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Cardiovascular Care for Older Adults · **Open Access** ·

Cardiovascular physiology in the older adults

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1 Introduction

In an aging society with persistent high prevalence of cardiovascular disease (CVD) in the elderly population, the health care system is facing an increasing challenge to effectively care for these patients. However, due to the under-representation of CVD patients over 75 years of age in clinical trials, assessing safety and efficacy of diagnostic and therapeutic approaches, the evidence for managing elderly CVD patients is especially limited. Physiological changes of aging intertwined with pathophysiology of CVD, and comorbid conditions often complicate clinical management. With the rapid adoption in older patients of invasive cardiovascular procedures, such as percutaneous coronary intervention and trans-catheter aortic valve replacement, the magnitude of this challenge is increasing. Understanding key aspects of cardiovascular physiology in older adults can serve as a foundation to guide interpretations of clinical presentation, diagnostic responses, formulating therapeutic strategies, and monitoring clinical efficacy in elderly patients with CVD.

Advanced age is an important risk factor for cardiovascular disease, and a powerful independent predictor of cardiovascular morbidity, mortality and disability. As a result of decades of complex molecular and cellular aging processes, cardiovascular physiology in the older adult is characterized by: (1) endothelial dysfunction, (2) increased arterial stiffness, (3) increased left ventricular (LV) stiffness, (4) altered coupling of LV and arterial stiffness and function, (5) attenuated baroreflex and autonomic reflexes, and (6) degenerative changes of the conduction system. These changes produce a cardiovascular system that has reduced maximal function compared to younger people and less reserve capacity, and can fail to meet needs when stressed. The purpose of this paper is to highlight the changes in the vasculature and heart that impact on the basal and stressed physiology of the older patient with cardiovascular disease.

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2 Endothelial dysfunction

2.1 Physiology and age-related changes

The endothelium plays an active role in maintaining vascular homeostasis by balancing vasodilation and vasoconstriction, growth inhibition and promotion, anti- and pro-thrombosis, anti- and pro-inflammation, and anti- and pro-oxidation. Endothelial cells secrete various vasoactive molecules such as the vasodilators, nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor, and vasoconstrictors, such as endothelin-1, angiotensin II and thromboxane A_2. The most frequently used tool to investigate age-related changes in endothelial function is NO mediated vasodilatation. Age-related decreases in NO-mediated vasodilatory responses are well documented at every level of the vasculature from the coronary micro-circulation to larger epicardial coronary arteries and the peripheral circulation.[1] Endothelial-dependent forearm va-

sodilation decreases progressively with advancing age in men, and notably occurs about ten years later in women.[2] The underlying mechanisms include: (1) increased oxidative stress with increased production of reactive oxygen species (ROS), which directly reduce NO production by inhibiting eNOS expression and inducing eNOS uncoupling; (2) increased level and activity of arginase, which directly limits the availability of eNOS substrate availability and decreases NO production; (3) increased production of vasoconstrictors, such as thromboxane, endoperoxide and endothelin-1; and also (4) reduced capacity of endothelial regeneration due to endothelial cell senescence and decreased availability of endothelial progenitor cells.

2.2 Clinical implications

The clinical impact of age-related endothelial dysfunction is to reduce the regulatory capacity of blood flow and promote atherosclerosis and thrombosis. Testing of endothelial function in the elderly is not usually performed clinically but is a useful clinical research tool. Importantly, age-related endothelial dysfunction is at least partially reversible by dynamic physical activity.[3] The older artery remains responsive to the effects of NO; direct NO donors, such as nitrates, do not rely on endothelial-mediated activity to stimulate NO and can ameliorate the impact of age-related changes in endothelial function. These and other vasodilatory agents, such as alpha-blockers, must be used with care in the elderly due to the potential for excessive vasodilatation and orthostatic hypotension. Statins, selective beta blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers also can improve endothelial dysfunction associated with systemic conditions such as hypertension, diabetes mellitus, inflammatory diseases etc, but efficacy on age-related changes has not been tested.

3 Increased arterial stiffness

3.1 Physiology and age related changes

Age-related changes occur throughout the arterial wall. The arterial tree is a visco-elastic tube. In younger individuals, the central arteries are more elastic and less stiff than the peripheral arteries. Compared to vessels from healthy younger individuals, arteries from older individuals are characterized by increased reactive oxygen species (ROS) content, inflammatory changes, decreased NO availability, and endothelial dysfunction. These changes produce a stiffness gradient along the arterial tree that is reversed, i.e., greater central artery stiffness than peripheral arteries. In general, arteries in older adults become longer, wider, thicker and stiffer. Decreased distensibility or increased stiffness of the large central arteries is a hallmark of vascular aging.[4,5] The processes involve complex molecular and cellular mechanisms as summarized in Figure 1, which include (1) migration and proliferation of vascular smooth muscle cells in the sub-endothelial space; (2) accumulation of collagen and proteoglycan in the intima, and decrease of hydrolytic turnover and elasticity of collagen due to increased cross-linking; (3) decreased production and accelerated degradation of elastin, and (4) increased calcification. Various pathways including inflammatory cytokines and cells, adhesion molecules, matrix metalloproteinases (MMPs) and transforming growth factor-β are also affected. These changes coupled with the endothelial changes, result in large artery stiffening, decreased compliance and recoil, and a diminished capacity to absorb the pulsatile wavefront produced by the ejecting heart.[6]

As a result of increased arterial stiffness, there is increased LV afterload, contraction and oxygen requirement. In older adults, LV afterload is increased due to (1) an enlarged aortic diameter creating more inertance (the pressure gradient in a fluid required to cause a change in

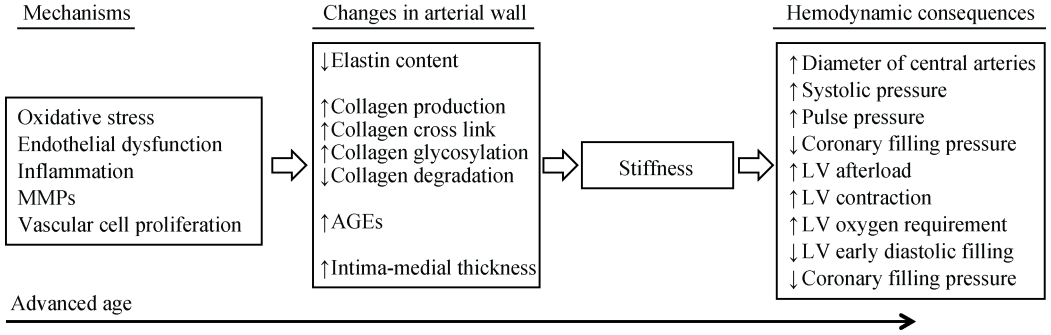

Figure 1. Summary of molecular mechanisms leading to increased arterial stiffness in the older adult and its' hemodynamic consequences. AGEs: advanced glycation end products; LV: left ventricular; MMPs: matrix metalloproteases.

flow-rate with time); (2) decreased aortic compliance requiring increased LV pressure to maintain cardiac output; (3) the premature reflection of the arterial pulse wave from the periphery; and (4) an increased in systemic vascular resistance. Decreased coronary blood flow results from both decreased aortic diastolic blood pressure and increased LV end diastolic pressure from ventricular stiffness, left ventricular hypertrophy and increased LV afterload.

3.2 Clinical implications

Regional and local arterial stiffness can be quantified invasively or by non-invasive measurement. The measurement of pulse wave velocity (PWV) is generally accepted as the most simple, non-invasive, robust and reproducible method to determine arterial stiffness. However, because PWV is conventionally measured when the artery is distended at diastolic pressure, it may underestimate the real stiffness increase with age. Carotid-femoral PWV is a strong predictor of cardiovascular mortality and morbidity.[7] In patients with hypertension, aortic stiffness measured by carotid-femoral PWV adds independent predictive value in addition to other CVD risk factors, such as those included in the Framingham risk score.[8] Longitudinal epidemiological studies have demonstrated the independent predictive value of arterial stiffness for cardiovascular events (all cause and cardiovascular mortalities, fatal and non-fatal coronary events, and fatal strokes) in patients with uncomplicated essential hypertension, type 2 diabetes, end stage renal disease, elderly subjects, and the general population.

The increased arterial stiffness and decreased distensibility in the elderly lead to the age-associated increase in systolic blood pressure, decrease in diastolic blood pressure (DBP) and widening of pulse pressure (PP). These changes can complicate the treatment of systolic hypertension in the elderly due to excessive DBP lowering and/or postural hypotension (in combination with reflex changes discussed below), and coronary hypoperfusion. Decreased central arterial compliance (increased arterial stiffness) also creates a system in which small shifts in intravascular volume create large changes in blood pressure.[9,10] Furthermore, an increased pulsatility (widened PP) is also harmful to end organs and increases the risk for renal disease, dementia, myocardial infarction, stroke, heart failure, arial fibrillation and mortality.

Antihypertensive medications (diuretics, angiotensin converting enzyme-inhibitors, angiotensin receptor blockers, calcium-channel blockers, and certain beta-blockers) have been shown to reduce arterial stiffness in investigational studies. Non-pharmacological interventions, including weight loss, low-sodium diet, and moderate alcohol consumption can reduce age-related arterial stiffness. Most importantly, regular moderate to vigorous intensity physical activities (brisk walking, jogging, aerobics, and other sports) attenuate arterial stiffening during aging. More recently, it has been demonstrated that light physical activity for longer durations can also reduce arterial stiffening, especially in older people who have not previously exercised regularly. Thus, all levels of exercise should be encouraged in older patients, as more vigorous physical activities are not feasible for some older individuals. Light physical activities to replace sedentary behavior may be a more practical and achievable preventive strategy for many elderly.[11]

4 Reduced LV compliance and cardiac reserve

4.1 Physiology and age-related changes

LV function is determined by myocardial contractility, preload, and afterload. It is also dependent on the "functional" coupling of the LV with the arterial system (ventricular-vascular coupling), represented by the ratio between arterial effective elastance (E_A) to end-systolic left ventricular elastance (E_{LV}). Primary changes in cardiomyocytes in older adults include an increase in size (progressive hypertrophy) and a decrease in the number (progressive loss of myocytes) with an alteration of myocyte to fibroblast ratio. While resting LV contractility is usually preserved in the absence of disease, LV stiffness increases and LV volume decreases during aging with the transition occurring between youth and middle-age, and becoming clinically manifest between the ages of 50 years to 64 years. Several other factors also lead to age-associated decreased LV compliance and alterations in contraction-relaxation, such as increased collagen accumulation and advanced glycation end products -mediated cross-links, fibrosis and infiltration of inflammatory cells and proteins. In addition, alterations in calcium signaling in the sarcoplasmic reticulum (SR) of cardiomyocytes also impair active LV relaxation. Hearts of healthy older adults have less cardiac SR calcium ATPase (the calcium pump), have lower SR calcium content, and are more dependent on trans-sarcolemmal calcium fluxes, including those through the L-type calcium channels and the sodium-calcium exchanger. This increased dependency on calcium entry through the L-type calcium channels may explain the increased sensitivity of older people to drugs that block these channels.

With advanced age, there is prolongation of LV isovolumic relaxation time, reduction in early diastolic filling, and augmentation of late diastolic filling. The percent filling of the LV during the early phase of diastole can diminish from 70% to 30%, and as the LV end diastolic volume

(LVEDV) does not change with age, LA volumes increase. Thus, the older heart is more dependent on active filling in late diastole from the atrial contraction, can contribute up to 70% of the LVEDV.

4.2 Clinical implications

LV compliance (stiffness) can be determined by the slope of LV diastolic pressure-volume curve derived from invasive left heart catheterization but is rarely done today, as noninvasive echocardiographic assessment of LV diastolic function has become the gold standard. Doppler measurement of mitral inflow velocity and tissue Doppler imaging assessment of mitral annular velocity are routinely done during transthoracic echocardiography to assess LV compliance and diastolic function.

Increased LV stiffness in the older adult contributes to the clinical presentations of heart failure with preserved ejection fraction. It also contributes to the dependence of LV filling from atrial systole, and explains the relative clinical intolerance of atrial fibrillation in an older adult compared with a younger patient. The older patient has a lower threshold for developing dyspnea and/or pulmonary edema, especially with acute onset episodes of atrial fibrillation or flutter and rapid ventricular responses. Early LV diastolic filling can also be compromised during any tachycardia. However, load-dependent BP lability and augmented LV wall stress can occur in response to relatively minor perturbations in heart rate, BP, intravascular volume, or cardiac dysfunction. Multiple factors can impact the supply and demand aspects of CV performance in older patients, tipping the balance to one dependent on cardiac reserve. In clinical practice, identifying and rectifying the factors that might have altered this balance can often stabilize an older patient and avoid a higher-risk intervention. Pharmacologic agents, such as ACE inhibitors and ARB, are effective in dilating vasculature and reducing after load, and potentially affecting myocardial relaxation and compliance by reducing interstitial collagen deposition and fibrosis. Calcium channel blockers improve LV compliance by decreasing cytoplasmic calcium concentration and increasing myocardial relaxation. These agents often improve exercise capacity and quality of life for the elderly, in particular, those who experience hypertensive response to exercise.

5 Impaired beta-adrenergic and parasympathetic function

5.1 Physiology and age-related changes

Physiological responses to autonomic input are keys to maintaining blood pressure when standing or during volume loss, and increasing cardiac output during exercise or stress. Decreased responses to beta adrenergic and parasympathetic stimulation and reflex responses are hallmarks of aging. Chronotropic, inotropic, and lusitropic responsiveness to beta-adrenergic agonists are decreased with advancing age. During aging, the heart rate response to atropine is decreased due to an elevated parasympathetic vagal tone and a reduced sympathetic responsiveness. In response to the administration of similar doses of isoproterenol, heart rate increased 25 beats/min in young healthy males, but only 10 beats/min in older healthy males. These changes are the results of suppressed cAMP generation, decreased beta-receptor numbers and function, and increased inhibitory G protein activity in the elderly. In contrast, the production and release of circulating catecholamine and exercise-stimulated levels of epinephrine and norepinephrine are higher in older adults in comparison to younger healthy adults. These changes in both limbs of the autonomic nervous system, contribute to the blunted reflex and baroreflex responses in the elderly, which in turn, diminish the potential for the body to respond to stressors.

5.2 Clinical implications

Normal responses to sudden lowering of pressure include increases in heart rate, peripheral vasoconstriction and venous return. The age-related reduction of responsiveness and blunted reflexes often diminish the normal response and can result in orthostatic hypotension and syncope.[12] Age-related changes in autonomic responses also contribute to the lack of CV reserve that can result in cardiac decompensation in older people faced with sudden or marked increases in cardiac workload, hypovolemia, fever, infection, or other stressors.

The age-related changes in heart rate are most evident for maximal and exercise-induced heart rates with negligible changes in resting heart rate. While vagal withdrawal may be responsible for increases in heart rate during the first minute of exercise in younger people, the reductions in maximal heat rate and reduced maximal cardiac output in the elderly are largely due to the blunted responsiveness to beta-adrenergic stimulation. In the setting of chronotropic incompetence, exercise-induced increases in cardiac output may depend substantially on augmented cardiac filling (preload). In addition to heart rate changes, the maximal increase in LV ejection fraction during exercise (i.e., EF reserve) is smaller in the older adult than in younger people. In addition, for a given increase in cardiac output in response to exercise, the concomitant rise in the systemic and pulmonary arterial pressures is also much greater. Many of the age-related changes described above and some of the

Table 1. Physiological changes of other organ systems and potential impacts on caring for CVD in the older adult.

Organ systems	Physiological changes in the older adult	Potential impact on caring for CVD in theolder adult
Kidney	↓ GFR ↓ Numbers of glomeruli ↑ Interstitial fibrosis ↑ Glomerulosclerosis	- Labile volume status in treating HTN and HF - ↑ Assess risk of contrast-induced nephropathy - Assess secondary cause of HTN and HF
Lung	↓ Alveoli ↓ Elastic recoil ↓ Gas exchange ↓ Maximal respiratory effort ↓ Tidal volume and minute ventilation ↑ V/Q mismatch ↓ Sensitivity of chemoreceptors to reduced O_2 and increased CO_2	- Monitoring and treatment of hypoxia and hypercapneic respiratory distress - Oxygen therapy if indicated
Endocrine	↓Estrogen (female) ↓Testosterone (male) ↓Growth hormone ↓Insulin-like growth factor 1 ↓Thyroid hormone ↑Total daily cortisol with disruption of circardian rhythm of cortisol	- Assess general wellness (nutrition, bone density, etc) - Risk stratification for CAD - Assess vascular related *vs*. endocrinology related erectile dysfunction of male - Assess secondary causes of CVDs
Gastrointestinal	↑Large bowel transit time susceptible for constipation	- Assess medical absorption - Assess GI bleeding risk while giving antiplatelet or anti-coagulation therapies
Neurological	↓ Brain size and weight ↓ Neuronal connectivity and size with unchanged numbers of neurons ↓ Cognitive function ↓ Memory ↓ Pyramidal tract function ↓ Postural sensation and control ↓ Special senses (hearing, vision, etc) ↓ Pain sensation ↓ Temperature regulation	- Assess medication adherence - Address communication barriers - Give instructions in direct and simple ways - Assess increased fall risk while giving anticoagulation or antiplatelet therapies - Anticipate atypical presentation of CVDs - Assess exercise capacity and provide assistance
Musculoskeletal	↓ Bone density ↓ Muscle mass and strength ↓ Ability to extract oxygen	- Assess fall risk while giving anticoagulation or anti-platelet therapies - Assess exercise capacity and provide assistance

CVD: cardiovascular disease; GFR: glomerular filtration rate; HF: heart failure; HTN: Hypertension.

autonomic age-related changes can be attenuated by exercise.

Aging is a systemic process involving all organ systems. Age-associated changes in other organ systems also greatly impact CV performance, endurance, and response to stress. Recognition of physiological changes of other organs associated with advanced age is critical in caring for CVD of the older adult (see Table 1).

6 Opportunities for future research and clinical pearls

The future research needs are: (1) defining exercise prescription for older patients; (2) establishing prediction schema based on data from older patients that incorporate measures of age-related changes; (3) discovering treatments that can ameliorate, antagonize, or prevent the cellular changes in cardiac myocytes with aging; (4) treatments that can restore endothelial function; (5) treatments that can selectively and directly reduce central arterial stiffening; and (6) physiological phenotyping and evidence-based management strategies for heart failure with preserved ejection fraction.

The clinical pearls are: (1) the only tool we currently have to attenuate age-related CV changes is exercise prescribe it! (2) direct vasodilators (nitrates and alpha-blockers), may precipitate excessive vasodilatation leading to orthostatic hypotension; (3) widened pulse pressure with significantly low diastolic pressure without the presence of aortic regurgitation or heart failure in an elderly person, is

suggestive of marked decrease of vascular compliance, associated with worse cardiovascular outcome; (4) decreased chronotropic, inotropic and lusitropic myocardial responses, as well as blunted baroreflexes explain why neurally-mediated and orthostatic types of syncope are the most common in older adults; and (5) heart rate control of atrial arrhythmias such as atrial fibrillation are critically important in the elderly, as these can significantly impair effective cardiac output and coronary perfusion.

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