ABSTRACT

Age is the dominant risk factor for cardiovascular diseases, and the age-associated changes in vascular structure and function are the likely culprits responsible, in large part, for the increased cardiovascular risks associated with aging. Insights from animal studies suggest that the links between vascular aging and vascular diseases stem from the fact that many of the biochemical, enzymatic, and cellular alterations that are operative in accelerated vascular aging, are involved in the pathogenesis and progression of arterial diseases such as hypertension and atherosclerosis. This establishes the interaction between arterial aging and these diseases and provides a basis for the epidemiological observations that aging confers increased risks for the occurrence of these diseases, lowers the threshold for their appearance, and influences the severity of their manifestation.

An important corollary of this is that age should no longer be viewed as an unmodifiable cardiovascular risk factor. It is our hope that a greater appreciation of the link between arterial aging and cardiovascular diseases will stimulate further investigation into strategies aimed at preventing or retarding arterial aging, with the hope that this would attenuate the appearance or the severity of cardiovascular diseases.

The risky components of aging have been attributed, in part, to an increased time of exposure to other established cardiovascular risk factors, which in turn may vary in number and severity with increasing age. Hopefully, combined diet and lifestyle changes in young people, associated with multiple drug combinations in adults, will demonstrate such effectiveness on endothelial vascular aging (EVA) and premature cardiovascular (CV) events. Change in diet and lifestyle from early age will retard endothelial cell dysfunction. At a later age, pharmacological intervention helps in improving endothelial cell function (ECF).

INTRODUCTION

Epidemiological studies have unequivocally shown that age is the dominant risk factor for cardiovascular diseases. Indeed, the incidence and prevalence of hypertension, coronary heart disease, congestive heart failure, and stroke all steeply increase with advancing age. However, most of the research efforts have focused on developing interventions that target "traditional" risk factors for coronary heart disease (e.g. hypertension, hypercholesterolemia, etc.) or identifying newer ones, whereas little attention has been devoted to aging. This is because age has usually been viewed as a chronological and unmodifiable, hence unpreventable or untreatable, risk factor.

These arguments expose our major shortcomings in understanding why age is such a potent risk factor for cardiovascular diseases, namely our poor insight into the specific elements that constitute the risky components of aging vis a vis the cardiovascular system. In other words, although we have always intuitively accepted age as being a risk factor and have taken this to be a "truism," we did not have, until recently, good mechanistic or molecular explanations as to why this would be the case.

ARTERIAL AGING IN APPARENTLY HEALTHY HUMANS

Cross-sectional studies show that elastic arteries, such as the central aorta, on an average, dilate with age, leading to an increase in lumen size. The thickness of the arterial wall, as indexed by the thickness of the intimal and medial layers, increases in a linear fashion nearly 3-fold between the ages of 20 and 90 years even in the absence of atherosclerotic plaques. Postmortem studies show that this age-associated increase in arterial wall thickening is caused mainly by an increase in intimal thickening, even in populations with low incidence of atherosclerosis. Not only the average intimal medial thickness (IMT) increases with advancing age, but that the range of values for IMT is greater at higher ages, suggesting significant heterogeneity in the magnitude of the age-associated thickening process among older individuals: some exhibit low values of IMT for their age and are termed "successful," whereas others have "accelerated” alterations.

The age-associated increase in thickness of the central arterial wall is accompanied by an increase in stiffness. This has been attributed to the repeated cycles of distensions and elastic recoils of the arterial wall, which are thought to accelerate the fragmentation and depletion of elastin, as well as the deposition of collagen. Endothelial cells play a pivotal role in regulating several arterial
properties, including vascular tone, vascular permeability, angiogenesis, and the response to inflammation. Endothelial-derived substances (eg, NO, endothelin-1) are determinants of large arterial compliance, suggesting that endothelial cells may also modulate central arterial stiffness. However, endothelial function in central arteries has not been directly assessed in humans. In the brachial artery, endothelial function, as assessed by agonist- or flow-mediated vasoreactivity, has been shown to decline with advancing age. However, in contrast to central arteries, the stiffness of muscular arteries does not increase with advancing age. Thus, the manifestations of arterial aging may vary among the different vascular beds.

AGING OF ENDOTHELIAL CELLS

Important alterations in the structure and function of endothelial cells accompany advancing age, including a higher prevalence of cells with polyplody nuclei, increased endothelial permeability, alterations in the arrangement and integrity of the cytoskeleton, the appearance of senescence-associated \( \beta \)-galactosidase staining, and the expression of several inhibitors of the cell cycle. Endothelial cells of aged arteries secrete more plasminogen activator inhibitor-1, favoring thrombosis formation. Furthermore, with aging, endothelial cell production of vasoconstricting growth factors such as angiotensin II (Ang II) and endothelin increases, and that of vasodilatory factors (eg, NO, prostacyclin, and endothelium-derived hyperpolarizing factor) is reduced. These age-associated alterations in the arterial wall create a metabolically and enzymatically active milieu that is conducive for the initiation or progression of superimposed vascular diseases (eg, atherosclerosis).

Endothelial cells exhibit shorter telomere lengths with aging and suppressed activity of telomerase reverse transcriptase. Senescence-like phenotypic changes in endothelial cells can also be induced in the absence of telomere length changes through glycation of collagen I. Advanced glycation end products, which accumulate with aging, increase the production of superoxide anion through the activation of NAD(P)H/oxidase. The coupling of advanced glycation end products to their receptors on endothelial cells also triggers inflammatory cell recruitment and activation and enhances thrombogenesis by stimulating platelet aggregation.

ARTERIAL AGING IN CARDIOVASCULAR DISEASES

Although the aforementioned changes in arterial structure and function with aging were thought previously to be part of normative aging, this concept was challenged when data emerged showing that these changes are accelerated in the presence of cardiovascular diseases. Patients with hypertension exhibit greater carotid wall thickness, central arterial stiffness, and central pressure augmentation than normotensive subjects, even after adjusting for age. Hypertensive individuals exhibit endothelial dysfunction, and the mechanisms underlying their endothelial dysfunction are similar to the ones that occur with normotensive aging, albeit they appear at an earlier age. The normotensive offspring of hypertensives also exhibit endothelial dysfunction, suggesting that endothelial dysfunction may precede the development of clinical hypertension. Among hypertensive men, shorter telomere length of circulating white blood cells is associated with greater arterial stiffness.

The metabolic syndrome, which is quite prevalent among older individuals, is associated with elevated carotid arterial thickness and stiffness. Diabetics also exhibit higher carotid IMT than nondiabetics, and they have accelerated progression of their IMT. Although their central arterial stiffness is increased, this is not accompanied by an increase in the central pressure augmentation. Diabetics also exhibit endothelial dysfunction, which can be found in their first-degree relatives who have insulin resistance. The circulating white blood cells of insulin-dependent diabetics have shorter telomere lengths than those from normoglycemic controls or noninsulin-dependent diabetics.

Patients with atherosclerosis have increased thickness, and stiffness of their central arterial walls, greater central pressure augmentation, and shorter telomere lengths on their circulating white blood cells. They also exhibit endothelial dysfunction, which has been implicated in the pathogenesis of atherosclerosis and is one of its earliest pathologic manifestations.

INTERVENTIONS TO RETARD OR PREVENT ACCELERATED ARTERIAL AGING

Diet and lifestyle modification

As with other cardiovascular risk factors, lifestyle modifications, including the prescription of aerobic exercise, dietary modifications, caloric restriction, and weight loss, can prevent or retard the progression of intimal medial thickening and arteriolar stiffening and improve endothelial function. Data from various studies reveal that nonhydrogenated unsaturated fats (olive, canola, mustard, groundnut, rice bran oils), whole grains, liberal fruits, vegetables, adequate omega 3 fatty acids (from fish or fish oil supplements or plant sources), red wine (moderate), black/green tea, nuts (almonds, walnuts, peanuts), liberal garlic, onion with daily exercise, maintaining normal weight and no smoking leads to healthy vasculature.

Regular exercise prevents the age-associated loss in endothelial cell function (ECF) in elderly and in patients with coronary artery disease (CAD). Exercise results in increased nitrite and nitrate levels, increased superoxide dismutase (SOD) activity and decreased oxidative stress. Weight loss in obese women (diet, exercise, liposuction) results in low cytokine concentration and improvement of ECF.

The aforementioned insights from animal models and human studies indicate that the components of arterial aging are modifiable, so the traditional view of arterial aging, which attributes the age-associated changes solely to passive sequelae of wear and tear from repetitive cycles of distension and recoil of central arteries, is no longer tenable. These insights also provide us with a growing list...
of putative factors that could be targeted by specific interventions aimed at retarding or preventing accelerated arterial aging.

Pharmacological interventions

Pharmacological treatments that are able to reduce arterial stiffness include the following: (1) antihypertensive treatment, e.g., diuretics, β-receptor blockers such as nebivolol, angiotensin-converting enzyme inhibitors, angiotensin II type 1 blockers, and calcium channel antagonists such as nifedipine; (2) treatment of congestive heart failure, e.g., angiotensin-converting enzyme inhibitors, nitrates, aldosterone antagonists, and β-blockers (3) hypolipidemic agents, e.g., statins; and (4) antidiabetic agents, e.g., thiazolidinediones and metformin.

Preventing vascular aging beyond BP reduction

Through the unloading of fibrous components of the arterial wall in response to BP reduction, many antihypertensive drugs have proven their ability to reduce arterial stiffness. However, significant differences were observed between classes of antihypertensive drugs, e.g., drugs interfering in the renin-angiotensin system are often more effective at reducing arterial stiffness than other drugs.

Tropeano et al. have shown a direct BP-independent effect of an angiotensin-converting enzyme inhibitor (perindopril) on carotid stiffness in patients with type 2 diabetes mellitus. Recently, similar results have also been reported for the reduction of aortic stiffness with an angiotensin II receptor antagonist (valsartan) in patients with type 2 diabetes mellitus.

Current alternatives to classic drugs

Novel therapeutic approaches could also contribute to reduce vascular aging and CV events. Several years ago it was demonstrated that EVA was frequently associated with age-associated (sex) hormonal decline. After menopause, women with reduced levels of estrogen experience a disproportionate increase in pulse pressure, a surrogate for aortic stiffness. In the Baltimore Longitudinal Study of aging, postmenopausal women taking hormonal replacement therapy have a smaller increase in systolic BP over time than those not taking hormonal replacement therapy, a difference that is intensified at older ages. In postmenopausal women not receiving estrogen, the increase in systolic BP may involve inhibition of NO bioavailability, thus, endothelial dysfunction in response to a high-salt diet. Many publications have documented that arterial stiffness was increased disproportionately after menopause (either post-surgery or chronological). It was, therefore, tempting to determine whether hormonal replacement therapy after menopause was accompanied by a slower progression of arterial stiffness. This has been addressed by some clinical trials. For instance, Rajkumar et al. compared postmenopausal women either treated or not treated with sex hormones with younger nonmenopausal women. They showed that treatment by sex hormones was accompanied by a lower aortic stiffness and systemic arterial compliance than those found in untreated women.

Osteoporosis is an increasingly common condition, not only in postmenopausal women, but also in elderly men, and one that is related both to increased CV risk and to EVA, as evidenced by increases in arterial stiffness. Selective treatments for osteoporosis may lead to a decrease in arterial stiffness and, thus, a decrease in CV events. It is important that patients with osteoporosis have their classic CV risk factors assessed, together with the measurement of arterial stiffness.

The role of advanced glycation end products in the age-associated increase in arterial stiffness has been underlined, especially in patients with altered glucose metabolism or overt diabetes mellitus. Collagen fibers and other structural proteins with long half-lives undergo nonenzymatic glycation.

Other possible alternatives to classic drugs

Telomerase inhibitors have been developed for the treatment of cancer, although their effect on tissue aging is unknown. Targeting telomerase activity for slowing aging is an active domain, and many patents are taken on telomerase activators, some of them having potential antiaging properties.

Lamin A has been implicated in physiological aging, leading to the concept that targeting the lamin A maturation pathway may be an effective antiaging pharmacotherapy. Progeria, which is associated with an abnormal lamin A, is probably the most severe syndrome of early aging. Affected patients exhibit a physical aspect of elderly patients and die before age 17 years. The major cause of death in progeria is CVD with ischemic heart disease and stroke. It has been shown that lamin A is a key protein for the mechanical integrity of the nucleus of cells, particularly in cells exposed to high mechanical stress, e.g., arteries and the skin.

CVD prevention remains an important issue in public health and preventive cardiology. Favorable age-adjusted trends in decreasing CVD incidence and better control of CVD and hypertension have been documented, a possible reflection of improving conditions for newborns and children. The ultimate goal is to find more effective ways for CVD prevention via aggressive decrease of atherosclerosis modifiers (ADAM). Current guidelines propose intensified risk factor control in patients at particularly high risk, e.g., patients with diabetes mellitus and established CVD. Because the risk often remains high in spite of therapeutic efforts in elderly, the general consensus of various workers is that new intervention trials are needed for early CVD prevention, based on screening for CVD in high-risk patients, e.g., those with a positive family history for CVD or impaired glucose metabolism. In families with a high risk for premature myocardial infarction and stroke, there is also a fair chance of finding family members with early signs of CV aging.

From both an ethical and a clinical perspective, it is fully acceptable to reach out and invite these individuals for a careful examination of CV risk factors, EVA, and other manifestations of target organ damage (TOD). Personal advice to improve lifestyle should be given and, in many cases, also targeted drug interventions according to guidelines.
REFERENCES


