Addressing Endothelial Dysfunction in Heart Failure: The Role of Endothelial Progenitor Cells and New Treatment Horizons

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Abstract

Heart failure (HF) is closely linked to endothelial dysfunction, which contributes significantly to its progression. Endothelial dysfunction in HF is marked by reduced nitric oxide bioavailability, increased oxidative stress and inflammation, all of which impair vascular function. Endothelial progenitor cells (EPCs) – vital for vascular repair – are particularly affected, with their dysfunction further exacerbating HF outcomes. Emerging therapies targeting these mechanisms, including antioxidants, gene therapies enhancing endothelial nitric oxide synthase activity and EPC-based strategies, hold promise. Recent advances show encouraging results, especially with treatments improving EPC mobilisation and function. Additionally, pharmacological agents such as statins and sodium–glucose cotransporter 2 inhibitors demonstrate pleiotropic benefits, enhancing endothelial health and EPC activity. This review emphasises the therapeutic potential of these approaches, highlighting the critical need for further research to optimise endothelial-targeted treatments and improve outcomes for HF patients.

Keywords

Endothelial dysfunction, heart failure, endothelial progenitor cells, nitric oxide, oxidative stress, vascular regeneration, novel therapeutic strategies

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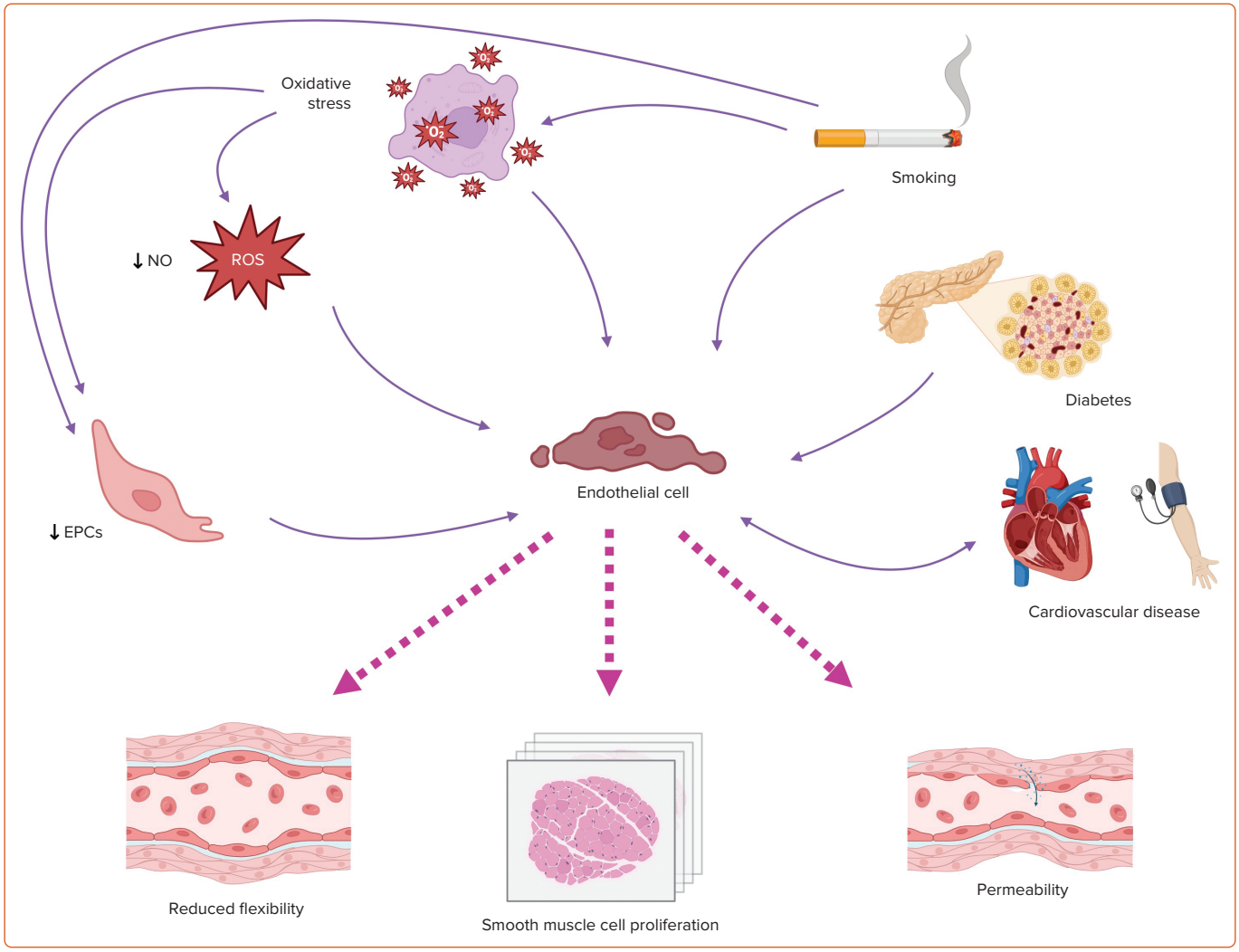
Heart failure (HF) is a clinical syndrome characterised by functional or structural alterations of the heart, resulting in inadequate cardiac output or increased intracardiac filling pressures at rest or under stress.[1,2] It is defined by the presence of cardinal symptoms (dyspnoea, asthenia) and signs (lower extremity oedema, pulmonary crackles, jugular turgor).[3] Historically, HF has been classified according to the left ventricular ejection fraction (LVEF), which is used to categorise HF as preserved (LVEF ≥50%), mildly reduced (41–49%) or reduced (≤40%) LVEF.[1,2] Conversely, the distinction between ischaemic and non-ischaemic forms can be made on the basis of their aetiology. HF is currently a significant global health concern, particularly in industrialised countries, to the extent that it is now regarded as one of the most significant health issues of the 21st century. Indeed, it has a high prevalence (estimated at between 1% and 2% in the general population and particularly in the elderly), affecting over 64 million people worldwide and associated with high morbidity and mortality rates.[4] Despite advances in medical therapy, the prognosis for patients with HF remains poor, underscoring the need for novel therapeutic strategies.[3] Among the mechanisms identified in the pathogenesis of HF, endothelial dysfunction (ED) is receiving increasing attention.[5] It refers to an impairment in the normal functioning of the endothelium, which plays a pivotal role in vascular homeostasis.[6] The endothelium not only acts as a barrier between the blood and the surrounding tissues, but it also regulates several critical vascular functions, including vasodilation, blood flow, immune response, coagulation and the balance between pro- and anti-inflammatory states.[6,7] In ED, there is reduced bioavailability of vasodilators and an increase in the production of vasoconstrictors and pro-inflammatory mediators.[6,7] This imbalance leads to increased vascular tone, oxidative stress and inflammation, contributing to the development of cardiovascular diseases such as atherosclerosis, hypertension and HF itself.[8] Risk factors such as hypertension, diabetes, hyperlipidaemia and smoking are commonly associated with ED, making it a significant marker for cardiovascular risk assessment and a potential therapeutic target for preventing disease progression.[8,9]

Figure 1: Impact of Cardiovascular Risk Factors on Endothelial Cells and Vascular Function



Cardiovascular risk factors, such as smoking and diabetes, induce oxidative stress, leading to increased production of ROS. These ROS reduce the availability of NO and impair the function of endothelial progenitor cells. The cumulative effect damages endothelial cells, promoting vascular stiffness, smooth muscle cell proliferation and increased vascular permeability, thereby driving the development and progression of cardiovascular diseases. NO = nitric oxide; EPC = endothelial progenitor cell; ROS = reactive oxygen species. Created in BioRender.

Endothelial progenitor cells (EPCs) are a subset of circulating cells that have the ability to differentiate into endothelial cells and contribute to vascular repair and regeneration.[10,11] These cells play a vital role in maintaining endothelial integrity and neovascularisation, particularly in response to vascular injury or ischaemic events.[12] EPCs are mobilised from the bone marrow into the bloodstream in response to various signals and they home to sites of endothelial damage, where they help to restore endothelial function and promote angiogenesis.[13] The number and function of EPCs in the bloodstream are inversely correlated with cardiovascular risk factors such as smoking, hypertension and diabetes, and reduced levels of EPCs are associated with poor cardiovascular outcomes.[1,2] The potential of EPCs in therapeutic angiogenesis has been explored in the context of conditions such as MI, peripheral artery disease and wound healing, where enhancing EPC mobilisation and function could improve vascular repair.[14] The aim of this review is to examine the current state of knowledge regarding the role that endothelial function plays in HF, with special emphasis on EPCs and on the possible future therapeutic prospective.

Endothelial Dysfunction in Heart Failure

Pathophysiology

In typical physiological conditions, the endothelium fulfils the function of a dynamic barrier between the blood and the vascular wall, regulating a multitude of processes that are vital for maintaining vascular health (*Figure 1*).[15] One of the most significant mediators of endothelial function is nitric oxide (NO), a gas transmitter that is synthesised by endothelial NO synthase (eNOS).[16] NO plays a crucial role in the relaxation of vascular smooth muscle cells, leading to vasodilation and thereby regulating blood pressure and ensuring adequate tissue perfusion.[16] Furthermore, NO exerts anti-inflammatory, antithrombotic and anti-proliferative effects, thus safeguarding the vasculature from injury.[16] Specifically, NO inhibits platelet aggregation, prevents leukocyte adhesion to the endothelial surface and suppresses smooth muscle cell proliferation, thereby maintaining vascular integrity and preventing the onset of atherosclerosis and thrombosis.[17] However, in the context of ED, this precisely regulated system is compromised.

A defining feature of ED is the reduction in the bioavailability of NO. This can occur as a result of either a reduction in the production of NO by eNOS or an increase in the degradation of NO by reactive oxygen species (ROS).[18,19] In conditions of elevated oxidative stress, there is an overproduction of ROS, particularly superoxide anions (O2–).[15,18] The reaction of superoxide with NO results in the formation of peroxynitrite (ONOO–), a highly reactive and damaging species that not only reduces NO levels but also induces direct oxidative damage to the endothelium

Table 1: Consequences of Common Cardiovascular Risk Factors on Endothelial Function

Risk Factor	Mechanism	Clinical Implications
Hypertension	Increased mechanical stress, inflammation, reduced NO availability	Increases vascular tone and contributes to hypertension
Diabetes	Formation of advanced glycation end-products, increased ROS	Decreases NO bioavailability and worsens endothelial dysfunction
Hyperlipidaemia	High LDL serum levels promote inflammation and atherosclerosis	Direct damage on endothelial cells and increased risk of cardiovascular events
Smoking	Increased oxidative stress and inflammation	Direct impact on endothelial function
Obesity	Increased free fatty acids, inflammatory cytokines	Induces inflammation and insulin resistance
Sedentary lifestyle	Increased oxidative stress and metabolic disturbances	Endothelial damage and increased cardiovascular risk

NO = nitric oxide; ROS = reactive oxygen species.

itself.[15,18] This oxidative modification of NO limits its availability to induce vasodilation, thereby increasing vascular tone, reducing blood flow and elevating arterial stiffness.[20] These are key features in the pathogenesis of cardiovascular diseases, including hypertension, coronary artery disease and HF.[21] In addition to reduced NO bioavailability, ED is associated with a shift towards a pro-inflammatory and pro-thrombotic phenotype. This is marked by an upregulation of adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1).[22] These molecules facilitate the recruitment and adherence of monocytes and other immune cells to the endothelial surface, thereby enabling their infiltration into the vascular wall.[22] This results in a localised inflammatory response that facilitates the development of atherosclerosis, which is characterised by the accumulation of lipids, the formation of foam cells and the development of plaques.[22,23] Moreover, ED is accompanied by an elevated production of vasoconstrictors, including endothelin-1 (ET-1) and angiotensin II.[24] Both molecules are potent vasoconstrictors, contributing to increased vascular tone and blood pressure. Additionally, ET-1 has been linked to the promotion of vascular smooth muscle proliferation and fibrosis, which contribute to arterial remodelling and stiffness.[25] Angiotensin II, produced via the renin–angiotensin system, not only induces vasoconstriction but also stimulates ROS production, thereby creating a vicious cycle of oxidative stress, ED and vascular damage.[25]

Risk Factors

It is established that several traditional cardiovascular risk factors contribute to the development of ED (*Table 1*).

Hypertension

Hypertension is a major risk factor for ED. Elevated blood pressure results in mechanical stress on the endothelium, which, over time, promotes inflammation, oxidative stress and a reduction in NO availability.[9,26] However, hypertension is both a cause and a consequence of endothelial dysfunction. In fact, the reduction in NO levels and the subsequent increase in vasoconstrictor production result in elevated vascular resistance, which, in turn, leads to sustained hypertension.[9,26]

Diabetes and Hyperglycaemia

In patients with diabetes, elevated blood glucose levels promote the formation of advanced glycation end-products, which interact with endothelial receptors and stimulate the overproduction of ROS.[27] This enhances oxidative stress, which in turn reduces NO bioavailability.[27]

Hyperlipidaemia

Increased levels of LDL cholesterol, especially oxidised LDL, contribute to endothelial damage by promoting inflammation, foam cell formation and atherosclerosis.[28] Nevertheless, once again, the relationship is reciprocal as long as a dysfunctional endothelium promotes plaque development by allowing LDL cholesterol to penetrate the arterial walls and triggering a local inflammatory response.[23,29] Over time, plaques can become unstable and lead to events such as MI or stroke.[23,29]

Smoking

The combustion of tobacco produces a multitude of oxidants and pro-inflammatory agents, collectively known as tobacco smoke, which elevate oxidative stress and inflammation levels.[21,30] This directly impairs endothelial function.[21,30]

Obesity

In individuals with an excess of adipose tissue, elevated levels of circulating free fatty acids, adipokines and inflammatory cytokines, including tumour necrosis factor (TNF)-α and interleukin (IL)-6, contribute to systemic inflammation, insulin resistance and erectile dysfunction.[31]

Sedentary Lifestyles and Unhealthy Diets

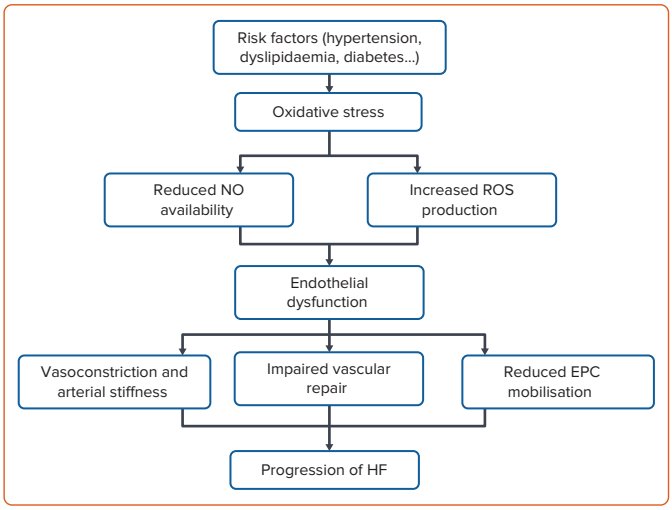
A paucity of physical activity and diets comprising a high proportion of processed foods, sugars and unhealthy fats have been associated with oxidative stress and metabolic disturbances, which can ultimately result in endothelial damage.[32,33]

Pathophysiological Role of Endothelial Dysfunction in Heart Failure

ED plays a pivotal role in the pathogenesis and progression of HF, contributing to both the worsening of cardiovascular symptoms and adverse outcomes.[34] In HF, the endothelium's capacity to regulate vascular tone, maintain fluid balance and control the inflammatory response is compromised.[5,35] This dysfunction is characterised by a reduction in NO bioavailability, an increase in oxidative stress and the overproduction of vasoconstrictive agents, all of which contribute to the worsening of the clinical picture of HF (*Figure 2*).[5,35] In HF, endothelial cells demonstrate a diminished capacity to produce NO, which is a vital mediator of vasodilation. As already mentioned, NO is synthesised by eNOS and is responsible for relaxing vascular smooth muscle cells, thus lowering vascular resistance and facilitating blood flow.[16,25] In HF, the production of NO is reduced because of the dysfunction of the enzyme eNOS and depletion of cofactors (such as tetrahydrobiopterin), which are essential for NO synthesis.[36] Furthermore, elevated oxidative stress levels result in the accelerated decomposition of NO by ROS, particularly superoxide anions, thereby further reducing its availability.[17,36] A reduction in NO results in impaired vasodilation, which in turn leads to an elevation in vascular tone, an increase in afterload and a compromise in organ perfusion.[35]

The term oxidative stress is used to describe a condition in which there is an imbalance between the production of ROS and the body's ability to detoxify and eliminate them.[37] Oxidative stress represents a pivotal mechanism

Figure 2: Pathophysiological Progression of Endothelial Dysfunction and Its Impact on Heart Failure



The flowchart illustrates the progression of endothelial dysfunction, starting from risk factors to impaired vascular repair and the progression of HF, including the role of EPCs. NO = nitric oxide; EPC = endothelial progenitor cell; HF = heart failure; ROS = reactive oxygen species.

underlying ED in the context of HF.[37] ROS, including superoxide and hydrogen peroxide, are overproduced in the failing heart as a consequence of both mitochondrial dysfunction and the hyperactivation of neurohormonal pathways, such as the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system, which are key parts of HF pathophysiology.[36,38] These ROS not only degrade NO but also directly damage the endothelium, thereby promoting endothelial inflammation and structural changes in the vascular wall. Furthermore, the formation of peroxynitrite, a toxic product of the interaction between NO and superoxide, exacerbates vascular damage by promoting lipid peroxidation and impairing the function of proteins that are essential for maintaining endothelial homeostasis.[22,36] Moreover, HF is associated with low-grade systemic inflammation, which is in part due to ED. The over-expression of adhesion molecules, ICAM-1 and VCAM-1, on endothelial surfaces facilitates the recruitment and adhesion of inflammatory cells (monocytes, neutrophils) to the vascular wall.[39] This inflammatory environment has the additional effect of impairing endothelial function and promoting vascular remodelling.

Additionally, the endothelium in HF tends to adopt a pro-thrombotic phenotype, characterised by increased expression of tissue factor and von Willebrand factor.[22,36,40] This leads to an elevated risk of thrombosis, which can further compromise clinical outcomes in HF patients by increasing the risk of events such as stroke and MI.[40] The clinical consequences of ED in HF are significant and far-reaching. As an outcome of impaired vasodilation and enhanced vasoconstriction, patients experience increased vascular resistance and decreased perfusion, particularly to critical organs such as the heart, kidneys and skeletal muscles.[41] This impaired perfusion results in the exacerbation of symptoms, including fatigue, dyspnoea and exercise intolerance, which are characteristic features of HF.[1] Furthermore, microvascular dysfunction can diminish coronary blood flow, intensifying myocardial ischaemia and facilitating additional cardiac injury, which may ultimately result in progressive fibrosis and worsening HF.[41,42] In addition, ED is a powerful predictor of unfavourable outcomes in patients with HF. It is correlated to an elevated risk of hospitalisation, cardiovascular events and mortality.[1] Several studies have demonstrated that markers of ED, such as reduced flow-mediated dilation or elevated ET-1 plasma levels, are associated with poorer outcomes in patients with HF.[43]

Therapeutic Implications

In light of the critical function of the ED in the development of HF, therapeutic strategies designed to improve endothelial function represent a significant area of interest. Several established therapies for HF have been shown to have the potential to enhance endothelial function (*Table 2*).[3]

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers (ARBs) have been demonstrated to possess therapeutic potential in this regard. The administration of these pharmaceutical agents is able to diminish the vasoconstrictor and pro-inflammatory effects of angiotensin-II, thereby facilitating enhanced endothelial function.[1,2,44] This objective is accomplished by reducing ROS production and augmenting NO bioavailability.

β-blockers have been demonstrated to reduce sympathetic overactivity, which can, in turn, lead to improvements in NO bioavailability and a reduction in oxidative stress, thereby exerting a beneficial effect on endothelial function.[45]

In addition to their cholesterol-lowering effect, which itself would be sufficient to explain their role in improving endothelial function by preventing atherosclerosis, statins also exert pleiotropic effects, including the reduction of oxidative stress and the enhancement of NO synthesis.[46]

Sodium–glucose cotransporter 2 inhibitors (SGLT2Is) exert anti-inflammatory effects through a reduction in body weight, the degree of inflammation in adipose tissue and uric acid serum concentrations.[47,48] Canagliflozin has been demonstrated to enhance endothelial function by inhibiting specific inflammatory pathways, namely the IL-1β-mediated production of cytokines and chemokines by the endothelial cells. In contrast, empagliflozin has been demonstrated to stimulate vascular regeneration, thereby facilitating the transition of EPCs to the M2 phase of polarisation.[1,2,49]

Vericiguat, a soluble guanylate cyclase (sGC) stimulator, has emerged as a promising therapeutic option for improving cardiovascular function in patients with HF with reduced ejection fraction (HFrEF) and in inflammatory conditions associated with oxidative stress, such as diabetes and atherosclerosis.[50] Vericiguat acts on the NO–sGC–cyclic guanosine monophosphate (cGMP) pathway, bypassing NO deficiency by stimulating cGMP production and activating protein kinase G (PKG), which supports vascular smooth muscle relaxation and improves microcirculation.[51,52] Consequently, vericiguat could represent a fifth pillar in HF management, as well as offering potential for treating chronic ED, expanding the therapeutic approach to cardiovascular disorders linked to reduced NO bioavailability.[53]

In terms of non-pharmacological approaches, it has been demonstrated in several studies that regular exercise has the capacity to enhance eNOS activity, increase NO production and reduce oxidative stress, thereby improving endothelial function in patients with HF.[33,54]

Among conventional therapies for HF, ACE inhibitors, ARBs, β-blockers and statins have shown secondary benefits on endothelial function, mainly via the modulation of oxidative stress pathways and improvement in NO bioavailability. These drugs indirectly support vascular homeostasis by attenuating inflammatory processes and reducing the burden of neurohormonal activation. Additionally, SGLT2Is have recently emerged not only as glucose-lowering agents but also as modulators of endothelial health, exerting anti-inflammatory effects and stimulating vascular

Table 2: Effects of Heart Failure Drugs on Endothelial Dysfunction and Endothelial Progenitor Cells

Therapy	Mechanism of Action	Role of Drug in Heart Failure	Role of Drug on Endothelium	Role of Drug on EPCs
ACE inhibitors	Decrease pro-inflammatory effects of angiotensin-II, increase NO availability	Improves endothelial function and reduces ROS production	Increases NO availability, reduces oxidative stress	Increases mobilisation of EPCs and vascular repair capacity
β-blockers	Reduce sympathetic hyperactivity, increase NO availability	Improves endothelial function by reducing oxidative stress	Reduces sympathetic hyperactivity, improves endothelial function	Anti-apoptotic effect and mobilisation of EPCs
Statins	Reduce oxidative stress, increase NO synthesis	Reduces inflammation and promotes neovascularisation	Reduces oxidative stress, promotes NO synthesis	Mobilises EPCs and improves their function
SGLT2Is	Reduce body weight and inflammation, stimulate vascular regeneration	Reduces cardiac workload and improves endothelial function	Reduces inflammation, improves endothelial function	Stimulates transition of EPCs to anti-inflammatory M2 phenotype
Vericiguat	Stimulates NO–sGC–cGMP pathway to improve smooth muscle relaxation	Improves microcirculation and reduces cardiovascular mortality	Improves endothelial relaxation	Potentially enhances mobilisation and function of EPCs

ACE = angiotensin-converting enzyme; cGMP = cyclic guanosine monophosphate; EPC = endothelial progenitor cell; NO = nitric oxide; ROS = reactive oxygen species; sGC=soluble guanylate cyclase; SGLT2I = sodium–glucose cotransporter 2 inhibitor.

regeneration. Notably, SGLT2Is have demonstrated the capacity to promote EPC mobilisation and induce a shift toward anti-inflammatory phenotypes, suggesting a potential bridging role between conventional pharmacotherapy and regenerative strategies.[47–49]

Nevertheless, novel therapeutic approaches, including antioxidant agents, gene therapy targeting eNOS and EPC-based therapies, are currently being investigated, with promising results, with the aim of directly improving the underlying mechanisms of ED in HF patients (*Supplementary Table 1*).[55,56] In comparison to conventional HF therapies, novel approaches such as EPC-based therapies and mitochondrial-targeted interventions aim to act more directly on the mechanisms of endothelial repair. While standard therapies reduce endothelial injury, regenerative approaches focus on restoring endothelial integrity through the enhancement of progenitor cell function and vascular regeneration. For instance, EPC infusion or mobilisation strategies have demonstrated encouraging results in preclinical models, showing improved neovascularisation and attenuation of adverse remodelling.[57,58] Furthermore, agents like vericiguat, through the activation of the NO–sGC–cGMP pathway, offer a complementary mechanism by bypassing upstream NO deficiency.[50,51,59] These therapies provide a more targeted correction of endothelial dysfunction, and their integration with standard HF treatment may offer synergistic effects, especially in patients with advanced disease and profound EPC impairment. Thus, structured comparisons highlight that, while conventional therapies remain essential for neurohormonal control, the incorporation of novel endothelial-targeted interventions may represent a paradigm shift toward precision vascular repair.

Endothelial Progenitor Circulating Cells in Endothelial Dysfunction

Definition of Endothelial Progenitor Cells

EPCs were first discovered by Asahara et al. in 1997, until then, it was previously assumed that endothelial cell differentiation was exclusive of embryonic development.[60,61] However, Asahara presented evidence indicating that CD34-positive haematopoietic progenitor cells isolated from adults could also undergo endothelial cell differentiation *in vitro* (*Supplementary Figure 1*).[61] EPCs, which originate in the bone marrow, play a pivotal role in the repair of damaged endothelium and the restoration of its structure and function.[61] The question of whether cells displaying characteristics of both the haematopoietic lineage and vasculogenic properties should be classified as EPCs remains a topic of on-going debate. The difficulty arises from the fact that CD34, a common marker, is expressed not only by haematopoietic stem cells but also by mature endothelial cells.[62] Additionally, research has investigated the potential of haematopoietic stem cells to express more primitive markers, such as CD133, which is not present on mature endothelial or monocytic cells.[63] For example, cells that are positive for both CD133 and vascular endothelial growth factor receptor 2 (VEGFR2) may indicate an immature progenitor cell, whereas cells that are positive for both CD34 and VEGFR2 are considered to be more mature.[64] EPCs thus represent a heterogeneous group of cells at various differentiation stages and no single marker or gene expression profile is sufficient to fully define them.[14] In laboratory settings, the challenge of defining EPCs is often addressed through cell culture. Peripheral mononuclear cells are cultured to form endothelial colony-forming units, which serve as a functional estimate of EPC activity after several days of growth.[60] This method assesses the ability of cells to proliferate and differentiate, which can be altered in different disease conditions.

The Role of Endothelial Progenitor Cells in Endothelial Dysfunction

We can reasonably state that EPCs constitute a particular subset of stem cells that originate from the bone marrow and circulate in the bloodstream.[65] They are capable of recognising and localising sites of endothelial injury, where they facilitate the regeneration of the vascular endothelium.[65] Their capacity to differentiate into mature endothelial cells and secrete factors that facilitate angiogenesis establishes them as pivotal contributors to the maintenance of endothelial health.[13,62]

Aetiopathogenesis of Endothelial Progenitor Cell Dysfunction

Mitochondria play a pivotal role in regulating cellular metabolism and energy production, which are indispensable for the survival and functionality of EPCs.[38] Recent research has indicated that cardiovascular risk factors, such as obesity, diabetes and chronic inflammation, can lead to mitochondrial dysfunction in EPCs, thereby impairing their ability to repair the endothelium.[66] Furthermore, oxidative stress exerts additional damage to mitochondria, thereby reducing the bioavailability and functionality of EPCs.[66] This vicious cycle of mitochondrial impairment and reduced endothelial repair capacity plays a significant role in the progression of ED and cardiovascular disease. Chronic inflammation represents another critical factor in EPC impairment. For example, in individuals with chronic HIV infection, systemic inflammation has been demonstrated to alter the phenotype of EPCs, reducing their angiogenic potential and contributing to elevated cardiovascular risk.[67] The presence

Table 3: Heart Failure Influence on Endothelial Dysfunction and Endothelial Progenitor Cells

Heart Failure Consequences	Effect on Endothelial Function	Impact on EPCs
Reduced nitric oxide availability	Reduced vascular tone regulation, increased vascular resistance	Limits EPC migration, reduces differentiation and vascular repair capacity
Increased oxidative stress	Accelerated endothelial damage, inflammation	Damages EPC proliferation, increases apoptosis and reduces survival
Chronic inflammation	Enhanced endothelial dysfunction, vascular remodelling	Inhibits EPC proliferation, reduces regenerative capacity
Impaired mobilisation	Compromised vascular repair and regeneration	Decreases EPC numbers at the injury site, limiting repair of damaged endothelium

EPC = endothelial progenitor cell.

of inflammatory cytokines and immune activation in conditions such as HIV and metabolic syndrome gives rise to a dysfunctional endothelial environment in which EPCs are less effective in maintaining vascular integrity.[67]

Endothelial Progenitor Cell Dysfunction in Cardiovascular Diseases

In patients with cardiovascular risk factors, such as hypertension, diabetes, smoking and hyperlipidaemia, the number and functional capacity of circulating EPCs are frequently diminished. This reduction in EPC numbers and functionality compromises the endothelium's capacity to repair itself, thereby accelerating the progression of ED-associated vascular diseases.[68] The role of EPCs in cardiovascular disease has been the subject of several studies, which have consistently demonstrated an inverse relationship between EPC levels and cardiovascular outcomes. Werner et al. observed that lower circulating EPC levels were associated with an elevated risk of cardiovascular events and a poorer prognosis in patients with coronary artery disease.[69] This finding indicates that EPCs not only facilitate vascular repair but also serve as a biomarker for cardiovascular risk. Similarly, research conducted by Hill et al. demonstrated a correlation between EPC levels and endothelial function, as measured by flow-mediated dilation.[10] This finding reinforces the hypothesis that EPCs are essential for maintaining endothelial health. In conditions such as atherosclerosis, where ED is a primary factor, EPCs serve a dual function: they facilitate the repair of damaged endothelium and promote the formation of new blood vessels (angiogenesis).[16,22,61] However, in advanced stages of the disease, the impaired functionality and reduced numbers of EPCs contribute to the progression of vascular lesions and plaque instability, thereby impeding the body's natural capacity to repair the damaged vasculature.[16,22,61]

Endothelial Progenitor Circulating Cells in Heart Failure

Pathophysiology and Mechanism

One of the emerging aspects of HF pathophysiology is ED, which plays a critical role in disease progression. EPCs have garnered significant attention due to their capacity for vascular repair and maintenance of endothelial integrity.[13,58] However, in HF, their number and functionality are significantly reduced, correlating inversely with disease severity as assessed by the New York Heart Association functional class.[58,60] In early stages, EPCs may increase in compensation, but chronic inflammation, oxidative stress and impaired mobilisation contribute to a marked decline in advanced stages.[57,58] Several factors contribute to EPC dysfunction in HF. NO bioavailability, essential for EPC migration, proliferation and neovascularisation, is diminished in HF due to endothelial NOS impairment, further compromising EPC functionality. Chronic inflammation, driven by elevated levels of cytokines such as TNF-α and IL-6, also plays a significant role.[36,57] These inflammatory markers inhibit EPC proliferation and impair their regenerative capacity. Additionally, oxidative stress, characterised by the excessive production of ROS, further damages EPCs, leading to increased apoptosis and reduced survival.[36] This combination of oxidative stress, reduced NO and chronic inflammation results in a significant decline in EPC function and number in advanced HF (*Table 3*).

Prognostic Value

EPC levels have been proposed as a potential biomarker for prognosis in HF. Different studies have shown that lower EPC counts are associated with worse outcomes, including increased mortality, higher hospitalisation rates and adverse cardiac remodelling.[11,55] Moreover, the reduction in EPC function, such as impaired migratory and colony-forming capacities, correlates with the severity of the disease.[60] Patients with higher levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP; a marker of HF) and lower EPC counts are at a higher risk of cardiovascular events and heart transplantation.[11,55] Therefore, EPCs not only reflect the degree of ED in this setting but also serve as an indicator of disease progression and overall prognosis in HF patients (*Supplementary Figure 2*).

Therapeutic Future Perspective of Endothelial Progenitor Cell Use in Heart Failure

Potential of Therapeutic Strategies

EPCs contribute to vascular repair both through direct integration into damaged vessels and by secreting factors that promote endothelial regeneration and reduce inflammation.[57] In cases of HF, dysfunction of EPCs is frequently associated with ED, which represents a significant factor in disease progression.[57] The mobilisation and functional enhancement of EPCs in patients with HF may lead to improvements in vascular health and – consequently – in cardiac function. Recent advances in this field suggest that EPC-based therapy could also prove beneficial in improving outcomes by mitigating the remodelling processes that exacerbate HF.[5,58] Moreover, it has been demonstrated that elevated levels of EPCs are associated with a reduced burden of coronary plaque and more favourable prognoses in patients with ischaemic heart disease, which is the most common aetiology of HF.[13,55]

Given the pivotal role of EPCs, enhancing their mobilisation and function represents an emerging therapeutic strategy in the treatment of cardiovascular diseases. Several approaches are currently being explored, including the following:

- Mitochondrial-targeted therapies. The implementation of interventions designed to enhance mitochondrial function, such as antioxidants or metabolic modulators, has the potential to restore EPC functionality and augment their capacity to repair the endothelium.[70]
- Stem cell therapies. The infusion of exogenous EPCs or stem cells with endothelial regenerative potential has demonstrated efficacy in preclinical studies.[70] The objective of this approach is to enhance the body's intrinsic repair mechanisms and reinstate endothelial functionality.

- Lifestyle and pharmacological interventions. It has been demonstrated that exercise, statins and agents that target oxidative stress are effective in increasing the levels of EPCs and improving their functionality.[32,33] Such interventions may offer a non-invasive method of enhancing endothelial repair and preventing cardiovascular events.

Limitations and Future Perspectives of Endothelial Progenitor Cell-based Therapeutic Strategies

Despite the promising indications of the potential of EPCs in vascular repair, several obstacles remain. Firstly, the precise characterisation of EPCs remains a topic of debate, given the identification of various subsets of progenitor cells with overlapping markers depending on their stage of differentiation. This heterogeneity complicates the identification of true EPCs with high regenerative capacity, limiting the reproducibility and consistency of therapeutic outcomes. Moreover, the clinical implementation of EPC-based therapies requires the resolution of issues pertaining to the harvesting, expansion and delivery of cells. Achieving enough functional EPCs is challenging, particularly in patients with HF who inherently present reduced EPC levels. Additionally, the *ex vivo* expansion of EPCs often results in cellular senescence or loss of regenerative capacity, compromising their clinical utility.

A further challenge is posed by the observation of variability in EPC function across different patient populations. It has been demonstrated that comorbidities such as diabetes and smoking impair the regenerative capacity of EPCs, thereby limiting their therapeutic potential. These conditions, associated with oxidative stress and mitochondrial dysfunction, not only decrease EPC numbers but also compromise their migratory and angiogenic abilities. Additionally, the long-term safety and efficacy of therapies aimed at enhancing EPC numbers or functions are not yet fully understood. Concerns have been raised about the potential for EPC-mediated neovascularisation to destabilise atherosclerotic plaques or promote tumour growth.

In the future, research will be focused on elucidating the molecular mechanisms that regulate EPC mobilisation, homing and differentiation. Enhancing homing signals through targeted modulation of chemotactic factors and improving EPC engraftment at injury sites are key areas of investigation. Furthermore, the combination of EPC-based strategies with other treatments, such as gene therapy or advanced drug delivery systems, may provide innovative avenues for addressing ED and its associated cardiovascular complications. Finally, large-scale clinical trials are needed to evaluate the long-term outcomes and safety profiles of EPC-based therapies.

Influence of Treatments for Heart Failure on Endothelial Progenitor Cells

Among the pharmacological strategies, statins – widely known for their lipid-lowering effects – have been demonstrated to enhance EPC mobilisation and improve endothelial function through mechanisms involving increased NO bioavailability via the PI3K/Akt pathway.[71] Statins have been shown to improve endothelial function, reduce inflammation and promote neovascularisation, making them a promising therapeutic option for restoring EPC function in HF.[71] In addition to statins, other agents and approaches, including ACE inhibitors, exercise and several growth factors (e.g. erythropoietin, granulocyte colony-stimulating factor), have been demonstrated to enhance EPC mobilisation and augment vascular repair capacity.[72] Erythropoietin, beyond its role in correcting anaemia, enhances EPC-mediated vascular repair, suggesting that it could be used as a therapeutic agent in HF patients with reduced EPC counts.[65,72] Physical exercise, on the other hand, has anti-apoptotic effects on endothelial cells, enhancing EPC mobilisation and endothelial function.[73] In clinical settings, EPCs have been used in cell-based therapies with the objective of regenerating damaged vasculature. For example, the TOPCARE-AMI trial demonstrated that the transplantation of autologous EPCs into patients with acute MI led to improved left ventricular function and reduced infarct size, thereby highlighting the potential therapeutic benefits of EPC-based therapies in ischaemic heart disease.[74]

Sodium–Glucose Cotransporter 2 Inhibitors and Endothelial Progenitor Cells: What Is Known and What Is Expected

SGLT2Is, commonly referred to as gliflozins, have emerged as promising agents in the treatment of HF. These agents reduce preload and afterload by promoting natriuresis (the excretion of sodium in the urine), resulting in improved cardiac function.[49] Beyond their glucose-lowering effects, gliflozins have been shown to improve endothelial function, potentially through mechanisms involving EPC mobilisation.[75] Several studies indicate that gliflozins can enhance the function and number of circulating EPCs. This is believed to occur via modulation of pathways that reduce oxidative stress and inflammation – two factors that impair EPC function.[75–77] Additionally, gliflozins improve vascular endothelial health by decreasing arterial stiffness and promoting vasodilation, which may indirectly support EPC-mediated repair processes.[78] More importantly, they can induce weight loss, reduce inflammation in adipose tissue and reduce uric acid serum concentrations leading to decreased cardiac inflammation and oxidative stress, which indirectly supports EPC-mediated vascular repair.[75–77] Furthermore, they can directly ascertain an inhibition of IL-1β-stimulated cytokine and chemokine secretion in vascular endothelial cells, which prompts EPCs to undergo a shift towards a polarisation into M2 macrophages, which are characterised by anti-inflammatory properties.[75–77] Recent studies suggest that gliflozins might also reduce the activity of the RAAS, a system that is often overactivated in HF and contributes to ED.[49,79] By modulating RAAS and reducing systemic inflammation, gliflozins create a more favourable environment for EPCs to operate and repair damaged vasculature.[49,79]

Combining EPC therapies with drugs such as gliflozins could represent a new frontier in the treatment of HF. Several on-going trials are exploring the synergistic effects of such combinations. For instance, therapies aimed at boosting EPC numbers through bone marrow stimulation or enhancing EPC function via cytokine administration may benefit from the endothelial and anti-inflammatory effects of gliflozins.[49,80] Additionally, advances in stem cell research are investigating the possibility of using autologous EPCs (derived from the patient's own body) to reduce the risk of rejection and enhance cardiac repair.[49,80] Combined with the metabolic and vascular benefits of gliflozins, this approach may prove to be highly effective in managing chronic HF.

Insights into the Emerging Role of Vericiguat

In circumstances where NO bioavailability is compromised, vericiguat has demonstrated the capacity to restore endothelial-dependent vasodilation and enhance microvascular integrity.[51,52] The presence of high glucose levels is often associated with the development of oxidative stress and inflammation, which subsequently results in a reduction in the availability of NO. This, in turn, leads to the impairment of endothelial cell function and the subsequent disruption of downstream signalling pathways.[51] Studies on human vascular smooth muscle cells exposed to high glucose levels have demonstrated that vericiguat can normalise cGMP and PKG

activity, which are essential for maintaining endothelial function.[51] This mechanism suggests potential benefits for vericiguat in the treatment of vascular disorders characterised by ED, including those associated with diabetes and chronic inflammatory diseases. In murine models, vericiguat demonstrated the capacity to enhance endothelial-dependent relaxation without affecting endothelial-independent responses, thereby further underlying its targeted mechanism of action.[52]

The efficacy of vericiguat in the treatment of HFrEF has been substantiated by the VICTORIA trial, which has demonstrated a reduction in cardiovascular mortality and hospitalisations due to HF-related complications.[81] In particular, this trial demonstrated that vericiguat significantly reduced above-mentioned endpoints in high-risk HFrEF patients, with greater efficacy observed in those with lower baseline NT-proBNP levels, indicating less advanced disease.[81] The drug's sGC stimulation selectively enhances sensitivity to endogenous NO without excessively lowering blood pressure, thereby rendering it a safe option for vulnerable patients prone to hypotension. Furthermore, vericiguat has been proposed as a prospective fifth pillar in the treatment of HFrEF, alongside standard treatments such as angiotensin receptor–neprilysin inhibitors, β-blockers, mineralocorticoid receptor antagonists and SGLT2Is, particularly in patients with comorbidities that restrict their tolerance to conventional therapies.[1,53]

The impact of vericiguat on EPCs is still under investigation; however, enhancing cGMP signalling shows promise for EPC mobilisation and function. It is conceivable that vericiguat may assist in the preservation of EPC functionality by enhancing the endothelial environment and supporting NO–cGMP signalling, thereby indirectly contributing to vascular repair processes. Further studies on the dynamics of EPCs in the context of vericiguat therapy may elucidate its potential role in promoting endothelial health through both direct vascular effects and enhancement of vascular progenitor cell activity. In conclusion, vericiguat provides a novel therapeutic avenue for addressing ED in cardiovascular disease and HFrEF, with benefits extending beyond the conventional haemodynamic effects.

Conclusion

ED plays a pivotal role in the pathophysiology of HF, contributing to progression of the disease and the development of associated clinical complications. ED is characterised by a reduction in NO bioavailability, an increase in oxidative stress and a pro-inflammatory, pro-thrombotic phenotype, which collectively impair vascular function. Furthermore, the impaired function of EPCs in HF further constrains vascular repair and regeneration, thereby intensifying the damage to the endothelium. As HF progresses, the pro-thrombotic changes in endothelial behaviour, such as increased expression of tissue factor and von Willebrand factor, elevate the risk of thrombotic events, including stroke and MI. From a therapeutic perspective, the enhancement of endothelial function and the targeting of EPC dysfunction represent promising strategies for the management of HF. It has been demonstrated that established treatments, including ACE inhibitors, ARBs, β-blockers, statins and SGLT2Is, have the potential to enhance endothelial health by increasing NO availability and reducing oxidative stress and inflammation. Meanwhile, emerging therapies that target EPC mobilisation and mitochondrial function offer new avenues for improving endothelial repair. ❑

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