Aging has become one of the most critical issues for industrialised nations, because population average age, and thus the incidence of age-associated disease, has markedly risen to create a major burden as patients draw heavily on the need for continuing medical treatment and hospital and other community services. Despite major advances in medicine in recent years, cardiovascular disease remains the greatest cause of morbidity and mortality. Age, per se, confers the major risk for cardiovascular disease because specific pathophysiological mechanisms that underlie these diseases become superimposed on cardiac and vascular substrates that have been modified by the aging process \[1–3\].

In healthy humans rigorously screened to exclude cardiovascular disease, non-human primates, and rodents, the large elastic arteries become dilated and stiffen and the intima thickens and exhibits cellular and sub-cellular features that resemble those that occur during vascular inflammation and injury \[1\]. Age-associated changes in cardiac structure (increased left ventricular myocyte size, reduced myocyte number, increased extracellular matrix remodelling, fibrosis) and resting function (reduced early diastolic filling) occur, in part, in response to aging of the arterial system \[2\].

Cardiovascular reserve function in advanced aged without cardiovascular disease is limited by suboptimal ventricular–vascular coupling due to an age-associated augmentation of vascular afterload and reduced myocardial contractility due, in part, to a diminished effectiveness of β-adrenergic modulation \[3,4\]. Senescent cardiac myocytes are characterized by altered metabolic, ionic, and electrical properties due partly to increased myocyte size, altered membrane composition, reduced capacity to maintain ion homeostasis, reduced Ca\(^{2+}\) tolerance, increased reactive O\(_2\) species levels in response to a variety of stressors, and reduced adaptive capacity to invoke “ischemic preconditioning-like” intracellular signal transduction for post-stress survival \[5–9\].

Age-targeted therapies such as those involving diet, exercise habits, gene therapy, or pharmacological agents that interfere with or beneficially regulate angiotensin II and other hormones, epigenetic factors, collagen cross-linking, metalloprotease regulation, inflammation, endogenous antioxidant systems, and mitochondria, are thus required to prevent or delay the structural and functional changes that accompany age-associated cardiovascular functional decline and the risk for disease \[10–15\]. However, the remarkable resilience and adaptive capacity of the heart and cardiovascular system to meet the rigorous and diverse demands of our ‘longer’ lives also offer us great opportunity to unravel nature’s molecular fabric.

Some of these themes have been treated in reviews or original articles that delineate new insights into the mechanisms underpinning cardiovascular aging in this Spotlight Issue of Cardiovascular Research dedicated to Cardiovascular Aging. This challenging issue features 12 reviews and 11 original articles that tackle cardiovascular aging at the level of the genome, myocardial metabolism and function, and the vasculature.

Volkova et al. \[16\] review cardiac transcriptome analysis techniques and their significance to determine pathways, regulatory sequences, and candidate genes implicated in...
aging and ultimately to identify genetic causes of aging in humans. Park and Prolla [17] review differential gene expression patterns determined via gene array analysis of mouse heart, brain, and skeletal muscle and caloric restriction, a dietary model that retards aging. Age-associated transcriptional patterns of genes required for energy metabolism resemble those patterns apparent with the development of cardiac hypertrophy. Caloric restriction effectively blocks these age-associated changes in gene expression whereas antioxidant diet with Coenzyme Q10 or alphalipoic acid does not, producing modest impact on expression; thus, it is proposed that oxidative stress contributes, but may not be causal, to cardiac aging.

Edo and Andrés [18] review the potential role of telomeres and telomere-related proteins in aging and, in particular, present studies that indicate that telomere integrity is eroded with age and that the reduction in telomere length (in smooth muscle, endothelial, and white blood cells) is a primary factor predisposing vascular tissue to atherosclerosis and the reduced capacity for neovascularisation. This exhaustion of telomere length is most prominent under conditions of high oxidative stress, but particularly in hypertensives, diabetics, and those with coronary artery disease. It is proposed that induction of increased human telomerase reverse transcriptase expression in progenitor cells or via transfection may offer post-infarct novel therapy for revascularisation. With regard to potential genomic therapies for treating age-related decline in cardiac function, Schmidt et al. [19] present original data that demonstrate that gene transfer of parvalbumin for its overexpression in Fischer 344 rats improves myocardial calcium handling and diastolic function in aging without augmenting energy consumption. In addition, Speer et al. [20], demonstrate that vascular calcification due to reduced cellular expression of osteopontin can also be targeted by a gene-transfer approach. Using a ‘knockout’ transgenic mouse model of osteopontin, these authors use retroviral transduction of osteopontin cDNA to rescue osteopontin−/− aortic smooth muscle cells from inorganic phosphate-induced calcification.

The delineation of the mitochondrial role in aging and in myocardial cell adaptation and survival in disease is highly controversial. In two reviews with differing emphases, Di Lisa and Bernardi [21] and Juhaszova et al. [22] update for us the role of mitochondrial permeability transition and the regulatory signalling that modulates mitochondrial capacity in cardioprotection. Willems et al. [23] appraise the regulatory role of endogenous adenosine in cardioprotection against ischemic stress and the impact of an age-associated decline in adenosine-dependent cardioprotective signal transduction mechanisms.

Although endogenous release of parathyroid hormone-related peptide (PTHrP; present in vascular smooth muscle, endothelial, and atrial myocardial cells) has been shown to contribute to protection of the isolated rat heart against ischemia-reperfusion injury in young adults, PTHrP has paradoxically opposite effects in aged or hypertrophied isolated rat hearts (Wistar and SHR) [24]. Ross and Schlüter [24] demonstrate that the reduced capacity for post-ischemic contractile recovery evident in aged or hypertrophied hearts from SHR can be abrogated by use of a cardiac-specific PTHrP antagonist delivered just prior to ischemia, and these authors propose that PTHrP post-receptor coupling is modified during aging independently of pressure-induced hypertrophy.

Kaye and Esler [25] review how the progressive, age-related changes in the human subcortical forebrain and the sympathetic nervous system that lead to increased norepinephrine ‘spillover’, reduced clearance of plasma catecholamines, and reduced neural reuptake of catecholamines may be important causal factors predisposing for essential hypertension, cardiac failure, and ventricular arrhythmias. Later in this issue, Vonend et al. [26] present an original study examining the renovascular effects of neuropeptide Y and ATP, which are co-transmitted with noradrenaline in sympathetic neurons that are overactive in hypertension.

The theme of age-associated remodelling is extended further to the atrial myocardium in an original study by Anyukhovsky and colleagues [27] in which they examine the induction of arrhythmogenesis in a canine model of rapid atrial pacing. Atrial fibrillation is the most common chronic arrhythmia responsible for an overwhelming burden of morbidities and continuing medical care. Atrial fibrillation is closely associated with increased age and remodelling of cellular electrical properties, extracellular matrix, and fibrosis.

A significant proportion of this spotlight issue on cardiovascular aging is focused on inflammatory signalling. Krichevsky et al. [28] review the expression of C-reactive protein, fibrinogen, IL-6, IL10, and TNFα in aging and the predisposition for coronary heart disease and stroke. Yamamoto and colleagues [29] review the role of elevated plasminogen activator inhibitor-1 with aging and the increased risk for thrombogenesis and inflammation. The importance of elevated inflammatory markers as risk factors for cardiovascular disease is also addressed in the original article by Deten et al. [30], who examine the role of IL-6 and IL-1b in aging and in the development of myocardial infarction.

The important role of endothelial remodelling in aging and the decline in endothelium-dependent regulation of vasodilation is reviewed by Brandes et al. [31]. They highlight this decline as being due partly to increased superoxide and peroxynitrite formation, diminished eNOS, estrogens, and dehydroepiandrosterone, and the increased inflammatory signalling that promotes iNOS. Dubey et al. [32] review the vascular consequences of menopause and relevance of estrogen therapy. Shipley and Muller-Delp [33] present experimental data that shows aging of Fischer 344 rats decreases the endothelium-dependant responsiveness of coronary arterioles to endothelin, potassium chloride, and pressure-induced myogenic responses. In an original study of the effects of endothelin-1 on constrictor
responses in Fischer 344 rat coronary arteries, Korzick et al. [34] examine the age-associated increase in coronary resistance and dysfunctional PKC-mediated signal transduction due to increased Ca\(^{2+}\)-sensitive PKCo, -βI, and -βII. Although Donato et al. [35] report an age-associated increase in gastrocnemius arteriole vasoconstrictor responsiveness and sensitivity to endothelin-1, they were unable to demonstrate that exercise training could reverse the age-associated effects of vasoconstrictor responsiveness to endothelin-1.

Vascular remodelling in aging is also emphasised in the review by Dao et al. [36] on the age-associated increase in large artery stiffness and resultant loss of capacitance and faster pulse wave velocity. The underlying vascular remodelling that ultimately predisposes for hypertension includes loss of smooth muscle cells and elasticity coupled with medial calcification and accumulation of advanced glycation end-products in collagen and elastin. The impact of age-associated remodelling of the extracellular matrix, under the regulation of metalloproteases, is examined in original studies by Defawe et al. [37] and Lindsey et al. [38].

**Conclusion**

As progress is made in further elucidating the diverse molecular mechanisms that underlie the cardiovascular alterations that accompany advancing age, novel therapies must emerge that will specifically retard or reverse “unsuccessful” cardiovascular aging [15]. The possibility of identifying factors that modify cardiovascular changes [2,9–11], including lifestyle factors, is reinforced by the substantial variability among older persons in the degree to which these cardiovascular changes that accompany aging occur. Treatments targeting structural factors have begun. ALT-711, a novel thiazolium agent that breaks non-enzymatic cross-links between glucose and amino groups which generate advanced glycation end-products in collagen and elastin. The impact of age-associated remodelling of the extracellular matrix, under the regulation of metalloproteases, is examined in original studies by Defawe et al. [37] and Lindsey et al. [38].

**References**


