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Current themes in myocardial and coronary vascular aging

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Abstract

Advancing age will affect every individual and its impact on cardiac health deserves significant attention. The age-related physiological changes occurring in the coronary vasculature, myocardium, and valves set the stage upon which cardiovascular disease can escalate in the elderly population. The overall focus of this review is to highlight new and noteworthy studies and to incorporate reviews related to cardiac senescence in the context of the current state of the field. Lastly, future directions in the field of cardiac aging and the development of novel therapeutics to treat pathophysiological conditions typically associated with advancing age will be discussed.

Keywords

aging; senescence; microvascular; perfusion; cardiac; coronary

Introduction

Advanced age, senescence, or the definition of elderly is typically characterized in developed countries by the chronological age of 65 and beyond. In 2003, Edward Lakatta [1–3] published a series of seminal review papers on how age-associated alterations in cardiac structure and function partner with pathophysiological disease mechanisms to determine the threshold, severity and overall outcome of cardiovascular disease (CVD) in the geriatric population. There are many factors that make the heart unique compared to other organs, but some clearly resonate more when coupled with these changes that naturally occur with aging. For example, since myocardial blood flow mainly occurs during diastole, chronic abnormalities in this phase of the cardiac cycle can significantly impact overall cardiac function and perfusion. Diastolic dysfunction is an increasing cause of hospital admissions and exercise intolerance in the elderly, but currently has no present treatment [4]. Interestingly, systolic function in the elderly is relatively preserved at rest, but decrements in cardiovascular reserve following exercise is apparent, likely due to age-related decreases in maximal heart rate and ejection fraction [5]. Even life-long exercising humans cannot escape the decrease in VO_2 max and maximum heart rate that accompanies old age [6].

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Common age-related pathologies that are cardiac-centric

The risk of developing heart failure (HF) increases with age, but so does the risk of HF with preserved ejection fraction (HFpEF), particularly in women. This clinical condition is characterized by the development of HF via age-associated physiologic cardiac changes mentioned by Lakatta [1] (diastolic dysfunction, ventricular hypertrophy and fibrosis), but is accompanied by near normal ejection fraction. HFpEF has steadily gained attention due to the fact that approximately 50% of HF patients are reported to have HFpEF [7*]. There are few evidence-based interventions to treat HFpEF, instead of relying on a robust history of empirical data. Neurohormonal blockade is typically used to treat HF patients and has been attempted as a carryover therapy in HFpEF patients. However, three large-scale prospective randomized clinical trials recently concluded there was no significant impact of blockade treatment in HFpEF and has left clinicians with an ongoing therapeutic dilemma [8]. Further, the difficulty in non-invasively identifying this large patient population led Dunlay and colleagues (2017) to describe the need for a simpler, but sensitive and specific method to accurately diagnose HFpEF. For example, developing novel biomarkers from blood samples or algorithms generated from electronic medical records may help stem this burgeoning clinical population [7*].

Studies identifying a protein mutation and the emergence of immunocardiology highlight some of the other recent research contributing to common age-related cardiovascular pathologies. Clinical presentations such as escalated concentric wall thickening, diastolic dysfunction with normal systolic function, and a reduced functional capacity are typical markers of cardiac disease in aging, but new research shows that these may actually be due to wild-type transthyretin amyloidosis (ATTRwt) [9]. ATTRwt is most commonly found in men and is responsible for causing the misfolding of amyloid proteins, resulting in excessive concentric geometric remodeling which can lead to a greater possibility of cardiovascular events or death [9]. Currently, ATTRwt cardiomyopathy is not accurately diagnosed because its clinical manifestations resemble various other cardiac pathologies that occur with aging, specifically, hypertensive or hypertrophic heart disease [9]. Overall, Connors et al. (2016) found that subjects with ATTRwt demonstrate more advanced age-related cardiac pathologies than what was indicated in the past [9]. Thankfully, there are emerging, ongoing therapies for ATTRwt already in late-phase clinical trials, but are seeing mixed success [10]. Liver transplantation in patients with ATTRwt delays, but does not cease cardiac dysfunction because ATTRwt continues to be deposited in the heart from the transplanted liver. This therapy is not preferred because of the insufficient attainable number of organs and the longing for lifelong immunosuppression [10]. Interestingly, green tea is rich in the flavonoid epigallocatechin gallate that arrests amyloid fibril formation in vitro, and is currently in open-label trials for the treatment of ATTRwt [10]. With this in mind, the drug Tafamidis is currently in trial with the Transthyretin Amyloid Cardiomyopathy Tafamidis Study that is predicted to end in 2018 with the prospect of gaining a U.S. Food and Drug Administration approved drug for ATTRwt [10].

Immunocardiology studies denote the importance of CD4⁺ T cells in the aged myocardium due to their effect on spontaneous local inflammation and heart dysfunction [11**]. Myocardial impairment correlates with changes in the architecture of tissue-resident

leukocytes and a buildup of activated CD4⁺ FOXP3⁻ (forkhead box P3) IFN- γ ⁺ T cells in the heart draining lymph nodes [11**] (Table 1). In the older population, increased cardiac-resident lymphocytes do not lead directly to myocardial deterioration, but rather amplify the myocardial inflammation which advances the structural changes of the myocardium in advancing age [11**]. Thus, myocardial aging is a combined result of cardiac and immunological factors [11**]. Ramos et al. established in 2017 that it is normal for the healthy myocardial parenchyma to contain both B and T lymphocytes for steady-state conditions, whereas prior to that study it was recognized that only macrophages seeded the myocardium under basal conditions. In essence, the healthy heart is immunologically active and the presence of lymphocytes detects changes in cardiac function and causes immune responses during aging.

Cardiomyocyte aging

A number of theories have been postulated for cardiac changes occurring in advanced age, such as short telomere defect, unregulated oxidative stress, subsequent mitochondrial damage, intracellular Ca²⁺ mishandling and excitation-contraction coupling [12] (Table 1). Since the heart is the most energy-dependent organ, it relies on the aerobic metabolism of fatty acids, glucose and lactate to produce sufficient ATP for normal heart function [13]. Mitochondria occupy about 30% of each cardiomyocyte, but advancing age leads to a malfunction of cardiac mitochondrial metabolism [14] and results in overproduction of reactive oxygen species (ROS) [13,14]. Increased mitochondrial ROS can damage mitochondrial components and activate oxidant-mediated signaling pathways, such as mitochondrial oxidative phosphorylation that results in cell death [14]. Despite having been studied in a variety of cell types, the functional role of matrix metalloproteinase (MMP)-9 in cardiomyocytes is not well understood. Nevertheless, a link between cardiac MMP-9 and aging is emerging, such as work by Tsai and colleagues that demonstrated how ROS could induce MMP-9 secretion in the vascular wall [15]. Other studies have shown that MMP-9 is involved in cardiomyocyte remodeling such as inflammation and fibrosis [16], and macrophage-specific MMP-9 acts to escalate left ventricle (LV) hypertrophy as well as suppress angiogenesis to elicit an inadequate number of blood vessels for sufficient oxygen supply to support normal cardiac function during aging [17*] (Table 1). Thus, overexpression of MMP-9 results in a hypoxic environment and further causes myocardium inflammation by activating traditional pro-inflammatory M1 macrophages and suppressing anti-inflammatory M2 macrophages [17,18*] (Table 1). At the same time, there is an increased number of macrophages in the LV with senescence. This feed-forward mechanism results in more MMP-9 and aids further aging of cardiomyocytes [18]. The impact of aging on the cardiac extracellular matrix, including MMP-9, were recently described and highlighted in a review by Meschiari et al. in 2017 [19]. In brief, myocardial MMPs play important roles in cell signaling during the aging process by modulating cytokines, chemokines, growth factors, hormones, and angiogenic factor expression and activity [19].

Controlled mitochondrial autophagy in cardiomyocytes is important for successful cardiac aging because it selectively targets and removes damaged or old mitochondria [20]. Obviously, mechanisms that downregulate autophagy could lead to cardiac dysfunction [21,22]. In 2017, it was reported that aging led to enhanced mitochondrial aldehyde

dehydrogenase, an enzyme which induces cardiac remodeling and contractile dysfunction by directly suppressing myocardial autophagy [12] (Table 1). Traditionally, aldehyde dehydrogenase is a gene which had previously been shown to regulate cardiac function in pathological settings, such as diabetes mellitus, alcoholism, ischemic heart disease and arrhythmias [12]. As such, therapies designed to minimize the actions of mitochondrial aldehyde dehydrogenase will have widespread cardiac implications, particularly in the aged patient population by possibly restoring balanced autophagy.

Valves and aging

Other notable degenerative changes in human cardiac aging include aortic stenosis as a result of fibrosis and valvular calcification [23], which prevents effective pumping of the blood through the aortic valve. The combination of enhanced MMP activity, scattered deposition of fibers, and hydroxylation of telopeptidyl lysine increases collagen content leading to collagen remodeling [24]. It is the remodeling of collagen that causes a change in valve architecture, resulting in valvular stiffness during aging [25]. As a way to compensate, LV wall thickening occurs in order to maintain sufficient systolic function. Over time, the pressure overload and wall stress causes LV dilation and will lead to systolic dysfunction. Aortic stenosis affects 2% of the general population >65 years of age and increases to 4.6% of the population aged 75 years and older [26**,27]. For decades, passive accumulation of calcium and progressive “wear-and-tear” were considered causes of valvular damage [27]. But for the same amount of aortic valve calcification, women have recently been shown to achieve hemodynamically more severe aortic stenosis than men (Figure 1) [26**]. This is because hemodynamic severity in patients with aortic valve calcification is dependent on valvular fibrosis, which is predominantly increased in women (Figure 1) [26**]. There is evidence that valve calcification proceeded by a pathological process that contributes to the development of fibrocalcific aortic valve stenosis is a process similar to that occurring in bone matrix [27].

The age-related valvular changes mostly occur in the mitral and aortic valves, as opposed to the tricuspid and pulmonary valves. Though less common than aortic stenosis, degenerative mitral valve disease still affects 2–3% of the general population [28**]. Degeneration of the mitral valve can cause severe mitral regurgitation and LV dysfunction [28**]. However, if repair of degenerative valve is performed before signs of LV dysfunction arises, surgical outcome has recently been shown to be significantly improved in the general population [28**]. Otherwise, the surgical repair may not be curative.

Coronary arteries and vascular aging

The ventricular and valvular changes that occur in senescence compromise the functional pumping reserve of the heart but also lower the threshold in which vascular dysfunction can manifest. In general, prominent structural changes to the vasculature that occur with aging include dilation and wall thickening of large elastic arteries [3,29], with a 2–3-fold increase in the intimal media layer between 20 and 90 years of age [30]. In the heart, stress echocardiography of the left anterior descending (LAD) artery in elderly patients can serve as an effective prognostic evaluation of coronary artery disease (CAD) [31]. Specifically,

Cortigiani and colleagues found that a decreased coronary blood flow reserve (CFR) of the LAD is a strong and independent indicator of mortality and major adverse cardiac events [32]. Furthermore, if CFR is preserved in octogenarians (> 1.93), it predicts a benign prognosis and is associated with a very low risk of major cardiac event of only 2.1% [32].

In the coronary microcirculation, the endothelial cell layer becomes deranged in senescence and may contribute to the decreased ability of the heart to increase CFR [33]. Local metabolic feedback, specifically the production of relaxing and constricting factors (such as nitric oxide (NO), prostacyclins, endothelin, and endothelium-derived hyperpolarizing factor), are still considered the primary regulators of coronary microvascular blood flow, but the response to these factors change as the heart ages. It's been widely recognized for two decades that a chronic loss of NO in the endothelial cell layer occurs with advancing age and in disease states, and recent evidence strongly supports compensatory mechanisms that act to preserve coronary blood flow by shifting NO-mediated dilation to hydrogen peroxide (H_2O_2)-mediated dilation [34]. In fact, aged coronary arterioles depend more on H_2O_2 (vs NO) to mediate basal coronary vascular tone [35]. Recently, Beyer et. al. described the temporal shift in the primary mediator of flow-induced vasodilation in coronary arterioles from humans [36*]. Specifically, the authors reported a transition from utilizing prostacyclin in youth, to NO in adulthood and middle-age, and finally to mitochondrial-derived- H_2O_2 with the development of CAD [36*].

Attempting to normalize the increased presence of ROS in the vascular wall has improved functional parameters such as flow-induced dilation in human coronary microvessels [37,38]. Freed et al. (2014) identified ceramide, a known inducer of mitochondrial ROS, as an integral player in the transition from NO to H_2O_2 . Inhibiting the production of ceramide worked to revert the mechanism of dilation back to NO [37]. Similarly, upregulation of mitochondrial antioxidant enzymes through activation of telomerase, an enzyme classically known to maintain telomere length in nuclear DNA, has been proven to restore NOS-mediated vasodilation in vessels from patients with CAD [39]. Whether these interventions improve overall cardiac perfusion has yet to be demonstrated in aged patients, but a study by Nevitt and colleagues (2016) suggests that this may be possible. By acutely inhibiting cell membrane receptor CD47, a known activator of cellular ROS in many cell types, the authors reported an increase in CFR in aged rodents compared to the old group treated with a control antibody [40]. Likewise, infusion of monoclonal antibody against CD47 has been shown to improve cutaneous blood flow in aged mice [41] and is garnering attention as a successful post-infarction/injury therapy [42]. Other therapeutic interventions, such as exercise, cell therapy and caloric restriction target specific age-dependent dysfunction and elicit improvements in microvascular health, in part, through an increase in ROS buffering. These interventions do not reverse senescence-induced vascular sequelae back to a youth-like state, but may position the aged heart to better withstand and/or recover from normal insults.

Potential for Therapies in Cardiac Aging

Developing cardiac-centric therapeutics have been limited to hearts with pathophysiological diagnoses, rather than creating therapies to treat strictly age-related alterations in the myocardium, valves, and/or coronary vessels. In the early 2000's, the widespread use of

angiogenic factors to treat ischemic hearts were largely shown to be ineffective due to the inability of newly created vessels to mature and successfully perfuse the infarcted area [43]. Within the past decade, stem cell therapy has arisen as a therapeutic approach for an acute myocardial infarction, chronic ischemia, and chronic HF. But a major disadvantage to this therapy is that stem cell self-renewable ability is distorted with aging [44–46]. Although, a recent study by Liu et al (2016) opens new avenues for treatment of myocardial infarction in the elderly population by demonstrating the role of hepatocytes growth factor (HGF) in cardiac stem cell (CSCs) proliferation and differentiation [47]. Specifically, the authors describe how adenovirus carrying hepatocytes growth factor gene activates endogenous c-kit CSCs to promote cardiomyocyte proliferation and angiogenesis through the induction of necroptosis, the programmed form of necrosis for inflammatory cells [47]. Additionally, readers are directed to a position paper published by the European Society of Cardiology that describes the most recent novel therapies for acute cardioprotection in the aged population [48**], including the status of ongoing clinical and experimental studies and identified areas of optimization for both.

Exercise has long been known to be beneficial to the heart, but it's been recently established that long-term exercise is especially favorable in the aging heart because it diminishes accumulation of collagen and fibrosis in cardiomyocytes, which lessens arrhythmias and maintains cardiac function [49**]. There is an age-related increase in the number of sodium calcium exchange channels and sarcoendoplasmic reticulum ATPase (SERCA), which raise the risk of arrhythmias and disrupts the calcium balance in advancing age [49]. SERCA activity is normally regulated by phosphorylated phospholamban (PLB), but this decreases with aging. As a result, the ratio of SERCA/PLB is increased [49]. Walton et al (2016) demonstrated that mice who undergo a chronic exercise regime beginning in middle age can actually halt further cardiomyocyte aging. This is because exercise causes SERCA and sodium calcium exchange expression to return to normal levels and PLB expression to increase, leading to a lower SERCA/PLB ratio and thus maintaining stability and improved dynamics of calcium handling during the remainder of the lifespan [49**]. Finally, this study promotes the old adage of “better late than never” regarding the initiation of an exercise regime.

Future Directions and Conclusions

Given that CVD is the leading cause of morbidity and mortality in western societies [50] and that advancing age is a main risk factor for CVD, future therapeutic studies that successfully reverse or prevent some of the age-related changes in the senescent heart could have a major health and financial impact. As described above, each area of the heart has age-related changes occurring and would benefit from tailored therapies to address each of these sections. For example, the growth of therapies related to reducing or restoring the balance of ROS in advancing age would affect multiple areas of the heart, as increased ROS plays a role in both the dysfunction of cardiomyocytes and the coronary microvasculature. Future directions of cardiac aging research will likely capitalize on the recent advances in our understanding of immunocardiology (T cells). It was an important and novel discovery for the field when a constitutive presence of CD4+ T cells were identified in the aging myocardium [11**]. Further, these constitutive immune cells were found to also mediate

cardiac inflammation and cause mild functional cardiac impairment in the elderly [11**], suggesting these T cells could serve as a disease-modifying factor in other age-related cardiac pathologies.

Sex-related differences in CVD research and clinical trials are being realized more frequently, likely instigated by the recent requirement to consider sex as a biological variable for NIH-funded research. The overall principle of men and women receiving equitable, high-quality care is an obvious unstated goal of any healthcare system, but consideration of unique sex-dependent physiological differences must be heeded in optimizing care. In patients with heart failure, we previously described a greater prevalence for women to exhibit HFpEF [7], while men are more likely to be diagnosed with ATTRwt cardiomyopathy [9]. This topic of gendered research as it applies to cardiovascular medicine has been recently reviewed [51*] and is particularly germane in developing therapeutics for aging men and women.

Lastly, if therapies are developed to treat age-related cardiac changes vs the pathological conditions that are associated with aging, such as myocardial infarctions and HF, perhaps the prevention of such CVDs are possible. In order for this to happen, however, delineation of these conditions, including an aging-specific research agenda, must be a vital part of strategic planning to improve the lives of all aging patients. In this theme, the National Institute of Aging (NIA) promotes and encourages applications designed to elucidate the physiological mechanisms underlying the process of aging and age-related changes in humans and animal models of human aging. Not only is the development and characterization of animal models of aging sought and funded by the NIA, but grants investigating novel interventions for the prevention and treatment of age-related conditions are identified areas of priority. Therefore, researchers are encouraged to pursue these funding opportunities in order to advance the known roadmap and intersection between cardiac physiology/pathology and senescence.

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Abbreviations

ATTRwt	Wild-type transthyretin amyloidosis
CAD	Coronary artery disease
CSCs	cardiac stem cell
CVD	Cardiovascular disease
H₂O₂	Hydrogen peroxide
HF	Heart failure

HFpEF	Heart failure with preserved ejection fraction
HGF	Hepatocytes growth factor
LV	Left ventricle
MMP-9	Matrix metalloproteinase-9
NO	Nitric oxide
PLB	Phosphorylated phospholamban
ROS	reactive oxygen species
SERCA	Sarcoendoplasmic reticulum ATPase

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Highlights

- This review highlights new and noteworthy studies and reviews related to cardiac senescence
- Cardiovascular disease can escalate especially in the elderly population

Figure 1.

(**A**) During aging, more valvular calcification changes happen in men than women. On the other hand, the aortic valve in women undergoes additional fibrotic changes as they age, which leads to aortic fibrocalcification and decreased valve opening. (**B**) Men develop less severe aortic stenosis even though they have more calcification on the aortic valve than women. Severity of aortic stenosis is increased in women compared to men, due to more fibrotic changes in the aortic valve. Adapted from reference [26]

Table 1

A summary of the cellular age-related changes in the myocardium and resultant cardiac outcome as mentioned in the review.

Cellular changes during aging in the myocardium	Cardiac outcome
Buildup of activated CD4 ⁺ FOXP3 ⁻ IFN- γ ⁺ T cells	Myocardial deterioration
Increased cardiac-resident lymphocytes	Myocardial deterioration
Intracellular Ca ²⁺ mishandling	Increase risk of arrhythmias
Mitochondrial damage	Myocardial deterioration
Short telomere defect	Cardiac remodeling and contractile dysfunction
Increased macrophage-specific MMP-9	Escalate left ventricle hypertrophy
Increased pro-inflammatory M1 macrophages	Suppresses anti-inflammatory M2 macrophages-causes myocardial deterioration
Enhanced mitochondrial aldehyde dehydrogenase	Cardiac remodeling and contractile dysfunction
Increase in the number of sodium calcium exchange channels and sarcoendoplasmic reticulum ATPase	Increase risk of arrhythmias