Aging and carotid remodeling

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Abstract

As we age, remodeling takes place in our body, and while some changes can be attributed to the mere aging process, others can be attributed to an early pathological process of subclinical changes typical in atherosclerosis. Aging is an imminent part of life and is a risk factor for atherosclerosis and cerebrovascular disorders in both sexes. Once established, cerebrovascular diseases are strong contributors in worldwide morbidity and mortality scales, and stroke is the worldwide leading cause of mortality and disability in adults. Cerebrovascular disorders in Croatia are the second leading cause of mortality and the first in adult disability. In this article, we attempt to present all the changes of aging in the common carotid artery thus distinguishing them from a pathological processes.

Keywords: Aging, IMT (intimal-medial thickness), Arterial Stiffness, Arterial Compliance, Endothelial Dysfunction

Sažetak

Starenje i remodeliranje karotida

Kako starimo, u našem se tijelu odvija preobrazba i dok se neke promjene mogu pripisati samom procesu starenja, druge se mogu pripisati ranom patološkom procesu subkliničkih promjena svojstvenih aterosklerozi. Starenje je neizbježan dio života i čimbenik je rizika za aterosklerozu i cerebrovaskularne poremećaje kod oba spola. Jednom uspostavljena, cerebovaskularna bolest je unutar prvih pet uzroka morbiditeta i mortaliteta u svijetu, a isto vrijedi i za Hrvatsku u kojoj je moždani udar među prvim uzrocima smrtnosti i invaliditeta u odraslih osoba. Cerebrovaskularni poremećaji u Hrvatskoj drugi su vodeći uzrok smrtnosti i prvi u invalidnosti odraslih osoba. U ovom smo članku pokušali prikazati sve promjene starenja u zajedničkoj karotidnoj arteriji kako bismo ih time od patoloških procesa.

Ključne riječi: starenje, IMT (debljina intime i medije), arterijska krutost, arterijska popustljivost, endotelna disfunkcija

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Aging

Since life expectancy increased over the past few decades, the proportion of elder people is increasing in many countries around the world. It is believed that proportion of people aged over 80 years will triple in the next 30 years.[1] The most common health problems in old age are chronic diseases, primarily cerebrovascular (more often in women) and cardiovascular (more often in men). Underlying condition in both conditions is atherosclerosis, but atheroslclerosis is not isolated, rather it affects all segments of the vascular system.

Previous research has established a positive connection between the reduced elasticity of the blood vessel wall and the frequency of stroke and other vascular diseases.[2] However, Nagai et al. showed it is more specialized for atherothrombotic stroke compared to other forms of stroke, for example lacunar stroke.[3] Furthermore, del Sol (2001) and Baldassare (2000) showed that a separate assessment of IMT in the common carotid artery (ACC) is useful as a surrogate for vascular disease risk assessment instead of recording risk factors.[4,5] The Tromso study showed that an increase in IMT (thickening of the intimal and medial part of the arterial wall) is an independent predictor of heart attack, stroke in general and ischemic stroke in particular.[6]

Still, there are some changes in the vascular system that can be attributed solely to the aging process. The most important contributor to this statement comes from the BLSA study (Baltimore Longitudinal Study on Aging). Researchers of the BLSA study distinguish vascular aging as a physiological process that does not necessarily imply the onset of vascular disease. On the other hand, vascular disease is a condition mostly favored by unsuccessful aging and the loss of the natural balance of body processes.[7]

Additionally, it seems that not only exposure to various risk factor, but the time of exposure is what makes the difference of successful as opposed to unsuccessful aging. Namely, some of the changes characteristic of aging, such as the loss of elastin thus diminishing vascular elasticity, are observed at an earlier age in the population exposed to hypertension, hyperlipidemia or other vascular risk factors. It is considered that these people would have the earliest or pre-clinical/sub-clinical development of the vascular disease. Therefore, it is important to find methods by which it is possible to distinguish between normal vascular aging from vascular disease.

Subclinical carotid disease is characterized by asymptomatic changes in the blood vessels, the development of which started an unfavorable chain of events that often ends in a stroke.[8] It is not entirely clear whether subclinical arterial changes represent a risk of developing the disease or a manifestation of an already developed disease. Subclinical changes represent a syndrome in which three main changes are recognized: the formation of carotid plaque, the occurrence of thickening of the IMT and distensibility disorder in the supply vessels of the brain.[9] The subclinical atherosclerotic process of the carotid tree is quantified by measuring IMT thickening[10], quantitative and qualitative analysis of carotid plaques[11] and by measuring elasticity indices such as arterial stiffness (AS), arterial compliance, extensibility ("distensibility") and wall shear stress.[2] Commonly, increased increased pulse pressure (PP) and pulse wave velocity (PWV) are used as AS measures. They are not synonyms, rather PWV will directly reflect the AS processes and PP will serve as a surrogate marker of AS.

Animal models

To accurately assess the function of the arterial wall, many simulations were performed using mathematical models of physiological conditions in which viscoelastic properties of blood, elastic modulus, shear stress of the wall and the degree of shear stress of the wall were investigated.[12-16]

However, in order to biologically evaluate vascular aging animal models such as rodents and non-human primates were initially used as models for the evaluation because they have been shown to be very similar to humans in terms of physiological and pathophysiological changes. The use of animal models has proven specific changes in the aorta of rodents that are regularly seen in the aging arteries are: increase in arterial diameter, arterial stiffness, and IMT. IMT increase is a process that involves the intimal layer, the medial layer and extracellular matrix. Following processes are specific for intimal changes: increase in smooth muscle cell thickness as well as extracellular matrix, increase in TGF-β (transforming growth factor - beta) with decreased anti proliferative response, increase in MMP-2 (metalloproteinase type 2 - zinc-dependent endopeptidase) and MMP-1 (metalloproteinase 1 – membrane type, MMP-2 activator), increased expression of ICAM-1 (interstitial adhesion molecule), increase in nitrates and nitrites as well as increased activity of ACE (angiotensin adhesion enzyme). Tunica media is involved with increase in layer thickness via increase in cell size, but decrease in cell number. The extracellular matrix is increased via increase in collagen content, increase in non-enzyme glycosylation processes that promotes greater number of collagen fibers, increase in fibronectin, increase in glycoasminoglycans and decrease in elastin by defragmentation and calcification. In addition to all this, endothelial dysfunction is promoted with specific changes in arterial vasoreactivity: decrease in nitric oxide (NO) with increase in superoxide and peroxinitrite and increased expression of adhesion molecules and permeability, decrease in angiogenesis with decrease in VEGF (vascular endothelial growth factor). All this predisposes overreactive response to arterial injury and overly active atherosclerotic process initiated with excessive lipid consumption.[2,17-19]

Furthermore, the expression of fibronectin and TGF-β are regulated with the help of angiotensin-II, and their role is to promote the formation of the extracellular matrix. Aortic MMP-2 is known to play a role in damage to the internal elastic

sheath, which occurs under the influence of several cytokines: interleukin-1 β, TNF-α and TGF-β. It was also experimentally confirmed that smooth muscle cell of the tunica media are more sensitive to chronic stimulation by cytokines than to acute stimulation, thus activating a stronger response to injury. Endothelial balloon injury model leads to accelerated migration of smooth muscle cells and increased secretion of the aforementioned molecules, which causes destruction of the internal elastic sheath (probably via MMP-2 activation) and neointimal proliferation under the influence of bone marrow-derived hematopoietic progenitor cells and platelet-derived growth factor (PDGF).[2]
Endothelin, oxygen radicals, PGH2 and angiotensin II have a vasoconstrictive effect on the walls of arteries. Vasodilating effects are, in turn, exerted by: NO, PGE1 (prostaglandin E1), PGE2 (prostaglandin E2), histamine, adrenomedurin and endothelial hyperpolarizing factor (EDHF). In old age the vasodilatory vascular response to NO stimulation is reduced, and the total amount of nitrites and nitrates in the blood is increased. Vasoconstrictor vascular response to angiotensin II stimulation is also slowed, but can be affected by inhibition of NO synthesis. In some studies, a reduced amount of NO due to aging was also recorded, which conditioned the increased expression of endothelial NO synthetase (eNOS). This response is associated, then, with increased production of mitochondrial superoxide, peroxynitrite and nitrosylated proteins that are evoked as cell protective mechanisms.[20]

Vascular aging

Age is the most significant risk factor for development of any chronic disease making the detection of sub-clinical manifestation of vascular disease so interesting today. Therefore, response to a certain stimulus is measured. To perform specific risk factor analysis, respondents to a certain stimulus are divided into age subgroups and according to the representation of a particular indicator. If an indicator is singled out for its positive or negative impact on health, the first or last quartile or quintile is usually determined. People in these subgroups are still not considered diseased, but are at an increased risk of developing the disease, and that is a criterion of "unsuccessful" aging.
The elasticity or AS of the carotid artery wall is a parameter used to test the mechanical ability of blood flow for adequate brain perfusion. Previous studies have established a negative relationship between the thickening of the blood vessel wall and the decrease in elasticity, thus explaining a predictive value for the occurrence of stroke. So far, studies have used the following approach: conventional ultrasound machines (M mode analysis), intravascular ultrasound, phase contrast magnetic resonance angiography, "cine" magnetic resonance angiography and mathematical modeling or studies on models. The indicators used to assess AS are numerous, and often better adapted to laboratory than clinical conditions: intraluminal and extraluminal diameter of the artery, compliance[21,22], extensibility ("distensibility")[23-27], stiffness[28-32], pulse wave velocity and shear stress[33-35].
A reflection of age-related changes is a trait of intrinsic AS. In addition to AS increase in aging, endothelial dysfunction and an increase in and arterial pressure (measured as pulse pressure) are, also, possible. Several indicators of AS have so far been validated as a measure of vascular age: β-stiffness, Ep and AC. The first two indices increase with increasing age, while the last one decreases. In addition to age, -stiffness is, also, associated with the chronic influence of smoking, and Ep with elevated blood pressure values.[36]
Combinations of individual factors create the personal vascular profile of each person and can help determine the degree of risk of developing arterial disease. Both changes occur simultaneously - endothelial dysfunction appears in the 6th decade, and at the same time there is a significant increase in PP or PWV.[2] PWV is a non-invasive indicator of AS that depends on mean arterial pressure and the intrinsic response to increased arterial mechanical exertion. It is considered that elevated PWV values indicate an increased collagen content, a reduced elastin content and calcification of the tunica media. A significant increase in PWV is possible without simultaneous atherosclerotic changes in blood vessels.[37] However, since PWV is also increased in hypertensive individuals, diabetics and people with atherosclerosis, it is believed that this connection does not only result from structural changes but also as a consequence of endothelial regulation of smooth muscle tone.
Recently, research has shown that endothelial dysfunction can be assessed, in addition to changes in the arterial wall, by quantifying hematopoietic progenitor (EPC) cells in the blood. An increased number of EPCs is associated with an increased risk of mortality from cardiovascular disease, occurrence of a first cardiovascular event in life, acute myocardial infarction, total number of hospitalizations, and mortality from any cause. Therefore, the number of EPC cells can, also, be considered an indicator and biomarker of endothelial dysfunction.[38]
A bond between reduced mitotic index of individual tissue and increasing age is, also, observed.[39] Endothelial aging is confirmed not only by enhanced α-galactosidase staining in the elderly, but, also, the expression of regulators of cell mitotic cycles such as telomere shortening and suppression of telomerase activity. Loss of telomere function promotes endothelial dysfunction, and suppression of telomere shortening has been shown to reverse endothelial dysfunction resulting from aging.[40] Loss of telomere function is associated with the higher degree of atherosclerosis, pulse pressure and PWV (more pronounced in men).[39,41]

The role of aging in the development of vascular disease

Aforementioned mechanisms of vascular aging lead to several consequences. First of all, vascular remodeling by means of reduces NO production leads to increased AS, early signs of atherosclerosis and hypertension. Furthermore, AS increase then

potentially leads to systolic hypertension, left cardiac hypertrophy, atherosclerosis and stroke. Lastly, decrease in physical activity will promote all those changes. Still, all the mechanisms of vascular aging are intertwined. Research has recently shown that all the aforementioned changes in metabolism, enzyme activity, cellular and endothelial changes have an important causal and promotional role in atherosclerosis, vascular inflammation, vascular remodeling and oxidative stress. Therefore, atherosclerosis is most likely a process resulting from the interaction of atherosclerotic process and the intrinsic arterial properties of aging. It means that the appearance of atherosclerosis at an earlier age is a reflection of accelerated aging on increased AS due to excessive exposure to classical risk factors (high blood pressure, smoking, increased amount of fat in the blood, diabetes, unhealthy diet, insufficient physical activity and genetics).[2] However, the Rotterdam study showed that there is an association of increased AS measured in the aorta and carotid artery with carotid IMT increase and the degree of stenotic changes measured in both the carotid arteries and the aorta.[30]

Morphological indicators of changes in arterial function in aging are increased diameter and thickening of the IMT. Changes called arterial remodeling are intimal hyperplasia and fibrocyte hypertrophy due to local changes in flow and wall loading forces – an adaptive mechanism that affects individual arterial segments and is not uniform along the entire length. They are characteristic of the aging process of large elastic arteries, and postmortem studies confirmed that thickened walls are the most common changes in the aorta associated with aging. Some authors believe that carotid IMT is only weakly associated with concomitant coronary disease, so it cannot be considered an accurate indicator of subclinical disease, but more likely a reflection of carotid remodeling.[42]

IMT measurement has been considered a marker of early atherosclerosis since the Dutch ARIC study, but it cannot be considered a risk factor for cerebrovascular diseases, as a reduction in IMT thickness does not lead to a reduction in risk. A French study showed that 66% of the variability of IMT ACC and 74.9% of ACI could be explained as a consequence of heredity.[43] Fox hypothesized that the genes for IMT could be located on the 12th chromosome.[10] Howard established on the data of the ARIC study that the IMT in men is always slightly higher - 0.8mm vs. 0.73 mm in women.[11] Using the same data, Blakenhorn observed that the annual progression of IMT thickness was the smallest in the ACC (0.01 mm), followed by the carotid bifurcation (0.025 mm), and the largest was observed in the ACI (0.036 mm).[44] Thirty eight percent of ACC IMT variability appears to be due to heritable factors.[10] Almost at the same time, a group of Chinese researchers showed in their work that the genes that determine the characteristics of angiotensin converting enzyme (ACE) are also responsible for IMT, the diameter of the internal carotid artery (ACI), the elasticity and stiffness of the arteries.[45]

The ARIC prospective study showed, by measuring the change in diameter, Ep, Young's EC (elasticity coefficient) and β-stiffness index, that a decrease in arterial elasticity by one standard deviation increases the risk of developing hypertension by 15%. This influence is independent of the initial values of blood pressure in the examined group.[46]

Although isolated systolic hypertension, most often after the age of 50 years, can be considered a good indicator, the Framingham study confirmed PP as a better predictor because it analyzes both systolic and diastolic pressure. Studies have shown that lowering the blood pressure values in hypertensive patients will not stop further vascular damage that has already started. In the future, we should aim to create medication with the potential to act not only on lowering blood pressure values, but, also, that would influence vascular remodeling and reduce AS.[2]

Bussy et al. investigated AS in carotid arteries by determining and comparing a group of normotensive and hypertensive subjects by determining Young's EC. The overall analysis did not indicate a difference, but the stratification of the subjects into tertile subgroups according to age showed that the intrinsic, or effective, AS of the material was increased only in younger hypertensive patients. Therefore, the influence of aging and hypertension does not have an additive effect on the increase in AS, and changes in elderly hypertensive patients directly correspond to increased blood pressure values. However, the increase in AS is observed with age, and a special place in research is occupied by the carotid artery, which is more susceptible to pathophysiological changes than some peripheral muscular arteries (eg. brachial or radial). At the age of 70, AS can have up to six times higher values than those at the age of 20, which is even more pronounced in the case of hypertension or diabetes.[47]

As the AS of large elastic arteries becomes more and more rigid, there is an increase in central systolic pressure, a decrease in diastolic pressure, and a consequent increase in pulse pressure. Numerous studies have so far identified increased pulse pressure as an independent predictor of cardiovascular disease. Therefore, an increase in PWV most likely reflects: increased central systolic pressure, increased pulse pressure, and a change in AS structure/state. In the latest research, it has been confirmed that an increase in PWV with a simultaneous decrease in total compliance are independent predictors of the onset of cardiovascular diseases. One of the incriminating events in the body for such a development can be non-enzymatic glycosylation, which is increasingly pronounced in old age, especially in diabetics, so recently experiments have been made with drugs that would break these bonds.[2]

IMT measurement, aging and cerebrovascular risk factors

The usual approach to vascular risk factors in a cerebrovascular patient is to determine their the non-modifiable and modifiable risk factors. Non-modifiable risk factors are age, sex, race/

ethnicity and genetics, while modifiable ones are: high blood pressure, heart disease, diabetes, smoking, alcohol abuse, use of oral contraceptives, history of TIAs (transient ischemic attacks), elevated red blood cell count, elevated blood cholesterol and lipids, unhealthy diet, obesity, and physical inactivity.
However, when all of them are excluded, about 60% of the causes of stroke remain unexplained. That is why nowadays the so-called "new" cardiovascular disease risk factors. These are, in order: lipid fractions, abdominal obesity, metabolic syndrome, elevated homocysteine levels in the blood, infection and inflammation, and subclinical carotid disease.[48]
In order to monitor IMT increase as a form of subclinical arterial wall changes, it is important to recognize the possible influence of the underlying cause. Elevated blood pressure is probably the most significant vascular risk factor, and by expressing systolic blood pressure values or PP, we can fairly accurately relate to the development of changes in IMT thickness in ACC.[49] Other main factors that cause subclinical changes in arterial walls are: age[9], diabetes or impaired glucose tolerance, unregulated blood pressure, dyslipidemia[50] and hyperhomocysteinemia[51]. Factors such as smoking and excessive consumption of alcoholic beverages also promote the occurrence of these changes. Among the important newly discovered factors that stand out are C reactive protein levels (especially high sensitivity type), lipoprotein (a), fibrinogen and homocysteine levels, repeated vascular spasm and hemodynamic trauma.[48,52]
For many years, neurologists have been researching and assessing risk for stroke by measuring IMT, and one of the first was the Finnish Kuopio study that observed an increase in risk with progressive IMT thickening.[53] The French IMMEDIAT study showed in 2002 that the risk of developing cerebrovascular diseases can be assessed by recording the presence of plaques and IMT > 0.7 mm.[54] In the same year, Cupini estimated that the risk of non-lacunar stroke increases by 26% for every 0.1 mm increase. It has also been noted in studies that the frequency of certain risk factors varies in different parts of the carotid tree. The most common in CCA (common carotid artery) are age, sex, increased blood pressure, increased LDL level in the blood and smoking; in carotid bifurcation, age and smoking; and in ACI age, sex, elevated blood pressure, diabetes and smoking.[55,56] In addition, systolic and pulse pressure have an influence on IMT thickening.[57]
Another significant factor influencing IMT thickening is diabetes and the length of its duration, i.e. insulin values measured on an empty stomach. The thickening is on average 0.05-0.08 mm greater than the control group.[57,58]
The increased amount of fat in the blood causes an average thickening of the IMT by 0.13 mm, and within two years men are more prone to thickening.[53,59] Here, the maximum concentration of triglycerides measured in the blood after a fatty meal, and not the average serum values, have a predictive value.[60]
The ARIC study showed an association between thickening of IMT and body mass index, especially if abdominal obesity as expressed by the waist-to-hip ratio is taken into account.[57,61] In the same study, the association of IMT thickening with elevated blood fibrinogen values was confirmed.[62] In addition to the harmful effects of smoking, there is a connection between thickening of the IMT and the regularly consumed amount of alcohol when it amounts to more than 30g per day when an elevated concentration of IL-6 can be measured in the blood.[63]
Among other inflammatory indicators, thickening of the IMT can be associated with an increase in the total number of leukocytes in the blood and an increased concentration of C reactive protein.[64] Some people are, also, seropositive for Cl. pneumoniae.[65] Elevated homocysteine values also cause IMT thickening in the ARIC study, and this is particularly useful in assessing early stage atherosclerosis.[59]
Regular physical activity and optimal nutrition are effective in preventing the progression of IMT thickening in non-smokers.[66] Other influences include the serum titer of antibodies to oxidized LDL cholesterol, increased copper values, and decreased selenium values in the blood as promoters of IMT thickening.
Research on the endocrine system began when, after the administration of sex hormones[28], it was proven that the endocrine system plays an important role in the thickening of IMT, and most likely also a significant role in preserving the elastic properties of arteries. Pentz Vidović observed that after the application of hormone replacement treatment in menopausal women for 6 or 12 months, the return of thickened IMT values to baseline values is measured.[67] Lack of thyroid hormone leads to a reversible thickening of IMT in ACC, so after the application of replacement treatment or after the normalization of thyroid gland function, a reduction of IMT to the value before the onset of the disorder is observed. Therapy with T4 hormone in hypothyroidism has the opposite effect.[68]
As for the medications use - Ca blockers in the ELSA and PREVENT studies, ACE inhibitors in the HOPE SECURE substudy, and beta blockers with statins in the ELVA study showed efficacy in reducing the progression of IMT thickening in patients who took these medications.[69-72] Many large clinical studies have shown that the use of statins enables the regression of early changes: ACAPS (lovastatin), CLAS (colestipol), PLAC-II (paravastatin), MARS (lovastatin) and REGRESS (pravastatin) . The ASAP study showed that atorvastatin is better than simvastatin.[73] The ASAP study showed that taking 250 mg of slow-release vitamin C and 136 IU of vitamin E daily significantly reduced the annual progression of IMT thickening in men in 33% of cases and in women in 14% of cases. This influence is more significant in those people who have carotid plaques before starting vitamin therapy.[73]
Measurement of IMT is established and widespread among clinicians because it is a simple and reproducible method.[74] Some authors use IMT measurement to assess the risk of cerebrovascular

and cardiovascular disease.[8,75] Zureik even proved that, by isolating certain serum enzymes, it is possible to biochemically monitor the frequency of carotid plaque occurrence. Namely, elevated values of elastase inhibitors in the serum of subjects during the four-year follow-up are proportional to the number of carotid plaques.[76]
The indicators that we measure in various places in the carotid tree can also be measured in the aorta, where the changes are visible even a little earlier in the timeline of pathological changes, and the measurement techniques do not differ.[31]
However, the thickening of the IMT can be a misleading indicator, because the changes on the walls do not take place evenly.[77] For this reason, it seems prudent not to focus solely on IMT measurement, but include other measures of vascular aging and arterial remodeling.

Conclusion

Arterial remodeling is a physiological process that is primarily influenced by aging. Whether it reflects the traits of successful aging or strays from it determines the potential for future development of pathophysiological processes and, eventually atherosclerosis with increased risk for cerebrovascular disease occurrence.

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