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The Evolving Role of Structural and Functional Imaging in Assessment of Age-Related Changes in the Body

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Aging is an extremely complex, multifactorial, and inevitable process that varies in rate from person to person and that is not fully understood at its most basic levels. Despite this complexity, knowledge of age-related changes and normal variation in organ structure and function is essential to differentiate them from alterations that are associated with pathology. Combined structural and functional imaging, which increasingly is used to assess a multitude of disorders, including cancer, cardiovascular disease, and central nervous system abnormalities, can be applied to study changes in structure and function related to aging. This article reviews the major theories of biological aging and presents our approach and rationale to study age-related changes through quantitative tomographic radiological and scintigraphic approaches.

In the series of articles that follow, we have made an attempt to determine age-related changes in volume, attenuation, and function as measured by computed tomography, magnetic resonance imaging, and position emission tomography in the following organs and systems: central nervous system, head and neck, heart and major arteries, lungs, abdominal and pelvic parenchymal organs, gastrointestinal tract, genitourinary tract, breast, bone and bone marrow, joints, and skin. The population examined includes a large number of subjects in all decades of life. We have also made an effort to introduce some new concepts such as partial volume correction and measurements of global metabolic activity of the organs examined, and emphasize the importance of quantitative techniques in such applications. It is our hope that this new initiative will further enhance the role of novel imaging techniques in the management of patients with cancer and other disorders.
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The introduction of tomographic imaging techniques in the 1960s and 1970s has allowed for the visualization of quantitative changes that take place in organ structure and function in normal aging and disease states. Because most modern imaging modalities originally were designed to examine brain structure and function, this organ has been the focus of investigation for determining the effects of age during the past 25 years. In fact, our group was among the first to quantitatively measure changes that occur in brain structure and function with normal aging by using magnetic resonance imaging (MRI) and positron emission tomography (PET), respectively. The results of these early research studies were quite impressive and revealed significant alterations in cerebral anatomy and metabolism during senescence.

Organ structure and function can be accurately visualized and quantified with a high degree of precision using modern tomographic imaging techniques in the entire body. Therefore, one can determine the effects of age on a multitude of organs. Interestingly, there is a paucity of data with regard to the effect of age on most organs as determined in vivo by these powerful imaging modalities. This has led us to initiate and explore the role of these imaging tools and methodologies to assess such alterations in the human organs during aging and has been the driving force for us to draft the articles that follow this introductory article.

Discussion

Biological aging is an extremely complex, multifactorial process and generally is defined by some as a decline in a per-

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son's fertility or survival through time.[1-4] As opposed to chronological aging (which is defined by the passage of time from birth onwards), biological aging is characterized by progressive change in tissues or organs of the body, which can be said to begin at or before the time of conception, with associated impairment to maintain homeostasis, a decrease in cell, tissue, and/or organ function, and increased susceptibility to disease and death.[2,4-6] The progression and rate of aging is highly variable in humans, as well as in an individual's organs and tissues, in different cell types within a tissue, in different subcellular compartments within a cell type, and in different macromolecules within a cell, adding to the complexity of the aging process.[2,7-9]

Furthermore, the basic mechanisms underlying aging are unknown, although numerous aging theories have been proposed, including those related to chronic "wear and tear," genetically programmed change, or cumulative stochastic damage.[2-4,6,10-13] Dental caries, cartilage thinning, postural changes caused by the effects of gravity, skin or lens changes resulting from sunlight and external radiation, and hearing loss caused by loud noises are examples of age-related changes that may occur through chronic "wear and tear."[4] An example of a genetically programmed change with age is that of the expression and activity of reverse transcriptase telomerase, which can protect and maintain telomeres (the repetitive DNA elements at the end of linear chromosomes that are essential for genome stability and chromosomal integrity), can alter the gene expression involved in cell proliferation and the development of degenerative lesions during aging, and can promote cell survival by protecting cells from DNA damage and apoptosis.[1,3,4,14-22] However, although telomere length is reduced with age in many tissues such as peripheral blood cells, liver, kidney, spleen, dermal fibroblasts, and mucosal keratinocytes and although some studies have demonstrated a correlation between telomere length and risk to succumb to cardiovascular disease and infection, the decline in telomere length is not constant over the course of aging, and there are tissues that do not show telomere shortening (eg, brain and myocardium) although they still undergo structural and functional changes with age.[19,23-26] Interestingly, in the overwhelming majority of human cancers, telomerase is aberrantly activated and is thought to provide cancers with unlimited growth potential.[25,27] Cumulative unrepaired biochemical alterations that impair the function of nucleic acids, proteins, and lipid membranes may include oxidation by free radicals principally generated by mitochondria, as well as nonenzymatic glycosylation or epigenetic changes such as DNA methylation and histone acetylation, leading to deterioration of organelle, cell, tissue, and organ function, although the specific molecular mechanisms leading to age-related functional impairment remain to be systematically investigated.[2,4,28-47]

Unfortunately, aging is an inevitable process that we all face despite its complexity and, therefore, it is logical to continue to study the potential etiologic factors and underlying mechanisms of aging as well as the resultant microscopic and macroscopic changes in structure and function that occur with aging. Continued investigation of aging is particularly important because (1) the elderly are forming an ever-increasing percentage of the population; (2) aging may be considered to be the underlying basis of almost all major human diseases, including atherosclerosis, cancer, cardiovascular defects, cataracts, diabetes mellitus, dementia, macular degeneration, neurodegeneration, osteoporosis, and sarcopenia; and (3) the prevention of the onset of age-related disease through deeper understanding and early intervention in the basic processes of aging may be the best solution to improve the quality of human life and its dignity in old age.[2,6,48] In fact, the concept of "successful aging" was first proposed by Cicero in 44 BC when he wrote that "old age is not a phase of decline and loss, but instead, if approached properly, harbors the opportunity for positive change and productive functioning."[49] With all of this in mind, our goals for this series of articles over the next two issues of *Seminars in Nuclear Medicine* are (1) to provide an overview of what is known about normal changes in structure and function of the major organ systems of the human body during aging, (2) to present novel noninvasive radiological and scintigraphic imaging methodologies to quantitatively study various manifestations of these changes, (3) to report quantitative preliminary data obtained from such approaches regarding changes in structure and function of the major organ systems with aging, and (4) to discuss issues relevant to quantitative imaging.

We believe that the study of age-related changes in normal structure and function through quantitative tomographic radiological and scintigraphic approaches (namely, computed tomography [CT], MRI, and PET) is important for many reasons. First, radiologists and nuclear medicine physicians interpret CT, MRI, and PET examinations on a daily basis that are obtained for a wide variety of clinical indications, including oncologic, inflammatory, traumatic, metabolic, and congenital disease processes. As such, it is important for the image interpreter to know what "normal" is in terms of tissue or organ structure and function, which often depends on the age of the subject undergoing imaging, to then be able to recognize what "abnormal" is for a particular subject. This is particularly important in this day and age of "personalized medicine," where intersubject differences in bodily structure and function may exist because of age, as well as variations in genetic makeup and gene expression, sex, body habitus, and environmental factors.[50-59]

Second, the majority of CT, MRI, and PET imaging interpretations generally are performed on a daily basis in a qualitative or semiquantitative fashion. Although this environment may be sufficient to arrive at the correct diagnosis in many cases, quantitative analysis of acquired imaging data sets through use of hand-tracings or semiautomated computer-aided quantitative software packages to perform tasks, including segmentation, image analysis, data mining, statistical analysis, and/or data integration may (1) provide additional information relevant to such issues as subject prognosis and detection of early therapeutic response; (2) improve on the sensitivity, specificity, and accuracy of CT, MRI, and PET for disease diagnosis in a more reproducible and less subjective standardized fashion; and (3) make the task of the interpreting physician less cumbersome.[54,60-63] These advantages also

apply in the setting of animal or human research to assess the potentially age-dependent pharmacokinetic and pharmacodynamic effects of new drugs or other therapeutic interventions as safely, efficiently, and effectively as possible.[53,64,65]

Third, there is a spectrum of changes in structure and function in the human body that generally occur during aging, and it is often difficult to determine when to classify such changes as pathological as opposed to a part of normal aging.[6,66] For example, although prostate carcinoma generally is considered to be a pathological process, one could consider prostate carcinoma as an expected change in structure and function of the prostate gland during normal aging. This is supported by a study of prostate glands obtained at autopsy from men who died of motor vehicle accidents that revealed the presence of intraepithelial neoplasia and prostatic carcinoma with low degrees of development even in subjects in their second decade of life, and is further supported by the fact that the majority of elderly American men (approximately two-thirds) develop this tumor and die with this tumor rather than from it.[67-70] As another example, atherosclerosis may occur asymptomatically during infancy and childhood as seen by the appearance of fatty streaks in the aorta, and may, in this sense, be considered to be an expected change in structure and function of the aorta with normal aging until such time that a clinically significant symptomatic event such as stroke or myocardial infarction occurs later in life.[71,72] Therefore, quantitative radiological and scintigraphic approaches may be useful to further define the boundary between "normal" and "abnormal" changes in bodily structure and function with aging.

Although philosophers and scientists have long been interested in the aging process, general interest in this subject was minimal before the 1960s.[10] Since then, many approaches to investigate various aspects of aging have been used, including basic science laboratory analyses (eg, genomics, proteomics, and histopathology), epidemiological and evolutionary analyses, and clinical analyses that span multiple fields of medicine including pediatrics, internal medicine, geriatrics, and gerontology.[2,3] A multitude of investigators have also reported the use of noninvasive radiological cross-sectional imaging (ie, CT, MRI, or ultrasonography [US]) to study structural changes with aging in a variety of specific organ systems in specific target populations.[54,55,73-115]

In our approach to the study of normal aging, we have expanded on the use of CT and MRI to quantitatively study the macroscopic structural changes in all of the major organ systems in humans from ages 0 to 90 years old and have incorporated PET to quantitatively study various accompanying molecular and metabolic functional changes in these organ systems of the same subjects as well. Interestingly, the use of PET in previous investigations of aging largely has been ignored. We have also taken advantage of the natural synergy that exists between CT/MRI and PET data sets to (1) provide partial volume correction of standardized uptake values from PET images via volumetric measurements on CT/MRI examinations, (2) improve anatomical localization of radiotracer uptake seen on PET via coregistration with CT/MRI images, and (3) combine quantitative structural data from CT/MRI with quantitative functional data from PET into single integrated quantitative parameters that are easy to use and that take into account both structure and function of an organ of interest. Finally, we have taken advantage of the benefit of in vivo whole-body or near whole-body imaging provided by CT, MRI, and PET to evaluate regional structural and functional changes with aging in the human body.

It is our hope that this effort to demonstrate the evolving role of imaging to study age-related changes in structure and function of the major human organ systems will serve as a springboard for those interested or involved in aging research and will ultimately aid those people involved in the clinical care of patients as well as patients themselves.

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