HIGHLIGHTED TOPIC | Perspectives in Innate and Acquired Cardioprotection

Aging and cardioprotection

Arshad Jahangir, Sandeep Sagar, and Andre Terzic
Marriott Heart Disease Research Program, Division of Cardiovascular Diseases, and Departments of Medicine, Molecular Pharmacology, and Experimental Therapeutics Mayo Clinic, Rochester, Minnesota

Jahangir A, Sagar S, Terzic A. Aging and cardioprotection. J Appl Physiol 103: 2120–2128, 2007; doi:10.1152/japplphysiol.00647.2007.—Advanced age is a strong independent predictor for death, disability, and morbidity in patients with structural heart disease. With the projected increase in the elderly population and the prevalence of age-related cardiovascular disabilities worldwide, the need to understand the biology of the aging heart, the mechanisms for age-mediated cardiac vulnerability, and the development of strategies to limit myocardial dysfunction in the elderly have never been more urgent. Experimental evidence in animal models indicate attenuation in cardioprotective pathways with aging, yet limited information is available regarding age-related changes in the human heart. Human cardiac aging generates a complex phenotype, only partially replicated in animal models. Here, we summarize current understanding of the aging heart stemming from clinical and experimental studies, and we highlight targets for protection of the vulnerable senescent myocardium. Further progress mandates assessment of human tissue to dissect specific aging-associated genomic and proteomic dynamics, and their functional consequences leading to increased susceptibility of the heart to injury, a critical step toward designing novel therapeutic interventions to limit age-related myocardial dysfunction and promote healthy aging.

despite advances in preventive and therapeutic strategies, cardiovascular disease remains the leading cause of death, disability, and morbidity in the elderly (133). The elderly account for >80% of patients with ischemic heart disease (Fig. 1), >75% of patients with congestive heart failure, and >70% of patients with atrial fibrillation (133). More than 80% of all acute myocardial infarction-related death occur in those 65 yr or older (9, 10, 113), with advanced age consistently identified as one of the strongest independent predictor for poor outcome in the population (55, 97, 151). It is projected that the number of elderly in the United States will double in the next 25 yr, and by the year 2030 >70 million people (~20% of the population) will be 65 yr and older (11). This change in population demographics, a worldwide phenomenon (Fig. 2), will result in a large increase in the prevalence of age-related cardiovascular disabilities (141) with a severe impact on the utilization of health care resources (49), underscoring the need to implement strategies that limit myocardial dysfunction in the elderly (Fig. 3). A critical step in the development of such approaches is the further understanding of mechanisms underlying age-dependent increase in the susceptibility of the heart to injury.

Elderly are prone to myocardial dysfunction due to multiple factors, including greater severity of atherosclerosis and the negative impact of comorbidities such as hypertension, diabetes mellitus, renal dysfunction, and age-related cardiovascular structural and physiological changes (50, 96). These include degenerative changes in myocytes, as well as alterations in structure and composition of the extracellular matrix, rheostatic factors, and neurohormonal and autonomic influences (13, 33, 50, 95). Furthermore, the responsiveness of the aged heart to stress is altered with a concomitant attenuation of endogenous protective mechanisms increasing vulnerability to injury (5, 23, 143). The fundamental processes underlying aging and increased vulnerability, however, remain ill defined (107). This synopsis summarizes clinical and experimental evidence implicating the increased vulnerability of the aging heart, and highlights potential mechanisms underlying loss of endogenous cardioprotective responses.

AGING WORSENS CLINICAL OUTCOMES IN ISCHEMIA-REPERFUSION

Advanced age is one of the major independent predictor of adverse events in patients with ischemic heart disease (28). With each 10-yr increase in age, the odds for in-hospital death following an acute coronary event augments by 70% (55). In clinical trials of acute myocardial infarction and thrombolytic therapy, age has been shown to be one of the strongest independent variables associated with increased mortality after a heart attack (151, 154). The overall mortality rate in the European Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico-2 trial was <2% among patients younger than 40 yr, compared with >30% in those 80 yr and older (151). In the GUSTO (Global Utilization of Streptoki-
AGING REDUCES ENDOGENOUS CARDIOPROTECTION

The greater vulnerability of the aged heart to metabolic insults has also been demonstrated in animal models. In isolated perfused heart preparations controlling for variables, such as collateral flow, cellular blood elements, and hemodynamic factors, the greater susceptibility of the senescent heart to ischemia-reperfusion injury has been confirmed in a number of species (5, 45, 96, 101, 144). This occurs without change in the threshold for myocardial ischemia, collateral flow, or area at risk for infarction, indicating an aging-related decreases in intrinsic myocardial resistance to ischemic injury (3, 45, 155). Two major endogenous protective responses, ischemic preconditioning and postconditioning, have been identified in the heart. Ischemic preconditioning has been recognized as one of the most powerful endogenous cardioprotective mechanisms, whereby transient non-lethal ischemic events render the myocardium resistant to subsequent prolonged ischemia limiting infarct size, myocardial dysfunction, and arrhythmogenesis following reperfusion (59, 119, 158). This protective response can also be activated by other noxious stimuli, such as heat-stress, rapid pacing, or exposure to endotoxin, cytokines or reactive oxygen species (ROS) (29). Brief exposure to ischemia results in two distinct phases of preconditioning: an early phase that develops within a few minutes and last for ~1–2 h and a late phase that develops over 6–12 h but may last for up to 4 days (29, 42, 109, 158). Complex signaling cascades are activated by a preconditioning stimulus, and they may involve rapid posttranslational modification of preexisting proteins that in turn activate effectors of the early preconditioning response (42, 58, 92). The late-phase protection occurs due to stress induced alteration in expression of a number of stress-responsive and protective proteins that act in concert to mediate cardioprotection (9, 29, 42). Brief repetitive interruptions in blood flow in the early minutes of reperfusion, the so-called postconditioning response have also been shown to be cardioprotective against reperfusion injury by limiting infarct size (58, 88, 140, 160). It appears that cardioprotection by both ischemic preconditioning and postconditioning recruit similar signaling pathways (34, 58, 68, 89).

Although the cardioprotective ischemic preconditioning response has been documented in every species tested (131), it is attenuated in the senescent heart (5, 45, 137, 144). Indirect evidence also indicate that the cardioprotective effect of transient ischemia before subsequent prolonged ischemia is attenuated in the aging human heart (23). Protection due to preinfarction angina within 48 h of the onset of myocardial infarction, a clinical correlate of ischemic preconditioning associated with a lower incidence of in-hospital mortality, heart failure, cardiogenic shock, and myocardial necrosis observed in younger patients has been reported to be lost in the elderly by most (3, 74, 89) but not all (107, 131) investigators. In addition, studies with biochemical markers of injury (31, 98), warm-up angina (120) or electrocardiographic ischemic changes during coronary angioplasty (78, 98) are also supportive of the apparent attenuation of the ischemic preconditioning response in the aging human heart.

MECHANISMS UNDERLYING INCREASED SUSCEPTIBILITY OF SENESCENT HEART

Advanced age is a major risk factor associated with poor cardiovascular outcome (9, 10, 95, 132), with aging associated with multiple comorbidities that increases the likelihood of myocardial damage (13, 96). Yet, the fundamental processes that lead to cardiac senescence and to loss of myocardial capacity to protect itself are not fully understood (6, 112, 142). Notwithstanding, elucidation of mechanisms underlying increased tolerance of the heart to ischemia and its loss with aging are of major clinical significance (159). Abnormalities in mitochondrial function, calcium handling, oxidative stress, and...
cardioprotective signaling have all been proposed to be potentially implicated (26, 39, 102, 105, 118, 126). A number of transducers of the cardioprotective pathway have been identified, including receptor- and protein kinase-mediated signal cascades that activate effectors of cardioprotection, yet a single final effector remains elusive (41, 67, 153, 156, 158). Considered critical in myopreservation is the preservation of ionic and energetic homeostasis, with mitochondria and cellular metabolic sensors playing a vital role (59, 84, 91, 118, 153, 159).

MITOCHONDRIAL DYSFUNCTION AND IMPAIRED ENERGETIC RESERVE IN AGING

Age-associated deficits in myocardial performance, which typically manifest on exposure to increased metabolic demand during stress, are multifactorial. Heart muscle, an aerobic tissue with high energy demand is dependent on adequate energy supply from mitochondrial oxidative phosphorylation that provides >70% of ATP (135). A dysfunction in mitochondrial electron transport or oxidative phosphorylation increases the susceptibility to injury by limiting energetic reserves under conditions of increased demand (39, 122). In addition mitochondria also help regulate cellular ionic homeostasis, ROS, generation and cell death-survival signals that initiate necrosis or apoptosis following injury (39, 46, 65, 121). An age-associated decrease in mitochondrial substrate oxidation and activity of the oxidative phosphorylation pathway has been documented (21, 63, 76) with reduction in the activity of the respiratory chain components, adenine nucleotide translocase activity and changes in mitochondrial matrix and membrane lipid pattern (35, 43, 100, 127). These changes are associated with a reduced energetic reserve and an increase in myocardial susceptibility to calcium overload and oxidative injury during stress precipitating myocardial dysfunction (20, 39, 47, 54, 76, 94, 157). Mitochondria are also central to endogenous cardioprotection and play a critical role in defining tolerance of the heart to noxious stimuli (34–36, 40, 118). A critical process in initiating cell death is the opening of the mitochondrial permeability transition pore (mPTP), a nonspecific high conductance channel in the inner mitochondrial membrane (40) that causes mitochondrial uncoupling and swelling resulting in energetic failure, disruption of ionic homeostasis, and promotion of cell death following ischemia-reperfusion injury (39, 54, 65). Prevention of mPTP opening protects the myocardium against lethal injury and appears to be involved in cardioprotection by ischemic preconditioning, but exact mechanisms underlying protection are not known (34–36, 64, 104, 138). An increased sensitivity to stress-mediated opening of mPTP has been demonstrated in senescent mitochondria from lympho-

![Fig. 2. World Health Organization projection of the geographical distribution of the elderly population. Today (A), and in year 2025 (B). Color code indicates the proportion of the country population exceeding 60 yr of age. The blue shade indicates countries with >20% of the population above 60 yr.](http://jap.physiology.org/DownloadedFrom/10.220.33.3)
cytes (134), liver and brain (53, 110), as well as heart (75); however, the underlying mechanisms are not known and could be related to aging-associated impairment in calcium handling capacity (76) or alteration in adenine nucleotide translocase (157), voltage-dependent anion channel (85), or cyclophilin D (90) structure or function. Whether aging-associated changes in mPTP sensitivity described in rodent mitochondria (53, 76, 110, 134) also occur in human cardiac mitochondria is not known, and it is unclear whether interventions that prevent mitochondrial calcium overload or mPTP opening during stress (36, 39, 69, 72) are effective in protecting the senescent human heart.

INCREASED OXIDANT DAMAGE IN AGING

Oxidative stress plays a major role in disease processes, especially in the senescent heart. Normally, a balance exists between oxidant production as a by-product of normal intracellular metabolism and the antioxidant defense system that counteracts and regulates overall free radical levels maintaining physiological homeostasis (46). The level of oxygen radical production increases following ischemia-reperfusion, perturbing the normal redox balance and shifting the cell into a state of oxidative stress (46, 130). The interruption of oxygen delivery to mitochondria during ischemia results in accumulation of electrons in the respiratory chain at redox centers susceptible to electron leak, such as the NADH dehydrogenase in the respiratory chain complex I and the ubiquinone in the respiratory chain complex III, which is then partially reduced to ubisemiquinone, which on reperfusion reacts with oxygen to produce superoxide anion. This in turn is rapidly transformed into hydrogen peroxide by superoxide dismutases (SOD) (99), and hydrogen peroxide is further reduced to the hydroxyl group. Superoxide anion, hydrogen peroxide, or hydroxyl group can directly affect respiratory chain components (complex I and III, ATPase and the adenine nucleotide translocase) or cause mitochondrial genomic damage that over time creates a progressive decline in mitochondrial function in the aging heart (66, 148, 149). Free radicals also react with key cellular constituents, including proteins, lipids, and nucleic acids, increasing their susceptibility to injury (46, 130). Activation of signaling pathways contributes to additional cellular dysfunction further impairing functional reserves and the responsiveness of cardiomyocytes to metabolic stress, compromising thereby their viability (46, 149). Interaction of ROS with nitric oxide causes incremental damage by generation of peroxynitrite and other reactive nitrogen species that produce irreversible nitration of mitochondrial and cellular proteins (24, 37). Among antioxidant defenses, the mitochondrial form of SOD or MnSOD (SOD-2) is particularly important in securing ROS clearance and its lack results in generalized mitochondrial dysfunction and organ damage (117). Similarly, the cytosolic isoform CuZnSOD (SOD-1) reduces superoxide anion to hydrogen peroxide, whereas catalase and glutathione peroxidase catalyze the reduction of hydrogen peroxide to water. Quinones, ascorbates, and tocopherols also form part of this antioxidant system and act as strong scavengers of free radicals. With aging, a decrease in the antioxidative capacity along with increased oxidant production occurs. A shift in the oxidant-antioxidant balance in favor of enhanced oxidation contributes to the increased sensitivity of cellular and subcellular structures to damage, overwhelming the cardioprotective signaling function of otherwise low ROS levels (46, 51, 80, 114, 150, 152).

CALCIUM OVERLOAD SUSCEPTIBILITY IN AGING

Aging results in a reduced threshold for calcium overload (20, 47). Postreperfusion, a greater myocardial dysfunction occurs in the senescent compared with adult hearts, with a delayed recovery of contractile function and increased susceptibility to arrhythmias (20). The functional recovery of the ventricle is inversely related to intracellular calcium loading during ischemia, and this appears more severe in aged heart.
Altered cytosolic calcium handling in the senescent heart is due to reduction in the density and activity of calcium regulating proteins both in the sarcolemma (\(Na^+/Ca^{2+}\) exchanger), and the sarcoplasmic reticulum (\(Ca^{2+}-\)ATPase and ryanodine receptor) (18, 26, 32, 86). This results in a reduction in calcium extrusion and impaired sequestration into sarcoplasmic reticulum, both at baseline and during stress leading to greater calcium overload (18, 87, 111). The increased calcium in the aged heart is deleterious because of direct cellular injury with activation of calcium-dependent phospholipases, proteases, and nucleases, and indirectly through depletion of cellular ATP by inhibition of oxidative phosphorylation (71) and enhanced consumption of ATP due to activation of calcium ATPases. In addition, modification of cardiolipin content and composition in mitochondria (128) impair calcium homeostasis, predisposing to increased mitochondrial calcium load and mitochondrial damage due to opening of the mPTP (64) precipitating energetic failure and cellular injury (39, 65, 118).

**PROTECTION OF THE SENESCENT HEART FROM INJURY**

Strategies to protect the heart against ischemic injury currently involve early reperfusion following acute myocardial infarction (9, 10) or interventions that reduce energy demands during ischemia, such as hypothermia or cardioplegic solutions during cardiac surgery or drugs, such as \(\beta\)-adrenergic receptor blockers that reduce cardiac workload by decreasing heart rate, afterload, and contractility (Fig. 3) (12). In addition to these established therapeutic strategies, activation of endogenous protective responses by stimuli applied immediately before ischemia (ischemic preconditioning) or at reperfusion (postconditioning) have been demonstrated to increase myocardial tolerance to ischemia-reperfusion injury (58, 80, 140). These innate cardioprotective responses that persist even after the initiating stimulus is withdrawn are attractive targets to achieve persistent cardioprotection by activating receptors, signaling cascade or effector(s) mediating cardioprotection (29, 34, 58, 68). Insights into mechanisms underlying ischemic preconditioning or postconditioning have resulted in the exploration of novel therapeutic avenues. This has included administration of exogenous or promotion of endogenous production of cardioprotective adenosine, nitric oxide, or opioids that trigger protective signal transduction pathways (29, 42, 52, 57). Similarly, drugs that directly activate or increase the synthesis of cardioprotective proteins have been considered to enhance tolerance of the senescent heart against injury. In this way, the cardioprotective effects of ischemic preconditioning can be mimicked by treatment with various drugs that precondition the heart to produce a similar degree of protection against ischemic injury as induced by transient ischemia (Fig. 3) (60, 61). These drugs, which include potassium channel openers (56, 77), volatile anesthetics (142) and various agonists of \(G\) protein-coupled receptors (29, 42, 93), need to be further evaluated in randomized clinical trials to assess their effectiveness in protecting the senescent human heart against ischemia-reperfusion injury (30, 77, 88, 159).

Recent findings that both short- and long-term regular exercise partially reinstate the ability of the senescent myocardium to tolerate ischemia-reperfusion injury reducing infarct size in animal models as well as improve outcomes following myocardial ischemia in humans and the improvement in cardiac tolerance with short-term caloric restriction (1, 4, 6, 7, 139) opens up an additional opportunity for lifestyle and dietary modulation to limit myocardial dysfunction in elderly patients (139). Interventions that target signaling cascades or receptors that restore endogenous cardioprotective responses with exercise, caloric restriction or ischemic pre- or postconditioning responses such as upregulation of heat shock proteins and regulatory kinases, ROS production, mPTP inhibition, and improvement in energetics of the heart during stress are all potential strategies that needs to be systematically studied in humans to identify their beneficial effect in reducing morbidity in the elderly following an acute coronary event (17, 29, 34, 38, 42, 104, 129).

A case in point is the modulation of the cardioprotective potential of ATP-sensitive \(K^+\) (\(K_{ATP}\)) channels. A value for targeting \(K_{ATP}\) channels, metabolic sensors that by virtue of nucleotide-dependent gating link cellular metabolic state to cellular excitability (59, 84, 123, 145), have been demonstrated through use of \(K_{ATP}\) channel openers that mimic and inhibitors that abolish protection afforded by ischemic preconditioning (59, 77, 83, 161). Overexpression of \(K_{ATP}\) channel genes confers increased resistance to cells otherwise vulnerable to stress (17, 62, 82, 116, 161), whereas deletion results in maladaptation and loss of protection (27, 62, 82, 106). In humans, \(K_{ATP}\) channel mutations have been associated with increased susceptibility to heart failure and/or increased arrhythmogenesis (106, 124). Therefore, further studies to delineate the role of modulators of \(K_{ATP}\) channel function in aging-associated loss of preconditioning are warranted (32, 76, 77, 79).

Mitochondrial uncoupling by protonophores (73) and potassium channel openers (48, 71) also protects against metabolic stress by reduction in mitochondrial calcium overload, inhibition of mPTP opening, and decrease in stress-induced increase in ROS production that translate into improved cardioprotection against ischemia-reperfusion injury (48, 70–72). A mitochondrial potassium conductance has been proposed within the inner mitochondrial membrane that contributes to cardioprotection against ischemia reperfusion injury (16, 48, 59). A multiprotein complex consisting of succinate dehydrogenase, mitochondrial ATP-binding cassette protein 1, phosphate carrier, adenine nucleotide translocase, and ATP synthase has been proposed to reconstitute this channel (15), providing additional opportunity for therapy.

The identification of stem cells in the heart or in peripheral tissues such as the bone marrow that have the potential to differentiate into myocardial, endothelial, and vascular tissue has provided the impetus for cell-based therapies as a strategy to replace damaged myocardium and/or promote endogenous cardioprotective responses (22, 25). These multipotent cells have been shown to improve cardiac function when transplanted in to scarred myocardium in experimental models (25, 44) and to be safe in human clinical trials indicating their potential usefulness as cell-based therapy (19, 136, 146). However, because of genomic instability from decreased telomerase activity and increased oxidant injury with aging, the ability of the progenitor cells to differentiate or replicate may decrease and limit their utility for cell-replacement therapy in the elderly (14, 22, 147). Therefore, long-term efficacy in improving clinical outcomes under physiological and pathological stresses...
associated with pressure or volume overload and atherosclerotic vascular disease present in the elderly needs to be further defined.

As the life expectancy increases and demographics continue to shift with increase in the number of elderly suffering from cardiovascular diseases (132, 133), there is a greater need to understand the biology of the aging heart and to apply strategies to limit the burden of cardiovascular disabilities in our most rapidly growing population, ultimately reducing the impact on health care resources. A wealth of information has been accumulated on the effect of aging on cardiovascular function in animal models and humans, yet the molecular basis for age-associated alteration in myocardial function and tolerability to stress is not fully understood. Because human cardiac aging is associated with a complex phenotype that cannot be completely replicated in animal models, key determinants of aging-associated myocardial dysfunction can be missed, necessitating a direct assessment of human tissue to detect aging-associated changes in gene expression, protein modification and functional alteration to understand the basis for increased susceptibility of the heart to injury and disease progression in elderly patients. Insights into age-associated molecular changes underlying altered cardiac energetics, sensitivity to oxidative stress and cardioprotective pathways will advance our understanding of the biology of the aging heart and provide targets for the development of novel therapeutics to prevent, slow, or reverse changes that increases vulnerability of the senescent heart to injury.

GRANTS

This work was supported by National Institute on Aging Grant AG-21201; National Heart, Lung, and Blood Institute Grants HL-64822 and HL-83439; the Mayo Clinic Robert and Arlene Kogod Program on Aging; and the Marriott National Heart, Lung, and Blood Institute Grants HL-64822 and HL-83439; the Mayo Clinic Robert and Arlene Kogod Program on Aging; and the Marriott National Heart, Lung, and Blood Institute Grants HL-64822 and HL-83439; and the Marriott National Heart, Lung, and Blood Institute Grants HL-64822 and HL-83439; and the Marriott National Heart, Lung, and Blood Institute Grants HL-64822 and HL-83439; and the Marriott National Heart, Lung, and Blood Institute Grants HL-64822 and HL-83439; and the Marriott National Heart, Lung, and Blood Institute Grants HL-64822 and HL-83439; and the Marriott National Heart, Lung, and Blood Institute Grants HL-64822 and HL-83439.

REFERENCES


Invited Review


cardiomyopathy is not a tumor but a disease of cellular memory.

Cardiac aging is characterized by age-related changes in mitochondrial function, including alterations in mitochondrial DNA, protein expression, and mitochondrial dynamics. These changes contribute to the increased risk of heart failure and other age-related cardiovascular diseases.

Age-related changes in mitochondrial biogenesis and function are potentiated by chronic inflammation, oxidative stress, and telomere shortening. These age-related changes in the heart lead to increased oxygen consumption, increased mitochondrial permeability, and increased production of reactive oxygen species.

The mitochondrial permeability transition pore (mPTP) plays a key role in the transition from delayed preconditioning to inadequate cardioprotection. The mPTP is a protein complex that is activated by depolarization of the inner mitochondrial membrane.

Antioxidant and anti-inflammatory treatments have been shown to protect against age-related increases in mPTP opening and improve cardioprotection. These treatments may be useful in the prevention and treatment of age-related heart disease.

In conclusion, aging is an important risk factor for cardiovascular disease. Age-related changes in mitochondrial function contribute to the increased risk of heart failure and other age-related cardiovascular diseases. Future research is needed to better understand the mechanisms underlying these changes and to develop new treatments for age-related heart disease.

Citing the image:


