

Aortic Stiffness and Neutrophil-to-Lymphocyte Ratio in Coronary Artery Disease: Pathophysiological Links and Clinical Implications

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Abstract

Background: Aortic stiffness (AoS) is one of the first obvious signs of detrimental structural and functional alterations in the arterial wall. It is a promising indicator of subclinical disease and a non-invasive way to measure maladaptive alteration and remodeling of aortic characteristics. Pathologically elevated AoS increases hemodynamic strain on the left ventricle and central systolic pressure. Furthermore, processes linked to AoS, such as inflammation and oxidative stress pathway activation, may be indicative of underlying vascular risk. The neutrophil-to-lymphocyte ratio (NLR) represents systemic inflammatory activity and has been associated with atherosclerosis and arterial stiffness. Coronary artery disease (CAD) is characterized by the development of atherosclerosis in the coronary arteries, and inflammatory processes have an important role in its underlying vascular pathology.

Aim: This review aims to highlight the pathophysiological links between aortic stiffness, systemic inflammation represented by the neutrophil-to-lymphocyte ratio, and coronary artery disease, with emphasis on vascular remodeling mechanisms and their potential clinical implications.

Conclusion: Aortic stiffness, systemic inflammation, and coronary atherosclerosis represent interconnected components of vascular pathological remodeling. Neutrophil activation, oxidative stress, extracellular matrix degradation, altered collagen and elastin balance, and loss of lymphocytic counter-regulation provide mechanisms through which inflammatory activity may contribute to progressive arterial stiffening. Assessment of aortic stiffness together with inflammatory biomarkers such as NLR may provide complementary information regarding vascular alterations associated with coronary artery disease.

Keywords: Aortic stiffness; Neutrophil-to-lymphocyte ratio; Coronary artery disease

Introduction

Aortic stiffness (AoS) represents an important structural and functional alteration of the arterial wall. The flexibility of the blood artery wall is measured by AoS, and elevated AoS may both cause and contribute to increased stress on the vessel walls. It is a promising indicator of subclinical disease and a non-invasive way to measure maladaptive alteration and remodeling of aortic characteristics. The arterial tree's mechanical characteristics vary along its length, mostly due to the different contributions of collagen and elastin to its structure [1].

The cardiac cycle's pulsatile hemodynamics produce pulse waves that flow down the large conduit arteries to the mid-sized arteries, where they encounter higher resistance because of branch points and elevated arterial tone. The periphery then reflects the incident waves in the direction of the central arteries. The velocity at which reflected waves return is determined by the stiffness of the central conduit arteries; higher AoS causes reflected waves to propagate more quickly, which defines the recorded pulse wave velocity (PWV) [2].

Pathologically elevated AoS increases hemodynamic strain on the left ventricle and increases central systolic pressure by enabling waves reflected from the periphery to return in phase with cardiac systole. Furthermore,

processes linked to AoS, such as inflammation and oxidative stress pathway activation, may be indicative of underlying vascular risk [3].

Inflammation is increasingly linked to alterations in vascular structure and function. Elevated AoS has been associated with persistent inflammatory conditions, while inflammatory biomarkers have been related to progressive vascular dysfunction and stiffness. The neutrophil-to-lymphocyte ratio (NLR) reflects the balance between neutrophil-mediated inflammatory activity and lymphocyte-mediated regulatory pathways. The relationship between an increased NLR and AoS depends on the equilibrium between active cellular degradation of structural tissues and the concurrent failure of vascular repair mechanisms.

Coronary artery disease (CAD) is characterized by atherosclerotic plaque accumulation within the coronary arterial system. Atherosclerosis itself involves endothelial dysfunction, lipid accumulation, inflammation, smooth muscle cell proliferation, extracellular matrix remodeling, and plaque formation. These processes provide an important pathophysiological intersection between coronary atherosclerosis, systemic inflammation, and alterations in arterial mechanical properties.

This review highlights the pathophysiological links between aortic stiffness, NLR, and CAD, focusing on the mechanisms by which inflammation, extracellular matrix degradation, oxidative stress, and vascular remodeling may connect these processes.

Aortic Stiffness

One of the first obvious signs of detrimental structural and functional alterations in the artery wall is arterial stiffness. Atherosclerosis, which is the occlusive consequence of endovascular inflammatory illness, lipid oxidation, and plaque development, should be distinguished from arteriosclerosis, which is the degenerative stiffness of the arterial beds. Both often coincide and describe a widespread, age-related, progressive process that affects all vascular beds [1].

The flexibility of the blood artery wall is measured by AoS. In addition to changing degrees of smooth muscle modulation, the arterial tree's mechanical characteristics vary along its length, mostly due to the different contributions of collagen and elastin to its structure. Pulse waves generated by pulsatile cardiac hemodynamics travel along the arterial tree and are reflected from peripheral sites. Higher stiffness of the central conduit arteries increases the velocity at which these reflected waves propagate [2].

Pathologically elevated AoS increases central systolic pressure and hemodynamic strain on the left ventricle. Carotid-femoral PWV (cfPWV) can capture a distinct measure of central hemodynamics that is not reflected by blood pressure alone. Processes associated with AoS, particularly inflammation and oxidative stress pathway activation, may additionally reflect underlying vascular risk [3].

Longitudinally monitored cohort research has shown that stiffening of the aorta, a sign of subclinical illness, can occur prior to the onset of hypertension [4]. Increased PWV has also been linked to atherosclerosis and poorer cardiovascular outcomes in high-risk conditions. AoS can predict cardiovascular events including coronary disease, heart failure, stroke, and cardiovascular mortality [5].

Assessment of Aortic Stiffness

AoS can be measured by PWV using different methods, including magnetic resonance imaging, Doppler ultrasonography, standard blood pressure cuffs, and tonometer transducer recording of pulse waves [1].

Carotid-femoral pulse wave velocity is considered a reliable indicator of aortic wall stiffness. CfPWV can be measured transcutaneously from pressure waveforms at the femoral and common carotid arteries. Doppler or MRI flow waveforms can also be used. The velocity component is calculated using the separation between the two surface sites and the time interval between the waveforms [6].

PWV and blood pressure are strongly connected, with greater mean arterial pressures being associated with higher AoS [2]. This relationship is important when interpreting arterial stiffness measurements.

Augmentation index (AI) represents another measurement of AoS. It is calculated as a percentage by dividing augmentation pressure by pulse pressure and multiplying the result by 100. However, variables including age, systolic blood pressure, heart rate, left ventricular ejection time, and height have a greater influence on AI than on PWV. Consequently, PWV, particularly cfPWV, is increasingly used in clinical investigations [7].

Determinants and Risk Factors of Aortic Stiffness

Age and Sex

An increase in AoS with age has been well documented. Central arterial stiffness reduces the arterial reservoir effect, resulting in increased pressure during systole and decreased pressure during diastole. This may contribute to poor myocardial perfusion, unfavorable ventricular and vascular hemodynamics, and cardiac remodeling [8].

Age-related arteriosclerosis involves intrinsic arterial remodeling and changes in mechanical properties, including maladaptive remodeling and increased collagen deposition. Cumulative exposure to vascular risk factors further influences the age-related increase in AoS.

Sex also has a complex relationship with AoS that changes with age. Hormonal changes appear to contribute to these differences. Elevated AoS in postmenopausal women may be related to a pro-inflammatory condition associated with reductions in estradiol, while female sex hormones such as progesterone and 17-beta estradiol promote elastin deposition [9].

Hypertension

Hypertension demonstrates a substantial relationship with AoS. Arterial stress produced by high pressure and elastin fractures associated with pulsatility can cause inflammation and maladaptive vascular remodeling. Increased vascular stiffness has been associated with both baseline blood pressure and blood pressure variability [10].

Higher blood pressure variability may facilitate oscillatory wall stress, vascular smooth muscle cell proliferation, and atherosclerosis. Higher AoS may consequently result from increased blood pressure variability, while stiffer arteries themselves may increase blood pressure, demonstrating an interdependent relationship.

Metabolic Syndrome and Diabetes Mellitus

AoS can be increased in metabolic syndrome, which includes obesity, insulin resistance, hypertension, and dyslipidemia. Increased PWV has been associated with components of metabolic syndrome, and progression of cfPWV may be accelerated when cardiovascular risk factors coexist [11].

Individuals with diabetes mellitus are more susceptible to cardiovascular disease. Elevated PWV has been associated with cardiovascular disease in patients with diabetes, making aortic PWV an additional tool for risk stratification. A pro-inflammatory environment produced by metabolic imbalance and direct vascular wall injury may mediate AoS in diabetes. Advanced glycation end products and increased RAAS activity may also contribute to these alterations.

Smoking, Nutrition, and Exercise

Smoking is an important modifiable cardiovascular risk factor. A single cigarette can acutely increase arterial wave reflection, brachial and aortic blood pressure, and AoS. Passive smoking has also been shown to reduce aortic flexibility. Cigarette smoking may influence AoS through endothelial damage, reduced vasodilatory ability, vascular remodeling, arterial calcification, elevated vascular tone, oxidative stress, inflammation, and elevated cholesterol [12].

Lifestyle modifications including smoking cessation, dietary changes, exercise, and weight reduction may influence AoS. Reduced salt intake has been linked to lower PWV independently of blood pressure. Exercise may reduce age-related increases in PWV and lower central PWV. Alterations in arterial wall tension, reductions in vasoconstrictors, and vasodilation through increased nitric oxide activity may contribute to these effects.

Inflammation and Aortic Stiffness

Serum biomarkers associated with AoS provide insight into its underlying mechanisms and may allow non-invasive assessment of vascular alterations [1]. Elevated AoS is linked to persistent inflammatory and infectious conditions. Increased arterial stiffness in chronic inflammatory disorders supports an important role for inflammation in vascular remodeling.

AoS has been associated with several inflammatory biomarkers. Sustained elevations in serum C-reactive protein (CRP) have been linked to longitudinal increases in PWV. A consistent relationship between CRP and AoS has also been observed after controlling for cardiovascular risk variables. Endothelial dysfunction represents one possible mechanism connecting inflammatory activity with vascular stiffness [13].

The association between inflammatory activity and AoS provides a mechanistic basis for investigating cellular inflammatory markers. Among these, NLR offers a representation of two different but interacting components of the inflammatory response: neutrophilic activation and lymphocytic regulation.

Neutrophil-to-Lymphocyte Ratio and Vascular Inflammation

NLR integrates information from circulating neutrophils and lymphocytes. Increased neutrophil activity represents an enhanced innate inflammatory response, whereas a reduction in absolute lymphocyte count may reflect increased apoptosis caused by systemic inflammatory signaling or a cortisol-driven physiological stress response.

Lymphocytes, particularly regulatory T-cell populations, perform important homeostatic functions through secretion of anti-inflammatory cytokines including interleukin-10 and transforming growth factor-beta. When lymphocytic containment declines, the local vascular microenvironment shifts toward unrestrained pro-inflammatory pathways. Absolute or relative lymphopenia may therefore compromise natural defenses against atherogenesis and promote vascular calcification and advanced wall remodeling [14].

Clinical observations described in the reviewed literature connect elevated NLR with increased PWV. In CAD, NLR has also been associated with anatomical complexity and multivessel obstruction, providing a link between systemic inflammatory activity and macrovascular structural abnormalities [15].

Pathophysiological Link Between NLR and Aortic Stiffness

The relationship between an increased NLR and AoS depends on the equilibrium between active cellular degradation of structural tissues and failure of vascular repair mechanisms.

Neutrophil Extracellular Traps and Luminal Remodeling

Neutrophils may cause aortic structural degradation through direct degranulation and NETosis. NETosis involves the extrusion of web-like structures known as neutrophil extracellular traps (NETs), composed of chromatin and cytotoxic proteins.

Within the aortic media and intima, NETs can act as scaffolding that gathers oxidized low-density lipoproteins and stimulates local endothelial cells. This process attracts additional circulating inflammatory leukocytes through upregulation of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1.

Intramural neutrophils can also produce free radicals including superoxide anions and hydrogen peroxide. These mechanisms reduce local nitric oxide bioavailability through impairment of endothelial nitric oxide synthase activity, contributing to vasospasm and functional mechanical stiffness [3].

Proteolytic Cleavage and Collagenous Fibrosis

The structural balance within the aortic media is maintained by vascular smooth muscle cells within highly organized elastic lamellae. Neutrophil-derived matrix metalloproteinases, particularly MMP-2 and MMP-9, can target and cleave elastin fibers. This enzymatic fragmentation compromises passive structural recoil of the vessel during diastole.

To stabilize the vascular wall against high intraluminal systolic pressure, vascular smooth muscle cells can shift from a contractile to a synthetic phenotype. Fragmented elastin is replaced by rigid, cross-linked type I and type III collagen, transforming the aorta from an elastic buffer into a more rigid and non-compliant conduit [16].

Loss of Lymphocytic Counter-Regulation

Lymphopenia represents a systemic shift toward a pro-inflammatory state. Regulatory T lymphocytes normally help prevent vascular remodeling by secreting IL-10, which reduces MMP production by tissue macrophages and neutrophils.

When absolute lymphocyte levels decrease, this protective feedback mechanism is diminished. The resulting inflammatory environment can promote vascular smooth muscle cell alterations, calcification, and remodeling [17]. Thus, both components responsible for an elevated NLR may participate in vascular structural changes: increased neutrophilic inflammatory activity and decreased lymphocytic counter-regulation.

Coronary Artery Disease and Atherosclerosis

CAD is characterized by the accumulation of atherosclerotic plaque within the coronary arterial lumen. Impaired blood flow reduces oxygen delivery to the myocardium. CAD encompasses a spectrum of clinical manifestations related to structural and functional abnormalities of coronary arteries and the coronary microcirculation.

Atherosclerosis represents an important underlying process in coronary disease. Both inherited and acquired risk factors can influence its development. Atherosclerotic plaques consist broadly of a fibrous cap surrounding a lipid-rich core containing cholesterol and cholesterol esters. Plaque rupture may result in obstructive vascular thrombosis [18].

Endothelial damage, lipid oxidation, lipid accumulation, and inflammation influence vascular healing and chronic inflammatory responses. T lymphocytes, macrophages, proliferating smooth muscle cells, and dysfunctional endothelial cells participate in atherogenesis. Early intimal plaques include smooth muscle cells, macrophages, and foam cells. With progression, cell death releases lipids and necrotic debris, while extracellular matrix produced by smooth muscle cells alters the developing atheroma.

Collagen becomes particularly prominent in the fibrous cap. A necrotic core containing lipid-laden cells, cholesterol crystals, foam cells, fibrin, thrombus, and other plasma proteins remains within advanced lesions, and calcification is frequently observed [19].

Inflammatory activity also influences plaque stability. Continuous remodeling of the fibrous cap can either stabilize the plaque or increase its vulnerability to rupture. Collagen represents a major structural component responsible for fibrous cap mechanical strength, and the integrity of the cap is affected by the balance between collagen synthesis and degradation.

Smooth muscle cells represent an important source of collagen within atherosclerotic plaques. Their loss can reduce fibrous-cap resistance. Matrix metalloproteinases regulate collagen turnover, and inflammatory processes can increase collagen degradation and reduce its production, thereby influencing the mechanical properties of the plaque [20].

The Pathophysiological Intersection of Aortic Stiffness, NLR, and CAD

Aortic stiffness, NLR, and CAD share several interconnected pathophysiological pathways. Inflammation, oxidative stress, endothelial dysfunction, extracellular matrix degradation, smooth muscle cell alterations, and changes in collagen and elastin are common mechanisms involved in both arterial stiffening and atherosclerotic vascular disease.

The aortic wall depends on organized elastic lamellae and vascular smooth muscle cells to maintain normal compliance. Neutrophil-mediated inflammatory activity can disturb this organization through oxidative injury and matrix metalloproteinase activation. Elastin fragmentation reduces the capacity of the aorta to recoil during diastole, while replacement with rigid collagen increases mechanical stiffness.

At the same time, similar inflammatory mechanisms participate in coronary atherosclerosis. Endothelial dysfunction facilitates lipid accumulation and inflammatory-cell recruitment. Macrophages, lymphocytes, and smooth muscle cells contribute to plaque development, while extracellular matrix synthesis and degradation influence plaque structure and stability.

NLR may consequently represent systemic inflammatory activity relevant to both processes. Increased neutrophilic activity promotes tissue injury, oxidative stress, NET formation, and extracellular matrix degradation. Reduced lymphocytic regulation diminishes anti-inflammatory control. Together, these changes create an environment favoring vascular remodeling.

The association is therefore biologically interconnected rather than representing isolated vascular abnormalities. Aortic stiffening reflects structural and functional changes within the central arterial circulation, whereas CAD represents atherosclerotic disease within the coronary circulation. Systemic inflammatory activity may contribute to both through overlapping molecular and cellular mechanisms.

Clinical Implications

AoS provides information about central vascular mechanical properties. PWV, particularly cfPWV, represents an important non-invasive approach for evaluating arterial stiffness. AoS can reflect hemodynamic abnormalities and structural vascular remodeling that may not be completely represented by conventional blood pressure measurements.

NLR, in contrast, represents an easily obtainable inflammatory index derived from circulating blood cells. Its biological relevance to vascular disease is supported by mechanisms involving neutrophil activation, lymphocytic regulation, oxidative stress, NET formation, matrix metalloproteinases, and vascular remodeling.

Because AoS and NLR represent different aspects of vascular pathology, their assessment may provide complementary information. AoS reflects mechanical and structural vascular changes, whereas NLR reflects systemic inflammatory balance. Their pathophysiological intersection with atherosclerosis supports continued investigation of these parameters in CAD.

However, AoS is influenced by multiple demographic, hemodynamic, metabolic, and lifestyle variables, including age, blood pressure, diabetes mellitus, smoking, diet, and physical activity. Interpretation of AoS and inflammatory biomarkers should therefore consider the wider cardiovascular risk profile.

Conclusion

Aortic stiffness represents an important structural and functional alteration of the arterial wall and is closely linked to central hemodynamics, vascular remodeling, inflammation, and oxidative stress. NLR reflects the balance between neutrophil-mediated inflammatory activity and lymphocyte-mediated regulatory mechanisms.

Neutrophil activation, NET formation, oxidative stress, matrix metalloproteinase activity, elastin degradation, collagen deposition, and reduced lymphocytic counter-regulation provide a pathophysiological framework linking systemic inflammatory activity with progressive loss of arterial elasticity.

CAD and aortic stiffness also share fundamental mechanisms, including endothelial dysfunction, inflammation, extracellular matrix remodeling, smooth muscle cell alterations, and changes in vascular structural proteins. Therefore, aortic stiffness and NLR represent complementary aspects of the vascular pathological processes associated with coronary atherosclerosis. Further evaluation of these interconnected mechanisms may improve understanding of vascular remodeling in patients with coronary artery disease.

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