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Review Article

Innovative Pharmacological Strategies Targeting Endothelial Dysfunction and Vascular Remodeling in Hypertension Management: A Narrative Review

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Abstract

Background: Hypertension is a worldwide health issue and an independent risk factor for cardiovascular disease. Endothelial dysfunction is an important mechanism for its pathogenesis, thus compromising vascular homeostasis and causing vascular remodeling. It is supported by reduced availability of nitric oxide, increased oxidative stress, and chronic inflammation, all of which contribute to hypertension as well as cardiovascular morbidity.

Objectives: The present narrative review is focused on exploring new pharmacological interventions to target endothelial dysfunction and vascular remodeling in the treatment of hypertension. The review brings molecular mechanisms to the forefront. It discusses new therapeutic drugs to target the reversal of endothelial function and improve vascular health, ultimately resulting in better control of hypertension.

Methodology: A narrative review of the literature was performed, including studies from preclinical studies, clinical trials, and new pharmacological advances. The review is focused on modulation of the nitric oxide pathway, anti-oxidant therapy, angiotensin receptor blockers, and new therapies for oxidative stress. New endothelial progenitor cell function therapies, hydrogen sulfide (H_2S) donors, and nanoparticle-based drug delivery systems were discussed.

Results: Recent evidence clearly shows that pharmacologic therapy for reversing endothelial dysfunction is effective for treating hypertension. H_2S donors reduce oxidative stress and increase vascular relaxation, and endothelial progenitor cells are explored for vascular repair. Nanoparticles enable targeted delivery of drugs into endothelial cells, with increased therapeutic impact. Further, nitric oxide generation modulating drugs, such as angiotensin receptor blockers, have been reported to improve vascular function and control hypertension.

Conclusion: Pharmacotherapy for endothelial dysfunction is extremely promising in improving hypertension management by targeting the very pathogenesis of the disease. Further research and clinical trials are required to improve these therapies further and establish their long-term clinical benefits.

Keywords

Antioxidants, endothelial progenitor cells, hydrogen sulfide donors, hypertension, nitric oxide, targeted drug delivery

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Introduction

Hypertension or high blood pressure is a significant global health issue, and over a billion people are affected worldwide. Hypertension is a decisive risk factor for most of the cardiovascular diseases (CVDs) like stroke, coronary heart disease, heart failure, and kidney disease.[1] Hypertension is one of the significant causes of global disease burden, as estimated by the World Health Organization (WHO), with a mortality of approximately 9.4 million annually. Hypertension burden is rising in the world, particularly in low- and middle-income countries, due to urbanization, unhealthy diet, physical inactivity, and rising stress.[2] Hypertension is a silent disease, but if untreated, it is a significant cause of public health

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problems. Chronic hypertension causes a cascade of pathological changes in the cardiovascular system, including arterial stiffening, vascular damage, and the development of atherosclerosis. These changes lead to increased workload of the heart, ultimately causing heart failure, stroke, and kidney disease.[3]

Endothelial dysfunction is the most important reason for the development of hypertension. Endothelium, a thin layer of cells coating blood vessels, is most importantly implicated in the mechanism of vascular homeostasis. Under physiological conditions, the endothelium secretes vasoactive factors such as nitric oxide (NO) that modulate the dilation of the blood vessels, sustain blood flow, and inhibit clotting.[4] On the contrary, in hypertensive patients, endothelial dysfunction impairs NO generation, causing decreased NO bioavailability, enhanced reactive oxygen species (ROS), and increased oxidative stress. This, in turn, causes vasoconstriction, vascular remodeling, and augmentation of a pro-thrombotic state, which enhances the development of hypertension.[5]

The molecular pathophysiology of endothelial dysfunction involves loss of NO, overproduction of ROS, and activation of inflammatory cascades. These synergistically decrease endothelial cell function and vascular injury, further exacerbating hypertension and cardiovascular risk.[6] Thus, therapeutic interventions for endothelial dysfunction have been of most interest since they can potentially treat the underlying causes of hypertension and enhance vascular function.[7]

Currently available pharmacologic agents for the treatment of hypertension, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers, and diuretics, are targeted at lowering blood pressure and are effective in managing hypertension.[8] None of these treatments, however, normalizes endothelial function or reverses chronic hypertension-induced vascular damage. This limitation has provoked interest in investigating the potential for using novel pharmacologic approaches to improve endothelial function, lower oxidative stress, and inhibit vascular remodeling.[9]

Recent advances have focused on new therapies that directly address endothelial dysfunction in hypertensive patients. Such therapies seek to restore NO bioavailability, inhibit oxidative stress, and promote endothelial repair. For example, hydrogen sulfide (H_2S) donors have been shown to enhance vasodilation, promote NO synthase expression, and reduce ROS levels.[10] Similarly, endothelial progenitor cells (EPCs) are being researched for their capacity to regenerate injured endothelial cells, thereby improving vascular integrity. Antioxidants are also being explored as a potential therapeutic intervention in scavenging ROS and endothelial cell protection against injury.[11] Although such therapies are still in the infancy of clinical scrutiny, preliminary preclinical and clinical evidence suggests they are hopeful candidates to augment endothelial function and vascular health in hypertensive patients.[12]

One such approach is a combination therapy with traditional anti-hypertensive drugs and endothelial-targeted therapy. This will address both the blood pressure and the pathological endothelial dysfunction.[13] Combination of ACE inhibitors or ARBs with EPC-targeted therapy, H_2S donors, or antioxidants might have the potential to improve endothelial function, reduce oxidative stress, and improve vascular health, with an outcome of better blood pressure control and reduced cardiovascular complications.[14]

The rationale for targeting endothelial dysfunction in treating hypertension is that it contributes to vascular remodeling and the development of CVD. Endothelial dysfunction increases vascular resistance, arterial stiffness, and atherosclerotic plaque formation. Restoration of endothelial function is a therapeutic target for new treatments to improve vascular function, inhibit further vascular damage, and reduce the long-term cardiovascular morbidity of hypertension.[15]

Several problems must be solved to establish endothelial-targeted therapies, such as effective vascular drug delivery systems, long-term efficacy and safety, and avoiding drug resistance and side effects. There would have to be preclinical and clinical trials to determine the best way to integrate the new therapies with existing protocols for treating hypertension.[16]

Personalized medicine is the future of the treatment of hypertension, where the treatment is tailored to the patient according to their genetic makeup, pathophysiology of the disease, and response to therapy. Identifying biomarkers, genetic profiling, and clinical trials will be the primary drivers in designing endothelial-targeted therapy and optimal patient outcomes.[17] A combination of conventional anti-hypertensive treatment and endothelial-targeted treatment will provide an integrated approach in the treatment of hypertension and its complications. With continued research, combination therapies can reduce blood pressure, enhance endothelial function, ultimately enhance patients' quality of life, and reduce the global burden of CVD.[18]

Review of Literature

Endothelial dysfunction and vascular remodeling are the core of hypertension, and new pharmacological strategies are necessary. Schiffrin[19] enumerated oxidative stress, inflammation, and extracellular matrix (ECM) remodeling as the significant causes of vascular remodeling. Gallo et al.[20] emphasized the clinical significance of endothelial dysfunction and new therapies. Baeyens[21] wrote about fluid shear stress participation in vascular remodeling. Thompson and Lawrie[22] wrote about molecular targets in pulmonary arterial hypertension. Spaczyńska et al.[23] wrote about new therapies for vascular remodeling, and Lemarié et al.[24] wrote about ECM participation. These articles emphasize the need for new endothelial-targeted therapies in hypertension, as shown in Table 1.

Table 1. Literature Review—Previous Work.[19–24]

Authors (Year)	Key Finding	Research Focus	Challenges/Limitations	Future Scope
Schiffrin (2012)	Vascular remodeling is driven by oxidative stress and inflammation.	Mechanisms of vascular remodeling in hypertension	Limited therapeutic options for reversing vascular remodeling	Development of drugs targeting oxidative stress and inflammation
Gallo et al. (2022)	Endothelial dysfunction is a significant factor in hypertension progression.	Clinical implications of endothelial dysfunction	Lack of endothelial-targeted treatments for hypertension	Exploration of novel pharmacological interventions restoring endothelial function
Baeyens (2018)	Fluid shear stress influences vascular homeostasis and remodeling.	Pharmacological targeting of mechanical forces in vasculature	Limited clinical translation of shear stress-modulating therapies	Developing therapies that modify endothelial responses to mechanical stress
Thompson and Lawrie (2017)	Targeting vascular remodeling improves outcomes in pulmonary hypertension.	Therapeutic strategies for pulmonary arterial hypertension	Complexity of remodeling mechanisms in different vascular beds	Precision medicine approaches for individualized hypertension treatment
Spaczyńska et al. (2020)	Emerging therapies show promise in reversing vascular changes in pulmonary arterial hypertension (PAH).	Pharmacological treatments for pulmonary arterial hypertension	High cost and accessibility of new treatments	Expanding research into cost-effective and widely available therapies
Lemarié et al. (2010)	Extracellular matrix (ECM) changes contribute to vascular remodeling.	Structural alterations in hypertensive blood vessels	Insufficient understanding of ECM-targeted interventions	Identification of ECM-modulating therapies for vascular protection

Note: Summary table of main findings, research emphasis, issues, and areas of future research on endothelial dysfunction and vascular remodeling in hypertension.

Methodology

Data Locating

A narrative search was conducted using the following academic databases: PubMed, Scopus, Google Scholar, and Web of Science. The search was focused on endothelial dysfunction, vascular remodeling, and hypertension treatment studies. Keywords such as "endothelial dysfunction," "vascular remodeling," "hypertension therapies," and MeSH terms were used to select articles. Peer-reviewed high-quality articles published in peer-reviewed journals were chosen for review.

Data Collection

Articles published between 2010 and 2024 were considered. Journal articles with high impact on pharmacological intervention, endothelial dysfunction mechanisms, and new therapeutic approaches to hypertension were preferred. Review articles, meta-analyses, and clinical trials were selected to provide an overall overview of recent research and advances in this field.

Data Extraction

Key information was derived from the chosen studies, such as study objectives, study types, primary findings, and limitations of the studies. The focus was on molecular mechanisms, drug agents, and the clinical significance of anti-hypertensive treatment, especially in treating endothelial dysfunction. The data abstracted from the chosen studies were presented to emphasize treatment approaches, molecular pathways, and their potential to maximize endothelial well-being in hypertensive individuals.

Data Synthesis

The evidence abstracted was synthesized to provide a rational account that identifies emerging trends, gaps in research, and probable avenues of endothelial-targeted therapies in hypertension. The evidence was critically analyzed to provide an evidence-based and balanced framework. Additional caution was exercised in synthesizing preclinical and clinical research evidence to provide a comprehensive overview of the state of the art in the field.

Results

Endothelial Dysfunction's Role in the Development of Hypertension

Endothelial dysfunction is an important mechanism of pathogenesis of hypertension and is responsible for vascular homeostasis disruption, vasoconstriction, arterial stiffness,

and vascular inflammation. Deficiency in NO, a potent vasodilator secreted by endothelial cells, is a primary cause of endothelial dysfunction.[25] Under normal physiological conditions, NO regulates vascular tone, prevents platelet aggregation, and reduces oxidative stress, ensuring vascular health and function. In hypertensive individuals, endothelial dysfunction of endothelial nitric oxide synthase (eNOS) and excessive overproduction of ROS significantly decrease NO bioavailability. The disequilibrium between NO deficiency and ROS overproduction facilitates augmented vasoconstriction, increases vascular resistance, and results in the development of chronic hypertension.[26]

Besides NO deficiency, chronic inflammation and oxidative stress are the prime drivers of endothelial dysfunction. Activation of ROS generation by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, mitochondrial dysfunction and angiotensin II signaling further reduces NO bioavailability and increases endothelial damage.[27] Inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukins (IL-6, IL-1β), and C-reactive protein (CRP) increase endothelial activation, leading to leukocyte adhesion and vascular remodeling activation. These actions increase vascular permeability, induce smooth muscle proliferation, and lead to arterial wall structural changes responsible for hypertension's progressive and irreversible nature.[28]

Endothelial dysfunction is an early biomarker of hypertensive complications such as atherosclerosis, left ventricular hypertrophy, and renal dysfunction. Recognition of molecular markers of endothelial dysfunction enables one to diagnose early and facilitate targeted pharmacologic intervention, reversing endothelial dysfunction.[29] These treatments have the potential to slow disease progression and decrease cardiovascular complication risk, as emphasized in Table 2.

Mechanisms and Consequences of Vascular Remodeling During Hypertension

Vascular remodeling is a hallmark of hypertension, which is caused by changes in blood vessel function and structure. It enhances arterial resistance and organ injury.[30] The central mechanism is remodeling of the ECM, where collagen, fibronectin, and proteoglycans are laid down in excess, making the arteries stiff and causing loss of vascular elasticity and dysfunctional blood vessels.[31] Hypertrophy and hyperplasia of vascular smooth muscle cell (VSMC) also cause thickening of the vessel wall and reduction in lumen size, enhancing vascular resistance and worsening the hypertension. This results in decreased control of blood flow, leading to ischemic damage in the target organs. The renin–angiotensin–aldosterone system (RAAS) is a critical mechanism of vascular remodeling.[32] Angiotensin II induces vasoconstriction, oxidative stress, and inflammation, inducing proliferation of VSMC and ECM deposition. Aldosterone induces vascular fibrosis and endothelial dysfunction. Inflammatory cytokines TNF-α, IL-6, and TGF-β further induce ECM remodeling and vascular inflammation, worsening the condition.[33] Clinical features of vascular remodeling are arterial stiffness, enhanced cardiac afterload, and organ damage, leading to stroke, myocardial infarction, and heart failure. It is important to understand these

Table 2. Role of Endothelial Dysfunction in Hypertension Progression.[25–29]

Authors (Years)	Mechanism	Consequence	Biomarker	Clinical Implication	Future Direction
Konukoglu and Uzun (2017)	Nitric oxide (NO) deficiency, oxidative stress	Increased vascular resistance, endothelial apoptosis	Reduced NO levels, increased oxidative stress markers	Early detection and intervention for endothelial dysfunction	Novel therapies to enhance NO bioavailability
Brandes (2014)	Increased reactive oxygen species (ROS), inflammation	Impaired vasodilation, vascular stiffness	Elevated ROS, inflammatory cytokines (IL-6, TNF-α)	Targeted antioxidant therapy to reduce oxidative stress	Combination therapy using antioxidants and anti-hypertensives
Perticone et al. (2001)	Endothelial dysfunction leading to hypertension progression	Increased cardiovascular risk, impaired endothelial repair	Endothelial-dependent vasodilation tests	Risk stratification for hypertensive patients based on endothelial function	Personalized medicine for hypertensive patients
Higashi et al. (2012)	Aging-related endothelial dysfunction, RAAS activation	Increased arterial stiffness, reduced vascular elasticity	Increased endothelin-1, decreased eNOS activity	Addressing age-related hypertension with endothelial-targeted therapy	AI-based predictive models for vascular aging
Gupta et al. (2011)	Chronic inflammation and endothelial dysfunction	Progressive vascular damage, atherosclerosis	High C-reactive protein (CRP) and adhesion molecules.	Anti-inflammatory strategies for managing early hypertension	Developing immunomodulatory therapies for vascular protection

Notes: This table summarizes key mechanisms of endothelial dysfunction in hypertension progression, highlighting biomarkers, clinical implications, and future directions for therapeutic development. AI, artificial intelligence; eNOS, endothelial nitric oxide synthase; IL-6, interleukin-6; RAAS, renin–angiotensin–aldosterone system; TNF-α, tumor necrosis factor-alpha.

molecular mechanisms to develop targeted therapies to remodel the ECM, block the RAAS, and use anti-inflammatory interventions to prevent vascular damage due to hypertension and improve patient outcomes,[34] as shown in Table 3.

Pharmacological Treatments Targeting Endothelial Dysfunction

Endothelial dysfunction is a significant cause of hypertension and a primary drug target. Current anti-hypertensive medications, such as ACE inhibitors, ARBs, CCBs, and beta-blockers, primarily reduce blood pressure but also confer some protection to the endothelium.[35] ACE inhibitors and ARBs reduce oxidative stress and inflammation and enhance NO bioavailability and endothelial function. CCBs block vasoconstriction, while beta-blockers reduce sympathetic tone and endothelial stress. These treatments do not, however, fully reverse endothelial dysfunction, suggesting the need for more targeted therapies.[36]

New therapies target endothelial protection and restoration directly. H_2S donors are of interest due to their potential to enhance NO signaling, reduce oxidative stress, and induce vasodilation.[37] EPCs are also of interest for research due to their potential to restore endothelial function. Antioxidants like resveratrol and *N*-acetylcysteine target ROS to prevent endothelial damage and maintain vascular homeostasis.[38]

Nanoparticle drug delivery systems offer a step ahead in endothelial-targeted therapy with enhanced drug bioavailability and fewer side effects. Nanoencapsulation of anti-inflammatory agents, NO donors, and RAAS blockers has been noted to have enhanced therapeutic efficacy in preclinical models.[39] These advances promise individualized, endothelial-targeted therapies ranging from traditional and new pharmacologic interventions, as outlined in Table 4.

Comparison of Standard and New Therapies in Hypertension

Traditional anti-hypertensive medications such as ACE inhibitors, ARBs, and CCBs easily reduce blood pressure but do not enhance endothelial function and vascular remodeling, the pathophysiologic substrates of hypertension. Although they reduce vascular stress and endothelial protection, they do not enhance endothelial function or reverse the chronic hypertension-induced damage.[40]

On the other hand, newer therapies such as H_2S donors and EPCs restore endothelial damage and reverse vasculature remodeling. H_2S donors enhance NO signaling, reduce oxidative stress, and cause vasodilation, offering a more direct route to vascular restitution of function. EPCs cause endothelial regeneration to heal and restore damaged blood vessels.[41] New treatments are only just emerging, but have massive potential for vasculature restoration in the long term. Nanotech drug delivery systems enhance such therapies further with targeted delivery to endothelial cells, increased bioavailability, and decreased side effects. While such emerging technologies have the potential to be dazzling, clinical trials need to be conducted to assess their safety and efficacy.[42]

Advancements in Reversing Vascular Remodeling

Hypertensive vascular remodeling is the etiology of arterial stiffness, raised vascular resistance, and chronic organ damage, which must be reversed by specific pharmacologic therapy in order to enhance vascular elasticity.[43] The conventional anti-hypertensive drugs, such as ACE inhibitors, ARBs, and CCBs, are partially effective in reversing vascular remodeling by decreasing VSMC growth and ECM deposition. These therapies

Table 3. Mechanisms and Impacts of Vascular Remodeling in Hypertension.[30–34]

Authors (Years)	Mechanism	Effect	Clinical Impact	Therapeutic Strategy	Future Direction
Renna et al. (2013)	Endothelial dysfunction, oxidative stress	Increased arterial stiffness, reduced vascular elasticity	Increased risk of cardiovascular events	Antioxidants, NO donors to reduce oxidative damage	Development of personalized endothelial-targeted therapies
Zeng and Yang (2024)	Activation of RAAS, inflammation	Vascular smooth muscle hypertrophy, ECM deposition	Hypertension-induced organ damage	RAAS inhibitors, anti-inflammatory agents	AI-driven predictive modeling for vascular remodeling
Song et al. (2022)	Exercise-induced vascular adaptation	Improved vascular compliance, reduced hypertrophy	Lower blood pressure reduces arterial stiffness	Exercise as an adjunct therapy to pharmacological treatment	Integrating exercise-based interventions in hypertension guidelines
Risler et al. (2005)	Fibrosis, collagen deposition in arteries	Reduced vascular flexibility, increased peripheral resistance	Accelerated progression of resistant hypertension	Fibrosis-targeting drugs, ECM-modifying agents	Exploring epigenetic regulation of vascular remodeling
Humphrey (2008)	Shear stress and intramural tension	Endothelial injury, vascular remodeling	Sustained arterial hypertension, increased cardiac workload	Mechanical unloading strategies, vasodilators	Biomechanical modeling for precision treatment

Notes: This table outlines the mechanisms of vascular remodeling in hypertension, highlighting key clinical impacts, therapeutic strategies, and future directions in hypertension management. AI, artificial intelligence; ECM: extracellular matrix; NO, nitric oxide; RAAS, renin–angiotensin–aldosterone system.

Table 4. Pharmacological Interventions Targeting Endothelial Dysfunction.[35–39]

Authors (Years)	Therapeutic Approach	Mechanism of Action	Effect on Endothelial Dysfunction	Clinical Implication	Future Direction
Balakumar et al. (2008)	Antioxidants and nitric oxide (NO) donors	Enhances NO) bioavailability, reduces oxidative stress	Improves vasodilation, reduces endothelial damage	Potential adjunct therapy for resistant hypertension	Development of targeted NO-releasing drugs
Sudano et al. (2006)	Nutritional and pharmacological interventions	Modulates inflammation, protects endothelial cells	Reduces oxidative stress and endothelial dysfunction	Lifestyle interventions combined with pharmacotherapy	Personalized nutrition-based pharmacology
Deshpande et al. (2011)	Anti-inflammatory agents	Inhibits endothelial activation and immune-mediated damage	Decreases cytokine-induced endothelial dysfunction	Prevents cardiovascular events linked to endothelial inflammation	Development of selective endothelial anti-inflammatory drugs
Kuldo et al. (2005)	Molecular targeting strategies	Targeting endothelial activation pathways (NF-κB, adhesion molecules)	Blocks the endothelial inflammatory response, prevents vascular remodeling.	Potential for chronic hypertension and atherosclerosis management	Precision-based endothelial-targeted therapies
Matsuzawa et al. (2015)	Coronary disease treatment	Improves endothelial repair mechanisms and vascular elasticity	Reduces cardiovascular risk and arterial stiffness	Endothelial function as a biomarker for treatment response	AI-guided endothelial-targeted drug development

Notes: This table summarizes pharmacological approaches targeting endothelial dysfunction, emphasizing their mechanisms, clinical implications, and future directions for improving cardiovascular health and hypertension management. AI, artificial intelligence; NF-κB, nuclear factor kappa B.

are ineffective in reversing endothelial integrity and vascular elasticity, warranting more specific pharmacologic therapies.[44]

New combination treatments will provide synergistic advantages by pairing blood pressure management with endothelial repair. NO-based therapy with H_2S donors enhances vascular compliance and reverses arterial fibrosis.[45] EPC therapy with angiogenic and vascular repair capabilities also holds promise. Nanoparticle-based delivery systems also increase bioavailability and targeted delivery of anti-inflammatory and anti-fibrotic drugs to remodeled vessels.[46]

Recent clinical trials have demonstrated regression of vascular remodeling by RAAS blockers, NO donors, and H_2S-releasing agents to improve arterial compliance, endothelial function, and vascular stiffness.[47] Recent research targets preventing and reversing hypertension-induced vascular remodeling by pathways like oxidative stress, inflammation, and ECM turnover. Future therapy will most likely include pharmacologic and regenerative medicine approaches for long-term vascular health in hypertensive patients.[48]

Challenges and Future Directions in Hypertension Pharmacology

Although there has been extensive progress in the treatment of hypertension, various hurdles continue to restrict the development of effective endothelial-targeted therapies. Vascular accessibility is a significant hurdle, in that most drug delivery systems currently used face difficulties reaching endothelial cells extremely efficiently, thus limiting their therapeutic potential.[49] Drug resistance is another hurdle, especially with long-term anti-hypertensive treatment, as patients become progressively less responsive. In addition, the long-term safety and efficacy of new treatments such as H_2S donors, EPCs, and nanotechnology-based treatments necessitate aggressive clinical trials to establish their capability to reverse endothelial dysfunction without causing unwanted effects.[50]

Precision pharmacology and personalized medicine are the future of pharmacology in hypertension. This model is centered on personalized therapies based on biomarkers, genetic markers, and endothelial function tests. Specific molecular targets like oxidative stress markers, NO bioavailability, and vascular stiffness should be the highest priority for early detection and monitoring of treatment effects so that the best drug can be chosen and side effects minimized.[51]

Additionally, artificial intelligence (AI) and machine learning (ML) can potentially revolutionize hypertension treatment by predicting drug response and identifying high-risk patients. Future studies must explore AI-driven methods to personalize therapy based on real-time patient data, optimize drug repurposing, target identification, and clinical trial design.[52] Combining new therapy with new drugs such as EPCs or H_2S donors and traditional pharmacotherapies will most likely have additive effects that would restore endothelial function and clinical features of hypertension. Overall, overcoming these obstacles will allow the design of more efficient, long-term, targeted hypertension therapies to restore vascular function and optimize patient outcomes.[53]

Discussion

Hypertension is a worldwide public health issue, with millions of individuals being affected, and is one of the most

significant causes of the cardiovascular burden of disease worldwide. Traditional anti-hypertensive treatment, such as ACE inhibitors, ARBs, CCBs, beta-blockers, and diuretics, has been effective in reducing blood pressure and treating hypertension.[54] These medications, however, are primarily focused on symptomatic control of hypertension and not treatment of the pathophysiologic processes of vascular dysfunction and remodeling that are responsible for the development of hypertension. Considering this in mind, although these medications lower blood pressure, they cannot reverse the structural and functional vascular adaptations responsible for cardiovascular morbidity in the long term.[55]

Two of the most pivotal processes engaged in the pathogenesis of hypertension vascular remodeling and endothelial dysfunction are the bedrock of the disease pathogenesis. Endothelial dysfunction is triggered by the disruption of the balance between vasoconstrictive and vasodilatory substances across blood vessels, mainly disrupting vascular homeostasis. One of the most pivotal aspects of endothelial dysfunction is impaired availability of NO, an essential molecule to regulate vascular tone, suppress platelet aggregation, and preserve vascular integrity.[56] eNOS malfunction and excessive overproduction of ROS in hypertensive individuals significantly disrupt NO availability. This imbalance sustains increased vasoconstriction, increased vascular resistance, and the establishment of chronic hypertension.[57] Moreover, oxidative stress and inflammation, promoted by mediators angiotensin II (Ang II), TNF-α, IL-6, and CRP, amplify endothelial damage, increase leukocyte adhesion, increase vascular permeability, and amplify VSMC growth. These effects collectively result in vascular remodeling, characterized by ECM deposition, vascular smooth muscle hypertrophy, and fibrosis, further impairing endothelial function, inducing arterial stiffening, and facilitating hypertension development.[58]

Conventional anti-hypertensive drugs, while effective in reducing blood pressure, do not reverse significantly the endothelial dysfunction and vascular remodeling that are involved in the pathogenesis of hypertension. ACE inhibitors and ARBs act through the modulation of the RAAS, reduce oxidative stress and inflammation, and increase NO bioavailability.[59] While such treatment confers some protective benefits to the endothelium, it does not reverse endothelial integrity and vascular elasticity to a significant extent. Similarly, CCBs and beta-blockers reduce vasoconstriction and sympathetic tone, thereby conferring partial protection to the endothelium. However, none of these drugs can reverse structural vascular damage due to chronic hypertension. This limitation has generated interest in new therapies that directly target endothelial dysfunction and vascular remodeling, which aim to reduce blood pressure, reverse endothelial function, and avert late cardiovascular complications.[60]

Among the promising paths to reverse endothelial dysfunction is the application of H_2S donors, which have been documented to enhance NO signaling, decrease oxidative stress, and induce vasodilation. H_2S donors such as sodium hydrosulfide (NaHS) and GYY4137 have been documented to increase eNOS expression, enhance mitochondrial function, and suppress pro-inflammatory cytokines, all of which are involved in vascular repair and enhanced endothelial function.[61] EPC therapy is another promising method for correcting endothelial integrity. EPC transplantation or stimulation of endogenous EPC mobilization has been found to induce angiogenesis, repair endothelial cell damage, and prevent endothelial dysfunction. EPCs thus provide a regenerative solution for vascular health by addressing endothelial repair and vascular regeneration at the source.[62]

In addition to these treatments, antioxidant-based treatments have also been studied as a mechanism of targeting ROS that cause endothelial damage and vascular remodeling. Antioxidants resveratrol, *N*-acetylcysteine, and vitamin C restored NO bioavailability and maintained endothelial function by removing ROS and decreasing oxidative stress. These medications shield the endothelium from damage after injury and thus maintain vascular homeostasis.[63]

Another development in endothelial-targeted therapy is drug delivery systems using nanoparticles. Drug delivery systems using nanoparticles enable targeted delivery of drugs to endothelial cells, which increases drug bioavailability and reduces systemic side effects. Nanoparticles with NO donors, RAAS inhibitors, or anti-inflammatory drugs have shown enhanced efficacy in preclinical models and support personalized endothelial-targeted therapy.[64] The drug delivery systems are a novel approach to endothelial dysfunction and vascular remodeling therapy, providing more effective and targeted regimens. Vascular remodeling is also a beneficial target for treating hypertension, irrespective of endothelial dysfunction. Vascular remodeling is characterized by the structural changes of the vasculature, including arterial stiffness, ECM deposition, and smooth muscle hypertrophy, which result in reduced vascular compliance and increased peripheral resistance.[65]

Although RAAS inhibitors and NO-based treatments have achieved limited success in reversing vascular remodeling, more potent treatments are necessary. Combination treatment with H_2S donors, EPC therapy, and nanotechnology-based treatment has excellent potential for synergistically enhancing vascular elasticity, reducing arterial fibrosis, and inhibiting smooth muscle proliferation.[66] Although potential exists for these novel therapies, various hurdles must be overcome in treating hypertension with endothelium-targeting therapies. Vascular accessibility is one such hurdle because drug delivery systems per se cannot effectively target endothelial cells, thus being ineffective. Furthermore, the blood–brain barrier, vascular permeability, and drug metabolism play a role in the efficacy and biodistribution of these therapies.[67]

Furthermore, the long-term efficacy and safety of novel pharmacologic agents such as H_2S donors, EPCs, and nanotechnology-based therapies are to be determined. Large-scale clinical trials are needed to determine their long-term impact and endorse them in treating chronic hypertension.

Furthermore, drug resistance and compensatory mechanisms are to be overcome because prolonged treatment with some of these therapies results in reduced efficacy.[68]

The future pharmacology of anti-hypertension is precision medicine, where therapies are individualized to the patient through biomarkers, genetic testing, and endothelial function testing. This will enable patient-specific pharmacologic therapy to be designed, maximizing drug selection and dosing and reducing side effects. ML and AI are also poised to transform the treatment of hypertension by predicting drug response, discovering new endothelial targets, and streamlining clinical trial designs. AI can also marry large patient databases, hemodynamic variables, and molecular markers to individualize hypertension therapy and maximize the efficacy of endothelially targeted therapy.

In brief, while conventional anti-hypertensive drugs remain the cornerstone in the management of hypertension, new pharmacological strategies for the reversal of vascular remodeling and endothelial dysfunction are promising to reverse vascular function and avert long-term cardiovascular morbidity. A combination of H_2S donor therapy, EPC therapy, antioxidants, and nanotechnology-based drug delivery systems is a new area of endothelial regeneration and vascular rehabilitation. Drug delivery, long-term efficacy, and clinical validation hurdles are in the way of these therapies becoming a reality. Combination therapies, AI-based pharmacology, and precision medicine strategies will be the solutions to close the gap between endothelial dysfunction and ideal hypertension control and ultimately to improve patient outcomes and reduce the global burden of CVD.

Conclusion

Hypertension is a global health problem, and it contributes significantly to the CVD burden. Traditional anti-hypertensive medications like ACE inhibitors, ARBs, CCBs, and beta-blockers effectively lower blood pressure but are ineffective on the underlying endothelial dysfunction and vascular remodeling. New therapies targeting these mechanisms, like H_2S donors, EPCs, and nanoparticle-based drug delivery systems, can potentially reverse vascular injury and promote vascular wellness.

However, initial results suggest that the therapies may restore endothelial function, and long-term clinical trials are required to determine if they are safe and effective. Drug resistance, vascular accessibility, and side effects must be overcome before the therapies can be used routinely in the clinic.

The future is with precision medicine, in which biomarkers and AI are used to deliver patient-specific therapy based on individual patient profiles. Integrating new therapy with established anti-hypertensives will likely deliver optimal therapy for disease management and cardiovascular complication prevention. With continued research, newer modalities can revolutionize the treatment of hypertension and promote long-term cardiovascular health globally.

Key Takeaways

Endothelial dysfunction is the most important determinant of hypertension and is the cause of elevated arterial resistance and vascular stiffness. Traditional anti-hypertensive agents reduce blood pressure without fully reversing vascular remodeling and endothelial dysfunction. New therapeutic strategies like H_2S donors, EPCs, and site-specific antioxidants hold promise in restoring vascular homeostasis. Nanoparticle-based drug delivery systems improve the efficacy of endothelial-targeted therapy, and AI and biomarker-guided treatments render hypertension treatment personalized. Drug resistance, vascular accessibility, and confirmation of long-term efficacy are the significant challenges for the transformation of hypertension drug treatment.

Abbreviations

ACE: Angiotensin-converting enzyme; **AI:** Artificial intelligence; **ARBs:** Angiotensin receptor blockers; **CCBs:** Calcium channel blockers; **CRP:** C-reactive protein; **CVDs:** Cardiovascular diseases; **ECM:** Extracellular matrix; **eNOS:** Endothelial nitric oxide synthase; **EPCs:** Endothelial Progenitor Cells; **H_2S:** Hydrogen sulfide; **IL-1β:** Interleukin-1 beta; **IL-6:** Interleukin-6; **ML:** Machine learning; **NaHS:** sodium hydrosulfide; **NF-κB:** Nuclear factor kappa B; **NO:** nitric oxide; **RAAS:** Renin–angiotensin–aldosterone system; **ROS:** Reactive oxygen species; **TGF-β:** Transforming growth factor beta; **TNF-α:** Tumor necrosis factor-alpha; **VSMC:** Vascular smooth muscle cell; **WHO:** World Health Organization.

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Ethical Approval

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