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REVIEW ARTICLE

VASCULAR AGING

ABSTRACT

The incidences of heart and vascular diseases increase with age and it is known to be the leading cause of mortality and morbidity in developed countries. Although aging is a chronological process, it is known that some environmental factors, chronic diseases and lifestyle may form and speed up the process of aging, especially of the cardiovascular system. Due to the changes that occur at structural and molecular levels in the vascular system of the elderly, the function of the cardiovascular system becomes impaired. Vascular aging is a normal physiological process, which develops gradually along with the age. The most known pathophysiological vascular changes are the ones beginning at the intimal level such as atherosclerosis. However, the other vascular pathologies leading to the thickness in media and adventitia and remodeling are also seen in aging even if atherosclerosis is not present. These changes include an increase in collagen fibers and covalent bonds, local inflammation, fibrosis, mucous matter storage, a marked decrease in the elastin composition and the classifications of elastic laminae. Aging related differences develop independently of the atherosclerosis. They create a cumulative effect by activating the atherosclerosis with contributions of other factors such as hypertension, dyslipidemia, diabetes mellitus, renal failure, dietary, genetic and smoking along with aging. When the format and the mechanism of occurrence of these changes in the growing elderly population are carefully managed today, we can take a considerable step towards protecting the community from cardiovascular events and diseases.

Key Words: Aging; Atherosclerosis; Blood Vessels.



DERLEME

DAMAR YAŞLANMASI

Öz

Kalp ve damar hastalıkları insidansının yaşlanmayla birlikte artış gösterdiği ve gelişmiş ülkelerdeki mortalite ve morbiditenin önde gelen nedenlerinin başında yer aldığı bilinmektedir. Yaşlanma kronolojik bir süreç olmakla beraber bazı çevresel faktörler, kronik hastalıklar ve yaşam şeklinin yaşlanmanın özellikler kardiyovasküler sistem üzerindeki etkilerinin meydana geliş şekli ve sürecini hızlandırabildiği bilinmektedir. Yaşlılıkta damar sisteminde meydana gelen yapısal ve moleküler düzeydeki değişiklikler nedeniyle kardiyovasküler sistem fonksiyonlarında bozulmalar meydana gelmektedir. Damar yaşlanması yaşla beraber yavaş yavaş gelişen normal fizyolojik bir süreçtir. Patofizyolojik vasküler değişikliklerin en bilinenleri ateroskleroz gibi intimal düzeyde başlayan değişikliklerdir. Bununla birlikte media ve adventisyada kalınlaşma ve remodelinge yol açan diğer vasküler patolojiler ateroskleroz yokluğunda dahi yaşlılıkla beraber ortaya çıkmaktadır. Bu değişiklikler kollajen lifleri ve kovalen bağlarında artış, lokal inflamasyon, fibrozis, mukoid madde depolanması, elastin içeriğinde belirgin azalma, elastik lamina kalsifikasyonları şeklindedir. Yaşlanmayla ilişkili bu değişiklikler aterosklerozdan bağımsız olarak gelişen bir süreçtir, çoğu zaman yaşlanmayla beraber, hipertansiyon, dislipidemi, diyabet, böbrek yetmezliği, diyet, genetik ve sigara kullanımı gibi diğer faktörlerin de katkılarıyla aterosklerozu da aktive ederek kümülatif bir etki oluşturmaktadır. Bu değişikliklerin oluş şekli ve mekanizması dikkatli incelendiğinde günümüzde artan yaşlı nüfusta meydana gelebilecek kardiyovasküler olaylardan korunmakta önemli bir adım atılabilecektir.

Anahtar Sözcükler: Yaşlanma; Aterosklerozis; Kan Damarları.



In developed countries, cardiovascular diseases play a major role as mortality and morbidity causes. Although cardiovascular disease and stroke incidences are under control by effective treatment methods for some risk factors such as hypertension and hypercholesterolemia. They have been known to increase with the age (1).

Aging occurs at molecular, cellular, tissue levels and in the systems of the organism. It advances with time independently of the causes such as any accident or disease and it includes all irreversible structural and functional changes (Table 1). Though aging is a chronological process, personal and environmental factors are mostly effective for this process to occur earlier or later. Therefore, the physiological changes occurring with age are also observed to different degrees in individuals (2).

While United Nations accepts aging population as the age of sixty and over, the World Health Organization accepts this at the age of sixty-five and over. The latter definition is mainly adopted in national and international aging studies(3). Many factors such as the changes in lifestyle by age, retirement, beginning of sedentary life and the diversity in the nutritional habits may be confused with the natural alterations of aging. In addition, the changes occurring in other organ systems also closely affect the changes in cardiovascular system as a result of aging. Therefore, while a variety in cardiovascular system is described, the genetic factors and life conditions should be considered.

The incidence of cardiovascular disease increases along with age, and the majority of mortality caused by cardiovascular system diseases has been observed in population over the age of sixty-five. Vascular aging is a normal physiological process, which develops gradually along with the age. The researchers throughout the world have recently started to figure out the intricate physiopathology of this occurrence. The most known pathophysiological vascular changes are the ones beginning at the intimal level such as atherosclerosis. However, the other vascular pathologies leading to the thickness in media and adventitia and remodeling are also seen in aging even if atherosclerosis is not present (1,3).

THE STRUCTURE OF NORMAL ARTERIES

1. Elastic Arteries; Aorta and its large branches are in this group. Their diameters are more than 7 mm but their walls are thin with regard to their diameters. The most developed layer in arteries is tunica media. Flexible laminas contract at systole and decrease the pressure alterations. At diastole, fle-

Table 1— Age-Associated Changes in Human Arterial Structure and Function.

Subendothelial collagen fibers and covalent bonds	↑
Local inflammation	↑
Arterial wall fibrosis	↑
Elastin composition	↓
Elastin fragmentations	↑
Proteoglycans	↑
Matrix metalloproteinase activity	↑
Intimal migration and proliferation of vascular smooth muscle cells	↑
Arterial distensibility	↓
Pulse wave velocity	↑
Total peripheral resistance	↑
Endothelial permeability	↑
Endothelial nitric oxide release	↓
Inflammatory markers and mediators	↑
β Adrenergic mediated vasodilatation	↓

xible contraction regulates the arterial pressure. Away from the heart, the flow rate of arterial pressure and the pressure changes decrease (4). Endothelium is a single-fold flat epithelium. Endothelia cells are 10-15mm in width and 20-25 mm in length. Cells are connected to each other with tight junctions and gap junctions and make up the barrier. They have rich pinocytotic vesicles. There are electron-dens bodies surrounded by membrane, known as Weibel-Palade bodies (von-Willebrand factor) which are 0,1 mm in diameter and 3 mm in length in endothelium cells. They also have structures that include Factor VIII (4,5).

The fibers helping the rhythmic contractions and relaxations are arranged longitudinally. Smooth muscle cells are present in this layer. They both contract and synthesize the extracellular inter-substance and fibrils. The amount of fiber increases while coming closer to tunica media. The flexible fibers intensify at the border of media, and constitute elastic internal membrane. But as it resembles media, it is difficult to differentiate it (5).

There are 40-70 flexible laminas that increase with age in tunica media. Gaps among the laminas are called as windows.

There are smooth muscles, reticular fibers, vasa vasorum and chondroitin sulfate among the flexible membranes. Elastic arteries do not have a real elastic external membrane. Tunica adventitia is slim and about half of the media thickness in size. It consists of fibro elastic connective tissue including flexible collagen fibers, vasa vasorum and nerves (4).



Muscular Arteries: It is the most common arterial type delivering the blood to the organs. Their diameters are 2,5-7 mm. Depending on the contraction of smooth muscle in media, the blood flow is regulated by local, hormonal and neural stimuli. From the flexible arteries to the muscular arteries, elastic material decreases, and smooth muscles increase. They have very clear elastic internal and external membranes (4,6).

Tunica Intima: It is thinner than elastic arterial intima and while a small number of smooth muscle cells exist in the sub-endothelial layer, internal elastical membrane is very clear. Rarely, two internal elastical membranes may co-exist (bifid internal elastic lamina). As in the elastic arteries, endothelium has prolongations passing to internal elastic membranes. These prolongations are attached to the smooth muscles located in media that is close to intima by means of gap junctions (7).

Tunica Media: It is mainly made up of smooth muscle cells. Smooth muscle cells here are smaller than in the internal organ walls. Several smooth muscle bands facing intima have longitudinal course. There are 40 layers of concentric smooth muscles in greater muscular arteries while there are only 3-4 layers of the smooth muscles in the small muscular arteries. As the vascular structures branch out, the number of layers decreases. Every smooth muscle cell is surrounded by external lamina, which is similar to basal lamina. Matrix of the tunica media reveals PAS positive reaction. There are elastic, reticular fibers, small amounts of collagen fibers and chondroitin sulfate among the smooth muscles in proteoglycan-structured matrix. Smooth muscles have a function in the production of matrix and fibers. Vasa vasorum exist among the muscle cells. They have a clear external elastic membrane that is made up of several thin elastic layers, but it is thinner than the internal elastic membrane. There are several windows existing among the layer (8).

Tunica Adventitia: Collagen tissue fibers, fibroblasts, lipid cells, vasa vasorum, lymphatic vessels, and nerve ends without myelin exist in this layer. The neurotransmitters released from the nerve ends depolarize some smooth muscle cells at the top by passing through the windows of the external elastic membrane and reaching media. The stimulus is transferred to other smooth muscle cells by gap junctions. Vasomotor nerves also exist. Intersubstance material is mostly made up of dermatan sulfate and heparan sulfate. Collagen and elastic fibers have a longitudinal course enough to facilitate the shrinking of the arteries when injured (9).

Arterioles: They are terminal arterial vessels regulating the blood flow to the capillaries. The width of their walls is simi-

lar to the diameter of their lumens. They are supported by sub-endothelial collagen tissue including endothelium, type III collagen and several elastic fibers. While thin and windowed internal elastic membrane exists in the small arterioles, 2-3 layers of smooth muscle exist in large arterioles. They have no external elastic membrane. Adventitia layer is the thin fibro elastic collagen tissue containing a few fibroblasts (10).

The arteries supplying blood to the capillary bed are called as metarteriols. Their smooth muscle layers have intervals. Smooth muscle cells are located separately from each other. Smooth muscle cells occur sphincter (precapillary sphincter) regulating the blood flow to the capillaries. It balances the pressure difference between arterial and venous systems.

STRUCTURAL CHANGES IN THE VASCULAR SYSTEM IN AGING

The vascular network normally sends the blood from the left ventricle to the tissue capillaries and in order to provide a continuous blood flow through the vascular system, it has a buffering property for the continuous injections of the ventricle, especially in aorta. This feature called "windkessel effect" is related to the high flexibility in aorta and other large arteries (11). Combined with aging, elongation and tortois- es occur in especially large arteries. Enlargement in lumen and wall thickness, including especially intima and media layers, are observed. Age associated morphological changes in the vascular wall are listed in table (Table 2). These changes result in an increase in vascular sclerosis, systolic blood pressure, pulse pressure and a decrease in diastolic pressure (12-15).

While the effect of aging in muscular arteries is at a lower level, the changes in elastic arteries are fairly clear. These changes include an increase in collagen fibers and covalent bonds, local inflammation, fibrosis, mucous matter storage, a marked decrease in the elastin composition and the classifications of elastic laminas (16,17). Aging related differences develop independently of the atherosclerosis. They create a cumulative effect by activating the atherosclerosis with contributions of other factors such as hypertension, dyslipidemia, diabetes mellitus, renal failure, dietary, genetic and smoking along with aging. Sclerosis in the vascular wall is related to the relative amount of elastin and collagen materials. Much more elastin exists at the proximal parts of the arterial system than the distal parts, therefore enlargement and sclerosis are evident in especially aorta and its branches (18). Depending on age, collagen accumulation and elastin degradation as well

**Table 2**— Age Associated Changes in Intima Media and Matrix.

Intima
Increased thickness (smooth muscle cells and matrix)
Increased Matrix metalloproteinase
Increased expression of adhesion molecules
Increased nitrite and nitrate levels
Decreased endothelial nitric oxide synthase activity
Increased Angiotensin converting enzyme activity
Media
Increased thickness
Increase in size but decrease in number of smooth muscle cells
Matrix
Increased collagen content
Increased collagen cross-linking (nonenzymatic glycation)
Increased fibronectin
Decreased elastin: calcification and fragmentation
Increased glycosaminoglycans

as intramural accumulation of proteins such as integrin, fibronectin and desmin in the vascular wall play an important role in the increase of sclerosis in vascular wall (17,18). As a result of the disappearance of the buffering effect of the vascular network, the increase in atherosclerosis may have a destructive effect especially on the microcirculation in brain, kidney and heart. Endothelium cells play an important role in regulating many arterial features such as vascular tonus, permeability, angiogenesis and the response to inflammation. In addition to sclerosis, enlargement and thickness in the vascular wall, the changes are also observed in endothelium layer of the vascular lumen along with aging. Irregularity and elongation are seen in the endothelial cells due to the high rate of laminar blood flow. Consequently, endothelium function and its regenerative capacity diminish along with age. Endothelial cells are exposed to risk factors such as hypertension, smoking and hyperlipidemia, lose their protective effects against the adhesion of thrombocyte, monocytes and neutrophils (19). By producing various autocooids apart from substance transportation, endothelium layer plays an important role in regulating many features such as vascular tonus, angiogenesis and response to inflammation (20). Nitric oxide (NO) is the most well-known endothelium derived autocooid. It has a protective action as a vasodilator, as an inhibitor of leukocyte adhesion, thrombocyte aggregation, and smooth muscle cells proliferation. It is known that the decrease in production and bioavailability of NO is observed by age. As a result of the decreased NO production and its effect, vasodilatation mecha-

nism related to the endothelium diminishes. In females, the decrease in the NO dependent vasodilatation mechanism occurs about ten years later than males, whereas it progresses very rapidly in males. Additionally, the decrease in the release of hyperpolarizing factor via endothelium, which is another effective substance, and the increase in the release of vasoconstrictor products such as endotheline-1 and thromboxane A2 are observed (21).

In addition to impaired endothelial function and chronic vascular inflammation, arterial stiffness increase. As the large conduit arteries stiffen, aortic pulse wave velocity and pulse pressure also increase. Increased aortic pulse wave velocity results in early return of the reflected pressure wave, which produces significant systolic pressure augmentation and a decrease in diastolic pressure. Decreased diastolic pressure results in decreased coronary artery blood flow. The sequelae of increases in systolic hypertension result in left ventricular remodeling, diastolic dysfunction, and accelerated development of atherosclerotic lesions, all of which create a potential risk factor for increased cardiovascular mortality in the elderly patients (18).

FUNCTIONAL CHANGES IN THE VASCULAR SYSTEM IN AGING

As a consequence of structural effects occurring in the vascular network along with aging, the changes in blood and pulse pressures are mainly observed. The main indicators of blood pressure are blood volume, atherosclerosis and peripheral vascular resistance. Depending on sclerosis developing in the arterial wall, diastolic blood pressure decreases and systolic blood pressure increases. In a study by Franklin et al., it was demonstrated that systolic and diastolic blood pressures increased together up to 5th decade, and that the diastolic blood pressure diminished in the later period (15). Thus, isolated systolic hypertension after the 6th decade is observed most commonly.

A large amount of systolic blood stays in aorta due to its elasticity and provides the continuity of blood flow during diastole. As a result of the disappearance of the elasticity of aorta along with aging, the pressure on aorta increases significantly especially during systole. Increases in pulse pressure as well as an increase of difference among systolic and diastolic pressures are also seen. Therefore, the pulse pressure is used as the effective indicator of atherosclerosis in especially elastic vessels (15).



HEMOSTATIC AND CLINIC FINDINGS

Though age is one of the most important factors of cardiovascular mortality, atherosclerosis also causes an important increase both in cardiovascular mortality and morbidity risk occurring with age and in cardiovascular mortality and morbidity risk independent from age. Owing to the post-atherosclerosis and structural changes occurring in especially elastic arteries, systolic hypertension develops with aging. Depending on hypertension, failure findings in the left ventricle will develop within time. The impairment in left ventricle diastolic functions seen most commonly in the old population leads to the main cause of heart failure findings. Additionally, the prolonged systolic ejection time is also the second factor causing the increase in wall thickness as well as the arterial pressure. As a consequence of all these factors, vascular damage increases and then the clinical picture such as the increase in workload of the heart, left ventricular hypertrophy, cerebrovascular events and deterioration in renal functions occur. The vascular changes that occur as a result of aging are also observed noticeably in coronary arteries. For this reason in older ages, the risk of coronary artery disease also increase (22).

DISCUSSION

With aging, structural changes such as fragmentation in elastic fibers, slimming and deterioration in arterial wall, as well as the disappearing in elastin fibers and elastic lamina are observed (23). Since the amount of elastic fibers in proximal ascending aorta is higher than the amount of collagen fibers, the changes occurring with aging become very prominent in this part.

Taking into account all of the data, it is seen that the structural changes in the large arteries and aging play an important role in cardiovascular mortality. It is primarily known that the changes occurring in the large vessels alter the left ventricle diastolic functions and cause diastolic heart failure. More than 50% of heart failure cases observed in the older population occur with this mechanism (24). Additionally, enhanced pulse wave velocity and prolonged ejection time lead to the increase in systolic blood pressure and pulse pressure. Therefore, it may lead to end organ damages such as renal damage or cerebrovascular event with the left ventricular hypertrophy and enhanced cardiac work load (16). The dysfunction occurring in endothelial cells is mostly observed in coronary arteries and they lead to coronary dysfunction (22). Another important matter is that the regression occurring in barore-

ceptor control of the cardiac rate increases the susceptibility to arrhythmia in the older population. In a study by Rodeheffer et al., it was shown that the regular exercise inhibited the regression in baroreceptor control of cardiac rate in the older population (25).

Currently, reducing pulse pressure is the most effective strategy to prevent arterial stiffness and decrease wave reflections in elderly patients with systolic hypertension. In addition, the roles of newer therapies targeting at breaking collagen cross-links or preventing their formation should be investigated (18).

Consequently, further studies on the effects of aging on structural, functional, and molecular levels in cardiovascular system should be prioritized. Through these studies, environmental cardiovascular occurrences can be minimized and therefore an important component of healthy aging would be provided.

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