Short Review

Vascular Disease as a Consequence of Impaired Endothelial Redox Adaptation

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Abstract

Endothelial dysfunction plays a central role in cardiovascular and cerebrovascular disease, but its portrayal as a simple imbalance associated with oxidative stress and nitric oxide (NO) deficiency has somewhat hindered therapeutic progress over the years. Accumulating evidence supports a conceptual shift towards endothelial redox plasticity, the capacity of vascular endothelium to dynamically regulate NO synthase activity and reactive oxygen species (ROS) production during various physio-pathological processes, including growth, repair, and ageing. Experimental, genetic, and clinical data exhibit that ROS are required for physiological adaptation, and that pathology emerges from a regulatory imbalance rather than oxidative stress alone. Mechanistic studies have further exhibited that redox-sensitive signalling networks tightly coordinate endothelial survival, mitochondrial function, and inflammatory activation, reinforcing the concept that oxidative signalling is integral to vascular homeostasis rather than merely deleterious. Distinct vessel-specific redox profiles, microenvironmental factors, progenitor cell dysfunction, and cellular senescence further determine vascular resilience. Hence, restoration of redox adaptability offers a sound foundation for precision vascular therapies.

Introduction

Endothelial dysfunction, characterised by impaired endothelium-dependent vascular relaxation, remains a central concept in the pathogenesis, progression, and exacerbation of cardiovascular and cerebrovascular disease [1,2]. However, its underlying mechanistic framework has changed remarkably little over the past few decades. Oxidative stress, stemming from an imbalance between pro-oxidant and antioxidant bioavailability and the consequent reduction in nitric oxide (NO) levels, has long been regarded as a principal driver of endothelial dysfunction [1]. Inevitably, this oversimplified view of endothelial dysfunction has contributed to the translational failures observed with antioxidant therapies over the years [3]. We propose that a more accurate interpretation, supported by experimental, genetic, and clinical evidence, is that vascular disease reflects a profound disruption of endothelial redox plasticity, defined as the capacity of endothelial cells to dynamically coordinate NO synthase (NOS) activity and reactive oxygen species (ROS) signalling in response to diverse physio-pathological processes such as growth, injury, and ageing.

Redox Regulation and Endothelial Growth

Early mechanistic studies revealed a close interplay between endothelial cell growth and redox regulation. In coronary endothelial cells, NOS and NAD(P)H oxidase appear to regulate proliferation and survival in a coordinated manner, rather than acting in opposition [4]. Subsequent studies demonstrated that the state of endothelial cell growth directly regulates the expression of a functionally critical NAD(P)H oxidase subunit, p22-phox, a membrane-bound subunit also required for enzymatic stability [5]. These findings refute the notion that ROS generation is inherently pathological and highlight the role of ROS as critical signalling mediators during endothelial adaptation and angiogenesis. These in turn suggest that the problem lies in the loss of regulatory balance, rather than in the bioavailability of ROS.

Experimental studies have further shown that endothelial redox signalling interacts with mitochondrial dynamics and apoptotic pathways, linking ROS generation to cell cycle progression and cell survival decisions [6,7]. Additional evidence demonstrates that ROS genetaed by NADPH oxidase modulate cardiomyocyte and endothelial growth responses in a context-dependent fashion, reinforcing the notion that tightly controlled oxidative signalling is critical for adaptive vascular remodelling [8].

However, in pathological conditions such as diabetes and hypertension, ROS signalling becomes poorly controlled, leading to endothelial NOS (eNOS) uncoupling. This process is accompanied by excessive production of superoxide anion (O_2^-), the foundation molecule of all ROS and reduced NO bioavailability [9].

Angiotensin II exemplifies the dual nature of redox signalling within the vascular endothelium. As the key effector peptide of the renin-angiotensin-aldosterone system (RAAS), angiotensin II plays a central role in the regulation of blood pressure, vascular tone, fluid

balance, and electrolyte homeostasis [10]. Beyond its well-documented classical haemodynamic actions, angiotensin II modulates intracellular and intercellular signalling pathways, particularly those mediated by ROS and NO. Through these interactions, it exerts context-dependent effects on endothelial cell function.

Notably, the influence of angiotensin II on NO generation changes according to the physiological state of the endothelium. In proliferating or remodelling endothelial cells, such as during angiogenesis or vascular repair, angiotensin II can induce a transient increase in ROS production. Under these conditions, ROS act as second messengers that activate redox-sensitive signalling cascades, supporting endothelial adaptation, cell migration, proliferation, and survival. In this adaptive setting, tightly regulated ROS production facilitates coordinated vascular growth and repair rather than eliciting injury.

Contrary to this, in quiescent or resting endothelial cells, sustained exposure to elevated levels of angiotensin II tilts the redox balance towards oxidative dominance. Chronic stimulation of NADPH oxidase leads to increased generation of O_2^- which rapidly reacts with NO to form another ROS called peroxynitrite and as a result reduces NO bioavailability and compromises vasodilatory, anti-proliferative, anti-aggregatory and anti-inflammatory functions. Moreover, peroxynitrite and related oxidative modifications promote eNOS uncoupling thereby inducing even more O_2^- production, exacerbating oxidative stress and establishing a self-perpetuating cycle in which ROS generation continues to rise at the expense of protective NO signalling [9,11,12].

Earlier human and experimental studies in hypertension similarly demonstrated that angiotensin II-driven oxidative stress impairs endothelium-dependent relaxation and enhances vascular superoxide production, thereby linking RAAS activation directly to functional endothelial decline [13,14].

Taken together, data from studies of angiotensin II illustrate that endothelial dysfunction does not result from ROS overproduction, but from an inability to effectively control redox balance in a context-dependent manner. Under physiological conditions, endothelial cells preserve NO-mediated vascular relaxation and equilibrium by meticulously regulating the balance between ROS and NO signalling and thus enabling short-lived oxidative signals to facilitate adaptive responses. However, when this regulatory flexibility is disrupted, such as during sustained activation of the RAAS activation in hypertension or metabolic disease, the redox balance cannot be appropriately adjusted. As a consequence, the endothelium becomes trapped in a persistent pro-oxidant state characterised by diminished NO bioavailability and elevated oxidative stress status. This loss of redox adaptability ultimately drives the progression from adaptive signalling to endothelial damage and vascular dysfunction.

Genetic Determinants of Basal Redox Tone

In this context, the findings of a previous genetic study were particularly important [15]. Rather than focusing on the consequences of acute activation of the pro-oxidant enzyme NADPH oxidase, this study investigated functional polymorphisms in the p22[phox] subunit encoded by the CYBA gene. The study showed strong associations between specific CYBA variants, vascular oxidative stress phenotypes, and cardiovascular risk. Allelic variants linked to enhanced enzymatic activity were associated with attenuated endothelium-dependent relaxation. This was in accordance with greater O_2^- generation and reduced NO bioavailability. These findings suggest that inherited differences in ROS-producing capacity can establish a basal vascular redox tone, predisposing certain individuals to oxidative imbalance and rendering them more susceptible to endothelial dysfunction even before environmental and haemodynamic stressors, such as hypertension, smoking or diabetes, are superimposed.

Genetic evidence further corroborates this adaptive redox framework. Namely, polymorphisms in the eNOS gene have been linked with ischaemic heart disease risk, signifying the importance of endogenous NO production in vascular health and protection [16]. Allelic variants that affect eNOS expression, enzymatic activity, and/ or susceptibility to uncoupling may diminish capacity to preserve NO signalling in settings associated with oxidative stress. Taken together with functional polymorphisms that induce excessive ROS production, a coherent picture emerges in that cardiovascular risk reflects the cumulative impact of genetically determined redox imbalance. In this model, predisposition to vascular disease is not triggered by a single defective mechanism, but by the combination of genetically determined reductions in NO bioavailability and elevations in oxidative status which significantly lower the threshold for vascular dysfunction in the presence of environmental and haemodynamic modifiers.

Gene–Environment Interactions in Vascular Disease

Genetic susceptibility becomes clinically relevant only when combined with adverse environmental influences. Ex vivo studies of human vessels have shown that endothelium-dependent relaxation in saphenous vein grafts and internal mammary arteries varies markedly according to sex, smoking status, hypertension, and diabetes [17]. Among these factors, smoking and hyperglycaemia enhance NADPH oxidase activity and promote eNOS uncoupling, whereas hypertension sustains angiotensin II–driven oxidative signalling. Through increased ROS generation, eNOS uncoupling, and persistent neurohormonal activation, these conditions directly impair endothelial integrity and function [2,18]. In individuals who are genetically predisposed, particularly those carrying high-activity variants of the CYBA gene or less effective alleles of the eNOS gene, such environmental stressors may overwhelm intrinsic redox-regulating mechanisms. The resulting imbalance can lock the vasculature into a maladaptive pro-oxidant state, thereby accelerating the progression toward ischaemic vascular disease.

Notably, vascular beds do not share the same structural and functional characteristics. For instance, vascular smooth muscle cells from internal mammary artery (IMA) exhibit greater intrinsic antioxidant capacity and reduced migratory capacity compared to their counterparts from other conduit vessels. These inevitably account, at least in part, for IMA's superior long-term graft patency [19]. This inherent resistance to oxidative stress and pathological remodelling may help explain why the IMA is considered as the best

conduit for coronary artery bypass grafting. These important findings imply that intrinsic, vessel-specific redox phenotypes, rather than systemic risk factors only, play a decisive role in determining vascular resilience to atherosclerotic disease. Susceptibility to oxidative injury and maladaptive remodelling is therefore, to a degree, intrinsically determined within the vascular wall itself. Therapeutic strategies that overlook this biological heterogeneity and treat the vasculature as a uniform system may be limited in their efficacy and fail to provide appropriate or long-lasting protection.

Endothelial Progenitor Cells and Impaired Vascular Repair

The concept of endothelial redox plasticity also extends to vascular repair mechanisms. Endothelial progenitor cells (EPCs) have emerged as potential biomarkers for the diagnosis and prognosis of ischaemic stroke [20]. EPCs are bone marrow-derived stem cells that play a crucial role in the maintenance of endothelial integrity and function by re-endothelialisation of blood vessels under both physiological conditions and pathological settings such as ischaemic injury [21,22]. Similar to embryonic angioblasts, EPCs possess an intrinsic capacity to circulate, proliferate and differentiate into mature endothelial cells Beyond vascular repair, EPCs can mitigate the detrimental consequences of ischaemic injury by inducing endothelial repair, angiogenesis and vasculogenesis, key physiological processes that are adversely affected by chronological ageing [21,22]. However, EPC dysfunction closely mirrors that of mature endothelial cells, characterised by perturbed NO signalling and increased oxidative stress. Recent work further indicates that oxidative imbalance disrupts EPC mobilisation, differentiation, and paracrine signalling capacity, thereby limiting their regenerative potential and compromising post-ischaemic vascular repair [23].

This parallel deterioration indicates that vascular disease involves not only damage to the endothelium but also a compromised capacity for endothelial regeneration. In this context, reduced NO bioavailability and excessive synthesis and release of ROS adversely influence both resident mature endothelial cells and their progenitors in systemic circulation. The impairment of vascular repair mechanisms reinforces the concept that atherosclerotic and ischaemic vascular disorders may derive from a general failure of redox adaptability rather than isolated or merely structural cellular damage.

Ageing, Senescence, and the Collapse of Redox Flexibility

Ageing represents the ultimate stress test for endothelial redox control. Endothelial cell senescence, characterised by the acquisition of senescence-associated secretory phenotype (SASP), chronic inflammatory and pro-oxidant states, and the breakdown of endothelial barrier integrity and function signals the end of flexible signalling [24]. Recent integrative analyses have highlighted that mitochondrial dysfunction, impaired autophagy, and persistent NADPH oxidase activation collectively drive senescence-associated redox imbalance in ageing vasculature, further supporting the concept that loss of redox plasticity is central to vascular ageing [25].

Recent evidence demonstrates that delaying endothelial senescence helps preserve the integrity of the cerebral vascular barrier and attenuates age-related dysfunction. Treatment with antioxidant vitamins, NADPH oxidase inhibitors and senotherapeutics, including both senolytics (that selectively eliminate senescent cells) and senomorphics (that suppress the SASP without killing the cells) have emerged as promising agents to mediate vascular ageing [26]. These findings propose a rethink of vascular therapeutics and pinpoint a prerequisite to prioritise strategies that can maintain or restore normal endothelial function throughout the lifespan as opposed to focusing on the downstream consequences of vascular disease.

Future Therapeutic Directions

Collectively, the evidence presented in this paper argues against reductionist approaches that target single ROS or isolated redox signalling molecules. This does not imply that oxidative stress is irrelevant despite repeated lack of success in large-scale antioxidant trials. Instead, it indicates that the indiscriminate suppression of ROS impairs physiological endothelial signalling processes. ROS function as seminal signalling molecules in the maintenance of overall vascular tone and homeostasis [1,12]. The assumption that they are merely damaging metabolic by-products is inaccurate. Therefore, broadly neutralising ROS can radically perturb endothelial function instead of restoring it [3].

Future therapeutic strategies should move beyond blanket antioxidant approaches and aim to re-establish redox balance in a more targeted manner. This ranges from preservation of eNOS coupling to maintain NO bioavailability, keeping NAD(P)H oxidase activity within physiological range to maintain necessary ROS signalling, regulating endothelial senescence process, rejuvenating endothelium to increasing both the number and functional capacity of EPCs.

Conclusion

In conclusion, endothelial dysfunction should be reframed as a pathology of redox adaptability. Genetic predisposition, environmental risk factors, cellular growth state, and ageing converge on a common failure to dynamically regulate NO and ROS signalling. Recognising endothelial redox plasticity as the defining feature of vascular health not only reconciles decades of experimental and clinical data, but also provides a rational framework for precision-based therapies in cardiovascular and cerebrovascular disease.

Declarations

Competing Interests

The authors declare that they have no competing interests.

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Author's Contributions

UB searched the literature and prepared the manuscript. FG edited the manuscript. Both authors read and approved the final manuscript.

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