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THE ROLE OF ENDOTHELIAL DYSFUNCTION IN THE DEVELOPMENT OF ARTERIAL HYPERTENSION

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Abstract
Arterial hypertension remains a leading cause of global cardiovascular morbidity and mortality, with its pathogenesis involving complex multifactorial mechanisms. The vascular endothelium, once regarded as a simple anatomical barrier, is now recognized as a dynamic endocrine organ that critically regulates vascular homeostasis. Endothelial dysfunction represents a pivotal early event in the development and progression of arterial hypertension, characterized by impaired endothelium-dependent vasodilation, reduced nitric oxide bioavailability, and a shift towards a proinflammatory and prothrombotic phenotype. This review examines the molecular mechanisms linking endothelial dysfunction to hypertension, including oxidative stress, uncoupling of endothelial nitric oxide synthase, imbalance between vasodilators and vasoconstrictors, and inflammatory pathway activation. We discuss current evidence from clinical and experimental studies demonstrating that endothelial dysfunction not only precedes the clinical manifestation of hypertension but also contributes to target organ damage. Furthermore, we evaluate diagnostic approaches for assessing endothelial function and explore therapeutic strategies targeting the endothelium. Understanding the complex bidirectional relationship between endothelial dysfunction and hypertension is essential for developing personalized prevention and treatment strategies.

Keywords: Endothelial dysfunction, arterial hypertension, nitric oxide, oxidative stress, endothelin-1, vascular inflammation, flow-mediated dilation, cardiovascular risk.

Introduction

Systemic arterial hypertension (SAH) constitutes one of the most prevalent cardiovascular disorders worldwide, affecting approximately one-third of the adult population and representing a major risk factor for myocardial infarction, stroke, chronic kidney disease, and heart failure [Giles et al., 2012, p. 2]. The pathophysiology of hypertension is remarkably complex and multifactorial, involving genetic predisposition, environmental factors, neurohormonal activation, renal dysfunction, and vascular abnormalities. Among these mechanisms, the role of the vascular endothelium has emerged as a central theme in understanding both the initiation and progression of hypertensive disease [Brandes, 2012, p. 4]. The endothelium, composed of a monolayer of endothelial cells lining the

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interior surface of all blood vessels, was historically considered merely a passive barrier separating blood from vascular smooth muscle. However, groundbreaking discoveries since the 1980s have revealed that the endothelium is a highly metabolically active organ that exerts profound regulatory functions over vascular tone, platelet aggregation, leukocyte adhesion, and smooth muscle cell proliferation [Konukoglu & Uzun, 2017, p. 512]. These diverse functions are mediated through the release of numerous vasoactive substances, including the vasodilator nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF), as well as vasoconstrictors such as endothelin-1 (ET-1) and angiotensin II [Giles et al., 2012, p. 3]. Endothelial dysfunction (ED) refers to a phenotypic alteration of endothelial cells characterized by reduced vasodilator capacity, particularly diminished NO bioavailability, accompanied by a proinflammatory and prothrombotic state [Wang & He, 2024, p. 2]. This dysfunctional state represents one of the earliest detectable abnormalities in the vasculature and precedes the development of clinically apparent atherosclerotic lesions by many years. Importantly, accumulating evidence indicates that endothelial dysfunction is not merely a consequence of elevated blood pressure but actively contributes to the pathogenesis of hypertension through multiple mechanisms [Brandes, 2012, p. 5]. The relationship between endothelial dysfunction and arterial hypertension is bidirectional and self-perpetuating. On one hand, impaired endothelium-dependent vasodilation increases peripheral vascular resistance, a hallmark of established hypertension. On the other hand, the hemodynamic forces associated with elevated blood pressure—particularly increased shear stress and pulsatile flow—can directly damage endothelial cells, further compromising their function and creating a vicious cycle [Konukoglu & Uzun, 2017, p. 520]. This intricate interplay has important clinical implications, suggesting that therapeutic strategies aimed at restoring endothelial function may offer benefits beyond blood pressure reduction alone.

Recent advances in molecular biology and vascular medicine have substantially enhanced our understanding of the mechanisms underlying endothelial dysfunction in hypertension. Oxidative stress, characterized by excessive production of reactive oxygen species (ROS) and reduced antioxidant capacity, appears to play a central role by scavenging NO and uncoupling endothelial NO synthase (eNOS) [Wang & He, 2024, p. 5]. Additionally, inflammation, endothelial cell senescence, and alterations in the endothelial glycocalyx contribute to the complex pathophysiology. The identification of circulating biomarkers of endothelial dysfunction, including asymmetric dimethylarginine (ADMA), soluble adhesion molecules, and endothelial microparticles, has provided new tools for risk stratification and monitoring of therapeutic interventions [Meena et al., 2025, p. 512]. This review aims to comprehensively examine the role of endothelial dysfunction in the development of arterial hypertension, with particular focus on molecular mechanisms, diagnostic approaches, and therapeutic implications. We synthesize current evidence from experimental models, clinical studies, and population-based investigations to provide a integrated perspective on this critical relationship.

LITERATURE REVIEW

Historical Perspective and Conceptual Evolution - The recognition of the endothelium as an active participant in cardiovascular regulation represents one of the most significant paradigm shifts in modern vascular biology. Prior to the 1980s, the endothelium was regarded as a inert lining with primarily barrier functions. The seminal work by Furchgott and Zawadzki in 1980, demonstrating

that acetylcholine-induced vasodilation required the presence of intact endothelial cells, fundamentally altered this view and led to the discovery of endothelium-derived relaxing factor, subsequently identified as nitric oxide [Brandes, 2012, p. 4]. This discovery earned the Nobel Prize in Physiology or Medicine in 1998 and opened an entirely new field of investigation.

The concept of endothelial dysfunction emerged from observations that various cardiovascular risk factors, including hypertension, diabetes, and hypercholesterolemia, were associated with impaired endothelium-dependent vasodilation. The Framingham Heart Study provided some of the first population-based evidence linking blood pressure to endothelial function, demonstrating an inverse correlation between systolic blood pressure and flow-mediated dilation (FMD) of the brachial artery [Brandes, 2012, p. 6]. While cross-sectional in nature, these findings established that endothelial dysfunction and hypertension are intimately connected, though the direction of causality remained uncertain.

Subsequent longitudinal studies have clarified that endothelial dysfunction often precedes the development of hypertension in normotensive individuals. Offspring of hypertensive parents, who are at increased genetic risk for developing hypertension, exhibit impaired endothelium-dependent vasodilation even when their blood pressure is normal, suggesting that endothelial dysfunction represents an early, possibly inherited, abnormality in the pathogenesis of hypertension [Konukoglu & Uzun, 2017, p. 515].

Endothelial Physiology and Vasoactive Mediators

The healthy endothelium maintains vascular homeostasis through the balanced release of vasodilator and vasoconstrictor substances. Understanding these physiological mechanisms is essential for appreciating how their disruption leads to hypertension.

Nitric Oxide: The Central Vasoprotective Molecule Nitric oxide is synthesized from L-arginine by endothelial nitric oxide synthase (eNOS) in the presence of oxygen and the cofactor tetrahydrobiopterin (BH4). Under physiological conditions, laminar shear stress is the primary stimulus for continuous NO production, which diffuses to underlying vascular smooth muscle cells and activates soluble guanylyl cyclase, increasing cyclic guanosine monophosphate (cGMP) and inducing relaxation [Giles et al., 2012, p. 4]. Beyond vasodilation, NO inhibits platelet aggregation, suppresses leukocyte adhesion molecule expression, and prevents smooth muscle cell proliferation—all critical atheroprotective functions.

The importance of NO in blood pressure regulation is dramatically illustrated by studies of eNOS-deficient mice, which develop hypertension and exhibit exaggerated vascular responses to vasoconstrictors. In humans, intra-arterial infusion of eNOS inhibitors such as NG-monomethyl-L-arginine (L-NMMA) causes significant increases in peripheral vascular resistance and blood pressure, confirming the tonic vasodilator influence of basal NO production [Konukoglu & Uzun, 2017, p. 518].

Endothelin-1: The Principal Vasoconstrictor

Endothelin-1 (ET-1), a 21-amino acid peptide, represents the most potent endogenous vasoconstrictor yet identified. Produced by endothelial cells in response to various stimuli including angiotensin II, vasopressin, and shear stress, ET-1 acts on two receptor subtypes: ETA receptors on vascular smooth

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muscle cells mediate vasoconstriction and proliferation, while ETB receptors on endothelial cells promote NO and prostacyclin release, providing a counter-regulatory vasodilator influence [Brandes, 2012, p. 8].

Circulating ET-1 levels are elevated in patients with hypertension, and the degree of elevation correlates with blood pressure severity. Moreover, hypertensive patients exhibit enhanced vasoconstrictor responses to ET-1 and reduced vasodilator responses to ETB receptor stimulation, indicating a shift in the balance between vasoconstrictor and vasodilator ET-1 pathways [Meena et al., 2025, p. 514].

Endothelium-Derived Hyperpolarizing Factor and Prostacyclin While NO dominates in conduit arteries, endothelium-derived hyperpolarizing factor (EDHF) plays a particularly important role in resistance vessels that determine peripheral vascular resistance. EDHF is not a single molecule but rather a family of factors including epoxyeicosatrienoic acids, hydrogen peroxide, and C-natriuretic peptide that act by opening potassium channels on smooth muscle cells, causing membrane hyperpolarization and relaxation [Giles et al., 2012, p. 5]. Prostacyclin (PGI2), produced by cyclooxygenase, synergizes with NO by increasing cyclic adenosine monophosphate (cAMP) in smooth muscle cells and inhibiting platelet aggregation.

Molecular Mechanisms of Endothelial Dysfunction in Hypertension

Oxidative Stress and eNOS Uncoupling - Oxidative stress represents the final common pathway through which diverse cardiovascular risk factors induce endothelial dysfunction. Reactive oxygen species (ROS), particularly superoxide anion ($O2^{\bullet-}$), are produced in the vasculature by several enzyme systems including NADPH oxidases (NOX), xanthine oxidase, and mitochondrial electron transport chain enzymes [Wang & He, 2024, p. 6].

In hypertension, multiple factors converge to increase ROS production. Angiotensin II, via AT1 receptor activation, potently stimulates NOX enzymes, particularly NOX1 and NOX2, in endothelial cells and vascular smooth muscle. The resulting superoxide rapidly scavenges NO in a diffusion-limited reaction, forming peroxynitrite ($ONOO^-$), a highly reactive oxidant that causes cellular damage and further impairs vascular function. Peroxynitrite oxidizes BH4, the essential eNOS cofactor, leading to eNOS uncoupling—a state in which the enzyme produces superoxide rather than NO, creating a self-amplifying cycle of oxidative stress [Brandes, 2012, p. 7].

Evidence supporting the role of oxidative stress in hypertensive endothelial dysfunction includes observations that antioxidant interventions improve endothelium-dependent vasodilation in experimental models and that genetic polymorphisms in antioxidant enzymes influence hypertension risk. However, clinical trials of antioxidant vitamins have yielded disappointing results, likely reflecting the complexity of vascular redox systems and the inability of nonspecific antioxidants to target critical pathways [Konukoglu & Uzun, 2017, p. 525].

Inflammation and Endothelial Activation

Chronic low-grade inflammation characterizes hypertension and both contributes to and results from endothelial dysfunction. Inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are elevated in hypertensive patients and directly impair endothelial function by

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activating kinases that phosphorylate eNOS at inhibitory sites and by increasing oxidative stress [Wang & He, 2024, p. 8]. Dysfunctional endothelial cells upregulate adhesion molecules including vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), promoting leukocyte adhesion and transmigration into the vascular wall. Infiltrating immune cells, particularly monocytes and T lymphocytes, release additional inflammatory mediators and ROS, further amplifying vascular damage. This inflammatory cascade contributes not only to impaired vasodilation but also to vascular remodeling and stiffness that characterize chronic hypertension [Meena et al., 2025, p. 513].

Endothelial Glycocalyx Disruption

The endothelial glycocalyx, a carbohydrate-rich layer covering the luminal surface of endothelial cells, has emerged as a critical determinant of vascular health. Composed of proteoglycans, glycosaminoglycans, and glycoproteins, the glycocalyx serves as a mechanosensor for shear stress, regulates vascular permeability, and shields adhesion molecules from circulating leukocytes [Brandes, 2012, p. 9]. Hypertension is associated with glycocalyx degradation, likely due to oxidative stress and enzymatic cleavage by matrix metalloproteinases and heparanase. Disruption of the glycocalyx impairs mechanotransduction, reducing shear stress-induced NO production, and exposes adhesion molecules, promoting leukocyte-endothelial interactions. Shed glycocalyx components, including syndecan-1 and hyaluronan, can be detected in the circulation and may serve as biomarkers of endothelial injury [Konukoglu & Uzun, 2017, p. 522].

Clinical Assessment of Endothelial Function

Flow-Mediated Dilation Flow-mediated dilation (FMD) of the brachial artery, measured by high-resolution ultrasound, represents the most widely used noninvasive technique for assessing endothelial function. Following temporary forearm ischemia, reactive hyperemia increases shear stress, stimulating NO release and consequent arterial dilation. FMD correlates with coronary endothelial function and predicts cardiovascular events independently of traditional risk factors [Brandes, 2012, p. 10].

In hypertensive patients, FMD is consistently impaired, and the degree of impairment correlates with blood pressure level, duration of hypertension, and presence of target organ damage. Importantly, FMD improves with successful antihypertensive therapy, particularly with agents that target the renin-angiotensin system, suggesting that serial FMD measurements may be useful for monitoring treatment efficacy [Meena et al., 2025, p. 515].

Circulating Biomarkers Numerous circulating molecules reflect endothelial status and may serve as accessible biomarkers. Asymmetric dimethylarginine (ADMA), an endogenous eNOS inhibitor, is elevated in hypertension and predicts adverse cardiovascular outcomes. ET-1 levels correlate with hypertension severity and pulmonary hypertension. Soluble adhesion molecules (VCAM-1, ICAM-1, E-selectin) indicate endothelial activation, while endothelial microparticles—small vesicles released from activated or apoptotic endothelial cells—provide a measure of endothelial injury [Wang & He, 2024, p. 9].

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Recent studies have identified endocan (endothelial cell-specific molecule-1) as a promising marker of endothelial dysfunction in hypertension. Endocan reflects glycocalyx disruption and inflammatory activation, and circulating levels are elevated in hypertensive patients compared to normotensive controls, with positive correlations with blood pressure [Meena et al., 2025, p. 514].

DISCUSSION

The Bidirectional Relationship: Cause or Consequence? A central question in understanding the role of endothelial dysfunction in hypertension is whether endothelial dysfunction causes hypertension or merely represents a consequence of elevated blood pressure. The available evidence supports both directions, suggesting a complex bidirectional relationship that likely varies among individuals and over the course of disease.

Several lines of evidence indicate that endothelial dysfunction can precede and contribute to the development of hypertension. First, as noted previously, normotensive offspring of hypertensive parents exhibit impaired endothelium-dependent vasodilation before any elevation in blood pressure, suggesting that endothelial dysfunction represents an inherited phenotype that increases susceptibility to hypertension [Konukoglu & Uzun, 2017, p. 515]. Second, experimental induction of endothelial dysfunction in animals—for example, by eNOS inhibition or genetic eNOS deletion—consistently produces hypertension. Third, longitudinal studies in humans have demonstrated that impaired FMD predicts incident hypertension over follow-up periods of several years, independent of baseline blood pressure and other risk factors.

Conversely, there is equally compelling evidence that hypertension causes or exacerbates endothelial dysfunction. Acute elevations in blood pressure in experimental settings impair endothelium-dependent vasodilation, likely through increased oxidative stress and mechanical endothelial injury. Chronically, the hemodynamic forces associated with hypertension—increased pulsatile stress, altered shear patterns, and elevated wall tension—promote vascular remodeling, inflammation, and oxidative stress that further compromise endothelial function [Brandes, 2012, p. 11]. This bidirectional interaction creates a self-perpetuating cycle: endothelial dysfunction increases peripheral resistance and blood pressure, and the resulting hypertension causes further endothelial damage, propagating disease progression.

The clinical implication of this bidirectional relationship is that effective hypertension management must interrupt this vicious cycle at multiple points. Blood pressure reduction alone, while essential, may not fully restore endothelial function if underlying mechanisms such as oxidative stress and inflammation persist. Conversely, interventions that directly improve endothelial health might lower blood pressure and enhance the benefits of antihypertensive therapy.

Therapeutic Implications: Targeting the Endothelium

Antihypertensive Drugs with Endothelial Effects

Different antihypertensive classes vary considerably in their effects on endothelial function, independent of their blood pressure-lowering efficacy. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have demonstrated particularly favorable effects on the endothelium. By reducing angiotensin II-mediated oxidative stress and inflammation, these agents improve NO bioavailability and enhance endothelium-dependent vasodilation [Wang & He,

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2024, p. 11]. Experimental studies show that ACE inhibitors prevent eNOS uncoupling by reducing oxidative degradation of BH4 and may directly activate eNOS through bradykinin-mediated pathways.

Calcium channel blockers also improve endothelial function, primarily through antioxidant effects and by reducing endothelial intracellular calcium overload. In contrast, beta-blockers have variable effects, with newer vasodilating beta-blockers (nebivolol, carvedilol) showing endothelial benefits through antioxidant properties and, in the case of nebivolol, through direct stimulation of endothelial NO release [Konukoglu & Uzun, 2017, p. 528].

Diuretics have minimal direct endothelial effects, though blood pressure reduction itself may indirectly improve endothelial function by reducing hemodynamic stress. Thiazide diuretics may even have adverse metabolic effects that could counteract any endothelial benefit.

Emerging Therapeutic Approaches Beyond traditional antihypertensive agents, several novel therapeutic strategies specifically targeting endothelial dysfunction are under investigation. Antioxidant approaches that go beyond nonspecific vitamins—including BH4 supplementation, NADPH oxidase inhibitors, and activators of antioxidant enzymes—have shown promise in experimental studies. BH4 supplementation improves endothelial function in some clinical studies, though effects on blood pressure have been inconsistent [Brandes, 2012, p. 12].

Endothelin receptor antagonists, already approved for pulmonary arterial hypertension, have been evaluated in essential hypertension. While effective in lowering blood pressure, their use has been limited by side effects including fluid retention and hepatotoxicity. Selective ETA receptor antagonists may offer advantages by preserving ETB-mediated vasodilator and clearance functions [Meena et al., 2025, p. 516].

Xanthine oxidase inhibitors, such as allopurinol, reduce vascular oxidative stress and improve endothelial function in hyperuricemic patients. Recent evidence suggests that the endothelial benefit derives primarily from reduced ROS production rather than uric acid lowering per se, and studies are evaluating whether these agents have a role in hypertension management independent of uric acid levels [Maruhashi & Higashi, 2024, p. 3312].

Non-Pharmacological Interventions Lifestyle modifications that improve cardiovascular health also enhance endothelial function. Aerobic exercise training consistently improves FMD in both healthy individuals and patients with hypertension, through mechanisms including increased eNOS expression, reduced oxidative stress, and enhanced shear stress-mediated NO release. The magnitude of improvement is comparable to that achieved with some pharmacological interventions [Wang & He, 2024, p. 12].

Dietary interventions, particularly those rich in polyphenols and nitrates, show endothelial benefits. The Mediterranean diet, characterized by high consumption of fruits, vegetables, olive oil, and nuts, improves endothelial function and reduces blood pressure. Beetroot juice, rich in inorganic nitrate that can be converted to NO via the nitrate-nitrite-NO pathway, acutely lowers blood pressure and improves endothelial function [Konukoglu & Uzun, 2017, p. 530]. Weight loss in obese individuals markedly improves endothelial function, with benefits proportional to the degree of weight reduction.

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Bariatric surgery produces dramatic improvements in both endothelial function and blood pressure, highlighting the importance of metabolic factors in vascular health

Sex Differences and Personalized Approaches

Emerging evidence indicates important sex differences in endothelial function and its relationship to hypertension. Premenopausal women exhibit better endothelial function than age-matched men, likely due to estrogen-mediated enhancement of eNOS activity and antioxidant effects. However, this advantage is lost after menopause, and the incidence of hypertension in women eventually exceeds that in men [Kopaliani & Deussen, 2024, p. 3]. These sex differences have therapeutic implications. Women may respond differently to antihypertensive agents that target endothelial pathways, and optimal management may require sex-specific approaches. ACE inhibitors and ARBs appear particularly effective in improving endothelial function in postmenopausal women, possibly by counteracting the adverse effects of angiotensin II in the context of estrogen deficiency [Kopaliani & Deussen, 2024, p. 5].

RESULTS

Evidence from Clinical Studies - Clinical investigations consistently demonstrate that endothelial dysfunction is both a marker and mediator of hypertensive vascular disease. A cross-sectional study by Meena and colleagues involving 40 hypertensive patients classified according to hypertension severity revealed significant associations between endothelial biomarkers and blood pressure levels [Meena et al., 2025, p. 514]. Nitric oxide levels showed a progressive decline across hypertension stages, with mean values of 30.8 ± 6.2 μmol/L in pre-hypertension, 24.6 ± 4.9 μmol/L in Stage 1 hypertension, and 18.2 ± 5.1 μmol/L in Stage 2 hypertension ($p < 0.001$). Conversely, ADMA levels increased with hypertension severity, from 0.54 ± 0.09 μmol/L in pre-hypertension to 0.86 ± 0.12 μmol/L in Stage 2 hypertension ($p < 0.001$). VCAM-1 concentrations similarly rose with increasing blood pressure, reaching 1124 ± 230 ng/mL in Stage 2 hypertension ($p = 0.002$).

Correlation analysis demonstrated a strong inverse relationship between NO levels and systolic blood pressure ($r = -0.52$, $p < 0.001$), while ET-1 showed positive correlation with both systolic and diastolic pressure. Multivariate regression identified NO ($\beta = -0.42$, $p < 0.001$) and ET-1 ($\beta = 0.39$, $p = 0.002$) as independent predictors of hypertension severity, suggesting that these biomarkers contribute to blood pressure elevation beyond traditional risk factors [Meena et al., 2025, p. 515]. Predictive modeling using machine learning approaches demonstrated that endothelial biomarkers significantly improved hypertension severity classification beyond clinical parameters alone. Random Forest models achieved an area under the curve (AUC) of 0.85, while Support Vector Machine models attained an AUC of 0.83, indicating excellent discriminatory capacity [Meena et al., 2025, p. 516].

Evidence from Interventional Studies

The therapeutic relevance of endothelial dysfunction is supported by studies demonstrating that interventions improving endothelial function also reduce cardiovascular events. A retrospective cohort study by Huang and colleagues followed 456 patients with essential hypertension initially free from subclinical target organ damage (STOD) for a median of 25 months [Huang et al., 2024, p. 2]. Patients with baseline endothelial dysfunction (FMD ≤ 7.1%) had significantly higher incidence of

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STOD compared to those with normal endothelial function. Importantly, patients whose endothelial function improved within three months of enrollment—termed early endothelial function improvement (EEFI)—had lower cumulative STOD incidence compared to those without improvement, regardless of baseline endothelial status ($p < 0.05$).

Multivariable Cox regression confirmed EEFI as an independent protective factor against STOD (hazard ratio approximately 0.6, $p < 0.05$), with particularly pronounced benefits in patients under 65 years, nonsmokers, and those with LDL cholesterol ≤ 3.4 mmol/L. These findings provide direct evidence that improving endothelial function translates into reduced target organ damage, supporting endothelial function as a therapeutic target [Huang et al., 2024, p. 4].

Biomarker Profiles and Clinical Correlations

The identification of reliable biomarkers has enhanced our ability to detect and monitor endothelial dysfunction. Endocan, a proteoglycan specifically secreted by endothelial cells, has emerged as a particularly promising marker. A systematic review and meta-analysis by Behnoush and colleagues demonstrated significantly higher circulating endocan levels in hypertensive patients compared to normotensive controls, with levels correlating positively with blood pressure [Maruhashi & Higashi, 2024, p. 3313]. Xanthine oxidoreductase (XOR) activity has also been linked to endothelial dysfunction independent of uric acid levels. Kurajoh and colleagues demonstrated that plasma XOR activity, but not serum uric acid, was significantly associated with FMD after adjustment for confounders, suggesting that XOR inhibitors may improve endothelial function primarily through reduced ROS production rather than uric acid lowering [Maruhashi & Higashi, 2024, p. 3312].

Genetic and Molecular Insights Genetic studies have provided additional evidence linking endothelial pathways to hypertension. Primary aldosteronism due to aldosterone-producing adenomas (APA) provides a model of severe hypertension with defined genetic etiology. Kishimoto and colleagues demonstrated that patients with APA and KCNJ5 mutations exhibited significantly impaired FMD and nitroglycerin-induced vasodilation at baseline, comparable to APA patients without the mutation [Maruhashi & Higashi, 2024, p. 3313]. However, following adrenalectomy, only patients with KCNJ5 mutations showed significant improvement in FMD, with reductions in plasma aldosterone correlating with improved endothelial function. These findings suggest that specific genetic subtypes of hypertension may have differential effects on the endothelium and that genetic information could guide treatment expectations.

CONCLUSION

The vascular endothelium plays a fundamental role in maintaining cardiovascular homeostasis, and its dysfunction represents a critical pathogenic mechanism in the development and progression of arterial hypertension. The evidence reviewed here establishes that endothelial dysfunction is not merely an epiphenomenon of elevated blood pressure but actively contributes to hypertensive disease through multiple interconnected mechanisms. Reduced nitric oxide bioavailability, resulting from oxidative stress, eNOS uncoupling, and accumulation of endogenous inhibitors such as ADMA, impairs endothelium-dependent vasodilation and increases peripheral vascular resistance. Concurrently, enhanced production of vasoconstrictors, particularly endothelin-1, and activation of

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proinflammatory pathways create a vascular phenotype characterized by vasoconstriction, remodeling, and end-organ vulnerability. The endothelial glycocalyx, increasingly recognized as a critical component of vascular health, is disrupted in hypertension, contributing to impaired mechanotransduction and enhanced leukocyte adhesion. The bidirectional relationship between endothelial dysfunction and hypertension—each promoting the other—creates a self-perpetuating cycle that drives disease progression and complicates treatment. This interdependence has important clinical implications, suggesting that optimal management must address both blood pressure elevation and the underlying endothelial pathology. Assessment of endothelial function, whether by noninvasive physiological techniques such as flow-mediated dilation or by measurement of circulating biomarkers including ADMA, ET-1, and endocan, provides valuable information for risk stratification and may guide treatment decisions. The demonstration that early improvement in endothelial function reduces subsequent target organ damage supports the concept of endothelial function as both a therapeutic target and a surrogate endpoint in hypertension management. Current therapeutic approaches with demonstrated endothelial benefits include ACE inhibitors and ARBs, which reduce angiotensin II-mediated oxidative stress and inflammation; calcium channel blockers with antioxidant properties; and lifestyle interventions including exercise, weight loss, and dietary modification. Emerging strategies targeting specific pathways—such as BH4 supplementation, NADPH oxidase inhibition, and endothelin receptor antagonism—hold promise but require further clinical validation. Sex differences in endothelial function and its response to therapy highlight the need for personalized approaches that consider individual patient characteristics, including genetic factors, hormonal status, and coexisting conditions. The integration of endothelial biomarkers with clinical parameters and advanced predictive modeling offers the potential for more precise risk stratification and targeted intervention.

Future research directions should include longitudinal studies to establish the temporal relationship between endothelial dysfunction and hypertension onset in diverse populations; investigation of sex-specific mechanisms and therapeutic responses; development of reliable, cost-effective methods for endothelial function assessment suitable for routine clinical use; and clinical trials to determine whether endothelial function-guided therapy improves cardiovascular outcomes beyond blood pressure control alone.

In conclusion, endothelial dysfunction occupies a central position in the pathogenesis of arterial hypertension, representing both an early pathogenic event and a potential therapeutic target. Recognition of the endothelium as an active participant in hypertensive disease rather than a passive bystander has fundamentally altered our understanding of hypertension and opened new avenues for prevention and treatment. As our understanding of endothelial biology continues to advance, the prospect of endothelial-targeted therapies for hypertension and its complications moves closer to clinical reality.

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