Basic & Clinical Pharmacology & Toxicology

BCPT Basic & Clinical Pharmacology & Toxicology

FOCUSED REVIEW OPEN ACCESS

Role of Inflammatory and Proresolving Mediators in Endothelial Dysfunction

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Received: 24 November 2024 | **Revised:** 20 February 2025 | **Accepted:** 10 March 2025

Funding: Work from the author's laboratory was supported by grants SAF2016-80305P and PID2020-116498RB-I00 funded by Agencia Estatal de Investigación (MCIN/AEI/10.13039/501100011033) and by 'ERDF A way of making Europe'; Comunidad de Madrid (B2017/BMD-3676 AORTASANA) FEDER-a way to build Europe; Fundación Española de Arteriosclerosis (Beca FEA 2021 Investigación Básica en Arteriosclerosis), CiberCV Instituto de Salud Carlos III (CiberCV CB16/11/00286, CiberCV CB16/11/00257, CiberCV CB16/11/00333; CiberCV CB/11/00222); the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement no. 954798; and Instituto de Salud Carlos III (AC23_2/00044) under the umbrella of the Partnership Fostering a European Research Area for Health (ERA4Health) (GA N° 101095426 of the EU Horizon Europe Research and Innovation Programme).

Keywords: cardiovascular diseases | endothelial dysfunction | hypertension | inflammation | specialized proresolvin mediators

ABSTRACT

Excessive local inflammation is a common mechanism in many cardiovascular diseases (CVDs) such as hypertension, atherosclerosis and aortic aneurysms. In endothelial cells, inflammatory cytokines such as interferons, tumour necrosis factor alpha or interleukins increase oxidative stress and contractile prostanoids and the expression of adhesion molecules that reduce nitric oxide (NO) availability and bind leucocytes, thereby impairing endothelial function. Despite this evidence, anti-inflammatory therapies are not yet indicated for the treatment of most CVD. Resolution of inflammation is mediated by a family of specialized pro-resolving mediators (SPMs) that act on cognate G protein–coupled receptors to limit immune cell infiltration and initiate tissue repair. SPMs, generated from omega-3 and omega-6 polyunsaturated fatty acids, belong to four major families: lipoxins, resolvins, protectins and maresins. SPM receptors are expressed in immune and vascular cells where they regulate important processes such as phagocytosis and polarization, production of cytokines, NO and prostacyclin, and modulation of smooth muscle cell phenotype. Growing evidence in animal models demonstrates that activation of SPM receptors can protect vascular function and structure and provide beneficial effects in various CVD. We will review recent advances in the role of inflammation and SPMs in vascular (dys)function in hypertension, atherosclerosis, and aortic aneurysms.

1 | Introduction

The vascular endothelium is a semipermeable barrier involved in critical physiological functions such as exchange of substances and fluids, control of vascular tone, mechanotransduction, haemostasia, angiogenesis, injury and repair and metabolism [1–3]. Endothelial cell (EC) function can be influenced by proximal cells such as immune cells, fibroblasts or cardiomyocytes, and similarly, EC can affect the behaviour of such cells. In response to various stressors including lipid products, inflammatory cytokines, changes in blood flow, oxidative stress, metabolic factors, some drugs or cardiovascular risk factors, the EC become

Summary

- Excessive inflammation in the arteries is a common feature of many cardiovascular diseases such as hypertension, atherosclerosis, and aortic aneurysms.
- Many inflammatory factors damage the vasculature by reducing the availability of key vasodilator factors and facilitating the recruitment of immune cells that further perpetuate the damage.
- Despite this evidence, anti-inflammatory therapies are not yet indicated for the treatment of most cardiovascular diseases.
- Specialized pro-resolving mediators are molecules that act on vascular and immune cells to regulate important processes involved in the proper functioning of the vasculature and can provide beneficial effects in several cardiovascular diseases.

dysfunctional and shift the production of protective molecules towards factors that promote major features of endothelial dysfunction that contribute to many cardiovascular diseases (CVDs) [1–3].

It is recognized that endothelial dysfunction is an initiating or contributing factor in many CVDs such as hypertension, atherosclerosis, diabetes, obesity or aortic aneurysms. This highlights the need to find therapeutic strategies to prevent or reverse endothelial dysfunction in order to maintain vascular health. In this context, many, if not all, CVDs associated with endothelial dysfunction are now considered low-grade inflammatory diseases with increased production of vascular inflammatory mediators locally or from infiltrated or circulating immune cells that negatively affect ECs [4, 5].

In this review, we will provide an overview of the role of inflammation in different features of endothelial dysfunction in hypertension and other CVDs. We also propose additional approaches to resolve the inflammatory response in EC as novel pharmacological tools to treat endothelial dysfunction with potential impact in various CVDs.

2 | Endothelial Dysfunction and Inflammation

Endothelial dysfunction is characterized by several features including inflammation, hyperpermeability, leukocyte adhesion, endothelial NO synthase (eNOS) uncoupling, altered EC metabolism, oxidative stress, injury and cell death, senescence, endothelial–mesenchymal transition and impaired vasodilation [1–3]. Chronic exposure to cardiovascular risk factors such as hypertension, hypercholesterolaemia, diabetes or obesity reduces endothelium-dependent relaxation, and this has a prognostic value for future cardiovascular events [6]. Therefore, targeting factors that impair vascular relaxation would have a major impact on cardiovascular morbidity and mortality. In healthy conditions, the endothelium releases NO, prostacyclin, and endothelium-derived hyperpolarizing factors (EDHF) such as hydrogen sulfide (H_2S), carbon monoxide, arachidonic acid metabolites, and hydrogen peroxide (H_2O_2), which, at physiological concentrations, are key factors in the regulation of the vascular tone. However, in cardiovascular comorbidities such as hypertension, the endothelium also releases vasoconstrictor molecules such as endothelin-1 (ET-1), angiotensin II (Ang II), thromboxane A_2, or superoxide anion, which contribute to the impaired vasodilator responses observed in these diseases [1–3]. Moreover, multiple risk factors including EC injury, lipids, peptides such as Ang II or ET-1, metabolic factors, and hormones such as aldosterone trigger the expression of cytokines, monocyte chemoattractant protein-1 (MCP-1), chemokines and cell adhesion molecules (vascular cell adhesion molecule-1 [VCAM-1], intercellular cell adhesion molecule-1 [ICAM-1] and selectins) by EC, which increase permeability and attract inflammatory immune cells into the sub-endothelial space, initiating local and systemic inflammation [4, 5, 7].

In the first part of the review, we will focus on the effect of different proinflammatory cytokines as mediators of impaired endothelial function in hypertension through the production of contractile factors such as reactive oxygen species (ROS) and prostanoids.

2.1 | Inflammatory Cytokines and Endothelial Dysfunction in Hypertension

It is recognized that low-grade immune response plays an important role in the initiation and maintenance of high blood pressure [4]. In hypertension, blood vessels are exposed to several insults that promote the release of the so-called damage-associated molecular patterns (DAMPs), which are recognized by pattern recognition receptors (PPRs); upon PPR activation, proinflammatory cytokines are produced by immune and vascular cells, and EC adopt a proinflammatory and prothrombotic phenotype, characterized by decreased release of vasodilator factors and increased release of vasoconstrictor factors, thereby reducing vasodilatory capacity [4]. Toll-like receptors (TLRs) are a well-characterized family of membrane-bound PRRs expressed in various cell types, including vascular cells. Several studies have demonstrated upregulation of TLR4 in various models of hypertension, contributing to hypertension-associated endothelial dysfunction through ROS-dependent mechanisms [8, 9].

Cytokines are mediators that coordinate innate and adaptive immune responses. They are produced by immune cells but also by EC, vascular smooth muscle cells (VSMC) and perivascular adipose tissue (PVAT). Cytokines have a major impact on the structure and function of blood vessels in hypertension. Alterations in the balance between pro- and anti-inflammatory cytokines can drive the host defence immune response towards either chronic inflammation or resolution and healing. In both patients and animal models of hypertension, levels of several proinflammatory cytokines are increased, whereas those of anti-inflammatory cytokines are decreased, and this is associated with end-organ damage, including altered blood vessels function [4, 10].

Tumour necrosis factor-α (TNFα) is produced by T lymphocytes, VSMC, EC, adipocytes, macrophages and fibroblasts. After interacting with its receptors, NADPH oxidase is activated, mainly producing superoxide anion, which reacts with NO to form peroxynitrite (ONOO−) [11]; this reduces NO bioavailability,

impairing vasodilation and increasing blood pressure. In addition, TNF-α negatively regulates the eNOS promoter and contributes to the destabilization of the eNOS mRNA structure, leading to the massive degradation of eNOS with a reduction in NO synthesis [12]. Furthermore, TNF-α increases ICAM-1 and VCAM-1 expression by activating the NF-κB pathway, facilitating immune cell recruitment and vascular dysfunction [13].

Interleukin-6 (IL-6), secreted by circulating leucocytes, EC, VSCM and fibroblasts, also induces endothelial dysfunction and contributes to the development of hypertension. IL-6 is thought to reduce eNOS activation by increasing the half-life of caveolin-1 and, consequently reducing Ser^{1177} phosphorylation (the eNOS stimulatory site) [14]. Additionally, experiments performed in Ang II-infused IL-6-deficient mice have shown that this cytokine also induces oxidative stress and reduces eNOS expression [15], thereby limiting NO bioavailability and vasodilation.

IL-1β is primarily derived from monocytes, T cells and neutrophils. It is released into the extracellular space after pro-IL-1β processing by inflammatory caspases. Its receptors are expressed on immune cells, VSMCs and ECs. IL-1β activates NADPH oxidase and ROS production and induces the expression of the inducible cyclooxygenase 2 (COX-2) [16, 17]. Various approaches targeting IL-1β prevented aldosterone-induced endothelial dysfunction [18]. Moreover, anakinra, an IL-1R1 receptor inhibitor, prevents endothelial dysfunction induced by macrophage-conditioned media from Ang II-induced hypertensive mice [19].

Activation of the mineralocorticoid receptor in CD8+T cells induces hypertension and endothelial dysfunction via Interferon-γ (IFN-γ) [20]. IFN-γ is mainly produced by T helper I cells, effector $CD8^+$ T cells and natural killer (NK) cells. Its receptor is expressed on most cells, and, when activated, it induces oxidative stress and inflammation, endothelial dysfunction, vascular remodelling and fibrosis in hypertension [21]. Moreover, IFN-γ stimulates interferon-stimulated genes, such as ISG15, which contribute to endothelial dysfunction and vascular remodelling in hypertension through inflammatory mechanisms and oxidative stress [22].

The proinflammatory cytokine IL-17A is derived from Th17 cells, an important subset of $CD4^+$ T cells. In EC, IL-17A inhibits eNOS by inducing Thr^{495} phosphorylation (the eNOS inhibitory site) and reducing Ser^{1177} phosphorylation, resulting in decreased NO production [23]. Moreover, Ang II infusion failed to induce endothelial dysfunction or to increase blood pressure in $17A^{-/-}$ mice, and this was associated with a reduced superoxide production and decreased T-cell infiltration [24].

IL-22, a member of the IL-10 cytokine family, is mainly produced by $CD4^+$ Th1, Th17 and Th22 cells, as well as NK and γδ T cells. Binding to specific cell surface receptors induces JAK/STAT3 signalling and subsequent eNOS phosphorylation at Thr^{495}, which contributes to impaired NO-dependent relaxation in Ang II-infused mice [25].

IL-10 is an anti-inflammatory cytokine with protective effects in hypertension and endothelial dysfunction. It is secreted by regulatory T cells (Tregs), monocytes, macrophages, dendritic cells, NK cells, and B cells and limits the host immune response. Through its receptor, IL-10 activates the JAK/STAT pathway and reduces the release of proinflammatory cytokines such as IFN-γ, IL-1β, TNF-α, and IL-6. Several reports have shown that IL-10 protects against Ang II-induced impaired vasodilation by suppressing oxidative stress [26, 27].

Taken together, these findings indicate that proinflammatory cytokines induce endothelial dysfunction in hypertension mainly by reducing eNOS activation and through oxidative stress–dependent mechanisms.

2.2 | ROS and Endothelial Dysfunction in Hypertension

High plasma and vascular levels of ROS have been extensively described in both animal models and hypertensive patients [28–31]. When produced at pathological levels by various cell types, ROS reduce NO bioavailability and function and are important second messengers in EC signalling. Indeed, an imbalance between antioxidant defence mechanisms and ROS production is considered a primary cause of endothelial dysfunction. A dysfunctional endothelium also exacerbates the production of ROS, which can activate redox-sensitive transcription factors (e.g., NF-κB and AP-1) involved in the expression of proinflammatory genes and cytokines that further perpetuate vascular inflammation and endothelial damage [30, 31].

The major source of ROS in hypertension is the NADPH oxidase family, whose expression and activity are increased at the vascular level. The NADPH oxidase isoforms Nox-1, Nox-2, Nox-4 and Nox-5, the latter of which is only expressed in humans, are expressed in fibroblasts, EC and VSMC and are regulated by growth factors, elevated intravascular pressure, proinflammatory mediators and vasoactive agents such as ET-1 and Ang II [30, 31]. Nox signalling involves activation of multiple pathways, including endoplasmic reticulum stress, NF-κB or various kinases, resulting in oxidative stress, inflammation, endothelial damage and high blood pressure [30, 31]. Other important sources of ROS in hypertension are mitochondria, xanthine oxidase and uncoupled eNOS. In hypertension, certain points in the electron transport chain can 'leak' electrons to oxygen, resulting in the formation of superoxide, which is rapidly converted to H_2O_2 by the enzyme superoxide dismutase 2 (SOD2). H_2O_2 can easily diffuse out of the mitochondria, contributing to cellular oxidative stress [32]. It has been observed that NADPH oxidase-derived ROS stimulates mitochondria ROS and vice versa, creating a vicious feed-forward cycle implicated in endothelial dysfunction and elevated blood pressure in hypertension [29, 32].

Endothelial NOS can also generate ROS in the absence of L-arginine substrate or tetrahydrobiopterin (BH4) cofactor. This phenomenon is referred to as eNOS uncoupling and has been demonstrated in several models of hypertension [30, 33]. Several factors, including oxidative stress and Ang II, reduce the bioavailability of BH4 by downregulating dihydrofolate reductase, which is involved in the synthesis of this cofactor [34]. In addition, superoxide anion and ONOO− oxidase BH4 to dihydropterin (BH2), leading to uncoupled eNOS and superoxide anion production rather than NO. [33]

The bioavailability of ROS is tightly regulated by the balance between generation and detoxification by several antioxidant mechanisms, including enzymes such as glutathione peroxidase (GPx), SODs, catalase or the thioredoxin system and non-enzymatic molecules, such as tocopherols or ascorbic acid [30]. Therefore, a disturbance in any of these mechanisms can lead to pathological levels of ROS. Reduced expression and activity of SOD, catalase and GPx have been described in hypertensive patients and models of hypertension [30, 35, 36]. Interestingly, activation of nuclear factor erythroid 2-related factor-2 (Nrf2), an oxidative stress-responsive factor that activates transcription of genes encoding several antioxidant and detoxifying proteins, such as NAD(P)H quinone reductase 1, heme oxygenase 1, SOD1/2, GPx and catalase [37], prevents endothelial dysfunction, inflammation and hypertension in several animal models [36, 37]. In addition, several studies have shown that various antioxidants and inhibitors of ROS production improve endothelial function in different models of hypertension. Similarly, genetic deletion of different NADPH oxidase isoforms or other sources of ROS preserve vascular function in response to hypertensive challenge. However, data from clinical trials with antioxidants have yielded mixed results, which may be due to different biological factors, inadequate or incomplete ROS measurement, chemical reactivity problems or pathophysiological or pharmacokinetic aspects. We will not discuss this aspect in detail, and the reader is referred to previous reviews [30, 31, 38].

2.3 | Prostanoids and Endothelial Dysfunction in Hypertension

Previous studies have shown that endothelium-derived vasoconstrictor prostanoids are major determinants of endothelial dysfunction in hypertension [1]. A role for constitutive COX-1 has been described for endothelium-derived contractile factor (EDCF) production in several animal models, including spontaneously hypertensive rats (SHR) [1]. Moreover, whereas inducible COX-2 is typically expressed at low levels in healthy blood vessels, its expression is significantly increased in vessels from hypertensive patients and hypertension models, probably due to the inflammatory phenotype. In these conditions, COX-2 plays a role in endothelial dysfunction, as demonstrated by the fact that selective COX-2 inhibitors restore impaired vasodilation to acetylcholine and reduce the increased EDCF responses [1, 28, 29, 39]. Prostanoids derived from COX-2 are considered EDCF in hypertension. For example, vascular $PGF_{2\alpha}$ production is increased in hypertension, and the increased endothelium-dependent contractility is abolished by a thromboxane A_2/prostaglandin H_2 (TP) receptor antagonist in a COX-2-dependent manner [29, 40, 41]. Interestingly, PGI_2, which in healthy vessels acts as an important endothelium-derived relaxing factor via the IP receptor in VSMCs, acts as a TP agonist to induce contraction in arteries from hypertensive animals [35]. In agreement, PGIS deficiency results in the exacerbation or appearance of endothelium-dependent constriction ex vivo and in vivo together with reduced NO-dependent relaxation and increased blood pressure [42].

Ang II and increased oxidative stress appear to be major contributors to the upregulation of vascular COX-2 in hypertension [29, 39]. On the other hand, COX-2 is a major source of vascular oxidative stress in hypertension, either directly through its enzymatic activity or indirectly through the effects of prostanoids in various ROS sources [28, 29, 43]. Thus, the COX-2–ROS axis may create a vicious cycle of self-perpetuating vasoactive substances that play a pathophysiological role in the altered vascular contractile and dilatory responses associated with hypertension [43]. These data suggest that COX-derived prostanoids may be a pharmacological target for vascular dysfunction in hypertension. However, both selective and non-selective non-steroidal anti-inflammatory drugs increase cardiovascular risk [44]. In this context, inhibition of specific prostanoid-generating enzymes or receptors may be a safer strategy. For example, microsomal prostaglandin E synthase-1 (mPGES-1), an inducible PGE_2-generating enzyme downstream COX-2, is upregulated in the aorta of Ang II-induced hypertensive mice, and its expression is also upregulated in peripheral blood mononuclear cells from hypertensive patients [45, 46]. Furthermore, the deletion of mPGES-1 or EP1 blockade prevented the Ang II-induced hypercontractility and endothelial dysfunction [45, 46], suggesting a role for this prostanoid in altered endothelial function in hypertension.

3 | Resolution of Inflammation and Endothelial Dysfunction

Resolution of inflammation is a critical process in tissue repair and restoration of tissue homeostasis. It is a highly orchestrated process mediated by the enzymatic conversion of ω-6 and ω-3 polyunsaturated fatty acids (PUFA), including arachidonic acid (AA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA), to a family of specialized pro-resolving mediators [SPMs: lipoxins (LX), resolvins (Rv), protectins, maresins (MaR)] by various enzymes such as 5- or 15-lipoxygenases (5-LOX, 15-LOX) [47, 48]. The production of SPMs is initiated by a temporal lipid mediator class switch in which COX-derived PGE_2 precedes the biosynthesis of lipoxins from AA. PGE_2 and PGD_2 induce 15-LOX in human neutrophils switching from leukotriene B4 to lipoxin production, which is a stop signal for polymorphonuclear neutrophils that limits further recruitment [47, 48]. SPMs are also produced by macrophages because they have all the biosynthetic enzymes. Moreover, SPMs are biosynthesized via cell–cell communication in a process termed transcellular biosynthesis [49]. Specifically, activated EC at sites of inflammation produce precursors of SPMs that are taken up by adherent neutrophils and converted into several SPMs [49], confirming the role of EC not only as major targets of inflammatory molecules but as key players in the resolution of inflammation programme. Interestingly, cardiovascular medications such as aspirin or atorvastatin trigger the formation of specific LXs, Rvs and protectins, as well as n-3 DPA-derived 13-series resolvins, which are produced during neutrophil–endothelial cell interactions [50, 51].

SPMs bind cognate G protein-coupled receptors such as ALX/FPR2 for RvD1 and LXA4, GPR32 for RvD1, GPR18 for RvD2, ChemR23 for RvE1, or LGR6 for MaR1, among others [47, 48]. These receptors are expressed on various immune cells such as neutrophils, monocytes, macrophages and T cells, where they exert protective functions such as decreased infiltration, chemotaxis and activation, decreased production of inflammatory cytokines, increased efferocytosis and phagocytosis capability and polarization of M2 macrophages. SPM receptors are also

expressed on platelets and VSMC and EC, facilitating reduced platelet aggregation and activation, reduced VSMC proliferation and migration, reduced EC activation and reduced expression/activation of proinflammatory pathways [47, 52, 53]. Overall, this limits immune cell infiltration and initiates tissue repair mechanisms [47, 48, 52–54]. Importantly, lack of resolution of inflammation is a major pathophysiology in common vascular diseases [52, 54]. Indeed, dysregulation of SPMs levels, enzymes or receptors has been shown in human atherosclerotic plaques and aortic aneurysms [55–59].

Recent evidence has demonstrated the beneficial effects of SPMs on cardiovascular injury in a variety of conditions by modulating immune cell infiltration and inflammation, as well as cardiovascular remodelling and extracellular matrix deposition [49, 60–62]. However, the effects of SPMs on endothelial function have been less explored. Initial studies demonstrated that one SPM, RvD2, increased the production of NO and PGI_2 in human umbilical vein EC [63]. In addition, RvD2 activates the PI3K/Akt pathway (which is key to NO production) to regulate the expression of the anti-inflammatory protein Del-1 in EC [64]. This may indicate potential effect of SPMs in the modulation of vascular tone. Interestingly, RvD1, RvD2 and RvE1 do not relax preconstricted rat thoracic aortic segments [65], and we have not observed acute relaxant effects of several SPMs in mouse aorta (unpublished). However, RvE1, RvD1 and RvD2 inhibit constriction of rat thoracic aorta and human pulmonary artery induced by the thromboxane mimetic U46619 [65], and, similarly, pretreatment of isolated human saphenous vein with RvE1, RvD1 and MaR1 significantly reduced the contractile responses to U46619 [66]. Interestingly, pretreatment with LXA4 and RvD2 had no significant effect on the vascular tone of saphenous vein [66], suggesting that there might be differences in SPM responses between arteries and veins.

3.1 | SPMs and Endothelial Dysfunction in Hypertension

As discussed above, a major feature of hypertension-induced endothelial dysfunction is a reduced NO availability. Based on the reported ability of RvD2 to increase NO and PGI_2 [63], we recently tested the effects of RvD2 treatment in vivo in Ang II-induced hypertension. RvD2 not only prevented but also reversed the impaired endothelium-dependent relaxation observed in resistance arteries from Ang II-infused mouse, which may contribute to its antihypertensive effects [67]. Interestingly, in the aorta, we did not observe an improvement in endothelial dysfunction by RvD2, but we did observe a prevention of hypercontractility, suggesting possible differences in RvD2 receptor expression or signalling between vascular beds [67]. The underlying mechanisms responsible for these effects likely include an increase in NO and PGI_2 availability without a change in the EDHF component. However, the contribution of other factors such as reduced vascular infiltration of immune cells or polarization of the macrophages phenotype towards a pro-resolving one cannot be excluded [67]. In addition, normalized endothelium-dependent vasodilation and contractility were induced by in vivo RvD2 treatment in a model of hypertension and obesity in both large and small arteries [59]. Similarly, ex vivo incubation with SPMs such as LXA4, RvD1 or RvE1 potentiated acetylcholine-induced relaxation in small arteries from SHR but failed to abolish acetylcholine-induced contraction [68]. In cultured EC, RvD2 also decreased the expression of VCAM, MCP-1, COX-2 or Nox5 induced by Ang II and IFNγ and restored the decrease in nitrite production induced by Ang II and IL-6 [59, 67], suggesting a direct effect of RvD2 in this cell type. In the saphenous vein, RvE1, RvD1 and MaR1, but not LXA4 and RvD2 pretreatment, reduced the release of MCP-1 and TNF-α [66].

The beneficial effects of RvD2 on endothelial function appear to be independent of VSMC sensitivity to NO, as responses to NO donors were similar in hypertensive mice treated or not with RvD2 [59, 67]. However, an effect of SPMs in VSMC in hypertension has also been demonstrated, as RvD2 improved vascular structure in lean or obese hypertensive mice [59, 67]. Moreover, RvE1 through the ChemR23 receptor ameliorated hypertension and vascular remodelling by activating AMPKα/Nrf2 signalling, which inhibited the canonical NF-κB/Ccl5 pathway and immune cell infiltration and regulated VSMC proliferation and phenotypic transformation [69]. In addition, RvD1 attenuated Ang II-induced hypertension by inhibiting VSMC proliferation, migration and phenotypic transformation by blocking the RhoA/MAPK pathway [70]. Taken together, these findings suggest protective effects of SPMs in specific features of endothelial dysfunction and vascular remodelling in hypertension.

As hypertension and endothelial dysfunction often accompany other cardiovascular conditions such as atherosclerosis and aneurysms, we will also discuss the beneficial effects of SPMs in these diseases.

3.2 | SPMs and Endothelial Dysfunction in Atherosclerosis

Endothelial dysfunction is an initiating event in atherosclerosis. As mentioned above, chronic exposure to cardiovascular risk factors results in endothelial dysfunction and subsequent increased endothelial permeability, which in turn promotes LDL-c transcytosis across the endothelium, leading to its accumulation and subsequent oxidation. This process triggers the expression of cell adhesion molecules, including VCAM1 and ICAM1, and selectins by EC, which in turn attract monocytes and lymphocytes into the sub-endothelial space [7]. Monocytes are converted into macrophages, which express scavenger receptors for modified lipoproteins. The ingestion of lipoproteins by macrophages induces the differentiation of these cells into foam cells, leading to the formation of fatty streaks, the initial lesion of atherosclerosis. Communication between the various cellular components of innate and adaptive immunity increases the release of pro-inflammatory cytokines, such as MCP-1, which sustain and amplify the inflammatory response. This chronic inflammatory response at the lesion site serves as a stimulus for the migration and proliferation of VSMCs from the media into the neointima layer, leading to the formation of a fibrous cap over the lipid core and the conversion of the fatty streak into a fibrofatty lesion [71].

The protective effects of activating resolution of inflammation in atherosclerosis have been demonstrated in many landmark studies [49, 51, 52, 54, 60]. Regarding specific features

of endothelial dysfunction, several reports demonstrate that SPMs reduce EC activation, inflammation and oxidative stress. For example, RvE1 downregulated the local expression of pro-atherogenic genes involved in cell adhesion such as Cd74, Cd44, Ccl2 or Ccr5 in the aorta and significantly inactivated IFN-γ and TNF-α signalling pathways in ApoE*3Leiden mice fed a hypercholesterolaemic diet [72]. In fat-fed Ldlr$^{-/-}$ mice, administration of RvD1 during plaque progression promotes plaque stability, reduces lesional oxidative stress and necrosis, improves lesional efferocytosis and thickens fibrous caps [55]. Aspirin-triggered LXA4 blocked atherosclerosis progression in the aortic root and thoracic aorta of ApoE$^{-/-}$ mice, reduced macrophage infiltration and apoptotic cells in atherosclerotic lesions and decreased the mRNA levels of several cytokines and chemokines (CCL2 and CXCL16) in the spleen and aorta [73]. In addition, diabetes-induced aortic plaque development and aortic tissue inflammation, including VCAM-1, MCP-1, IL-6 and IL-1β expression, were significantly attenuated by both LXA4 and a synthetic LX analogue, Benzo-LXA4 [74]. On the other hand, RvD2 and MaR 1 treatment does not significantly affect endothelial ICAM-1 and VCAM-1 expression in ApoE$^{-/-}$ mice fed a high-fat diet for 4 months [75]. These findings suggest that SPMs might be protective in the early stages of atherosclerosis by improving endothelial function. Furthermore, an additional contribution of the immune cell modulation induced by SPMs cannot be excluded. Indeed, a protective role of several SPMs receptors specifically expressed in macrophages has been demonstrated in atherosclerosis [57, 76–78]. Most likely, the protective effects of SPMs in vivo involve multiple cell types, which also represent very exciting pharmacological perspectives to reprogramme the immune response with additional protective vascular effects.

3.3 | SPMs and Endothelial Dysfunction in Abdominal Aortic Aneurysm

Atherosclerosis and abdominal aortic aneurysm (AAA) share several risk factors and aetiopathogenic mechanisms [79]. However, although endothelial dysfunction is a critical feature of atherosclerotic disease, its contribution to AAA has been somewhat underestimated and insufficiently investigated. In patients with AAA, endothelial function, measured as endothelium-dependent flow-mediated vasodilation, is negatively correlated with aneurysm diameter, whereas it is improved after surgical repair [80, 81], suggesting a close relationship between endothelial dysfunction and AAA. Indeed, major risk factors for the development of AAA, such as smoking, ageing or hypertension, are closely associated with endothelial dysfunction, and therefore, many features of endothelial dysfunction are also found in AAA. For example, decreased NO bioavailability has received increasing attention as a critical player in the development of AAA, and the association between AAA, impaired NO bioavailability, oxidative stress and endothelial NADPH oxidases and inflammation has been extensively explored, postulating new therapeutic strategies for AAA [79, 82, 83]. With regard to SPMs, a protective role of the ALX/FPR2 receptor pathway has been proposed in the progression of AAA [56]. Moreover, several studies have shown that treatment with RvD2, RvD1 or MaR1 protects against AAA in various animal models, in particular by reducing inflammation and oxidative stress and modulating the phenotype of macrophages towards a proresolving one [84–88]. Unfortunately, endothelial (dys)function was not assessed in these studies. In this context, we have recently reported that in a model of aortic dilation induced by high-fat diet plus hypertension by Ang II infusion, RvD2 not only prevented the impaired endothelium-dependent relaxation and the altered contractility of aortic segments but also improved endothelial function in small mesenteric arteries, and these effects were associated with reduced expression of some proinflammatory markers [59]. These results suggest that the beneficial effects of SPM in AAA might be due not only to effects on inflammation and VSMC, but also on endothelial function. Future studies are needed to further investigate the potential of resolution of inflammation in endothelial dysfunction in this devastating disease.

4 | Targeting Inflammation in Endothelial Dysfunction and Cardiovascular Disease in Humans

As discussed above, inflammation is a major contributor to endothelial dysfunction in hypertension. Drugs used to treat hypertension are also associated with a reduced inflammatory response in the vasculature [89]. However, patients who achieve adequate blood pressure control still have an increased risk of cardiovascular events compared with their untreated counterparts with similar levels of blood pressure [90]. A possible explanation for this residual risk is that the inflammatory response is undertreated in these hypertensive patients. Anti-inflammatory or immunomodulatory approaches are not currently considered therapeutic options for reducing blood pressure and associated cardiovascular disease. However, targeting inflammation could lead to a reduction in cardiovascular events in hypertensive patients, probably by improving vascular function. Several studies have shown that statins have beneficial effects on endothelial function, possibly attributed to their antioxidant and anti-inflammatory properties rather than their lipid-lowering effects [91, 92]. In addition, clinical trials such as CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) or LoDoCo2 (Low Dose Colchicine-2) have shown that antiinflammatory therapies such as canakinumab, a monoclonal antibody targeting IL-1β, or colchicine, a broad anti-inflammatory drug, reduce cardiovascular events [93, 94]. Of note, inflammation assessed by high-sensitivity CRP was a stronger predictor for risk of future cardiovascular events and death than cholesterol assessed by LDL-C [95]. These data suggest that inflammation-inhibiting therapies may be needed to further reduce cardiovascular mortality. However, some of these therapies can induce immunosuppression, and they should preserve tissue repair but also maintain the immune physiological response.

Over the past decades, numerous studies have investigated the role of ω-3 PUFA in CVD. Cardiovascular outcome trials on ω-3 fatty acids have generated contradictory results likely due to the heterogeneity of the study population, the proportion of the two ω-3 PUFA, EPA and DHA, and the formulation of the ω-3 PUFA used, as well as the relatively low dose used in most trials (up to approximately 1 g ω-3 PUFA) [62]. Several clinical trials such as JELIS (Japan EPA Lipid Intervention), REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl Intervention Trial) or EVAPORATE (Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy) have shown that treatment of patients with either EPA or

the purified ethyl ester of EPA resulted in reduced clinical cardiac events and significant plaque regression [96–98]. The underlying mechanisms appear to include more than just triglycerides lowering such as modulation of endothelial function, attenuation of intraplaque inflammation and oxidative stress, and reduction of macrophage accumulation that can result in plaque stabilization [62, 99]. As mentioned, EPA is the precursor of E-series resolvins, which have antiinflammatory and vasoprotective effects in a number of CVDs such as atherosclerosis, AAA, obesity, hypertension and heart failure. Whether the beneficial effects of ω-3 fatty acids may be partially due to SPMs is still under investigation.

5 | Conclusions

Since the seminal observations of Robert Furchgott on the importance of the endothelium for vasodilator responses and the many findings demonstrating the presence of endothelial dysfunction in various CVD [1], efforts have focused on elucidating the underlying mechanisms responsible for EC damage. Proinflammatory cytokines such as ILs, IFNs or TNF-α, produced by circulating or locally infiltrated immune cells, are elevated in hypertension and other CVD and reduce NO availability through multiple processes including excessive oxidative stress, eNOS uncoupling, production of vasoconstrictor prostanoids or activation of EC that attract and retain leucocytes that further perpetuate endothelial damage. Antihypertensive and lipid-lowering drugs improve endothelial function, which may be due, at least in part, to their pleiotropic anti-inflammatory effects. However, many patients remain at residual cardiovascular risk despite effective pharmacological treatment. Strong evidence demonstrate that some anti-inflammatory drugs can provide further reduction in cardiovascular events, but they should also preserve the physiological immune response. In this sense, recent studies with specific formulations of ω-3 PUFA have shown beneficial effects on cardiovascular outcomes, probably through effects on vascular and immune cells. SPMs are a family of lipid mediators derived from of ω-6 and ω-3 PUFA, that protect EC and VSMC and reprogram immune cells to exert beneficial effects in vascular function in hypertension and other CVD such as atherosclerosis and AAA. As we learn more about the biology of SPMs, the interest of these compounds as therapeutic strategies to preserve endothelial function and treat cardiovascular disease is an area of active research.

Acknowledgements

Work from the author's laboratory was supported by grants SAF2016-80305P and PID2020-116498RB-I00, funded by Agencia Estatal de Investigación (MCIN/AEI/10.13039/501100011033) and by 'ERDF A way of making Europe'; Comunidad de Madrid (B2017/BMD-3676 AORTASANA) FEDER-a way to build Europe; Fundación Española de Arteriosclerosis (Beca FEA 2021 Investigación Básica en Arteriosclerosis); CiberCV Instituto de Salud Carlos III (CiberCV CB16/11/00286, CiberCV CB16/11/00257, CiberCV CB16/11/00333 and CiberCV CB/11/00222); the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement no. 954798; and Instituto de Salud Carlos III (AC23_2/00044) under the umbrella of the Partnership Fostering a European Research Area for Health (ERA4Health) (GA N° 101095426 of the EU Horizon Europe Research and Innovation Programme).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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