardial infarction; NO, nitric oxide; RV, right ventricle; TAC, transverse aortic constriction; VCI, vascular cognitive impairment.

or high-carbohydrate diets (cp. *Table 1*). The nutrition-based conditions may represent more relevant pathophysiological models of the human disease. However, as in humans, the cardiac impact of diet is highly dependent on its composition and caloric intake.[215] For example, if C57BL/6 mice are fed with a high-fat diet, they develop vascular dysfunction and atherosclerosis in which the interaction between perivascular AT and vessels can be easily studied. Additional strains are characterized by genetic modifications that correspond to an entire new range of transgenic mice, including knock-out and knock-in strains (for more details, consult[140,216]).

In the *in vitro* setting, collecting conditioned medium obtained from AT provides a useful means to study the impact of factors secreted by AT on other organs or tissues (vessels, myocardial strips, cardiomyocytes, fibroblasts or endothelial cells, among others) after performing co-cultures and subsequent functional studies.[31,225]

It is currently accepted that therapeutic interventions or other strategies that delay or limit AT turnover, redistribution, or dysfunction are associated with improved lifespan.[226] These strategies include dietary and lifestyle changes, such as increasing physical activity, anti-obesity drugs, or bariatric surgery.[226] A short-term weight loss, for up to six months, is usually achieved but is more difficult to maintain in the long term. Thus, weight loss approaches must be individually tailored, taking into account age, sex, race, the degree of obesity, individual health risks, metabolic characteristics, and environmental and genetic factors.[181]

10. The immune system and the heart

This section summarizes the main directions of how the immune system may interact with cardiac diseases. Data on elevated levels of inflammatory mediators in heart failure patients and experimental studies repeatedly indicate the activation of inflammation to be causally related to left ventricular remodelling and dysfunction.[227] Chronic ischemic heart failure results in a shift of the immune phenotype of circulating immune cells with altered transcript profiles, as indicated by single-cell sequencing. An increase in fatty acid-binding protein-5 (FABP5) and Wnt signalling pathways partially contributed to enhanced monocyte activation, as recently revealed to occur in human heart failure.[228] Further, single-cell RNA sequencing to map the cardiac immune composition in experimental mouse models of either pressure-overload induced HF[229] or auto-immune myocarditis[230] indicate that a large diversity of cardiac immune cells—macrophages, B cells, T cells and regulatory T cells, dendritic cells, Natural Killer cells, neutrophils, and mast cells—is activated in the failing heart, thereby further potentially widening the therapeutic window in cardioimmunology.

Although phase III clinical trials antagonizing inflammatory mediators have been negative thus far, the most recent CANTOS trial indicates that specific patients with a cardiac inflammatory phenotype may still positively respond to therapies that target immune cells and inflammation. In the CANTOS trial, patients with post-myocardial infarction were treated with canakinumab, an antibody that targets the interleukin-1β innate immunity pathway. This approach led to a significantly lower cardiovascular event rate independent of a lipid-level lowering effect.[80] In view of the increased prevalence of heart failure in auto-immune diseases—with cardiovascular diseases being the number one cause of death in auto-immune diseases[231]—understanding the interaction between the immune system, T cells and monocytes in particular, and the heart is of outmost importance.

10.1 T cells

Various T-cell subsets play separate roles in the failing heart depending on the inflammation-triggering event, with specific chemokines and adhesion molecules in the heart, and circulating epitopes activating their cardiac recruitment. Inhibition of anti-inflammatory T-regulatory cells as part of anti-cancer treatment with check-point inhibitors leads to de-repression, or activation, of aggressive inflammatory responses (T cells and macrophages) against cross-epitopes in the heart. Two percent of the cancer patients getting check-point inhibitors are likely to develop heart failure due to fulminant myocarditis.[232] Abatacept, an FDA-approved drug that inhibits T-cell co-stimulation through T-regulatory cells, reduces severity, and delays progression of pressure overload-induced cardiac hypertrophy and fibrosis in mice, even when this commences at a later stage of disease.[233] Abatacept also prevents this immune checkpoint inhibition—T-reg de-repression-mediated myocarditis and heart failure.[234]

In chronic heart failure, a systemic expansion of inflammation-related cell types ($CD4^+$ and $CD8^+$ T cells, $CD4^+$ Th1, Th2, Th17, and various Treg subsets) takes place in the failing heart, the circulation, and also in lymphoid organs.[235] Activated CD4+ T cells drive heart failure progression in ischemic HF and, interestingly, CD4+ T-cell ablation partially halts pathological LV remodelling in ischemic heart failure.[235]

10.2 Monocyte/macrophages

A recent review summarizes the ontogeny and function but also specifically the interplay of both tissue-resident as well as monocyte-derived macrophages in numerous organs.[236]

10.3 Resident cardiac macrophages

Resident cardiac macrophages are derived from different embryonic lineages, are long-lived, and persist independent of blood monocyte input. Their behaviour is different from the blood-derived macrophages. Recent data indicate that those resident macrophages mainly proliferate upon external pathological stimuli to stimulate cardiomyocyte regeneration and physiological hypertrophy, prevent adverse monocyte recruitment, and stimulate vascular expansion.[237] As such, those resident macrophages may, therefore, aim to protect the heart against damage and failure at the initial stage of the disease.[237]

10.4 Invading cardiac monocytes

Invading cardiac monocytes, on the other hand, are required to heal the injured myocardium,[238] but they have the negative side effect of stimulating fibrosis, pathological hypertrophy, and vessel regression, thereby overall leading to heart failure.[239] Whereas others have provided first evidence that indicates a role of resident macrophages in preventing cardiac systolic failure upon ischemic injury,[236,239,240] the implication of resident macrophages in non-ischemic cardiomyopathy—particularly in heart failure with preserved ejection fraction (HFpEF)—remains completely unknown.

Overall, these findings indicate an involvement of the immune system in cardiac dysfunction and arrhythmias. Future trials with novel therapeutic modalities to target the cardiac immunity are warranted.

11. Animal models to study cardiac/extracardiac interactions

Table 1 compiles animal models that are currently available for the study of cardiac/extracardiac interactions in heart failure. However, despite the availability of numerous animal models, there is a need to develop more clinically realistic models. In the case of animal studies, this would indicate the use of older or aged animals and add 'risk factors' or initiate parallel additional non-cardiac diseases in such models. Importantly, most current models use 'acute' rather than chronic scenarios. This is in great contrast to clinical reality and may explain weak translational power. Thus, the use of more chronically acting disease stimuli rather than acute toxic applications to create an artificial organ failure model are required. For example, certain drugs may only best work in animals/patients with a certain disease, as recently proposed.[241] But even despite better developed animal models, they still are animal models with certain uncertainties for translation to human beings. Thus, importantly, we must additionally develop better *in vitro* or *ex vivo* systems to study inter-organ interactions. For example, it is now possible to also utilize human living cardiac tissue to study intercellular interactions in a very clinically relevant context.[242]

12. Conclusion

In this position paper, we provided a brief overview of known organ interactions during heart failure. Of course, there are multiple further interactions of the heart and other organ systems that are not discussed in this review, such as interactions with bone marrow, pancreas, and diabetes in general, skin, sex hormones, or others. This is illustrated by the fact that HF prevalence increases after menopause in women and particularly often results in HFpEF, a fact that has been extensively reviewed.[243] Clearly, heart failure must be viewed as a multifactorial clinical syndrome that affects and involves multiple organs, with numerous subtypes based on additional leading organs involved. This holds true particularly in an aging population where HF as a syndrome is more frequent.[244] More clinical and experimental research is urgently needed to understand individual molecular mechanisms and, based on that, the development of more tailored therapeutic interventions that not only target the heart but also other related affected organ systems. This position paper aims to enable the provision of an overview regarding potential interactions between the heart and other organ systems, the clinical evidence, their underlying mechanisms, available animal models, and finally potential new drug interventions to be developed in the future. It also suggests that new therapeutic strategies aiming at the root of HF—either directly in heart tissue or indirectly on diseased other organs contributing to HF—are necessary. We also strongly advise that more research funds must be generated for HF research not just nationally but also by the European Union, as HF remains a deadly condition and main cause of death in industrialized nations.

Authors' contributions

M.C., D.D., I.F.P., M.G., N.H., S.H., C.G.T., J.v.d.V., S.Z., and T.T. designed the concept and structure of the position paper. M.C. drafted the section entitled *Heart and Kidney*; D.D. and N.H. drafted the section entitled *Heart and Lung*; I.F.P. drafted the section entitled *Heart and Adipose Tissue*; M.C. and S.Z. drafted the section entitled *Heart and Skeletal Muscle*; S.H. drafted the section entitled *Heart and Innate Immunity*; A.H., A.L., D.H., and J.v.d.V. drafted the section entitled *Heart and Brain*; C.G.T. drafted the section entitled *Heart and Intestine*; and T.T. drafted the sections entitled *Heart and Liver*, Introduction, Animal Models, and Conclusion. J.v.d.V. and T.T. provided substantial revisions to the draft manuscript. All authors revised the manuscript and approved the version to be published.

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