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Review Article

ELECTRO-PHYSIOLOGICAL IMPLICATIONS OF CONTROLLING ARTERIAL STIFFNESS THROUGH INTEGRATED APPROACH OF YOGA THERAPY

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ABSTRACT

Arteries are not as simple as we may think. As per World Health Organization (WHO), 80% of non- communicable diseases followed by death due to an abnormality with the arteries. Most of the part of the arteries may be small or large, made up by smooth muscle controlled by autonomic nervous system (Sympathetic and Parasympathetic) which gets hardened at any age depending upon mainly our life style. Yoga or Physical exercise can bring down the hardening characteristics of the arteries but significant findings are noted from IAYT (Integrated Approach of Yoga Therapy). We can survive more; we can have healthy life style if we accept this therapy as one of the main component like eating food or drinking water. Electrophysiological implications (measurement of electrical activities in the neurons or VSMC) on arterial stiffness are unknown to all of us. In this review, electrical events have been correlated with the mechanical events of VSMCs & activities of autonomic nervous system, eventually, the mechanical events of vascular smooth muscle cells are being modified, reflected to hardening characteristics have been highlighted.

Keywords: Cardiovascular disease; Arterial stiffness; Yoga Therapy; Depression & Anxiety.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death globally, affecting an estimated 17.9 million lives each year. CVDs come from the disorders of blood vessels. Coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease and other ischemic conditions in the heart comes under CVDs(1). Most of the CVD deaths are due to an abnormality with the blood vessels gets hardened in people of all the age groups. The most important risk factors are unhealthy diet, physical inactivity, stress, sedentary life style, tobacco use and harmful use of alcohol. The effects of these risk factors may show up in subjects with every age as raised blood pressure, raised blood glucose, raised blood lipids, and overweight and obesity. Cessation of tobacco use, reduction of salt in the diet, eating more fruit and vegetables, regular physical activity and avoiding harmful use of alcohol have been shown to reduce hardening characteristics of blood vessels which actually reduce the risk of cardiovascular disease. Health policies that create conducive environments for making healthy choices affordable and available, like Yoga therapy, is very much required for rectification, and action must be taken so that people are to adopt and sustain healthy behaviors. IAYT program is defined as the use of yoga practices for the prevention and treatment of medical conditions, includes therapies based on yoga, ayurveda and naturopathy (2). We have conducted few experiments and observed that arterial stiffness is more reduced if IAYT is followed as compared to Yoga or Physical exercise. Arterial stiffness can be measured easily at any aged of individuals from the value of pulse wave velocity (PWV) with the help of PC based cardiovascular analyzer (3). PWV is produced by systolic pumping of the heart travels along the aorta & other vasculature throughout the body, has come out as a marker for arterial stiffness indicating abnormalities in the cardio respiratory system. PWV becomes faster in stiffed arteries. Hence from the value of PWV we can estimate our characteristic of the arteries present in our bodies. If anybody has a facility to determine PWV, must go for after IAYT and before IAYT. Abnormalities with the structural components of the arteries can lead to an increase with the arterial stiffness which can be reversible if treated. Many options are there as far as treatment aspect is concerned but IAYT is most effective because IAYT can involve autonomic nervous system (4-5). The resting membrane potential (RMP) is being maintained adequately. In this review, role of autonomic nervous system on electrophysiological alterations have been brought, just to understand about why IAYT is more effective and not costly to treat patients suffering from CVD.

ARTERIAL STIFFNESS

As per common language, this stiffness is termed as hardening of arteries. Another way we can say “increased tension in the arteries” or decreased “elastic characteristic” which appear from the observation showing predominantly athermanous calcified plaques in the various layers of blood vessels (6-8). The more recent description of ‘arterial stiffening’ relates to alterations of structural components of the blood vessels, leading to reduced dispensability and stability of the arterial wall, and so decreasing the buffering capacity of arteries to pulsatile cardiac ejection during systole and diastole (Figure-1). Arterial stiffness describes the rigidity of the arterial wall also means failure to relaxation with the arterial or venous smooth muscle (vascular smooth muscle or VSMCs).

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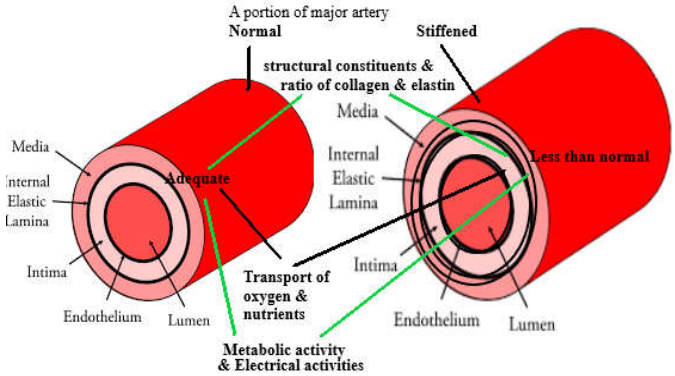

Figure-1: Major differences between normal & stiffened arteries

Stiffening of the arterial wall is determined by common mechanisms including reduced elastin/collagen ratio, production of elastin cross-linking, reactive oxygen species–induced inflammation, amount of calcification, contraction and relaxation of vascular smooth muscle cells, and endothelial dysfunction (9-10). Several studies have confirmed that advanced age, diabetes mellitus, dyslipidemia, hypertension, male gender, cigarette smoking and renal disease are risk factors of intimal calcification, resulting formation of fibro fatty plaques, formation of synthetic cells from contractile state of VSMCs which all together can increase the thickness of the blood vessel and reduce the diameter of the vessel. In this case(atherosclerosis 0r arteriosclerosis), vessel elasticity & stability are reduced. Mechanical integrity of blood vessel is reduced; hence the blood vessels become hardened. Clinically this condition is called vasculitis disease. According to the nature & appearance, vacuities is divided into three: 1) Monckeberg medial calcific sclerosis (patches of calcification in intima), 2) Atherosclerosis (hardening of all the major arteries with the loss of elasticity & stability) and 3) Arteriosclerosis (all minor arteries & veins). Most of the Western people are suffering from atherosclerosis which is very dangerous because blood vessel wall gets thickened and lumen of blood vessels become narrow, elastic nature of the vessel becomes zero. Body tissues did not get proper nutrition & oxygen (Figure-2). We can see these in all ischemic heart diseases, stroke, and hypertension (3-5).

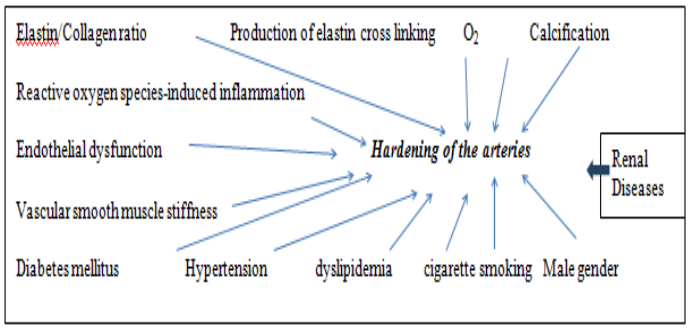

Figure-2: Cause of hardening the arteries both major & small.

IAYT

Best possible way to reduce hardening characteristic of the blood vessels is Integrated Approach to Yoga Therapy (IAYT). In this IAYT,we have 1) an opportunity to inhale huge oxygen through pranayama, 2) can improve the mobility of the body tissues 3) can provide adequate nutrition by taking vegetarian diet 4) can involve central nervous system(CNS) through meditation 5) can make friendship with various people in the society (4,5,8). As a whole, in IAYT, we have an opportunity to understand about life style modification which remain absent in taking physical exercise only or yoga alone. Let us understand one by one about why IAYT is the only and best way to manage hardening characteristic of the arteries. Physiological aspect is described here which I think most important for us (4).Five layered existence of human beings (components of IAYT) are:

1. Annamayakosha: Diet, kriyas, exercise and asana are the techniques at the physical level.
2. Pranamayakosha: Breathing exercise, pranamaya techniques
3. Monomayakosha: Various kinds of meditation like MSRT,MENT,CyclicMeditation,Om meditation etc.
4. Vijnamaya and 5. Anandamayakosha: Self-analysis, happy assembly, Yogic counseling and karma Yoga.

In this integrated approach of yoga therapy, one individual is a) actively involved in taking physical exercise, b) following/practicing yoga and meditation, c) regularly taking satvic food, d) attending daily prayer, and e) involved actively/like to participate in social gathering. All these have a possibility to stimulate parasympathetic nervous system (part of autonomic nervous system), tissue perfusion with oxygen increases, metabolic activities in a cell increases, resilience with the content structurally and functionally, resulting arterial stiffness or hardening characteristic of arteries remain absent or can be reduced.

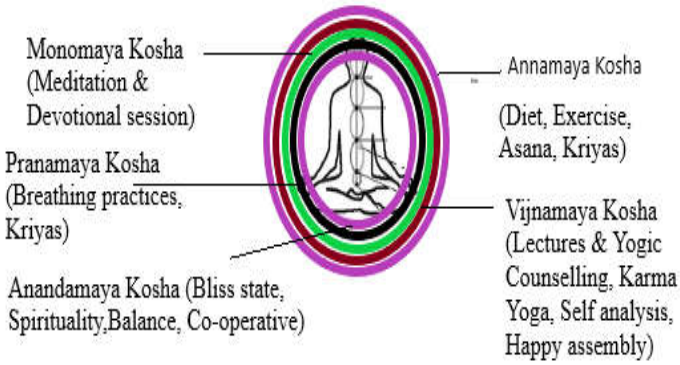

Figure-3: Various components of IAYT

VSMC

Hardening of the arteries comes from the abnormal or defective structural components as well as active mechanical events (contraction and relaxation of smooth muscle). Mechanical event depend upon generation of electrical events called slow waves and spike potentials (8).

Electrical events of VSMC/ICC –like cell: Resting membrane potential becomes -60 mv in both ICC-like cells and smooth muscle cells which can go on contraction followed by relaxation, due to the presence of electrically coupled gap junctions, generate rhythmic and simultaneous contractions by an involvement of entry of Ca^{++} channel (depolarization) and exit of voltage gated K^{+}channel (repolarization) respectively (Figure-4).

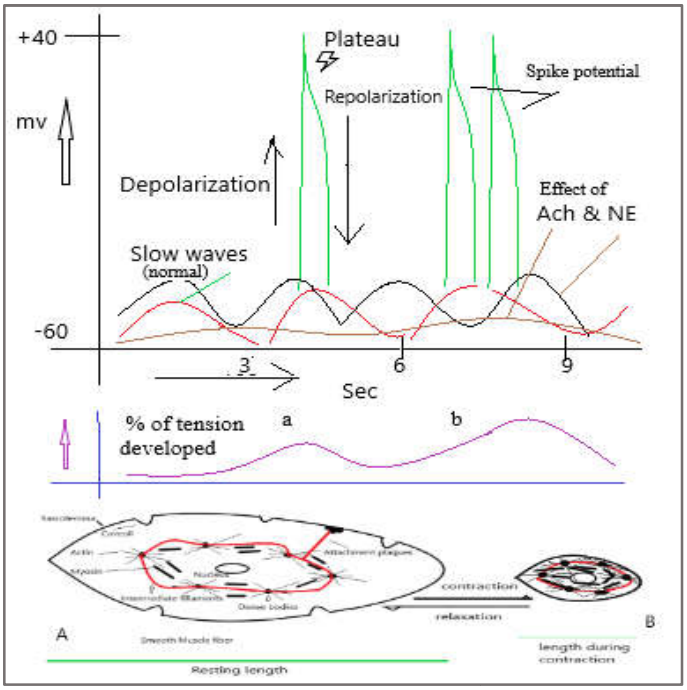

Figure-4: Co-relation between electrical (Slow waves & Spike potential) & mechanical events (A & B) of VSMC. a & b is the amount of tension developed.

A complete depolarization events consist of initial development of slow wave, followed by a development of spike potential/action potential (quick depolarization, membrane potential to reach +40 mv by an involvement of both slow and 'L' type Ca^{++} channel, then plateau phase by an involvement of both exit K^{+} and entry of Ca^{++} through 'L' type, and then repolarization by voltage gated K^{+} channel) (Figure-4). Various phases of spike potential have been noted (Figure-5).

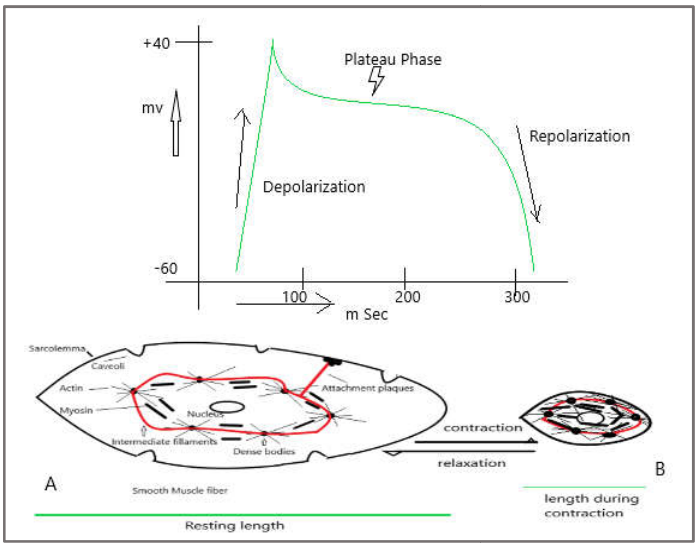

Figure-5: Various phases of spike potential shown with large scale

They result when a slow wave passes over an area of smooth muscle that has been primed by exposure to neurotransmitters released in their vicinity by neurons of the autonomic nervous system. The neurotransmitters, acetylcholine (Ach) or nor- epinephrine (NE) or both, are released in response to a variety of local stimuli, including distension of the wall of the digestive tube and serve to "sensitize" the muscle by making its resting membrane potential more positive. Acetylcholine is inhibitory for VSMC, has a tendency to hyperpolarize the VSMCs and opposite in response to an availability of nor-adrenaline from the nerve ending of sympathetic. Accordingly number of spike potential developed in VSMCs, less or no spike potential against parasympathetic stimulation and more and more spike potential against sympathetic stimulation (Figure-4). Tension developed (stiffness) in the VSMCs also depends upon number of spike potential being formed and again number of spikes depends upon strength of stimuli (Figure-4). As a whole, tension would be more when sympathetic is stimulated and the same would be less when parasympathetic is stimulated which can also be reflected in mechanical events of VSMCs. Length of the fiber during contraction has drastically reduced (B of figure-4), coming back to normal length during relaxation (A of figure-A). The actin filaments are stretched between dense bodies in the cytoplasm and attachment plaques at the cell membrane. The myosin filaments lie between the actin filaments(1,11-12). Furthermore intermediate filaments made by two proteins, one is desmin and another is vimentin support the cell structure. Smooth muscle cells contract slower than skeletal muscle cells, on the other hand they are stronger, more sustained and require less energy. Myofibroblasts represent a special type of smooth muscle cell which additionally have qualities of fibrocytes. They produce connective tissue proteins such as collagen and elastin for which reason they are also referred to as fixed (or stationary) connective tissue cells (8). Isolated single smooth muscle cells have been observed contracting in a spiral corkscrew fashion or squeezing of different protein present in VSMCs. Smooth muscle-containing tissue needs to be stretched often, so elasticity is an important attribute of smooth muscle. Smooth muscle cells may secrete a complex extracellular matrix (ECM) containing collagen (predominantly types I and III), elastin, glycoproteins, and proteoglycans. Smooth muscle also has specific elastin and collagen receptors to interact with these proteins of the extracellular matrix. These fibers with their extracellular matrices contribute to the viscoelasticity of these tissues. For example, the great arteries are viscoelastic vessels that act like a Windkessel, propagating ventricular contraction and smoothing out the pulsatile flow, and the smooth muscle within the tunica media contributes to this property(13-14).

Mechanical events of VSMC/ICC- like cell:

Contraction (B) and relaxation (A) in VSMC is a very complex process(Figure-4 &5).Smooth muscle is phosphorylated during its activation, which creates a potential difficulty in that simply reducing calcium levels will not produce muscle relaxation. Myosin light chain phosphatase (MLCP), instead, is responsible for de-phosphorylation of the myosin light chains, ultimately leading to smooth muscle relaxation. Contraction and complete relaxation also depend upon the ideal composition extracellular matrix (ECM), allowing it to withstand a wide range of tensile stresses, while preserving its shape and integrity due to have complex composition. Another important clinical aspect of smooth muscle relaxation is the mechanism of nitric oxide. Nitric oxide forms via nitric oxide synthase in endothelial cells; it is then able to diffuse out of the endothelium into smooth muscle cells. Nitric oxide then stimulate the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) by binding to and activating the enzyme guanylylcyclase. In smooth muscle cells, the increase in cGMP will lead to stimulation of cGMP-dependent protein kinase, which in turn activates MLCP, leading to dephosphorylation of myosin light chains and eventual smooth muscle relaxation. Electrical alteration

Steps involved in smooth muscle cell contraction (Step-1 to3):

1) Depolarization of membrane or hormone/neurotransmitter activation 2) L-type voltage-gated calcium channels open 3) Calcium-induced calcium release from the SR 4)Increased intracellular calcium 5) Calmodulin binds calcium 6) Myosin light chain kinase

activation 7) Phosphorylation of myosin light chain 8)Increase myosin ATPase activity 9) Myosin-P binds actin 10) Cross-bridge cycling leads to muscle tone (Power stroke) (Figure-5).

Steps involved in smooth muscle cell relaxation (Step-4):

Muscle fiber can go on relaxation if no further stimulus is there (Figure-5), Concentration of ca^{++} falls, resulting cross-bridge activity ends when phosphate is removed from the head due to stimulation of myosin light chain phosphatase (MLC Phosphatase). Calmodulin becomes inactive; a fresh molecule of ATP can join which again go for hydrolysis to form energized head for participating next contraction.

Interaction of VSMCs within the extracellular matrix (ECM):

Contraction & relaxation of VSMC depend upon structural constituents of ECM because interaction between ECM & mechanical behavior (Complete contraction followed by complete relaxation) trigger significant variations of stiffness. Again, this mechanical events as well as structural characteristics of ECM depend upon electrical events (slow waves & spike potential). The intermediate filaments network is one of the important cytoskeleton systems (vimentin), widely distributed from the plasma membrane to nucleus, providing mechanical and structural integrity for the VSMC, In conjunction with other associated proteins, intermediate filament support cell shapes, able to adjust contraction/relaxation states.

Effect of exercise/Physical activity:

Physical activity/ exercise improve endothelial function by reducing inflammatory and oxidative damage signaling with an increase in antioxidant enzymes and NO availability. These improvements prevent or delay the onset of frailty and decrease clinical cardiovascular disease. Mitochondrial function in the VSMC is improved, ROS (Reactive Oxygen Species) production is also inhibited, protein synthesis is increased and protein degradation is reduced. All these effects depend upon electrical activities like resting membrane potential followed by spike potential. One of the best studied marker of physical fitness is maximal oxygen uptake (VO_2 max), which can decrease mortality rate, demonstrated that the endothelium of veins and the aorta are hydrophobic due to a coating of surface-acting substances and that bubbles can be stable more of less indefinitely on a hydrophobic surface. Since it has been shown that NO is released from the endothelial cells following exercise, and that NO inhibits leucocytes and platelet adhesion and aggregation. It is reported that an increase in NO will also reduce the hydrophobicity of the endothelial wall, thereby reducing the number of nuclei. It has been demonstrated that NO can act both as a mediator for cell injury and as a cytoprotective agent. The mechanism for the preventive effect of a single bout of exercise on bubble formation may be linked to NO production and repolarization of nodal cell/VSMC

AUTONOMIC INNERVATION ON VSMC/ICC –LIKE CELLS:

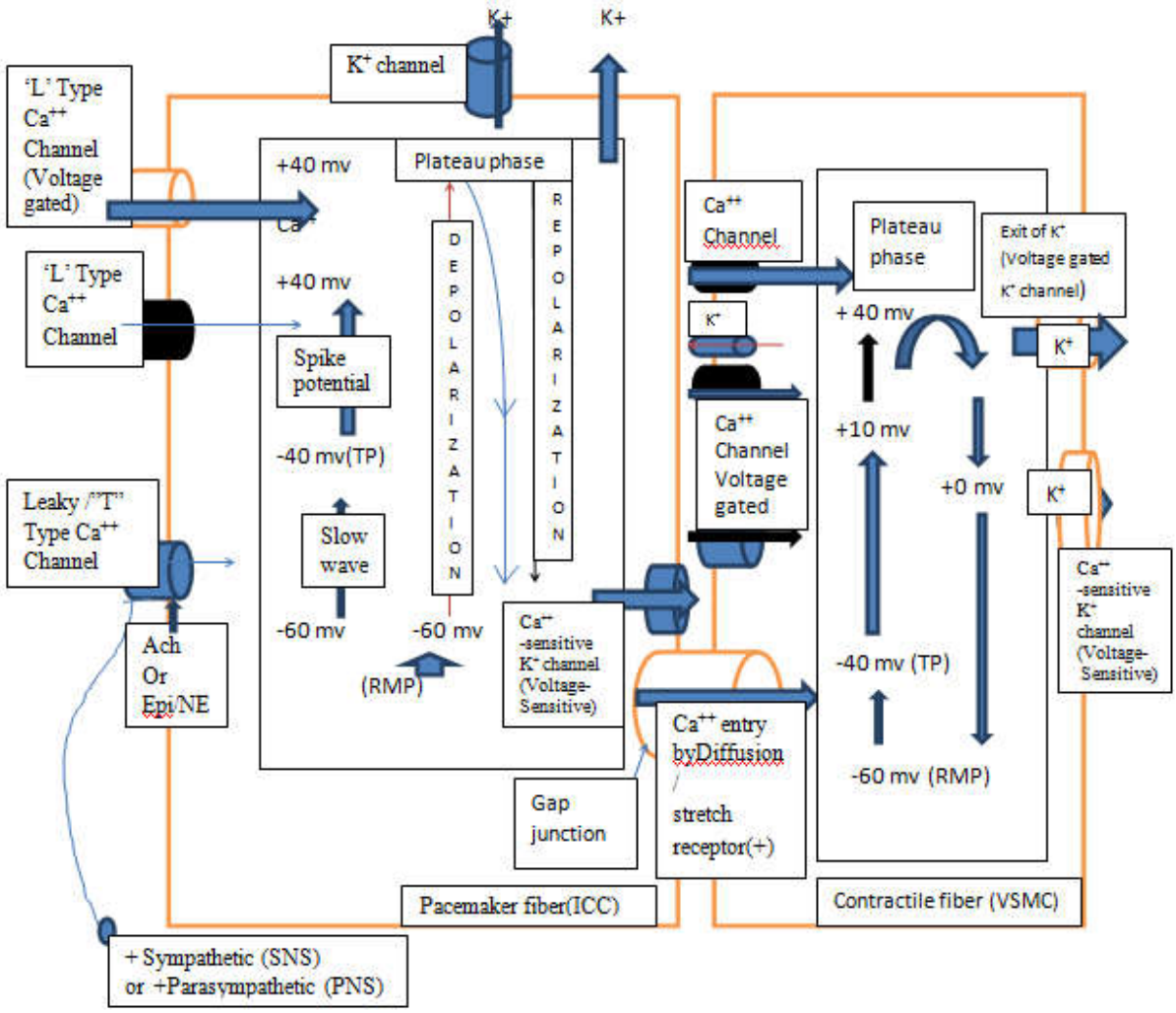

Figure-6: Electrophysiological events in VSMC and factors affecting electrophysiological events.

The autonomic nervous system (Sympathetic & parasympathetic) plays a vital role in the regulation of vascular wall contractility. There is a big possibility of availability of more acetylcholine when person go on following IAYT. Acetylcholine can bind with cholinergic receptor (Muscarinic type-3), will inhibit entry of Ca ⁺⁺ into the VSMC/ICC –like cells, instead of depolarization, hyperpolarization may be seen. Therefore VSMC will not go for contraction. Once, there is no contraction, relaxation also will remain absent. Elasticity will remain (Figure-6).Molecular steps (Figure-7) of contraction and relaxation will not be involved if parasympathetic is involved in IAYT.

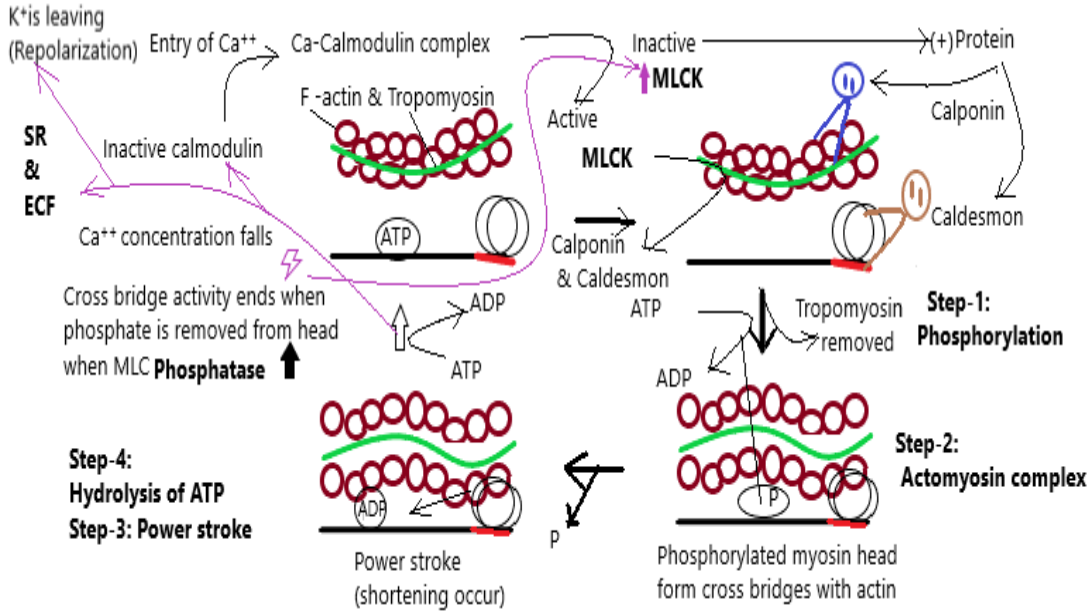

Figure-7: Molecular steps of muscle contraction and relaxation.

Factors modulating hardening characteristics by sympathetic & parasympathetic:

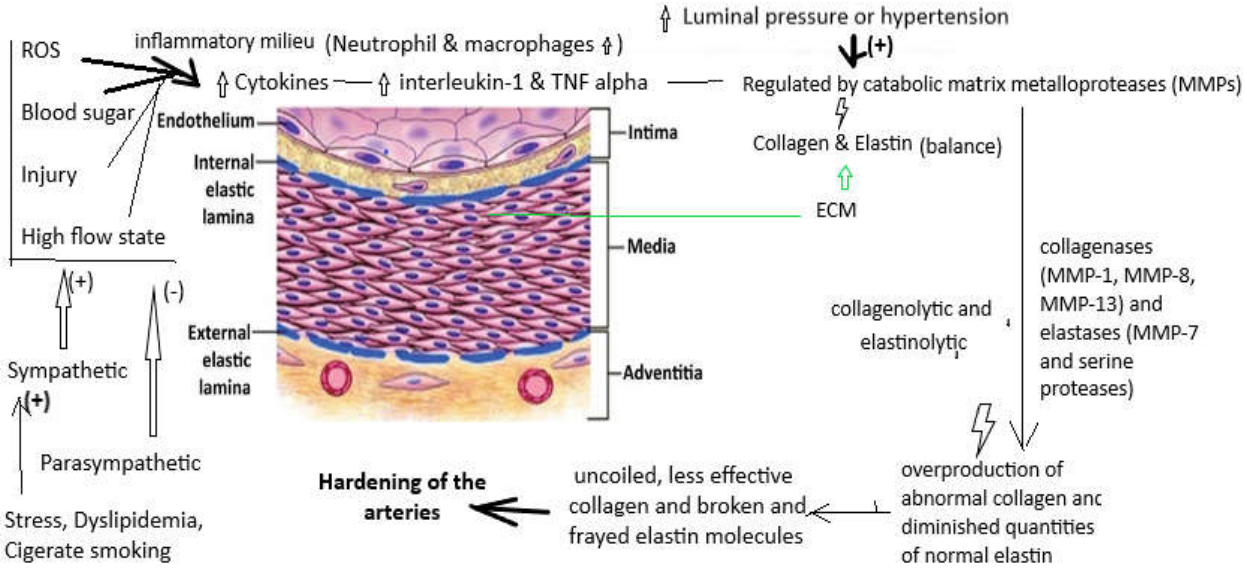

Figure-8: Factors affecting hardening characteristics of the blood vessels

Sympathetic is activated by stress, dyslipidemia, cigarette smoking which can increase blood sugar, ROS level, high flow state leading to inflammation (increased number of neutrophils and macrophages). Concentration of interleukin -1 and TNF-α are increased, regulated by MMPs (matrix metalloproteases), MMPs are more secreted in hypertension or to increased luminal pressure, which actually increase the production of collagen and diminish the quantities of elastin through collagenolytic and elastinolytic properties(8, 15-20). Therefore, uncoiled less effective collagen and broken frayed elastin molecule will never contribute to elastic properties of the blood vessels. Opposite effect will be there if parasympathetic is involved. IAYT is the best to operate parasympathetic; hence elasticity of the blood vessels will remain (Figure-8).Parasympathetic is involved on the phosphorylation events,leading to a decrease in intracellular calcium (inhibit L type Calcium channels, inhibits IP3 receptor channels, stimulates sarcoplasmic reticulum Calcium pump ATPase), a decrease in the 20kd myosin light chain phosphorylation by altering calcium sensitization and increasing myosin light chain phosphatase activity, a stimulation of calcium sensitive potassium channels which hyperpolarize the cell(ICC-like /VSMC)(21-29).

CONCLUSION

IAYT is a very simple and reliable process to make ourselves healthy. Every day, we must accept IAYT as a routine work. We must arise early in the morning, must go for running, jogging etc, go for asana, joined with groups for open interaction, and must be looking for satvic food. This actually hit our parasympathetic nervous system which releases acetylcholine from their nerve ending. Acetylcholine is secreted from the nerve ending of parasympathetic and makes VSMC in resting state without much involving the contracting and relaxing machinery. We feel happy and tension Free State.

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Conflict of Interest: None

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