Evidence supporting the hypothesis that age-associated changes in cardiovascular structure/function are implicated in the markedly increased risk for cardiovascular disease in older persons has been presented in the preceding 2 articles in this series. It follows that therapies to prevent or delay cardiovascular changes that accompany aging may reduce the risk for age-associated cardiovascular diseases. Understanding the nature and effectiveness of such therapies, however, requires an understanding of heart and arterial aging at the cellular and molecular levels. Fortunately, many of the age-associated changes in cardiac and arterial structure or function that have been observed in humans also occur across a wide range of other species. Insights gained from cellular and molecular studies in these animal models may hold clues that will assist in directing future efforts toward developing novel therapies for age-associated arterial and cardiac structural and functional remodeling in humans.

Vascular Aging
Age-associated remodeling of the walls of large arteries of rodents (Table 1) and nonhuman primates is quite similar to that observed in humans and includes luminal dilation, intimal and medial thickening (Figure 1), vascular stiffening, and endothelial dysfunction.

Intimal Changes
The thickened intima in older rats (Figure 1A) is composed of matrix molecules including collagen, fibronectin, and proteoglycans, as well as vascular smooth muscle cells (SMCs), and it exhibits increased immunostaining for transforming growth factor-beta (TGF-β), interstitial cell adhesion molecule (ICAM-1), the zinc-dependent endopeptidase type-2 metalloproteinase (MMP-2), and its activator, membrane type metalloproteinase-1 (Figure 1B). Aortic MMP-2 is active in situ (Figure 1C) and accumulates in areas surrounding SMCs that are located near breaks in the internal elastic lamina, suggesting that it may play a role in the observed fragmentation of the elastic lamina.

Vascular Responses to Injury
The intimal growth occurring during aging in rodents and nonhuman primates in the absence of experimental injury resembles, in some ways, the late stages of neointimal formation observed after vascular injury induced by arterial catheter balloon inflation or after aortocoronary saphenous vein graft implantation. Atherosclerotic plaques and inflammatory cells, however, are conspicuous in their absence. Neointimal growth in response to injury is markedly enhanced in older versus younger rats and is due to factors intrinsic to the vessel wall, because the excessive intimal hyperplasia is still observed when aortae from old animals are transplanted into younger ones.

After balloon injury to the rat carotid artery, medial SMCs are activated and they begin to proliferate, and subsequently migrate to the intimal layer, invading the complex extracellular matrix of the vessel wall through discontinuities in the internal elastic lamina. In addition to the migration of medial SMCs, recent evidence suggests that hematopoietic stem cells that originate in the bone marrow also contribute to the neointimal proliferation after arterial injury by migrating into the subendothelial layer from the luminal side of the vascular wall and differentiating into vascular SMC. The dissolution or hyperpermeability of the basement membrane that enables the transmigration of circulating stem cells or SMCs from the media may result from the action of elastases and gelatinases (such as MMP-2), which are themselves secreted by the activated SMC (see below).

Studies of cultured vascular SMC have demonstrated that chemotactic invasion of a reconstituted basement membrane requires activated MMP-2, potentially derived from cytokine stimulated vascular SMCs. Early-passage vascular SMCs from aged aortae secrete more MMP-2 than those from young aortae when stimulated with the cytokines interleukin-1α (IL-1α), tumor necrosis factor-α (TNF-α), or TGF-β. This suggests that enhanced MMP-2 levels in the thickened intima of aortae from aged rats may, in part, reflect a chronically enhanced level of cytokine stimulation in vivo. It is also noteworthy that early passage aortic vascular SMCs of old rats exhibit an exaggerated chemotactic response to platelet-derived growth factor (PDGF), whereas cells from young aortae require several additional passages in culture to generate an equivalent response (Figure 1D). Thus, the exaggerated response of old vessels to experimental injury in vivo may be attributable, in part, to enhanced SMC chemotaxis or proliferation in response to growth factors such as PDGF.

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Excessive neointimal formation observed after balloon injury to the rat carotid artery can be prevented by cleaving the mRNA of the early growth response gene, Egr-1, a zinc-finger transcription factor that modulates a host of stress-responsive genes, including PDGF and TGF-β, which impact cellular proliferation, migration, and apoptosis. Although the antiproliferative actions of TGF-β decrease with age, TGF-β suppresses the activity of proteases, activates tissue inhibitors of MMP, and is a potent factor for the synthesis of extracellular matrix proteins. An increase in the expression of TGF-β can therefore promote matrix formation. TGF-β accumulation in the intima of older rats may be related to the age-associated increase in arterial fibronectin and collagen. Fibronectin and TGF-β expression are both regulated by angiotensin II. An age-associated increase in aortic angiotensin converting enzyme (ACE) activity occurs in rats and nonhuman primates; aortic angiotensin II is increased and co-localizes with both increased ACE and MMP-2. Importantly, many of the age-associated intimal and matrix changes can be markedly delayed by chronic administration of ACE inhibitors, suggesting that age-associated changes in the local vascular angiotensin system may play a central role in age-associated vascular remodeling.

**Endothelial Structure/Function**

Aging is also associated with enhanced expression of adhesion molecules in aortae of rats and increased adherence of monocytes to the endothelial surface in rabbits. It is thus of great interest that the serum-soluble levels of these adhesion molecules also display age-associated alterations in humans. Aging in rodents is also associated with an increased arterial permeability; the intima of older rabbits accumulates glycosaminoglycans, which play an important role in regulating several arterial properties, possibly including vascular permeability.

Aging rats exhibit elevated plasma levels of nitrite and nitrate, and nitric oxide-dependent mechanical and agonist-mediated endothelial vasodilation is attenuated in older rats versus younger rats as is the case in humans. Interestingly, the vasoconstrictor response to angiotensin II is attenuated in aging rats, and this response is normalized by the inhibition of nitric oxide synthesis. In some studies in rats and rabbits, the activity of the endothelial nitric oxide synthase (eNOS) isoform has been shown to be markedly reduced with aging, whereas other studies in rats have observed a marked age-associated reduction in NO in the context of an increase in eNOS expression in the aged aorta, which has been interpreted to reflect enhanced mitochondrial superoxide production coupled to enhanced peroxynitrite formation, as evidenced by increased levels of nitrosylated proteins, eg, MnSOD.

Endothelial cellular aging has been characterized by the appearance of senescence-associated β-galactosidase (SA-β-gal) staining, expression of several regulators of the cell cycle, attrition of telomeres, and suppression of telomerase activity. Telomere length is a marker of cellular turnover and is inversely associated with age, and pulse pressure. Loss of telomere function was recently shown to induce endothelial dysfunction in vascular endothelial cells, whereas inhibition of telomere shortening was shown to suppress the age-associated dysfunction in these cells.

Endothelial cells play a pivotal role in angiogenesis, which requires the migration and proliferation of endothelial cells in response to cytokines. Angiogenesis is impaired with advancing age in animal models. Expression of TGF-β and the matrix protein type-I collagen are decreased in microvascular endothelial cells from aged mice and are associated with alterations in MMP-1 and tissue inhibitor of metalloproteinase-1. Angiogenesis can be modulated with the administration of angiogenic growth factors such as vascular endothelial growth factor (VEGF). Interestingly, expression of VEGF and hypoxia inducible factor 1 (HIF-1) activity are decreased with aging. The activity of growth factors required for endothelial proliferation and angiogenesis is modulated by advanced glycosylation end-products. Glycation of collagen 1 induces premature senescence-like phenotypic changes in endothelial cells in the absence of telomere length changes. Thus, the age-associated impairment in angiogenesis is due, in part, to changes in the

**TABLE 1. Age-Associated Aortic Changes in Rodents**

<table>
<thead>
<tr>
<th>Intima</th>
<th>Wall thickness</th>
<th>Thickness: SMC and matrix</th>
<th>TGF-β, but antiproliferative effects</th>
<th>MMP-II levels and activity</th>
<th>Expression of adhesion molecules</th>
<th>Nitrite and nitrate</th>
<th>Activity of ACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Media</td>
<td>Thickness</td>
<td>SMC: size, number</td>
<td>Collagen content</td>
<td>Collagen cross-linking</td>
<td>Elastin: calcification</td>
<td>Glycosaminoglycans</td>
<td></td>
</tr>
<tr>
<td>Matrix</td>
<td>Collagen content</td>
<td>Collagen cross-linking</td>
<td>Elastin: calcification</td>
<td>Glycosaminoglycans</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
<td>Vasoreactivity</td>
<td>Free NO, superoxide, peroxynitrite</td>
<td>Expression of adhesion molecules</td>
<td>Permeability</td>
<td>Angiogenesis, VEGF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exaggerated wound repair response</td>
<td>Exaggerated atherosclerosis in response to a high lipid diet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SMC indicates smooth muscle cells; TGF-β, transforming growth factor beta; MMP-II, type 2 matrix metalloproteinase; eNOS, endothelial nitric oxide synthase; ACE, angiotensin converting enzyme; and VEGF, vascular endothelial growth factor.

*In rabbits.
levels of extracellular enzymes, matrix proteins, and growth factors, which affect endothelial cell proliferation and migration.

**Links Between Arterial Aging and Atherosclerosis**

Findings from the rodent and nonhuman primate models of arterial aging clearly indicate that central arterial intimal-medial thickening is an age-associated process that is separate from atherosclerosis, because both of these animal models are devoid of atherosclerosis. The age-associated cellular, enzymatic, and molecular mechanisms that underlie the phenotypic appearance of intimal medial thickening, including the migration of activated vascular SMCs into the intima and the elevated levels or activity of molecules such as MMP-2, membrane type-1–MMP, angiotensin II, TGF-β, and ICAM-1, create a metabolically active environment that induces, contributes to, or is a result of endothelial dysfunction and its attendant endothelial permeability. These same metabolic, enzymatic, cellular, and endothelial alterations are increasingly recognized as playing a critical role in the genesis and promotion of atherosclerosis, vascular inflammation, vascular remodeling, and oxidant stress. In other words, many of the same factors that underlie the age-associated structural and functional intimal and medial alterations are also implicated in the pathogenesis of clinical cardiovascular diseases. These culprits could thus represent the missing links that explain the “risky” component of arterial aging in humans.

The blurring of the boundaries between the aging and the atherosclerotic processes may have been fueled and aggra-
vated, in part, by a poor selection of terminology. The age-associated intimal-medial thickening that is observed in humans is often ascribed to "subclinical atherosclerosis." This concept has become so pervasive that intimal-medial thickening is now widely thought of by epidemiologists and clinicians as a valid surrogate measure of atherosclerosis. Indeed, referring to age-associated intimal-medial thickening as "subclinical atherosclerosis" gives the false impression that the atherosclerotic process is already present in the arterial wall, whereas, as noted above, intimal-medial thickening and endothelial dysfunction clearly occur in the absence of atherosclerosis. In other words, excessive intimal-medial thickening in humans is not necessarily synonymous with "early" or "subclinical" atherosclerosis. Rather, as the arterial wall becomes remodeled during aging, it becomes super-sensitive to risk factors (eg, high-lipid diets, etc) not usually encountered by animals. The interaction of these risk factors with the age-altered vascular substrate is clearly exemplified by the reduced threshold for or accelerated development of experimental atherosclerosis in older animals subjected to an atherogenic diet.

Cardiac Aging

Cellular and molecular mechanisms that may be implicated in age-associated changes in myocardial structure and function in humans have also been studied largely in rodents (Table 2).

---

### Table 2. Myocardial Changes With Adult Aging in Rodents

<table>
<thead>
<tr>
<th>Structural Δ</th>
<th>Functional Δ</th>
<th>Ionic, Biophysical/Biochemical Mechanisms</th>
<th>Molecular Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Myocyte size</td>
<td>Prolonged contraction</td>
<td>Prolonged cytosolic Ca(^{2+}) transient</td>
<td>↑ SR Ca(^{2+}) pump mRNA</td>
</tr>
<tr>
<td>↓ Myocyte number</td>
<td></td>
<td>↓ SR Ca(^{2+}) pumping rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ Pump site density</td>
<td></td>
</tr>
<tr>
<td>Prolonged action potential</td>
<td>↓ l(_{Ca}) inactivation</td>
<td>No Δ calsequestrin mRNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ l(_{Ca}) density</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diminished contraction velocity</td>
<td>↓ α MHC protein</td>
<td>↓ MHC mRNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ β MHC protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ Myosin ATPase activity</td>
<td>Shift in myosin isoform mRNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ RxR(β1) and γ mRNA</td>
<td>↓ RxR(β1) and γ mRNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ RxR(β1) and γ protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ Thyroid receptor protein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diminished β-adrenergic contractile response</td>
<td>↓ Coupling βAR-acylase</td>
<td>↓ βAR mRNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No Δ G, activation</td>
<td>No Δ βARK mRNA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No Δ βARK activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ TNI phosphorylation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ Phospholamban phosphorylation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ l(_{Ca}) augmentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ Ca(^{2+}) transient augmentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ Enkephalin peptides</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ Proenkephalin mRNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ Matrix connective tissue</td>
<td>↑ Myocardial stiffness</td>
<td>↑ Hydroxyline proline content</td>
<td>↑ Collagen mRNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Activity of myocardial RAS</td>
<td>↑ Fibronectin mRNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Atrial natriuretic peptide</td>
<td>↑ AT, R mRNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ Atrial natriuretic peptide mRNA</td>
<td></td>
</tr>
<tr>
<td>↓ Growth response</td>
<td></td>
<td>↓ Induction of immediate early genes</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ Heat shock response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Opioid peptides</td>
<td>↑ Proenkephalin mRNA</td>
</tr>
</tbody>
</table>

SR indicates sarcoplasmic reticulum; SERCA, sarco/endoplasmic reticulum calcium ATPase; Ca\(^{2+}\), calcium ions; NaCa, sodium calcium; MHC, myosin heavy chain; mRNA, messenger RNA; RXR, retinoid X-receptor; βAR, β-adrenergic receptor; βARK, β-adrenergic receptor kinase; G\(_i\), inhibitory G protein; TNI, troponin-I; l\(_{Ca}\), calcium influx; Ca\(^{2+}\), intracellular calcium concentrations; HSF, heat shock factor; RYR\(_{2}\), cardiac ryanodine receptor; AT\(_i\), angiotensin AT-1 receptor; and RAS, renin-angiotensin system.

This concept has become so pervasive that intimal-medial thickening is now widely thought of by epidemiologists and clinicians as a valid surrogate measure of atherosclerosis. Intimal-medial thickening, however, is only weakly associated with the extent and severity of coronary artery disease. Indeed, referring to age-associated intimal-medial thickening as "subclinical atherosclerosis" gives the false impression that the atherosclerotic process is already present in the arterial wall, whereas, as noted above, intimal-medial thickening and endothelial dysfunction clearly occur in the absence of atherosclerosis. In other words, excessive intimal-medial thickening in humans is not necessarily synonymous with "early" or "subclinical" atherosclerosis. Rather, as the arterial wall becomes remodeled during aging, it becomes super-sensitive to risk factors (eg, high-lipid diets, etc) not usually encountered by animals. The interaction of these risk factors with the age-altered vascular substrate is clearly exemplified by the reduced threshold for or accelerated development of experimental atherosclerosis in older animals subjected to an atherogenic diet.
The altered cardiac structural phenotype that evolves with aging in rodents includes an increase in LV mass due to an enlargement of myocyte size, and focal proliferation of the matrix in which the myocytes reside, which may be linked to an altered cardiac fibroblast number or function. The number of cardiac myocytes becomes reduced because of necrosis and apoptosis, with the former predominating. Putative stimuli for cardiac cell enlargement with aging in rodents include an age-associated increase in vascular load due to arterial stiffening and stretching of vessels caused by drop out of neighboring myocytes. Stretch of cardiac myocytes and fibroblasts initiates growth factor signaling (eg, angiotensin II/TGF-β), which, in addition to modulating cell growth and matrix production, also leads to apoptosis. The expression of atrial natriuretic and opioid peptides, molecules that are usually produced in response to chronic stress, is increased in the senescent rodent heart.

Coordinated changes in the function or expression of proteins that regulate several key steps of the cardiac cell excitation-contraction coupling process occur in the rodent heart with aging and result in a prolonged action potential (AP), a prolonged cytosolic calcium (Ca) transient after excitation, and a prolonged contraction (Table 2). Both the apparent number and the activity of individual cardiac L-type Ca channel increases with age in the rat. The ensemble L-type current inactivates more slowly in myocytes from older rats versus those in younger rats, and this, as well as reductions in outwardly directed K currents, could account, in part, for the prolonged AP of the former. The imposition of a shorter AP to myocytes from the old rat heart reduces the Ca transient amplitude, an effect attributable to a reduction in sarcoplasmic reticulum Ca2+ load, which is presumably due to a reduced L-type Ca channel current (Ical) integral and likely also to an increased net Ca2+ extrusion via sarcosommal Na+–Ca2+ exchanger.

The prolonged Ca that occurs with aging is explained, in part, by a reduction in the rate of Ca2+ sequestration by the sarcoplasmic reticulum (Figure 2D). This is attributable to a reduced transcription of the gene coding for the sarcoplasmic reticulum Ca2+ pump, SERCA2 (see for review). The abundance of transcripts of the cardiac Na+–Ca2+ exchanger (NCX-1), which serves as the main trans-sarcolemmal Ca2+ extrusion mechanism, is increased ~50% in senescent (24-month) compared with the young adult (6-month) rat hearts. The age-associated prolonged Ca2+ transience and contraction may impair myocardial relaxation during early diastole and, in part, may underlie the reduction in early diastolic filling rate that accompanies advancing age. Studies in rodents that have employed gene therapy or exercise conditioning to increase the level of SERCA2 have demonstrated that impaired relaxation and Ca2+ sequestration that occur with aging can be reduced by these interventions.

Marked shifts occur in the cardiac myosin heavy chain (MHC) isoforms in the senescent rat heart, with the β1-isofrom becoming predominant; myosin Ca2+–ATPase activity declines with the decline in α-MHC content (see reference 59 for review). MHC gene expression is regulated, in part, via binding of thyroid hormone receptors, members of a superfamily of receptors that includes retinoic acid receptors, vitamin D receptors, and retinoid X receptors, to thyroid response elements in gene 5' flanking regions. A significant reduction (approximately 50%) in the levels of thyroid hormone receptor-β and retinoid X receptor-γ proteins between 6 and 24 months and in mRNA encoding these receptor subtypes has been observed in hearts of senescent rats.

The altered composite cellular profile (Table 2), which results in a contraction that exhibits reduced velocity and a prolonged time course due to prolonged elevation of cytosolic [Ca] after a prolonged AP (Figure 1), can be considered to be adaptive rather than degenerative because myocardial shortening at reduced velocity is energy-efficient. This altered pattern of Ca2+ regulation and myosin protein expression allows the myocardium of older hearts to generate force and active stiffness for a longer time after excitation. The prolonged isovolumic relaxation period that occurs in the healthy human heart with aging (see 2 for review) may be in part attributable to such prolonged contractile protein Ca2+ activation, enabling the continued ejection of blood during late systole, a beneficial adaptation with respect to enhanced central arterial stiffness and early reflected pulse waves.

**Reduced Acute Response to Stress**

Acute excess myocardial Ca2+ loading leads to dysregulation of Ca2+ homeostasis, impaired diastolic and systolic function, arrhythmias, and cell death. The cell Ca2+ load is determined by membrane structure and permeability characteris-
tics, the intensity of stimuli that modulate Ca\(^{2+}\) influx or efflux via their impact on regulatory function of proteins within membranes, and reactive oxygen species (ROS), which affect both membrane structure and function. Excessive cytosolic Ca\(^{2+}\) loading occurs during physiological and pharmacological scenarios that increase Ca\(^{2+}\) influx (eg, neurotransmitters, postischemic reperfusion, or oxidative stress).\(^6\)\(^8\)\(^9\) In hearts or myocytes from the older heart, enhanced Ca\(^{2+}\) influx, impaired relaxation, and increased diastolic tone occur during pacing at an increased frequency.\(^6\)\(^2\)\(^3\)\(^7\)\(^0\)\(^1\) This is a “downside” of the aforementioned age-associated adaptation that occurs within the cells of senescent heart (and also of young animals chronically exposed to arterial pressure overload). Causes of reduced Ca\(^{2+}\) tolerance of the older heart include changes in the amounts of proteins that regulate Ca\(^{2+}\) handling, caused in part by altered gene expression (Table 2), and to an age-associated alteration in the composition of membranes in which Ca\(^{2+}\) regulatory proteins reside, which includes an increase in membrane ω\(^6\)-ω\(^3\)-polysaturated fatty acids (PUFAs).\(^2\)\(^5\) ω\(^6\) PUFAs are protective of cardiac calcium regulation. An additional potential cause of the reduced threshold of senescent myocytes for Ca\(^{2+}\) overload is an enhanced likelihood for intracellular generation of ROS\(^6\)\(^9\)\(^7\)\(^3\) in cells from the senescent versus the younger adult heart during stress. In this regard, the older cardiac myocyte and endothelial cells\(^2\)\(^9\) share common “risks” with aging.

**Cellular β-Adrenergic Signaling**

Age-associated deficits in the myocardial β-adrenergic receptor (βAR) signaling cascade also occur with aging (see 59 for review). A reduced myocardial contractile response to either β\(_1\)AR or β\(_2\)AR stimulation is observed with aging.\(^2\)\(^4\)\(^–\)\(^7\)\(^6\) This is due to failure of βAR stimulation to augment Ca\(^{2+}\), to the same extent in cells of senescent hearts that it does in those from younger adult hearts,\(^2\)\(^4\) an effect attributable to a deficient increase of L-type sarcolemmal Ca\(^{2+}\) channel availability, which leads to a lesser increase in Ca\(^{2+}\) influx.\(^7\)\(^4\) The richly documented age-associated reduction in the postsynaptic response of myoccardial cells to βAR stimulation seems to be due to multiple changes in the molecular and biochemical steps that couple the receptor to postsynaptic effectors. However, the major limiting modification of this signaling pathway that occurs with advancing age in rodents seems to be the coupling of the β-adrenergic receptor to adenyl cyclase via the Gs protein and changes in adenyl cyclase protein, which lead to a reduction in the ability to sufficiently augment cell cAMP and to activate protein kinase A to drive the phosphorylation of key proteins that are required to augment cardiac contractility.\(^7\)\(^5\) In contrast, the apparent desensitization of βAR signaling that occurs with aging does not seem to be mediated via increased β-adrenergic receptor kinase (βARK) or increased G, activity.\(^7\)\(^5\) A blunted response to βAR stimulation of the cells within older myocardium can, in one sense, be viewed as adaptive with respect to its effect to limit the risk of Ca\(^{2+}\) overload and cell death in these cells.

**Reduced Chronic Adaptive Capacity of the Older Heart**

Many of the multiple changes in cardiac structure, excitation, myofilament activation, contraction mechanisms, Ca\(^{2+}\) dysregulation, deficient βAR signaling, and altered gene expression of proteins involved in excitation-contraction coupling that occur with aging (Table 2) also occur in the hypertrophied myocardium of younger animals with experimentally induced chronic hypertension\(^5\)\(^9\)\(^7\)\(^7\) and in failing animal or human hearts, in which they have been construed as an adaptive response to a chronic increase in LV loading. When chronic mechanical stresses that evoke substantial myocardial hypertrophy (eg, pressure or volume overload) are imposed on the older heart, the response in many instances is reduced. There is evidence that transcriptional events associated with hypertrophic stressors become altered with advancing age, eg, the nuclear binding activity of the transcription factor nuclear factor-κB is increased and that of another transcription factor, Sp1, is diminished.\(^7\)\(^8\) Because these transcription factors each influence expression of a number of genes, they may contribute to the pattern of gene expression observed in the hearts of senescent rodents and may also dictate the limits of adaptive responses to the imposition of additional chronic stress. The acute induction of both immediate-early genes and later responding genes that are expressed during the hypertrophic response is blunted in hearts of aged rats after aortic constriction.\(^7\)\(^9\)\(^8\)\(^0\) Similarly, the acute induction of heat shock 70 protein genes in response to either ischemia or heat shock is reduced in hearts of senescent rats.\(^8\)\(^1\)\(^8\)\(^2\) A similar loss of adaptive capacity is observed in younger rats that have used a part of their reserve capacity before a growth factor challenge.\(^8\)\(^3\)

**Conclusion**

The recent advances in our understanding of the age-associated alterations in vascular and cardiac structure and function, at both the cellular and molecular levels, provide valuable clues that will hopefully assist in directing future efforts to develop effective therapies to prevent, delay, or attenuate the cardiovascular changes that accompany aging. These age-associated changes are themselves increasingly recognized as risk factors for cardiovascular diseases, and future efforts to modulate them will require the close collaboration of a consortium of researchers, including molecular cardiologists, cardiovascular physiologists, and translational clinical trialists.

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