Vascular (dys)function in the failing heart

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Abstract

Heart failure (HF) is not confined to contractile failure of cardiomyocytes or myocardial fibrosis. Coronary and systemic vascular dysfunction contributes to the initiation and progression of HF with or without reduced ejection fraction. Furthermore, HF compromises vascular function, creating and sustaining a vicious cycle with deranging effects on coronary blood flow, cardiac metabolism and cardiac function. In HF, systemic arterial dysfunction, characterized by increased arterial stiffness and resistance, raises cardiac afterload and impedes myocardial contractile function. Reduced coronary blood flow impairs myocardial oxygen delivery and consequently cardiomyocyte metabolism and function. Coronary microvascular dysfunction is heterogeneous in its pathogenesis and manifestations, complicating the diagnosis and management across different HF phenotypes. Understanding the alterations in function in different segments of the vasculature, from the aorta to the capillary level, offers mechanistic insights into disease drivers and therapeutic interventions. Interventional approaches can improve vascular haemodynamics, whereas established and emerging pharmacotherapies target the neurohumoral axis, reduce extravascular compression, inflammation and oxidative stress, thereby improving vascular function and HF-related outcomes. In this Review, we provide a mechanistic framework of vascular dysfunction in the pathogenesis of HF with or without reduced ejection fraction, pointing towards integrated therapies that consider the vascular implications of contemporary HF management across HF phenotypes.

[H1] Introduction

Arterial inflow, in both the coronary and the systemic circulation, provides the essential substrates and oxygen necessary for all metabolic processes occurring in each tissue, which is vital for proper organ function. Concurrently, venous outflow removes metabolic waste products, including carbon dioxide and other byproducts, ensuring a continuous supply and clearance cycle. This flow-in, flow-out homeostasis sustains metabolic flux, because metabolism relies on constant exchange by adequate blood flow. Metabolic derangements caused by alterations in coronary and systemic vascular function contribute to the onset and progression of heart failure (HF), independently of its cause. Furthermore, HF alters metabolic and vascular function, thereby creating and sustaining a vicious circle (Fig. 1). Of note, vascular dysfunction has a crucial role in HF with reduced ejection fraction (HFrEF), HF with mildly reduced EF (HFmrEF) and HF with preserved ejection fraction (HFpEF). In HFrEF, particularly in post-ischaemic HF, coronary microvascular dysfunction (CMD) is causal to contractile failure, whereas in HFpEF, microvascular dysfunction is the key driver of metabolic disturbances in the heart.

In this Review, we provide a comprehensive and translational perspective on the pivotal role of vascular dysfunction across different HF phenotypes, regardless of aetiology. We discuss evolving concepts, including the role of pericytes in the capillary circulation and the involvement of lymphatic vessels. We critically assess advanced imaging techniques that capture the interaction between (micro)vascular, metabolic and contractile function. Finally, we explore the effect of established and emerging HF therapies — both pharmacological and interventional — on vascular function and metabolism, emphasizing their potential to improve personalized treatment strategies. We identify knowledge gaps in these notions and outline unmet needs, a necessity to refine disease concepts and eventually identify novel therapeutic targets.

[H1] Coronary vascular function in the healthy and failing heart

[H2] Heterogeneity in the control of coronary blood flow

Our understanding of the mechanisms controlling coronary blood flow dates back more than five decades[1-3], but the heterogeneity and spatial intricacy of this control, specifically as it relates to the mechanisms that operate in different segments of the coronary microvasculature across different HF phenotypes, have not been comprehensively summarized and might differ from those of systemic circulation (Box 1). Indeed, the most distal part of the coronary microcirculation, the capillary bed, is not a passive structure but is more actively involved in the regulation of myocardial perfusion than was initially thought[4-6] (Fig. 2). Contractile function of the heart is crucially dependent on the supply of oxygen and nutrients to cardiomyocytes, which is achieved by a tight and dynamic regulation of coronary blood flow. Physical, metabolic, endothelial and neurohumoral signals regulate coronary blood flow via changes in coronary vascular resistance, which primarily resides in the microcirculation.

The exact mechanisms integral to the control of coronary blood flow across different HF phenotypes, for example in response to perturbations such as physical exercise, are still incompletely understood and remain an important topic for future research. Epicardial coronary arteries have only a small capacitance, a low degree of endothelium-dependent dilatation in response to shear stress, pose little resistance to blood flow and, therefore, contribute little to the regulation of physiological coronary blood flow[1,2,7,8] (Fig. 2). Small arteries and particularly arterioles, with their unique capacity to adjust their diameter dynamically, have long been considered as the primary sites for the regulation of coronary blood flow[1,2,8,9] (Fig. 2). By contrast, capillaries, which lack the smooth muscle cell (SMC) layer that is characteristic of arteries and arterioles, have long been viewed as principally passive channels[1,2,10] (Fig. 1). However, capillaries are surrounded by pericytes that have contractile properties, which challenges this notion. Pericytes and SMCs are derived from shared embryonic progenitor cells, and pericytes surrounding capillaries have a contractile phenotype, given that they express α-smooth muscle actin[4-6]. Therefore, pericytes seem to have a relevant role in the control of blood flow and its distribution in the capillaries (such as via K^+ channels and adenosine) and might influence flow distribution between capillaries and their oxygen extraction[10]. Pericytes interact directly with endothelial cells and are important not only for capillary diameter but also for capillary integrity and formation[4-6]. In the capillaries, the proximity of circulating blood cells, endothelial cells and pericytes to cardiomyocytes enables an exchange of metabolites that does not occur in arterioles and larger vessels, and the interaction between all these cell types maintains the homeostasis of capillary fluid and substance exchange[4] (Fig. 2). Future research focusing specifically on the coronary capillary bed is needed. In addition to capillary vasomotion, the physical properties of blood can also affect microcirculatory blood flow and oxygen utilization[11]. Blood cell count and red blood cell deformability and aggregation as well as the rheological properties of blood plasma determine blood viscosity, cell–cell interactions and myocardial perfusion at the capillary level[6] (Fig. 3). Indeed, myocardial perfusion is actively regulated at the capillary level — a paradigm shift from the concept that arterioles were the smallest regulatory unit of blood flow.

[H2] CAD and HF: a complex relationship

Alterations in coronary vascular structure and function in the context of different HF phenotypes, including ischaemic and dilated cardiomyopathy, Takotsubo syndrome, cardiotoxicity-induced HF and right ventricular HF, have been reviewed in detail previously[12-14]. Indeed, coronary abnormalities are invariably present in HF of a variety of origins, including those that have been classically considered as being non-ischaemic, such as hypertrophic and dilated cardiomyopathy[15,16]. What is still not fully understood is whether these perturbations in coronary blood flow are a cause or a consequence of HF[13]. To illustrate this complex relationship, we examine ischaemic heart disease, caused by either obstructive coronary artery disease (CAD) or non-obstructive CAD, and its relationship to HFrEF and HFpEF.

The initial phase of atherosclerosis is tightly linked to endothelial dysfunction, which can occur across all segments of the coronary vascular bed[17]. In the larger epicardial arteries, endothelial dysfunction can trigger focal or diffuse atherosclerotic lesions. Obstructive CAD can result in regional myocardial ischaemia. Its sequelae, including myocardial stunning, myocardial hibernation[18], coronary microembolisation[19] and acute myocardial infarction, constitute important causes of HFrEF. In non-obstructive CAD, endothelial dysfunction in arterioles and in capillaries manifests in CMD, a major driver of HFpEF[3,13,20,21]. However, the relationship between obstructive and non-obstructive CAD is complex, and the separation between these entities is somewhat artificial. Indeed, many patients with non-obstructive CAD have diffuse atherosclerosis[17,22-24]. In animal studies, the coronary microcirculation undergoes functional alterations and structural remodelling distal to the coronary stenosis[25], whereas clinical data suggest that lower levels of coronary blood flow due to dysfunction of the distal microvasculature promote atherosclerosis in epicardial arteries[26].

Both obstructive and non-obstructive CAD, and therefore HFrEF and HFpEF, result from long-term exposure to risk factors, such as hypertension, chronic kidney disease and several metabolic disorders, including obesity, diabetes mellitus and dyslipidaemias[27,28]. These cardiovascular risk factors promote a low-grade, chronic inflammatory state mediated by circulating immune cells, cytokines and adipokines, resulting in oxidative stress in all cellular compartments of the myocardium[29]. This chronic, low-grade inflammation not only drives atherosclerosis in the epicardial arteries[30,31] but also impairs coronary microvascular function and structure, a shared mechanism between most forms of HFrEF, HFmrEF and HFpEF[3]. For example, long-term hypertension is not only a well-known risk factor for atherosclerosis and HFrEF but also induces functional and structural alterations in the coronary microcirculation and is a risk factor for HFpEF[20].

[H2] HF-associated cellular and molecular alterations in the coronary circulation

Alterations in coronary blood flow regulation can occur through abnormalities in vascular cells (endothelial cells, SMCs and pericytes) but can also be secondary to abnormalities in non-vascular cells, such as changes in cardiomyocyte[32,33], fibroblast[34,35] and lymph endothelial cell[33,36] function (Fig. 3). Changes in myocardial metabolism are characterized by substrate shifts (increased glucose utilization in HFrEF and increased free fatty acid utilisation in HFpEF) (Figs 2,3), as well as mitochondrial dysfunction in cardiomyocytes[37] and endothelial cells[38]. Fibroblast activation and the resulting production of extracellular matrix can lead to increased myocardial and vascular stiffness, thereby increasing left ventricular (LV) diastolic pressure and limiting coronary vasodilatation, respectively.[34] Perturbations in lymph vessel function and structure in HF can impede coronary blood flow via the formation of oedema[33,36].

[H3] Small arteries and arterioles. In patients with HF, structural alterations in small arteries and arterioles are characterized by inward vascular eutrophic or hypertrophic remodelling and perivascular fibrosis, resulting in elevated vascular stiffness and increased minimum microvascular resistance[20,21,39,40]. The presence of an obstructive coronary lesion can aggravate abnormalities in coronary microvascular function and structure[41].

The functional control of small arteries and arterioles involves several neurohormonal mechanisms[1-3,42]. Sympathetic activation modulates coronary tone via (nor)adrenaline, neuropeptide Y and ATP released from sympathetic nerves and the adrenal medulla. α-Adrenergic receptor-derived vasoconstriction is predominantly mediated by α_1-adrenergic receptors in arteries and small arteries and by α_2-adrenergic receptors in arterioles and possibly capillaries[43], whereas β-adrenergic receptor-derived vasodilatation is predominantly mediated by β_1-adrenergic receptors in arteries and small arteries and by β_2-adrenergic receptors in arterioles (Fig. 2). Parasympathetic nerves release vasoactive acetylcholine. M_1, M_2 and M_3 muscarinic receptors have been identified in the human coronary vasculature[44-46]. The response to acetylcholine seems to be species-specific, with vasodilatation in healthy human and canine coronary arteries and arterioles, but coronary constriction in swine (reviewed previously[1-3,42,47]). HF is associated not only with an increased central sympathetic drive but also with local sympathetic nerve growth and resultant sympathetic hyperinnervation of the coronary arteries, and little or no desensitization of vascular α_1-adrenergic and β_2-adrenergic receptors[48,49]. These observations suggest an altered balance of autonomic control of coronary blood flow, with an increased sympathetic and reduced parasympathetic influence on the coronary microcirculation that is particularly pronounced in HFrEF but also present in HFpEF[48,49].

A variety of blood-derived and tissue-derived metabolites exert vasodilator and vasoconstrictor influences on the coronary vasculature and, again, the segments of the coronary vasculature differ in their responsiveness. Serotonin (5-HT) produces vasodilatation of coronary arterioles through endothelial 5-HT_1 receptors, and vasoconstriction of coronary arteries through 5-HT_1 and 5-HT_2 receptors located on SMCs[50]. Whereas nitric oxide (NO) predominantly mediates endothelium-dependent vasodilatation in large and small arteries, the endothelium-derived hyperpolarizing factors hydrogen peroxide (H_2O_2), epoxyeicosatrienoic acids and prostaglandin I_2 (also known as prostacyclin) mediate endothelium-dependent vasodilatation in coronary arterioles[2,42] (Fig. 2). Expression levels and specific functions of the potassium ion (K^+) channels differ depending on the vessel size and location in the coronary circulation. In arteries, K_{Ca} channels are more important, whereas in arterioles, K_{ATP}

and K_v channels have a predominant role in vasodilatation in response to various stimuli, including adenosine and NO[2,42] (Fig. 2). Many of these vascular control mechanisms are present on both endothelial cells and SMCs, including the α_2-adrenergic and 5-HT_1 receptors as well as various K^+ channels, making studies of their importance in coronary blood flow regulation and changes that occur in HF complex and difficult[1,2]. In small arteries and arterioles, two major functional alterations occur in HF. First, impaired endothelium-dependent vasodilatation is caused to reduced bioavailability of NO, with a shift towards H_2O_2 (possibly due to mitochondrial dysfunction in vascular cells[38]) and other endothelium-derived hyperpolarizing factors. Second, SMC dysfunction is caused by reduced vasodilator responsiveness to NO and adenosine, increased vasoconstrictor responsiveness to noradrenaline and endothelin, as well as K^+ channel dysfunction, which together increase coronary microvascular tone (Figs 2,3). The contribution of K_{ATP} channel activity to coronary blood flow regulation is increased in experimental models of HFrEF, whereas K_{ATP} and K_V channel activity is blunted in animal models of, and humans with, HFpEF[13,51].

[H3] Capillaries. Evidence is increasing that capillary dysfunction is a hallmark of both HFrEF and HFpEF, but that it is particularly prominent in HFpEF[13,52]. These abnormalities in capillary function are likely to result from pericyte dysfunction, with impaired pericyte responsiveness to changes in metabolic demands of the surrounding myocardium owing to altered signalling[4-6]. Pericytes express α_2-adrenergiv and β_2-adrenergic, thromboxane and endothelin receptors[53,54], and pericytes are therefore likely to actively regulate capillary diameter in response to neurohumoral activity. However, a causal involvement of pericyte dysfunction in perturbations to the coronary microcirculation is still largely hypothetical, principally based on observations in other organs[53]. Pericyte dysfunction also seems to have a key role in the process of capillary rarefaction[52]. Functional and structural alterations in the capillary bed can result in impaired capillary inflow and flow distribution[10], thereby potentially precipitating or aggravating cardiomyocyte hypoxia[4,52]. How pericyte function is altered in HFrEF compared with HFpEF is not well understood and is an important topic for future research.

Changes in blood viscosity and cell–cell adhesion are of particular importance in the capillary bed. Associated with HF, the expression of cellular adhesion molecules is generally increased[55], and red blood cell aggregation is increased and deformability is decreased[56] (Fig. 3). HF-associated comorbidities are associated with platelet hyperactivation[57,58]. In HF, the production of reactive oxygen species (ROS) by blood cells is increased[56,57,59], and the production of NO by red blood cells is decreased, which further impairs endothelial cell function[56,60]. Leukocytes mediate inflammation, cause proteolytic and oxidative damage to the endothelial cells, and promote blood cell plugging in the microvasculature[61]. All these phenomena point to an alteration in the microcirculation through blood-derived changes in HF, but no clear evidence of a causal involvement is so far available.

The fundamental cellular and molecular changes in the coronary vasculature that occur with HF show substantial overlap between HFpEF and HFrEF, with a few differences, as discussed above. However, genetic and therefore primordial determinants were reported to differ considerably between patients with HFpEF and those with HFrEF, suggesting that unidentified metabolic differences might exist that could affect the coronary vascular system differently in HFrEF compared with HFpEF[62]. Therefore, the complex interaction between various cell types (including endothelial cells, SMCs and blood cells) and neuronal and humoral factors in the coronary microcirculation in HFrEF and HFpEF, as well as the molecular signalling pathways involved, remains an important area of study to improve our understanding and treatment of HF.

[H1] Systemic and pulmonary vascular (dys)function

Arterial resistance determines LV afterload, and pulmonary resistance determines right ventricular afterload; afterload opposes ejection of blood from the respective ventricle. Arterial dysfunction, often secondary to metabolic diseases (such as obesity and diabetes) and atherosclerosis, manifests in endothelial dysfunction, increased vasomotor tone and arterial stiffness, ultimately producing higher arterial resistance and LV afterload[63,64] (Fig. 1). Neurohumoral activation through catecholamines and the renin–angiotensin–aldosterone system (RAAS) further increases vasomotor tone and inflammation[65]. A drug-induced decrease in afterload improves cardiac output and reduces myocardial work and oxygen consumption[66,67].

The systemic venous circulation contains ~70% of the total blood volume, located mainly in the splanchnic circulation, and determines venous return and right ventricular preload. Sympathetic system-induced venoconstriction increases venous return and thereby cardiac output. The venous return to the left ventricle is dependent on respiratory fluctuations in intrathoracic pressure and volume. In HF, excessive fluid retention elevates filling pressures to both the left and right ventricles, causing congestion and peripheral and pulmonary edema[68] (Fig. 1). Chronic venous hypertension increases oxidative stress and predisposes individuals to thrombosis, further impairing cardiac output[69,70]. Normalizing preload through pharmacotherapy, splanchnic nerve modulation or intermittent caval flow occlusion can reduce ventricular filling pressures and help to normalize cardiac output[71,72].

Pulmonary hypertension can cause right ventricular failure directly, or the right ventricle can be secondarily affected by left-sided HF independently of ejection fraction[73]. The resulting right ventricular dysfunction aggravates systemic congestion and multiorgan failure[74]. Pulmonary vascular remodelling and neurohumoral dysregulation further impair oxygen exchange and cardiac function[75,76]. Ultimately, dysregulated preload and afterload perpetuate HF progression, and most drug therapy for HF targets vasomotion and blood volume to optimize cardiac function and systemic perfusion.

[H1] The lymphatic system

Fluid overload and congestion in HF affect both the venous and lymphatic systems. In HF, the thoracic duct size and flow increase as a compensatory mechanism. At advanced stages, capillary hydrostatic pressure is elevated and lymphatic drainage impaired[77], driven by structural changes in lymphatic vessels, such as valve insufficiency, disrupted endothelial junctions, impaired SMC contractility and reduced compression by fatigued skeletal muscle[78]. Ageing and HF-related metabolic alterations, such as obesity and diabetes, worsen these effects through chronic inflammation[79]. Conversely, a functional cardiac lymphatic system stimulates resolution of inflammation after acute myocardial infarction[80]. Lymphatic dysfunction not only results from HF but also contributes to its progression by exacerbating chronic inflammation, fluid imbalance and impaired vasomotor regulation[81]. Local lymphatic dysfunction, including in the kidneys[82] and heart itself[83], further contributes to HF. Emerging strategies to treat lymphatic congestion include promoting lymphangiogenesis through delivery of vascular endothelial growth factor, and device-based or pharmacological interventions[84,85].

The lack of comprehensive tools to assess lymphatics in HF limits our understanding of its precise role. Lymphoscintigraphy is minimally invasive and visualizes deep lymphatics, but the images are not dynamic and their resolution is low[86]. Indocyanine green lymphangiography captures primarily superficial lymphatics and requires standardization[87]. Pedal and inguinal lymphangiography are more invasive, and dynamic contrast-enhanced magnetic resonance lymphangiography is time-consuming, costly and quite invasive[88,89].

Emerging strategies to treat lymphatic congestion include the promotion of lymphangiogenesis and device-based or compression therapies[84,85]. By acting on common molecular mediators, including NO and prostaglandins, several drugs can influence the contractile function of lymph vessels, but their specific effects remain unclear. No approved therapies for HF target the lymphatic system directly. Advances in imaging modalities and more precise identification of specific lymphatic functions will be essential to target the lymphatic system as an effective therapeutic approach in HF.

[H1] Imaging coronary vascular (dys)function and cardiac metabolism in HF

Imaging coronary vascular dysfunction and cardiac metabolism in HF requires a multimodal approach. Each imaging modality has unique strengths and limitations. Echocardiography and coronary computed tomography angiography (CCTA) remain essential for first-line assessment, whereas positron emission tomography (PET) and cardiac magnetic resonance imaging (CMR) offer detailed insights into perfusion and metabolism. The choice of technique should balance diagnostic accuracy, patient safety, availability and cost-effectiveness, with non-invasive methods preferred for diagnosis and research. In this section, we summarize contemporary imaging modalities, comparing the strengths and limitations of non-invasive imaging techniques, and provide guidance on their optimal clinical application (Table 1).

[H2] Non-invasive modalities

Fig. 4 illustrates a workflow using available imaging modalities to support a rational diagnostic approach for the optimal treatment of HF, both in clinical practice and for mechanistic research.

[H3] Echocardiography. Echocardiography is the first-line imaging modality in HF because it allows the assessment of structural abnormalities, ventricular function and myocardial viability. A lack of response to low-dose dobutamine suggests non-viable myocardium, whereas a biphasic response indicates hibernating myocardium[90,91]. Doppler echocardiography is used to evaluate coronary flow velocity, which correlates with coronary flow reserve as a marker of CMD[92]. Myocardial contrast echocardiography is used to visualize microvascular function, correlates well with PET and CMR, and provides real-time imaging, although accuracy depends on operator expertise[93].

[H3] CMR. With high spatial and temporal resolution, CMR can be used to assess cardiac structure, function and perfusion. First-pass perfusion with gadolinium detects ischaemia and CMD. Late gadolinium enhancement differentiates viable from non-viable myocardium[91]. T1/T2 mapping provides insights into fibrosis, oedema and lipid content, whereas magnetic resonance spectroscopy quantifies myocardial energy metabolites involved in myocardial energy production (the phosphocreatine-to-ATP ratio[94]), which is reduced in HF[95] and linked to worse outcomes[96]. Magnetic resonance spectroscopy also detects intramyocardial lipid accumulation, which is common in conditions such as diabetic cardiomyopathy, contributing to mitochondrial dysfunction and worsening HF[97]. Hyperpolarized magnetic resonance spectroscopy enables real-time tracking of metabolic tracers, providing further insights into HF pathophysiology[98,99].

[H3] CCTA and CT–MPI. CCTA is the first-line imaging modality for assessing CAD as the underlying cause of HF. A normal scan has a high negative predictive value, reducing the need for invasive angiography in patients at low-to-intermediate risk[100]. Computed tomography (CT)-derived fractional flow reserve (FFR) is used to evaluate the clinical significance of atherosclerotic lesions and correlates closely with invasive FFR[101,102-104]. CT–myocardial perfusion imaging (MPI) can be used to assess myocardial perfusion and CMD, especially in patients with HFpEF. CT–MPI integrates stress imaging and contrast techniques but requires advanced scanners and precise execution and is not routinely used in clinical practice. Dynamic CT–MPI quantification of myocardial blood flow aligns well with measurements by PET, CMR–MPI and invasive FFR[105,106].

[H3] SPECT. Single-photon emission computed tomography (SPECT) is used to assess regional ischaemia but can now also be used for the absolute quantification of myocardial blood flow and coronary flow reserve through dynamic imaging and improved tracer kinetics[107]. Despite advances in SPECT, clinical experience remains limited.

[H3] PET. PET is used to quantify myocardial perfusion and metabolism and can be used to distinguish between CAD and microvascular dysfunction. The gold-standard tracer, ^{15}O-water, requires a cyclotron, whereas ^{82}Rb is as a more accessible alternative tracer. PET evaluates metabolic substrate uptake, with ^{18}F-FDG identifying viable myocardium and ^{11}C-palmitate revealing impaired fatty acid metabolism in HF[108-111].

[H2] Invasive modalities

Non-invasive imaging modalities provide valuable diagnostic information, but invasive modalities might be either preferred or necessary to complement non-invasive approaches in some disease states. Invasive modalities offer direct and detailed insights into coronary haemodynamics, endothelial function, myocardial metabolism and myocardial structural disarray, enabling a more comprehensive assessment of cardiovascular pathology. The use of invasive modalities depends on the need for greater diagnostic precision, the limitations of non-invasive modalities, and their effect on clinical decision-making and patient outcomes. In this section, we discuss the most commonly used invasive modalities and explore their role in disease characterization, risk stratification and therapeutic decision-making.

[H3] Coronary angiography and integrated physiological coronary measurements. In addition to detecting CAD, coronary angiography can be used to assess myocardial perfusion and coronary flow via the corrected thrombolysis in myocardial infarction (TIMI) frame count and myocardial blush grade[112]. FFR is an index used to assess the severity of coronary artery stenosis using a pressure wire and hyperaemia (induced by adenosine)[113], whereas the instantaneous wave-free ratio (iFR) provides a pharmacology-free alternative by measuring pressure gradients during diastole[114].

Coronary flow reserve evaluates CMD in the absence of epicardial stenosis, particularly in HFpEF, whereas the index of microvascular resistance quantifies microvascular resistance during hyperaemia[114]. Angiography-derived microcirculatory resistance, a wire-free and adenosine-free method, uses 3D modelling and TIMI frame count, offering similar accuracy to that of the index of microvascular resistance[115]. Although not an imaging modality, right heart catheterization can be a supplementary examination to measure pulmonary capillary wedge pressure, right atrial pressure and pulmonary artery pressures to differentiate between HFpEF and non-cardiac dyspnoea.

[H3] Intracoronary imaging. Intravascular ultrasonography (IVUS) provides cross-sectional imaging of the coronary wall, assessing plaque burden and arterial remodelling to distinguish ischaemic from non-ischaemic HF[116]. Optical coherence tomography (OCT) complements IVUS by offering high-resolution imaging of plaque characteristics and endothelial integrity[117]. IVUS provides deeper penetration and is ideal for assessing plaque burden, large vessels and diffuse disease. OCT offers higher resolution and is better for evaluating fine plaque details and thrombus and optimizing coronary intervention. OCT requires the use of contrast agent, whereas IVUS does not, making IVUS preferable in patients with renal dysfunction.

[H3] When are invasive modalities needed? Invasive haemodynamic assessment with imaging (coronary angiography) and procedures (right heart catheterization or endomyocardial biopsy) is required when precise measurements and specific treatment decisions are necessary. These techniques have a crucial role in advanced HF, pulmonary hypertension, uncertain diagnoses or treatment-resistant cases, in which non-invasive methods might not provide definitive answers.

If ischaemic cardiomyopathy is suspected, coronary angiography is necessary to evaluate the need for revascularization. FFR and iFR enable functional assessment of coronary stenoses, offering specific guidance during revascularization. Intracoronary imaging modalities (IVUS or OCT) are not routinely required in patients with HF. However, these modalities can be useful in selected patients, particularly when guiding coronary interventions.

Right heart catheterization is the gold standard for diagnosing pulmonary hypertension and for distinguishing between pre-capillary causes (group 1, pulmonary artery hypertension) and post-capillary causes (group 2, pulmonary hypertension related to left-sided HF). Invasive haemodynamic assessment might also be required to differentiate between HFpEF, constrictive pericarditis and restrictive cardiomyopathy.

Coronary sinus sampling, measuring myocardial substrate exchange through metabolite and biomarker analysis[118], is used for research into myocardial metabolism. Endomyocardial biopsies aid in diagnosing HF aetiologies, such as amyloidosis or myocarditis, and can be used to evaluate myocardial energy stores and mitochondrial function for research purposes[119,120].

[H2] Implications of improved detection of CMD

Standardized diagnostic criteria for CMD remain undefined owing to the inability to directly visualize the coronary microcirculation and the lack of animal models replicating all aspects of human disease. CMD is typically detected using indirect non-invasive or invasive methods and characterized by reduced vasodilator capacity. This impairment, caused by either inadequate microvascular dilatation or partial dilatation at rest[121,122], is increasingly recognized as a key contributor to chronic CAD[123]. Experimental studies have linked impaired coronary reserve to non-obstructive CAD[124], obstructive CAD[125,126] and microembolization[19]. Despite its importance, CMD lacks widespread clinical acceptance. Studies emphasize the value of microvascular resistance reserve, a quantitative and operator-independent method calculated as coronary flow reference divided by FFR corrected for driving pressures[127]. Microvascular resistance reserve has shown diagnostic and prognostic utility, with a microvascular resistance reserve >3 being predictive of cardiovascular events at 5 years, according to an analysis of the ILIAS registry[128]. Additionally, microvascular resistance reserve has been used to predict symptomatic and perfusion benefits of revascularization in patients with moderate CAD[129]. Multiple imaging modalities have been discussed, but head-to-head comparisons assessing their diagnostic accuracy, prognostic value and cost-effectiveness in specific HF phenotypes (such as HFpEF versus HFrEF) are lacking. Despite the diagnostic and prognostic importance of CMD, its assessment (via PET, Doppler echocardiography or CMR) is not routinely included in clinical practice.

[H1] Vascular effects of pharmacotherapies for HF

Neurohumoral activation affects vascular structure and function and drives the initiation and progression of HFrEF, HFmrEF and HFpEF[65,130,131]. Indeed, systemic and local perturbations of the arterial, venous and lymphatic systems, including low-grade inflammation, oxidative stress and altered NO signalling, have a major effect on endothelial cells, SMCs and immune cells. These pathways mainly operate in the vasculature and are important drivers of HF pathogenesis, meaning that they are important targets for therapeutic intervention to improve myocardial function (Fig. 5; Table 2). The effects of HF drugs on the lymphatic system have been comprehensively reviewed previously[132].

[H2] Loop diuretics and thiazides

Loop diuretics and thiazides are essential for the management of HFrEF, HFmrEF and HFpEF, primarily to reduce congestion and symptom burden, whereas evidence from randomized trials on hard cardiovascular end points remains very limited[133,134]. Loop diuretics (such as furosemide or torasemide (also known as torsemide)) act by inhibiting the renal Na^+–K^+–$2Cl^-$ cotransporter in the thick ascending limb of the loop of Henle, whereas thiazides target the distal convoluted tubule, providing an additive effect. All diuretics reduce preload and congestion by reducing extracellular volume overload and intracardiac filling pressures, which are hallmarks of decompensated HF, thereby improving dyspnoea and exercise capacity. However, their effect on vascular function is likely to extend beyond simple fluid transfer[135].

Acutely infused furosemide does not alter arterial function in humans, even if supratherapeutic doses are used, but directly exerts venodilatation, which can be reversed by the prostaglandin inhibitor indomethacin[136]. However, excessive use of loop diuretics impairs endothelial function, disturbs electrolyte homeostasis (resulting in hypokalaemia and/or hypomagnesaemia) and aggravates HF-related RAAS activation, which can exert detrimental downstream effects, including exacerbated vascular remodelling[137]. In rat kidneys, torasemide inhibited the interaction between aldosterone and its receptor, whereas furosemide had no effect[138], suggesting an anti-aldosteronergic effect of torasemide. However, HF-related outcomes were similar in patients with HF randomly assigned to furosemide or torasemide in the large-scale TRANSFORM-HF trial[139], questioning the translational value of these preclinical observations. Our understanding of the direct vascular effects of diuretic therapy remains scarce, but in vivo data suggest a predominant venodilatory effect on the venous system[136].

In the management of patients with worsening HF, persistent congestion and hospital admissions for volume management remain major public health concerns: in the setting of persistent congestion, identifying underlying mechanisms can guide diuretic therapy. Sequential nephron blockade by thiazide-like diuretics (such as metolazone) boosts diuresis, although the dose of loop diuretics at which combination nephron blockade is most effective remains an area of uncertainty[140]. Intermittent intravenous diuretic therapy in multidisciplinary outpatient settings might facilitate the early treatment of congestion and decrease HF hospitalizations in selected patients[141], but evidence on hard cardiovascular end points remains scarce[142]. Conversely, the use of high-dose loop diuretics might be linked to worse outcomes in some patients with acutely decompensated HF[143], although the results of the randomized, controlled DOSE study[144] do not support this notion. Therefore, the optimization and individualization of diuretic therapy, including tailoring the dose and combinations to achieve a net negative sodium balance to maintain euvolaemia, to minimize adverse vascular effects (aggravated neurohumoral activation and subsequent vascular remodelling), and to relieve the signs and symptoms of congestion, remains a cornerstone of contemporary management in HFrEF, HFmrEF and HFpEF. Fig. 6 displays a personalized approach to the initiation and optimization of pharmacological and device therapy for patients with HF.

[H2] Mineralocorticoid receptor antagonists

Mineralocorticoid receptor antagonists (MRAs) are highly effective for the treatment of (resistant) arterial hypertension and slowing of HF progression. Steroidal MRAs (spironolactone and eplerenone) and non-steroidal MRAs (finerenone) reduce the risk of HF hospitalization or cardiovascular death in patients with HFrEF, but the benefits of steroidal MRAs have not been consistently observed in patients with HFpEF[145], although some regional variation might exist, as suggested by a post-hoc analysis of the landmark TOPCAT trial[146]. Conversely, the cardiovascular benefits of non-steroidal MRAs extend to patients with HFmrEF or HFpEF (Fig. 6), irrespective of geographical region, potentially because of their distinct molecular structure with fewer off-target effects[147]. Both types of MRA reduce preload and afterload by antagonizing aldosterone-induced sodium reabsorption in exchange for potassium wasting in the distal tubule, thereby alleviating volume overload and lowering arterial pressure, reducing ventricular wall stress and vascular tone[148]. MRAs also antagonize aldosterone-induced vascular remodelling independently of electrolyte homeostasis, favouring the involvement of local effects on SMCs[149]. Vascular benefits of MRAs involve mechanisms at both the systemic and cellular levels, the former probably being independent of the type of MRA[150].

In cultured SMCs, spironolactone prevented the aldosterone-induced decrease in K_{Ca} expression, thereby reducing myogenic tone, with blood pressure-lowering effects[151]. Mineralocorticoid receptors expressed by SMCs contribute importantly to perivascular fibrosis, oxidative stress and vascular tone, with modulatory effects on coronary flow reserve[152]. In support of this notion, aged mice lacking mineralocorticoid receptors in SMCs have reduced vascular tone, agonist-dependent contraction, and expression and activity of L-type calcium channels, indicating that mineralocorticoid receptors in SMCs contribute to angiotensin II-induced vascular oxidative stress, vascular contraction and hypertension[149]. In parallel, endothelial aldosterone antagonism counteracts endothelial dysfunction by increasing NO bioavailability and mitigating ROS formation, thereby improving endothelium-dependent vasodilatation[153]. MRAs also mitigate inflammation in the vascular wall by reducing the production and release of inflammatory mediators such as C-C motif chemokine 2 (CCL2; also known as MCP1), IL-6, transforming growth factor-β and tumour necrosis factor (TNF), limiting immune cell recruitment and infiltration, thereby preserving vascular integrity[154-156]. Overall, MRAs stabilize endothelial function, reduce oxidative stress and decrease the myogenic tone of SMCs, while exerting anti-inflammatory properties, making them essential in preserving vascular homeostasis and improving outcomes in HFrEF, HFmrEF and (for non-steroidal MRAs) HFpEF.

[H2] β-Blockers and ivabradine

In HFrEF, β-blockers reduce rehospitalizations and mortality, but no data support their use without a secondary indication in HFmrEF or HFpEF[157] (Fig. 6). After acute myocardial injury, β-blockers are effective in reducing reinfarctions and mortality in those with reduced LV ejection fraction (LVEF)[157] but do not reduce mortality in patients with a LVEF ≥50%[158]. Moreover, a secondary analysis of the TOPCAT trial found that β-blocker use in patients with a LVEF ≥50% was associated with an increased risk of HF hospitalizations[159], raising concerns about their routine use in HFpEF. In a crossover, randomized trial, β-blocker withdrawal in patients with HFpEF and chronotropic incompetence (the inability of the heart to increase its rate adequately in response to exercise or other physiological demands) significantly improved maximal functional capacity[160]. Indeed, higher heart rates in patients with HFpEF have been associated with a reduction in LV end-diastolic pressure, thereby improving myocardial relaxation and coronary perfusion[161]. This highlights the stark contrast between HFrEF, in which β-blockers are essential to improve prognosis, and HFpEF, in which the role of β-blockers remains uncertain and potentially harmful in certain subsets of patients.

The mechanisms by which β-blockers affect vascular function are multifaceted but involve indirect effects (mainly through a reduction in heart rate[162]) and direct, drug-specific pleiotropic effects (antioxidative, anti-inflammatory, antiproliferative and NO-potentiating effects), the latter mainly confined to third-generation drugs[163,164-168]. Contemporary HF therapy involves β_1-adrenergic receptor-selective second-generation drugs (bisoprolol or metoprolol) or β_1-adrenergic receptor-selective plus vasodilating (nebivolol) or non-selective plus vasodilating (carvedilol) third-generation drugs, which modulate heart rate, myocardial metabolism, contractile function and vasomotor tone. β_1-Adrenergic receptor antagonism also reduces renin release in specialized SMCs (located in the afferent arterioles of the juxtaglomerular apparatus), resulting in prolonged diastole and reduced afterload[169]. Carvedilol also blocks β_2-adrenergic receptors, but its α_1-adrenergic receptor antagonism offsets this effect, causing coronary and systemic vasodilatation rather than vasoconstriction; by contrast, non-selective β-blockade induces unopposed α-adrenergic vasoconstriction during sympathetic activation such as exercise[170,171]. The vasodilatory effects of L-nebivolol involve a β_3-adrenergic receptor agonism-mediated increase in NO bioavailability[163].

Carvedilol also attenuates lipid peroxidation, scavenges ROS, inhibits ROS formation and prevents the depletion of endogenous antioxidants in SMCs[164,165]. Most β-blockers also reduce systemic inflammation, as measured by plasma levels of IL-6 or C-reactive protein, which are important determinants of endothelial function, vascular leakage and all-cause mortality after a diagnosis of HF[166,167]. In addition to potent antioxidative effects, the chiral β-blocker nebivolol also mitigates proliferation of endothelial cells and SMCs in vitro[168]. In optimally treated but symptomatic patients with a LVEF ≤35% and sinus rhythm ≥70 bpm, ivabradine (an inhibitor of the hyperpolarization-activated cyclic nucleotide-gated channel responsible for the pacemaker or 'funny' current, I_f) reduces the risk of HF hospitalization and HF-related death[172]. Ivabradine exerts no direct effects on inotropy, vascular resistance or blood pressure, but confers clinical benefits through negative chronotropy, with each 5-bpm reduction in heart rate equating to a 16% reduction in the risk of HF hospitalization and HF-related death in the SHIFT trial[172]. Vascular benefits conferred by ivabradine are dependent on heart rate. In support of this notion, an ivabradine-induced reduction in heart rate lowers vascular oxidative stress, improves endothelial function and slows atherosclerotic plaque formation in hyperlipidaemic mice, but does not provide vasculoprotection ex vivo[173]. However, in pigs, ivabradine also exerts a direct cardioprotective action and reduces infarct size[174]. Although the vascular benefits of β-blockers and ivabradine are well established in selected patients with HFrEF, no data are available to support the routine use of these agents in patients with HFmrEF or HFpEF without a secondary indication[157].

[H2] RAAS and neprilysin inhibitors

In patients with HFrEF, pharmacological RAAS inhibition by angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs) and angiotensin II receptor–neprilysin inhibitors (ARNIs) results in a 16%, 12% and 29% reduction in mortality, respectively, compared with placebo[175]. Prespecified, pooled analyses of the PARAGLIDE-HF and PARAGON-HF trials support the use of RAAS-inhibiting pharmacotherapies to improve cardiovascular and cardiorenal events in patients with HFmrEF or HFpEF[176], but the guideline recommendations on their use are mixed[177,178] (Fig. 6). In addition to the many systemic effects of RAAS inhibition (including reductions in cardiac afterload, preload and systolic wall stress, resulting in increased cardiac output[179]), ACE inhibitors, ARBs and ARNIs exert direct cellular effects through their actions on endothelial cells, SMCs and immune cells, contributing to their broad vascular benefits.

ACE inhibitors (such as enalapril and ramipril) reduce the angiotensin II-mediated synthesis of oxidative, pro-inflammatory and profibrotic mediators, while simultaneously increasing the bradykinin-dependent induction of NO, resulting in improved endothelial cell function[180]. ACE inhibitor-driven reductions in ROS generation limit the migration and proliferation of SMCs, favourably affecting vascular remodelling[180,181]. ACE inhibitors also lower immune cell recruitment to the vascular wall by suppressing the release of cytokines such as IL-6 and TNF, and reducing the angiotensin II-mediated upregulation of endothelial adhesion molecules[181,182].

Similarly, through the selective blockade of angiotensin II type 1 receptors on endothelial and SMCs, ARBs (such as candesartan and valsartan) improve endothelial cell-dependent vasodilatation and attenuate SMC proliferation. However, unlike ACE inhibitors, ARBs do not interfere with the degradation of bradykinin and, compared with ACE inhibitors, are associated with an approximately twofold to threefold lower risk of angio-oedema[183]. Similar to the anti-inflammatory effects of ACE inhibitors, ARBs dampen immune cell activation and infiltration, thereby reducing vascular inflammation and subsequent remodelling[184].

The ARNI sacubitril–valsartan amplifies the effects described above by synergistic inhibition of neprilysin, thereby increasing natriuretic peptide signalling with vasodilator, antifibrotic and antihypertrophic effects[185]. The increased bioavailability of these vasoactive natriuretic peptides promotes the endothelial release of NO, limits the proliferation of SMC and reduces vascular wall stiffness in mice[186], although central aortic stiffness was not significantly different in patients randomly assigned to receive the ARNI compared with those receiving an ACE inhibitor in the EVALUATE-HF trial[187]. Through these coordinated effects on endothelial cells, SMCs and immune cells, ACE inhibitors, ARBs and ARNIs preserve vascular homeostasis, mitigate inflammation and improve vascular compliance, making them an important pillar in the contemporary management of HFrEF, with accumulating evidence supporting their use in the management of HFmrEF and potentially also HFpEF[176] (Fig. 6).

[H2] SGLT2 inhibitors

Sodium–glucose cotransporter 2 (SGLT2) inhibitors, such as canagliflozin, dapagliflozin and empagliflozin, provide vasculoprotective effects independently of their glucose-lowering properties[188]. The use of SGLT2 inhibitors is associated with a reduced risk of HF hospitalizations and cardiovascular death in patients with HFrEF, HFmrEF or HFpEF[189] (Fig. 6). In humans, SGLT2 is predominantly expressed in the proximal tubule of the nephron[188,190], but SGLT2 inhibitors improve vascular function through their metabolic effects and by directly acting on cells in the vessel wall. Systemically, SGLT2 inhibitors reduce preload and afterload by transiently inducing natriuresis and osmotic diuresis, resulting in blood volume redistribution, reduced ventricular filling pressures and improved vascular compliance[188]. Through increased urate excretion and attenuated urate production, reductions in plasma uric acid levels occur[191], further limiting oxidative stress, low-grade inflammation and endothelial dysfunction[188]. SGLT2 acts as a nutrient surplus sensor, and its inhibition restores autophagic flux via activation of a variety of hub molecules involved in nutrient deprivation signalling (such as serine/threonine-protein kinase mTOR, NAD-dependent protein deacetylase sirtuin 1 and hypoxia-inducible factor 2α, thereby preventing endothelial senescence and diminishing the susceptibility to atherosclerotic plaque initiation and progression[192]. SGLT2 inhibitors might also improve autonomic balance by increasing vagal tone as a compensatory response to urinary glucose loss, addressing the autonomic dysfunction that often persists in patients with HF, even with optimal therapy[193].

In endothelial cells, SGLT2 inhibitors contribute to 5′-AMP-activated protein kinase (AMPK) activation and restore endothelial NO synthase (eNOS) function[194], thereby increasing endothelial NO bioavailability, with pleiotropic downstream effects[195]. Through the attenuation of low-grade inflammation and angiotensin II-induced NADPH oxidase activation, SGLT2 inhibitors reduce intracellular ROS synthesis, thereby dampening endothelial senescence and dysfunction[196]. Through their AMPK-activating effects, SGLT2 inhibitors stabilize mitochondrial membrane potential, prevent mitochondrial DNA damage, and modulate fission–fusion dynamics[194]. SGLT2 inhibitors also preserve mitochondrial health by reducing mitochondrial Ca^{2+} overload, increasing ATP synthesis and reducing ROS leakage[197]. In microvascular dysfunction, a condition that is particularly relevant to HFpEF, SGLT2 inhibitors alleviate TNF-mediated ROS accumulation, restore endothelial NO delivery and improve endothelium-dependent vasodilatation, at least partly mediated by their sodium–hydrogen exchanger 1 (NHE1)-inhibiting effects[198,199]. Anti-inflammatory effects of SGLT2 inhibitors involve suppression of the NLRP3 inflammasome in SMCs (through which the migration and proliferation of these cells is attenuated[200]) and the dampening of nuclear factor-κB (NF-κB)-dependent and IL-6-dependent signalling in endothelial cells[201].

Through these highly interconnected pathways — preserved mitochondrial function, antioxidative and anti-inflammatory properties, increased NO bioavailability, re-instated energy homeostasis and alleviated microvascular dysfunction — SGLT2 inhibitors exert a variety of vascular benefits in patients with HF, irrespective of LVEF[189].

[H2] GLP1 receptor agonists

Glucagon-like peptide 1 (GLP1) receptor agonists reduce adverse vascular events and composite HF end points in patients with obesity (body mass index ≥27 kg/m^2) and established CAD across subtypes of HF, as reported in a prespecified analysis of the SELECT trial[202]. First discovered as a regulator of β-cell-mediated insulin release and with known anti-inflammatory properties, GLP1 is expressed by endothelial cells, SMCs and macrophages, which are all present in the vasculature[203]. Through their pancreatic and extrapancreatic effects[203], GLP1 receptor agonists have a substantial effect on plasma glucose lowering and weight loss, mediated via one canonical GLP1 receptor. Although GLP1 receptor agonists might also improve cardiovascular outcomes by reducing visceral adiposity (a major driver of vascular dysfunction[204]), the vascular benefits of GLP1 receptor agonists are predominantly mediated by the endothelial GLP1 receptor[203].

In support of this notion, the GLP1 receptor agonist liraglutide attenuated angiotensin II-induced endothelial dysfunction, oxidative stress and vascular inflammation in myeloid cell-specific *Glp1r*$^{-/-}$ mice but not endothelial cell-specific *Glp1r*$^{-/-}$ mice[205]. Indeed, agonism of GLP1 receptors on endothelial cells increases NO bioavailability, at least in part via AMPK-mediated phosphorylation of eNOS, thereby promoting vasodilatation and improving endothelial function[206,207]. Simultaneously, GLP1 receptor agonists blunt NADPH oxidase activity and suppress intracellular ROS production, while dampening NF-κB signalling in TNF-stimulated human umbilical vein endothelial cells[208].

Stimulation of rat SMCs with liraglutide inhibited angiotensin II-induced proliferation by activating AMPK signalling and inducing cell cycle arrest, mechanisms possibly contributing to the GLP1 receptor agonist-induced attenuation of atherosclerotic plaque progression in hyperlipidaemic mice[207]. Exposure of mouse macrophages to a GLP1 receptor agonist in vitro blunted the release of CCL2, IL-6 and TNF[209], whereas continuous infusions of a GLP1 receptor agonist in hyperlipidaemic mice in vivo attenuated monocyte adhesion and infiltration into atherosclerotic plaque[210]. These experimental data are in accordance with observational evidence obtained in patients with obesity and type 2 diabetes, in whom 12 weeks of treatment with exenatide (10 μg twice daily) decreased plasma levels of CCL2, IL-6 and serum amyloid A protein[211]. GLP1 receptor agonists have emerged as key modulators of the functional and structural homeostasis of the human vasculature in patients with obesity and HF, with important therapeutic potential in both HFrEF and HFpEF.

[H2] Targeting sGC

NO signals via soluble guanylate cyclase (sGC)–cGMP-dependent mechanisms, with sGC stimulators (such as vericiguat) acting on this pathway in an NO-independent fashion, and sGC activators (such as ataciguat) exerting their effects by sensitizing sGC to endogenous NO[212]. Neurohumoral activation during HF progression accelerates oxidative stress in the vasculature, resulting in the loss of the sGC prosthetic haem group and preventing its activation by NO, which makes direct sGC stimulation a promising avenue to improve HF-related outcomes[213]. In the landmark VICTORIA trial[214], vericiguat reduced the risk of HF hospitalization or cardiovascular death in patients with worsening HFrEF, suggesting that a subgroup of patients with HFrEF benefit from stimulation of the sGC pathway. In a phase II study, ataciguat tended to slow the progression of calcific aortic valve disease[215], an important cause of HF for which no medical therapy is available[216].

Importantly, sGC stimulators and activators induce vasodilatation of both the pulmonary and systemic circulations, resulting in decreased right ventricular and LV afterload, and have beneficial effects on endothelial cells and SMCs. Indeed, in a rat model of ischaemic HFrEF, reductions in endothelium-dependent vasorelaxation and NO sensitivity were reversed by the sGC activator ataciguat[217]. By reducing endothelial P-selectin expression, sGC activation by BAY 41-2272 reduced leukocyte rolling and endothelial adhesion in IL-1β-treated mice, suggesting potent anti-inflammatory effects[218]. Importantly, platelet-derived growth factor (PDGF) reduces sGC expression in SMCs[213], with ataciguat-mediated sGC activation attenuating platelet aggregation in rats with ischaemic HFrEF[217]. Interestingly, in a mouse model of non-alcoholic steatohepatitis, the sGC stimulator praliciguat suppressed NLRP3 inflammasome activation in the liver, with attenuated release of IL-1β by liver macrophages[219]. In support of the potent anti-inflammatory effects of sGC stimulation, 12 weeks of treatment with vericiguat dose-dependently reduced plasma C-reactive protein levels in patients with HFrEF in the SOCRATES-REDUCED study[220]. By reversing some of the sequelae of impaired NO signalling, including vasoconstriction, inflammation and platelet aggregation, stimulation of the sGC–cGMP pathway is a multifaceted strategy to improve vascular outcomes in selected patients with worsening HFrEF; however no data support the use of this approach in patients with HFmrEF or HFpEF[221,222].

[H2] Metabolic modulation

Metabolic modulation is an emerging approach for the treatment of HF, aiming to optimize myocardial energy metabolism and improve cardiac function. Strategies include inhibiting free fatty acid oxidation and increasing glucose utilization with trimetazidine[223] or ranolazine[223]; optimizing mitochondrial function with Coenzyme Q_{10}[224] or elamipretide[223]; and modulating substrate competition with ketone bodies[225], butyrate[226] or α-ketoglutarate[227]. In addition to their effects on myocardial metabolism, these strategies also offer vascular benefits, such as improving endothelial function, increasing vasodilation, reducing vascular resistance and mitigating oxidative stress[223-227].

[H1] Vascular effects of interventional and surgical approaches in HF

[H2] Ischaemic HF

The importance of coronary revascularization in patients with HFrEF and potentially hibernating myocardium[18] has been investigated in randomized, controlled trials and registry-based studies. The major question was whether revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery was superior to optimal medical therapy. In the STICH trial[228], no significant difference in all-cause mortality was found between CABG surgery and optimal medical therapy at 4.7 years, but patients treated with CABG surgery had a significant survival benefit at a median of 9.8 years. Similarly, in the REVIVED-BCIS2 trial[229], no significant difference in survival was found between PCI and contemporary optimal medical therapy at 3.4 years, but the rate of myocardial infarction was higher in the medical therapy group. Unfortunately, the REVIVED-BCIS2 trial was not powered to detect differences in all-cause mortality owing to the short duration of follow-up, small sample size and low event rates. In a registry-based comparison between CABG surgery and PCI in more than 2,000 patients with HFrEF, CABG surgery was associated with improved long-term survival rates, starting to become apparent at 3–4 years after the procedure[230]. One reason for the survival benefit associated with CABG surgery compared with PCI might be the use of conduit vessels rather than stents. Multi-arterial revascularization is preferred to saphenous vein grafts in patients aged <70 years, although a strategy of bilateral internal thoracic artery grafts was not superior to single internal thoracic artery grafts in terms of survival at 10 years in the ART trial[231].

Another reason for the improved survival with CABG surgery compared with PCI could be the completeness of revascularization, which is normally the objective of any surgical approach but not necessarily of PCI, in which often only the culprit lesion is treated. The benefits of complete versus incomplete revascularization are still under debate. In the ISCHEMIA trial[232], patients with chronic CAD were randomly assigned to a conservative treatment group (optimal medical therapy) or an invasive treatment group (PCI or CABG surgery). Complete revascularization was achieved in approximately 50% of patients in the invasive treatment group. Health status improved significantly in patients with complete revascularization compared with those with incomplete revascularization or who received conservative medical treatment[232]. This effect of complete revascularization probably also explains the differences in outcomes observed in the randomized, controlled COURAGE[233] and ORBITA[234] trials involving patients with stable angina. In the COURAGE trial[233], PCI of one coronary vessel did not reduce the risk of death, myocardial infarction or other major cardiovascular events when added to optimal medical therapy compared with optimal medical therapy alone at a median follow-up of 4.6 years. Similarly, in the ORBITA trial[234] involving patients with medically treated angina and serve coronary stenosis, PCI did not significantly increase exercise time compared with a placebo procedure. The consequences of incomplete revascularization were addressed in a study that used non-invasive myocardial stress perfusion and coronary flow reserve measured by PET to produce maps of coronary flow capacity and predict the 10-year survival in patients with CAD with or without revascularization[235]. The researchers concluded that the coronary flow capacity reflects the cumulative physiological expression of risk factors, CAD severity and the potential positive effects of revascularization[235].

In summary, evidence from randomized, controlled trials comparing contemporary PCI versus CABG surgery for the treatment of patients with ischaemic HF and multivessel disease is lacking. This deficit will hopefully be addressed by two ongoing randomized, controlled trials involving this specific patient population. In the STICH3C trial[236], the primary end point is the composite of all-cause death, stroke, spontaneous myocardial infarction, urgent repeat revascularization or HF rehospitalization. The key hierarchical end point is time to death and frequency of hospitalizations for HF. The planned median duration of follow-up is 5 years. The UK-focused BCIS4 trial[237] will compare PCI versus CABG surgery in the same patient population, with a minimum duration of follow-up of 4 years . Until the results of these two trials are available, recommendations based on an analysis of the SWEDEHEART registry[238,239] support the favourable long-term results of CABG surgery. In this real-world study, CABG surgery was associated with lower risks of myocardial infarction, repeat revascularization, HF and death compared with PCI in patients with non-ST-segment elevation myocardial infarction[238,239]. This difference was greatest in patients with LV dysfunction (LVEF <35%), left main CAD and those aged <70 years[238].

[H2] HF of valvular origin

HF can result from untreated valvular heart disease. In most cases, the underlying pathology is aortic (and less commonly mitral) valve stenosis or regurgitation. The aetiology is either degenerative, rheumatic, ischaemic or infective in nature. At the cellular level, both aortic valve stenosis and regurgitation ultimately induce (concentric and/or eccentric) hypertrophy of cardiomyocytes and progressive interstitial fibrosis[240]. The consequence is a progressive mismatch between the growing myocardium and the microvasculature, resulting in minimal coronary vascular resistance per gram of myocardium, increased diffusion distances, focal ischaemia and necrosis, which further exacerbates HF progression. Pharmacotherapy for aortic valve disease remains elusive[216], and interventional treatment is successful only if the appropriately timed. Both experimental and clinical data support LV unloading to reduce LV mass[241]. However, whether the extracellular matrix undergoes reverse remodelling and whether CMD is improved remains uncertain[241].

In mitral valve stenosis, mostly seen in patients with end-stage rheumatic heart disease, the left ventricle is not properly loaded and consequently does not generate substantial pressure–volume work (the mechanical work done by the ventricle as it contracts and ejects blood, represented by the area within the pressure–volume loop)[242]. Conversely, in mitral valve regurgitation, the left ventricle is filled regularly but a progressively increasing regurgitant volume leaks into the left atrium during the LV ejection phase[243]. Therefore, the left ventricle becomes progressively functionally inefficient, with potential backward failure into the pulmonary system, compromising right ventricular function. Surgical or interventional correction is the only cure, when performed before the ejection fraction deteriorates.

[H2] Acute HF and cardiogenic shock

In acute HF with cardiogenic shock, inotropes and mechanical assist devices are crucial. The causes are often ischaemic (for example, papillary muscle rupture) or infective (for example, acute endocarditis of the aortic valve), with toxic origins being rare. Rapid onset leads to inadequate cardiac output, decreased coronary perfusion and worsening underperfusion due to progressively increasing diastolic radial wall stress[244]. Effective treatment involves addressing the underlying cause (for example, valve replacement or coronary revascularization) and supporting the heart with inotropes and unloading to reduce wall stress and improve perfusion. All ventricular assist devices use a vascular approach and effectively unload the failing heart from its afterload and, in the case of veno-arterial extracorporeal membrane oxygenation (ECMO) and microaxial pumps, also from preload. The use of an intra-aortic balloon pump is now less common[245]. VA-ECMO is increasingly used for full cardiopulmonary support but is associated with the intrinsic problems of limb ischaemia, thromboembolism and bleeding, as well as an increased LV afterload from retrograde aortic perfusion[246]. Microaxial flow pumps for LV unloading alone or in combination with VA-ECMO can overcome the increased LV afterload. A meta-analysis showed lower in-hospital mortality in the combination group compared with VA-ECMO alone[247]. Multicentre data show that these approaches can promote recovery in infarct-related cardiogenic shock[248] or serve as a bridge to ventricular assist devices or heart transplantation[249]. To monitor treatment efficacy (and overall prognosis), the arterial lactate level is a dynamic biomarker providing real-time feedback on tissue perfusion in acute HF[250]. However, lactate levels can also be influenced by non-cardiac factors such as sepsis or liver dysfunction and so must be interpreted in combination with other clinical findings.

[H1] Conclusions

The heart functions as both a motor and a pump that drives cardiac output throughout the vasculature to provide the entire organism with oxygen and nutrients and remove the waste products. The heart itself depends on adequate fuel delivery via the coronary circulation. However, contractile function is dependent not only on intrinsic cardiomyocyte contractility but also on preload from venous return and afterload from arterial impedance. In HF, the focus is naturally on the cardiomyocytes, which have a failure in excitation–contraction coupling and are dysfunctional. However, HF is a systemic disease in which perfusion through the arteries and veins is inadequate, and many of the manifestations of HF are vascular, such as inadequate perfusion of parenchymal organs, congestion and thrombosis. Therefore, both the coronary circulation and the systemic circulation must be carefully considered in the context of HF. In this Review, we have discussed the role of the coronary and systemic circulation in the pathogenesis of various phenotypes of HF of different origins, as well as its diagnosis and treatment. Of note, we have highlighted when HF treatment relies on primarily on vascular approaches, either pharmacological or interventional. The treatment of HF is more effective with approaches that increase coronary blood flow and unload the heart primarily via systemic vascular effects than with approaches that primarily improve excitation–contraction coupling in cardiomyocytes.

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Author contributions

The authors contributed substantially to all aspects of the article.

Competing interests

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Key points

- Heart failure (HF) is a systemic disease involving coronary and systemic vascular dysfunction; the coronary circulation sustains myocardial metabolism by delivering oxygen and nutrients while removing waste, whereas the systemic circulation defines preload and afterload for cardiac contraction.
- Cellular and molecular changes in the coronary vasculature overlap in HF with preserved ejection fraction and HF with reduced ejection fraction, but distinct genetic determinants suggest unidentified metabolic mechanisms in each condition.
- Vascular dysfunction in HF impairs blood flow to cardiomyocytes; increases afterload; impairs venous return; induces pulmonary hypertension; triggers multiorgan congestion and lymphatic dysfunction; and perpetuates inflammation, oxidative stress and neurohormonal dysregulation, thereby accelerating cardiac and systemic HF progression.
- Both non-invasive and invasive imaging modalities are used experimentally and clinically to evaluate the contribution of coronary vascular structural and functional disturbances to the pathogenesis of a wide spectrum of HF.
- Contemporary pharmacotherapies for HF, such as β-blockers, renin–angiotensin–aldosterone system and neprilysin inhibitors, sodium–glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists and soluble guanylate cyclase stimulators, improve vascular function by targeting endothelial cells, smooth muscle cells and immune pathways, reducing inflammation, oxidative stress and vascular remodelling.
- Interventional or surgical revascularization improves coronary blood flow in ischaemic HF; ventricular assist devices unload the heart in acute HF.

Table 1 | Imaging of vascular dysfunction in heart failure

Feature	Echocardiography	CMR	CCTA and CT-MPI	SPECT	PET
Strengths	Widely available, cost-effective, and real-time imaging. Evaluates structure, geometry and contractile function. Doppler echocardiography assesses CFV, which correlates with CFR. MCE provides insights into microvascular function and perfusion.	High-resolution evaluation of structure, geometry and contractile function. High-resolution, non-contrast and contrast-based perfusion imaging. LGE identifies infarcted versus viable myocardium. T1 and T2 mapping assesses fibrosis, oedema and tissue characteristics. MRS and hyperpolarized MRI provide metabolic insights (such as PCr:ATP ratio and metabolic flow).	High negative predictive value for CAD, reducing unnecessary invasive angiography. FFR_{CT} assesses lesion significance non-invasively. CT-MPI can detect CMD and integrate functional assessment with anatomical visualization.	Well-established for detecting ischaemia via perfusion deficits. Advances now enable absolute MBF and CFR quantification. Improved resolution and dynamic imaging increase diagnostic accuracy.	Gold standard for absolute quantification of MBF and myocardial metabolism. High spatial resolution and ability to distinguish CAD from CMD. Assesses metabolic remodelling (such as glucose and fatty acid metabolism).
Limitations	Operator-dependent, with variable accuracy. Limited sensitivity in detecting subtle microvascular dysfunction. No standardized diagnostic criteria for CMD.	Time-consuming and expensive. Contraindications in patients with metallic implants or severe claustrophobia. Hyperpolarized MR can directly measure metabolic processes but not to the same extent as PET.	Requires advanced CT scanners and optimized imaging protocols. Radiation exposure and contrast-related risks. CT–MPI is technically demanding.	Lower spatial resolution than PET. Limited clinical experience with newer quantification techniques. Potential radiation exposure concerns.	Requires access to specific tracers (such as ^{15}O-water, ^{82}Rb or ^{18}F-FDG). Cyclotron dependency for certain radiotracers. High cost and limited availability.
Clinical applications	First-line assessment for HF classification (HFrEF versus HFpEF). Screening for CMD in patients with suspected microvascular dysfunction.	Comprehensive structural and functional assessment in HF. Perfusion imaging for ischaemia and CMD evaluation. Research applications in myocardial energetics and metabolism.	First-line for excluding clinically significant CAD in patients at low to intermediate risk. FFR_{CT} enables functional assessment of intermediate stenoses.	Assessment of CAD-related ischaemia and myocardial viability. Emerging role in quantifying MBF and CFR in CMD diagnosis.	CMD diagnosis and ischaemia evaluation. Assessment of myocardial viability for revascularization planning. Research tool for metabolic and pathophysiological insights in HF.
Utility in HFpEF versus HFrEF	HFpEF: detects diastolic dysfunction and CMD (Doppler). HFrEF: assesses left ventricular systolic function and ejection fraction.	HFpEF: CMD evaluation. T1 mapping for fibrosis. HFrEF: LGE for infarct characterization and viability assessment.	HFpEF: CMD assessment possible with CT–MPI. HFrEF: first-line modality for CAD exclusion.	HFpEF: limited use. HFrEF: detects ischaemia but PET preferred.	HFpEF: CMD detection (gold standard). HFrEF: viability and metabolic assessment.

Diagnostic accuracy	Doppler CFV correlates with CFR; MCE assesses microvascular function (CMD) but is operator-dependent.	High-resolution perfusion and ischaemia imaging, including CMD. T1 mapping for diffuse fibrosis. MRS and hyperpolarized MR for metabolism.	Highest sensitivity and specificity for CAD. FFR_{CT} has a better diagnostic accuracy than PET, SPECT or CMR as a second-line test in patients with documented CAD on CCTA. CT–MPI correlates well with PET or CMR for MBF but is not used routinely.	Traditional ischaemia assessment but might miss balanced ischaemia. Newer tracers allow absolute MBF quantification but limited use.	Gold standard for CMD assessment by MBF and CFR. ^{18}F-FDG evaluates metabolic shifts in HF.
Prognostic value	E/A ratio and global longitudinal strain predict HF outcomes.	LGE predicts HF mortality. Fibrosis burden correlates with prognosis.	FFR_{CT} predicts ischaemic events. MBF quantification correlates with prognosis.	CFR via dynamic SPECT correlates with mortality in HFpEF.	CFR <2 predicts MACE and HF hospitalization. ^{18}F-FDG identifies viable myocardium.
Cost-effectiveness	Low cost, first-line bedside test, but less precise for CMD.	Expensive, limited availability, contraindicated in severe chronic kidney disease.	Medium cost, radiation exposure, requires advanced scanners.	Cheaper but lower resolution than PET. Might miss microvascular disease.	Expensive. Requires cyclotron for ^{15}O-water. ^{82}Rb is more accessible.

CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CFR, coronary flow reserve; CFV, coronary flow velocity; CMD, coronary microvascular dysfunction; CMR, cardiovascular magnetic resonance; CT, computed tomography; E/A ratio, ratio of the peak velocities of early and late diastolic filling; FDG, fluorodeoxyglucose; FFR_{CT}, computed tomography-derived fractional flow reserve; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LGE, late gadolinium enhancement; MACE, major adverse cardiovascular events; MBF, myocardial blood flow; MCE, myocardial contrast echocardiography; MPI, myocardial perfusion imaging; MR, magnetic resonance; MRS, magnetic resonance spectroscopy; PCr, phosphocreatine; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

Table 2 | Vascular effects of heart failure drugs in clinical trials

Drug class	Drug	Initial / target dose[a] (mg)	RCT or meta-analysis	Patients	End points	Risk estimate (95% CI)	Dilatory effects on coronary circulation	Dilatory effects on systemic circulation
β-Blocker	Bisoprolol	1.25 / 10	CIBIS-II[251]	NYHA III or IV, LVEF ≤35%	All-cause mortality	HR 0.66 (0.54–0.81)	–[b]	–[b]
					All-cause hospital admission	HR 0.80 (0.71–0.91)		
	Metoprolol	25 or 12.5 / 200	MERIT-HF[252]	NYHA II or IV, LVEF ≤40%	All-cause mortality	RR 0.66 (0.53–0.81)	–[b]	–[b]
					Cardiovascular mortality	RR 0.62 (0.50–0.78)		
	Carvedilol	2 × 12.5 / 2 × 50	Carvedilol Heart Failure Study[253]	LVEF ≤35%	All-cause mortality	HR 0.35 (0.20–0.61)	+++ (– –)[c]	++ (– –)[c]
					Rehospitalization for cardiovascular causes	HR 0.73 (0.55–0.97)		
	Nebivolol	1.25 / 10	SENIORS[254]	LVEF ≤35%; age ≥70 years	All-cause mortality or cardiovascular hospital admission	HR 0.86 (0.74–0.99)	+++	++
					All-cause mortality	HR 0.88, (0.71–1.08)		
RAAS inhibitor or ARNI	Sacubitril–valsartan[d]	2 × 100 / 2 × 200	PARADIGM-HF[255]	NYHA II–IV, LVEF ≤40%	Composite of death from cardiovascular causes or hospitalization for HF	HR 0.80 (0.73–0.87)	++	+++
					All-cause mortality	HR 0.84 (0.76–0.93)		
	Enalapril	2.5–20	SOLVD[256]	LVEF ≤35%	All-cause mortality	RR 0.84 (0.74–0.95)	+	++
					Composite of death or hospitalization for HF	RR 0.74 (0.66–0.82)		
	Valsartan	2 × 40 / 2 × 160	Valsartan Heart Failure Trial[257]	NYHA II–IV, LVEF <40%	All-cause mortality	RR 1.02 (0.88–1.18)	+	++
					Composite of death, cardiac arrest, hospitalization for HF, or need for vasoactive substances	RR 0.87 (0.77–0.97)		
MRA	Spironolactone	25 / 50	Randomized Aldactone Evaluation Study[258]	LVEF ≤35%	All-cause mortality	HR 0.70 (0.60–0.82)	+	++
					Hospitalization for cardiac causes	RR 0.70 (0.59–0.82)		
	Finerenone	20 / 40	FINEARTS-HF[259]	LVEF ≥40%	Composite of total worsening heart failure events and cardiovascular death	Rate ratio 0.84 (0.74–0.95)	+	++
					Cardiovascular mortality	HR 0.93 (0.78–1.11)		
SGLT2 inhibitor	Empagliflozin	10 / 10	EMPEROR-PRESERVED[260]	NYHA II–IV, LVEF >40%	Cardiovascular death or hospitalization for HF	HR 0.79 (0.69–0.90)	++	++
					Hospitalization for worsening HF	HR 0.73 (0.61–0.88)		

		10 / 10	EMPEROR-REDUCED[261]	NYHA II–IV, LVEF ≤40%	Composite of cardiovascular death or hospitalization for worsening HF	HR 0.75 (0.65–0.86)	++	++
					Hospitalization for worsening HF	HR 0.70 (0.58–0.85)		
	Dapagliflozin	10 / 10	DELIVER[262]	NYHA II–IV, LVEF >40%	Composite of worsening heart failure or cardiovascular death	HR 0.82 (0.73–0.92)	++	++
					Cardiovascular death	HR 0.88 (0.74–1.05)		
		10 / 10	DAPA-HF[263]	NYHA II–IV, LVEF ≤40%	Composite of worsening heart failure or cardiovascular death	HR 0.74 (0.65–0.85	++	++
					Cardiovascular death	HR 0.82 (0.69–0.98)		
GLP1 receptor agonist	Semaglutide	2.4 once weekly	SELECT[264]	HFpEF, ASCVD and overweight or obese	Composite of cardiovascular death or worsening HF	HR 0.69 (0.53–0.89)	+	++
		1.0 once weekly	FLOW[264]	HFpEF, T2DM and CKD	Worsening HF events	HR 0.59 (0.41–0.82)		
		2.4 once weekly	STEP-HFpEF[264]	Obesity-related HFpEF	Cardiovascular death	HR 0.82 (0.57–1.16)		
		2.4 once weekly	STEP-HFpEF DM[264]	Obesity-related HFpEF				

ARNI, angiotensin receptor–neprilysin inhibitor; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; GLP1, glucagon-like peptide 1; HF heart failure; HFpEF, heart failure with preserved ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; RAAS, renin–angiotensin–aldosterone system; RR relative risk; SGLT2, sodium–glucose cotransporter 2; T2DM, type 2 diabetes mellitus. [a]Refers to daily doses unless otherwise stated. [b]Unopposed α-adrenergic vasoconstriction. [c]Non-selective β-blockade can result in peripheral vasoconstriction (mainly through β_2-blockade, allowing unopposed α-adrenergic vasoconstriction). [d]The reported risk estimates used the placebo group as the reference but, in the PARADIGM-HF trial[255], the reported hazard ratios refer to the comparison between the ANRI (200 mg twice daily) and enalapril (10 mg twice daily).

Fig. 1 | The vicious cycle between vascular (dys)function and the failing heart. (1) As a consequence of metabolic disturbances and endothelial dysfunction, activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system, vasomotor tone and systemic vascular resistance are increased. (2) Sustained elevated vascular resistance is associated with structural stiffening of the arterial wall. The systemic increase in arterial resistance determines the increase in left ventricular (LV) afterload. (3) Aortic valve stenosis also increases LV afterload. (4) Systemic venous circulation determines venous return and right ventricular preload. Systemic venous dysfunction leads to congestion and fluid overload. (5) Pulmonary vascular dysfunction, including arterial remodelling and increased resistance, leads to right ventricular overload. (6) Excessive systemic fluid retention increases filling pressures in both the left and right ventricles, leading to congestion and peripheral and pulmonary oedema. (7) Chronic venous hypertension predisposes to thrombosis, which further reduces cardiac output. (8) Fluid overload and congestion in heart failure also affect the systemic lymphatic system. Lymphatic dysfunction impairs fluid transport and exacerbates both cardiac and systemic congestion. (9) Coronary vascular and lymphatic dysfunction contribute to impaired vasomotor function, myocardial inflammation and oedema. Therefore, coronary and systemic vascular dysfunction contribute to the development and progression of heart failure, whereas heart failure compromises vascular function, creating and maintaining a vicious circle with perturbing effects on coronary blood flow, cardiac metabolism and cardiac function.

Fig. 2 | Heterogeneity in the responsiveness to physical, metabolic, autonomic, endocrine, paracrine and endothelial factors in the various segments of the coronary vascular tree. The figure shows the responsiveness of various segments of the coronary vascular tree to metabolic perturbations under physiological conditions (solid lines) and in heart failure (shading above or below the solid lines). The coronary vasculature responds actively to changes in perfusion pressure and shear stress with changes in vascular tone, via myogenic responses (MR) and flow-mediated dilatation (FMD), respectively. Coronary small arteries and arterioles have a functional smooth muscle cell (SMC) layer, whereas capillaries are surrounded by special mural cells (pericytes). FMD primarily affects the vasomotor tone of small arteries and larger arterioles. Pressure-mediated, stretch-induced myogenic mechanisms affect larger arterioles, whereas the smallest arterioles are particularly sensitive to cardiomyocyte-derived metabolic stimuli, such as adenosine (Ado). Several receptors and ion channels are crucial for coronary vasomotion, and the relative responsiveness to their agonists is highly heterogeneous. The interaction between these receptors, their associated signalling pathways and ion channels creates the complex integrated coronary vascular response, termed coronary vasomotion (reviewed previously[1,2]). Although many details are known about the epicardial conductance arteries and the resistance arteries (small arteries and arterioles), the importance of actively regulating coronary capillary diameters, as well as the underlying molecular mechanisms, are still incompletely understood (indicated with grey dashed lines). Capillaries might have an active role in the control of the coronary blood flow and its distribution in the coronary capillary bed, but how the mechanisms controlling capillary structure and function are affected in heart failure is still mostly hypothetical and extrapolated from other vascular beds. 5-HT_1, serotonin receptor 1; 5-HT_2, serotonin receptor 2; α_1, α_1-adrenergic receptor; α_2, α_2-adrenergic receptor; β_1, β_1-adrenergic receptor; β_2, β_2-adrenergic receptor; EDHF, endothelium-derived hyperpolarizing factor; H_2O_2, hydrogen peroxide; K_{ATP}, ATP-sensitive potassium channel; K_{Ca}, calcium-activated potassium channel; K_V, voltage-gated potassium channel; NO, nitric oxide; PGI_2, prostacyclin.

Fig. 3 | Structures of arterioles and capillaries and similarities and differences in their cellular and molecular control mechanisms. Heart failure (HF) increases sympathetic nervous system activity, coronary arterioles become hyperinnervated, and vascular adrenoceptors become desensitized. In contrast to arterioles, capillaries lack autonomic innervation, whereas the direct cell–cell contact (such as between blood cells and endothelial cells (ECs)) in the capillaries might facilitate intercellular signalling. Pericytes — specialized mural cells that surround capillary ECs and provide vascular stability — seem to take over the role that smooth muscle cells (SMCs) have in arterioles. Indeed, many of the receptors and ion channels found on arteriolar SMCs have also been described on pericytes. Lymphoid vessel structures, which run parallel to the arterioles, are absent in the capillaries. The underlying cellular and molecular changes due to the underlying risk factors in obstructive coronary artery disease (CAD) or HF with reduced ejection fraction (HFrEF) compared with non-obstructive CAD or HF with preserved ejection fraction (HFpEF) are shown on the right of the figure. Note that many of the molecular changes are shared between the two disease phenotypes, although several differences are also apparent. Both phenotypes of HF are characterized by impaired endothelium-dependent vasodilatation, a chronic inflammatory state not only in vascular ECs and lymphatic ECs (LECs) but also in leukocytes, dysfunctional red blood cells (RBCs), activated platelets and metabolic perturbations in cardiomyocytes. Concentrations of myeloperoxidase (MPO) and neutrophil extracellular traps (NETs) are elevated; nitric oxide (NO) and ATP availability are reduced; production of reactive oxygen species (ROS) and hydrogen peroxide (H_2O_2) is increased; and adenosine (Ado), angiotensin II (A_{II}), endothelin receptor (ET) and thromboxane A_2 (TXA_2) signalling is increased. The general pro-inflammatory environment is often more intermittent in obstructive CAD and HFrEF (such as during an acute myocardial infarction) and more constant in non-obstructive CAD and HFpEF. In HF, SMC dysfunction occurs, including reduced vasodilator responsiveness to NO and to Ado, increased vasoconstrictor responsiveness to noradrenaline (NA) and endothelin 1 (ET-1), as well as K^+ channel dysfunction, which together increase coronary microvascular tone. ATP-sensitive potassium (K_{ATP}) channels contribute to coronary blood flow regulation in HFrEF, whereas the activity of both K_{ATP} and voltage-dependent potassium (K_V) channels is blunted in HFpEF. Systemic metabolic disorders and ischaemic sequelae result in modified cardiomyocyte glucose and free fatty acid (FFA) metabolism, but substrate shifts occur in opposite directions in obstructive CAD and HFrEF (increased FFA metabolism) compared with non-obstructive CAD and HFpEF (increased glucose metabolism). Lymphoid collecting vessels undergo inward remodelling and rarefaction, possibly due to increased oxidative stress, which might contribute to the formation of oedema. Blood viscosity and blood cell–EC interactions are of crucial importance to capillary blood flow. With both phenotypes of HF, plasma viscosity is increased, the expression of cellular adhesion molecules (CAMs) is upregulated, and RBC aggregation is increased and deformability is decreased. Leukocytes promote a chronic inflammatory state, thereby aggravating blood cell plugging in the microvasculature, whereas the various HF risk factors are associated with platelet hyperactivation. Increased blood viscosity can not only impair perfusion in the microcirculation but might also impair intercellular signalling and oxygen (O_2) exchange in capillaries. Pericytes surrounding the capillaries seem to be very similar to SMCs in terms of function and molecular control mechanisms, and so it is likely (but still hypothetical) that the changes observed in coronary arteriolar SMCs also occur in capillary pericytes. Collagen deposition is increased in both HF phenotypes, with an increased ratio of collagen III (Col III) to collagen I (Coll I) in obstructive CAD and HFrEF, and an increased Coll I:III ratio in non-obstructive CAD and HFpEF. Changes in white text are uncertain or have not been described in the context of the coronary circulation. A, adrenaline; α, α-adrenergic receptor; AT_1, angiotensin II receptor type 1; β, β-adrenergic receptor; EDHF, endothelium-derived hyperpolarizing factor; EV, extracellular vesicle; GC, guanylate cyclase; 5-HT, serotonin; LDN, low-density neutrophil; M, muscarinic receptor; MMP, matrix metalloproteinase; P1, piezo-type mechanosensitive ion channel 1; PKG, protein kinase G; RDW, red blood cell distribution width; TGFβ1, transforming growth factor-β1; TIMP, tissue inhibitors of metalloproteinase.

Fig. 4 | Workflow for the use of imaging modalities in HF. The figure shows a proposed workflow for the use of imaging modalities to support a rational diagnostic approach for optimal management and treatment of patients with heart failure (HF), both in clinical practice and for studying mechanisms in research. CABG, coronary artery bypass graft; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CFR, coronary flow reserve; CFV, coronary flow velocity; CMD, coronary microvascular dysfunction; CMR, cardiovascular magnetic resonance; FDG, fluorodeoxyglucose; FFR, fractional flow reserve; FFR_{CT}, CT-derived fractional flow reserve; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICA, intracoronary angiography; iFR, instantaneous wave-free ratio; LGE, late gadolinium enhancement; MBF, myocardial blood flow; MPI, myocardial perfusion imaging; PCI, percutaneous coronary intervention; PET, positron emission tomography; PYP, pyrophosphate; SPECT, single-photon emission computed tomography.

Fig. 5 | Contemporary pharmacotherapies and their effect on vascular function in heart failure. **a**, Overview of vascular effects mediated by the renin–angiotensin (Ang)–aldosterone system (RAAS) and targeted interventions. Activation of RAAS leads to increased cardiac workload and vascular remodelling, which is mitigated by β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs) and glucagon-like peptide 1 (GLP1) receptor agonists. Sodium–glucose cotransporter 2 (SGLT2) inhibitors further reduce vascular tone and systemic inflammation and improve microvascular function. **b**, Effects on endothelial cell function. L-Nebivolol improves nitric oxide (NO) bioavailability through β_3-adrenergic receptor signalling. SGLT2 inhibitors improve mitochondrial health and increase autophagic flux, whereas GLP1 receptor agonists, ACE inhibitors and angiotensin receptor–neprilysin inhibitors (ARNIs) reduce inflammation and vascular adhesion molecule expression. β-Blockers and MRAs favour the homeostatic state with reduced oxidative stress, inflammation, apoptosis and mitochondrial derangement. **c**, Actions on vascular smooth muscle cells. β-Blockers other than carvedilol and nebivolol augment vasoconstriction by unopposed α-adrenergic effects. Agents such as vericiguat increase cGMP signalling via soluble guanylate cyclase (sGC), whereas neprilysin inhibitors increase natriuretic peptide signalling, thereby reducing nuclear factor-κB (NF-κB)-mediated inflammatory pathways and myogenic tone. SGLT2 inhibitors, MRAs and GLP1 receptor agonists attenuate oxidative stress (ROS), cellular migration and proliferation. **d**, Modulation of macrophage polarization. GLP1 receptor agonists, SGLT2 inhibitors and MRAs modulate macrophage phenotype towards a resident, reparative state, reducing vascular inflammation and promoting tissue repair. AMPK, 5′-AMP-activated protein kinase; ANP, atrial natriuretic peptide; AT_1, angiotensin II receptor type 1; BK_{Ca}, large-conductance calcium-activated potassium channel; BNP, B-type natriuretic peptide; eNOS, endothelial nitric oxide synthase; GLUT1, glucose transporter type 1; NPR, natriuretic peptide receptor; P, phosphorylation; SIRT, NAD-dependent histone deacetylase sirtuin; TGFβ, transforming growth factor-β; VCAM1, vascular cell adhesion protein 1.

Fig. 6 | Stepwise initiation and optimization of therapy for patients with HFrEF, HFmrEF or HFpEF. The figure outlines a stepwise approach to the management of heart failure (HF) based on ejection fraction. In HF with reduced ejection fraction (HFrEF), therapy begins with quadruple pharmacological treatment, followed by optimization, additional therapies and reassessment of cardiac function. In HF with mildly reduced ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF), treatment starts with sodium–glucose cotransporter 2 (SGLT2) inhibitors and diuretics (if congested), with evolving evidence supporting the use of glucagon-like 1 peptide (GLP1) receptor agonists in patients with a body mass index ≥27 kg/m^2. This step is followed by additional guideline-directed medical therapy and comorbidity management. Irrespective of HF subtype, reassessment of patient status determines further interventions, including referral to specialty HF care if symptoms persist or worsen. Treatments are colour-coded based on guideline recommendations and evidence levels[265]. [a]Patients with HFmrEF or HFpEF might derive greater clinical benefit from non-steroidal MRAs than from steroidal MRAs[147], although some regional variation in the benefits of steroidal MRAs in the setting of HFpEF exist[146]. Irrespective of the type of MRA used, close laboratory monitoring of serum potassium levels is required. [b]β-Blockers should be subject to a thorough risk–benefit assessment in the setting of HFmrEF and HFpEF, particularly in patients with chronotropic insufficiency[159,160]. ARNI, angiotensin receptor–neprilysin inhibitor.

Box 1 | Differences in coronary and systemic circulation in heart failure

Coronary circulation

- Extravascular compression impedes coronary blood flow, which therefore occurs only in diastole.
- Autoregulation maintains coronary blood flow at different perfusion pressures.
- The heart has near-maximal oxygen extraction at rest. Therefore, increased myocardial oxygen consumption depends on increased coronary blood flow.
- Metabolic vasomotion determines coronary blood flow; mediators involve adenosine, prostaglandins, nitric oxide, superoxide ions, carbon dioxide, H^+ and K^+, but are ultimately not clear.
- The coronary circulation is a terminal perfusion territory with minimal collateral blood supply. Insufficient blood flow causes injury, either reversible or irreversible.
- In heart failure, tachycardia (shortened diastole) and increased left ventricular diastolic pressure impair coronary blood flow, even at early stages.

Systemic circulation

- Autoregulation maintains arterial pressure and ensures perfusion to the brain, heart and kidneys.
- Skeletal muscle perfusion depends on metabolism (active state) and sympathetic vasoconstrictor tone (resting state).
- The venous system contains most of the circulating blood volume, and blood volume and venous vasomotor tone determine mean systemic filling pressure.
- Neuronal and endocrine pathways (catecholamines, the renin–angiotensin–aldosterone system, vasopressin, atrial natriuretic peptide and others) regulate vasomotor tone and blood volume.
- Perfusion is impaired only in severe heart failure when cardiac output is reduced.
- Vasomotor tone and blood volume are the main targets for drug therapy in heart failure.

ToC

Coronary and systemic vascular dysfunction contributes to the initiation and progression of heart failure (HF) with or without reduced ejection fraction and, vice versa, HF compromises vascular function. In this Review, Liberale and colleagues discuss vascular dysfunction in the pathogenesis of HF and how pharmacological, interventional and surgical management of HF can improve vascular function.