Myocardial oedema: pathophysiological basis and implications for the failing heart

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Abstract

Myocardial fluid homeostasis relies on a complex interplay between microvascular filtration, interstitial hydration, cardiomyocyte water uptake and lymphatic removal. Dysregulation of one or more of these mechanisms may result in myocardial oedema. Interstitial and intracellular fluid accumulation disrupts myocardial architecture, intercellular communication, and metabolic pathways, decreasing contractility and increasing myocardial stiffness. The widespread use of cardiac magnetic resonance enabled the identification of myocardial oedema as a clinically relevant imaging finding with prognostic implications in several types of heart failure. Furthermore, growing experimental evidence has contributed to a better understanding of the physical and molecular interactions in the microvascular barrier, myocardial interstitium and lymphatics and how they might be disrupted in heart failure. In this review, we summarize current knowledge on the factors controlling myocardial water balance in the healthy and failing heart and pinpoint the new potential therapeutic avenues.

Keywords Heart failure; Myocardial oedema; Cardiac microcirculation; Cardiac pericytes; Cardiac lymphatics; Myocardial interstitium; Extracellular matrix

Introduction

The adequate compartmentalization of water in the myocardium is essential to maintain normal cardiac function.1 Despite several mechanisms known to regulate cardiomyocyte and interstitial volume,2 the myocardium remains particularly susceptible to oedema formation due to its dense microvascular network and high interstitial flow rate.

Myocardial oedema (MO), defined by the accumulation of cardiac water in interstitial and/or intracellular compartments, has been shown to induce cardiomyocyte injury, dysfunction3–6 and remodelling.3,4

The recent introduction of magnetic resonance imaging (MRI) techniques (e.g. myocardial T1 and T2 mapping) has enabled the non-invasive assessment of the extracellular component, namely, the myocardial water content, suggesting that MO negatively affects the prognosis across acute and chronic heart failure (HF).7–9 Moreover, advances in the understanding of the myocardial microvascular barrier and lymphatics suggest that myocardial fluid balance disturbances are key determinants of the extent and duration of myocardial injury. These aspects may recast MO as a therapeutic target yet to explore in clinical practice.

The present review aims to summarize the current knowledge on the pathophysiological mechanisms of MO formation and their contribution to the disruption of cardiac homeostasis in the failing heart, also discussing future perspectives on therapeutic targeting of MO.
Basic concepts

Myocardial fluid balance and myocardial oedema

To maintain fluid homeostasis, microvascular fluid filtration into the myocardium must be matched by its removal rate via myocardial lymphatic vessels. Microvascular fluid exchange is governed by the Starling principle, expertly reviewed elsewhere, summarised by the revised Starling equation:

\[ J_V = L_P S \left[ \left( P_C - P_I \right) - \sigma \left( \Pi_C - \Pi_G \right) \right] \]

where \( L_P \) is the hydraulic conductivity, \( S \) is the filtration surface area, \( P_C \) and \( P_I \) are the intracapillary (C) and interstitial (I) hydrostatic pressures, \( \sigma \) is the protein reflection coefficient and \( \Pi_C \) and \( \Pi_G \) are the intracapillary and subglycocalyx (G) colloid osmotic pressures, respectively (Figure 1). In order to keep a stable interstitial volume \( (V_I) \) and defend against oedema formation, several physiological mechanisms counteract primary perturbations in \( P_C \), \( \Pi_C \) and endothelial barrier function—oedema safety factors.

Figure 1. The disruption of myocardial fluid balance in the failing heart. Multiple mechanisms can contribute for oedema formation in the failing heart and are differentially observed in several types of acute and chronic heart failure. Myocardial ischaemia, inflammation and volume overload negatively impact on microvascular barrier function by promoting the glycocalyx degradation and pericyte detachment, resulting in excessive fluid filtration. The resulting increase in interstitial volume and pressure disrupt the extracellular matrix (ECM) architecture, pulling cardiomyocytes away from capillaries and increasing oxygen diffusion distance. Moreover, ECM degradation and high central venous pressure impair lymphatic recruitment and drainage, leading to the accumulation of inflammatory cells, cytokines and metabolic waste products in the myocardial interstitium. Collectively, these mechanisms can impair myocardial contractility and bioenergetics, increase myocardial stiffness and promote cardiomyocyte apoptosis.
Myocardial oedema develops when fluid filtration rate exceeds lymphatic fluid removal and can be generated by increased ΔP or S, decreased ΔΠ or alterations of microvascular membrane properties (increased Lp or decreased σ) (Figure 1). Increased Pc can be driven by high pre-capillary pressure in the setting of acute arterial hypertension, or high post-capillary pressure in coronary sinus occlusion, pulmonary hypertension or in acute HF with increased central venous pressure. Moreover, increased S, caused by increased capillary recruitment or vasodilation, promotes MO formation and is particularly relevant in inflammatory HF aetiologies (e.g. myocarditis and sepsis). Finally, as albumin is the major determinant of Πc, states of hypoalbuminemia facilitate fluid filtration and global interstitial oedema. This is particularly relevant in crystalloid coronary perfusion during cardiac surgery and in shock management (e.g. septic and cardiogenic) in which, excessive fluid resuscitation worsens prognosis.

Myocardial oedema dramatically reduces energetic efficiency, impairing both contraction and relaxation. However, increased VI and P have been shown to primarily affect myocardial viscoelastic properties, resulting in higher diastolic stiffness. Due to its low interstitial compliance, small interstitial volume expansions create high interstitial pressures, making the myocardium particularly sensitive to oedema formation. The experimental increase in myocardial water content by 3.5% was associated with a 40% drop in cardiac output. In addition, MO directly opposes filtration, by decreasing ΔP and physically compressing the capillaries and disrupting nutrient and oxygen delivery. The disruption of the extracellular matrix structure, increased oxygen diffusion distance and accumulation of metabolic waste products are additional proposed mechanisms of MO-associated functional deterioration (Figure 2).

In summary, myocardial fluid balance is largely dependent on microcirculation dynamics, microvascular barrier, interstitial architecture and lymphatic drainage. Disruption of any of these components may disturb myocardial fluid homeostasis. In this review, each factor will be addressed in detail regarding its physiological role and how it may be disrupted in the failing heart.

**Coronary microcirculation**

The healthy myocardium is one of the most densely vascularized tissues in human body, possessing a high density capillary network (3,000–4,000/mm²) closely disposed around cardiomyocytes (Figure 2). Such proximity between cardiomyocytes and capillaries is of utmost importance to maintain a short diffusion distance not only for oxygen, but also for potentially toxic byproducts of cellular metabolism. Moreover, the high metabolic rate of the myocardium, which primarily depends on oxidative phosphorylation, translates in an elevated oxygen demand that is matched by a very high oxygen extraction rate (70%–80% in resting conditions). Consequently, in stress conditions, additional increments in oxygen demand are predominantly met by parallel increases in myocardial blood flow (MBF). This metabolic contribution to MBF autoregulation is made possible by the close contact...
between cardiac muscle and vasculature, enabling cardiomyocyte-derived mediators (CO$_2$, lactate) and microenvironmental factors (pH, extracellular K) to modulate local vasomotor tone and haemoglobin dissociation curve. Therefore, pathological conditions limiting the close communication between cardiomyocytes and vasculature, namely, the expansion of the interstitial space due to oedema or fibrosis, as well as arteriolar and capillary rarefaction, common features in chronic HF, impair diffusional transport and MBF autoregulation, contributing to oxygen supply/demand mismatch (Figure 2).

Another consequence of the proximity between coronary microvasculature and cardiomyocytes is their mechanical interactivity. Previously considered an important modulator of contractility (i.e. Gregg phenomenon), the effect of coronary perfusion was later shown to be negligible within the autoregulatory pressure-flow range. Extravascular forces are not uniform across the ventricular wall and a gradual increase in interstitial pressure and vascular compression is observed from the subepicardium to the subendocardium. This is partly compensated by a higher arteriolar density at the subendocardium so that, in physiological conditions, MBF is similar in both myocardial layers. Yet, the distinct mechanical cross-talk between different myocardial layers, makes arterio-venous pressure gradient (i.e. pressure force) at the subendocardium about half of that of subepicardium. Consequently, in the setting of decreased coronary pressure (e.g. coronary artery disease), the subendocardial perfusion is predominantly affected. This intricate relation between microcirculation and perfusion may underly, at least partially, the existence of clearly distinct patterns of MO distribution associated with different kinds of myocardial injury: in acute inflammatory conditions (e.g. viral myocarditis, sepsis) oedema is generally evident in the subepicardial layers whereas in acute ischaemia, the oedema is transmural or predominantly affects the subendocardium.

Coronary vasculature also influences myocardial tissue properties. Higher coronary perfusion pressure is associated with increased myocardial stiffness, shifting diastolic pressure-volume relationship left and upwards, even in the absence of oedema formation. The underlying mechanism resides in the fact that cardiomyocyte contraction increases the cell diameter, which happens at the expense of coronary vascular diameter, contributing to the abovementioned systolic vascular compression. Accordingly, higher intravascular volume and pressure, caused by increased coronary perfusion or venous outflow pressure, oppose intravascular fluid displacement, and therefore impair muscle contraction and relaxation. This has been shown to be especially relevant in the setting of increased coronary sinus pressure, seen in acute and chronic HF, where increased intravascular and interstitial volume act cooperatively to impair systolic function and diastolic compliance.

**Coronary microvascular barrier**

Overlooked in the past, the cardiac microvascular barrier became increasingly recognized as highly active and complex structure, composed of a continuous non-fenestrated endothelial cell monolayer, which is internally coated with a negatively charged gel-like mesh (i.e. glycocalyx) and externally covered by pericytes and basement membrane (Figure 3).

**Interendothelial junctions**

Endothelial cells (EC) are tightly bonded by interendothelial junctions (IEJ), mostly comprised by tight (occludins, claudins and JAMs) and adherens junctions (VE-cadherin), which define endothelial pore size and can be dynamically regulated at the expression level and through internalization, to finely tune endothelial permeability and regulate the passage of macromolecules and cells (Figure 3). Accumulating evidence suggests IEJ disruption as a potential pathophysiological mechanism in cardiac diseases. Importantly, endothelial expression of claudin-5, a critical player in size-selective barrier function, is reduced in human end-stage HF hearts. This was also shown in experimental diastolic dysfunction induced by western diet, where claudin-5 and occludin down-regulation was associated with increased vascular permeability, an effect attenuated by amiloride, suggesting an important role for endothelial ENaC expression and sodium overload. Regarding adherens junctions, reduced VE-cadherin/β-catenin expression in dilated cardiomyopathy was associated with endothelial cell degeneration, whereas in post-ischaemic MO, Src inhibition prevented VEGF-mediated disruption of Flk/VE-cadherin/β-catenin complex and attenuated post-ischaemic MO, fibrosis and mortality. In addition, key risk factors for HF development and progression have been shown experimentally to promote endothelial hyperpermeability by disrupting EJ, namely, renin-angiotensin-aldosterone system activation, inflammation, hypoxia, cardioplegic arrest, hyperglycaemia, oxidative stress, increased circulating LDL and free fatty acid levels.

**The endothelial surface layer**

The endothelial glycocalyx (eGC) covers the apical side of endothelial cells and consists of a complex meshwork of varied membrane-associated macromolecules (Figure 3). These include proteoglycans and glycoproteins, forming a backbone in which soluble proteins, plasma- or endothelial-derived, are incorporated. eGC proteoglycans are constituted by linear core proteins, mostly Syndecan-1, to which multiple glycosaminoglycans (GAGs) side chains can be covalently attached.
Figure 3 Molecular interactions in myocardial fluid balance. The myocardium is composed by cardiomyocytes, microvascular capillaries enclosed by pericytes and lymphatic capillaries. Fluid is filtrated in microvascular capillaries, through the endothelial surface layer and interendothelial junctions. In the myocardial interstitium, fluid entry is limited by type I and type III collagen fibres and GAGs, extracellular matrix components that act as a buffer for Na⁺ and water. Interstitial and intracellular water are in delicate balance, maintained by cardiomyocyte volume regulators. Interstitial fluid (IF) and solutes are collected by initial lymphatic capillaries, enabling a continuous IF renovation, which is returned ultimately to the venous circulation. (A). Cardiomyocyte ionic transporters: cardiomyocytes closely regulate intracellular water entry and extrusion. Water enters through aquaporins or passively diffuses through the cell membrane, according to osmotic gradients established by ionic and solute concentrations. (B). Endothelial cell–pericyte interaction: these cells establish close paracrine and physical (N-cadherin) interactions regulating microvascular stability. Endothelial cells secrete PDGF-BB that binds to PDGFR-β, promoting pericyte recruitment and microvascular integrity, whereas pericytes secrete angiopoietin 1 (Ang-1), which acts on Tie-2 and stabilizes endothelial cells. (C). Endothelial surface layer and interendothelial junction: the endothelial surface layer is composed by endoluminal glycocalyx, which binds plasma proteins and protects endothelial cells. Furthermore, endothelial cells establish varied connections, maintaining cohesiveness and cell survival. (D). Lymph drainage in initial lymphatic capillary: fluid enters the lymphatic vasculature via lymphatic capillaries, which are blunt-ended vessels attached to the extracellular matrix by anchoring filaments. Lymphatic endothelial cells overlap, creating valve-like structures that promote unidirectional lymph flow. These vessels converge progressively from the subendocardium to the subepicardium, forming epicardial lymphatic collectors. ALK-1 and -5, anaplastic lymphoma kinase-1 and -5; Ang-1, angiopoietin-1; AngII, angiotensin II; Aqp, aquaporins; GAG, glycosaminoglycans; HA, hyaluronic acid; JAMs, junctional adhesion molecules; NBS, Na+/HCO₃⁻/CO₂ Symporter; NCX, Na⁺/Ca²⁺ exchanger; NHE, Na⁺/H⁺ exchanger; PDGF-BB, platelet-derived growth factor BB; PDGFR-β, PDGF receptor β; TGF-β, transforming growth factor β; TGFR-β2, TGF receptor β2; Tie-2, angiopoietin-1 receptor.

GAGs are highly polyanionic compounds composed of disaccharide repeating units which can be non-sulfated [hyaluronic acid (HA)] or sulfated (chondroitin sulfate, dermatan sulfate, keratan sulfate and heparan sulfate). Together, they form a negatively charged surface that will enable electrostatic interactions with plasma cations, mostly with divalent metal cations (e.g. Ca²⁺), but also with Na⁺ due to its high plasma concentration.⁷⁵,⁷⁶ The resulting high cation concentration at the interface with the plasma enables negatively charged circulating proteins (albumin, antithrombin III and thrombomodulin), that would otherwise not be able to electrically interact with the glycocalyx, to approach and incorporate this layer, forming together the endothelial cell surface layer (ESL).⁷⁷,⁷⁸ The ESL, measuring between 0.2 and 2.0 mm in vivo, is therefore a highly complex structure with critical functions in microvascular physiology by (i) physically shielding the underlying endothelium from luminal aggressions; (ii) regulating microvascular flow by transmitting shear-stress forces; (iii) constituting a barrier for plasma proteins and ions, thereby maintaining intravascular oncotic...
pressure; (iv) avoiding platelet aggregation by accumulating platelet-inhibitory factors (antithrombin III and thrombomodulin) and physically restricting its interaction with subendothelium at the endothelial gaps; (v) inhibiting endothelial proinflammatory activation (i.e. increased permeability and adhesiveness) by binding circulating cytokines; and (vi) limiting the access and adhesion of circulating immune cells to the EC surface.79,80,81

The ESL structure is maintained by a fragile balance between flow and enzymatically mediated shedding, and de novo production of its components.82 Not surprisingly, most pathological mechanisms shown to increase microvascular barrier permeability act concomitantly on IEJ and ESL, namely, in inflammation, ischaemia–reperfusion,83 hypoxia84 and hyperglycaemia.85 Importantly, the activity of glycosalyx-degrading enzymes (i.e. hyaluronidases, heparanase and MMPs) is increased in the setting of inflammation, which, in combination with endothelial CAM overexpression, facilitates leukocyte adhesion and diapedesis.86 The importance of the permissive effect of ESL degradation on cardiac leukocyte infiltration has been shown in myocardial infarction,87,88 viral myocarditis89 and sepsis,90,91 aggravating the myocardial inflammatory injury. Moreover, degradation of eGC components (hyaluronan92 and heparan sulfate93) has been shown to promote MO by increasing microvascular permeability to water and proteins.

Perhaps, the more striking association between eGC and HF is the fact natriuretic peptides (NP), mostly produced by cardiomyocyte stretching in the setting of hypervolemia and ventricular overload, have been repeatedly shown to promote eGC degradation.94–98 This effect seems to act concurrently with Na+ overload, which also leads to the destabilization and collapse of the eGC, mainly through loss of heparan sulfate residues, an effect attenuated by the use of spironolactone.99 This can be interpreted essentially as a compensatory mechanism, by enabling the escape of excessive intravascular fluid and sodium to the interstitium, which has a high Na+ buffering capacity due to its GAG content,100 and acting in conjunction with NP-mediated venodilation to reduce cardiac overload. However, eGC degradation in the setting of myocardial functional impairment might also carry some drawbacks. In addition to eGC degradation being an inherently proinflammatory stimuli for EC,101,102,103 the impairment of glycosalyx Na+ buffering capacity may increase the amount of Na+ presented to the endothelium, promoting intracellular endothelial Na+ overload and increased transport to the interstitium, resulting in endothelial dysfunction and aggravated interstitial oedema, respectively.104,105,106 Furthermore, this combined effect of hypervolemia and Na+ overload also has important implications in the critical care setting (e.g. cardiogenic and septic shock),107,108 where the frequently excessive crystalloid resuscitation might disrupt microvascular barrier function and complicate haemodynamic management and prognosis. Despite its proposed pathophysiological importance, a direct observation of ESL disruption in HF is still lacking.

## Cardiac pericytes

Cardiac pericytes (CPC) are a highly heterogeneous population of perivascular contractile cells that ensheathe and intimately interact with underlying endothelial cells, forming a microvascular syncytium.109,110 Despite conflicting reports, recent data suggest that CPC cover up to 99% of the length of the myocardial microvasculature.111 CPC share the basement membrane with EC and establish numerous physical interactions, ensuring an adequate control of microvascular permeability. Moreover, an intense reciprocal communication between CPC and EC takes place through gap junctions and paracrine factors, which has been shown to be especially relevant for angiogenesis and stabilization of newly formed vessels101 (Figure 3). Importantly, multiple pericyte phenotypes with distinct cell-surface marker signatures and variable expression of contractile proteins have been shown to be differentially distributed across the arteriolar, microvascular and venular sections of coronary vasculature.99,112 Such diversity probably underlies distinct pathological roles attributed to pericytes in the context of myocardial injury and remodeling.

Extensive evidence supports a key role for CPC in the regulation of myocardial microvascular flow and permeability. Indeed, the disruption of key trophic and homeostatic pathways for CPC, namely, PDGF-β/PDGFR-β,113,114 Ang-1/Tie2,115,116 Sirtuin-3117,118 and Notch3,119,120 has been shown to decrease CPC density and EC coverage, resulting in increased microvascular permeability in response to injury, MO and functional impairment. Importantly, common observations in genetic and drug-induced CPC dysfunction are increased microvascular tortuosity and decreased coronary reserve in response to vasodilator challenge, with cardiac up-regulation of hypoxia-related genes.121 In knockout mouse models, the genetic ablation of Notch3122 and Sirtuin-3123 impairs microvascular maturation and pericyte/EC interaction, exacerbating ischaemic injury and hindering post-ischaemic functional recovery. Similar observations were made in experimental models of endotoxemia and diet-induced obesity, in which Sirtuin-3 has been shown to be down-regulated.124,125 Accordingly, in the setting of ischaemic injury, cardiomyocyte-derived proNGF activates p75 neurotrophin receptor, causing pericyte process retraction, resulting in a lack of support of the microvascular endothelium and perivascular oedema.126 Moreover, Hypoxia-Induced Endoplasmic Reticulum Stress Regulating (HypER) lncRNA, which promotes pericyte proliferation, viability and interactions with EC, is down-regulated in human HF,127 supporting pericyte degeneration as a potentially important pathophysiological mechanism.

ESC Heart Failure 2022; 9: 958–976
DOI: 10.1002/ehf2.13775
In line with the diversity of CPc phenotypes and functional roles in the setting of myocardial ischemia, CPc have also been implicated in the no-reflow phenomenon.\(^{128}\) Importantly, some pericyte subpopulations express variable amounts of myosin and actin isoforms (\(\alpha\)-SMA and \(\gamma\)-actin), having the ability to contract and relax in response to multiple paracrine factors (catecholamines and adenosine).\(^{129,130}\) Being circumferentially disposed around capillaries, CPc contraction can decrease microvascular flow and theoretically reduce capillary luminal diameter enough to impede the passage of leukocytes. Indeed, in an ischaemia/reperfusion injury model, post-ischaemic capillary blockage sites have been shown to be disproportionately close to pericytes, suggesting ischemic CPc contraction, probably mediated by an increase in intracellular Ca\(^{2+}\),\(^{131}\) as an important mediator of impaired reoxygenation of ischemic tissue following myocardial revascularization.\(^{132}\)

In inflammatory conditions, CPc detachment from EC surface was associated with differentiation into myofibroblasts and increased production of ECM, potentially contributing to pathological myocardial remodelling.\(^{134,135}\) In fact, galectin-3, a well-validated biomarker and mediator of cardiac fibrosis in HF patients,\(^{136}\) has been shown to stimulate pericyte proliferation and procollagen I secretion.\(^{137}\) This is in accordance with observations in angiotensin II-induced myocardial hypertrophy model, in which Gli1+ cells were shown to be a subpopulation of pericytes that, in the setting of injury, differentiate into myofibroblasts and produce ECM in perivascular and interstitial spaces.\(^{138}\) Further supporting this role of CPc, in a clinically relevant rat model of HF with preserved ejection fraction (ZSF1 obese rats), decreased EC coverage was associated with subendocardial foci of CPc proliferation, which colocalized with ECM deposition and inflammatory cell infiltration.\(^{139}\) Consistently with this finding, pericytes have been shown to respond to proinflammatory stimuli with overexpression of cytokines, chemokines and CAMs,\(^{140}\) regulating immune cell diapedesis.\(^{141}\) In the setting of experimental sepsis, inflammatory-mediated CPc loss facilitates the infiltration of immune cells in cardiac interstitium.\(^{142}\) These findings highlight the fact that, beyond being key determinants in the microvascular barrier, pericytes may detach from endothelial cells and promote interstitial remodelling in inflammatory injury.

**Myocardial interstitium**

The myocardial interstitium is a highly organized and compact structure, comprised by fibrillar collagen, non-collagen matrix proteins, proteoglycans, GAGs and a wide array of bioactive signalling molecules\(^{143}\) (Figure 3). Cardiomyocytes are enclosed in a basement membrane, mostly constituted by integrins, laminin and fibronectin, behaving as anchoring points for fibrillar collagen and other matrix components (proteoglycans and GAG) attachment. Collagens (type I and III) are the predominant components of cardiac ECM, and their high tensile strength is assumed to be the main contributor for ECM structural integrity.\(^{144}\) Cardiac ECM architecture enables an effective force summation of individually contracting cardiomyocytes, allowing a coordinated myocardial tissue contraction, while at the same time maintaining adequate spatial relationships between cells, which prevents cardiomyocyte overstretching, preserves intercellular connections and opposes microcirculatory collapse.

Cardiac ECM composition is an important determinant of interstitial space volume and pressure. The interstitial space is densely crowded with intertwined components, which occupy the available physical space and limit the entrance of plasma proteins or cells, a phenomenon called steric interstitial exclusion.\(^{2}\) Given their polyanionic nature, interstitial GAGs further contribute to limit the entrance of plasma proteins, while also binding free ions (mostly Na\(^+\)) and annulling their osmotic force.\(^{93}\) Interestingly, changes in sulfated GAG conformation are associated with decreased Na\(^+\) buffering capacity and interstitial oedema.\(^{93}\) Moreover, the high stiffness of cardiac ECM not only preserves cardiomyocyte function by generating passive tension and avoiding tissue overstretching but also confers a low interstitial compliance to the myocardium and opposes interstitial space expansion.\(^{145}\) Consequently, in the setting of increased transcapillary filtration, interstitial fluid (IF) buildup stretches the ECM, causing a steep increase in interstitial pressure, which, in turn, forces IF into the lymphatic system.\(^{2}\)

Alterations in ECM architecture or composition critically influence myocardial function. Increased ECM deposition, mainly in the form of collagen, has been recognized as an important mechanism of increased stiffness and diastolic dysfunction in most forms of chronic HF.\(^{16}\) However, mechanical and enzymatic disruption of the ECM also significantly impairs myocardial systolic and diastolic function by compromising force transmission by displacing collagen struts from their anchoring points and breaking intercellular connections.\(^{146,147}\) Moreover, inflammation-driven up-regulation of ECM-degrading enzymes promotes both ECM and basement membrane degradation, decreasing interstitial exclusion effect and facilitating the interstitial passage of fluid, proteins and immune cells.\(^{148}\) ECM degradation has been shown in acute high-grade myocardial inflammation, especially in experimental myocarditis\(^{149}\) and sepsis,\(^{150}\) where a significant acute decrease in total myocardial collagen content and collagen degradation were observed and associated with MO, systolic and diastolic dysfunction. Further supporting this experimental observation, post-mortem evaluation of human septic myocardium found significant ECM disruption and interstitial oedema at the subepicardium, which colocalized with macrophage infiltration and cardiomyocyte apoptosis.\(^{45}\) Importantly, disruption of collagen struts may also increase coronary microvasculature susceptibility.
bility to external compression, which might compromise MBF in the setting of oedema-associated increased interstitial pressure.\textsuperscript{36,123}

Interestingly, chronic oedematous states produced by increased microvascular filtration or decreased lymphatic drainage are associated with increased myocardial collagen deposition.\textsuperscript{3,4} The interstitial remodelling may be interpreted as a compensatory mechanism, by decreasing interstitial compliance and preventing interstitial expansion, therefore minimizing the disruption of cardiac architecture. However, increased collagen deposition also causes long-term detrimental effects on overall myocardial compliance and function.\textsuperscript{151}

Impaired turnover of non-collagen ECM elements can also promote fibrosis and have detrimental effects on myocardial function. HA is observed in healthy cardiac ECM in its high-molecular-weight HA form and has a unique capacity to bind and retain water molecules.\textsuperscript{152} Interestingly, while eGC HA degradation has been consistently associated with endothelial dysfunction, increased microvascular permeability and MO,\textsuperscript{153} cardiac interstitial accumulation of HA, has similarly been shown to promote MO and structural remodelling.\textsuperscript{154} Cardiac interstitial accumulation of HA is normally associated with increased interstitial water content and MO, and is observed in myocardial infarction,\textsuperscript{155} hypertrophic cardiomyopathy,\textsuperscript{156} myocarditis\textsuperscript{157} and experimental cardiac transplant rejection.\textsuperscript{158,159} Curiously, hyaluronidase treatment was able to decrease MO in rejected heterotopic transplants,\textsuperscript{160} whereas accumulation of low-molecular-weight HA (LMWHA) in hypertrophic cardiomyopathy is not associated with increased water content,\textsuperscript{161} raising the possibility of distinct contributions of high-molecular-weight HA and LMWHA for oedema generation. Indeed, in the setting of inflammation and myocardial injury, production of LMWHA is preponderant and has been shown to stimulate TLR inflammatory signalling pathways.\textsuperscript{127} Collectively, these results underscore the importance of GAG structure, composition and regional distribution for IF balance.

Cardiac lymphatic system

The cardiac lymphatic system is essential in maintaining myocardial fluid balance and immunological homeostasis.\textsuperscript{139} It represents the main route for the removal of cellular metabolites, allowing the continuous IF renewal while avoiding the buildup of interstitial volume and pressure.\textsuperscript{2} Additionally, an immunomodulatory role has also been attributed to cardiac lymphatics due to the washout of proinflammatory mediators and immune cells from the myocardial interstitium in the setting of myocardial injury.\textsuperscript{162,163}

Lymphatic capillaries are highly specialized blind-ended structures, composed by oak-leaf shaped lymphatic endothelial cells (LEC), which mostly lack basement membrane and are connected by permeable flap-like intercellular junctions that favour unidirectional passage of IF, solutes and immune cells\textsuperscript{164,165} (Figure 3). Moreover, cardiac LEC are connected to the surrounding ECM and cardiomyocytes by structures designated as anchoring filaments, constituted by type VII collagen projections, integrins and focal adhesion kinases. Anchoring filaments maintain lymphatic patency by exerting tensile forces and opening the lumen of lymphatic capillaries, facilitating lymphatic flow.\textsuperscript{166,167} Anatomically, the lymphatic capillaryplexus progressively converges from the subendocardium to the subepicardium, suffering structural alterations along the way, namely, the appearance of a continuous basement membrane, intraluminal valves to promote unidirectional flow, tight junctions, and, in larger trunks outside the myocardium, an adventitial layer and surrounding smooth muscle cells to help pump lymph.\textsuperscript{168,169} Subepicardial lymphatic pre-collectors converge to form epicardial lymphatic collectors that transport cardiac lymph via lymph nodes towards thoracic ducts, ultimately draining into the superior vena cava.\textsuperscript{170}

Several factors influence cardiac lymph flow, most of which known to be unique to the heart. A distinctive feature of the intramyocardial lymphatic system is the absence of smooth muscle in intramyocardial vessels. Therefore, lymph flow is highly dependent on external forces, namely, muscle contraction and deformation along the cardiac cycle, heart rate and contractility.\textsuperscript{1} However, factors not intrinsic the heart function also impact lymph drainage. By concentrating interstitial metabolic products and proteins, lymph oncotic pressure exceeds interstitial oncotic pressure, promoting water osmotic dragging and fluid drainage.\textsuperscript{1} Coronary venous pressure is also an important regulator of lymph flow. Experimental coronary sinus blockade increases capillary hydrostatic pressure and promotes fluid filtration upstream, which requires compensatory lymphatic dilation and increased lymph flow to maintain fluid homeostasis.\textsuperscript{13,14,147} On the other hand, downstream, because lymph is ultimately drained into the venous circulation, increased central venous pressure acts synergically with decreased contractility to impair lymph flow in acute HF, promoting MO.\textsuperscript{16,93}

The frequent observation of MO in several aetiologies of HF suggests that cardiac lymphatic inability to respond to increased filtration is a rather common finding. Despite the recognized ability of the healthy heart to respond to an increased capillary filtration by increasing lymph drainage severalfold,\textsuperscript{1} multiple disease mechanisms may render the cardiac lymphatic system incapable to cope. In this setting, lymphatic dysfunction will not only promote accumulation of a protein-rich IF, which contributes to microvascular and cardiomyocyte stress, but will also have a proinflammatory effect by decreasing the clearance of proinflammatory cytokines and immune cells.\textsuperscript{171} Prolonged residence of cellular debris, inflammatory mediators and cells in myocardial interstitium will aggravate and prolong myocardial

ESC Heart Failure 2022; 9: 958–976
DOI: 10.1002/ehf2.13775
inflammation, especially in the setting of myocardial infarc-
tion and myocarditis. Furthermore, the distortion of in-
terstitial architecture mediated by oedema and the acti-
vation of collagen and GAG-degrading enzymes may have a negative
impact on anchoring filaments and initial lymphatics, further
compromising lymphatic patency and function. Whereas
acute lymphatic obstruction leads to oedema, chronic ob-
struction is associated with interstitial fibrosis and ECM
remodelling. Moreover, given the close proximity of the
lymphatic and electrical conduction system, lymphatic dys-
fuction has also been shown to be associated with electrical
disturbances.

Lymphangiogenesis, the process of producing new ly-
mpathic vessels is known to be a dynamic process mainly re-
gulated by VEGF-C and VEGF-D binding to lymphatic-specific
receptor VEGFR3, and to be affected by inflammation and
other cardiovascular factors (diabetes and obesity). In
acute inflammation and in myocardial infarction, higher
fluid filtration increases the need for lymph drainage, with
resulting up-regulation of lymphangiogenic factors. However,
this endogenous response appears to be insufficient and to
result in deficient lymphangiogenesis, with a predominance
of lymphatic capillaries and lack of pre-collectors. In fact, in
post-infarct mouse models, stimulating lymphangiogenesis
with exogenous VEGF-C or adrenomedullin increases lymph
flow, decreases MO, attenuates myocardial inflammation
and fibrosis and improves cardiac function. Still, this
promising therapeutic avenue has been recently questioned
by the absent impact of genetic blockade of lymphangiogen-
esis on cardiac function after experimental myocardial
infarction.

Cardiomyocyte volume regulation

The cardiomyocyte membrane is highly permeable to water,
which moves passively according to osmotic gradients and di-
rectly sets cell volume. Normal cell function requires a sta-
ble volume and excessive water entry may disrupt membrane
and cytoskeleton integrity. To prevent abrupt cell volume al-
terations, intracellular osmolarity is highly controlled, either
with active ionic fluxes or the synthesis/degradation of os-
motically active solutes (Figure 3).

In the isotonic steady-state, intracellular osmotic pressure
exceeds extracellular osmotic pressure due to cellular con-
centration of organic phosphates and proteins, thus favouring
passive water entry. To maintain the volume constant, the
membrane Na+/K+ ATPase promotes the exit of 3 Na+ and en-
try of 2 K+ ions, a phenomenon known as the ‘Pump and
Leak’ concept. Together with low Na+ membrane permeabili-
ity, both mechanisms contribute to maintain a low
intra cellular [Na+] and a constant transmembrane gradient,
on which many ionic transporters that regulate cell volume
are highly dependent. In myocardial ischaemia, Na+/K+ ATPase
dysfunction results in extracellular accumulation of K+, intra-
cellular accumulation of lactate, Na+ and Cl− and consequent
cell swelling and membrane depolarization. Furthermore,
aerobic metabolites accumulate in extracel-
lular and intracellular spaces. Following reperfusion of the
coronary vessels will re-establish water delivery and wash
out extracellular, but not intracellular, metabolic products,
creating an osmotic gradient that promotes cell swelling.
Highlighting the pathophysiological importance of cardio-
myocyte oedema in ischaemia/reperfusion injury, reperfusion
with a hypertonic solution limited MO and infarct size, when
compared with isotonic solution.

Cell swelling depolymerizes actin filaments and disrupts cy-
toskeleton interactions with membrane proteins. Of note,
cardiomyocyte swelling induced by ischaemia–reperfusion in-
jury was associated with variable degrees of mitochondrial
damage, cytoskeleton abnormalities and significant increases
in sarcomere length, radial distance between myofibrils and
distance between mitochondria and myofibrils, repercussing
on maximal tension and calcium sensivity. Accordingly,
swelling of isolated cardiomyocytes induced by hypotonic
medium was associated with lower contractility and activated
NO/cGMP/PKG pathway.

Despite most of myocardial water being confined to the in-
tracellular compartment, few studies have addressed the
pathophysiological role of cardiomyocyte swelling in HF.

Clinical perspective

In clinical research and practice, MRI stands out as the
gold-standard method for non-invasive MO evaluation,
based on its ability to identify the tissue ‘free’ water pool.
‘Free’ water molecules rotate very rapidly when subjected
to a magnetic field and produce long T1 and T2 relaxation
times, whereas ‘bound’ water molecules have their motion
restricted due to hydrogen bonding with macromolecules,
producing short T2 relaxation time values. The recent intro-
duction of parametric mapping techniques—T1, T2 and
extracellular volume, has enabled the detection of subtle
changes in myocardial free water content and precise
estimation of the interstitial fraction volume and com-
position.

Making use of aforementioned MRI capabilities, evidence
supporting the disruption of myocardial water balance has
been shown in a broad range of cardiac and systemic diseases
(Table 1). Overall, the increase in myocardial free water con-
tent is generally associated with depressed left ventricular
function, increased NP plasma levels, disease progression
and severity, and poor prognosis (Table 1). Nevertheless,
due to the observational nature of these studies, a causal as-
sociation between the presence of MO, LV dysfunction and
cardiac prognosis could not yet be drawn.
| Disease                                  | Myocardial oedema | CMR imaging | Analytical associations | Clinical associations | References |
|------------------------------------------|-------------------|-------------|-------------------------|-----------------------|------------|
| Acute heart failure                      | Global            | T2 mapping  | —                       | (+) PAWP              | 16,188     |
| Myocardial infarction/Ischaemia-reperfusion | Focal            | T2-weighted imaging, T1, T2 and ECV mapping | (+) Troponin           | (+) Infarct extension (+) MACE (+) LV dilatation | 189,190 |
| Aortic stenosis                          | Global            | T1 and T2 mapping | —                       | (--) LVEF             | 191        |
| Cardiomyopathies                         |                   |             |                         | (+) Disease progression (+) Risk of Syncope | 194,195 |
| Non-ischaemic dilated cardiomyopathy     |                   |             |                         | (+) Myocardial macrophages | 196,197 |
| Hypertrophic cardiomyopathy              | Focal            | T2-weighted imaging, T2 mapping | (+) Troponin (+) BNP   | (+) ECG Changes (+) Clinical worsening | 202       |
| Takotsubo cardiomyopathy                 | Focal            | T1 and T2 mapping (USPIO enhancement) | (+) Myocardial macrophages | —             | 196,197 |
| Peripartum cardiomyopathy                | Global            | T1 and T2 mapping | —                       | (--) LVEF             | 198        |
| Infiltrative diseases                    |                   |             |                         | (+) Anrhymia (+) MACE (+) Death | 9,203–205 |
| Cardiac amyloidosis                      | Global            | T2 and ECV mapping | (+) NT-proBNP           | (+) Mortality (AL)    | 199        |
| Cardiac sarcoidosis                      | Focal            | T1 and T2 mapping | —                       | —                     | 200,201    |
| Fabry disease                            | Focal            | T1 and T2 mapping | (+) Troponin            | (+) ECG Changes (+) Clinical worsening | 202       |
| Viral myocarditis                        | Focal, subepicardial | T2-weighted and LGE imaging, T2 mapping | (+) Troponin           | (+) Anrhymia (+) MACE (+) Death | 9,203–205 |
| COVID-19                                 | Focal            | T2-weighted and LGE imaging, T2 mapping | (+) Troponin           | —                     | 206–209    |
| Sepsis                                   | Focal            | T2-weighted imaging | (+) EMB macrophages    | —                     | 45,210     |
| HIV                                      | Global            | T2-weighted and LGE imaging, T1 mapping | —                       | (+) Adverse cardiovascular events | 211       |
| Chagas disease                           | Focal            | T2-weighted and LGE imaging | —                       | (+) Disease severity | 212        |
| Inflammatory diseases                    |                   |             |                         | (+) Disease activity (+) Circumferential Strain | 213       |
| Rheumatoid arthritis                     | Focal            | T1 and ECV mapping | —                       | (--) Circumferential Strain | 214,215    |
| ANCA-associated vasculitides             | Diffuse          | T1 and T2 mapping | —                       | (+) Cold pressor test (+) Disease activity (+) Circumferential Strain | 216,217    |
| Systemic sclerosis                       | Focal            | T1 and T2 mapping | —                       | (+) Disease activity | 218,219    |
| Systemic lupus erythematosus             |                   |             |                         | (+) Reversal of acromegalic cardiomyopathy (+) Stroke volume (+) Cardiac index | 220,221    |
| Endocrine diseases                       |                   |             |                         | (+) Transplant rejection | 222,223 |
| Acromegaly                               |                   |             |                         | (+) Stroke volume (+) RV dilatation | 224       |
| Hypothyroidism                           |                   |             |                         | (+) RV function (+) RV dilatation | 225–228    |
| Pulmonary arterial hypertension          |                   |             |                         | (+) Uremic Cardiomyopathy | 225–228    |
| Cardiac surgery                          |                   |             |                         | (+) Transplant rejection | 222,223 |
| Chronic kidney disease                   |                   |             |                         | (+) Uremic Cardiomyopathy | 225–228    |

(Continues)
Myocardial oedema has been particularly well-studied in the acute setting of ischemic heart disease, in which it may have a role on early injury during reperfusion and also late tissue healing.\textsuperscript{165–171} During the initial phase of reperfusion, MO may contribute to the pathophysiological process of microcirculation compression and perfusion defects underlying the ‘no-reflow’ phenomenon.\textsuperscript{171,172} MO is also detectable later, at the time of tissue healing and collagen deposition,\textsuperscript{166} which discloses the complex interplay between myocardial fluid balance and inflammation and underscores the need for a cautious interpretation of MRI assessment of infarcted and at-risk myocardium.\textsuperscript{171,173} Interestingly, patient comorbidities might impact on the development of MO in a disease-specific and somewhat unpredicted way, underscoring the lack of clinical knowledge on this topic. As an illustration, diabetes was shown to aggravate post-ischaemic MO,\textsuperscript{174,175} whereas the opposite effect may be present in Takotsubo cardiomyopathy.\textsuperscript{176}

Myocardial oedema has not been evaluated as an endpoint in HF randomized clinical trials, and the effect of most drugs on myocardial fluid balance is currently unknown. However, pre-clinical evidence supports the beneficial effect of spironolactone\textsuperscript{92} and SGLT2 inhibitors\textsuperscript{177} by protecting endothelial glycocalyx. Interestingly, these two drug classes were shown to provide clinical benefit across a wide ejection fraction range in HF,\textsuperscript{178–181} supporting a possible role for myocardial fluid balance among their mechanisms of action. Other drugs have proved useful to protect microvascular barrier in distinct clinical scenarios and may oppose MO formation. Of note, aprotinin, a fibrinolysis inhibitor, preserves adherens junctions and reduces MO in experimental cardioplegic arrest,\textsuperscript{65} whereas in sepsis, hydrocortisone\textsuperscript{182} and sulodexide, a mixture of GAGs (heparan and dermatan sulfates),\textsuperscript{183} may protect the glycocalyx and diminish oedema formation.

In contrast, some drugs may facilitate the development of MO by impacting on microvascular filtration and ESL preservation. NP are known disruptors of the ESL\textsuperscript{89,91} and BNP levels correlate with myocardial water content across several clinical scenarios (Table 1), an association not yet known to be causal. However, it is tempting to speculate that this effect might have contributed to the somewhat disappointing results of BNP analogue nesiritide in the setting of acute HF treatment.\textsuperscript{184} In line with this, nepirilysin is a known regulator of microvascular permeability by increasing the half-life of NP and bradykinin,\textsuperscript{185} suggesting that sacubitril may also perturb microvascular barrier function.\textsuperscript{230} Preclinical evidence suggests that beta-blockers\textsuperscript{186} and calcium channel blockers\textsuperscript{187} may increase microvascular permeability, an effect not yet observed in the myocardium.

Finally, experimental data suggest that stimulators of lymphangiogenesis (e.g. VEGF-C and adrenomedullin) may accelerate oedema resolution after myocardial

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Disease} & \textbf{Myocardial oedema} & \textbf{References} \\
\hline
Breast cancer/chemotherapy & (+) & \end{tabular}
\caption{Table 1 (continued)}
\end{table}
in infarction, but clinical studies are needed before considering this therapeutic pathway in HF.

**Conclusion**

In the failing heart, myocardial fluid balance is disrupted due to alterations in microcirculation dynamics, microvascular barrier, extracellular matrix composition and lymphatic function. Experimental data suggest that MO significantly impairs cardiac performance, affecting systolic and diastolic properties and promoting long-term adverse remodelling. In the last decade, CMR has been increasingly used for HF phenotyping and data suggest the increase in myocardial free water content as relevant pathophysiological mechanism of cardiac injury and dysfunction, also representing an important prognosticator across multiple cardiac and systemic diseases. The recent advances in the knowledge of microvascular barrier and lymphatic function open the prospect for novel therapeutics targeting myocardial fluid disturbances in HF.

**Funding**

This study was funded by national funds through FCT - Portuguese Foundation for Science and Technology, under the scope of the Cardiovascular R&D Center – UnIC (UIDP/00051/2020 and UIDP/00051/2020).

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