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Review Article

Medical Science

PATHOPHYSIOLOGY OF AORTIC STIFFNESS AND NEW INSIGHTS INTO HEALTH AND DISEASE

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ABSTRACT Aging is defined as age associated decrease in physiological function essential for the endurance of wellbeing and fertility .Cardiovascular aging is an prime factor that determines duration of the life. Aging of aorta, associated with an adaptation to morphological and functional variations, mainly increase in diameter, thickness, Altered Endothelial function, cytoskeleton structural remodeling, attenuation in the buffering nature of high pressure and flow wave of proximal aorta . This makes end organs at failure due to the deleterious effects of speedy pulse wave on microcirculation especially on brain, liver, spleen, pancreas, kidney . Overtime this also increases work load on heart, left ventricular remodeling, increased heart rate, decreased diastolic filling time, hypertrophy of the Heart. The vessel wall compliance is determined by the ratio of elastin and collagen fibers. Aging is associated with a decreased ratio of elastin/collagen due to more degradation of elastin and/or increased accumulation of tougher collagen fibers. Elastin degradation is associated with progressive aortic stiffening. Age associated neuro hormonal changes which includes, increase in sympathetic activity, decreased baro receptor reflex sensitivity(short term regulatory mechanism for blood pressure), increased sensitivity of salt intake, up regulation of renin angiotensin mechanism, associated aldosterone dysfunction promotes vascular stiffening. Transmission of speed of pressure wave along the vessel wall is pulse wave velocity (PWV). Aortic PWV measurement is the gold standard test of aortic stiffness. units are meter/sec. Speed of PWV is increased with aging and pulse wave velocity is the index of the aotic stiffness.

KEYWORDS : vascular smooth muscle(VSMC), extracellular matrix (ECM). pulse wave velocity (PWV), Aortic Stiffness(AS), focal adhesion (FA) complexes matrix metalloproteinases (MMP) ,Advanced glycation end products (AGEs), nitric oxide (NO)

INTRODUCTION

Aortic Stiffening is a consequence of biological aging due to continous cycles of mechanical stress. Increase in pulse pressure is an indicator of aortic stiffness. Stiffness increases with pressure oscillations for each time when heart beats. It is leading cause of morality due to cardiovascular risks like Ischemic Heart Disease and Cerebrovascular Accidents, fast cognitive decline. WHO represents it as a global health problem. Vascular changes due to aging include increase in the content of collagen proteins partially as a compensatory mechanism against the loss of arterial elastin and partially due to the fibrosis. Glycation of structural proteins of the cell and extra cellular matrix to form advanced glycation end products. This makes cross linkages between collagen and other proteins and cell to cell adhesions. This further increases stiffness of the vessel wall.

Pathophysiology:

Vascular aging and vascular pathology interrelated by many mechanical biochemical, enzymatic, and cellular modifications that run in ↑/↓ manner. Alterations from the normal involves in the pathogenesis and progression of arterial diseases such as hypertension and atherosclerosis. Each cardiac cycle events involves mechanical stimuli, such as transmural pressure, velocity of the flow, vascular shear stress due to pulsatile pressure, and circumferential wall tension and all increase with age. Hemodynamic changes enhance VSM cytoskeletal remodeling, change in membrane conductance and biochemical signal activation that finally lead to functional changes in VSM tone. Cadherin junctions transmit mechanical signals from one cell to the next. mechanotransduction brings progressive age related changes in structural anatomy of the vascular bed[1] . Mechanical forces from inside or outside of the cell can affect the activity of regulatory factors of actin remodeling . The Arp2/3 complex forms new branched actin networks under the influence of nucleation promoting factor. This helps in cell locomotion. The polymerization and depolymerization of actin filaments and microtubules helps the cell, in carrying out essential functions include contraction ,cell shape changes, locomotion, force transduction, and adhesion[2]. γ - isoform of cytoplasmic actin, present in the cell cortex, lies near plasma membrane. Histamine and Potassium depolarization increase actin polymerization.

Activation of Rho signaling system helps in actin polymerization through phosphorylation. This promotes treadmilling, elongation and branching of filaments. This aids in the regulation of cell shape and stiffness and force transmission. Integrin-mediated adhesions regulate matrix remodeling, in relation to the cues of the chemical and mechanical stimuli of the vasculature. With in the physiological limits synergistic activity of FA ,actin and Integrin helps to auto regulate and maintain vascular tensile pressure and vascular shear stress near normal. [3,4] Aging involves ↑↑RhoA-Rho kinase signaling, promotes more stiffness.[5,6] Transforming growth factor(TGF-β), modulate endothelial cell differentiation, matrix production, and

apoptosis.[7]. Transmembrane integrin protein helps in mechanochemical transduction between cytoskeletal signaling complex and FA. As newtons 3rd law, balance of a force between the contractile myocardium and the resisting elastin bundles within the ECM of must be equal and opposite to achieve normal cardiac and vascular function[8]. "Half of the cell secrets lies out side of the cell". That is in the extracellular matrix (ECM). Vascular aging is allied with impaired endothelial function, low-grade inflammation of intimal layer. Stiffness of the aortic wall is contributed by vascular smooth muscle cell(VSMC) and from outside by extracellular matrix (ECM). Cross bridges among VSMC and ECM transmits mechanical force throgh focal adhesion (FA) complexes. The stiffness of the cytoskeleton regulatory protein, Neural Wiskott-Aldrich syndrome protein N-WASP, promote linear actin polymerization. Src-dependent signaling pathway that enhances tyrosine phosphorylation of FA proteins and FA remodeling. Talin-vinculin, involved in linkage with intigrin FA to actin of the CSK. Releasing stiffness of this interphase decreases FA size. Releasing the interface at Talin-vinculin and N-WASP is effective in decreasing aortic stiffness by directly inhibiting actin polymerization[9]. Smooth muscle focal adhesions stands future probable therapeutic site in preventing or reversing increases in aortic stiffness[10]

DISCUSSION:

Extracellular matrix (ECM) composition represents as pre-atherogenic state. Intima is the innermost layer, with a layer of endothelial cells hyperplasia and dysfunction and increased amounts of collagen. The media is composed of ↑ collagen, ↓elastin, ↑VSM contraction, ↓VSM relaxation, inflammation, calcification, The outermost artery layer is the adventitia, which is composed of ECM remodeling with ↑fibroblasts, ↑collagen, ↑proteoglycans. ECs are sensitive to matrix stiffness and increased intimal stiffness causes endothelial dysfunction. Aging cause disintegration and up regulation of matrix metalloproteinases (MMP) leads to degradation of elastin fibers and marked raise in arterial stiffness. Pulsatile wall stress also can cause elastin disintegration throughout the lifetime. Direct binding of calcium ions to elastin fibers causing calcification, elasto-calcinosis. ↑Elastases activity seen with age. The amounts of desmosine and isodesmosine and their crosslinks, important for cross linking elastin fibers also decrease with age. Increased collagen synthesis and collagen cross linking precipitated by non-enzymatic glycation process, which increases arterial stiffness with age. Glycation is a reaction between reducing sugars and proteins/fats, stiffens tissues and produce Advanced glycation end products (AGEs). They clogs up the blood vessels. AGEs disturb vascular homeostasis by decreasing nitric oxide bioavailability, an important vasodilator for maintain vascular tone and show anti inflammatory effects on the endothelium. ↑AGEs and ↓NO favors Atherogenesis and Atherosclerosis. VSMCs move from the media into the thickened intima in response to increased ECM matrix stiffness, EC-cell junction size↑ with polyploidy ,permeability↑, more activation of Rho kinase pathway to increase cellular contractile forces with loss of cell-cell junction integrity which enhances leukocyte transmigration. loss of endothelium integrity also cause hypertension[11]. Metabolic disorders precipitate Aging-related Arterial Stiffening , which include dyslipidemia, hypertension, insulin resistance, and hyperglycemia. Aging associated with ↑visceralfat, ↑circulating leptin are linked with an ↑in blood pressure. Hyperglycemia and dyslipidemia are the source of vascular endothelial dysfunction and oxidative stress. they initiates MMP2 activity. An enzyme ,calpain-1 also upregulated with aging, which trigger MMP2 resulting in elastin degradation, and ↑production of collagen as a pavement to vascular remodeling and arterial stiffening. Aging is associated with elevated sympathetic nervous activity and which may favour increased inflammation in aging to produce inflammatory cytokines and chemokines to cause tissue damage. Aging is also associated with deregulation of aldosterone and its receptors also cause inflammatory responses and T cell infiltration. Cardiotrophin 1 (CT-1), a cytokine of the interleukin-6 family, potent fibrotic factor, may be involved in aging-related arterial stiffening. Klotho gene was identified as an aging-suppressor gene which extends lifespan also decreases with aging [12].vascular smooth muscle cells produce monocyte chemoattractant proteins, damage the ECM and enhances atherosclerosis[13]. L-selectin, recruits neutrophil during microvasculature inflammation[14]. Nitric oxide (NO), a potent vasodilator, is synthesized from l-arginine by the enzyme NO synthase (NOS). Aging associated with ↓ amounts of l-arginine and endogenous endothelial eNOS inhibitors. Reduced nitric oxide (NO) bioavailability is either due to↓ NO synthesis or ↑NO degradation by oxidative stress, peroxynitrite formation (ONOO−)2, a cellular marker for oxidative stress. Asymmetric dimethylarginine (ADMA), initiates many cardiovascular pathologies and also blocks synthesis of NO. Tetrahydrobiopterin (BH4) is a cofactor essential for NOS activity is also ↓ with aging. Cyclooxygenase (COX) keeps an check in balance between secretion of vasodilators and vasoconstrictor. Aging associated with a move in favor of increased contractile secretors. Ageing also associated with increased activity of the renin-angiotensin-aldosterone system (RAAS) produces adverse vascular effects. Many vascular pathologies connected with up regulation of Ang II and ACE. Ang II initiates production reactive oxygen chemicals by activating NADPH, leading to inactivation of telomerase and damaging vascular bed[15,16] . Calpain-1,an enzyme, increases with aging. Its activation initiates Ang II up regulation, MMP2 expression and its cascade mechanism. Involves VSMC migration, elastin degradation, and collagen deposition proteolysis of vimentin and spectrin. Key factor in the damage of the normal vascular structural intrigity[17]. Vascular mitochondrial function impairs with aging and cause mitochondrial genomic instability[18]. Membrane/lipid rafts interconnect with cytoskeleton involves vascular diseases[19]. Telomere-induced vascular and cellular senescence may be enhanced in older individuals, due to less expression of telomerase[20].Vasa vasorum, a perivascular bed limits blood flolw in the vessel with atherosclerosis ,aging and precipitates aortic stiffness[21]. Arterial stiffness measurement is done from peripherally acquired waveforms using tonometry. Pulse wave velocity (PWV) measurement is non-invasive test. This involves measuring PWV, arterial distensibility ,assessments of peripheral arterial pressure waveforms . Using ultrasound, PWV measurements, distensibility, and compliance measurements are also obtained. Measurment of intimal stiffening helps in the better understanding of the underlying mechanisms to know the affinity in between arterial stiffening and cardiovascular disease.[22]

CONCLUSION

Vascular aging process, can be minimized by bringing Changes in mode of life, food habits, being fit, caloric restriction, and weight loss, particularly practicing yoga and aerobic exercise may inhibit or slow down the onset of vascular wall changes related to aortic stiffness. New research work on therapeutic advances in way of releasing age related stiffness in between cytoskeletal system and extra cellular matrix also should come clinical bed side.

Recognition of the relationship between vessel wall aging and cardiovascular diseases will give a great ray of hope in promising therapeutic advances for treating stiffness related heart disorders.

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