

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 'HF_rEF', 'HF_mrEF', or 'HF_pEF', 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

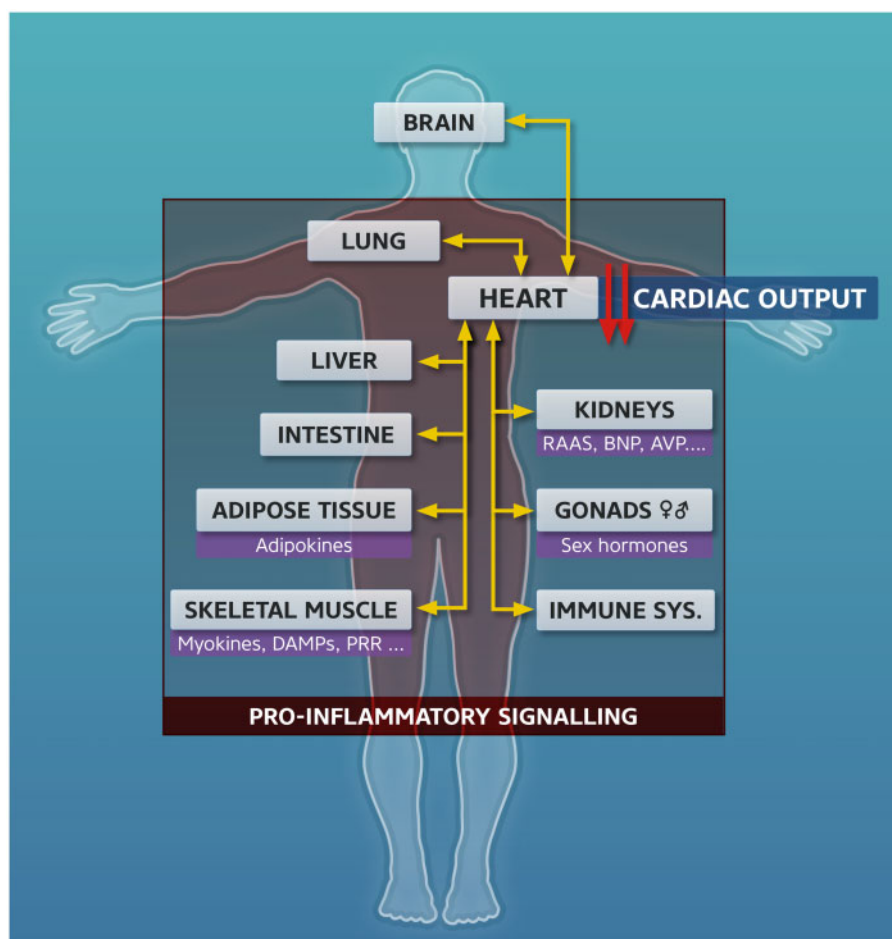


Figure 1 Diagram of postulated organ crosstalk in heart disease—namely between the heart, kidneys, brain, lung, skeletal muscle, intestine, liver, adipose tissue, gonads, and the immune system. Details are elaborated in the respective subsections. RAAS, renin–angiotensin–aldosterone system; BNP, natriuretic brain peptide; AVP, arginine 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 cells²³ 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 intricately regulated 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.clinicaltrials.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, TNF α —was found to increase in cerebral vascular smooth muscle cells of the MI mice six weeks after intervention. Interrupting the TNF α 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 (IL1 β , 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 IL1 β 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 TNF α —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 genes⁸⁴ 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 TNF α , IL-1 β , 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 TNF α and TWEAK (TNF-like weak inducer of apoptosis)—activate NF- κ B 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, nor-epinephrine, and angiotensin II levels.¹⁰⁵ Chronic epinephrine and nor-epinephrine exposure results in reduced β 2-adrenergic receptor signalling and persistent β 1-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- κ B 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 descending (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 TNF α was higher in HFrEF while IL-1 β 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 O₂ 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 gp130R β /IL-6R α , 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 caldesmon (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-1 β , 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 mice¹³⁰), 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 pacing¹⁴² or intracoronary microembolization¹⁴³ 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 cardio-circulatory system by indirectly ameliorating the activity of the gut barrier by stimulating mucus production; activating olfactory receptor 51E2 (OR51E2; also known as OLF78) 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

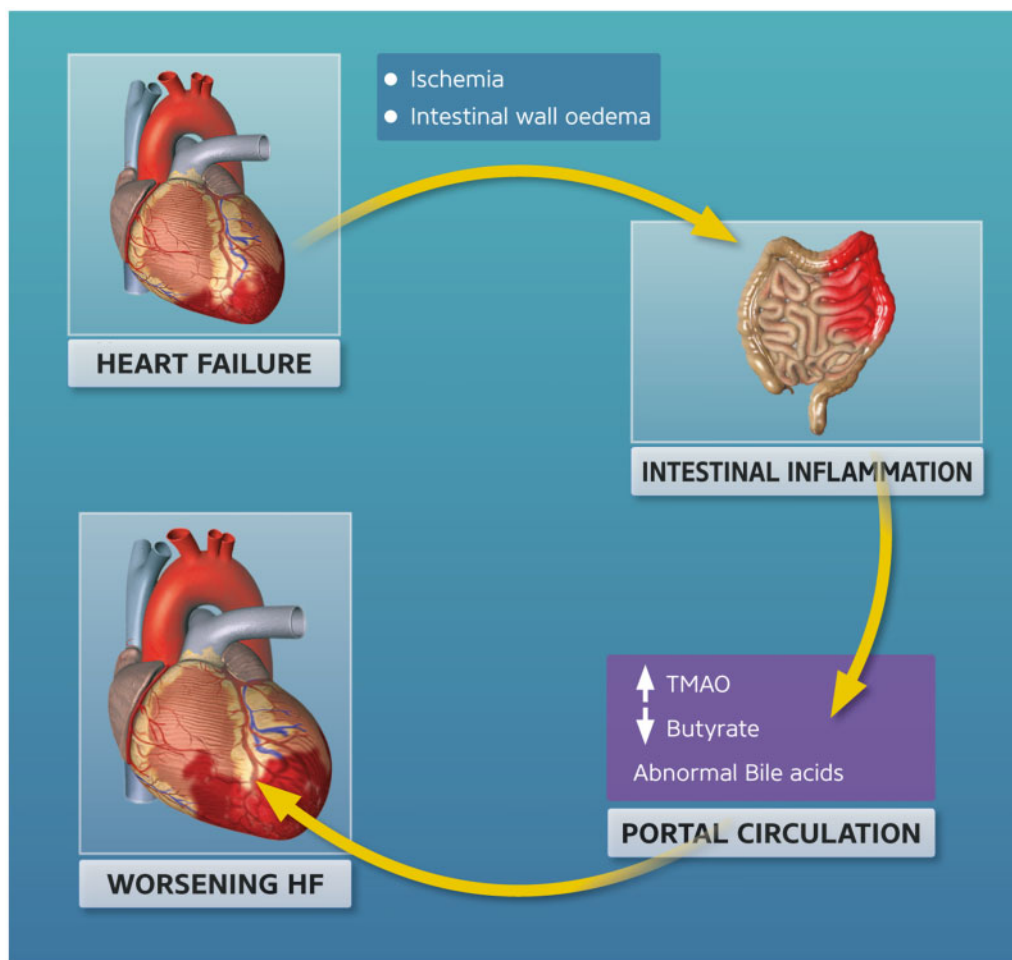


Figure 2 Display of the hypothesized interaction between the failing heart and the intestine. TMAO, trimethylamine N-oxide.

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 (CB₂-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 CB₂-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 depots¹⁹¹ (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 pro-inflammatory 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.

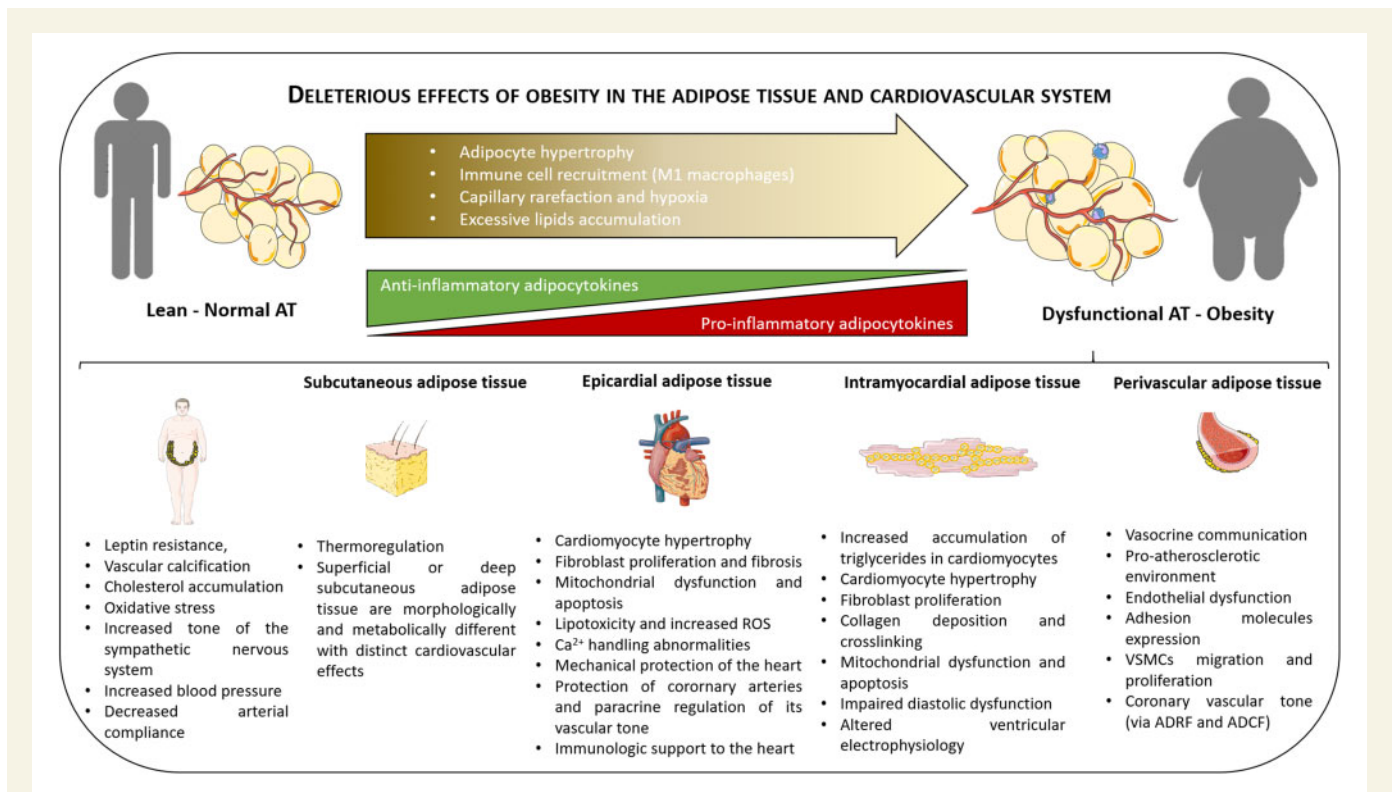


Figure 3 Obesity-induces adipose tissue dysfunction (upper panel). The cardiac consequences of dysfunctional visceral, subcutaneous, epicardial, intramyocardial, and perivascular adipose tissue are depicted in the lower panel. Of note, certain cardiovascular actions are shared by distinct fat pads. ADRF, 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, remodeling, 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* mutation¹⁹⁴ 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 HFpEF,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) OLETF 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* mice²¹³) or with a mutation in the leptin receptor (*db/db* mice²¹⁴) 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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • Bilateral common carotid artery occlusion 	34
Rat	Model of pulmonary hypertension: <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • rapid ventricular pacing • sequential intracoronary microembolization 	142 143
Sheep	Model of VCI: <ul style="list-style-type: none"> • Middle cerebral artery occlusion 	41
Baboon	Model of VCI: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • <i>ob/ob</i> mice • <i>db/db</i> mice 	213,214,222
Rat	Genetic models for studying AT-myocardial interaction in obese animals: <ul style="list-style-type: none"> • 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 HF²²⁹ or auto-immune myocarditis²³⁰ 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-1 β 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 diseases²³¹—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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References

- Husain-Syed F, McCullough PA, Birk HW, Renker M, Brocca A, Seeger W, Ronco C. Cardio-pulmonary-renal interactions: a multidisciplinary approach. *J Am Coll Cardiol* 2015;**65**:2433–2448.
- Bang C, Thum T. Exosomes: new players in cell-cell communication. *Int J Biochem Cell Biol* 2012;**44**:2060–2064.
- Bar C, Thum T, de Gonzalo-Calvo D. Circulating miRNAs as mediators in cell-to-cell communication. *Epigenomics* 2019;**11**:111–113.
- Bang C, Batkai S, Dangwal S, Gupta SK, Foinquinos A, Holzmann A, Just A, Remke J, Zimmer K, Zeug A, Ponimaskin E, Schmiedl A, Yin X, Mayr M, Halder R, Fischer A, Engelhardt S, Wei Y, Schober A, Fiedler J, Thum T. Cardiac fibroblast-derived microRNA passenger strand-enriched exosomes mediate cardiomyocyte hypertrophy. *J Clin Invest* 2014;**124**:2136–2146.
- Virzi GM, Day S, de Cal M, Vescovo G, Ronco C. Heart-kidney crosstalk and role of humoral signaling in critical illness. *Crit Care* 2014;**18**:201.
- Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008;**52**:1527–1539.
- Liu S. Heart-kidney interactions: mechanistic insights from animal models. *Am J Physiol Renal Physiol* 2019;**316**:F974–F985.

8. Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, Krumholz HM. Renal impairment and outcomes in heart failure. Systematic review and meta-analysis. *J Am Coll Cardiol* 2006;**47**:1987–1996.
9. Park JW, Yang PS, Bae HJ, Yang SY, Yu HT, Kim TH, Uhm JS, Joung B, Lee MH, Pak HN. Five-year change in the renal function after catheter ablation of atrial fibrillation. *J Am Heart Assoc* 2019;**8**:e013204.
10. Liu JJ, Liu S, Gurung RL, Ang K, Ee Tang W, Sum CF, Tavintharan S, Hadjadj S, Lim SC. Arterial stiffness modulates the association of resting heart rate with rapid renal function decline in individuals with type 2 diabetes mellitus. *Arterioscler Thromb Vasc Biol* 2019;**39**:2437–2444.
11. Ito T, Yoshimura M, Nakamura S, Nakayama M, Shimasaki Y, Harada E, Mizuno Y, Yamamuro M, Harada M, Saito Y, Nakao K, Kurihara H, Yasue H, Ogawa H. Inhibitory effect of natriuretic peptides on aldosterone synthase gene expression in cultured neonatal rat cardiocytes. *Circulation* 2003;**107**:807–810.
12. Imamura T, Kinugawa K, Hatano M, Fujino T, Inaba T, Maki H, Kinoshita O, Nawata K, Kyo S, Ono M, Komuro I. Low cardiac output stimulates vasopressin release in patients with stage D heart failure. *Circ J* 2014;**78**:2259–2267.
13. Niizuma S, Iwanaga Y. Revisiting vasopressin and heart failure. *Expert Rev Cardiovasc Ther* 2013;**11**:1451–1454.
14. Hatamizadeh P, Fonarow GC, Budoff MJ, Darabian S, Kovacs CP, Kalantar-Zadeh K. Cardiorenal syndrome: pathophysiology and potential targets for clinical management. *Nat Rev Nephrol* 2013;**9**:99–111.
15. Verkaik M, Oranje M, Abdurrahim D, Goebel M, Gam Z, Prompers JJ, Helmes M, Ter Wee PM, van der Velden J, Kuster DW, Vervloet MG, Eringa EC; the NIGRAM Consortium. High fibroblast growth factor 23 concentrations in experimental renal failure impair calcium handling in cardiomyocytes. *Physiol Rep* 2018;**6**:e13591.
16. Szymanski MK, Buikema JH, Veldhuisen DJ, Koster J, Velden J, Hamdani N, Hillege JL, Schoemaker RG. Increased cardiovascular risk in rats with primary renal dysfunction; mediating role for vascular endothelial function. *Basic Res Cardiol* 2012;**107**:242.
17. Johnson RJ, Nangaku M. Endothelial dysfunction: the secret agent driving kidney disease. *J Am Soc Nephrol* 2016;**27**:3–5.
18. Reddy MA, Natarajan R. Recent developments in epigenetics of acute and chronic kidney diseases. *Kidney Int* 2015;**88**:250–261.
19. Beckerman P, Ko YA, Susztak K. Epigenetics: a new way to look at kidney diseases. *Nephrol Dial Transplant* 2014;**29**:1821–1827.
20. Xiao D, Dasgupta C, Chen M, Zhang K, Buchholz J, Xu Z, Zhang L. Inhibition of DNA methylation reverses norepinephrine-induced cardiac hypertrophy in rats. *Cardiovasc Res* 2014;**101**:373–382.
21. Lorenzen JM, Thum T. Long noncoding RNAs in kidney and cardiovascular diseases. *Nat Rev Nephrol* 2016;**12**:360–373.
22. Rana I, Kompa AR, Skommer J, Wang BH, Lekawanvijit S, Kelly DJ, Krum H, Charchar FJ. Contribution of microRNA to pathological fibrosis in cardiorenal syndrome: impact of uremic toxins. *Physiol Rep* 2015;**3**:e12371.
23. Godwin JG, Ge X, Stephan K, Jurisch A, Tullius SG, Iacomini J. Identification of a microRNA signature of renal ischemia reperfusion injury. *Proc Natl Acad Sci U S A* 2010;**107**:14339–14344.
24. Zarjou A, Yang S, Abraham E, Agarwal A, Liu G. Identification of a microRNA signature in renal fibrosis: role of miR-21. *Am J Physiol Renal Physiol* 2011;**301**:F793–F801.
25. Zhong X, Chung ACK, Chen H-Y, Meng X-M, Lan HY. Smad3-mediated upregulation of miR-21 promotes renal fibrosis. *J Am Soc Nephrol* 2011;**22**:1668–1681.
26. Adam O, Lohfelm B, Thum T, Gupta SK, Puhl S-L, Schafers H-J, Bohm M, Laufs U. Role of miR-21 in the pathogenesis of atrial fibrosis. *Basic Res Cardiol* 2012;**107**:278.
27. Cardin S, Guasch E, Luo X, Naud P, Le Quang K, Shi Y, Tardif J-C, Comtois P, Nattel S. Role for MicroRNA-21 in atrial profibrillatory fibrotic remodeling associated with experimental postinfarction heart failure. *Circ Arrhythm Electrophysiol* 2012;**5**:1027–1035.
28. Kolling M, Kaucsar T, Schauerte C, Hubner A, Dettling A, Park J-K, Busch M, Wulff X, Meier M, Scherf K, Bukosza N, Szenasi G, Godo M, Sharma A, Heuser M, Hamar P, Bang C, Haller H, Thum T, Lorenzen JM. Therapeutic miR-21 silencing ameliorates diabetic kidney disease in mice. *Mol Ther* 2017;**25**:165–180.
29. Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Bussen M, Galuppo P, Just S, Rotbauer W, Frantz S, Castoldi M, Soutschek J, Kotliarsky V, Rosenwald A, Basson MA, Licht JD, Pena JTR, Rouhanifard SH, Muckenthaler MU, Tuschl T, Martin GR, Bauersachs J, Engelhardt S. MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. *Nature* 2008;**456**:980–984.
30. Mahaffey KW, Jardine MJ, Bompont S, Cannon CP, Neal B, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Capuano G, de Zeeuw D, Greene T, Levin A, Pollock C, Sun T, Wheeler DC, Yavin Y, Zhang H, Zinman B, Rosenthal N, Brenner BM, Perkovic V; on behalf of the CREDESCENCE Study Investigators. Canagliflozin and cardiovascular and renal outcomes in type 2 diabetes mellitus and chronic kidney disease in primary and secondary cardiovascular prevention groups. *Circulation* 2019;**140**:739–750.
31. Juni RP, Kuster DWD, Goebel M, Helmes M, Musters RJP, van der Velden J, Koolwijk P, Paulus WJ, van Hinsbergh VWM. Cardiac microvascular endothelial enhancement of cardiomyocyte function is impaired by inflammation and restored by empagliflozin. *JACC Basic Transl Sci* 2019;**4**:575–591.
32. Baartscheer A, Schumacher CA, Wüst RCI, Fiolet JWT, Stienen GJM, Coronel R, Zuurbier CJ. Empagliflozin decreases myocardial cytoplasmic Na⁺ through inhibition of the cardiac Na⁺/H⁺ exchanger in rats and rabbits. *Diabetologia* 2017;**60**:568–573.
33. Pabel S, Wagner S, Bollenberg H, Bengel P, Kovács Á, Schach C, Tirilomis P, Moustroph J, Renner A, Gummert J, Fischer T, Van Linthout S, Tschöpe C, Streckfuss-Bömeke K, Hasenfuss G, Maier LS, Hamdani N, Sossalla S. Empagliflozin directly improves diastolic function in human heart failure. *Eur J Heart Fail* 2018;**20**:1690–1700.
34. Washida K, Hattori Y, Ihara M. Animal models of chronic cerebral hypoperfusion: from mouse to primate. *Int J Mol Sci* 2019;**20**: 6176.
35. Bink DI, Ritz K, Aronica E, van der Weerd L, Daemen MJAP. Mouse models to study the effect of cardiovascular risk factors on brain structure and cognition. *J Cereb Blood Flow Metab* 2013;**33**:1666–1684.
36. Bosch L, de Haan JJ, Bastemeijer M, van der Burg J, van der Worp E, Wesseling M, Viola M, Odille C, El Azzouzi H, Pasterkamp G, Sluijter JPG, Wever KE, de Jager SCA. The transverse aortic constriction heart failure animal model: a systematic review and meta-analysis. *Heart Fail Rev* 2020 Apr 25. doi: 10.1007/s10741-020-09960-w. Online ahead of print.
37. Yang J, Noyan-Ashraf MH, Meissner A, Voigtlaender-Bolz J, Kroetsch JT, Foltz W, Jaffray D, Kapoor A, Momen A, Heximer SP, Zhang H, van Eede M, Henkelman RM, Matthews SG, Lidington D, Husain M, Bolz S-S. Proximal cerebral arteries develop myogenic responsiveness in heart failure via tumor necrosis factor- α -dependent activation of sphingosine-1-phosphate signaling. *Circulation* 2012;**126**:196–206.
38. Kaplan A, Yabluchanskiy A, Ghali R, Altara R, Booz GW, Zouein FA. Cerebral blood flow alteration following acute myocardial infarction in mice. *Biosci Rep* 2018;**38**: BSR20180382.
39. Hay M, Vanderah TW, Samareh-Jahani F, Constantopoulos E, Uprety AR, Barnes CA, Konhilas J. Cognitive impairment in heart failure: a protective role for angiotensin-(1-7). *Behav Neurosci* 2017;**131**:99–114.
40. Shibata M, Ohtani R, Ihara M, Tomimoto H. White matter lesions and glial activation in a novel mouse model of chronic cerebral hypoperfusion. *Stroke* 2004;**35**:2598–2603.
41. Hainsworth AH, Allan SM, Boltze J, Cunningham C, Farris C, Head E, Ihara M, Isaacs JD, Kalaria RN, Lesnik Oberstein SAMJ, Moss MB, Nitzsche B, Rosenberg GA, Rutten JW, Salkovic-Petrisic M, Troen AM. Translational models for vascular cognitive impairment: a review including larger species. *BMC Med* 2017;**15**:16.
42. van der Flier WM, Skoog I, Schneider JA, Pantoni L, Mok V, Chen CLH, Scheltens P. Vascular cognitive impairment. *Nat Rev Dis Prim* 2018;**4**:18003.
43. Gathright EC, Dolansky MA, Gunstad J, Josephson RA, Moore SM, Hughes JW. Examination of attention, executive function, and memory as predictors of mortality risk in adults with systolic heart failure. *Eur J Cardiovasc Nurs* 2019;**18**:729–735.
44. Currie K, Rideout A, Lindsay G, Harkness K. The association between mild cognitive impairment and self-care in adults with chronic heart failure: a systematic review and narrative synthesis. *J Cardiovasc Nurs* 2015;**30**:382–393.
45. McLennan SN, Pearson SA, Cameron J, Stewart S. Prognostic importance of cognitive impairment in chronic heart failure patients: does specialist management make a difference? *Eur J Heart Fail* 2006;**8**:494–501.
46. Gallagher R, Sullivan A, Burke R, Hales S, Gillies G, Cameron J, Saliba B, Toftler G. Mild cognitive impairment, screening, and patient perceptions in heart failure patients. *J Card Fail* 2013;**19**:641–646.
47. Frey A, Sell R, Homola GA, Malsch C, Kraft P, Gunreben I, Morbach C, Alkonyi B, Schmid E, Colonna I, Hofer E, Müllges W, Ertl G, Heuschmann P, Solymosi L, Schmidt R, Störk S, Stoll G. Cognitive deficits and related brain lesions in patients with chronic heart failure. *JACC Hear Fail* 2018;**6**:583–592.
48. Harkness K, Demers C, Heckman GA, McKelvie RS. Screening for cognitive deficits using the montreal cognitive assessment tool in outpatients <65 years of age with heart failure. *Am J Cardiol* 2011;**107**:1203–1207.
49. Vogels RLC, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: a systematic review of the literature. *Eur J Heart Fail* 2007;**9**:440–449.
50. Hooghiemstra AM, Bertens AS, Leeuwis AE, Bron EE, Bots ML, Brunner-La Rocca H-P, de Craen AJM, van der Geest RJ, Greving JP, Kappelle LJ, Niessen WJ, van Oostenbrugge RJ, van Osch MJP, de Roos A, van Rossum AC, Biessels GJ, van Buchem MA, Daemen MJAP, van der Flier WM; on behalf of the Heart-Brain Connection Consortium. The missing link in the pathophysiology of vascular cognitive impairment: design of the heart-brain study. *Cerebrovasc Dis Extra* 2017;**7**:140–152.
51. Hooghiemstra AM, Leeuwis AE, Bertens AS, Biessels GJ, Bots ML, Brunner-La Rocca H-P, Greving JP, Kappelle LJ, van Oostenbrugge RJ, van Rossum AC, van der Flier WM; Heart-Brain Connection Consortium. Frequent cognitive impairment in patients with disorders along the heart-brain axis. *Stroke* 2019;**50**:3369–3375.
52. Vogels RLC, van der Flier WM, van Harten B, Gouw AA, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Brain magnetic resonance imaging abnormalities in patients with heart failure. *Eur J Heart Fail* 2007;**9**:1003–1009.
53. Cogswell RJ, Norby FL, Gottesman RF, Chen LY, Solomon S, Shah A, Alonso A. High prevalence of subclinical cerebral infarction in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail* 2017;**19**:1303–1309.
54. Havakuk O, King KS, Grazette L, Yoon AJ, Fong M, Bregman N, Elkayam U, Kloner RA. Heart failure-induced brain injury. *J Am Coll Cardiol* 2017;**69**:1609–1616.

55. Hassell MEC, Nijveldt R, Roos YBW, Majoie CBL, Hamon M, Piek JJ, Delewi R. Silent cerebral infarcts associated with cardiac disease and procedures. *Nat Rev Cardiol* 2013;**10**:696–706.
56. Ferro D, van den Brink H, Amier R, van Buchem M, de Bresser J, Bron E, Brunner-La Rocca HP, Hooghiemstra A, Marcks N, van Rossum A, Biessels GJ. Cerebral cortical microinfarcts: a novel MRI marker of vascular brain injury in patients with heart failure. *Int J Cardiol* 2020;**310**:96–102.
57. Leeuwis AE, Benedictus MR, Kuijer JPA, Binnewijzend MAA, Hooghiemstra AM, Verfaillie SCJ, Koene T, Scheltens P, Barkhof F, Prins ND, van der Flier WM. Lower cerebral blood flow is associated with impairment in multiple cognitive domains in Alzheimer's disease. *Alzheimers Dement* 2016;**13**:531–540.
58. Alcoso ML, Gunstad J, Jerskey B, A, Xu X, Clark US, Hassenstab J, Cote DM, Walsh EG, Labbe DR, Hoge R, Cohen RA, Sweet LH. The adverse effects of reduced cerebral perfusion on cognition and brain structure in older adults with cardiovascular disease. *Brain Behav* 2013;**3**:626–636.
59. Leeuwis AE, Hooghiemstra AM, Bron EE, Kuipers S, Oudeman EA, Kalay T, Rocca HB, Kappelle LJ, Van Oostenbrugge RJ, Greving JP, Niessen WJ, Van Buchem MA, Van Osch MJ, Van Rossum AC, Prins ND, Biessels G, van der Flier WM. Cerebral blood flow and cognitive functioning in patients with disorders along the heart–brain axis. *Alzheimers Dement* 2020;**6**:e12034.
60. Vogels RLC, Oosterman JM, van Harten B, Gouw AA, Schroeder-Tanka JM, Scheltens P, van der Flier WM, Weinstein HC. Neuroimaging and correlates of cognitive function among patients with heart failure. *Dement Geriatr Cogn Disord* 2007;**24**:418–423.
61. Tublin JM, Adelstein JM, Monte F, Combs CK, Wold LE. Getting to the heart of Alzheimer disease. *Circ Res* 2019;**124**:142–149.
62. Britton KA, Gaziano JM, Djousse L. Normal systolic blood pressure and risk of heart failure in US male physicians. *Eur J Heart Fail* 2009;**11**:1129–1134.
63. Hawkins NM, Petrie MC, Macdonald MR, Jhund PS, Fabbri LM, Wikstrand J, McMurray JJV. Heart failure and chronic obstructive pulmonary disease the quandary of beta-blockers and beta-agonists. *J Am Coll Cardiol* 2011;**57**:2127–2138.
64. Dzau VJ, Antman EM, Black HR, Hayes DL, Manson JE, Plutzky J, Popma JJ, Stevenson W. The cardiovascular disease continuum validated: clinical evidence of improved patient outcomes: part I: pathophysiology and clinical trial evidence (risk factors through stable coronary artery disease). *Circulation* 2006;**114**:2850–2870.
65. Le Jemtel TH, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol* 2007;**49**:171–180.
66. Barnes PJ. Chronic obstructive pulmonary disease. *N Engl J Med* 2000;**343**:269–280.
67. Jessup M, Brozena S. Heart failure. *N Engl J Med* 2003;**348**:2007–2018.
68. Rutten FH, Cramer M-JM, Grobbee DE, Sachs APE, Kirkels JH, Lammers J-WJ, Hoeks AW. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J* 2005;**26**:1887–1894.
69. Macchia A, Rodriguez Moncalvo JJ, Kleiner M, Comignani PD, Gimeno G, Arakaki D, Laffaye N, Fuselli JJ, Massolin HP, Gambarte J, Romero M, Tognoni G. Unrecognised ventricular dysfunction in COPD. *Eur Respir J* 2012;**39**:51–58.
70. Scally C, Rudd A, Mezincescu A, Wilson H, Sriwanasan J, Horgan G, Broadhurst P, Newby DE, Henning A, Dawson DK. Persistent long-term structural, functional, and metabolic changes after stress-induced (Takotsubo) cardiomyopathy. *Circulation* 2018;**137**:1039–1048.
71. Sin DD, Man SFP. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003;**107**:1514–1519.
72. Willemse BW, ten Hacken NHT, Rutgers B, Lesman-Leegte IGAT, Postma DS, Timens W. Effect of 1-year smoking cessation on airway inflammation in COPD and asymptomatic smokers. *Eur Respir J* 2005;**26**:835–845.
73. Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010;**137**:1091–1097.
74. Poulain M, Doucet M, Major GC, Drapeau V, Series F, Boulet L-P, Tremblay A, Maltais F. The effect of obesity on chronic respiratory diseases: pathophysiology and therapeutic strategies. *CMAJ* 2006;**174**:1293–1299.
75. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? *Lancet* 2007;**370**:797–799.
76. Scally C, Abbas H, Ahearn T, Srinivasan J, Mezincescu A, Rudd A, Spath N, Yucel-Finn A, Yucel R, Oldroyd K, Dospinescu C, Horgan G, Broadhurst P, Henning A, Newby DE, Semple S, Wilson HM, Dawson DK. Myocardial and systemic inflammation in acute stress-induced (Takotsubo) cardiomyopathy. *Circulation* 2019;**139**:1581–1592.
77. Steele P, Ellis JH, Van Dyke D, Sutton F, Creagh E, Davies H. Left ventricular ejection fraction in severe chronic obstructive airways disease. *Am J Med* 1975;**59**:21–28.
78. Hetzel M, Kochs M, Marx N, Woehrl H, Mobarak I, Hombach V, Hetzel J. Pulmonary hemodynamics in obstructive sleep apnea: frequency and causes of pulmonary hypertension. *Lung* 2003;**181**:157–166.
79. O'Hearn DJ, Gold AR, Gold MS, Diggs B, Scharf SM. Lower extremity edema and pulmonary hypertension in morbidly obese patients with obstructive sleep apnea. *Sleep Breath* 2009;**13**:25–34.
80. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;**377**:1119–1131.
81. Rain S, Andersen S, Najafi A, Gammelgaard Schultz J, da Silva Goncalves Bos D, Handoko ML, Bogaard H-J, Vonk-Noordegraaf A, Andersen A, van der Velden J, Ottenheim CAC, de Man FS. Right ventricular myocardial stiffness in experimental pulmonary arterial hypertension: relative contribution of fibrosis and myofibril stiffness. *Circ Heart Fail* 2016;**9**:e002636. doi: 10.1161/CIRCHEARTFAILURE.115.002636.
82. Rain S, Handoko ML, Trip P, Gan CT-J, Westerhof N, Stienen GJ, Paulus WJ, Ottenheim CAC, Marcus JT, Dorfmueller P, Guignabert C, Humbert M, Macdonald P, Dos Remedios C, Postmus PE, Saripalli C, Hidalgo CG, Granzier HL, Vonk-Noordegraaf A, van der Velden J, de Man FS. Right ventricular diastolic impairment in patients with pulmonary arterial hypertension. *Circulation* 2013;**128**:2016–2025.
83. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell* 2014;**157**:121–141.
84. van der Bruggen CE, Happe CM, Dorfmueller P, Trip P, Spruijt OA, Rol N, Hoevenaars FP, Houweling AC, Girerd B, Marcus JT, Mercier O, Humbert M, Handoko ML, van der Velden J, Vonk-Noordegraaf A, Bogaard HJ, Goumans M-J, de Man FS. Bone morphogenetic protein receptor type 2 mutation in pulmonary arterial hypertension: a view on the right ventricle. *Circulation* 2016;**133**:1747–1760.
85. CIBIS II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13.
86. Wikstrand J, on behalf of the MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**:2001–2007.
87. de Man FS, Handoko ML, van Ballegoij JJJ, Schalij I, Bogaards SJP, Postmus PE, van der Velden J, Westerhof N, Paulus WJ, Vonk-Noordegraaf A. Bisoprolol delays progression towards right heart failure in experimental pulmonary hypertension. *Circ Heart Fail* 2012;**5**:97–105.
88. Bhatt SP, Wells JM, Kinney GL, Washko GRJ, Budoff M, Kim Y-I, Bailey WC, Nath H, Hokanson JE, Silverman EK, Crapo J, Dransfield MT. Beta-blockers are associated with a reduction in COPD exacerbations. *Thorax* 2016;**71**:8–14.
89. Du Q, Sun Y, Ding N, Lu L, Chen Y. Beta-blockers reduced the risk of mortality and exacerbation in patients with COPD: a meta-analysis of observational studies. *PLoS One* 2014;**9**:e113048.
90. van Campen JSJA, de Boer K, van de Veerdonk MC, van der Bruggen CEE, Allaart CP, Rajmakers PG, Heymans MW, Marcus JT, Harms HJ, Handoko ML, de Man FS, Vonk-Noordegraaf A, Bogaard H-J. Bisoprolol in idiopathic pulmonary arterial hypertension: an explorative study. *Eur Respir J* 2016;**48**:787–796.
91. Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, Harrington D, Kox WJ, Poole-Wilson PA, Coats AJ. Wasting as independent risk factor for mortality in chronic heart failure. *Lancet* 1997;**349**:1050–1053.
92. Mancini DM, Walter G, Reichel N, Lenkinski R, McCully KK, Mullen JL, Wilson JR. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. *Circulation* 1992;**85**:1364–1373.
93. Poole DC, Hirai DM, Copp SW, Musch TI. Muscle oxygen transport and utilization in heart failure: implications for exercise (in)tolerance. *Am J Physiol Heart Circ Physiol* 2012;**302**:H1050–H1063.
94. Fulster S, Tacke M, Sandek A, Ebner N, Tschöpe C, Doehner W, Anker SD, von Haehling S. Muscle wasting in patients with chronic heart failure: results from the studies investigating co-morbidities aggravating heart failure (SICA-HF). *Eur Heart J* 2013;**34**:512–519.
95. von Haehling S, Doehner W, Anker SD. Nutrition, metabolism, and the complex pathophysiology of cachexia in chronic heart failure. *Cardiovasc Res* 2007;**73**:298–309.
96. Houstis NE, Eisman AS, Pappagianopoulos PP, Wooster L, Bailey CS, Wagner PD, Lewis GD. Exercise intolerance in heart failure with preserved ejection fraction: diagnosing and ranking its causes using personalized O₂ pathway analysis. *Circulation* 2018;**137**:148–161.
97. Montero D, Diaz-Canestro C. Skeletal muscle O₂ diffusion and the limitation of aerobic capacity in heart failure: a clarification. *Front Cardiovasc Med* 2019;**6**:78.
98. Deswal A, Petersen NJ, Feldman AM, Young JB, White BG, Mann DL. Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). *Circulation* 2001;**103**:2055–2059.
99. Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol* 1996;**27**:1201–1206.
100. Zhang L, Pan J, Dong Y, Twardy DJ, Dong Y, Garibotto G, Mitch WE. Stat3 activation links a C/EBPdelta to myostatin pathway to stimulate loss of muscle mass. *Cell Metab* 2013;**18**:368–379.
101. Dogra C, Changoua H, Wedhas N, Qin X, Wergedal JE, Kumar A. TNF-related weak inducer of apoptosis (TWEAK) is a potent skeletal muscle-wasting cytokine. *FASEB J* 2007;**21**:1857–1869.

102. de Alvaro C, Teruel T, Hernandez R, Lorenzo M. Tumor necrosis factor alpha produces insulin resistance in skeletal muscle by activation of inhibitor kappaB kinase in a p38 MAPK-dependent manner. *J Biol Chem* 2004;**279**:17070–17078.
103. Cai D, Frantz JD, Tawa NEJ, Melendez PA, Oh B-C, Lidov HGW, Hasselgren P-O, Frontera WR, Lee J, Glass DJ, Shoelson SE. IKKbeta/NF-kappaB activation causes severe muscle wasting in mice. *Cell* 2004;**119**:285–298.
104. Garnham JO, Roberts LD, Caspi T, Al-Owais MM, Bullock M, Swoboda PP, Koshy A, Gierula J, Paton MF, Cubbon RM, Kearney MT, Bowen TS, Witte KK. Divergent skeletal muscle mitochondrial phenotype between male and female patients with chronic heart failure. *J Cachexia Sarcopenia Muscle* 2020;**11**:79–88.
105. Mentz RJ, O'Connor CM. Pathophysiology and clinical evaluation of acute heart failure. *Nat Rev Cardiol* 2016;**13**:28–35.
106. Rosca MG, Tandler B, Hoppel CL. Mitochondria in cardiac hypertrophy and heart failure. *J Mol Cell Cardiol* 2013;**55**:31–41.
107. Bacurau AVN, Jardim MA, Ferreira JCB, Bechara LRG, Bueno CRJ, Alba-Loureiro TC, Negrao CE, Casarini DE, Curi R, Ramires PR, Moriscot AS, Brum PC. Sympathetic hyperactivity differentially affects skeletal muscle mass in developing heart failure: role of exercise training. *J Appl Physiol* 2009;**106**:1631–1640.
108. Voltarelli VA, Bechara LRG, Bacurau AVN, Mattos KC, Dourado PMM, Bueno CRJ, Casarini DE, Negrao CE, Brum PC. Lack of beta2-adrenoceptors aggravates heart failure-induced skeletal muscle myopathy in mice. *J Cell Mol Med* 2014;**18**:1087–1097.
109. Inoue N, Kinugawa S, Suga T, Yokota T, Hirabayashi K, Kuroda S, Okita K, Tsutsui H. Angiotensin II-induced reduction in exercise capacity is associated with increased oxidative stress in skeletal muscle. *Am J Physiol Heart Circ Physiol* 2012;**302**:H1202–H1210.
110. Bechara LRG, Moreira JBN, Jannig PR, Voltarelli VA, Dourado PM, Vasconcelos AR, Scavone C, Ramires PR, Brum PC. NADPH oxidase hyperactivity induces plantaris atrophy in heart failure rats. *Int J Cardiol* 2014;**175**:499–507.
111. Brink M, Wellen J, Delafontaine P. Angiotensin II causes weight loss and decreases circulating insulin-like growth factor I in rats through a pressor-independent mechanism. *J Clin Invest* 1996;**97**:2509–2516.
112. Yoshida T, Semprun-Prieto L, Sukhanov S, Delafontaine P. IGF-1 prevents ANG II-induced skeletal muscle atrophy via Akt- and Foxo-dependent inhibition of the ubiquitin ligase atrogin-1 expression. *Am J Physiol Heart Circ Physiol* 2010;**298**:H1565–H1570.
113. Bowen TS, Rolim NPL, Fischer T, Baekkerud FH, Medeiros A, Werner S, Bronstad E, Rogmo O, Mangner N, Linke A, Schuler G, Silva GJJ, Wisloff U, Adams V; on behalf of the Optimex Study Group. Heart failure with preserved ejection fraction induces molecular, mitochondrial, histological, and functional alterations in rat respiratory and limb skeletal muscle. *Eur J Heart Fail* 2015;**17**:263–272.
114. Seiler M, Bowen TS, Rolim N, Dieterlen M-T, Werner S, Hoshi T, Fischer T, Mangner N, Linke A, Schuler G, Halle M, Wisloff U, Adams V. Skeletal muscle alterations are exacerbated in heart failure with reduced compared with preserved ejection fraction: mediated by circulating cytokines? *Circ Heart Fail* 2016;**9**:e003027. doi: 10.1161/CIRCHEARTFAILURE.116.003027.
115. Adams V, Alves M, Fischer T, Rolim N, Werner S, Schutt N, Bowen TS, Linke A, Schuler G, Wisloff U. High-intensity interval training attenuates endothelial dysfunction in a Dahl salt-sensitive rat model of heart failure with preserved ejection fraction. *J Appl Physiol* 2015;**119**:745–752.
116. Dhakal BP, Malhotra R, Murphy RM, Pappagianopoulos PP, Baggish AL, Weiner RB, Houstis NE, Eisman AS, Hough SS, Lewis GD. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. *Circ Heart Fail* 2015;**8**:286–294.
117. Kitzman DW, Nicklas B, Kraus WE, Lyles MF, Eggebeen J, Morgan TM, Haykowsky M. Skeletal muscle abnormalities and exercise intolerance in older patients with heart failure and preserved ejection fraction. *Am J Physiol Heart Circ Physiol* 2014;**306**:H1364–H1370.
118. Lee JF, Barrett-O'Keefe Z, Nelson AD, Garten RS, Ryan JJ, Nativi-Nicolau JN, Richardson RS, Wray DW. Impaired skeletal muscle vasodilation during exercise in heart failure with preserved ejection fraction. *Int J Cardiol* 2016;**211**:14–21.
119. Pedersen BK, Febbraio MA. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. *Physiol Rev* 2008;**88**:1379–1406.
120. Biasucci LM, Vitelli A, Liuzzo G, Altamura S, Caligiuri G, Monaco C, Rebuzzi AG, Ciliberto G, Maseri A. Elevated levels of interleukin-6 in unstable angina. *Circulation* 1996;**94**:874–877.
121. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* 2000;**101**:1767–1772.
122. Seki M, Powers JC, Maruyama S, Zuriaga MA, Wu C-L, Kurishima C, Kim L, Johnson J, Poidomani A, Wang T, Munoz E, Rajan S, Park JY, Walsh K, Recchia FA. Acute and chronic increases of circulating FSTL1 normalize energy substrate metabolism in pacing-induced heart failure. *Circ Heart Fail* 2018;**11**:e004486.
123. Nakayama H, Otsu K. Mitochondrial DNA as an inflammatory mediator in cardiovascular diseases. *Biochem J* 2018;**475**:839–852.
124. Cho MC, Rapacciuolo A, Koch WJ, Kobayashi Y, Jones LR, Rockman HA. Defective beta-adrenergic receptor signaling precedes the development of dilated cardiomyopathy in transgenic mice with calsequestrin overexpression. *J Biol Chem* 1999;**274**:22251–22256.
125. Geng T, Li P, Yin X, Yan Z. PGC-1alpha promotes nitric oxide antioxidant defenses and inhibits FOXO signaling against cardiac cachexia in mice. *Am J Pathol* 2011;**178**:1738–1748.
126. Li P, Waters RE, Redfern SI, Zhang M, Mao L, Annex BH, Yan Z. Oxidative phenotype protects myofibers from pathological insults induced by chronic heart failure in mice. *Am J Pathol* 2007;**170**:599–608.
127. Dahl LK, Knudsen KD, Heine M, Leitl G. Effects of chronic excess salt ingestion. Genetic influence on the development of salt hypertension in parabiotic rats: evidence for a humoral factor. *J Exp Med* 1967;**126**:687–699.
128. Kato T, Niizuma S, Inuzuka Y, Kawashima T, Okuda J, Kawamoto A, Tamaki Y, Iwanaga Y, Soga T, Kita T, Kimura T, Shioi T. Analysis of liver metabolism in a rat model of heart failure. *Int J Cardiol* 2012;**161**:130–136.
129. Tanada Y, Shioi T, Kato T, Kawamoto A, Okuda J, Kimura T. Branched-chain amino acids ameliorate heart failure with cardiac cachexia in rats. *Life Sci* 2015;**137**:20–27.
130. Song T, Manoharan P, Millay DP, Koch SE, Rubinstein J, Heiny JA, Sadayappan S. Dilated cardiomyopathy-mediated heart failure induces a unique skeletal muscle myopathy with inflammation. *Skelet Muscle* 2019;**9**:4.
131. Caforio AL, Rossi B, Risaliti R, Siciliano G, Marchetti A, Angelini C, Crea F, Mariani M, Muratorio A. Type 1 fiber abnormalities in skeletal muscle of patients with hypertrophic and dilated cardiomyopathy: evidence of subclinical myogenic myopathy. *J Am Coll Cardiol* 1989;**14**:1464–1473.
132. Hajahmadi M, Shemshadi S, Khalilipour E, Amin A, Taghavi S, Maleki M, Malek H, Naderi N. Muscle wasting in young patients with dilated cardiomyopathy. *J Cachexia Sarcopenia Muscle* 2017;**8**:542–548.
133. Stitt TN, Drujan D, Clarke BA, Panaro F, Timofeyeva Y, Kline WO, Gonzalez M, Yancopoulos GD, Glass DJ. The IGF-1/PI3K/Akt pathway prevents expression of muscle atrophy-induced ubiquitin ligases by inhibiting FOXO transcription factors. *Mol Cell* 2004;**14**:395–403.
134. Song Y-H, Li Y, Du J, Mitch WE, Rosenthal N, Delafontaine P. Muscle-specific expression of IGF-1 blocks angiotensin II-induced skeletal muscle wasting. *J Clin Invest* 2005;**115**:451–458.
135. Schulze PC, Fang J, Kassik KA, Gannon J, Cupesi M, MacGillivray C, Lee RT, Rosenthal N. Transgenic overexpression of locally acting insulin-like growth factor-1 inhibits ubiquitin-mediated muscle atrophy in chronic left-ventricular dysfunction. *Circ Res* 2005;**97**:418–426.
136. Steffen BT, Lees SJ, Booth FW. Anti-TNF treatment reduces rat skeletal muscle wasting in monocrotaline-induced cardiac cachexia. *J Appl Physiol* 2008;**105**:1950–1958.
137. Ahn B, Empinado HM, Al-Rajhi M, Judge AR, Ferreira LF. Diaphragm atrophy and contractile dysfunction in a murine model of pulmonary hypertension. *PLoS One* 2013;**8**:e62702.
138. Molinari F, Malara N, Mollace V, Rosano G, Ferraro E. Animal models of cardiac cachexia. *Int J Cardiol* 2016;**219**:105–110.
139. deAlmeida AC, van Oort RJ, Wehrens XHT. Transverse aortic constriction in mice. *J Vis Exp* 2010;38:1729.
140. Gomes AC, Falcão-Pires I, Pires AL, Brás-Silva C, Leite-Moreira AF. Rodent models of heart failure: an updated review. *Heart Fail Rev* 2013;**18**:219–249.
141. Helies-Toussaint C, Moinard C, Rasmussen C, Tabbi-Annani I, Cynober L, Grynberg A. Aortic banding in rat as a model to investigate malnutrition associated with heart failure. *Am J Physiol Regul Integr Comp Physiol* 2005;**288**:R1325–R1331.
142. Rosca MG, Hoppel CL. Mitochondrial dysfunction in heart failure. *Heart Fail Rev* 2013;**18**:607–622.
143. Sabbah HN, Stein PD, Kono T, Gheorghide M, Levine TB, Jafri S, Hawkins ET, Goldstein S. A canine model of chronic heart failure produced by multiple sequential coronary microembolizations. *Am J Physiol* 1991;**260**:H1379–H1384.
144. Anker SD, Egerer KR, Volk HD, Kox WJ, Poole-Wilson PA, Coats AJ. Elevated soluble CD14 receptors and altered cytokines in chronic heart failure. *Am J Cardiol* 1997;**79**:1426–1430.
145. Krack A, Sharma R, Figulla HR, Anker SD. The importance of the gastrointestinal system in the pathogenesis of heart failure. *Eur Heart J* 2005;**26**:2368–2374.
146. Tang WHW, Li DY, Hazen SL. Dietary metabolism, the gut microbiome, and heart failure. *Nat Rev Cardiol* 2019;**16**:137–154.
147. Russo M, Guida F, Paparo L, Trinchese G, Aitoro R, Avagliano C, Fiordelisi A, Napolitano F, Mercurio V, Sala V, Li M, Sorriento D, Ciccarelli M, Ghigo A, Hirsch E, Bianco R, Iaccarino G, Abete P, Bonaduce D, Calignano A, Berni Canani R, Tocchetti CG. The novel butyrate derivative phenylalanine-butylamide protects from doxorubicin-induced cardiotoxicity. *Eur J Heart Fail* 2019;**21**:519–528.
148. Paparo L, Calignano A, Tocchetti CG, Di Scala C, Russo R, Bonaduce D, Berni Canani R. The influence of fiber on gut microbiota: butyrate as molecular player involved in the beneficial interplay between dietary fiber and cardiovascular health. In: R. A. Samaan (ed) *Dietary Fiber for the Prevention of Cardiovascular Disease*. London: Elsevier, 2017;61–71.
149. Schuett K, Kleber ME, Schramagl H, Lorkowski S, März W, Niessner A, Marx N, Meinitzer A. Trimethylamine-N-oxide and heart failure with reduced versus preserved ejection fraction. *J Am Coll Cardiol* 2017;**70**:3202–3204.
150. Mujumdar VS, Tummalapalli CM, Aru GM, Tyagi SC. Mechanism of constrictive vascular remodeling by homocysteine: role of PPAR. *Am J Physiol Cell Physiol* 2002;**282**:C1009–C1015.

151. Brown AJ, Goldsworthy SM, Barnes AA, Eilert MM, Tcheang L, Daniels D, Muir AI, Wigglesworth MJ, Kinghorn I, Fraser NJ, Pike NB, Strum JC, Steplewski KM, Murdoch PR, Holder JC, Marshall FH, Szekeres PG, Wilson S, Ignar DM, Foord SM, Wise A, Dowell SJ. The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *J Biol Chem* 2003;**278**:11312–11319.
152. Le Poul E, Loison C, Struyf S, Springael J-Y, Lannoy V, Decobecq M-E, Brezillon S, Dupriez V, Vassart G, Van Damme J, Parmentier M, Detheux M. Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. *J Biol Chem* 2003;**278**:25481–25489.
153. Ali FY, Armstrong PCJ, Dhanji A-RA, Tucker AT, Paul-Clark MJ, Mitchell JA, Warner TD. Antiplatelet actions of statins and fibrates are mediated by PPARs. *Arterioscler Thromb Vasc Biol* 2009;**29**:706–711.
154. Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolph MS, Mackay F, Artis D, Xavier RJ, Teixeira MM, Mackay CR. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature* 2009;**461**:1282–1286.
155. Li L, Hua Y, Ren J. Short-chain fatty acid propionate alleviates Akt2 knockout-induced myocardial contractile dysfunction. *Exp Diabetes Res* 2012;**2012**:1–10.
156. Kim MH, Kang SG, Park JH, Yanagisawa M, Kim CH. Short-chain fatty acids activate GPR41 and GPR43 on intestinal epithelial cells to promote inflammatory responses in mice. *Gastroenterology* 2013;**145**:396–396.
157. Gil-Cruz C, Perez-Shibayama C, De Martin A, Ronchi F, van der Borgh K, Niederer R, Onder L, Lütge M, Novkovic M, Nindl V, Ramos G, Arnoldini M, Slack EMC, Boivin-Jahns V, Jahns R, Wyss M, Mooser C, Lambrecht BN, Maeder MT, Rickli H, Flatz L, Eriksson U, Geuking MB, McCoy KD, Ludwig B. Microbiota-derived peptide mimics drive lethal inflammatory cardiomyopathy. *Science* 2019;**366**:881–886.
158. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, Knight R. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A* 2010;**107**:11971–11975.
159. Goodrich JK, Waters JL, Poole AC, Sutter JL, Koren O, Blekhan R, Beaumont M, Van Treuren W, Knight R, Bell JT, Spector TD, Clark AG, Ley RE. Human genetics shape the gut microbiome. *Cell* 2014;**159**:789–799.
160. Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, Li Y, Xia Y, Xie H, Zhong H, Khan MT, Zhang J, Li J, Xiao L, Al-Aama J, Zhang D, Lee YS, Kotowska D, Colding C, Tremaroli V, Yin Y, Bergman S, Xu X, Madsen L, Kristiansen K, Dahlgren J, Wang J. Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host Microbe* 2015;**17**:690–703.
161. Kinross JM, Darzi AW, Nicholson JK. Gut microbiome-host interactions in health and disease. *Genome Med* 2011;**3**:14.
162. Sherlock S. The liver in heart failure; relation of anatomical, functional, and circulatory changes. *Br Heart J* 1951;**13**:273–293.
163. Lefkowitz JH, Mendez L. Morphologic features of hepatic injury in cardiac disease and shock. *J Hepatol* 1986;**2**:313–327.
164. Giallourakis CC, Rosenberg PM, Friedman LS. The liver in heart failure. *Clin Liver Dis* 2002;**6**:947–967, viii–ix.
165. Dichtl W, Vogel W, Dunst KM, Grander W, Alber HF, Frick M, Antretter H, Laufer G, Pachinger O, Polzl G. Cardiac hepatopathy before and after heart transplantation. *Transplant Int* 2005;**18**:697–702.
166. Poelzl G, Eberl C, Achraier H, Doerler J, Pachinger O, Frick M, Ulmer H. Prevalence and prognostic significance of elevated gamma-glutamyltransferase in chronic heart failure. *Circ Heart Fail* 2009;**2**:294–302.
167. Allen LA, Felker GM, Pocock S, McMurray JJV, Pfeffer MA, Swedberg K, Wang D, Yusuf S, Michelson EL, Granger CB, for the CHARM Investigators. Liver function abnormalities and outcome in patients with chronic heart failure: data from the Candesartan in Heart Failure: assessment of Reduction in Mortality and Morbidity (CHARM) program. *Eur J Heart Fail* 2009;**11**:170–177.
168. Batin P, Wickens M, McEntegart D, Fullwood L, Cowley AJ. The importance of abnormalities of liver function tests in predicting mortality in chronic heart failure. *Eur Heart J* 1995;**16**:1613–1618.
169. Poelzl G, Ess M, Mussner-Seeber C, Pachinger O, Frick M, Ulmer H. Liver dysfunction in chronic heart failure: prevalence, characteristics and prognostic significance. *Eur J Clin Invest* 2012;**42**:153–163.
170. Liu H, Jayakumar S, Traboulsi M, Lee SS. Cirrhotic cardiomyopathy: implications for liver transplantation. *Liver Transpl* 2017;**23**:826–835.
171. Blendis L, Wong F. The hyperdynamic circulation in cirrhosis: an overview. *Pharmacol Ther* 2001;**89**:221–231.
172. Cazzaniga M, Salerno F, Pagnozzi G, Dionigi E, Visentin S, Cirello I, Meregaglia D, Nicolini A. Diastolic dysfunction is associated with poor survival in patients with cirrhosis with transjugular intrahepatic portosystemic shunt. *Gut* 2007;**56**:869–875.
173. Matyas C, Erdelyi K, Trojnar E, Zhao S, Varga ZV, Paloczi J, Mukhopadhyay P, Nemeth BT, Hasko G, Cinar R, Rodrigues RM, Ait Ahmed Y, Gao B, Pachter P. Interplay of liver-heart inflammatory axis and cannabinoid 2 receptor signaling in an experimental model of hepatic cardiomyopathy. *Hepatology* 2020;**71**:1391–1407.
174. Wiese S, Hove JD, Bendtsen F, Moller S. Cirrhotic cardiomyopathy: pathogenesis and clinical relevance. *Nat Rev Gastroenterol Hepatol* 2014;**11**:177–186.
175. Gupta SK, Itagaki R, Zheng X, Batkai S, Thum S, Ahmad F, Van Aelst LN, Sharma A, Piccoli M-T, Weinberger F, Fiedler J, Heuser M, Heymans S, Falk CS, Forster R, Schrepfer S, Thum T. miR-21 promotes fibrosis in an acute cardiac allograft transplantation model. *Cardiovasc Res* 2016;**110**:215–226.
176. Piccoli M-T, Gupta SK, Viereck J, Foinquinos A, Samolovac S, Kramer FL, Garg A, Remke J, Zimmer K, Batkai S, Thum T. Inhibition of the cardiac fibroblast-enriched lncRNA Meg3 prevents cardiac fibrosis and diastolic dysfunction. *Circ Res* 2017;**121**:575–583.
177. Stojkovic S, Koller L, Sulzgruber P, Hulsmann M, Huber K, Mayr M, Hengstenberg C, Wojta J, Niessner A. Liver-specific microRNA-122 as prognostic biomarker in patients with chronic systolic heart failure. *Int J Cardiol* 2020;**303**:80–85.
178. Viereck J, Thum T. Circulating noncoding RNAs as biomarkers of cardiovascular disease and injury. *Circ Res* 2017;**120**:381–399.
179. Derda AA, Pfanne A, Bar C, Schimmel K, Kennel PJ, Xiao K, Schulze PC, Bauersachs J, Thum T. Blood-based microRNA profiling in patients with cardiac amyloidosis. *PLoS One* 2018;**13**:e0204235.
180. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol* 2009;**53**:1925–1932.
181. Neeland IJ, Poirier P, Després J-P. Cardiovascular and metabolic heterogeneity of obesity: clinical challenges and implications for management. *Circulation* 2018;**137**:1391–1406.
182. Guglielmi V, Sbraccia P. Epicardial adipose tissue: at the heart of the obesity complications. *Acta Diabetol* 2017;**54**:805–812.
183. Ha EE, Bauer RC. Emerging roles for adipose tissue in cardiovascular disease. *Arterioscler Thromb Vasc Biol* 2018;**38**:e137–e144.
184. DeClercq V, Taylor C, Zahradka P. Adipose tissue: the link between obesity and cardiovascular disease. *Cardiovasc Hematol Disord Drug Targets* 2008;**8**:228–237.
185. Falcão-Pires I, Castro-Chaves P, Miranda-Silva D, Lourenço AP, Leite-Moreira AF, Leite-Moreira AF. Physiological, pathological and potential therapeutic roles of adipokines. *Drug Discov Today* 2012;**17**:880–889.
186. Hajer GR, van Haeflten TW, Visseren FLJ. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. *Eur Heart J* 2008;**29**:2959–2971.
187. Northcott JM, Yeganeh A, Taylor CG, Zahradka P, Wigle JT. Adipokines and the cardiovascular system: mechanisms mediating health and disease. *Can J Physiol Pharmacol* 2012;**90**:1029–1059.
188. Fuster JJ, Ouchi N, Gokce N, Walsh K. Obesity-induced changes in adipose tissue microenvironment and their impact on cardiovascular disease. *Circ Res* 2016;**118**:1786–1807.
189. Bergman RN, Kim SP, Catalano KJ, Hsu IR, Chiu JD, Kabir M, Hucking K, Ader M. Why visceral fat is bad: mechanisms of the metabolic syndrome. *Obesity* 2006;**14**:165–195.
190. Nava E, Llorens S. The paracrine control of vascular motion. A historical perspective. *Pharmacol Res* 2016;**113**:125–145.
191. Bays HE, González-Campoy JM, Bray GA, Kitabchi AE, Bergman DA, Schorr AB, Rodbard HW, Henry RR. Pathogenic potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. *Expert Rev Cardiovasc Ther* 2008;**6**:343–368.
192. Iacobellis G. Epicardial and pericardial fat: close, but very different. *Obesity (Silver Spring)* 2009;**17**:625–625, author reply 626–627.
193. Rabkin SW. Epicardial fat: properties, function and relationship to obesity. *Obes Rev Off J Int Assoc Study Obes* 2007;**8**:253–261.
194. Ernsberger P, Koletsky RJ, Baskin JS, Collins LA. Consequences of weight cycling in obese spontaneously hypertensive rats. *Am J Physiol* 1996;**270**:R864–R872.
195. McCune SA, Baker PB, Stills HF. SHHF/Mcc-cp rat: model of obesity, non-insulin-dependent diabetes, and congestive heart failure. *ILAR J* 1990;**32**:23–27.
196. Lourenço AP, Falcão-Pires I, Leite-Moreira AF. In vivo experimental assessment of cardiac function. In D. Cokkinos (eds). *Introduction to Translational Cardiovascular Research*. Switzerland: Springer International, 2015. pp. 389–411.
197. Aldiss P, Davies G, Woods R, Budge H, Sacks HS, Symonds ME. 'Browning' the cardiac and peri-vascular adipose tissues to modulate cardiovascular risk. *Int J Cardiol* 2017;**228**:265–274.
198. Meyer MR, Fredette NC, Barton M, Prossnitz ER. Regulation of vascular smooth muscle tone by adipose-derived contracting factor. *PLoS One* 2013;**8**:e79245.
199. Szasz T, Bomfim GF, Webb RC. The influence of perivascular adipose tissue on vascular homeostasis. *Vasc Health Risk Manag* 2013;**9**:105–116.
200. Gollasch M. Vasodilator signals from perivascular adipose tissue. *Br J Pharmacol* 2012;**165**:633–642.
201. Mendizábal Y, Llorens S, Nava E. Vasoactive effects of prostaglandins from the perivascular fat of mesenteric resistance arteries in WKY and SHROB rats. *Life Sci* 2013;**93**:1023–1032.
202. Ozen G, Daci A, Norel X, Topal G. Human perivascular adipose tissue dysfunction as a cause of vascular disease: focus on vascular tone and wall remodeling. *Eur J Pharmacol* 2015;**766**:16–24.
203. Qi X-Y, Qu S-L, Xiong W-H, Rom O, Chang L, Jiang Z-S. Perivascular adipose tissue (PVAT) in atherosclerosis: a double-edged sword. *Cardiovasc Diabetol* 2018;**17**:134.
204. Yudkin JS, Eringa E, Stehouwer CDA. 'Vasocrine' signalling from perivascular fat: a mechanism linking insulin resistance to vascular disease. *Lancet* 2005;**365**:1817–1820.
205. Samanta R, Pouliopoulos J, Thiagalingam A, Kovoor P. Role of adipose tissue in the pathogenesis of cardiac arrhythmias. *Heart Rhythm* 2016;**13**:311–320.

206. Ahmad AA, Randall MD, Roberts RE. Sex differences in the role of phospholipase A(2)-dependent arachidonic acid pathway in the perivascular adipose tissue function in pigs. *J Physiol* 2017;**595**:6623–6634.
207. Conti M, Renaud IM, Poirier B, Michel O, Belair M-F, Mandet C, Bruneval P, Myara I, Chevalier J. High levels of myocardial antioxidant defense in aging nondiabetic normotensive Zucker obese rats. *Am J Physiol Regul Integr Comp Physiol* 2004;**286**:R793–R800.
208. Christoffersen C, Bollano E, Lindegaard MLS, Bartels ED, Goetze JP, Andersen CB, Nielsen LB. Cardiac lipid accumulation associated with diastolic dysfunction in obese mice. *Endocrinology* 2003;**144**:3483–3490.
209. Hye Khan MA, Neckář J, Cummins B, Wahl GM, Imig JD. Azilsartan decreases renal and cardiovascular injury in the spontaneously hypertensive obese rat. *Cardiovasc Drugs Ther* 2014;**28**:313–322.
210. Heyen JRR, Blasi ER, Nikula K, Rocha R, Daust HA, Friedrich G, Van Vleet JF, De Ciechi P, McMahon EG, Rudolph AE. Structural, functional, and molecular characterization of the SHHF model of heart failure. *Am J Physiol Heart Circ Physiol* 2002;**283**:H1775–H1784.
211. Yu Y, Ohmori K, Chen Y, Sato C, Kiyomoto H, Shinomiya K, Takeuchi H, Mizushige K, Kohno M. Effects of pravastatin on progression of glucose intolerance and cardiovascular remodeling in a type II diabetes model. *J Am Coll Cardiol* 2004;**44**:904–913.
212. Hamdani N, Franssen C, Lourenço A, Falcão-Pires I, Fontoura D, Leite S, Plettig L, López B, Ottenheijm CA, Becher PM, González A, Tschöpe C, Díez J, Linke WA, Leite-Moreira AF, Paulus WJ. Myocardial titin hypophosphorylation importantly contributes to heart failure with preserved ejection fraction in a rat metabolic risk model. *Circ Heart Fail* 2013;**6**:1239–1249.
213. Ingalls AM, Dickie MM, Snell GD. Obese, a new mutation in the house mouse. *J Hered* 1950;**41**:317–318.
214. Hummel KP, Dickie MM, Coleman DL. Diabetes, a new mutation in the mouse. *Science* 1966;**153**:1127–1128.
215. Mirzaei H, Di Biase S, Longo VD. Dietary interventions, cardiovascular aging, and disease: animal models and human studies. *Circ Res* 2016;**118**:1612–1625.
216. Falcão-Pires I, Leite-Moreira AF. Animal models of cardiovascular disease. In: Cokkinos D. (eds) *Introduction to Translational Cardiovascular Research*. Cham: Springer International Publishing; 2015. pp. 335–369.
217. Falcão-Pires I, Leite-Moreira AF. In vitro experimental assessment of cardiac function. In: Cokkinos D. (eds) *Introduction to Translational Cardiovascular Research*. Cham: Springer International Publishing; 2015. pp. 371–387.
218. Gaborit B, Jacquier A, Kober F, Abdesselam I, Cuisset T, Boullu-Ciocca S, Emungania O, Alessi M-C, Clément K, Bernard M, Dutoir A. Effects of bariatric surgery on cardiac ectopic fat: lesser decrease in epicardial fat compared to visceral fat loss and no change in myocardial triglyceride content. *J Am Coll Cardiol* 2012;**60**:1381–1389.
219. Frantz Z, Falcão-Pires I, Balligand J-L, Bauersachs J, Brutsaert D, Ciccarelli M, Dawson D, de Windt LJ, Giacca M, Hamdani N, Hilfiker-Kleiner D, Hirsch E, Leite-Moreira A, Mayr M, Thum T, Tocchetti CG, van der Velden J, Varricchi G, Heymans S. The innate immune system in chronic cardiomyopathy: a European Society of Cardiology (ESC) scientific statement from the Working Group on Myocardial Function of the ESC. *Eur J Heart Fail* 2018;**20**:445–459.
220. Abplanalp WT, John D, Cremer S, Assmus B, Dorsheimer L, Hoffmann J, Becker-Pergola G, Rieger MA, Zeiher AM, Vasa-Nicotera M, Dimmeler S. Single cell RNA sequencing reveals profound changes in circulating immune cells in patients with heart failure. *Cardiovasc Res* 2021;**117**:484–494.
221. Martini E, Kunderfranco P, Peano C, Carullo P, Cremonesi M, Schorn T, Carriero R, Termanini A, Colombo FS, Jachetti E, Panico C, Faggian G, Fumero A, Torracca L, Molgora M, Cibella J, Pagiatakis C, Brummelman J, Alvisi G, Mazza EMC, Colombo MP, Lugli E, Condorelli G, Kallikourdis M. Single-cell sequencing of mouse heart immune infiltrate in pressure overload-driven heart failure reveals extent of immune activation. *Circulation* 2019;**140**:2089–2107.
222. Hua X, Hu G, Hu Q, Chang Y, Hu Y, Gao L, Chen X, Yang P-C, Zhang Y, Li M, Song J. Single-cell RNA sequencing to dissect the immunological network of autoimmune myocarditis. *Circulation* 2020;**142**:384–400.
223. Kerkhof PLM, Khamaganova I. Sex-specific cardiovascular comorbidities with associations in dermatologic and rheumatic disorders. *Adv Exp Med Biol* 2018;**1065**:489–509.
224. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, Hicks M, Puzanov I, Alexander MR, Bloomer TL, Becker JR, Slosky DA, Phillips EJ, Pilkinton MA, Craig Owens L, Kola N, Plautz G, Reshef DS, Deutsch JS, Deering RP, Olenchock BA, Lichtman AH, Roden DM, Seidman CE, Korolnik JJ, Seidman JG, Hoffman RD, Taube JM, Diaz LA Jr, Anders RA, Sosman JA, Moslehi JJ. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med* 2016;**375**:1749–1755.
225. Kallikourdis M, Martini E, Carullo P, Sardi C, Roselli G, Greco CM, Vignali D, Riva F, Ornbostad Berre AM, Stølen TO, Fumero A, Faggian G, Di Pasquale E, Elia L, Rumio C, Catalucci D, Papait R, Condorelli G. T cell costimulation blockade blunts pressure overload-induced heart failure. *Nat Commun* 2017;**8**:14680.
226. Salem JE, Allenbach Y, Kerneis M. Abatacept for severe immune checkpoint inhibitor-associated myocarditis. *N Engl J Med* 2019;**380**:2377–2379.
227. Bansal SS, Ismail MA, Goel M, Patel B, Hamid T, Rokosh G, Prabhu SD. Activated T lymphocytes are essential drivers of pathological remodeling in ischemic heart failure. *Circ Heart Fail* 2017;**10**:e003688.
228. Honold L, Nahrendorf M. Resident and monocyte-derived macrophages in cardiovascular disease. *Circ Res* 2018;**122**:113–127.
229. Bajpai G, Bredemeyer A, Li W, Zaitsev K, Koenig AL, Lokshina I, Mohan J, Ivey B, Hsiao HM, Weinheimer C, Kovacs A, Epelman S, Artyomov M, Kreisel D, Lavine KJ. Tissue resident CCR2- and CCR2+ cardiac macrophages differentially orchestrate monocyte recruitment and fate specification following myocardial injury. *Circ Res* 2019;**124**:263–278.
230. Heymans S, Luttun A, Nuyens D, Theilmeier G, Creemers E, Moons L, Dyspersin GD, Cleutjens JPM, Shipley M, Angellilo A, Levi M, Nüjße O, Baker A, Keshet E, Lupu F, Herbert J-M, Smits JFM, Shapiro SD, Baes M, Borgers M, Collen D, Daemen MJAP, Carmeliet P. Inhibition of plasminogen activators or matrix metalloproteinases prevents cardiac rupture but impairs therapeutic angiogenesis and causes cardiac failure [In Process Citation]. *Nat Med* 1999;**5**:1135–1142.
231. van der Laan AM, Ter Horst EN, Delewi R, Begieneman MP, Krijnen PA, Hirsch A, Lavaei M, Nahrendorf M, Horrevoets AJ, Niessen HW, Piek JJ. Monocyte subset accumulation in the human heart following acute myocardial infarction and the role of the spleen as monocyte reservoir. *Eur Heart J* 2014;**35**:376–385.
232. Christen T, Nahrendorf M, Wildgruber M, Swirski FK, Aikawa E, Waterman P, Shimizu K, Weissleder R, Libby P. Molecular imaging of innate immune cell function in transplant rejection. *Circulation* 2009;**119**:1925–1932.
233. Gupta SK, Foinquinos A, Thum S, Remke J, Zimmer K, Bauters C, de Groote P, Boon RA, de Windt LJ, Preissl S, Hein L, Batkai S, Pinet F, Thum T. Preclinical development of a microRNA-based therapy for elderly patients with myocardial infarction. *J Am Coll Cardiol* 2016;**68**:1557–1571.
234. Perbellini F, Thum T. Living myocardial slices: a novel multicellular model for cardiac translational research. *Eur Heart J* 2020;**41**:2405–2408.
235. Sabbatini AR, Kararigas G. Menopause-related estrogen decrease and the pathogenesis of HFpEF: JACC review topic of the week. *J Am Coll Cardiol* 2020;**75**:1074–1082.
236. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail* 2020;**22**:1342–1356.
237. Reddy V, Bhandari S, Seymour A-ML. Myocardial function, energy provision, and carnitine deficiency in experimental uremia. *Am Soc Nephrol* 2007;**18**:84–92.
238. Raine AE, Seymour AM, Roberts AF, Radda GK, Ledingham JG. Impairment of cardiac function and energetics in experimental renal failure. *J Clin Invest* 1993;**92**:2934–2940.
239. Homma T, Sonoda H, Manabe K, Arai K, Mizuno M, Sada T, Ikeda M. Activation of renal angiotensin type 1 receptor contributes to the pathogenesis of progressive renal injury in a rat model of chronic cardiorenal syndrome. *Am J Physiol Renal Physiol* 2012;**302**:F750–F761.
240. Bongartz LG, Braam B, Gaillard CA, Cramer MJ, Goldschmeding R, Verhaar MC, Doevendans PA, Joles JA. Target organ cross talk in cardiorenal syndrome: animal models. *Am J Physiol Renal Physiol* 2012;**303**:F1253–F1263.
241. Surwit RS, Feinglos MN, Rodin J, Sutherland A, Petro AE, Opara EC, Kuhn CM, Rebuffe-Scrive M. Differential effects of fat and sucrose on the development of obesity and diabetes in C57BL/6j and A/J mice. *Metabolism* 1995;**44**:645–651.
242. Fellmann L, Nascimento AR, Tibirica E, Bousquet P. Murine models for pharmacological studies of the metabolic syndrome. *Pharmacol Ther* 2013;**137**:331–340.
243. Ishizuka T, Ernsberger P, Liu S, Bedol D, Lehman TM, Koletsky RJ, Friedman JE. Phenotypic consequences of a nonsense mutation in the leptin receptor gene (fak) in obese spontaneously hypertensive Koletsky rats (SHROB). *J Nutr* 1998;**128**:2299–2306.
244. Bray GA. The Zucker-fatty rat: a review. *Fed Proc* 1977;**36**:148–153.