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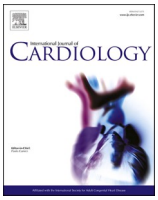

Review

Disturbed hemodynamics and oxidative stress interaction in endothelial dysfunction and AAA progression: Focus on Nrf2 pathway

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ABSTRACT

Hemodynamic shear stress is one of the major factors that are involved in the pathogenesis of many cardiovascular diseases including atherosclerosis and abdominal aortic aneurysm (AAA), through its modulatory effect on the endothelial cell's redox homeostasis and mechanosensitive gene expression. Among important mechanisms, oxidative stress, endoplasmic reticulum stress activation, and the subsequent endothelial dysfunction are attributed to disturbed blood flow and low shear stress in the vascular curvature and bifurcations which are considered atheroprone regions and aneurysm occurrence spots. Many pathways were shown to be involved in AAA progression. Of particular interest from recent findings is, the (Nrf2)/Keap-1 pathway, where Nrf2 is a transcription factor that has antioxidant properties and is strongly associated with several CVDs, yet, the exact mechanism by which Nrf2 alleviates CVDs still to be elucidated. Nrf2 expression is closely affected by shear stress and was shown to participate in AAA. In the current review paper, we discussed the link between disturbed hemodynamics and its effect on Nrf2 as a mechanosensitive gene and its role in the development of endothelial dysfunction which is linked to the progression of AAA.

1. Introduction

Cardiovascular diseases (CVDs) rank as the leading cause of death and morbidity among chronic diseases worldwide [1]. An aortic aneurysm is a major form of CVD with high incidence. Disease is defined as a persistent and irreversible focal dilation of the aorta including its composing three layers (the intima, the media, and the adventitia) [2]. Aortic aneurysm which takes place in the infrarenal aortic region has a higher rate of incidence than any other type of aneurysm and it is called an abdominal aortic aneurysm (AAA) [3]. It is documented that the AAA prevalence rate has declined since the nineties worldwide and this might be accredited to smoking control programs, and as recorded recently in some screening studies, it is approximately 8% [4,5] [6]. Also during the last 30 years, many studies have demonstrated the decline in the incidence of ruptured AAA in the USA and in some European countries [7–10]. On the other hand, the AAA prevalence rate is elevated with the advance of age, and this pattern is universally conserved as well [11]. Several studies have mentioned that AAA prevalence in women is threefold to fourfold lower than in men [12,13]. Increasing prevelance requires advancing diagnosis and therapies.

At present, AAA is diagnosed and assessed using ultrasound (US), computed tomography angiograms (CTA), and magnetic resonance imaging (MRI). To diagnose and stratify patients according to their risk, the maximum axial aortic diameter is measured. Expanded aortic diameter compared to the initial diameter is a very useful independent predictor [14,15]. AAA diagnosis is based on the aortic diameter. Conventionally, an infrarenal aorta with a traversal diameter greater than or equal to 30 mm is defined as AAA [3,16]. This definition has some weaknesses and does not apply to women, since it depends on a threshold value of the increase in the infrarenal aortic diameter to be greater than or equal to 30 mm, as this definition is derived based on the median diameter in males ≥65 years old, which is approximately 20 mm, though the same measured parameter in females ≥65 years old is 17.5 mm. Hence the potential for lower AAA thresholds in women may be addressed by

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lowering the diameter threshold by 3 mm [17,18]. This is supported by a community-based cohort study that aimed to state the definition of the diameters of the normal aorta in asymptomatic men and women, which proved that the average diameter of the abdominal aorta in a normal individual is larger in men than women [19]. Moreover, in some Asian populations lower measurement threshold is more appropriate for defining an AAA [20]. Additionally, dependence on the mentioned definition is subject to be affected by various factors which may introduce variability because of the different imaging procedures used, including the internal or the external wall diameters in measurement for the intervention criteria, and different technical details, particularly in the ultrasound measurement affecting the reproducibility for the procedure [21–23]. Therefore, it was recommended to diagnose AAA when the increase of the diameter of the measured infrarenal aorta is not <150% of the adjacent normal suprarenal aorta [2]. Additionally, if the aorta diameter growth rate is >5 mm/year, the patient is considered at high risk [24]. Despite these clinical reccommendations, small aneursysm may rupture hence a better understanding of the disease progression is needed.

AAA is caused by many factors. There has been a debate over whether atherosclerosis triggers the onset of AAA since the same risk factors of atherosclerosis specifically smoking, male gender, and hypertension are involved in the etiology of AAA [25]. Additionally, oxidative stress, and endothelial dysfunction, are implicated in the development of atherosclerosis and AAA. All of these factors are closely related to the hemodynamic stress acting on endothelial cells. More specifically, low shear stress from disturbed oscillatory flow was shown to trigger and govern these biological events eventually leading to AAA [26–30]. There are geometrical irregularities in the vascular tree, as a result, different patterns of flow dynamics are developed in specific areas. Laminar blood flow with a high magnitude of shear stress occurs in straight vessels that are referred to as atheroprotective areas. In vessel curvatures and bifurcations, the disturbed or oscillatory pattern of flow with a low magnitude of shear stress occurs and these areas are known as atheroprone or atherosusceptible areas, where oxidative stress, the endoplasmic reticulum stress and unfolded protein response (UPR) are triggered. These all together lead to the onset of endothelial dysfunction in these locations which is a primary step in the pathogenesis of CVDs such as AAAs [31,32]. Here, disturbed hemodynamics is known to influence atheroprone gene expression.

Many genes and molecular mediators were shown to be involved in AAA progression such as Nitric oxide, which has been thoroughly studied [33]. Another mechanism is through Nuclear factor erythroid 2-related factor 2 (Nrf2)/Keap-1 pathway, where Nrf2 is a transcription factor that has antioxidant properties and is strongly associated with several CVDs, yet, the exact mechanism by which Nrf2 alleviates CVDs still to be elucidated [34]. Nrf2 expression is closely affected by shear stress and was shown to participate in AAA [35–37]. The pathophysiology of AAA onset and progression is still not fully understood, where progressive inflammatory response, oxidative stress, activation of proteolytic pathways, and vascular smooth muscle cells(VSMCs) apoptosis take place. A stress-responsive transcription factor, Nrf2, regulates most of these processes by activating genes associated with cytoprotection, antioxidant activity, and detoxification [38]. A variety of Nrf2-dependent pathways are also shown to suppress cardiovascular disorders by retaining the contractile state of VSMCs, regulating vascular tone, reducing lipid accumulation, and inhibiting the formation of vascular calcifications, which are considered AAA major hallmarks [39]. Hence Nrf2-dependent pathways may have important contributory or preventive roles for CVD progression that requires further investigation.

In the current paper, we have reviewed the major mechanisms by which different hemodynamic shear stress induce endothelial dysfunction, the critical primary step of the onset of atherosclerosis and AAA. Moreover, we discussed the effect of different flow patterns on the expression of the antioxidant-dependent gene expression, particularly the under-explored Nrf2, and eventually the protective role of Nrf2 on endothelial cells. The paper is organized as follows:

ENDOTHELIAL CELLS (ECs) IN THE PATHOPHYSIOLOGY OF AAA, Endothelial dysfunction and AAA, Major Mechanoreceptors and mechanosening in AAA.

ER stress and oxidative stress interaction in AAA,DISTURBED HEMODYNAMICS FOR AAA PROGRESSION,AAA treatment available drugs and their effect on the Nrf2 signaling pathway,conclusions and future directions.

2. Endothelial cells (ECs) in the pathophysiology of AAA

2.1. Function of endothelial and vascular smooth muscle cells in normal physiology

Endothelial cells (ECs) compose the inner face of the cellular monolayer that lines the vasculature [40], functioning as a barrier between blood fluid and vascular smooth muscle cells (VSMCs) [41]. ECs are directly in contact with dynamic changes of the vascular lumen (e.g., shear stress and injuries), and ECs respond to such signals by secreting cytokines and growth factors, leading to endothelial dysfunction and consequently triggering the progression of cardiovascular complications [42]. Additionally, ECs are considered a whole dynamic organ, functioning via both autocrine and paracrine signaling [41]. Furthermore, ECs play fundamental roles in the preservation of the fluidity of the bloodstream and the regain of the integrity of the vascular wall, leading to balancing the thrombotic and the fibrinolytic systems. Moreover, ECs are responsible for the production and the secretion of several chemical mediators that promote vascular homeostasis and blood vessels vasodilation (Nitic Oxide(NO), prostacyclin (PGI_2),Endothelium derived hyperpolarizing factor (EDHF)), and vasoconstriction (endothelin 1, Thromboxane) [43]. Consequently, ECs are considered to be the key player in controlling vascular tone by keeping the balance between vasodilation and vasoconstriction [41,44]. Furthermore, at very early embryonic stages, ECs which are deno Novo developed are responsible for the formation of the initial vascular plexus. Also, ECs are influenced by different signaling pathways that make them key elements in angiogenesis and further differentiation into arterial and venous ECs [45].

As ECs and VSMCs are the primary cellular elements of the vasculature, these two cell types have intimate communication via several routes which is pivotal to maintaining vascular homeostasis [42,46,47]. At the embryonic stage, the interaction between VSMCs and ECs is crucial for the maturation of vascular cords during blood vessel morphogenesis [48]. Secreted vasoactive molecules like NO, arachidonic acid, peptides, and prostacyclin from healthy ECs represent a necessity for keeping the efficient contractile phenotype of VSMCs [43,49]. Nevertheless, damaged or injured ECs will negatively affect the communication between ECs and the VSMCs, eliciting VSMCs' phenotypic switching to the synthetic phenotype which is associated with cardiovascular pathological manifestations [46]. An AAA is characterized by an altered structural and physiological role of resident cells in the arterial vascular intima and media together with the ECs and VSMCs [50]. Multiple layers of VSMCs with the associated connective tissue compose the vascular media [51]. It is well-reported that VSMCs apoptosis plays a key role in the degeneration of the medial layer of an artery which is considered a hallmark of AAA [51,52]. VSMCs undergo switching into two distinct phenotypes: the contractile and the synthetic [53]. The contractile VSMCs have lower migratory potential and have less proliferative capacity when compared to the synthetic phenotype [53,54] and are involved in the alteration of the diameter of arterial lumen and maintaining vascular tone [50,55]. Aorta and other large arteries consist of several layers of VSMCs which are interwoven in elastin - collagen constructed matrix, this unique structure came to endure the pulsatile flow and pressure of blood during circulation [46]. VSMCs of synthetic phenotype harbor the ability of vascular extracellular matrix (ECM) degradation through the production of

metalloproteases, enhancing their migratory feature [56], it is reported that VSMCs switching to synthetic phenotype is a key factor behind the degeneration of ECM which leads to the development of thoracic abdominal aneurysm in murine animal models [57].

The combination between the phenotypic switching to synthetic VSMCs and Endothelial dysfunction is among the hallmarks of AAA development [57,58]. Communication between ECs and VSMCs is a crucial step in the onset and endothelial dysfunction significantly triggers the advancement of disease-associated vascular remodeling [42].

2.2. Endothelial dysfunction and AAA

A ubiquitous characteristic almost in all AAAs is a thick sheet of intraluminal thrombus which is accompanied by damage to adjoining endothelial lining. The significant role of endothelial dysfunction and endothelial phenotypic modifications in the progression of AAA has been poorly investigated [59]. Endothelial dysfunction (ED) is known as the inadequacy and insufficiency of the response of ECs following stimulation by chemical mediators or blood flow disturbances [60].

ED is mainly characterized by reduced NO bioavailability, augmented production of adhesion molecules and pro-inflammatory markers, increased aggregation of platelets, and changed control of VSMCs proliferation and growth [44,60]. Moreover, ED is counted as an autonomous prognosis for cardiovascular complications such as atherosclerosis [44]. Endothelium-generated NO is a pivotal vasodilator and its deficiency leads to vasoconstriction and most significantly leads to endothelial dysfunction. Additionally, NO reduced bioavailability leads to increased inflammatory machinery activation via the stimulation of intracellular adhesion molecule-1 (ICAM-1), macrophage chemoattractant peptide-1 (MCP-1), *E*-selectin, and vascular adhesion molecule-1 (VCAM-1) [61,62].

Biomechanical stress is implicated significantly in CVD progression, including atherosclerosis and AAA. Shear stress is the resulting tangential force that blood flow and friction exerted on the blood vessel [63]. In straight blood vessels, the blood shear stress is high approximately >10 dynes per cm square with a unidirectional laminar pattern of flow till blood reaches the areas of curvature and bifurcation where shear stress go to the lowest magnitude as it reaches the 2 dynes per cm squared and the laminar flow pattern is deteriorated and oscillatory or disturbed flow develops there. The development of aneurysms has the chance to occur in any area along the aorta, though, aneurysms usually form in the proximal region to the aortic branching point of the infrarenal aortic section or the curved arch of the thoracic aorta. The bifurcation region in the infrarenal aorta manifests a region of oscillatory blood flow with low shear stress. Persistent growth of localized aneurysms can trigger the onset of an aneurysm in adjacent regions which are subjected to low shear stress and localized recirculation of flow [32,64]. Endothelial dysfunction and its contribution to the development of AAA and associated wall thinning and expansion has gained much attention, one study reported that localized therapy using autologous ECs in a rat model resulted in the reduction of AAA generation and restrained the already developed AAA concluding that reestablishing ECs is essential for the AAA dynamics regulation. Another study investigated the role of endothelial NO synthase (eNOS) which is produced by healthy ECs, in the advancement of atherosclerosis and associated cardiovascular complications such as AAA. In a study it was demonstrated that mice with Apolipoprotein E/Endothelial Nitric Oxide Synthase Double-Knockout (apoE/eNOS-DKO) had accelerated advancement of atherosclerosis and AAA, when compared to apoE-KO mice, highlighting the significance of the ECs dysfunction involvement in developing AAA [65]. Recently, a study came in line with previous studies where researchers highlighted the significant role of ECs Krüppel-like factor 11 (KLF11) deficiency in triggering VSMCs phenotype switching and apoptosis aggravating AAA in elastase- and Pcsk9/AngII-induced AAA mice [66].

Major Mechanoreceptors and mechanosening in AAA.

As mentioned before,ECs and VMCs sense the alterations in the flow patterns and shear stress, as ECs harbor at their membrane, a wide variety of sophisticated mechanosensing machineries, comprising the shear stress sensing ion channels, like the transient receptor potential isoform-4 (TRPV4) ion channels by which via Ca2+ influx, it releases vasodilators mediators (NO, Prostaglandin I2 (PGI2)) and subsequently affecting VSMCs where vascular remodling and aoertic inflammation takes place at the oncet of AAA,(TRPV4) occur in ECS and also VSMCs [67].

Additionally, G protein-coupled receptors (GPCRs), ECs and VSMCs contain many GPCRs, such as the b2AR (b2-adrenergic receptor) and AT1R (angiotensin II type I receptor), which regulate a variety of functions, including vascular tone, angiogenesis, and cell proliferation [67]. It was demonstrated that under excess mechanical stretch, AT1R activates functioning as a mechanosensor in ECs.Also it was shown that VSMCs demonstrated a AAA growth augmentation following the AT1R mechanical activation in a hypertensive mouse model lead [68]. Also, primary cilia structure that protrude from endothelial cells surfaces, act as mechanosensors that detect blood flow, where pulsatile flow stimulates endothelial cilia to oscillate, activating endothelial nitric oxide synthase, which produces NO and regulates vascular tone [69].

Moreover, it is well documented that tyrosine kinase receptors and integrins are involved significantly in ECs mechanosensing to different shear stress cues [70].

2.3. ER stress and oxidative stress interaction in AAA

As mentioned earlier, a major manifestation of endothelial dysfunction is the decreased NO bioavailability, which leads to alteration in the endothelium-dependent vasodilation of the main arteries, representing a profound prognosis of CVDs including AAA [71]. One of the key factors that lead to the decline of NO bioavailability in the endothelium is accelerated ROS-mediated NO degeneration [72]. Several mechanisms contribute to AAA, including metalloproteinase over-activation, inflammation, shear stress, and excessive ROS generation within the vascular walls [73].

According to recent studies, oxidative stress is involved in several underlying mechanisms of AAA [71,74,75]. Shear stress, NADH/NADPH oxidase, and nitric oxide synthase are among the well-known ROS sources in the cardiovascular system [76]. In a murine model of AAA formation induced by CaCl2, iNOS deficiency, and NADPH oxidase inhibition protected the aortic walls against AAA formation indicating the pivotal role of ROS and oxidative stress in the development of AAA [77]. Also, infrarenal AAA tissue segments of patients going through elective aneurysm repair demonstrated elevated amounts of (O2·) and increased activity of NADPH oxidase [78].

Clinically, in a study conducted by Pincemail and coworkers, it was confirmed that oxidative stress has a potential role in the pathogenesis of AAA and the increase of its size, where AAA patients with higher serum antioxidants levels demonstrated a lower size of AAA when compared to the AAA patients with lower antioxidant levels in their sera [79]. Moreover, many research works investigated the presence and significant role of ROS in the surveillance of AAA in human subjects [80,81].

The endoplasmic reticulum (ER) is the largest cellular organelle and is considered a signaling organelle, it harbors multifunctional roles most significantly cell homeostasis, protein proper folding via the resident molecular chaperones and foldases, proteins translocation, and protein integration to the cellular membrane, ER is the site of posttranslational modification of synthesized proteins and calcium homeostasis conservation [44,82,83], the imbalance in the demand for folding newly synthesized proteins and the capacity of the cellular folding machinery leads to ER stress status activation followed by the unfolded protein response (UPR), where cellular pro-survival pathways are switched on [44,84]. Cells ameliorate the ER stress through many mechanisms of UPR like the reduction of general proteins translation decreasing the entrance of new proteins to ER lumen, increasing the production of

molecular chaperones enhancing the correction of the misfolded proteins, stimulation of ER-associated degradation machinery (ERAD) to eliminate any atypical proteins [44,85,86]. In the case of prolonged chronic ER stress, the activation of UPR will trigger pro-apoptotic and pro-inflammatory pathways, leading to apoptotic cell death [87]. Several studies confirmed the pivotal role that ER stress plays in the pathology of certain diseases including cardiovascular diseases (CVD) [88,89], moreover, ER stress and/or inflammatory reactions may contribute significantly to the initiation or deterioration of the pathological condition [90]. Prolonged ER stress and UPR activation lead to the disturbance of cell redox homeostasis and calcium equilibrium, also, the overwhelmed protein folding machinery results in oxidative stress [91]. Oxidative stress is the status in which an imbalance between the endogenous antioxidant defense machinery and the generation of reactive oxygen species (ROS) [92]. Many factors are responsible for the excess generation of ROS inside the endothelium including the upregulation of the processes of nitric oxide synthase uncoupling, mitochondrial respiration, and the enzymes nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and xanthine oxidase [93]. ROS excessive generation and buildup in the cell, stimulate signaling pathways that lead to oxidative damage of DNA, Protein, vital enzymes and consequently the endothelium, additionally, these highly reactive free radicals may interact with DNA and proteins leading to destructive modifications, significantly contributing to the development of disease [86,94]. An intimate association between ER stress and oxidative stress, in a vicious manner, contributes to the onset and development of (ED) [95].

The ER lumen is the place where newly translated proteins are exposed to post-translational modifications, initially, the majority of the proteins are subjected to N-glycosylation, followed by the formation of disulfide bonds stabilizing the proteins to acquire their proper tertiary structure [44,96]. The redox status homeostasis of the ER lumen is crucial in maintaining the oxidative folding of proteins, and catalyzing the formation of disulfide bonds in proteins by a family of protein disulfide isomerase (PDI) accompanied by the availability of high concentrations of reduced glutathione (GSH) keeping the thiol/disulfide machinery redox status in the oxidized form [96–98]. Additionally, ER harbors the complete machinery of foldases and molecular chaperones including Glucose-regulated protein 94,78 (GRP94 and GRP78) represents a strict strategy to ensure the proper folding of synthesized proteins [99,100].

The incorrect pairing of cysteine residues between polypeptide chains during the process of protein folding will lead to the formation of non-native disulfide bridges, causing the buildup of misfolded proteins. Under the typical conditions of the protein folding process, generating a native disulfide bond involves the transfer of electrons from the second cysteine residue to the electron acceptor, in this case, it is the molecular oxygen producing hydrogen peroxide, this reaction is catalyzed by PDI and ER oxidoreductase (ERO)-1α [101].

On the other hand, as in metabolic diseases, there is an overwhelming demand for protein folding leading to the increased development of erroneous disulfide bridges that needs to be reduced via GSH leading to excess consumption of GSH which in turn depletes the GSH pool which is responsible for scavenging ROS, putting the cell under oxidative stress, moreover, the ratio between the reduced form of glutathione GSH and the oxidized one GSSH will be decreased, disturbing the redox homeostasis in ER [44,95,101]. Also, it was found that ROS are involved in the inactivation of ER resident isomerases which aggravate the formation of misfolded proteins [102]. A subsequent event that occurs after the accumulation of misfolded proteins in the ER is the leakage of calcium ions in a high gradient inside the mitochondria via MAMS, triggering the ROS generation through the mitochondrial oxidative phosphorylation system, meanwhile, calcium ions excessively diffuse into the mitochondria blocking complex III which induce the leakage of electrons and the generation of ROS at the end [103,104].

It is well established that persistent ER stress, UPR, and oxidative stress are connected to the onset of some diseases including CVD and ED [31,105–107]. In a recent study, a higher expression of endoplasmic reticulum stress markers was also observed in the aortic walls of humans dissecting AAAs [108]. Many in vitro and in vivo studies have also demonstrated that ER stress inhibition can prevent the progressive growth of abdominal aneurysms [28,109].

3. Disturbed hemodynamics for AAA progression

3.1. Hemodynamics in the aorta

The aorta is the major artery in the body and is characterized by it is ability for dilation and its reduced resistance to the stream. During the systolic cycle, a stretching and expansion occur to the aortic wall, whereas in the diastolic cycle, the aortic wall recoils pushing blood in the entire cardiovasculature. AAA is the most prevalent aortic aneurysm type. The majority of AAAs develop in the infrarenal region of the abdominal aorta, where this region is located just below the renal arteries and above the bifurcation of the aorta. Throughout the length of the aorta, hemodynamic conditions vary prominently, this is thought to contribute to making the distal aorta predisposed to aneurysms. The major variation that occurs between the suprarenal and infrarenal segments of the aorta is the difference in the vessel wall shear stress.

In suprarenal aortic region, the blood flow is anterograde and laminar during the whole cardiac cycle, exerting continuous, directed shear stress on the vascular wall. As the cardiac contraction (systolic cycle) begins, the infrarenal aorta demonstrates an anterograde blood flow. While systole is being completed and during diastole, a reverse, disturbed recirculating flow associated with low and oscillatory shear stress is established on the vascular wall of the infrarenal aorta [110].

The disturbance of blood flow demonstrated in AAA, affects directly the ECs lining the vascular tube which are in direct contact with flow and are very sensitiveto any change in the flow pattern of the bloodstream. As indicated by many studies mentioned before in this review, disturbed flow with low and oscillatory shear stress leads to the activation of inflammatory pathways in the endothelium and subsequently leads to endothelial dysfunction and VSMCs apoptosis, eventually reducing the integrity, and the degeneration of the arterial wall, progressing toward AAA [16,111].

3.2. Endothelial pathophysiology and hemodynamic shear forces

ECs are subject to an unsteady hemodynamic force due to the pulsatile nature of the heartbeats. As a result, diverse patterns of fluid shear stress and cyclic circumferential stretch act on the blood vessels [112]. Fluid shear stress is the key determining factor in the physiology and pathophysiology of ECs through the specific feature of ECs harboring unique mechanotransducers which translate the hemodynamic physical cues into biochemical signals maintaining the redox homeostasis [36,113]. ECs mechanosensing process is mediated via putative mechanotransducers that have been investigated, particularly, mechanosensing ion channels, integrins, glycocalyx, focal adhesion complexes, cilia, receptor tyrosine kinases, and heterotrimeric G protein [112,114].

The vasculature tree differs geometrically from region to region which causes the spatial variation of flow patterns and shear stresses that ECs sense, the straight regions demonstrate unidirectional laminar flow with relatively high shear stress of >10 dynes per squared cm, on the contrary, the areas of bifurcations and inner curvature demonstrate a pattern of oscillatory disturbed flow with a low magnitude of shear stress <2 dynes per squared cm [32]. ECs sense such variations in shear stress and respond via the regulation of the redox signaling pathways, triggering the altered gene expression of antioxidant and prooxidant pathways, cell inflammatory features, and cell alignment [36].

3.3. Disturbed hemodynamics and endothelial dysfunction interaction

As mentioned above, disturbed hemodynamics in the vasculature is implicated significantly in major alterations in specific gene expressions. Here in this section, we will focus on the mechanosensitive genes in the endothelium which are involved in triggering endothelial dysfunction. The excessive expression of adhesion molecules including I-CAM and V-CAM is an important feature of endothelial dysfunction [115].

Since the late nineties, substantial research was conducted investigating the dynamic response of endothelial cells to different forms of shear stress [116,117]. Moreover, It is believed that increased Nfκb activity occurs in regions of disturbed flow in athero-susceptible regions and is associated with the expression of Nfκb-dependent genes, such as the adhesion molecules ICAM-1, VCAM-1, and *E*-selectin, contributing to the emigration of monocytes to the nascent plaque [116,118]. Also, it was reported that the expression of I-CAM and V-CAM, and VEGFR2 is altered when endothelial cells are exposed to different magnitudes of shear stress, supporting the fact that these molecules are implicative in mechanosensing [119]. It was well established that disturbed flow shear stress leads to increased nuclear localization of c-jun, Nfκb, and c-fos, consequently, the stimulation of these transcriptional factors triggers the expression of genes that are implicated in the inflammation and atherogenesis, including MCP-1, *E*-selectin, interleukin (IL)-1a, platelet-derived growth factor (PDGF)-BB, bone morphogenic protein-4 (BMP-4), (ET-1)and as previously mentioned I-CAM and V-CAM [120].

Another important hallmark of endothelial dysfunction is the reduced NO bioavailability, NO is a vital molecule involved in both vasodilation and anti-inflammatory response [121]. in turn, endothelial cells respond to shear stress in several ways, and exposing ECS to persistent oscillatory disturbed flow shear stress stimulates the excessive generation of ROS mainly O. As well as being highly diffusible, NO is highly reactive and contains an unpaired electron, particularly O. easily reacts with NO to form peroxynitrite (ONOO−) consuming NO leading to its deficiency in the cell [120]. Furthermore, It was demonstrated that oscillatory flow triggered the expression of the NADPH subunit Nox4 inducing the generation of O2 •-, this increase of O generation leads to the disturbance of redox homeostasis in cells augmenting the production of (ONOO−) which is a key player in inducing endothelial dysfunction and pathological events associated with atherogenesis [122].

3.4. Disturbed hemodynamics with ER stress / oxidative stress interaction and Involvement of NRF2 in AAA progression

ECs lining the arterial inner wall are subject to different patterns of blood flow shear stress including laminar shear stress like in large arteries with uniform geometry and turbulent or oscillatory shear stress near arterial branching and bifurcations and curvatures [123]. Blood shear stress occurs as a result of the tangential frictional force of blood flow on ECs [124]. ECs have the feature of sensing the slight variations of vascular wall shear stress, hence the mechanism by which ECs sense these variations remain elusive [32,125]. Many risk factors for AAA mainly include diabetes mellitus, hypertension, and coronary artery disease which are linked to metabolic disturbances and activated inflammatory status [126]. It is well documented that the endoplasmic reticulum (ER) stress response is triggered in cardiovascular diseases [26,127].

ECs of atheroprone areas with oscillatory patterns of shear stress showed an upregulation of genes involved in ER stress and the UPR [128]. Many studies supported the fact of the stimulatory effect of oscillatory flow shear stress on UPR markers in ECs, it was demonstrated that the molecular chaperone GRP87, associated with the ER stress sensing element (ERSE1) stimulation, was upregulated substantially in ECs exposed to oscillatory flow shear stress compared to laminar flow in the studied in vitro model [129]. Also, it was reported that oscillatory patterns of shear stress triggered the XBP-1 splicing which is encoding the XBP-1 transcription factor leading to its nuclear translocation to selectively activate the proapoptotic downstream genes as to the nucleus to activate selective pro-apoptotic target genes as part of UPR preceded by chronic ER stress [130]. ER homeostasis is closely related to normal cardiovascular function, and ER stress is considered a trigger and a consequence of a wide range of CVDs, including ischaemic heart disease, hypertension, stroke, heart failure, and cardiomyopathies, in a fashion of a vicious cycle [131].

Particularly speaking, ECs in the regions of oscillatory disturbed flow demonstrate altered gene expression of prooxidant and oxidant pathways, triggered ER stress accompanied by UPR activation [30]. Nrf2 has been extensively studied for its role in regulating the expression of a group of genes encoding phase II detoxification enzymes and antioxidants including Sestrin 2(Sesn2), heme oxygenase-1 (HO-1), glutathione-S-transferase, peroxiredoxin 1 (Prx-1), quinone oxidoreductase-1 (NQO1) and nicotinamide adenine dinucleotide phosphate (NADPH) [132,133]. Oxidative stress-related diseases such as CVDs are protected by Nrf2 which is ubiquitously expressed in various tissues and cells via the transcriptional modulation of the downstream antioxidant genes [134,135]. It has been found that Nrf2, is tightly linked to the UPR sensor PERK in neonatal mouse cardiomyocytes. Maintaining ER homeostasis and cardiac function during ischaemic preconditioning might require activation of the Nrf2-antioxidant response element cascade [136]. Moreover, Nrf2 is colocalized in the cytosol with its repressor Keap-1 during the resting state, where it is subjected to proteasomal degradation [137].

As demonstrated in both in vitro and in vivo studies, ECs exposed to oscillatory disturbed flow shear stress compared to cells exposed to unidirectional flow patterns have higher nuclear factor-B (**Nfκb**) activity and deficiency of the Nrf2 antioxidant pathway, which are implicated in proinflammatory states due to increased generation and reduced scavenging of ROS [138]. The disturbed oscillatory flow shear stress patterns are known to modulate ECs' redox state and inflammatory phenotype in atheroprone vasculature regions. Therefore, the laminar flow may protect EC against atherosclerosis and endothelial dysfunction by increasing Nrf2 activity and expression of the antioxidant genes [120,139]. There have been relatively few in vitro hemodynamic culture models demonstrating Nrf2's role as a shear-responsive transcription factor in EC that have been conducted using primarily HUVEC, which are not relevant to studying atherosclerosis, and in vivo models of atherosclerosis in mice.

There is substantial evidence, that indicates the stimulatory effect of laminar flow shear stress on the Nrf2 pathway and associated antioxidant genes. It was demonstrated that laminar shear stress has triggered the gene expression of HO-1, NQO1, GCLM, ferritin H, and SQSTM/A170 in HUVEC and HAEC cells, which also was significantly attenuated by silencing the Nrf2 gene [33,140]. Also, it was demonstrated that exposing ECs under laminar flow shear stress to inhibitors of an antioxidant nature, suppressed the Nrf2 laminar flow shear stress-mediated activation [33,141]. It was demonstrated, as with Laminar flow shear stress, atherogenic oscillatory flow shear stress increased Nrf2 nuclear accumulation, but did not lead to the induction of Nrf2 target gene expression [140], because of additional epigenetic modulation which occurs by histone deacetylases and mechanosensitive microRNAs as summarized in Fig. 1 [142]. Moreover, recently crosstalk was revealed between the glycocalyx sialic acid (SIA) and Nrf2 signaling in human primary ECs exposed to laminar and oscillatory flow shear stresses, and it was demonstrated that oscillatory flow shear mediated SIA modifications reduced atheroprotective Nrf2 signaling affecting the cells redox homeostasis. On the other hand, ECs exposed to laminal flow shear stress demonstrated heavier glycocalyx and enhanced Nrf2 antioxidant signaling and accompanied with thicker glycocalyx [143]. Another study indicates the important role of KLF2 which augment Nrf2 and antioxidant-dependent gene expression and enhance their role in ROS scavenging in ECs model exposed to laminal flow shear stress [144]. In a study of combined in vitro and in vivo models, it was demonstrated that HUVEC intracellular redox state is regulated by laminar flow-mediated

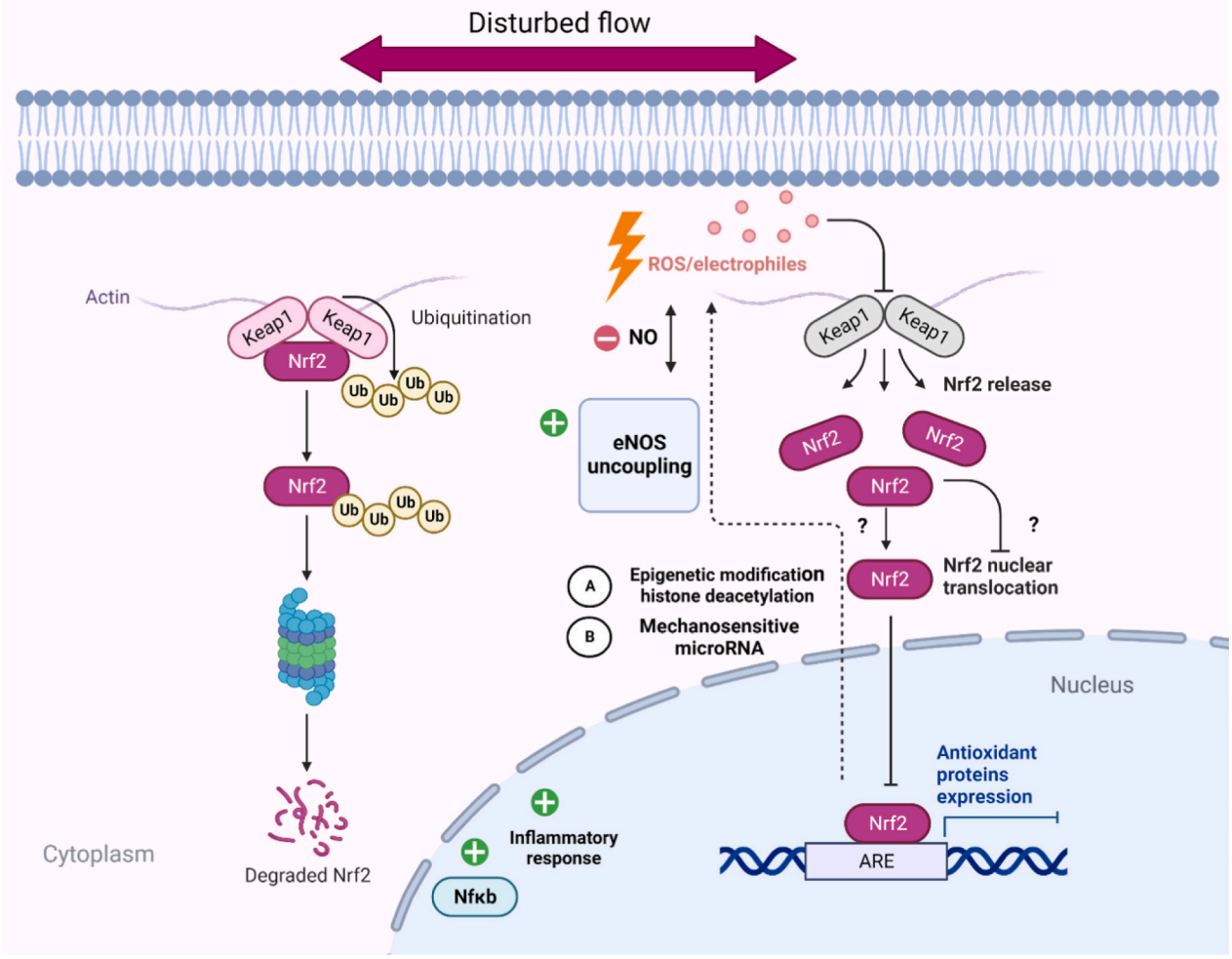

Fig. 1. Disturbed hemodynamics and Nrf2/Keap-1 pathway. When disturbed flow occurs, Nuclear factor erythroid 2-related factor 2 (Nrf2) transcriptional activity is reduced because Keap-1 modulates Nrf2 proteasomal degradation, or via attenuated Nrf2 nuclear translocation or if translocation occurs, Nrf2 will be accumulated with no induction of its target gene expression because of additional epigenetic modulation which occurs by histone deacetylases and mechanosensitive micro-RNAs·As a result of attenuated Nrf2 antioxidant activity, the oxidative stress is aggravated through the elevated production of reactive oxygen species (ROS) and endothelial nitric oxide synthase (eNOS) uncoupling, reducing nitric oxide (NO) bioavailability, also nuclear factor kappa b (Nfκb) expression is elevated triggering the inflammatory response. Together leading to endothelial dysfunction. This figure is created using:biorender.com.

Nrf2 activation, allowing cells to withstand oxidative stress, as elevated Nrf2 nuclear translocation was demonstrated in the areas where atheroprotective flow shear stress in mice aortae. Additionally, it was shown that the laminar flow shear stress modulates the EC's redox homeostasis via activating Nrf2 dependently on the PI3K/Akt pathway and independently from NO [145]. Proving that Nrf2 and associated antioxidant genes function in scavenging ROS and maintaining the Redox Homeostasis of ECs are significantly stimulated by laminar flow shear stress.

On the contrary, ECs that are subjected to persistent oscillatory flow shear stress manifest augmented generation of ROS including H2O2 and O_2^- which are resulting mainly from NAPPH oxidases and eNOS uncoupling, Further, elevated levels of ROS lead to a significant reduction in NO bioavailability, which is a hallmark of ED and it is associated with oscillatory flow shear stress. Moreover, ROS/RNS are capable of promoting post-translational modifications on regulatory proteins (such as S-glutathionylation, S-nitrosylation, and tyrosine nitration), which provide chemical signals associated with cardiovascular pathophysiology [121].

Furthermore, it is well reported that oscillatory flow shear stress aggravates oxidative stress through the elevated production of ROS and oxidizing BH4 leading to eNOS uncoupling which in turn decreases NO bioavailability deliberately inducing endothelial dysfunction [146,147]. Oxidative stress induced by ROS accumulation and lipid peroxidation strongly aggravates endothelial dysfunction, which stimulates Nrf2, retaining its protective role in ECs [148].

Exceeding the number of antioxidant 200 genes, are the downstream genes associated with Nrf2 activity, including the genes with vital functions for the redox status homeostasis, glutathione homeostasis, and phase II detoxifying enzymes [149,150]. Moreover, it was demonstrated that stimulating Nrf2 in human aortic endothelial cells triggers the expression of intracellular HO-1 which in turn protects ECs from the cytotoxic effect of tumor necrosis factor TNF-alpha used to induce atherogenesis in the ECs studied model, exhibiting an anti atherogenesis function of nrf2 [151]. Laminar flow shear stress modulates endothelial Nrf2 signaling, while arterial areas exposed to low oscillatory flow shear stress demonstrates declined expression of eNOS and reduced antioxidant and anti-inflammatory functions of Nrf2 [143]. Endothelial dysfunction is a critical risk factor for many CVDs and it is considered the first step toward CVD pathogenesis, specifically, atherosclerosis [152].

As mentioned before, numerous studies have indicated the key role of oxidative stress and ROS in AAA progression and demonstrated key sources of ROS in the aortic tissues of human and in vivo AAA models [153]. Several human studies came in agreement with the above, research has confirmed the association between AAA development and oxidative stress and endothelial dysfunction [35]. As Nrf2 is a master

transcription factor that harbors a pivotal role in cellular defense machinery with its antioxidant and anti-inflammatory roles. In a very recent study, it was demonstrated in a study where AAA mice models were employed, that treating AAA mice with the natural compound betanin constrained the enlargement of the aortic diameter in the experimental model when compared to the control group, associated with the augmentation of the Nrf2 expression and its downstream target HO-1 leading to the significant drop in ROS that was measured in betanin treated group, indicating that Nrf2/HO-1 pathway had a pivotal role in scavenging ROS and alleviating the AAA progression and aortic enlargement [154]. Relying on many in vitro and in vivo research works and several clinical studies, Nrf2 may be capable of targeting the oxidative stress triggering CVDs [155].

Based on these findings, involvement of shear responsive Nrf2 expression in AAA progression can be summarized as demonstrated in Fig. 1.

AAA treatment available drugs and their effect on the Nrf2 signaling pathway.

In AAA, medical therapy is indicated for two purposes: managing cardiovascular risk and stabilizing AAA with pharmaceutical drugs. Beta-blockers are believed to hamper aortic aneurysm progression, yet, further studies and clinical trials are needed to prove this type of drugs efficacy in hindering AAA growth. Based on non-randomized studies Propranolol which is a Beta-blockers reduces aortic aneurysm growth. Beta-blockers had demonstrated antioxidant and anti inflammatory features, through the beta blocking action reducing catecholamine which triggers the ROS generation in the myocardium and through the inhibition of nfkb, respectively [156,157]. Statins also, based on many cohort studies of AAA patients who underwent statin therapy after open surgery,demonstrated that statins significantly improved the survival of those patients [158,159]. these data are of great interest for understanding the mechanism of action by which statins can cease AAA progression. It is well proven by in vitro and in vivo studies that statins (e.g., Rosuvastatin and Mevastatin)harbor antioxidant and anti-inflammatory properties, acquired through the modulation of Nrf2 and its target-downstream genes including HO-1 [160,161]. Statins have been shown to stimulate the binding of Nrf2 to DNA and increase the expression of its target genes, HO-1 and GPX, shielding the cells from oxidative stress [162]. Moreover, statins were found to reduce endothelial dysfunction primarily through the enhancement of endothelial nitric oxide bioavailability, and also activating antioxidant enzymes like catalase [163].

4. Conclusions and future directions

A large piece of evidence from in vitro / in vivo and human studies indicated the pivotal role of disturbed hemodynamic-induced ROS and ER stress in endothelial cell dysfunction which is the first step in the onset and pathogenesis of several CVDs including AAA.

Also, the protective role of Nrf2 in CVDs and particularly AAA is spotting the light on it as a therapeutic target, and much more studies are needed to investigate more mechanisms and pathways crosstalk that involve Nrf2, also, investigating Nrf2-associated upstream regulators as well.Moreover, further clinical trials are needed to investigate the potential of drugs that are used in other CVDs and their effect is proved to be Nrf2 mediated, as they can be beneficial in hindering the AAA progression in AAA pateints.

Additionally, more suitable models must be investigated and employed for studying the hemodynamic effect on the suspected mechanosensitive genes.

Author statement

The authors confirm their contribution to the paper as follows.

Maram Hasan: contributed to the review conception and design, writing the original manuscript draft and the final version, Hassan Al-Thani: Critically revised the manuscript, Ayman El-Menyar: writing—review and editing:, Asad Zeidan: writing—review and editing, Asmaa Al-Thani: writing—review and editing, Huseyin C Yalcin: study conception and design, critically revised the manuscript, Approved the final version to be published.

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