HUMAN AGING; EMERGING TRENDS IN BIOCHEMICAL ALTERATIONS IN THE HEART

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ABSTRACT
The cardiac muscle is unique because it contracts tirelessly throughout the life and is highly resistant to fatigue. The amazing nature of the cardiac muscle is attributed to its matrix that maintains structural and functional integrity and provides the ambient micro-environment required for mechanical, cellular and molecular activities in the heart. The aging heart has three critical elements i.e Na+K+ATPase enzyme, hypoxia inducible factors and matrix metalloproteinases (MMPs) which are affected and heart muscle starts to become weakened and ageing process occurs causing biochemical alterations in myocytes. Cardiac matrix regulates myocyte contractility by endothelial myocyte (EM) coupling and calcium transients and also directs miRNAs required for precise regulation in the matrix homeostasis due to induction of MMPs, altered expression of specific miRNAs or impaired signaling for contractility of cardiomyocytes may lead to deleterious effects. This review article examines these features in the aging cardiac muscle.

INTRODUCTION
The increased age-dependent exposure time to various risk factors including hypertension, diabetes, hypercholesterolemia and smoking is accompanied by age associated interactions of the intrinsic aging of heart with progressive structural changes and functional decline occurring with age. Further, the changes in Cardiac structure and functions due to the intrinsic aging increase susceptibility to oxidative stress related injury and contribute to increased cardiovascular morbidity and mortality. Changes in the matrix homeostasis due to induction of MMPs, altered expression of specific miRNAs or impaired signaling for contractility of cardiomyocytes may lead to deleterious effects.1,2 Even without associated systemic risk factors, intrinsic cardiac aging leads to structural and functional deteriorations of the heart in elderly individuals. Therefore, interventions to combat cardiac aging will not only improve health span of the elderly but can also extend lifespan by delaying cardiovascular disease-related deaths. Although there is currently no specific treatment for cardiac aging, recent advances in the understanding of the mechanisms of cardiac aging have provided new insights, and we are now poised on the threshold of development. The cardiac matrix is intricately affected by hypoxia inducible factors (HIF) and may be important for senescence in the cardiac myocytes.3 An imbalance of MMP/TIMP has been implicated in structural and functional changes in hypertensive heart disease. The pathological role of MMPs in left ventricular remodeling and heart failure has been extensively reported in both pre-clinical and clinical studies. In spontaneously hypertensive rats, MMP inhibition was shown to attenuate pathological cardiac remodeling during hypertension. Another important enzyme according to us which has not received due attention is the Na+K+ATPase which basically regulates cardiac contractility. This review therefore will focus on these three elements important for cardiac functioning and its eventual aging leading to pathological disorders.

Structural changes in the aging heart
In humans, cardiac aging is associated with left ventricle hypertrophy, fibrosis, and diastolic dysfunction, resulting in reduction of diastolic filling and cardiac output ejection fraction.4 Although the underlining mechanisms are yet to be fully unravelled, studies suggest that cardiomyocyte apoptosis and vascular stiffness were associated with aging-induced structural and functional modifications. For instance, in the elderly, atherosclerotic plaques tend to be larger with increased vascular stenosis. The progressive accumulation of lipids, collagen, and calcification often occur in the plaques of the elderly as compared with younger people. Like atherosclerosis, cellular and vascular alterations are also critical to the evolution of stroke. Aging-induced endothelial dysfunction and impaired end diastolic diameter (EDD) have been linked to the etiology of stroke in elderly patients. Aging-induced modifications of brain microvasculature and white matter often facilitate ischemic brain damage. The alterations in neuronal...
conductivity by axolemma and white matter dysfunction could increase vulnerability to stroke. At the microscopic level, cardiac hypertrophy is associated with a high loss of myocytes.\(^5\) Earlier studies indicate that the number of ventricular myocytes was reduced with aging as a result of apoptosis. The study conducted by Olivetti et al\(^6\) reported a loss of about 45 million myocytes per year in the left ventricle of aging men. Although aging is accompanied by cardiomyocytes loss, studies have shown an increase in the ventricular myocyte volume.\(^7\)

Thus, it was hypothesized that the age-related myocyte loss can increase the mechanical load on the remaining myocytes, resulting in compensatory hypertrophy. In addition to the reduction in the cardiomyocytes number, the peripheral vascular stiffening may contribute to progressive hypertrophy in aged hearts. On the other hand, autophagy is an important intracellular process that controls lysosomal degradation of pathogens, aged or damaged proteins, and organelles to protect cells.\(^8,9\) In the heart, autophagy played an essential role against structural and functional dysfunction during basal state and hemodynamic stress. The autophagy inhibition shortens lifespan and exacerbates aging-associated cardiomyopathies. The rapamycin-induced autophagy (rapamycin as an inhibitor of mTOR signaling) extended longevity and promoted cardiac performance such as improvement of ejection fraction and reduction in ventricular hypertrophy in aged mice.\(^10,11\)

**Hypoxia inducible factor and aging heart**

In all metazoan species, hypoxia-inducible factor 1 (HIF-1) functions as a master regulator of oxygen homeostasis by controlling both the delivery and utilization of O\(_2\).\(^12\) When hearts from wild type (WT) mice were exposed to an ischemic preconditioning (IPC) stimulus and were immediately subjected to prolonged ischemia-reperfusion, infarct size was dramatically decreased, whereas the IPC stimulus afforded no protection in hearts from Hif1a\(^{+/}\) mice. In contrast, adenosine perfusion induced acute cardioprotection in both WT and Hif1a\(^{+/}\) mice, indicating a specific defect in IPC.\(^13\) These results were surprising because early-phase cardioprotection was generally thought to involve posttranslational modification of existing proteins or metabolic alterations, whereas late-phase cardioprotection was thought to involve new protein synthesis HIF-1 is a heterodimer that is composed of an O\(_2\)-regulated HIF-1\(\alpha\) subunit and a constitutively expressed HIF-1\(\beta\) subunit (Refer Fig.2). Further studies revealed that conditional knockout of HIF-1\(\alpha\) or HIF-1\(\beta\) expression in endothelial cells of the heart also resulted in a lack of acute cardioprotection following an IPC stimulus.\(^14\) This result was also surprising because IPC was generally thought to primarily involve responses in cardiomyocytes, leading some investigators to develop cell-based models. The requirement for both HIF-1\(\alpha\) and HIF-1\(\beta\) strongly suggested a requirement for HIF-1 transcriptional activity, despite the rapidity of the protective response.\(^15\) Furthermore, when WT hearts were infused immediately prior to the IPC stimulus with acriflavine, a drug that inhibits the dimerization of HIF-1\(\alpha\) and HIF-1\(\beta\), cardioprotection was also blocked, indicating that acute induction of HIF-1 activity was required and thus ruling out a more trivial role for HIF-1 in the baseline expression of a protein that was subsequently modified in response to the IPC stimulus.

**Na\(^+\)K\(^+\)ATPase and aging heart**

Na\(^+\)K\(^+\)ATPase is an important enzyme regulating cardiac contractility as shown in Fig.1.\(^16\) Digitalis glycosides inhibit this enzyme. It has been demonstrated that the aging process propagates cellular oxidative stress, senescence, and apoptosis, activating inflammatory pathways and cellular signaling pathways, such as Na/K-ATPase, which exacerbates the pathophysiological condition. Aging-induced oxidative stress also leads to alterations of adipocyte phenotype and dysfunction in an obese state, while causing cardiac vasculature damage and fibrosis, further amplifying cardiovascular diseases.\(^17\) The recently established role of activated Na/K-ATPase signaling in the production of excessive ROS contributes to the pro-oxidant state of cells, affecting cellular mechanisms. Further investigating the role of Na/K-ATPase signaling in perpetuating aging could provide potential therapeutic targets for developing anti-aging intervention strategies. In this regard, the peptide, pNaKtide, has demonstrated profound effects as an antagonist of Na/K-ATPase signaling, contributing towards the inhibition of oxidant amplification loop and preventing disease progression.\(^18\) The determination of magnitude of cardiac fibrosis, in the heart tissue of aging mice, was shown to be excessive with a clear demonstration of fragmented degraded myofibers. However, the Na/K-ATPase antagonist through pNaKtide attenuated this cardiac damage. Protein carboxylation and Src phosphorylation, in vivo, suggests the importance of the Na/K-ATPase oxidant amplification loop in aggravating the detrimental cardiovascular damage in aging.

**Adverse Extracellular Matrix (ECM) Remodeling and prevention**

ECM is a complex collection of proteins located exterior to the cells and provides structural and biological supports to the surrounding cells.\(^19\) Cardiac fibroblasts are the primary sources of cardiac ECM proteins, including collagen types I, II, III, IV, V, and VI, elastin, fibronectin, laminin, and fibrinogen as described by DeQuach et al.\(^20\) Cardiac ECM aligns cardiomyocytes and provides structural support to the heart; however, excessive ECM deposition increases the stiffness of the myocardium and mediates diastolic dysfunction.\(^21\) ECM composition is dynamically remodeled by the balance of the synthesis and degradation of ECM proteins by matrix metalloproteinases (MMPs) and other proteases (Refer Fig.3). Cardiac aging is associated with myocardial fibrosis, and deregulation of ECM synthesis and degradation has both been observed in aging hearts.\(^22,23\) MMP inhibitors are classified as specific and non-specific inhibitors. Non-specific inhibitors act through...
chelation of Zn2+ ion. Nonspecific inhibitors such as batimastat, marimastat, GM-6001 (ilomastat or gelardin), PD-166793 and ONO-4817 have been extensively used in various experimental models of disease.\textsuperscript{[24,25]} Tetracyclines are a group of antibiotics that are found to have MMP inhibition property. Chemically modified tetracyclines (CMTs) are devoid of antimicrobial property but retain the MMP inhibition function. CMT 3 has been shown to inhibit MMP-2 and -9 activities along with collagenase activity and ameliorate pathological cardiovascular remodeling. This is the only CMT which has been administered to humans in clinical trials.\textsuperscript{[26]}

**Cardiac Stem-Cell or Progenitor-Cell Therapy**

The recent discovery that the heart is able to regenerate although cardiac stem cells and cardiac progenitor cells has attracted enormous attention to the potential of stem-cell therapy for cardiovascular diseases and aging.\textsuperscript{[27]} Two approaches for stem-cell therapy are direct delivery of cardiac stem cells/cardiac progenitor cells i.e with or without treatment to enhance cardiac differentiation or regenerative capacity to the heart, and delivery of agents that enhance the function of endogenous cardiac stemcells or progenitor cells as shown by Ballard and Edelberg. Potential therapeutic agents for enhancing endogenous stem-cell or progenitor-cell function include stromal-cell-derived factor (SDF)-1, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and IFG-1.\textsuperscript{[28]} Furthermore, a very recent meta-analysis in patients with refractory angina showed that cell-based therapy improves anginal episodes, reduces the use of antianginal medications, ameliorates exercise tolerance and myocardial perfusion, and reduces the risk of major adverse cardiac events and arrhythmias compared with maximal medical therapy.\textsuperscript{[29,30]} For direct stem cell or progenitor-cell delivery, the therapeutic effects are limited by the proliferation, engraftment, survival, and persistence of the transplanted cells. In light of current research and advances, it seems plausible that in near future, cardiac stem cells will play an important role in the treatment and prevention of cardiac dysfunction and cardiac aging.

CONCLUSION

Cardiovascular anomalies are some of the most common disorder afflicting mankind. Older age has more propensity for cardiac structural alterations. The current estimates suggest that elderly population in developed countries is expected to double in the next 25 years, therefore there is an urgent need for interventions to attenuate or reverse cardiac impairment and the concomitant negative physiological consequences in the elderly. Recent studies show promising results of multiple novel interventions to delay or reverse cardiac aging. More in-depth understanding of the molecular mechanisms of intrinsic cardiac aging and the mechanistic effects of these interventions will be required to guide the development and future translation of these novel therapies to clinical application of new interventions to attenuate or reverse cardiac aging.

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