Impact of Aging on the Body's Vascular System

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In this review, the effect of aging on the body's vascular system is considered in terms of potential mechanisms involved in target organ damage. First, the effects of aging on body fluid compartments, including changes that occur in subdivisions of the interstitial space (quite heterogeneous among organs), are described, with particular reference to the macromolecular composition of the fluid compartments. Second, the structure and function of different segments of the vascular system during aging are examined, with emphasis on: (1) large arterial conduits responsible for isolated systolic hypertension; (2) arteries most responsible for peripheral resistance (the "resistance arteries"); (3) microcirculation networks, including the vasa vasorum; and (4) large collecting veins that can have such an important effect on the cardiac output. Third, a detailed discussion is provided of the heterogeneous macromolecular composition of interstitial fluid compartments that are involved in the critical traffic of vital substrates, including pharmacologic agents, in transit from the systemic circulation to the various organs. The strategic position of interstitial fluid compartments, situated as they are between microcirculation networks and vital organs, is considered to be critically involved in the morbidity and mortality caused by the vascular diseases afflicting elderly persons. Finally, with respect to "physiological" and/or "morbid" aging, a re-examination is undertaken of the target organ damage observed in elderly individuals who suffer from isolated systolic hypertension, type II diabetes mellitus, peripheral vascular disease, chronic heart failure, and renal failure. Potentially new and noninvasive approaches available to clinicians for early detection of large artery rigidity are considered, along with the possible benefits of nonpharmacologic and/or pharmacologic interventions.

IN MOST mammalian species, aging is associated with a significant reduction in total body water, mainly in the intracellular and interstitial fluid compartments. The vascular volume, however, remains relatively constant (5%) in relation to total body weight.[1,2] Maintenance of internal fluid and electrolyte balance between extracellular (vascular/interstitial) and intracellular compartments involves a number of complex and sensitive mechanisms, including active and passive movements across heterogeneous cell membranes. In addition, delicate structural and functional endothelial properties of the microcirculation networks are responsible for the transfer of fluid, solutes, and macromolecules from the vascular to the interstitial compartments.[3,4] Overall fluid and electrolyte balance is principally maintained by the kidneys, with the upper gastrointestinal tract serving as the normal portal of entry for these constituents. The gastrointestinal tract is responsible for the intake and an appreciable fraction of the output of such divalent ions as calcium and phosphate. With aging, both the kidneys and the digestive tract adapt in surprising fashion. For example, the renal response to an acute isotonic saline load is remarkably efficient in normal elderly subjects, despite the fact that renal plasma flow and glomerular filtration rate are both reduced.[5] However, in the elderly, more delicate tubular functions requiring complex hemodynamic/tubular epithelial relationships such as urinary dilution and concentration mechanisms do not operate optimally.[6,7]

Although the neurohumoral mechanisms involved in renal and digestive tract adaptations to the nutritional environment have been relatively well described, the potential adaptive role of extravascular fluid volumes—in particular the heterogeneous interstitial compartments adjacent to all capillary networks—has not been extensively explored. Recent data[8,9] indicate that interstitial macromolecular components, particularly glycosaminoglycans (GAGs) may play a significant role in "buffering" water and cations. In fact, the hydrophilic and polyanionic properties of GAGs are capable of sequestering water and cations (sodium being the most abundant) in several interstitial compartments,[4,10] including, of course, that of the renal medulla, where GAGs are approximately 10-fold more abundant than in the cortex.[11] It has been shown, in fact, that medullary osmotic pressure influences the production of GAGs by renal interstitial fibroblasts.[12] Aging is associated with significant changes in the relative composition of renal GAGs.[11] The above-mentioned physicochemical properties of these macromolecules mainly depend on their degree of sulfatation, chondroitin/dermatan sulfate-containing GAGs being the sulfated moieties (SO_4-GAGs), and hyaluronan being the nonsulfated molecule (NS-GAGs); hence, it appears that the ratio between these 2 types of GAGs should reflect these important properties. As shown in Fig 1, it is interesting to note that the renal profile of SO_4-GAGs/NS-GAGs ratio varies significantly with age, with newborn and old-age values being quite similar.[11] If comparable values reported for the newborn and aging kidney interstitial tissue are representative of those reported for other organs (the skin, for example, being a major interstitial fluid reservoir), this could explain—at least in part—the abnormally low response to an acute isotonic saline load, observed in young and old rats, as compared to mature animals, as shown in Fig 2.[13] These findings raise interesting physiological questions about the potential role played by interstitial compartments of organisms, via GAG's unique properties. In some ways, these properties are comparable to renal peritubular Starling forces, operating passively with minimal energy expenditure.

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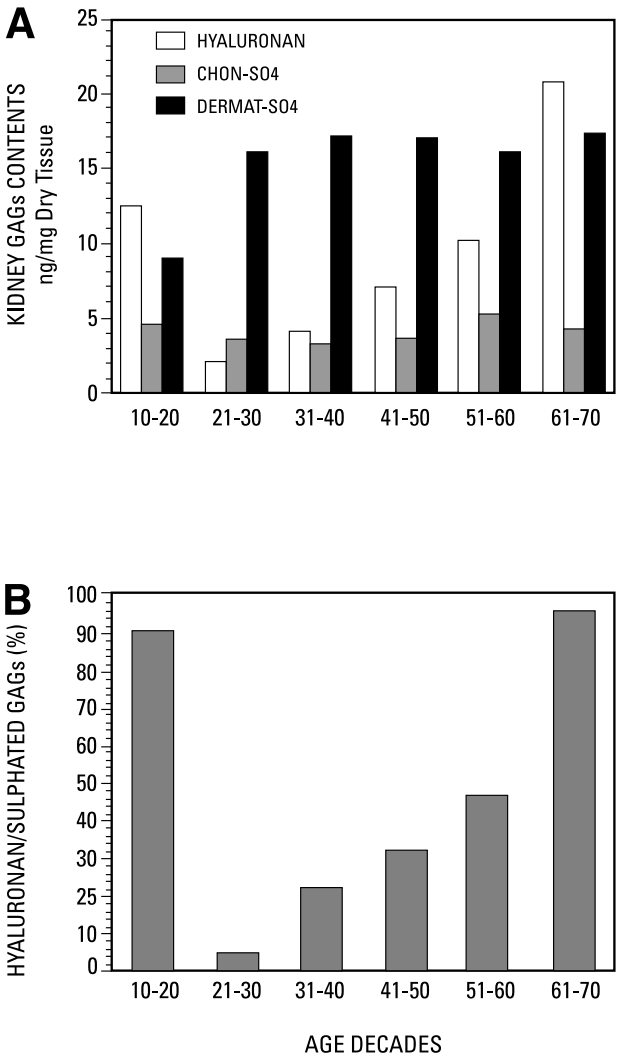

Fig 1. (A) Kidney hyaluronan and sulfated GAGs (chondroitin and dermatan sulfate) measured in kidney specimens obtained from human subjects of different ages (data from Murata and Horiuchi[11]). (B) The ratios between hyaluronan and total sulfated GAGs. It should be noted that, during early and late phases of life, kidney tissue ratios are comparable.

VASCULAR SYSTEM

All segments of the vascular system are affected by aging, but more and more observations are being focused on the abnormalities of the large arterial conduits responsible for isolated systolic hypertension and increased pulse pressure, and the potential consequences of these abnormalities on the left ventricle upstream as well as on the arteries responsible for peripheral resistance and the microcirculation networks downstream.[14] Also, it appears that aging is associated with a different profile of constriction of the aorta, mesenteric artery, and vena cava in response to angiotensin II. In vitro studies performed in normal rabbits of different ages reveal in fact that angiotensin II augments isometric aortic vascular smooth muscle contraction in old rabbits, compared to young animals, whereas the reverse phenomenon is observed on the mesenteric artery and the large veins, in which the vasoconstriction response is diminished with aging.[15] Enhanced contractility of the aortic tissue in response to angiotensin II could contribute to increased rigidity of this conduit vessel, leading to isolated systolic hypertension, whereas decreased vena cava contraction observed with aging could contribute to the changes in cardiac preload, diastolic blood pressure, and pulse pressure that commonly occur in the elderly.[14] Of interest, abnormal large central vein compliance has been reported in untreated hypertensive human subjects of different ages following acute administration of isotonic saline, suggesting a potential contribution of cardiac preload in the development of this condition.[16]

Aging is also associated with significant alterations in the microcirculation. Enhanced endothelial permeability to macromolecules has been documented in segments of the thoracic aorta.[17] Most of the albumin accumulation that occurs in the aortic wall is due to enhanced endothelial permeability arising from abnormalities in the aortic microcirculation, including the vasa vasorum located in the adventitia.[18] A major consequence of these endothelial functional abnormalities is the accumulation of macromolecular material in the media of large arteries. It is also likely that abnormal penetration of macromolecules, including lipoproteins from either the luminal or antiluminal sides of the aorta, contributes to atherogenesis.[19] Much less explored are the endothelial permeability alterations that develop in microcirculation networks of splanchnic and peripheral organs with aging. It becomes more and more evident that, as a result of increased pulse pressure owing to increased

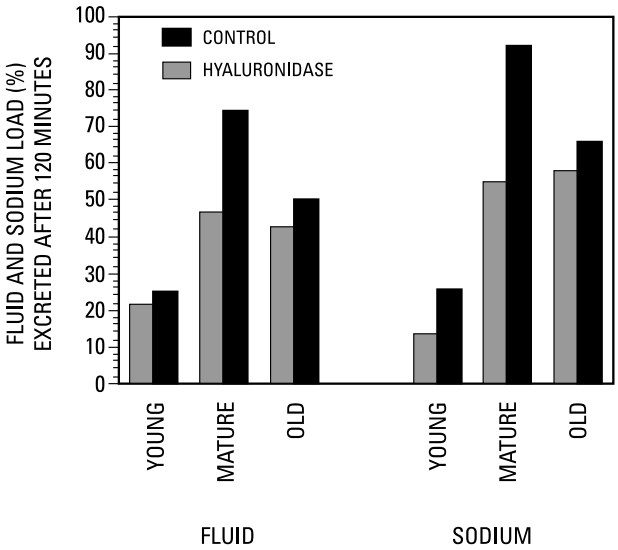

Fig 2. Cumulative excretion of fluid and sodium following acute isotonic saline volume expansion in normal rats of different ages, is shown for control rats pretreated with hyaluronidase, as an indirect method of evaluating the global tissue GAGs. Only in mature rats was a significant difference between control and hyaluronidase-treated animals observed, as if, in this group total tissue GAGs were abundantly present. In young and old groups of rats, hyaluronidase failed to influence mobilization of fluid and sodium from"bound" reservoirs. This observation is compatible with the low renal contents of sulphated glycosaminoglycans reported in these 2 opposite age groups, shown in Fig 1.

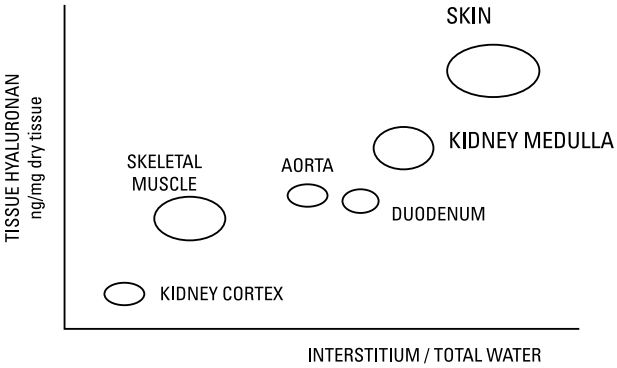

Fig 3. Relationship between interstitial fluid volumes representative of individual tissues (x-axis), and the corresponding measured total hyaluronan values (y-axis). A linear relation between these 2 parameters is obtained for most tissue examined. Of interest, in 2 different kidney compartments (cortex and medulla), tissue hyaluronan contents differ markedly (unpublished personal data).

rigidity of large vascular conduits, both "resistance arteries" and capillary networks are affected.[20] Observations obtained from both in vivo and in vitro experiments indicate that increased pulse pressure affects endothelial integrity, as other examples of abnormal shear stress-related phenomena have shown. The endothelial layer reorganization that develops in response to the traumatic effects of sustained arterial hypertension during aging may well lead to enhanced permeability to macromolecules. Such shear stress phenomena have even been demonstrated in the proximal renal tubular epithelium—effects that could well contribute to functional deterioration of this organ with aging.[21]

INTERSTITIAL COMPARTMENTS

For years, the interstitial fluid volume has been considered to be a more-or-less inert body compartment. It has been described as being associated with 2 histologically distinct components, fibrillar and amorphous. Tissue remodeling of vascular walls in proximity to the interstitium is now believed to be related to structural changes that promote collagen deposition and collagen/elastin ratio imbalance.[22] More recently, the biochemical composition of the so-called amorphous interstitial component has attracted the attention of physiologists, mainly on the basis of the above-mentioned physical-chemical properties of GAGs.[4,10] The regional distribution of this class of macromolecules is quite heterogeneous, as illustrated in Fig 3. Interestingly, there is an apparent relationship between the size of the interstitial compartment of individual organs and the amount of GAGs. For example, skin, which contains the largest fraction of interstitial water per absolute gram of tissue, contains the largest amount of GAGs, compared to the skeletal muscle in which most of the tissue water is intracellular and contains small absolute amounts of GAGs. The cortical and medullary regions of the kidney differ markedly in GAG content. In the cortex, where the interstitial space occupies approximately 10% of the total tissue weight, GAGs represents less than 20% of the amount measured in the medulla, where the interstitial space in relation to total tissue weight is in the range of 50%.[23]

The effect of aging on regional tissue distribution of GAGs, especially in organs considered to be fluid reservoirs, such as skin, skeletal muscle, and gastrointestinal tract, has not been extensively studied, but indirect evidence suggests that the profile should resemble that observed for the aging kidney, as described above.[11] In fact, the extrarenal response to acute saline administration during control conditions and then following destruction of GAGS with hyaluronidase (an indirect approach to evaluate tissue content of GAGs), in young and older normal rats, suggests that fluid and sodium mobilization from these reservoirs is superimposed upon the measured contents of these macromolecules in the kidney, as shown in Fig 1. The structural and functional characteristics of the interstitial fluid compartment, quite heterogeneous from one organ to the other, have been summarized in recent reviews,[12,24] which emphasize the strategic role played by this fluid compartment in normal physiology and in pathophysiology. It becomes evident that the traffic of vital substrates from blood to cellular mass of any organ, and the removal of waste products in the opposite direction for excretion, require relative integrity of the interstitium. Changes in size and/or biochemical composition of this compartment adversely affect cellular function.[24] For example, when interstitial oxygen pressure is measured from the luminal toward the antiluminal side of the aortic wall in normal and atherosclerotic animals, changes in the matrix composition are found to be associated with significant decreases in tissue oxygen tension—a valuable marker of target organ damage.[25]

CLINICAL ASPECTS

Target organ damage in patients suffering from primary vascular diseases (arterial hypertension, vasculitis, senescence, etc) or secondary vascular disorders (types 1 and 2 diabetes mellitus, chronic renal failure, congestive heart failure, dyslipidemia, morbid obesity, etc) represents a major challenge for scientists who are attempting to develop drugs capable of abating the pathophysiological cascade responsible for so much of the morbidity and mortality associated with these disorders.[19]

In a search for a common denominator involved in target organ damage, our investigative group has focused on segments of the vascular system containing the largest fraction of the blood volume; namely, microcirculation networks (capillaries and postcapillary venules) in which more that 50% of the entire vascular volume is contained in close proximity to the cellular mass of vital organs. The heterogeneous characteristics of these networks with respect to volume and composition may explain some of the wide variations in target organ damage observed in an array of vascular diseases of differing etiologies, such as primary arterial hypertension, chronic uremia, and congestive heart failure.[24] Yet, differences in etiology need not give rise to corresponding differences in organ damage. To the contrary, the primary abnormality common to these diverse conditions appears to be the endothelial dysfunction found in capillary and postcapillary networks. Studies from our laboratory indicate that enhanced endothelial permeability to albumin exists in conditions as different in appearance as diabetes mellitus, chronic uremia, heart failure, and vascular aging. This endothelial dysfunction leads to extravasation of plasma into the

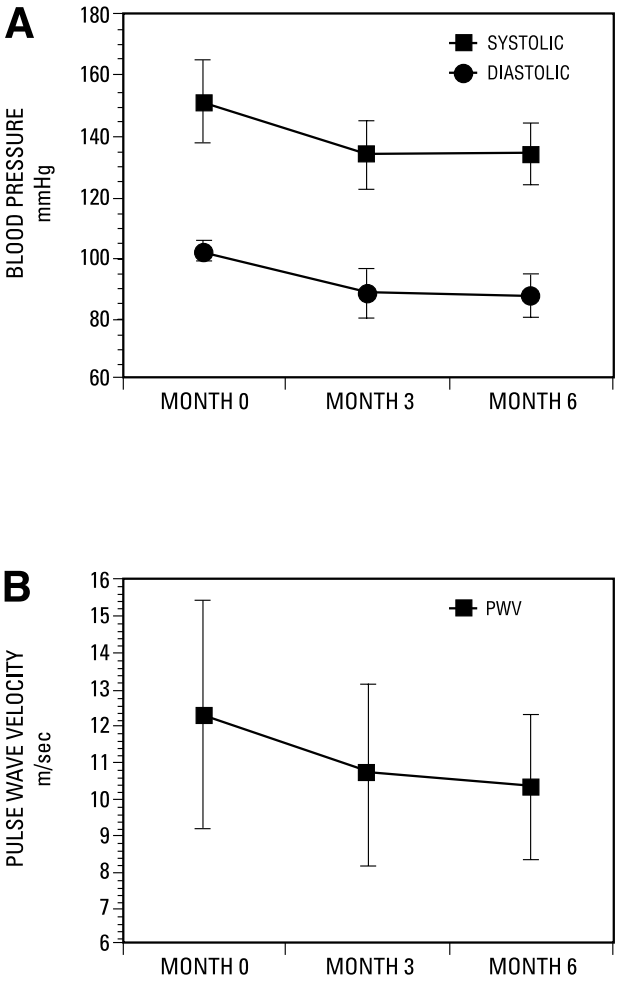

Fig 4. Preliminary results obtained from the Complior Study performed in several Canadian hypertension centers illustrate the beneficial effects of perindopril on large artery compliance noninvasively measured by pulse wave velocity, independently of the effect of this drug regimen on blood pressure. Note that blood pressure reduction is maximal after 3 months of treatment, while pulse wave velocity which decreased significantly after this period of active treatment, continued to decrease during the following months, and blood pressure remained stable, suggesting improvement of arterial compliance independent of blood pressure–lowering effects.

adjacent interstitial compartments. As a consequence, the interstitium is modified in size and composition, leading to disturbances in the traffic of fluid and vital substrates to the cellular mass, and in the removal of waste products in the opposite direction.[24]

The burden of vascular complications and target organ damage imposed by the above-described diseases urgently calls for the attention of health care authorities on a worldwide basis. If the sequence of morbid events leading to target organ damage described in several animal models of disease, in particular primary hypertension and type 1 diabetes mellitus, is shown to occur in human populations as well, the opportunity exists for the development of novel pharmacologic interventions designed to prevent or ameliorate vascular endothelial damage—particularly in microcirculation networks. In parallel, development of noninvasive methods[26-28] to evaluate the structure and function of large conduit vessels, particularly in elderly populations, will allow the early detection of vascular rigidity. Early diagnosis would permit timely nutritional and/or pharmacologic intervention.[14] In this regard, recent clinical studies have shown that some of the most widely employed drug treatments of arterial hypertension give rise to profoundly beneficial effects on the physical properties of large conduit vessels, independently of blood pressure control, as illustrated in Fig 4.[29] Such positive pharmacological actions on blood vessels in human beings are consonant with findings obtained in animal models of systemic vascular diseases.

In conclusion, when one looks at the evolution of systemic diseases such as arterial hypertension, diabetes mellitus, obesity, dyslipidemia, chronic renal and heart failure, and diseases of cognition, it becomes increasingly evident that the blood vessel structural and functional disturbances which characterize vascular aging, as described in the present review, make a major contribution to aging-related target organ damage.[24] During the millions of years of evolution of living organisms, a vascular system, beginning with primitive vessels such as those described in *Octopus dofleini*,[30] and increasing in complexity, was indispensable to the emergence of highly developed animal species. At the same time, perturbations of the complex (and hence correspondingly vulnerable) vascular system required for the proper function of the body's vital organs, are now considered to make an important contribution to the pathologic changes associated with aging in higher mammals, including—most notably—human beings.

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