



Clinical Implications of Age-Related Cardiovascular Modifications

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ABSTRACT

Cardiovascular aging encompasses such a wide and complex range of phenomena at the structural, functional, and molecular levels that its study has come to be viewed as a distinct branch of physiology, whose advances will be crucial to understand the functioning of an increasingly larger section of the population and will help to succeed in the difficult task of defining the border between normality and disease. Aging is associated with a mild increase in heart weight, reflecting some degree of left ventricular hypertrophy. An additional change described in the aging heart is a partial degeneration of cardiac sympathetic nerve supply. Vascular stiffness, defective endothelial function, arterial wall thickening to verify whether lifestyle or pharmacological interventions (exercise, sodium restriction, interference with lipid metabolism or the renin-angiotensin system) shown to have favorable effects on arterial structure and function in humans may also prevent cardiovascular events and mortality in apparently healthy elderly humans.

KEYWORDS

Cardiovascular Aging, Structural and Functional changes.

1. Introduction

Aging is associated with complex and diversified changes of cardiovascular structure and function. The heart becomes slightly hypertrophic and hyporesponsive to sympathetic (but not parasympathetic) stimuli, so that the exercise-induced increases in heart rate and myocardial contractility are blunted in older hearts. The aorta and major elastic arteries become elongated and stiffer, with increased pulse wave velocity, evidence of endothelial dysfunction, and biochemical patterns resembling early atherosclerosis. The arterial baroreflex is sizably altered in aging, but different components are differentially affected: there is a definite impairment of arterial baroreceptor control of the heart but much better preserved baroreceptor control of peripheral vascular resistance. Alterations at the afferent, central neural, efferent, and effector organ portions of the reflex arch have been claimed to account for age-related baroreflex changes, but no conclusive evidence is available on this mechanistic aspect. Reflexes arising from cardiopulmonary vagal afferents are also blunted in aged individuals. The cardiovascular and reflex changes brought about by aging may have significant implications for circulatory homeostasis in health and disease.

2. Structural and Functional changes of Aging heart

Aging is associated with a mild increase in heart weight, reflecting some degree of left ventricular hypertrophy cause to hypertension and increased afterload. Studies have shown an age-dependent change in cardiac shape has been described, with a rightward shift in the ascending aorta and a proximal bulge in the interventricular septum, which entail a narrowing of the left ventricular outflow tract. Cardiomyocyte dimensions are somewhat increased, whereas their numbers are decreased; collagen may become more prominent because of both quantitative and qualitative changes, with focal deposits and diffuse increases in the cross-linking between adjacent fibers (see Figure-1 & 2). An additional change described in the aging heart is a partial degeneration of cardiac sympathetic nerve supply .

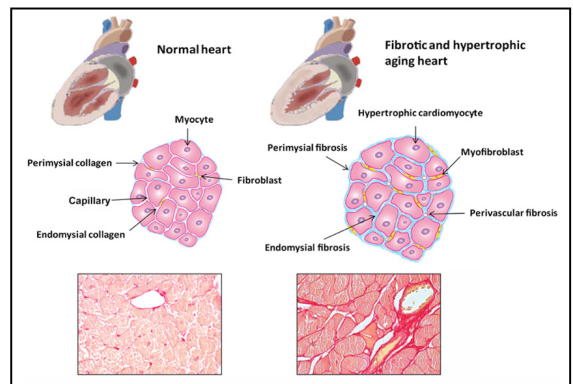


Figure-1 (structural changes in normal heart and aging heart.)

In the resting aging heart, there are largely no alterations of systolic function, with preserved ejection fraction and stroke volume; because resting heart rate is unchanged or only minimally reduced with aging, cardiac output is also preserved. Instead, diastolic function does undergo significant age-related changes, with a reduction in early diastolic filling compensated for by increased end-diastolic filling and a consequent progressive reduction of the echocardiographic early wave/atrial wave (E/A) velocity ratio .

Aging also alters cardiac responsiveness to -adrenergic stimuli, be they pharmacologically or physiologically determined. Both the catecholamine- or exercise-induced increases in heart rate and myocardial contractility are definitely blunted in elderly subjects . Thus, for cardiac output to be increased in proportion to the body's metabolic needs despite inadequate contractile and chronotropic reserves, the aging left ventricle mainly engages the Frank-Starling mechanism, i.e., it undergoes marked increases in volume, both end-diastolic and end-systolic. Via such hemodynamic a pattern, the aging heart can significantly increase its maximum output and allows elderly subjects to perform vigorous exercise, although not up to the same intensity as a younger individual can sustain. Overall, the peak cardiac output attained in response to maximal effort is blunted by some 20–30% in elderly compared

with young healthy subjects, the blunting being largely attributable to a lesser degree of effort tachycardia rather than to altered stroke volume . To draw an overall picture of modified cardiac exercise physiology in aging, it was suggested that the heart of the elderly behaves like a younger heart subjected to -blocker treatment .

Further age-related cardiac alterations relate to lusitropic function, with delayed relaxation as a consequence of enhanced duration of contraction. The latter results from prolonged action potential and active state rather than from changes in passive mechanical properties or myocardial catecholamine content . The above-mentioned alterations may be of considerable clinical importance as a possible functional substrate of the notorious propensity of elderly individuals to develop diastolic heart failure. The aged heart also shows a reduction in the inotropic responses to digitalis but not to calcium ions, indicating that the defect involves the signaling processes rather than the contractile machinery itself .

3. Age related Vascular Status

Aging large arteries are elongated and tortuous and have an enlarged lumen and a thickened wall, the thickening mainly affecting the intima and the media . In the former, arteries from healthy elderly subjects show no endothelial lesions or discontinuities; endothelial cells may, however, be irregular in shape and have increased height; there may be migration and/or proliferation of vascular smooth muscle cells, with infiltration in the subendothelial space, exaggerated deposition of collagen, elastin, and proteoglycans, along with abnormal abundance of leukocytes and macrophages (see Figure-2).

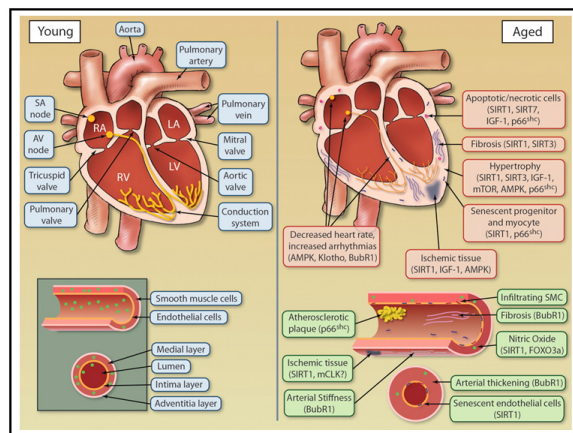


Figure-2(structural changes in normal heart with blood vessel and aging heart with blood vessel.)

The fundamental age-related change in arterial function is impairment of distensibility and thus of the cushioning function of the aorta and its major branches, associated with an enhancement in pulse wave velocity; such changes have been suggested to be nonuniform throughout the arterial tree with more marked alterations in elastic-type vs. muscle-type arteries . Increased stiffness is not solely dependent on structural alterations but also is majorly affected by humoral and endothelial regulation of vascular smooth muscle tone: aged vessels show an increased endothelial permeability and a reduced nitric oxide-dependent vasodilator response to acetylcholine .

Although the above-mentioned age-related functional alterations have been observed in atherosclerosis-free normotensive individuals, most of them are also present in atherosclerotic vessels, which are also known to be stiffer than normal but in which, unlike in aging, focal lesions, vessel stenosis, and plaque rupture eventually develop. Thus, because aging and atherosclerosis run along very similar biochemical pathways and determine many similar vascular alterations, vessel aging may be viewed as representing the prodromal stage of atherosclerotic disease or, conversely, atherosclerosis may be viewed as a form of accelerated arterial aging (probably favored by

coexisting noxious stimuli such as e.g., dyslipidemia, smoking, or hypertension).The systemic hemodynamic consequences of age-related vascular hypertrophy and stiffness include a moderate increase in total peripheral resistance and the well-known tendency to increased systolic and pulse pressure. In turn, elevated pressure is a stimulus for further development of vessel wall hypertrophy and stiffness, so that adverse phenomena beget each other and a more or less rapidly progressing vicious circle is established.

4. Cardiovascular Homeostasis with Clinical Implications

Age-related changes may affect cardiovascular homeostasis and be more or less directly relevant to geriatric medicine will be briefly discussed. Physiological age-related alteration in left ventricular diastolic function is a predisposing factor to the development of diastolic heart failure, which is indeed highly prevalent in elderly patients, accounting for up to 50% of all heart failure patients in this age range according to some reports. Combined occurrence of enhanced pulse wave velocity and prolonged ejection time critically facilitates summation of antegrade and retrograde arterial waves, which may contribute to elevation of systolic pressure and pulse pressure in aged subjects. This has obvious implications as a powerful mechanism favoring onset and/or progression of vascular damage and increased risk of adverse physiological or clinical outcomes, including excessive cardiac workload and oxygen demand, left ventricular hypertrophy, further arterial stiffening itself, (cerebro)vascular events, and decline of renal function. Diastolic function does undergo significant age-related changes, with a reduction in early diastolic filling compensated for by increased end-diastolic filling and a consequent progressive reduction of the echocardiographic early wave/atrial wave (E/A) velocity ratio .

Aging also alters cardiac responsiveness to -adrenergic stimuli, be they pharmacologically or physiologically determined. Both the catecholamine- or exercise-induced increases in heart rate and myocardial contractility are definitely blunted in elderly subjects. Aging large arteries are elongated and tortuous and have an enlarged lumen and a thickened wall, the thickening mainly affecting the intima and the media. Increased stiffness is not solely dependent on structural alterations but also is majorly affected by humoral and endothelial regulation of vascular smooth muscle tone: aged vessels show an increased endothelial permeability and a reduced nitric oxide-dependent vasodilator response to acetylcholine.

Altered endothelial function in aging coronary vessels is a further element that causes advanced age to be listed among coronary risk factors. Likewise, there is now convincing evidence that increased carotid intima or media thickness (by ultrasound) predicts occurrence of cardiovascular events . The observation of slowed arterial baroreceptor-mediated blood pressure responses in advanced age may impair moment-to-moment adjustments of sympathetic nerve activity and peripheral vascular resistance, with increased propensity of elderly subjects to postural or postprandial hypotension as well as to inordinate blood pressure peaks. Even in lack of such clinically significant phenomena, the age-related changes in neural cardiovascular control are likely to be responsible for the increased spontaneous blood pressure variability (with concomitant reduction of heart rate variability) typical of aged subjects. It is tempting to extrapolate from studies linking reduced baroreceptor control of heart rate to the risk of life-threatening arrhythmias in cardiac patients and envisage that the adverse potential of this alteration may also extend to the aging condition. In this regard, it is interesting to recall that habitual exercise is well known to exert an antiarrhythmic effect and that in elderly populations it was shown to oppose many age-related alterations , including impairment of the arterial baroreflex . Ongoing studies in our human laboratory suggest that similar benefits may be obtained by training elderly individuals to slow breathing. Impaired effectiveness of the cardiopulmonary reflex in aging may contribute to altered electrolyte and fluid homeostasis and facilitated dehydration: these changes may also be among the factors that dictate

caution in prescribing and dosing diuretic therapy in elderly patients.

5. Conclusion

Cardiovascular aging encompasses such a wide and complex range of phenomena at the structural, functional, and molecular levels that its study has come to be viewed as a distinct branch of physiology, whose advances will be crucial to understand the functioning of an increasingly larger section of the population and will help to succeed in the difficult task of defining the border between normality and disease. Early structural or functional alterations typical of aging, such as left ventricular diastolic dysfunction, sympathetic overactivity, vascular stiffness, defective endothelial function, arterial wall thickening to verify whether lifestyle or pharmacological interventions (exercise, sodium restriction, interference with lipid metabolism or the renin-angiotensin system) shown to have favorable effects on arterial structure and function in humans or experimental animals may also prevent or delay cardiovascular events and mortality in apparently healthy elderly humans.

6. Acknowledgements

Author would like to thank to Dr. Sonal Tanwar, Dr. R. Mathur Prof Physiology and Dr. S. Surana Prof Pathology . They provide lot of support to get learnings and related articles.

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