Invited Review: Aging and the cardiovascular system

Ferrari, Alberto U., Alberto Radaelli, and Marco Centola. Invited Review: Aging and the cardiovascular system. J Appl Physiol 95: 2591–2597, 2003; 10.1152/japplphysiol.00601.2003.—Aging is associated with complex and diversified changes of cardiovascular structure and function. The heart becomes slightly hypertrophic and hyporesponsive to sympathetic (but not parasympathetic) stimuli, so that the exercise-induced increases in heart rate and myocardial contractility are blunted in older hearts. The aorta and major elastic arteries become elongated and stiffer, with increased pulse wave velocity, evidence of endothelial dysfunction, and biochemical patterns resembling early atherosclerosis. The arterial baroreflex is sizably altered in aging, but different components are differentially affected: there is a definite impairment of arterial baroreceptor control of the heart but much better preserved baroreceptor control of peripheral vascular resistance. Alterations at the afferent, central neural, efferent, and effector organ portions of the reflex arc have been claimed to account for age-related baroreflex changes, but no conclusive evidence is available on this mechanistic aspect. Reflexes arising from cardiopulmonary vagal afferents are also blunted in aged individuals. The cardiovascular and reflex changes brought about by aging may have significant implications for circulatory homeostasis in health and disease.

Senectus ipsast morbu [senescence is a disease in itself].
Terentius Afer, Phormio, 575

Concepts and suggestions from Latin wisdom are often confirmed by modern knowledge, and the one mentioned above undoubtedly carries some truth: advanced age may induce a decline in bodily functions and overall cardiovascular performance even in the absence of overt disease. On the other hand, two major arguments stand against Terentius’ statement. 1) Although quite a few cardiovascular features of the elderly most likely depend on aging per se, in many instances impaired performance is not only the consequence of advanced age but also results from various combinations of more or less apparent cardiovascular or noncardiovascular illnesses: thyroid dysfunction, diabetes, heart failure, borderline hypertension, and others may be good examples of such situations, in which it is thus difficult to discriminate between disease-related and age-related alterations. 2) The issue is further complicated by the fact that age-related changes by no means consist of a uniform and generalized structural degeneration and/or functional decline; rather, different components of the cardiovascular system may be affected quite heterogeneously, which means that in aging at least some functions not only fail to show an impairment but may indeed be paradoxically enhanced. This also has the obvious methodological implication that age-related changes have to be systematically analyzed and their various elements and underlying mechanisms carefully dissected before any safe conclusions can be reached, which makes this area of research a particularly demanding one.

On the basis of the above premises, the present discussion will address the effects of aging on the heart, the blood vessels, and the reflex control of the cardiovascular system. Whenever relevant information is available, attention will be given to the mechanisms responsible for the age-related modifications as well as to their homeostatic and clinical implications. Conventionally, a cutoff point for advanced age in humans may be set at 65 yr, and this is adopted in the present article as well as in most quoted references dealing with human studies. A corresponding cutoff point for rats may be set at age above 18 mo. A summary of the major age-related effects in the cardiovascular system is provided in Table 1.
AGING AND THE HEART

Structural changes. Even in subjects apparently free of hypertension or other causes of increased afterload, aging is associated with a mild increase in heart weight, reflecting some degree of left ventricular hypertrophy (16). In some studies (17), an age-dependent change in cardiac shape has been described, with a rightward shift in the ascending aorta and a proximal bulge in the interventricular septum, which entail a narrowing of the left ventricular outflow tract. Cardiomyocyte dimensions are somewhat increased, whereas their numbers are decreased; collagen may become more prominent because of both quantitative and qualitative changes, with focal deposits and diffuse increases in the cross-linking between adjacent fibers. Because of the concomitant cardiomyocyte enlargement, however, no increase in the collagen-to-myocyte ratio is observed. Such changes are believed to be of functional importance, especially for diastolic events (see below). An additional change described in the aging heart is a partial degeneration of cardiac sympathetic nerve supply (33).

Functional changes. In the resting aging heart, there are largely no alterations of systolic function, with preserved ejection fraction and stroke volume; because resting heart rate is unchanged or only minimally reduced with aging, cardiac output is also preserved (38).

Instead, diastolic function does undergo significant age-related changes, with a reduction in early diastolic filling compensated for by increased end-diastolic filling and a consequent progressive reduction of the echocardiographic early wave/atrial wave (E/A) velocity ratio (34).

Aging also alters cardiac responsiveness to β-adrenergic stimuli, be they pharmacologically or physiologically determined. Both the catecholamine- or exercise-induced increases in heart rate and myocardial contractility are definitely blunted in elderly subjects (15). Thus, for cardiac output to be increased in proportion to the body’s metabolic needs despite inadequate contractile and chronotropic reserves, the aging left ventricle mainly engages the Frank-Starling mechanism, i.e., it undergoes marked increases in volume, both end-diastolic and end-systolic. Via such hemodynamic a pattern, the aging heart can significantly increase its maximum output and allows elderly subjects to perform vigorous exercise, although not up to the same intensity as a younger individual can sustain. Overall, the peak cardiac output attained in response to maximal effort is blunted by some 20–30% in elderly compared with young healthy subjects, the blunting being largely attributable to a lesser degree of effort tachycardia rather than to altered stroke volume (15). To draw an overall picture of modified cardiac exercise physiology in aging, it was suggested that the heart of the elderly behaves like a younger heart subjected to β-blocker treatment (23).

Further age-related cardiac alterations relate to lusitropic function, with delayed relaxation as a consequence of enhanced duration of contraction. The latter results from prolonged action potential and active state rather than from changes in passive mechanical properties or myocardial catecholamine content (25). The above-mentioned alterations may be of considerable clinical importance as a possible functional substrate of the notorious propensity of elderly individuals to develop diastolic heart failure.

The aged heart also shows a reduction in the inotropic responses to digitalis (but not to calcium ions, indicating that the defect involves the signaling processes rather than the contractile machinery itself) (28).

AGING AND THE VASCULATURE

Structural changes. Aging large arteries are elongated and tortuous and have an enlarged lumen and a thickened wall, the thickening mainly affecting the intima and the media (44). In the former, arteries from healthy elderly subjects show no endothelial lesions or discontinuities; endothelial cells may, however, be irregular in shape and have increased height; there may be migration and/or proliferation of vascular smooth muscle cells, with infiltration in the subendothelial...
space, exaggerated deposition of collagen, elastin, and proteoglycans, along with abnormal abundance of leukocytes and macrophages. Numerous substances involved in inflammatory and/or atherosclerotic processes such as adhesion molecules, matrix metalloproteinases, transforming growth factor-β, and others, such as proinflammatory cytokines, are also more abundant in aging arterial intima (3, 30).

**Functional changes.** The fundamental age-related change in arterial function is impairment of distensibility (37) and thus of the cushioning function of the aorta and its major branches, associated with an enhancement in pulse wave velocity; such changes have been suggested to be nonuniform throughout the arterial tree with more marked alterations in elastic-type vs. muscle-type arteries (43). Increased stiffness is not solely dependent on structural alterations but also is majorly affected by humoral and endothelial regulation of vascular smooth muscle tone: aged vessels show an increased endothelial permeability and a reduced nitric oxide-dependent vasodilator response to acetylcholine (41); this was consistently observed in different regional beds of both animals and humans including the coronary bed (10). Also the vasodilator responses to β2-adrenoceptor agonists are clearly attenuated because of reduced number and affinity of specific receptors; albeit to a probably lesser extent, vasoconstrictor responses to α-receptor stimulation are also diminished in aged arteries (11).

Although the above-mentioned age-related functional alterations have been observed in atherosclerosis-free normotensive individuals, most of them are also present in atherosclerotic vessels, which are also known to be stiffer than normal but in which, unlike in aging, focal lesions, vessel stenosis, and plaque rupture eventually develop. Thus, because aging and atherosclerosis run along very similar biochemical pathways and determine many similar vascular alterations, vessel aging may be viewed as representing the prodromal stage of atherosclerotic disease or, conversely, atherosclerosis may be viewed as a form of accelerated arterial aging (probably favored by coexisting noxious stimuli such as e.g., dyslipidemia, smoking, or hypertension).

One may on the other hand maintain that the two processes are distinct in origin because in many senescent subjects the age-related alterations are clearly present but apparently fail to ever progress to overt focal disease. This conceptual alternative may be to some extent academic, however. The real challenge, in the genomic era, will rather be to identify (and ultimately to control) the genetic and/or molecular mechanisms governing the transition from largely benign age-related changes to pathological atherosclerotic degeneration. For further details on this highly complex and rapidly expanding issue, the reader is referred to a recent and comprehensive review series (24, 26, 27).

The systemic hemodynamic consequences of age-related vascular hypertrophy and stiffness include a moderate increase in total peripheral resistance and the well-known tendency to increased systolic and pulse pressure. In turn, elevated pressure is a stimulus for further development of vessel wall hypertrophy and stiffness, so that adverse phenomena beget each other and a more or less rapidly progressing vicious circle is established.

**AGING AND BARORECEPTOR REFLEXES**

**Arterial baroreflexes.** An age-related decline in the ability of arterial baroreceptors to modulate cardiac chronotropic activity was repeatedly documented in experimental animals and in humans by different technical approaches: when baroreceptors are stimulated via a transient phenylephrine-induced elevation in blood pressure, the reflex slowing of the heart is less in aged compared with younger individuals (12, 19). The same is true for the cardioacceleration after baroreceptor deactivation via intravenous bolus administration of a peripheral vasodilator. Even using more sophisticated, nonpharmacological approaches such as the computer-based cross-spectral evaluation of the R-R interval to systolic blood pressure power ratio or the sequence technique (2), the derived indexes of so-called “dynamic” baroreflex sensitivity invariably were smaller in aged compared with younger individuals (36).

The wealth of data documenting age-related depression of the baroreceptor-heart rate reflex tended to be generalized and gave rise to the notion of age-related depression of the baroreflex at large; however, this represents just one more example of unsafe extrapolation and was indeed not confirmed when the effects of aging on baroreflex components other (and physiologically more important) than control of the sinus node were directly examined. Microneurographic evaluation of the baroreceptor control of efferent muscle sympathetic nerve activity (8, 18), studies employing the neck chamber technique to manipulate carotid baroreceptor activity in humans (see below), as well as various approaches employed in animals to elicit arterial baroreceptor-mediated reflex responses (12, 32), did on the one hand confirm that in advanced age the baroreceptor-heart rate reflex is impaired but on the other hand revealed much better preserved control of blood pressure and sympathetic activity. Animal models, particularly the aging rat, may be valuable in this area because in this species there is virtually no age-related increase in blood pressure nor development of atherosclerotic disease. To take advantage of these features, we compared in 3- to 6-mo-old and 24-mo-old rats the pressor responses to bilateral carotid artery occlusion obtained in the unanesthetized animal via chronically implanted pericarotid balloon occluders. A representative example of the observed responses is shown in Fig. 1. It is notable that the magnitude of the pressor response to baroreceptor deactivation is largely similar in the adult and senescent animal; it is also apparent, however, that in the latter the time course of the response is definitely prolonged (12). Interestingly, this pattern is qualitatively similar to that observed in a fairly large population of human subjects with a wide age range in whom the baroreceptor control of blood
pressure was examined by the neck chamber technique: when carotid baroreceptor deactivation was produced by applying positive neck pressure for 2-min periods, the late, steady-state reflex blood pressure rise was largely similar in the different age groups, whereas the early response was significantly attenuated in the older compared with the younger subjects (14). Although based on different techniques, the parallel findings on age-related effects obtained in humans and rats do support the notion that, with aging, baroreceptor control of blood pressure is quantitatively preserved but has a significantly slowed time course.

More recently, a novel approach to quantitate the blood pressure-buffering ability of arterial baroreflexes was used to compare this function in older vs. younger humans (22): transient blood pressure elevations were produced by intravenous administration of phenylephrine in the control condition and during ganglionic blockade by trimetaphan, the potentiation of the response under the latter condition being taken as a measure of the reflex blood pressure buffering capability. Older subjects clearly showed attenuated potentiation of the pressor responses during trimetaphan blockade, and the authors concluded that aging is associated with impaired baroreflex buffering; this conclusion may not be definitive, however, because this albeit ingenious approach is not devoid of limitations, as discussed by the authors themselves, insofar as phenylephrine is not selectively acting on resistance arterioles. Even more importantly, trimetaphan drastically lowered systemic blood pressure and did so to a quite different extent in the two age groups (much more markedly and indeed almost to shock-like levels in aged subjects), which may complicate the interpretation of the results. Thus the issue of the age-related baroreflex modifications remains in need of further assessment, especially as far as the baroreflex control of the peripheral circulation is concerned, to reconcile the sizeable discrepancies existing between the results and interpretations of different studies.

Lack of consensus on the merely descriptive aspects of age-related baroreflex modifications makes it even harder to address their underlying mechanisms. The issue is intrinsically difficult because of the multiplicity of the factors potentially involved; indeed, reduced distensibility of the arterial walls hosting the baroreceptors, blunted transduction of the stretch signal by the mechanosensitive elements, altered central neural processing of the afferent input, abnormal prevailing levels of efferent neural sympathetic or parasympathetic outflows, changes in end-organ (cardiac and vascular) responsiveness to neural stimuli, i.e., changes at virtually every portion of the reflex arc, have all been claimed to characterize aged compared with younger individuals.

As to the possible alterations at the afferent limb of the reflex, recent findings based on beat-to-beat assessment of carotid artery diameter supported reduced strain in vessels from aged individuals, compatible with reduced stimulus to baroreceptors and reduced afferent signal (20). It is to be noted, however, that the above-mentioned study suggested that arterial stiffening alone could not entirely account for the baroreflex blunting and that neural age-related alterations also gave a significant contribution. Even more intriguing, classical studies performed some 20 years ago on an isolated rat aortic arch-aortic nerve preparation had also reported reduced strain of the aged aortas, but this was accompanied by unchanged rather than depressed baroreceptor activity (1). Obviously, applicability of such in vitro evidence to in vivo functioning is to be considered with caution, and we have thus to admit that the all issue is far from being settled.

Disparate findings have also been reported as to the age-related changes in effector organ responsiveness. We mentioned above that adrenergically mediated cardiac responses are attenuated with aging, and this notion can be viewed as being experimentally well supported. Concerning the parasympathetic autonomic limb, cardiac vagal modulation was extensively explored by use of many different approaches (Valsalva maneuver, cough, baroreflex stimulation, heart rate variability, etc.), and age-related blunting of this function was invariably observed; all such studies, however, could not address the issue of whether the age-related defect depends on neural vagal discharge to the sinus node or on the ability of the cardiac pacemaker itself to respond. Indeed, studies directly testing cardiac responsiveness to parasympathetic stimuli in aging have been limited. We therefore addressed this issue by using adult and senescent rats in which the bradycardic responses to electrical stimulation of the peripheral end of the cut right vagal trunk were evaluated. Although on the basis of the available evidence the expectation was that the bradycardic responses would have been observed in the aged animals, the results...
arterial stiffening if one considers that sympathetic representations are a further factor contributing to age-related peripheral vessels would be implied (9). It may also experimentally verified, and thus cardiac hyperresponsiveness to their activations, one may hypothesize that chronically attenuated (13). To account for these somewhat surprising findings, one may hypothesize that chronically attenuated cardiac muscarinic receptors were pharmacologically activated by graded intravenous bolus injections of acetylcholine, the results went in the same direction, with much larger acetylcholine-induced bradycardic responses in old compared with adult rats (13). To account for these somewhat surprising findings, one may hypothesize that chronically attenuated cardiac parasympathetic drive in advanced age brings about sinus nodal muscarinic receptor upregulation and thus cardiac hyperresponsiveness to their activation; obviously, this albeit plausible explanation is admittedly speculative and indeed hardly amenable to be experimentally verified, at least in the rat species.

Identifying and mechanistically characterizing age-related modifications in the central neural mechanisms controlling the cardiovascular system at large and the baroreflex in particular is a tremendously difficult and as yet largely unmet goal. A few points are nonetheless fairly well documented: The age-related increase in circulating levels of norepinephrine (46) as well as the direct evidence of a clear-cut age-related increase in efferent sympathetic nerve activity obtained via microneurographic recordings from the peroneal nerves (45) support the notion of a physiological sympathetic overactivity in advanced age. Sympathetic overactivity (qualitatively similar to that chronically occurring in hypertension or acutely arising during the defense reaction) might per se account for reduced vagal efferent drive and partly suppressed baroreflex control of the heart, whereas less prominent (if any) interference with baroreflex control of the peripheral vessels would be implied (9). It may also represent a further factor contributing to age-related arterial stiffening if one considers that sympathetic activity tonically restrains arterial distensibility (31). The mechanisms responsible for increased sympathetic activity and central suppression of the baroreflex in advanced age are unknown and may operate at many possible sites in the brain (4, 42).

Cardiopulmonary reflexes. These reflexes have generally been given lesser attention than the arterial baroreflexes: their physiological role may, however, be quite relevant in the setting of aging if one considers their ability to control plasma renin activity and renal function alongside with the limited ability of elderly individuals to cope with fluid and electrolyte balance challenges. Indeed, although only few studies systematically addressed the issue of cardiopulmonary reflexes in aging, the evidence is largely in favor of a blunting in the hemodynamic and even more so in the humoral component of the cardiopulmonary reflex in aged compared with younger human subjects (5, 21). The question remains open, however, whether the impairment depends on defective cardiopulmonary receptor modulation of sympathetic activity or on reduced forebrain vascular responsiveness to neural stimuli (7). In addition, there have been studies that came to conclusions at variance with the above and reported preserved rather than attenuated cardiopulmonary reflex control of forearm vascular resistance in elderly compared with young healthy subjects (40).

HOMEOSTATIC AND CLINICAL IMPLICATIONS OF AGE-RELATED CARDIOVASCULAR MODIFICATIONS

In the following, final section, the way age-related changes may affect cardiovascular homeostasis and be more or less directly relevant to geriatric medicine will be briefly discussed. This has obviously no ambition to be exhaustive and rather intends to provide some significant examples.

First, there should be little question that a physiological age-related alteration in left ventricular diastolic function is a predisposing factor to the development of diastolic heart failure, which is indeed highly prevalent in elderly patients, accounting for up to 50% of all heart failure patients in this age range according to some reports.

Second, combined occurrence of enhanced pulse wave velocity and prolonged ejection time critically facilitates summation of antegrade and retrograde arterial waves, which may contribute to elevation of systolic blood pressure and pulse pressure in aged subjects. This has obvious implications as a powerful mechanism favoring onset and/or progression of vascular damage and increased risk of adverse physiological or clinical outcomes, including excessive cardiac workload and oxygen demand, left ventricular hypertrophy, further arterial stiffening itself, (cerebro)vascular events, and decline of renal function.

Third, altered endothelial function in aging coronary vessels is a further element that causes advanced age to be listed among coronary risk factors. Likewise, there is now convincing evidence that increased carotid
intima or media thickness (by ultrasound) predicts occurrence of cardiovascular events (35).

Fourth, the observation of slowed arterial baroreceptor-mediated blood pressure responses in advanced age may impair moment-to-moment adjustments of sympathetic nerve activity and peripheral vascular resistance, with increased propensity of elderly subjects to postural or postprandial hypotension as well as to inordinate blood pressure peaks. Even in lack of such clinically significant phenomena, the age-related changes in neural cardiovascular control are likely to be responsible for the increased spontaneous blood pressure variability (with concomitant reduction of heart rate variability) typical of aged subjects.

Fifth, it is tempting to extrapolate from studies linking reduced baroreceptor control of heart rate to the risk of life-threatening arrhythmias in cardiac patients and envisage that the adverse potential of this alteration may also extend to the aging condition. In this regard, it is interesting to recall that habitual exercise is well known to exert an antiarrhythmic effect and that in elderly populations it was shown to oppose many age-related alterations (38), including impairment of the arterial baroreflex (20). Ongoing studies in our human laboratory suggest that similar benefits may be obtained by training elderly individuals to slow breathing.

Sixth, impaired effectiveness of the cardiopulmonary reflex in aging may contribute to altered electrolyte and fluid homeostasis and facilitated dehydration: these changes may also be among the factors that dictate caution in prescribing and dosing diuretic therapy in elderly patients.

In conclusion, cardiovascular aging encompasses such a wide and complex range of phenomena at the structural, functional, and molecular levels that its study has come to be viewed as a distinct branch of physiology, whose advances will be crucial to understand the functioning of an increasingly larger section of the population and will help to succeed in the difficult task of defining the border between normality and disease. More specifically, future research efforts should in the authors' opinion pursue the following objectives: 1) to extend and refine risk factor characterization, i.e., to qualitatively and quantitatively define those clinical-functional features of elderly individuals that are most tightly associated with development of cardiovascular disease; 2) to identify (in this case, with no restriction to elderly populations) genetic polymorphisms able to predict development of most marked and/or early structural or functional alterations typical of aging, such as left ventricular diastolic dysfunction, sympathetic overactivity, vascular stiffness, defective endothelial function, arterial wall thickening, and so forth; and 3) to verify whether lifestyle or pharmacological interventions (exercise, sodium restriction, interference with lipid metabolism or the renin-angiotensin system) shown to have favorable effects on arterial structure and function in humans or experimental animals (29, 39) may also prevent or delay cardiovascular events and mortality in apparently healthy elderly humans. Such epidemiological, experimental, and clinical knowledge will form the basis for growing numbers of elderly subjects to be allowed to perpetuate their independence and well-being as late as possible in life (so-called successful aging; Ref. 26) and for modern societies and health professionals to become increasingly effective in providing prevention, diagnosis, and treatment of the cardiovascular disease epidemic worldwide.

REFERENCES


