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The Aging of the Heart and Blood Vessels: A Consideration of Anatomy and Physiology in the Era of Computed Tomography, Magnetic Resonance Imaging, and Positron Emission Tomographic Imaging Methods With Special Consideration of Atherogenesis

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Physicians have long told their patients that the doctor's job is to help patients "get as old as they can." As physicians, we have been aided in this objective by many other scientists in other disciplines. The entity of aging and its related changes blends imperceptibly with a variety of age-related diseases. However, these entities do appear to be separate though interrelated. Curing disease is important and a goal that we all work toward to add years to life expectancy. Here, we consider aging as it affects the heart and great vessels and as it serves to influence and support, if not cause, age-related cardiac diseases. This relationship is drawn as cardiac mechanics, hemodynamics, perfusion, metabolism and innervation, anatomy, and pathophysiology are each considered. The effects of aging are presented in 2 sections related to the early and recent "spikes" in aging related information. The latter is largely based in recent developments in chemistry, genetic engineering, molecular biology and the new imaging methods. The purpose of this manuscript is to present these new imaging methods, especially PET, and their impact on the second "spike." This is emphasized particularly in the second half of this review. As a method of demonstrating these imaging tools and their finest potential application, we decided to "showcase" atherosclerosis as the age-related disease for which these methods have made their greatest impact, for which yet more is promised, and for which the influence on longevity is most obvious. The application of positron emission tomography and other imaging methods to the characterization and image identification of atherosclerotic plaques and particularly the "vulnerable" plaque is emphasized. Yet, even with the eradication of coronary disease, the potential for very long life would not be likely. Only with the identification and eradication of the causative factors of aging can this possibility have a chance of becoming reality.

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It has been almost 20 years since "old age" has been removed from the list of possible causes of death.[1] Yet, the changes related to aging are numerous, basic, and clearly quite influential in the development of pathologies that are, too often, named as primary or contributing causes of death. So-called "age-related changes" present greater cardiovascular risk than others identified by epidemiological studies. Both overt cardiovascular disease[2] and occult pathology[3] increase geometrically with age.

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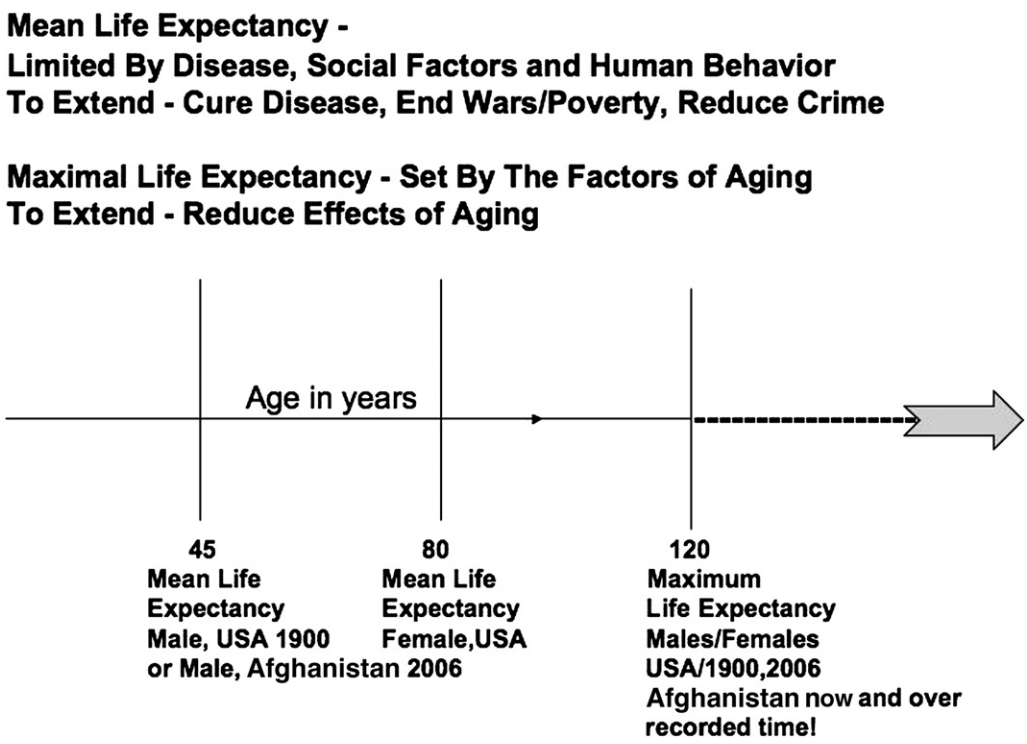

Figure 1 Life expectancy: difference between mean and maximal age and factors that determine them. Current values demonstrate factors involved.[5,7]

The parameters that define aging are as much philosophical as scientific.[4] Typically, 65 years is the age beyond which the changes of aging apply. However, this number has more to do with actuarial studies, insurance rates, economic, retirement policies and social practice, and less to do with pathophysiology. Although there are more than 35 million people 65 years of age or older in the United States and although that population will double by 2030,[5] the issue is more generic. The changes considered here are ongoing and dynamic. They do not begin or even necessarily prevail at age 65, and evidence suggests that they begin with life itself. Conceptually and clinically, we can think of development as the period between conception and birth, maturation as the early years of life to adulthood, and aging as the process thereafter.

The likelihood of dying increases exponentially with age after maturity. But the species-related and age-related life expectancy differences are extensive, and the fact that a rodent is old at 3, a horse at 35, and a human at 80 years is unexplained. Why different genders age differently is also unclear. It has been postulated by Best[6] that in the absence of disease and senescence, the only causes of death would be accident, suicide, and homicide. Under such conditions it is estimated that a 12-year-old child would have a median lifespan of 1,200 years and a maximum measured in the thousands! This seems good, but think about it. Darwin thought increased aging would put a species at a disadvantage with an eventual competition for resources across generations and would be gravely concerned were such numbers to become a reality. Two theories of aging can be summarized as "programmed aging," related to internal, possibly genetic mechanisms about which the individual can do little, and "wear-and-tear" aging, the effects of environment.[6] Neither appears to explain all the features of the condition.

There are evident changes that we all identify as age related, ranging from reduced body strength, to poor eyesight, to declining sexual activity and productivity, and loss of dentition. A multitude of other changes occur at the molecular, cellular, and organ levels. Although not clearly diseases in themselves, many of these have been influenced by behavioral changes, medications, or interventions with a significant impact on individual afflictions and with a recent increase in mean life expectancy. However, many of the changes are relatively superficial and simply remove the blight, as with cataract surgery, or cure the disease, with antibiotics. Although this has increased the mean life expectancy, it has done nothing for the maximum which has been steady at 115 to 120 years. That is, we have done a lot to maximize the potential for longevity but have not actually influenced the aging process which seems to put a limit on the maximum life duration (Fig. 1).[5,7] This suggests that the effects of aging are separate from disease and pathology and that their secrets will be more difficult to expose. Yet, expose them we must and will, given the development of tools available and the similarities between age related changes and the pathology we know all too well. Pushing back the barriers to aging is an ongoing effort.

Caloric restriction with adequate nutrition, not starvation or malnutrition, is one of the few interventions that extends the maximum life expectancy in laboratory animals.[6] However, it is an extremely difficult, or impossible, intervention to implement in humans, who have no idea just how little it

takes to maintain nutrition. The terms "successful" and "unsuccessful" aging refer to those individuals where potentially detrimental age-related factors, which may serve as risk factors for subsequent disease, are rare or frequent, respectively. There must be factors then, that we as scientists and physicians can influence or treat to retard or stop the process, and with this the recognized disease, morbidity, and mortality with which they are associated. Once overcome, we would then need to deal with the societal problems and social pressures which they could engender.

How Is Aging Characterized Biologically or Medically?

Aging presents a spectrum of changes at the molecular level that damage molecules or promote the development and deposition of damaging molecules, which then influence the structure and function of cells and organs.[6] These changes occur unpredictably with varying pace as the organism ages and have been said to appear different in their degree, progression, and consequences from the so-called "diseases of old age," including coronary artery disease, cardiomyopathy, osteoporosis, arthritis, cancer, and dementia. Of course, even this summary is a misnomer because the target population for coronary disease is men ages 40 to 60 and women ages 50 to 70, which are not really "old" populations by current standards. Furthermore, owing to improved identification and therapy of coronary disease, hypertension, and hyperlipidemia, the incidence of cardiomyopathy is increasingly and adversely influencing the quality and length of life such that the character and mix of the diseases of old age is itself evolving. If not themselves the early stages of disease, "age-related" changes certainly parallel and mimic the disease entity. Certainly, age-related damage provides an unfortunate "leg up" on pathology and increases the probability, if not the severity, of experiencing the disease and its complications. This relationship between age-related damage and pathologic disease of aging is nowhere more compelling than in the relationship between the early vascular changes of aging and the evolved changes of atherosclerosis and advanced vascular (and specifically coronary) disease.

Aside from recognized diseases of premature aging, the molecular basis of aging has been thought to relate to several possible causes, including the effect of free radicals; mitochondrial changes; protein damage by glycation; DNA damage; changes in telomeres and the genetic material; cellular senescence and apoptosis; and genetic silencing.[6] None of these will be considered here as we review those age-related changes evident to the clinician, which may be visible with application of the new and powerful imaging methods now available.

More now than ever, we are able to consider these "aging" changes as individual entities, which precede the development of the clinical syndrome. Combined with echocardiography, the development and clinical application of advanced imaging tools, magnetic resonance imaging (MRI) and computed tomography (CT), have made possible a deeper and more accurate evaluation of cardiac anatomy. However, only with a combined appreciation of both anatomic and pathophysiologic or functional changes can the true nature of aging-related changes be scientifically approached. To this point, pathophysiologic evaluation has been limited by our tools and methods. The application of positron emission tomography (PET) to the elucidation of cardiac pathophysiology promises to add many needed pieces to the solution of the puzzle that is "aging." Rather than attribute their cause to aging per se, here we will refer to "age-related" changes. As will become clear from the presentation herein, the aging-related knowledge base is biphasic. Much of what is known regarding age-related changes has long been known, gathered with clinical and research tools long applied. This early information spike is now joined by a new one, related to data contributed by new technology and the interplay of new and established methods.

Established "Age-Related" Changes: The First Aging Information Spike

Aging is related to a varied array of complex changes in cardiovascular structure and function that are expressed heterogeneously and unpredictably.[4]

Myocardium

Myocardial Mass and Thickness

An increased left ventricular (LV) chamber mass, modest LV hypertrophy characterized on echocardiography in populations of varying age,[8] a change in chamber shape or remodeling, tortuosity of the aorta, a bulge in the intraventricular septum, and narrowing the aortic outflow tract are noted.[9] Additionally, cardiomyocyte size appears to increase whereas the number decreases and focal collagen deposits grow with increased cross-linkage.[4] These changes may lead to increased myocardial stiffness, with the development of diastolic dysfunction that is well appreciated on echocardiography and frequently reported as "normal for age."[10] These changes add to myocardial oxygen demands and place a burden on the vasculature that is increasingly unable to respond to these demands of stress.

Diastolic Function

The myocardial changes described previously, combined with intrinsic stiffening of the vasculature overall, lead to an increased myocardial stiffness or reduced compliance, causing increased resistance to LV filling. Somewhat surprisingly, however, diastolic dysfunction in the aged subject appears to relate strongly to a prolonged action potential with increased duration of the active state of contraction or a reduction in the rate and magnitude of myocardial relaxation and not to the intrinsic mechanical characteristics of the myocardium or the effect of catecholamines.[11] This characteristic resembles the pathophysiology of diastolic dysfunction, which is the major aspect of dysfunction in those with diastolic heart fail-

ure. This feature is dominant in one-third to one-half and a significant aspect of the pathophysiology in many of the remaining patients presenting with heart failure,[12] which now is the largest cause of cardiac-related hospitalization and death. Often related to and predated by hypertension, LV hypertrophy and fibrosis add to the causes of such dysfunction and morbidity.[13]

Also, it must be remembered that the earliest functional effect of myocardial ischemia, the initial step in the ischemic cascade,[14] is diastolic dysfunction. Beyond this, the myocardial and the vascular changes related to aging provide a ready milieu for arrhythmia induction and propagation. In particular, atrial fibrillation (AF) is a growing source of morbidity and related stroke in the elderly.[15] "Lone AF," or AF without identifiable cardiac or other cause, also is related to an increased risk of stroke and is seen in as many as 10% of those with supraventricular tachycardia having a mean age of 70.[16] How then do these aged hearts respond when confronted with the common pathologies of hypertension and myocardial ischemia? They form a ready and all-too-willing foundation for the clinical effects of these common maladies of the elderly.

Systolic Function

Systolic function of the LV has not per se been found to be influenced by age. However, the response of the LV to stress, such as exercise, is blunted in part due to the age related effects of neuroregulation.

Blood Vessels

Vascular Compliance and Contour

The aorta and major elastic arteries become increasingly elongated and tortuous with increasing age. They dilate, and the enlarged internal diameter relates to a thickened intima and media or hypertrophied wall.[17,18] Increased carotid artery thickness seen with aging appears to be a risk factor for coronary events.[19] Animal work shows that intimal cells demonstrate an increasingly irregular shape and increasing height with increased numbers of leukocytes and macrophages, and deposition of collagen, elastin, cytokines, adhesion molecules, metalloproteinases, transforming growth factor β, and other substances, in some ways mimicking the milieu of inflammation and atherosclerosis.[20,21] Perhaps, as in diabetes, increased cellular cross-links caused by nonenzymatic glycation contribute to the increasing vascular stiffness with age.[22] Paradoxically, evidence exists that arterial stiffness precedes hypertension rather than occurring as a secondary effect of hypertension.[23]

With age, the major elastic vessels become stiffer and less compliant.[24] This relates in part to the structural changes noted previously and also to an altered vascular smooth muscle tone with a reduced nitric oxide-dependent vasodilator response to acetylcholine, an increased endothelial permeability, reduced vasodilation in response to β_2 stimulation, and a lesser blunting of the response to α-receptor-mediated vasoconstriction.[25,26] As noted by Ferrari and coworkers,[4] these changes parallel those seen in early atherosclerosis where the latter go on to develop focally with plaque formation, rupture, and vascular obstruction. Although vascular stiffening can be seen in the absence of atherosclerotic changes, it is also a feature of atherosclerosis and diabetes.[4] Is aging the precursor of atherosclerosis and coronary disease, or is coronary disease accelerated and malignant aging? More importantly, what governs the development of the process and the change from benign to malignant forms?

Increased Pulse Wave Velocity

The increase in vascular hypertrophy and stiffness influences the resistance vessels, ie, the arterioles and precapillaries, which are the last vessels with smooth muscle in their walls, and an increased peripheral resistance results. This age-related increase in peripheral resistance results in an increased systolic and pulse pressures and generates an increased pulse wave velocity. These latter changes result again in increased wall thickening and stiffness, resulting in increased peripheral resistance and increased systolic and pulse pressure, a classic example of a "vicious cycle." In fact, although normal systolic blood pressure values clearly increase with age, they are continuously being revised downward so that what was considered as normal for the elderly subject in the past is now considered as hypertensive. Because we now recognize the serious prognostic risk inherent in elevated systolic blood pressure and recognize its need for treatment, it is obvious how the rising normal systolic blood pressure of the aging blends into the pathologic entity requiring treatment.

A summation of antegrade and retrograde arterial pulse waves caused by the combined effects of increased pulse wave velocity and increased ejection duration could well contribute to an elevated systolic blood pressure and widened pulse pressure in the older patient. Although diastolic pressure has been found to increase to age 50 and then plateau and decrease thereafter, systolic pressure continues to rise with progressive changes in the arterial wall, the leading determinant beyond vascular resistance of blood pressure in the elderly. Hypertension increases vascular trauma and stiffness and promotes left ventricular hypertrophy, work of the heart and myocardial oxygen demands, with an adverse effect on myocardial function, renal function and an increase in risk of cerebrovascular events.

Endothelial Dysfunction: Altered Vasoreactivity and Coronary Flow Reserve

The coronary arteries have the highest resting resistance of any vascular system. With demand, a reduction in this resistance permits the coronary circulation to augment flow in response to increased requirements. With age, there is increasing evidence of endothelial dysfunction producing an inability of the coronary resistance vessels to dilate with blunting of the hyperemic response and an inability of the coronary circulation to augment flow consistent with demands. This is the earliest pathophysiologic change in atherosclerotic vessels and likely leads to and is amplified by the anatomic obstruction of atheromatous plaque. Along with this altered vasoreactivity, permeability is affected and lipids gain access to the intima and media. These early changes of aging blend imperceptibly with those of early pathology, and are some of many age related changes that place the patient at

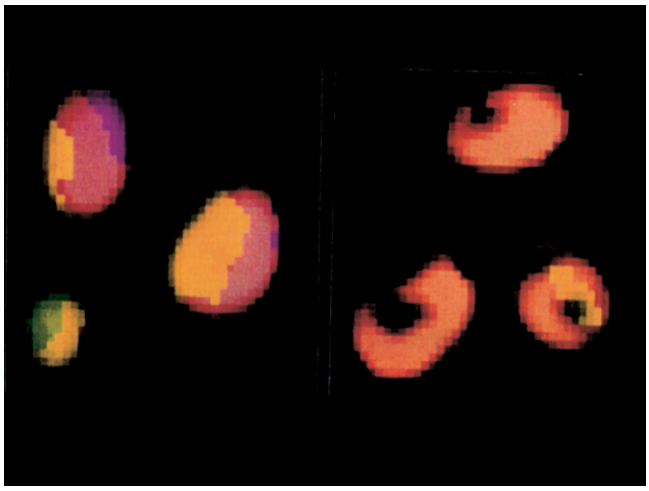

Figure 2 Sympathetic maturation: myocardial slices from newborn (left) and 3-month-old (right) puppies that were given ^{123}I MIBG and ^{201}Tl before sacrifice. These autoradiographs demonstrate ingrowth and maturation of myocardial sympathetic innervation where nerves have been demonstrated by several methods to grow from cardiac base to apex after birth.[34] Pink represents balanced amounts of radionuclides, and yellow and green indicate excess of ^{201}Tl with reduced innervation at birth. (Courtesy of M. Dae, MD, University of California San Francisco, San Francisco, CA.)

greater risk from coronary disease. Endothelial changes are a known accompaniment of atherosclerosis, diabetes, and hypertension.[27]

Altered Biochemistry and Calcium Deposition: Early Atherosclerosis?

Biochemical patterns develop with age that are similar to those found with atherosclerosis. Calcium deposited in the intima and media appears to increase with age and is again a finding of early coronary disease. Are the changes in structure, vasoreactivity, and biochemistry the early stages of atherosclerosis, or do the processes related to aging, with additional interactions and contributions of hypertension, diabetes, hyperlipidemia, diet, and genetics, "morph" unpredictably into those of well-known pathology? In fact, vascular wall thickening is an independent predictor of coronary events. Yet, this is clearly not the only or the pivotal risk factor, as the difference in risk between young and old without vascular thickening or between the young and the "successful" older population far exceeds the difference in risk between elderly groups with and without vascular thickening.[19]

Neuroregulation

Sympathetic Responsiveness

The myocardium becomes less responsive to β-adrenergic stimulation because heart rate and contractility augmentation with extrinsic catecholamines or exercise is blunted in the elderly.[28] Contractility is compensated by the Frank–Starling mechanism and the augmentation of contractility with increased volume. End-diastolic and end-systolic volumes both increase at rest and with exercise, increasing output. Yet, maximal cardiac output, heart rate × stroke volume (end-diastolic volume − end-systolic volume), remains blunted with age in response to exercise because of the inability of the stroke volume to fully compensate for the deficiency in heart rate augmentation.[28] Julius and coworkers compare the response of the aging heart to exercise as one of progressive β-blockade.[29]

Arterial Baroreflex: Definition and Description

The arterial baroreflex is greatly altered with age, whereas the mechanism modulating peripheral resistance is better preserved. Pharmacologically induced vasoconstriction and resultant hypertension produces a blunted slowing of the heart rate in the older compared with the younger individual. Conversely, peripheral vasodilation with a relative deactivation of baroreceptors results in a blunting of the acceleration response.[30] Ferrari and coworkers took a closer look at this baroreceptor response in rats, where there is no age-related increase in blood pressure or atherosclerosis.[31] They found that the baroreceptor response was not actually depressed because deactivation produced by transient bilateral carotid occlusion was of similar magnitude in adult and aged rats. However, the time course of the hypertensive response was blunted with age. This is similar to the pattern of response in a large human population where baroreceptor deactivation was produced with external neck pressure.[4] The complexities of this response and their alterations with age remain a subject of continued debate and evaluation.

Sympathetic Activity

We know from animal studies that sympathetic innervation of the myocardium is immature at birth and increases in the first months of life with an ingrowth of nerves from the base to the ventricular apex (Fig. 2).[32-34] This process repeats itself after heart transplantation.[35] Recently, we evaluated the ^{123}I-MIBG uptake in 41 children ages 3 months to 19 years who had studies for neuroblastoma evaluation, without tumor uptake, and without known heart disease. We found a steady

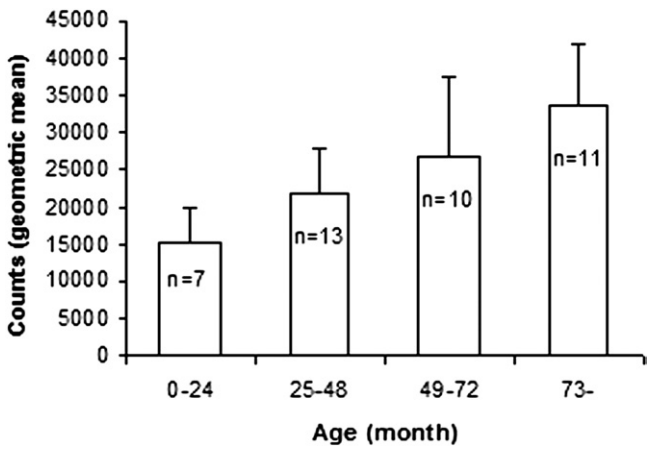

Figure 3 Myocardial sympathetic activity in children: geometric mean of ^{123}I MIBG counts calculated in studies of 41 children with normal MIBG images performed for clinical indications. Findings suggest continued increase in sympathetic innervation and activity in early years.

Table 1 Imaging Modalities Used For Assessment of Human Atherosclerotic Plaque

Imaging Modality	% Stenosis	Wall	Lipid	Fibrosis	Thrombus	Macrophage (Inflammation)	Ca^{++}	Apoptosis
Invasive methods								
Selective coronary angiography	++++	–	–	–	+	–	++	–
IVUS	++++	+++	++	++	++	–	++	–
OCT	+	+	+	+	+	–	+	–
Thermography	–	–	–	–	–	+	–	–
Noninvasive methods								
US	–	–	–	–	–	–	+	–
MRI	+	+++	+++	+++	++	–	++	–
EBCT/MSCT Coronary Ca^{++} Score (CACS)	–	–	–	–	–	–	++	–
CT coronary angiography (CTCA)	+++	+++	++	++	++	–	++	–
Scintigraphy	–	–	+	+	++	++	–	++

Relative advantages of each imaging modality used for assessment of human atherosclerotic plaque are shown. The findings may be extrapolated to other applications, and are generally determined by physical characteristics and biological "fit" of each imaging method.
Ability to image pathology noted expressed on scale of 1-4, where – = unable to image or not studied.
EBCT, electron beam computed tomography; IVUS, intravascular ultrasound; MRI, magnetic resonance imaging; MSCT, multislice computed tomography; OCT, optical coherence tomography; US, ultrasound.
Adapted and reprinted from Davies et al,[75] with permission from the American Society of Nuclear Cardiology.

increase in ^{123}I-MIBG uptake, measured as the total geometric mean counts, during these early years (Fig. 3). However, this data must be normalized to mediastinal activity as is the standard. Cardiopulmonary vagal efferent reflexes are blunted with age. This may relate only in part to altered neuroresponsiveness, with reduced sensitivity caused by intrinsic changes in wall stiffness.[36] The parasympathetic limb of the reflex arc has been studied in many ways, all demonstrating an age related blunting of the effector response. However, it remains unclear as to whether this blunting is caused by a change in vagal discharge to the sinus node or a suppression of the intrinsic cardiac pacemaker function. Yet, experiments stimulating the vagal input demonstrated a greater sensitivity and a paradoxically greater slowing in elderly rats compared with younger rats,[31] and the mechanism of age-related alterations in neurogenic cardiac control remain unclear. Although the central mechanism is unclear,[37,38] circulating levels of norepinephrine are increased with age,[39] as is sympathetic activity. This is similar to the pattern seen in chronic hypertension and may be a cause of the reduced vagal efferent activity with suppression of the cardiac baroreflex with less effect on the neurogenic control of peripheral vessels. The increased sympathetic activity also increases vascular tone and contributes to increased arterial stiffness.[40]

Circulatory Effects

The age-related vascular and reflex changes could have important effects on the maintenance of normal circulatory function and its responses. With age, the vasculature is increasingly unable to respond to the demands of stress in the setting of sympathetic neurodegeneration, further altering the cardiac stress response and requiring compensatory adjustments.[41,42] With increasing age, there is a slowing of blood pressure responses to physiologic variations in volume, position, activity, emotion and other factors, based on the sluggish baroreceptor response noted above. This reduces the ability of the vasculature to adjust to neural activity and provide appropriate vascular tone. This could lead to increased blood pressure lability with reduced heart rate variability and a greater incidence of postural and postprandial hypotension, intolerance to volume shifts, temperature variations, and blood pressure spikes that are classically seen in the elderly. Reduced heart rate variability and the altered neurologic activity in the elderly may also predispose them to arrhythmia. Interestingly, exercise appears to reverse or delay many of the age related changes noted above.[42,43]

Cardiopulmonary Reflexes

Definition and Description. Ferrari and coworkers[4] reported blunting of the hemodynamic and humoral aspects of the cardiopulmonary reflexes in the aged.[44] It remains unclear whether this is caused by an altered modulation of sympathetic activity by the cardiopulmonary receptor or by reduced peripheral vascular responsiveness to neural stimuli.[45]

Circulatory Effects. These reflexes influence plasma renin activity and related renal function and could be quite important in the elderly subject with reduced ability to manage fluid and electrolytes. Their alteration could lead to an increased tendency toward dehydration with diuretic sensitivity in the elderly.

Further characterization of the alterations of aging is needed, particularly of the underlying mechanisms and relationships to recognized pathology and disease entities. We need to identify the tendency of these traits to be transmitted in the genetic structure in an effort to influence that transmission or manage those with the greatest predisposition. Most critically, we need to determine whether these changes are amenable to treatment by alteration of environment or

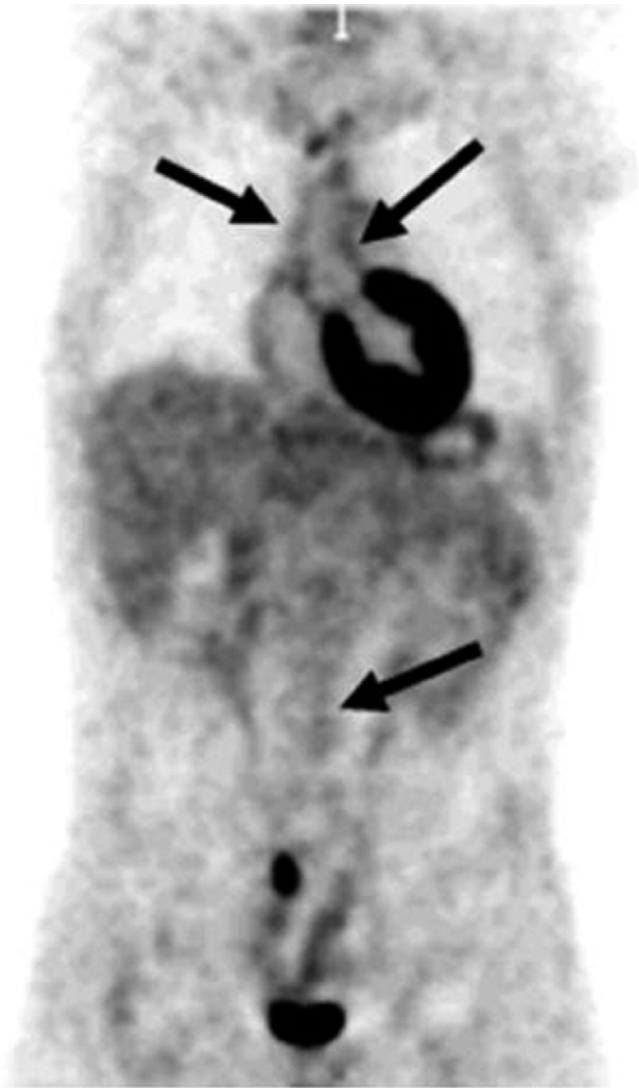

Figure 4 Aortic FDG activity. There is visible FDG uptake in walls of ascending and abdominal aorta (arrows) in this 23-year-old patient. Mean SUVs for ascending aorta were 1.3 and 1.2 for the abdominal aorta. (Reprinted with permission.[62])

behaviors, or with the implementation of medical treatment because diet control, weight control, activity level, smoking cessation, and medical alterations in lipid metabolism and the renin-angiotensin system appear to favorably influence vascular structure, potentially providing plaque stability, reversal of vascular remodeling, and plaque regression, as well as improvement of vascular function with improved vasoreactivity and potentially increased longevity.[42,43,46]

Advanced Imaging Methods for the Evaluation of Aging: The Second Aging Information Spike

The Contributions of CT and MRI

Virtually every aspect and advantage of each imaging method can be applied to assess one or another of the varied aspects of age-related changes. The use of MRI and CT has developed strongly, and they are now practical tools in clinical cardiology (Table 1). Beyond other methods, they provide exquisite anatomic resolution in the assessment of congenital heart disease; supply important anatomic information required by cardiac electrophysiologists regarding atrial anatomy, cardiac veins, and the composition of the right ventricle; provide structural evaluation of pericardial disease; and most recently provide an evaluation of the coronary anatomy. Specifically, CT coronary angiography is being heralded as a possible method for noninvasive clinical coronary evaluation. The evaluation of "soft plaques" by this method promises some insight into the pathophysiology of atherosclerosis, coronary disease, and related events. The identification and quantification, using CT, of vascular and coronary calcification as the coronary calcium score has been correlated with age and has been heralded as an early indicator of atherosclerosis.[47] This measurement, initially developed for the electron beam CT scanner, can be as accurately calculated with the current generation of multislice CT scanners. Not yet approved for clinical indications because of relatively broad diagnostic and prognostic variation, the method has been advocated as a tool to assess coronary related risk and to guide therapy, both in symptomatic as well as in the roughly 53,000,000 asymptomatic individuals at a low but finite coronary risk. However, radiographic methods, in general, provide little pathophysiologic or functional data. This method promises a refinement in measurements and can document some of the atherosclerotic and aging related processes. New software and new hardware including dual-energy CT may permit

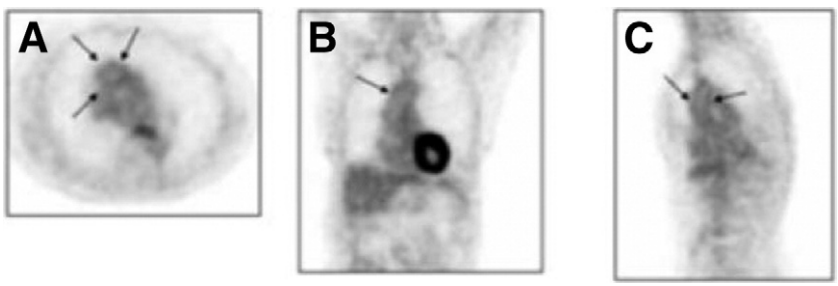

Figure 5 Aortic SUV measurement: the method of SUV measurement is illustrated. Axial image (A) was used to calculate mean SUVs in region indicated (arrows). On sagittal (B) and coronal (C) slices, there is visible FDG uptake in wall of ascending aorta (arrows). Mean SUV in this segment was 2.3. (Reprinted with permission.[62])

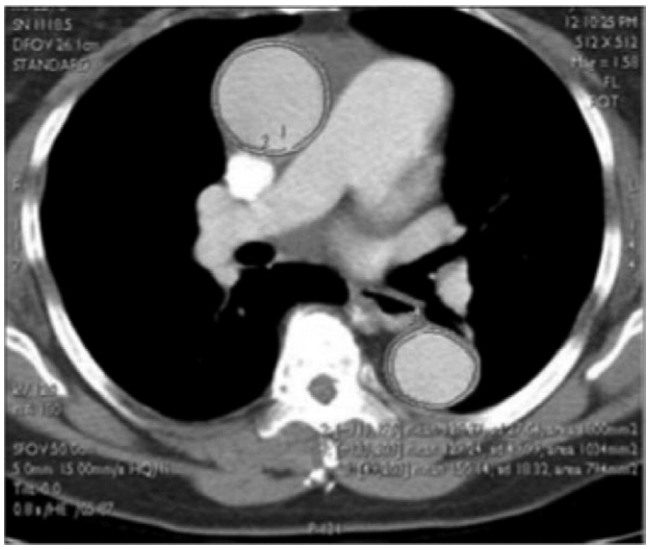

Figure 6 Aortic wall volume calculation. Aortic walls are delineated with a ROI on axial thoracic CT image. Inner ROIs were drawn around the aortic lumen. Outer ROIs were placed on the outer contour of the aortic wall. Net cross-sectional area values were calculated by subtracting the inner from the outer areas. Aortic wall volumes were then calculated by multiplication of area values by slice thickness. (Reprinted with permission.[62])

plaque characterization based on differential attenuations of lipid, fibrous tissue, and calcium.

MRI, with its lack of ionizing radiation, absence of iodinated contrast agents, and high repeatability is a useful imaging method, particularly since it also presents a strong ability to characterize soft tissue and separate lipid, fibrous tissue, calcium and thrombus.[48] Although T2-weighted images best differentiate the plaque collagen cap from the lipid core, a combination of proton density-weighted, T1-weighted, and T2-weighted images best differentiates calcification, hemorrhage, and the necrotic core of carotid plaques.[49,50] Although it has already been applied to determine vascular structure, detect subclinical atherosclerosis in high-risk patients, and help guide therapy in specific subjects, the use of MRI is somewhat limited by technical factors.[51] In particular, although it is robust when applied to study large and stationary vessels and has been applied to determine plaque size, and composition in large arteries,[50,52] MRI of the coronary arteries is somewhat limited by the small size, depth, and motion of the coronary arteries. MRI also has been successfully applied to monitor the vascular effects of lipid-lowering therapy and has demonstrated objective evidence of atherosclerotic regression, something which has been very difficult to prove and harder to demonstrate with angiography.[53,54]

Currently, gadolinium-based contrast agents improve the MRI detection of vascular plaques.[55] To image small plaques, contrast agents must be densely packed with a large amount of contrast material. A variety of novel agents, including ultrasmall particles of iron oxide and gadolinium-based agents that bind low-density lipoprotein (LDL) receptors[56] and high-density lipoprotein (HDL),[57] have been developed for this purpose.[58] Endovascular MRI probes promise to provide exquisite anatomic resolution of atherosclerotic tissue distribution in coronary and other vascular beds currently out of reach. A self-contained MRI probe has been designed for the direct visualization of atherosclerotic disease.[51] Current MRI planar resolution of coronary arteries is approximately 0.46 mm with a 2- to 5-mm slice thickness. A catheter-based MRI probe in development promises a cylindrical grid image display with z resolution of 1.5 mm and angular resolution of 60° and a radial resolution of 250 μm.[51] For now, the focus of hybrid systems is focused on PET/CT. However, the combination of MRI with PET, the latter a method to target biologic processes and pathophysiology on the molecular and cellular level, is highly sought after but delayed because of issues related to device compatibility and other technical factors.

A rigorous MRI-based study allowed researchers to quantitate the normal values of LV function and mass,[59] which are critically important for assessment of patients with cardiovascular disease. Among 800 randomly selected subjects without known major cardiac risk factors, there were significant differences in LV volume and mass (both $P < 0.05$) between men and women, where volumes, excluding LV end-systolic volume index, were generally inversely related to age. LV mass was inversely related to age in men but was not associated with age when corrected for body surface area. Neither LV mass nor LV mass index was related to age in women. LV mass was largest in black men (181.6 ± 35.8 g) and women (128.8 ± 28.1 g) and was smallest for Asian-American men (129.1 ± 20.0 g) and women (89.4 ± 13.3 g). Does this data conflict with earlier findings?

The Contributions of PET

The improved spatial resolution and functional localization of PET radiotracers provides great potential to add insight into a variety of biological processes related to aging. In comparison with other imaging techniques, PET is a quantitative imaging method with the potential to measure the concentration of the radiotracer in tissue, linking anatomy with biology and biochemistry and identifying pathophysiology from nascent to advanced stages with very high sensitivity. PET images, now acquired with CT images, permit more exact localization and quantitation of radiotracer uptake to

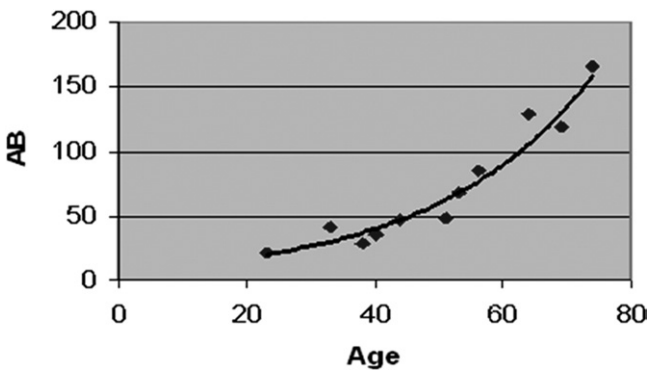

Figure 7 Relationship of AB with age. An exponential relationship of AB (units of SUV per milliliter) with age is shown. (Reprinted with permission.[62])

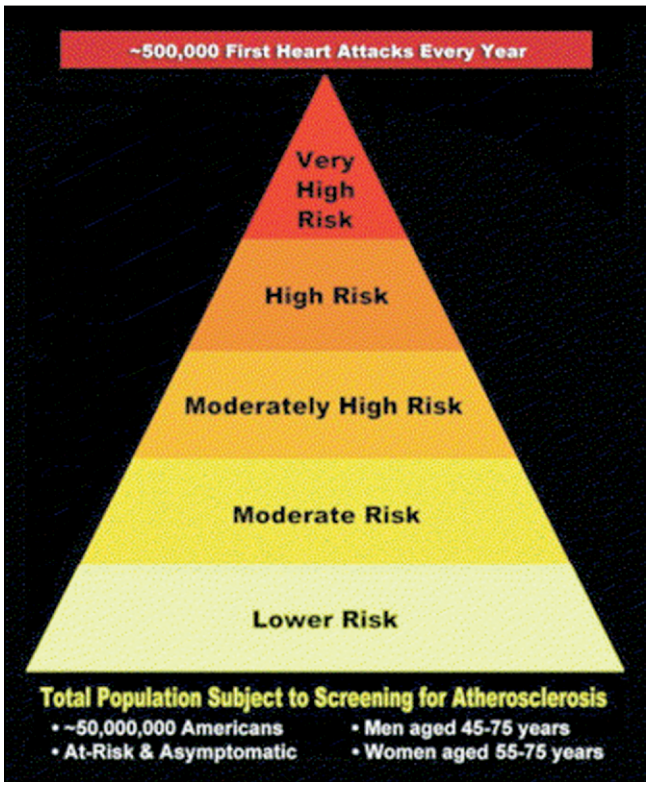

Figure 8 Searching for the vulnerable patient: this "pyramid" plots numbers of patients at risk for coronary events in ascending order of risk. Those at the apex are those with significant symptomatic coronary stenoses and greatest related risk for myocardial infarction and death. The largest population, at the pyramid base, has the smallest risk but largest numbers. There are 53,000,000 asymptomatic people with low-but-increased risk for coronary events. It is this population that contributes the greatest number of patients with events. There is a great need to develop methods to identify those within this population who are at greatest risk for these relatively rare, but devastating, events. Hence, methods to identify the "vulnerable" plaque and the "vulnerable" patient could make a great impact. (Reprinted with permission.[65]) (Color version of figure is available online.)

specific structures of the whole body. Specifically, ^{18}F-fluorodeoxyglucose (FDG) is transported across cell membranes by glucose transporters, is phosphorylated by hexokinase in the first step of the glycolytic pathway, and becomes trapped in cells in proportion to cellular metabolic activity. It serves as a competitive substrate and imaging marker for glucose, the major metabolite of the myocardium, and provides an in vivo map of glucose utilization, a surrogate for glycolytic rate throughout the body, a process that may be amplified with ischemia, inflammation, and malignancy and preserved with myocardial viability. In atherosclerotic plaque, FDG localizes primarily in macrophages[60] in proportion to their number.[61]

Bural and coworkers[62] in our laboratory developed a method to quantify the extent of atherosclerosis in the aorta. Four matched aortic segments were selected in 18 patients with age spanning 6 decades, on both FDG-PET and CT of the chest and abdomen. All CT studies were contrast enhanced, permitting visualization and measurement of aortic wall thickness. Inner and outer wall contours of the aortic wall were generated on each axial CT image and related wall areas were measured. Net aortic wall areas were multiplied by the slice thickness to calculate the aortic wall volume for each segment. FDG activity was homogeneous in each segment. The products of aortic wall volumes and mean standard uptake values (SUVs) were calculated for each segment and called the "atherosclerotic burden" or "atheroburden" (AB) values as means of integrating structural and functional data into single quantitative values (Figs. 4-6).[62] Aortic wall volumes, mean SUVs, and ABs in each segment were compared in 3 age groups spanning the population. The volume, SUVs, and ABs in each aortic segment increased linearly with age and, in this small population, demonstrated statistically significant differences in segmental mean SUV between age groups 21 to 40 and 61 to 80 as well as between ages 41 to 60 and 61 to 80. Similar age group differences were found for segmental ABs as well as significant differences in ABs between each age group over the entire aorta. Interestingly, the age related progression in mean SUV and volume appeared linear whereas the progression of AB with age appeared exponential (Fig. 7),[62] suggesting a major escalation in the atherosclerotic process with increasing age.

Imaging of the Vulnerable Plaque: A Pathologic Correlate of Aging

Overview

The clinical course of atherosclerosis is punctuated by events based in the instability of the related vascular plaque. If not themselves the early stages of atherosclerosis, the changes related to aging clearly parallel and mimic those early atherosclerotic changes. Again, age-related changes provide an un-

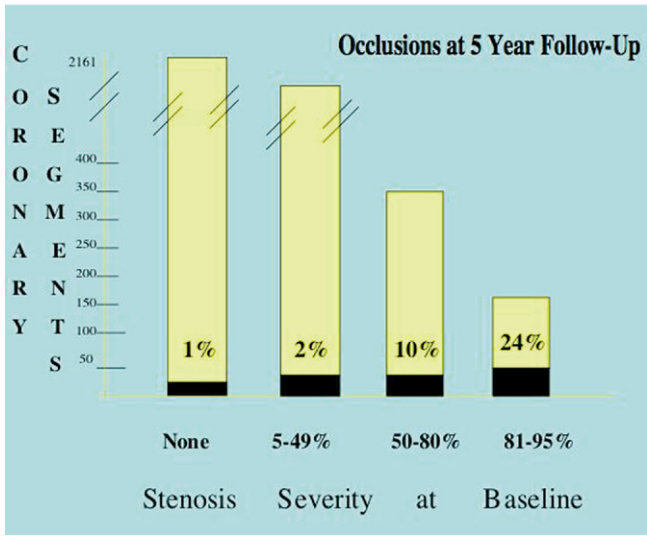

Figure 9 Frequency of coronary occlusion related to percentage baseline stenosis. Analyzed quantitatively on a vessel-by-vessel basis, the likelihood of event precipitated by occlusion of a tightly stenotic vessel far exceeds that related to occlusion of more numerous insignificantly stenotic vessels. (Adapted and reprinted with permission from the American College of Cardiology Foundation.[66]) (Color version of figure is available online.)

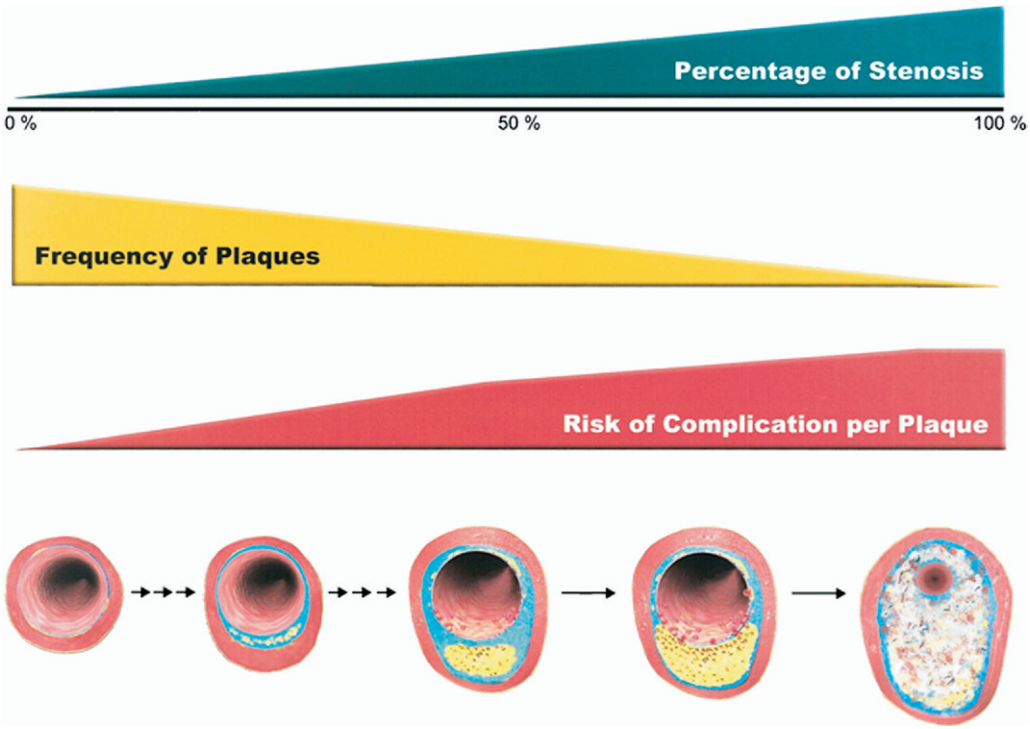

Figure 10 Plaque stenosis severity, frequency, and complication risk. Correlation between the frequency of plaque with given degree of stenosis and the risk of complication as a function of plaque progression. Although average absolute risk of severely stenotic plaques may be greater than the average absolute risk of mildly stenotic plaques, there are more mildly stenotic plaques and thus many more related events. Detection of non- or mildly stenotic plaques at risk is difficult at present. (Reprinted with permission.[67])

fortunate "leg up" for pathology and increases the probability of atherosclerosis. The pathology of the atherosclerotic plaque, in all of its vascular domains, has always been related to the expanded or "ruptured" plaque, which is associated with clinical events via its stenotic and obstructive nature. Here, rupture of the plaque "cap" removes the protective endothelial wall with exposure of the underlying thrombogenic components to circulating blood clotting elements and factors. In the coronary circulation, flow-limiting stenosis would relate to anginal chest pain whereas thrombosis would be the underlying cause of acute myocardial infarction and death. This focus places the coronary event at a time far removed from the changes of aging, which, by definition, do not extend to vascular narrowing and obstruction. Thus, there is focus on methods to identify the presence, severity, and extent of flow limiting coronary lesions with stress testing, single photon emission computed tomography (SPECT)/PET perfusion scintigraphy, stress echocardiography, and invasive coronary angiography and interest in applying CT and MRI with stress and performing coronary CT angiography. Although these methods have been quite successful, now more than ever it is recognized that although those with flow limiting stenoses bear the greatest individual coronary risk, the greatest number of patients suffering coronary events and related death derive from the large population with nonflow limiting atheromatous plaques (Figs. 8-10).[63-67]

The risk related to plaque rupture relates to plaque location and the amount of myocardium subtended, as well as lumen diameter, percent stenosis, and blood and myocardial characteristics. In addition, the likelihood of plaque rupture depends more on plaque composition and activity, ie, vulnerable plaque, the culprit responsible for the morbidity and mortality of the majority of those asymptomatic patients who suffer unexpected infarction and/or death. Vulnerable plaque frequently bears a thin necrotic cap, is rich in lipids, inflammatory cells, matrix metalloproteinases, and other inflammatory products, with a reduced component of smooth muscle cells (Figs. 11 and 12).[67,68]

Pathophysiology Determines the Imaging Targets

The vascular pathology of atherosclerosis presents an admixture of fatty deposits, connective tissue, and inflammatory cells. The vessel wall thickens as fat-laden macrophages engorge the intima with and cellular elements lead to fibrous deposition, vessel expansion, and deformity (remodeling) while initially preserving luminal diameter.[69] These findings are not dissimilar to those findings attributed to age alone. An "age-related " progression of coronary and aortic calcification[70] as well as a direct relationship between calcium accumulation, coronary artery disease and related risk, and peripheral vascular disease, have been established. FDG accumulation, either as the result of inflammation or other cellular activity, can potentially detect an earlier stage in the process, which likely relates to atherogenesis, coronary and other vascular disease, and related risk, and potentially serve as a biomarker for progression and regression with appropri-

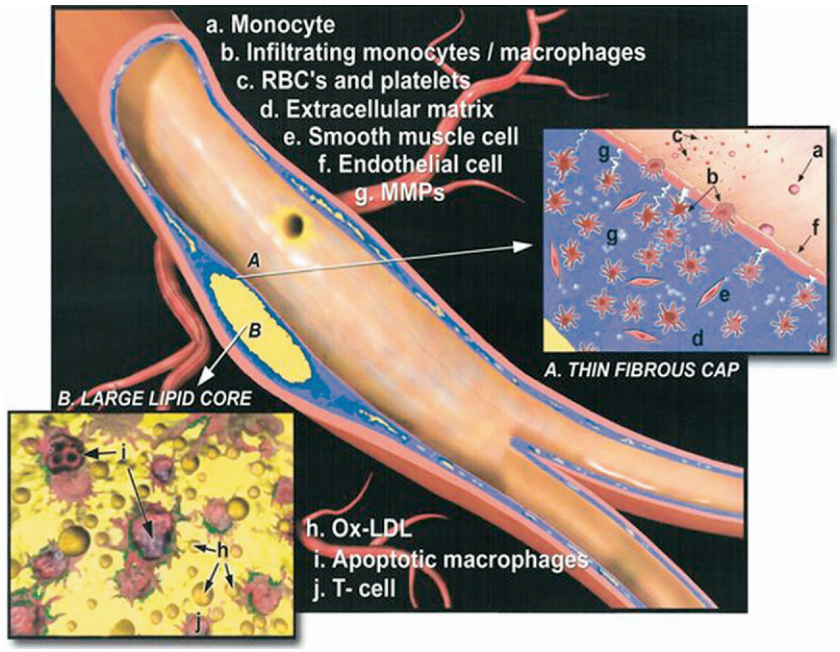

Figure 11 The "vulnerable plaque." Shown are the most common features of the vulnerable plaque, including its thin fibrous cap, extensive infiltration by macrophages, sparcity of smooth muscle cells, and large lipid core. Note, at this stage of development, a lack of luminal narrowing. Calcification could also occur before narrowing, presenting a discrepancy between atherosclerotic pathology and pathophysiology. MMP, matrix metalloproteinases; Ox-LDL, oxidized LDL. (Reprinted with permission.[67])

ate intervention. The development and evolution of atherosclerotic vascular changes during aging may provide clues to the onset and control of atherosclerosis.

Initially, endothelial cell dysfunction permits cholesterol-rich LDL to infiltrate the vascular intimal layer, where it is oxidized and acts as an inflammatory focus.[71] Circulating monocytes are then targeted to endothelial adhesion molecules of the intimal layer.[72] Here, they are transformed into scavenger macrophages and take up the oxidized LDL to become "foam" cells. These macrophages, and less frequently

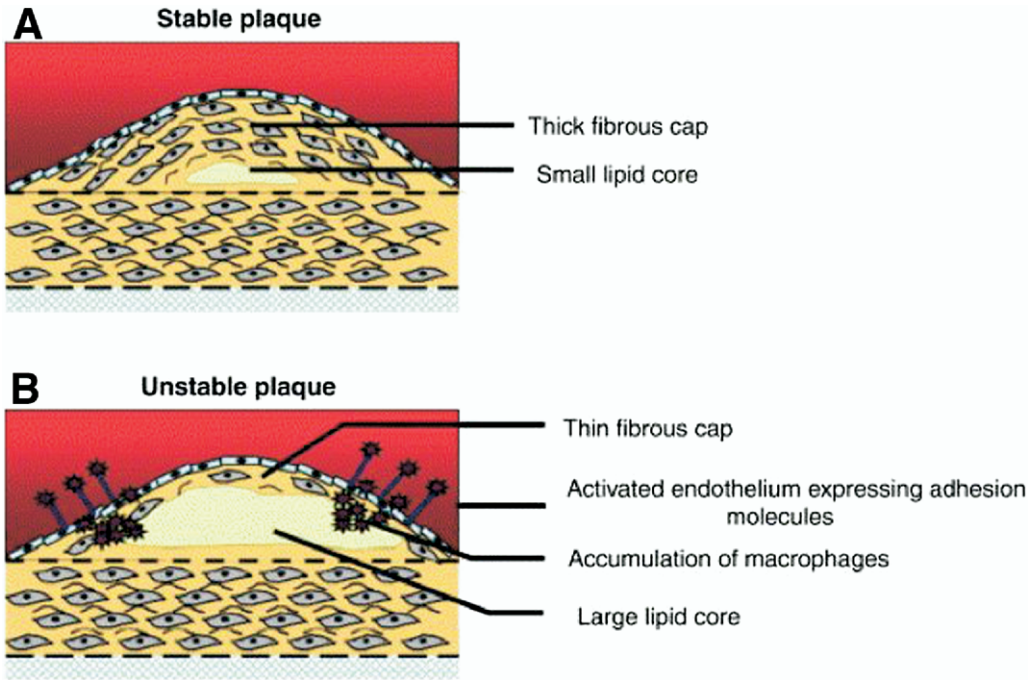

Figure 12 Structure of stable and unstable "vulnerable" plaques: characteristic features of stable (A) and unstable (B) plaques. (Reprinted with permission.[67])

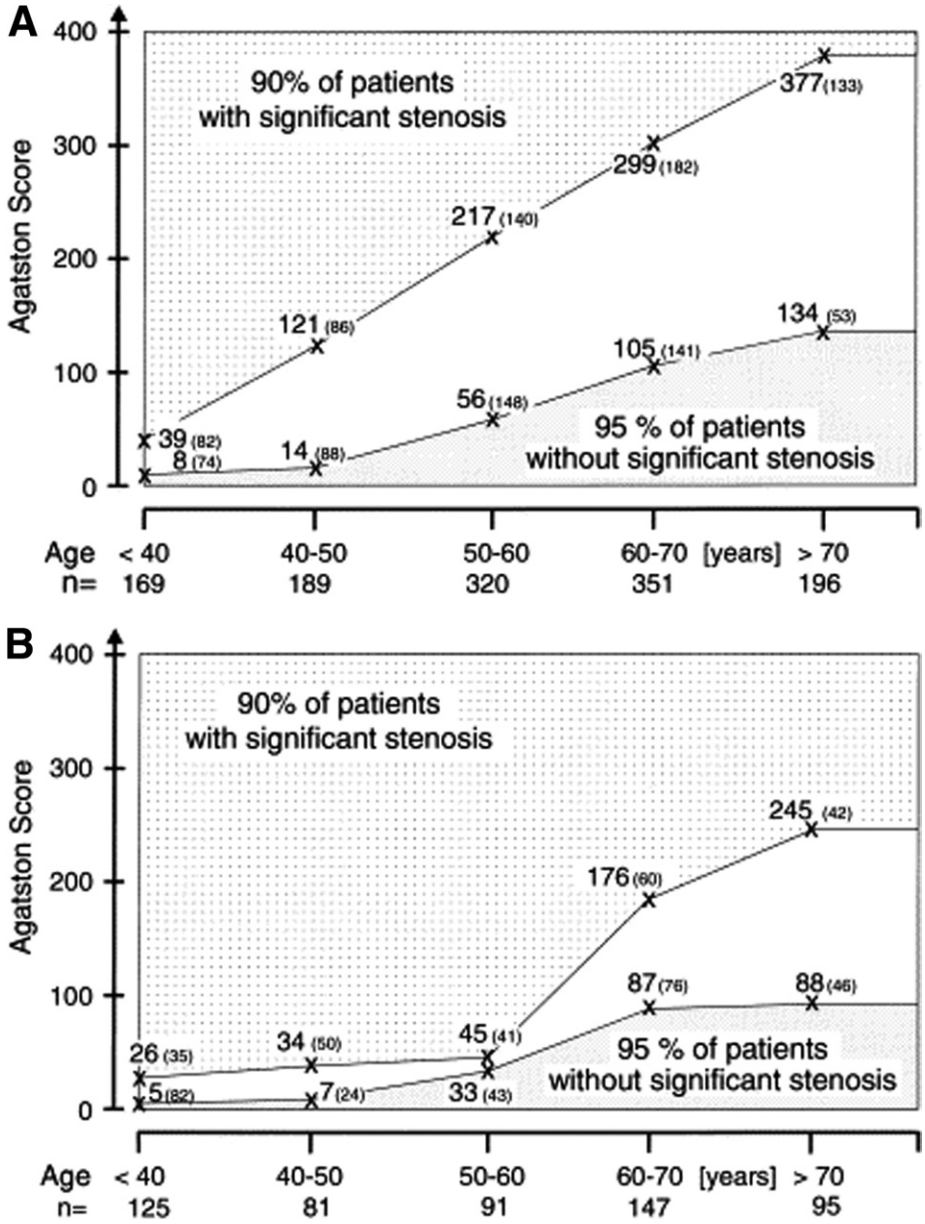

Figure 13 Age-related diagnostic yield of calcium screening in symptomatic patients. In a study of 1,764 symptomatic patients who underwent both electron beam computed tomography (EBCT) and coronary angiography, EBCT generated calcium score, an indication of density and extent of calcium deposition, correlated with age and likelihood of coronary disease within broad limits. Shown in (A) and (B) are age related 90% and 95% calcium score thresholds (CST) for men and women, respectively. (Reprinted with permission from the American College of Cardiology Foundation.[47])

lymphocytes, release a variety of proinflammatory materials, accelerating the inflammatory response, and additionally release metalloproteinases, which breakdown the supporting matrix.[73] Cell death and release of cholesterol esters and other products contribute to plaque core formation. Continued inflammation and breakdown of the matrix may then lead to plaque fragility and eventual plaque rupture. Alternatively, macrophage derived cytokines may lead to intimal migration of vascular smooth muscle cells which synthesize extracellular matrix proteins that strengthen and protect the fibrous cap. This balance of inflammatory macrophage and vascular smooth muscle cell activity determines plaque stability and fate.[74] Similarly, the thrombotic effects of plaque rupture, with exposure of the underlying thrombogenic materials, is countered by fibrinolytic elements seeking to prevent thrombus formation.Despite advances in imaging of atherosclerotic plaque, there is currently no imaging method or agent that provides a definitive identification of "vulnerable plaque."[75,76]

Conventional Structural Imaging Techniques of Atherosclerosis

Invasive methods to image atherosclerotic plaques include conventional coronary angiography, intravascular ultrasonography, optical coherence tomography, and thermography. Conventional angiography images the vessel lumen and

not the vessel wall and can detect no atherosclerotic changes in the absence of luminal abnormality. Although the other methods present varying amounts of information regarding components of the vessel wall, only thermography, with the placement of a thermistor adjacent to the plaque, has shown potential for the identification and quantification of its inflammatory component.[77,78] Here, the device senses heat generated from the inflammatory plaque activity, which is greater in unstable plaques. Ultrasonography, CT, and MRI can each image atherosclerotic plaques in large arteries and can define components of the plaque. Conventional ultrasonography is limited by its resolution, operator dependence, and inability to image deep small- to medium-sized vessels, in particular the coronary vessels. The use of intravascular ultrasonography (IVUS) can reveal nonstenotic plaques and provide some differentiation of fatty or soft plaque from fibrous or calcified plaque. In a recent study, the method applied the percent atheroma volume, the most significant IVUS-derived measure of disease change, to document the regression of atherosclerotic plaque with statin therapy.[79] CT permits the quantitation of the volume and distribution of atherosclerotic calcium (Fig. 13),[47] but limited evidence exists directly linking the regional calcium score with plaque vulnerability. CT multislice coronary angiography can visualize "soft plaque" and discriminate plaque components but is hampered by beam hardening artifact in the presence of calcium and by issues of resolution, motion, and other artifacts. The method can differentiate fat, fibrous tissue, and calcium components of lesions or arterial walls. MRI is probably best able to differentiate plaque components and image plaque rupture but predominantly in large and medium sized vessels. When applied after the administration of ultrasmall superparamagnetic iron oxide nanoparticles, the use of MRI has the potential ability to image macrophages as a marker for inflammation.[80]

The Importance of Inflammation and the Role of FDG-PET Imaging

The inflammatory nature of atherosclerosis is well recognized.[81] Falk defines atherosclerosis as a "multifocal, smoldering, immunoinflammatory disease of medium-sized and large arteries fueled by lipids."[82] Evidence of active inflammation has been proposed as an important indicator of "the vulnerable [atherosclerotic] plaque" related to greatest atherosclerotic risk, and the related concept of the "vulnerable [coronary] patient" has evolved.[65,67,83]

PET can detect small amounts of radiotracer uptake with very high sensitivity in pathophysiologically important processes in and around atherosclerotic plaque (Fig. 14).[67] However, PET tracers must overcome the difficulties intrinsic to imaging small plaques with accumulations in the vessel wall as well as the labeled blood pool, myocardial wall, and background structures. Tracers with the highest possible sensitivity and specificity for the atheromatous components, with rapid clearance and a high target-to-background ratio are needed, and the imaging instrument must have a high contrast resolution, best accomplished with PET methods. PET also has the greatest number of possible radionuclides to bind with plaque components in an attempt to label specific components.

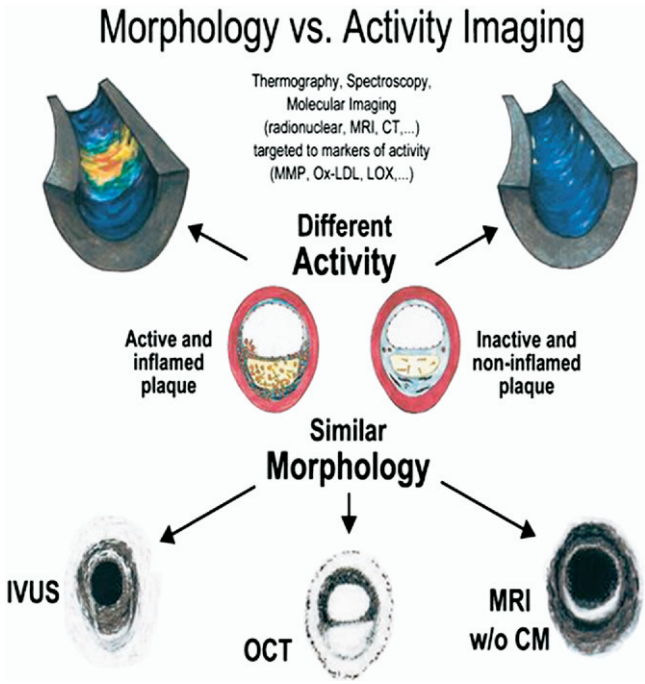

Figure 14 Differences between anatomy and pathophysiology of atherosclerotic plaque identified by imaging. Plaques with similar morphology in terms of lipid core and fibrous cap (middle panel) may look similar with diagnostic imaging aimed at morphology alone (bottom panel) but look very different using diagnostic methods capable of detecting plaque activity and pathophysiology. Top left plaque is hot as evidenced by thermography and FDG uptake, whereas plaque at top right is inactive and detected as cool plaque. (Reprinted with permission.[67])

FDG-PET Vascular Imaging

^{123}I or ^{99m}Tc-labeled autologous LDL has been used in animals and humans to identify the stage of foam cell accumulation.[84] However, the agent has a slow blood clearance, and an agent with better kinetics is needed. Macrophages take up oxidized LDL via the scavenger receptor, and radiolabeled oxidized LDL gives a better target/background ratio than labeled LDL alone with more rapid blood clearance.[85] Imaging of synthetic peptides resembling the apolipoprotein B portion of LDL was performed in the rabbit aorta, and radiolabeled antibodies to portions of LDL appear to relate to avid, high level uptake. However, signal-to-noise ratios were somewhat suboptimal and toxic effects were evident.[62] With the imaging of radiolabeled monocytes, an attempt is made to image the actual macrophage cellular component responsible for plaque rupture.[86] The peptides that recruit and attract these cells to the vessel wall also have been labeled and imaged in postmortem specimens.[87]

Similarly, matrix metalloproteinase (MMP) and MMP inhibitors have been radiolabeled and imaged in a small animal model (Fig. 15).[76,88] Apoptotic vascular smooth muscle cells, as might be found in the cap of a "vulnerable plaque," express

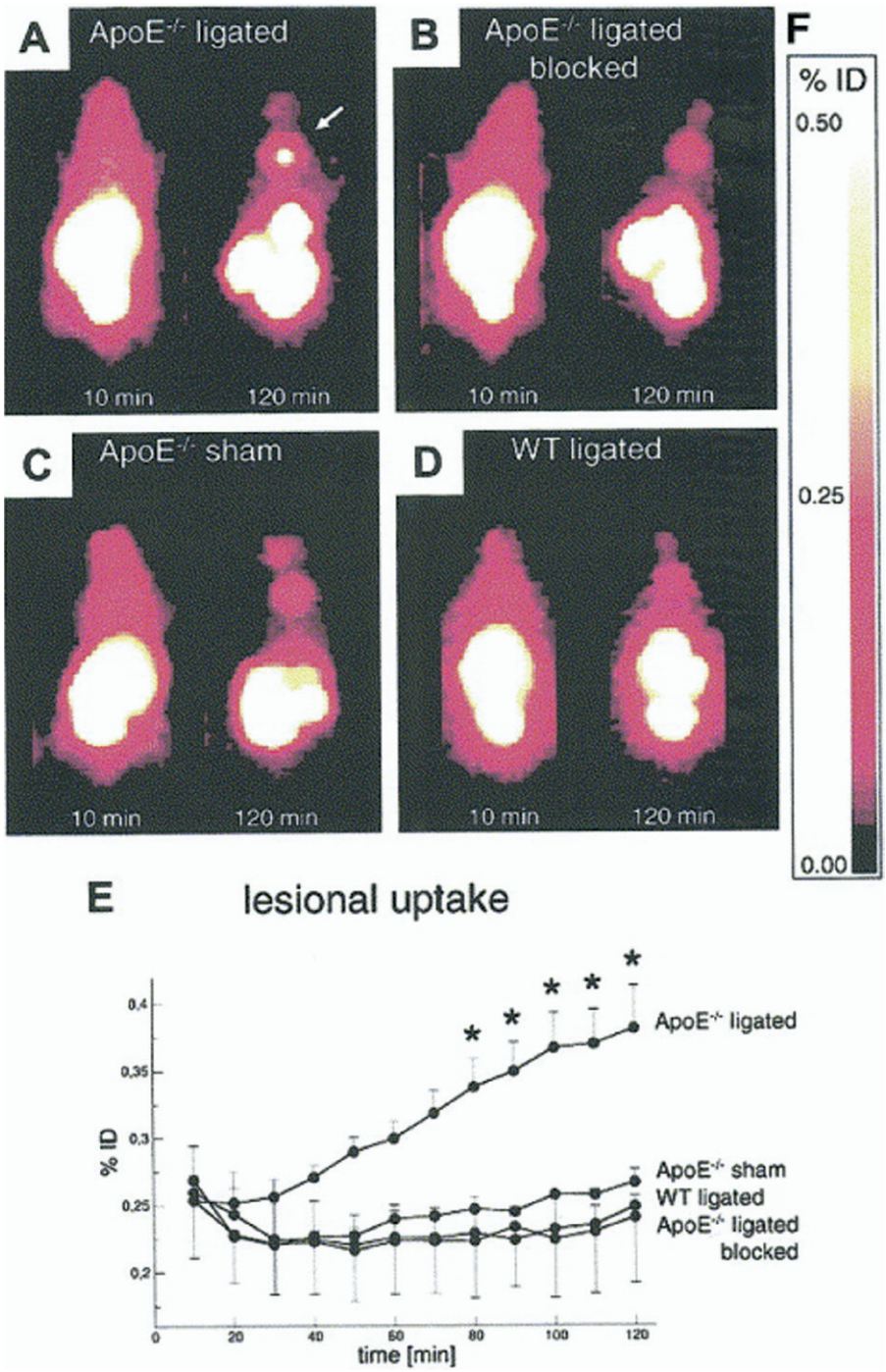

Figure 15 MMP uptake in plaque. In vivo SPECT imaging and quantitation of MMP activity in experimental carotid lesions in mice with tracer ^{123}I-HO-CGS-27023A is shown. Apolipoprotein E (ApoE) is a member of a family of soluble lipoproteins that interacts with LDL receptors, providing key role in lipid transport. Representative planar images taken 10 minutes (left) and 120 minutes (right) after injection in (A–C) ApoE-deficient (ApoE−/−) mice and (D) wild-type (WT) mice 4 weeks after carotid ligation: (A) unblocked; (B) after predosing with 6 mmol/l ^{123}I-HO-CGS-27023A; (C) sham operated; (D) WT; (E) quantitative uptake of radioligand in carotid lesion; and (F) tissue uptake over time expressed as percent injected dose. Predosing with unlabeled ligand prevented uptake indicating a high level of specific activity. There was a significant difference between unblocked and predosed lesional uptake, and tracer uptake into lesioned carotid arteries was significantly higher than in normal arterial tissue from the contralateral carotid artery or in carotid arteries from sham and control mice. Uptake in abdominal cavity is nonspecific and probably reflects the metabolism of the original compound as there is no inhibition after predosing in all experiments. (Reprinted with permission from the American College of Cardiology Foundation.[76])

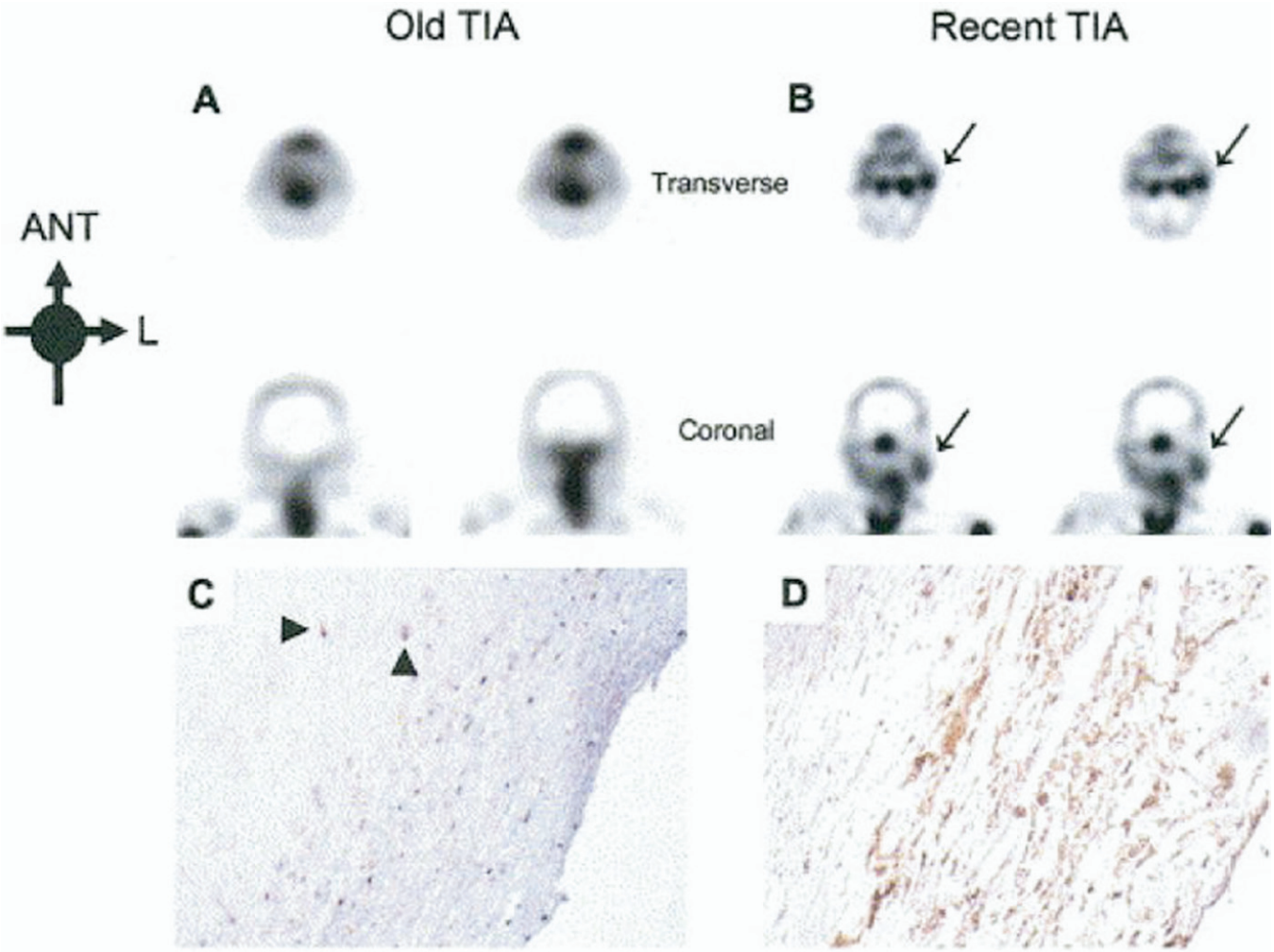

Figure 16 Annexin labeling of atherosclerotic plaque. SPECT images of "unstable" atherosclerotic carotid artery lesions obtained with ^{99m}Tc annexin A5 are shown. (A) SPECT images of a patient who had right-sided transient ischemic attack (TIA) 3 months earlier do not show annexin A5 uptake in carotid region on either side. Doppler ultrasonography revealed a hemodynamically significant obstructive lesion on the affected side. (B) SPECT in second patient with left-sided TIA 3 days earlier. There was significant stenosis of both arteries. However, the uptake of ^{99m}Tc annexin A5 is evident only in the culprit lesion (arrows). Histopathologic analysis of endarterectomy specimen from first patient (C) shows lesion rich in smooth muscle cells with negligible binding of annexin A5. Histopathology of endarterectomy specimen from second patient (D) stained with antiannexin A5 antibody shows substantial infiltration of macrophages into neointima with extensive binding of annexin A5 (brown staining). (Reprinted with permission.[89])

phosphatidyl serine on their surface, and radiolabeled annexin V with ^{99m}Tc has a high affinity for phosphatidyl serine expressed on cell surfaces (Fig. 16).[75,89] The agent had 10 times greater uptake in atheromatous than nonatheromatous aortic walls, correlating with plaque pathology in aortic plaques of rabbits.[90] Annexin V has been applied, as well, to image the plaque in human carotid arteries with uptake present only in lesions in symptomatic patients. The amount of radiotracer plaque localization correlated with the macrophage content of the plaque and was absent in smooth muscle dominant plaques.[89] Annexin V also has recently been radiolabeled and imaged with isotopes ^{18}F and ^{124}I. Unlike other agents for plaque imaging, annexin V is not taken up by the normal myocardium or vasculature and can be used for coronary plaque evaluation. Endothelin 1 is a cytokine involved in vascular tone and mitogenesis whose biologic effects are mediated through membrane receptors. Most recently, endothelin 1 receptors have been radiolabeled with ^{18}F and show promise as a PET imaging agent for atherosclerotic plaque.[91] There are also evolving scintigraphic methods to image thrombus.

As a more specific agent to image the atherosclerotic process, Zhang and coworkers[92] were the first to show adequate FDG localization in macrophage rich atherosclerotic lesions to permit imaging by conventional PET scanners (Fig. 17).[93] In a series of 156 patients with FDG-PET studies for oncologic evaluation, we found that roughly 50% were seen to have increased FDG uptake in the walls of large arteries.

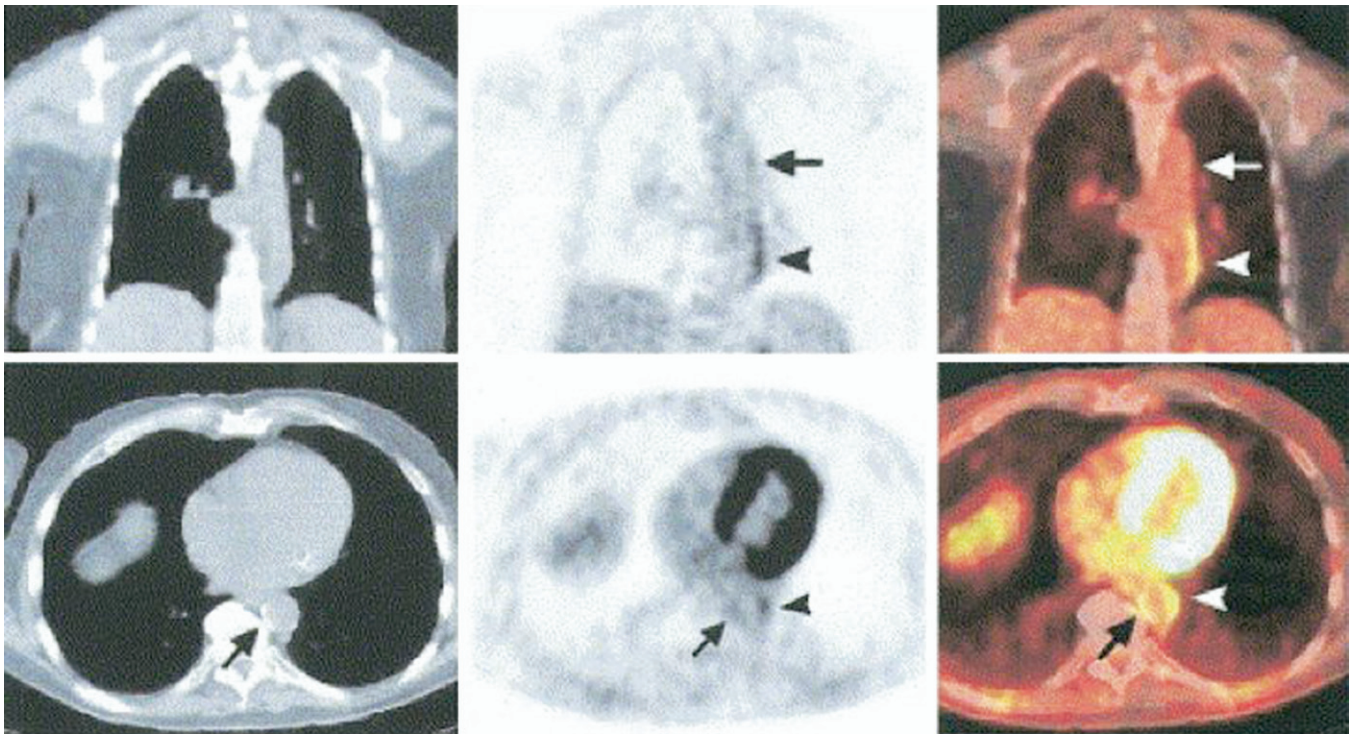

Figure 17 Visualization of aortic atheroma on PET/CT. PET and CT images acquired after administration of FDG in patients with aortic atheroma. Top row: coronal CT (left), FDG-PET (middle), and fused PET/CT images (right). There is no calcium present in the aortic wall on CT. On PET and fused images, mild (arrows) and moderate (arrowheads) grades of FDG uptake are seen in the aortic wall. Bottom row: axial CT (left), FDG-PET (middle), and fused PET/CT images (right). CT image shows calcification on the right side of the descending aortic wall (arrows), which on PET and fused images demonstrate mild (arrows) uptake indicating mild inflammation. Higher level FDG activity is also seen on the left side of the descending aortic wall (arrowheads) indicating a higher level of inflammation in this segment of noncalcified vessel wall. (Reprinted with permission.[93])

These patients had a much higher incidence of coronary risk factors compared with those without increased FDG.[94] Interestingly, age was the factor which best correlated with vascular FDG activity.

Rudd and coworkers used autoradiography to demonstrate localization of tritiated glucose in macrophages but not in neighboring vascular smooth muscle cells or the remaining aortic mural constituents. These same workers[60] subsequently demonstrated increased FDG accumulation in carotid plaques of symptomatic patients with significantly less uptake in vessels in asymptomatic patients. This and subsequent studies noted below, demonstrate that FDG-PET imaging can potentially measure the inflammatory component in atherosclerotic plaques. Confirmation is presented in a study demonstrating a close correlation between FDG uptake and plaque macrophage content in atherosclerotic rabbits.[61]

FDG appears to accumulate only in those plaques with the most active inflammation. Three studies[95] comparing the amount of vascular calcium on CT compared with FDG uptake in oncology patients demonstrated a major disparity between CT-positive and PET-positive studies. Because calcium indicates the presence of atherosclerosis, the findings suggest that calcium and FDG uptake accumulate at different stages of the atherosclerotic process. Calcium tends to occur with more chronic atherosclerosis, whereas FDG uptake indicates active inflammation, although both may be present simultaneously.

The severity of stenosis of the internal carotid artery is thought to represent the greatest identifiable risk for death or repeat ischemic cerebrovascular event.[96] Endarterectomy reduces this risk by 16% in symptomatic patients but by only 7% in asymptomatic patients. This difference in risk between symptomatic and asymptomatic patients indicates the risk related to factors other than lesion severity.[97] Prior studies have shown that plaque inflammation and specifically the degree of macrophage infiltration are important predictors of plaque rupture and occlusive or embolic events.[98] Macrophages in the vascular plaque will eventually bring about dissolution of the extracellular matrix and apoptosis of the smooth muscle cells that formed it,[99,100] leading to thinning of the fibrous cap and plaque instability with potential plaque rupture.[74] Given the relationship between plaque vulnerability and inflammation,[75,87,101,102] imaging methods that identify active inflammation are sought, and scintigraphic methods to image inflammation in such plaques are under development.[75]

One study evaluated 12 patients with recent transient ischemic attack and severe carotid artery stenoses in the ipsilateral carotid artery who were awaiting endarterectomy of the most severely stenotic lesion.[102] A semiquantitative method was applied to the identification and quantitation of all ca-

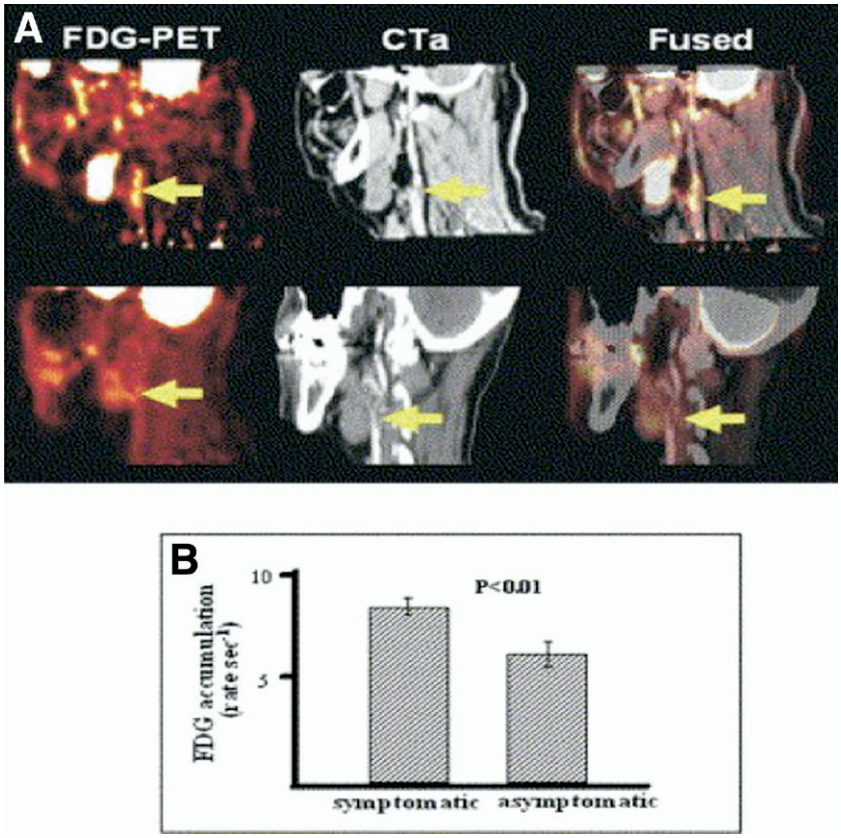

Figure 18 Symptomatic versus asymptomatic stenotic plaque. (A) FDG-PET (left column), CT angiography (middle column), and fused PET/CT (right column) images from patient with symptomatic carotid stenosis (top row) and contralateral asymptomatic carotid stenosis (bottom row) are shown. Arrows in the top row highlight areas of intense FDG uptake corresponding to stenotic plaque. Arrows in the bottom row highlight mild FDG localization in the plaque of the asymptomatic patient. Stenosis does not necessarily imply activity or underlying cause. (B) Graph of FDG activity in active symptomatic and inactive asymptomatic plaques. FDG uptake in symptomatic plaque was significantly higher. (Reprinted with permission from the American Society of Nuclear Cardiology.[75])

rotid plaques by a combination of high resolution magnetic resonance imaging and FDG-PET. Seven of the 12 had high FDG uptake in the lesion targeted for endarterectomy, and 3 of the others had FDG uptake in another less severely stenotic carotid plaque, which nonetheless subtended the vascular region of the embolic event compatible with the patients' symptoms (Figs. 18-20).[75,102] These findings suggest that inflammation as seen by regional FDG uptake may be a valuable marker for the culprit lesion that is more specific than the degree of angiographic stenosis. These same imaging methods to identify inflammation in stenotic and nonstenotic plaques may also be of value in identifying culprit lesions responsible for embolic events.

To determine the relationship between serum markers of atherosclerosis and vascular FDG uptake, Matsunari and coworkers[103] evaluated FDG-PET images, high-sensitivity C-reactive protein (hs-CRP) levels, lipid profiles, and HbA1c levels in 62 volunteers without known cardiovascular, inflammatory, or malignant disease. Peak and mean aortic SUVs were calculated for the most active site in the ascending, arch and descending aorta, and correlated with hs-CRP ($r = 0.66$ and $r = 0.50$, both $P < 0.01$, respectively). Peak segmental hs-CRP levels also correlated significantly with HbA1c and LDL levels ($r = 0.37$, $P < 0.01$ and $r = 0.28$, $P < 0.05$, respectively). Yun and coworkers in our group[94] have presented a correlation between aortic FDG uptake and atherosclerotic risk factors. FDG localization may be a method to link inflammation and atherosclerotic risk, and aid in the identification of the "vulnerable patient." Serial imaging in the same subjects can potentially document the temporal and spatial superimposition of these processes, and has potential to serve as a useful biomarker to monitor therapeutic efficacy for atherosclerosis.

As measured by SUV, FDG localized to a greater degree in the large arteries of diabetics then those of age-matched controls.[104] Such FDG localization likely represents an acceleration of the atherosclerotic process in diabetics in the early decades of life, and this finding is strengthened by our similar findings of increased SUVs in the aortas of hyperlipidemic, nondiabetic patients with normal body habiti, as well as in obese normolipemic patients compared with age-matched controls.[105,106]

In another study,[105] we quantitated the extent of aortic atherosclerosis in terms of aortic AB values in 17 patients ages 24 to 77 years who had PET/CT studies for oncologic indications. The wall areas of 4 aortic segments (ascending, arch,

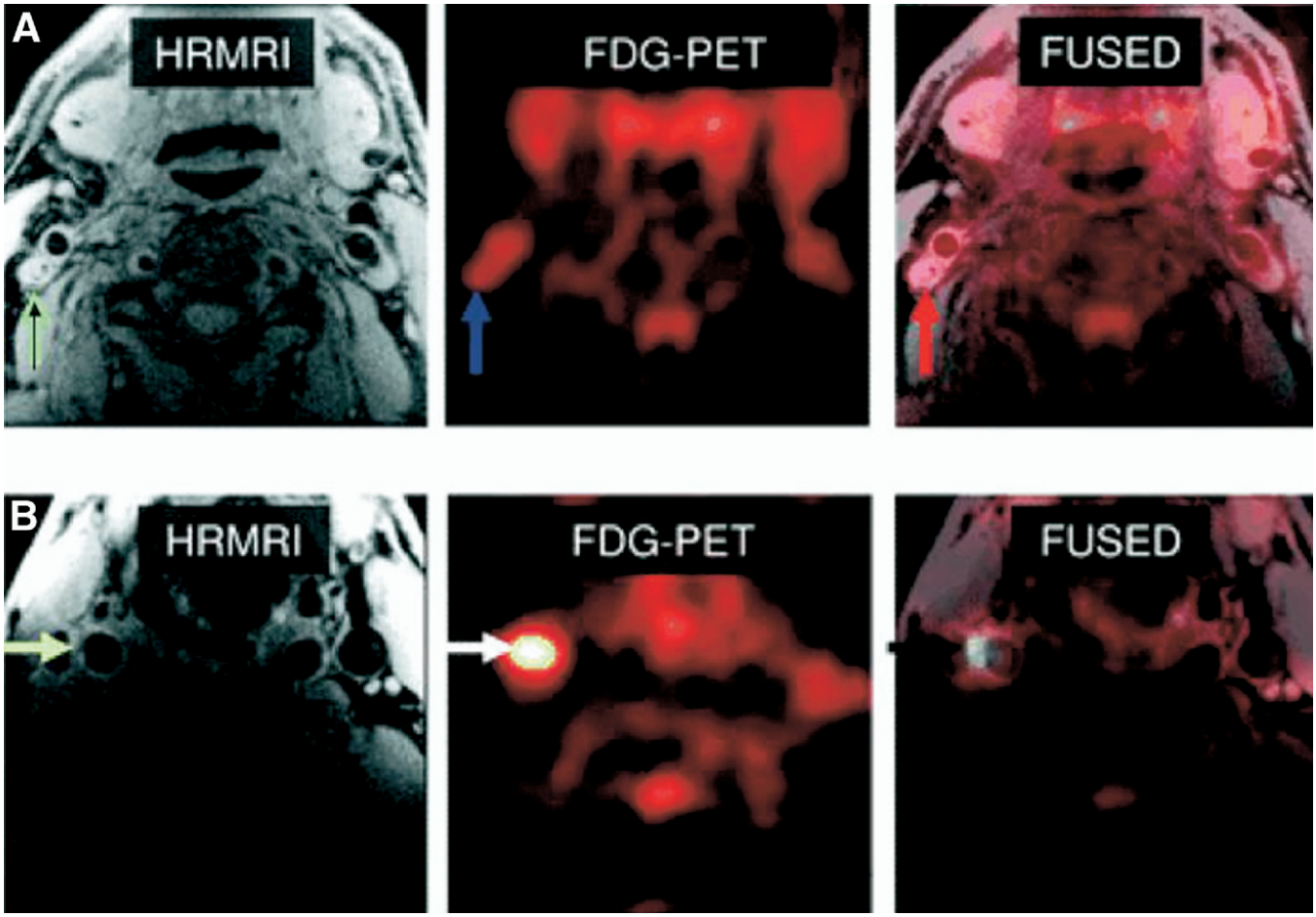

Figure 19 Identification of "vulnerable" carotid plaques. High-resolution MRI and FDG-PET scans in patient with recent right carotid territory stroke. (A) Axial images at the level of the proximal right internal carotid artery (RICA) show large atherosclerotic plaque in the RICA causing severe luminal stenosis (black arrow) with low FDG uptake (blue and red arrows). (B) Axial images at the level of the proximal common carotid arteries (CCA) show nonstenotic plaque (yellow arrow) in the wall of the CCA with associated high FDG uptake (white arrow). Active and "vulnerable" plaque may not necessarily be largest or most stenotic. (Reprinted with permission.[102])

descending, and abdominal) were calculated as net wall areas (calculated by differences between inner and outer aortic wall areas) from CT and were then multiplied by the slice thickness to yield net aortic wall volumes. These were then corrected for the volumes of regional wall calcium seen on CT to yield corrected net aortic wall volumes. Subsequently, these corrected wall volumes were multiplied by the corresponding mean SUVs over each segment. The sum of these values over all aortic segments represented the global metabolic activity or corrected AB of the aorta, which was then compared among 3 age groups (20-40, 41-60, and 61-80 years of age). The degree of correlation of mean SUV with total calcification volume in the entire aorta also was compared in each age group. There was a positive correlation of both aortic calcium and FDG uptake with age ($r = 0.65$ and 0.82, respectively). AB values also increased with increasing age. Although no mural calcium was evident in the youngest age group, the calcification volume measured on CT increased from 1,947 mm^3 in the middle age group to 20,744 mm^3 in the oldest with a positive correlation between age and calcium deposition. The authors concluded that both FDG uptake, representing an early and active atherosclerotic process, and calcification, representing a late and irreversible stage of the disease process, can be well quantified on FDG-PET studies and may allow a more optimal assessment of the atherosclerotic process.

This same group[107] quantitated the background subtracted FDG and methylene diphosphonate (MDP) activity of 40 patients ages 25 to 84 who had both FDG-PET and bone scans within 3 months of each other. Although FDG accumulation is related to inflammation, background subtracted MDP activity is related to calcification. Femoral artery SUV/background ratios increased significantly with age ($P < 0.05$), whereas femoral artery MDP/background ratios increased without statistical significance. The inflammatory atherosclerotic component increased more rapidly with age than did atherosclerotic calcification. However, Lee and coworkers[108] studied serial FDG and calcium distributions in the aorta, carotid arteries, and iliac arteries on serial PET/CT studies performed one year apart in 21 healthy adults with a mean

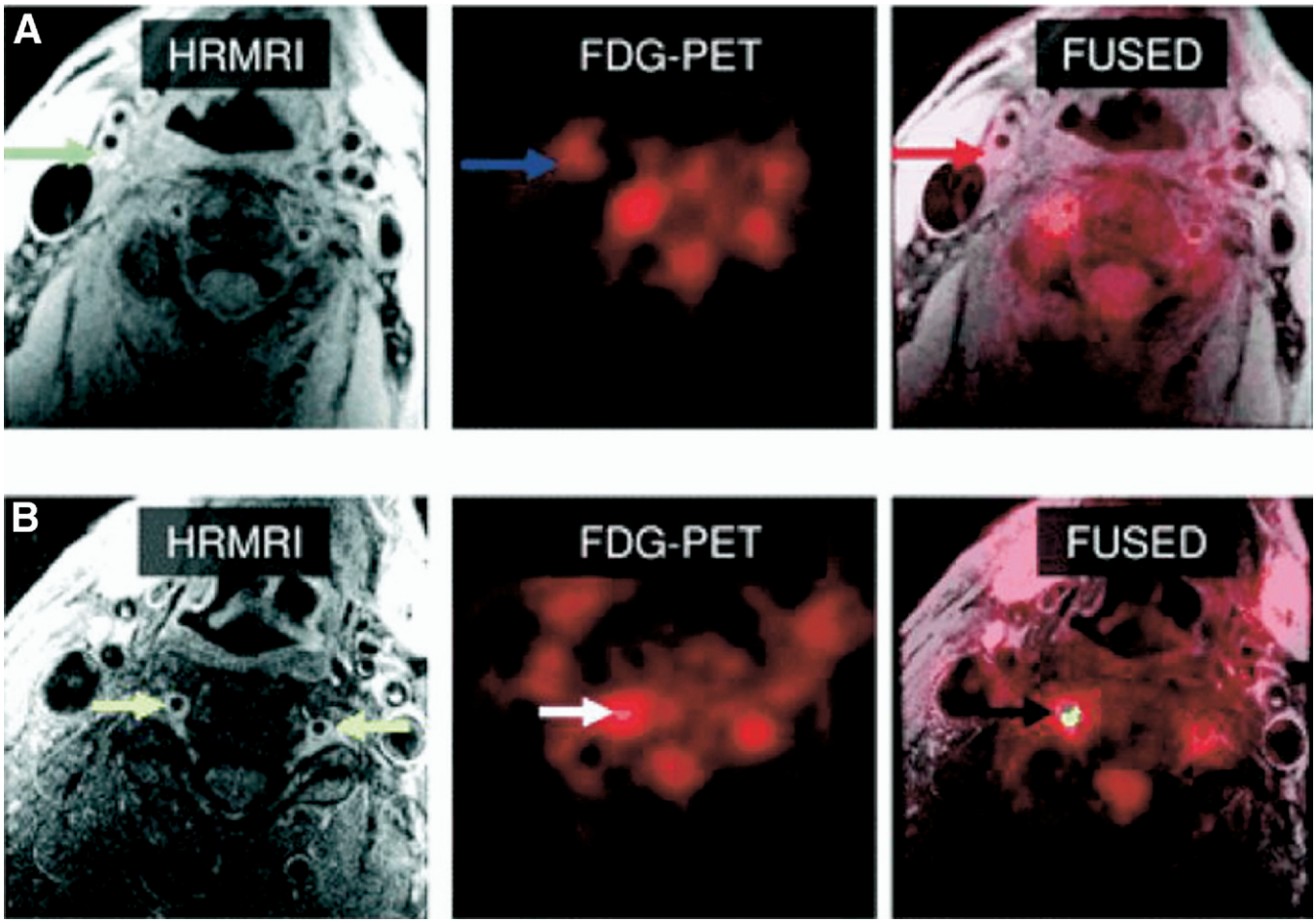

Figure 20 Identification of "vulnerable" carotid plaques. High-resolution MRI and FDG- PET scans in a patient with recent right carotid territory stroke soon after a transient visual disturbance in conjunction with a stenosis of the RICA on conventional angiography are shown. (A) Axial images at a level of the proximal RICA demonstrate RICA plaque targeted for endarterectomy (green arrow). Despite its supposed importance and appropriate location, only low FDG uptake is demonstrated (blue and red arrows). (B) Axial images 3 cm above those in (A). Vertebral arteries (yellow arrows) are well seen. White arrow on FDG-PET image highlights an area of high FDG uptake, which overlies the right vertebral artery on PET/CT image (black arrow). Inflamed vertebral artery plaque may likely be a cause of the patient's symptoms. Active and "vulnerable" plaque may not necessarily be the largest, most stenotic, or even located in the most likely culprit vessel. (Reprinted with permission.[102])

age of 56. In this study, the ratio of peak SUV lesion/peak SUV aortic lumen was measured, and calcification was assessed visually in a qualitative manner. Areas of arterial FDG uptake and calcium deposition were commonly found in these healthy adults, but these regions rarely corresponded to each other, suggesting that they represent somewhat independent components of the atherosclerotic process. The number of sites with calcium deposition increased serially, whereas FDG localization decreased with increasing age, again indicating that regional FDG uptake could be a marker for transient inflammation which occurs early in atherosclerosis, whereas the increase in calcification tends to be a more permanent remnant of the inflammatory process.

FDG PET Myocardial Imaging

In animals, age seems to bring a reduction of myocardial fatty acid metabolism with an increase in glucose metabolism[109,110] There have been few studies of glucose metabolism using quantitative kinetic models specifically focused on the effects of aging in the myocardium. Kates and coworkers[111] studied 36 normal volunteers, 17 subjects ages 26 ± 5 years old and 19 subjects ages 67 ± 5 years old with fasting quantitative PET at rest. Myocardial blood flow, oxygen consumption, myocardial fatty acid utilization and oxidation, as well as glucose utilization were quantitated with PET ^{15}O water, ^{11}C acetate, ^{11}C palmitate, and ^{11}C glucose, respectively. Rates of myocardial fatty acid utilization and oxidation, corrected for myocardial oxygen consumption, were significantly lower in older subjects compared with younger subjects. Although there was no change in the absolute myocardial glucose utilization rate normalized for blood flow, the authors concluded that there is likely a relative increase in the contribution of glucose utilization to total substrate metabolism with increasing age.

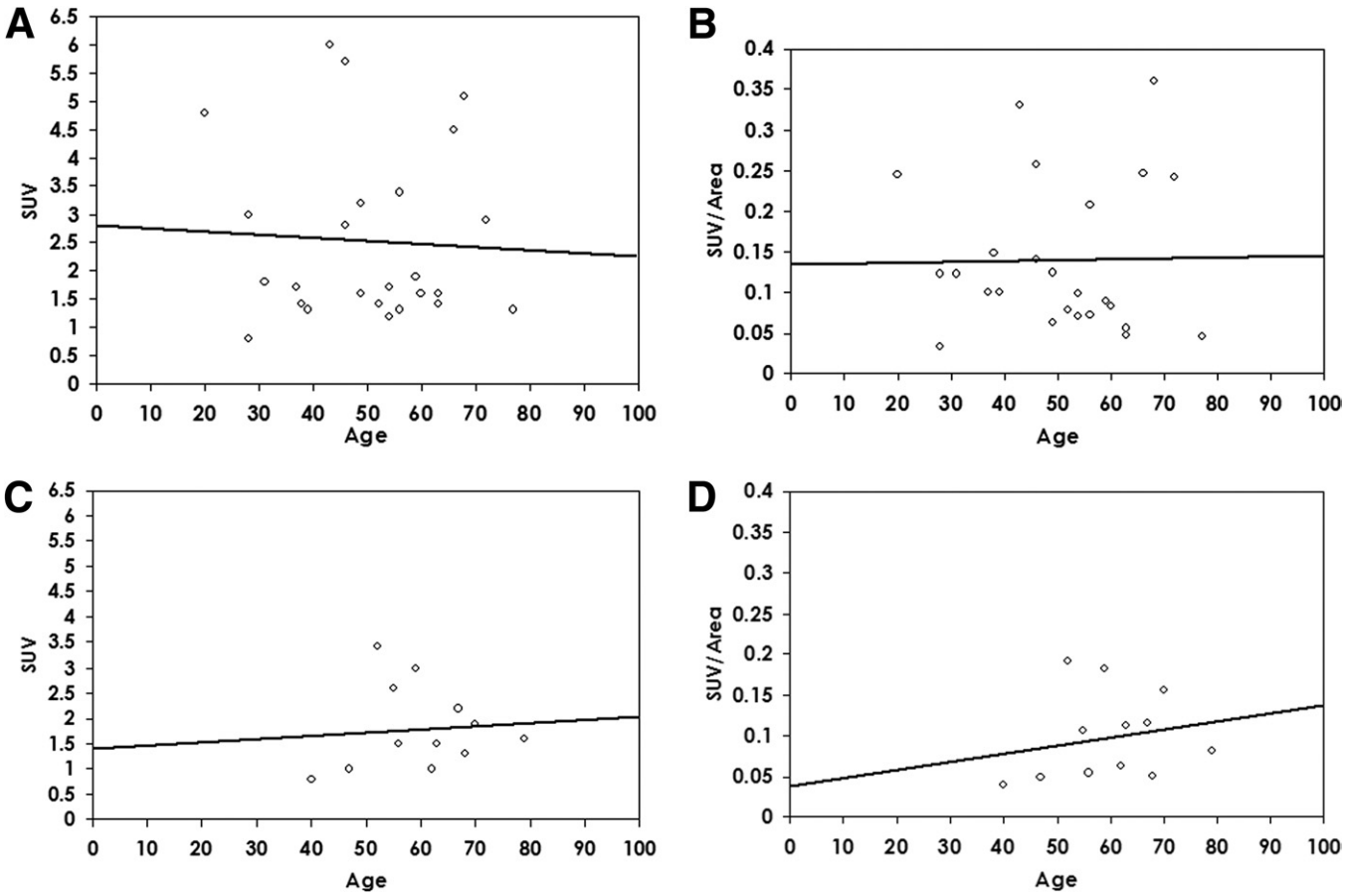

Figure 21 Myocardial FDG uptake with age. In those with coronary risk factors, mean SUV and SUV/cm^2 of mid-ventricular axial myocardial slice appeared to decrease slightly with age (panels at upper and lower right, respectively). When those with coronary risk factors were compared with those without risk factors, mean SUV in mid-ventricular axial myocardial slice differed from those without risk factors ($P = 0.058$) as did the SUV/cm^2 ($P = 0.051$), each approaching statistical significance.

Although of unclear significance, this shift in substrate metabolism toward glucose utilization could make the myocardium more resistant to ischemia. However, it may also detrimentally accentuate the metabolic shift already in place with pressure overload induced left ventricular hypertrophy and dilated cardiomyopathy. Acikgoz and coworkers[112] retrospectively studied 74 patients who underwent both fasting FDG-PET scans for malignancy evaluation and SPECT stress myocardial perfusion scans for preoperative risk assessment within 2 months of each other. Blood glucose levels were used to confirm the fasting state. The average maximum myocardial SUV in those with cardiac disease was significantly greater than in those with none although blood sugar levels were similar in the two groups, again supporting a relative shift toward glucose metabolism in the presence of ischemic disease.

In a recent retrospective study, we used methods to evaluate the aortic and myocardial FDG uptake in terms of mean and maximal SUVs in a consecutive patient population. We retrospectively reviewed the FDG-PET/CT scans in 33 patients who also had contrast-enhanced CT studies acquired from neck to thighs studied for oncologic indications. Patients were excluded if they had any history of cardiac disease. Whole-body PET/CT scans were acquired by 3-D technique using the Philips Gemini TF (Philips Inc; Nuclear Medicine Division, Milpitas, CA). Image acquisition began at a mean of 60 minutes after injection of 68 μCi/kg (2.5 MBq/kg). All patients fasted for 4 hours or more and had blood sugar levels of <150 mg/dL. There were 4 emission frames of 25 cm length with an overlap of 12.8 cm covering an axial length of 64 to 76.8 cm. Image reconstruction was performed with an iterative ordered subsets expectation maximization algorithm with 4 iterations and 8 subsets. Attenuation-corrected images were obtained based on unenhanced low-dose CT images. Thirty-eight scans were performed in the study patients and analyzed in this study. The mean interval between the PET/CT and the CECT studies was 165 days.

Patient age ranged from 20 to 79 years old with 18 (54.6%) males and 15 (45.4%) females. Three (9%) had diabetes mellitus, 5 (15%) had dyslipidemia, 10 (30%) had hypertension, and 26 (79%) had received chemotherapy. There were 17 (52%) nondiabetic patients also without hypertension and dyslipidemia. From the PET/CT scans, FDG uptake was calculated in the LV myocardium and in the ascending, arch, and descending segments of the thoracic aorta. The mean SUV was measured in the midventricular LV slice as well as in

4 to 6 axial regions of interest of each aortic segment where maximum SUVs also were measured. The SUVs for all transverse sections for each aortic segment were summed, and the arithmetical mean of values for each anatomic site was calculated for each patient. From the CECT scans, we measured the area of the LV myocardial wall on the midventricular axial slice. A ratio of glucose metabolism per unit area (SUV/cm^2) also was obtained. All data acquired from quantitative analysis were recorded into a computerized database (Microsoft Excel; Microsoft Corporation, Redmond, WA). Patients were divided into 3 groups based on age (20-39, 40-59, and 60-79 years old). The values were plotted in scatter diagrams and linear regressions performed. Pearson *r* coefficients were calculated to evaluate for linear correlations between aging and mean SUV of the myocardium and aortic segments, myocardial area, and SUV/cm^2. The mean and standard deviation of all parameters were also determined and *t*-tests were performed, comparing the parameters across the age groups in the patients without diabetes, hypertension, or dyslipidemia. Subgroup analysis also compared the aforementioned parameters in patients with and without risk factors for coronary artery disease. $P < 0.05$ was used as the threshold for statistical significance for both the t-tests and Pearson r coefficients.

In patients without coronary risk factors, the mean myocardial SUV, slice area, and SUV/area ratios showed no statistically significant difference across age groups. There was, however, a subtle trend toward increasing mean SUV values in all segments of the thoracic aorta with increasing age. In those with coronary risk factors, the mean SUV of the midventricular axial myocardial slice appeared to decrease slightly with age. Mean SUV and mean SUV corrected for myocardial area, calculated from the associated CT study, showed no initial linear correlation with aging. However, when those with coronary risk factors were compared with those without risk factors, mean SUV in midventricular axial myocardial slices differed from those without risk factors ($P = 0.058$) as did the SUV/cm^2 ($P = 0.051$), approaching statistical significance (Fig. 21). Although mean aortic SUVs again failed to correlate with increasing age in the ascending aorta and arch, SUVs in the descending aorta reached statistical correlation with aging in those with risk factors. When all the aortic segments were combined, there was a strong trend toward increasing SUV with age (Fig. 22).

These findings are quite similar to those of Yun and coworkers[94] and are in parallel with those of others who have similarly applied FDG analysis to correlate myocardial SUV with age. Kaneta and coworkers[113] studied 159 nondiabetic patients ages 11 to 81 years who were imaged with PET/CT for oncologic indications. Three-dimensional regions of interest (ROIs) were drawn on the fused images and the maximum SUV of the entire left ventricle was calculated. The authors found no significant relationship between myocardial uptake and age or fasting period in this population. Similarly, de Groot and coworkers[114] studied 175 nondiabetic patients with malignant diseases who had related imaging with routine whole body PET/CT. Age, blood glucose level, fasting duration, and myocardial FDG uptake were recorded.

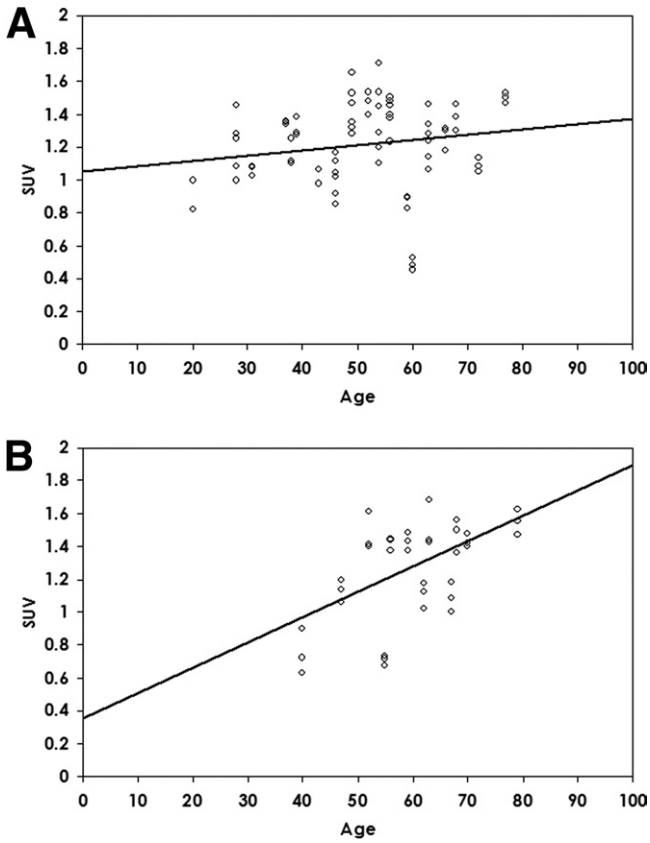

Figure 22 Aortic FDG uptake with age. There was a subtle trend toward increasing mean SUV values in all segments of thoracic aorta with increasing age (A). The mean aortic SUVs did not correlate with increasing age in the ascending aorta and arch, but SUVs in the descending aorta statistically correlated with aging in those with risk factors (not shown). When all the aortic segments were combined, there was a strong trend toward increasing mean SUV with age (B).

Qualitative visually assessed myocardial FDG uptake was not correlated to the blood glucose level, duration of fasting, or age. Here, as in our study, age did not appear to influence myocardial FDG uptake.

Issues with Myocardial Quantitation

FDG-PET has poor anatomic resolution and so must be combined with an anatomic map, generally provided by CT or perhaps, in the future, MRI with its greater ability to resolve the components of atherosclerotic plaque. Also, a host of factors, even if carefully controlled, can influence myocardial FDG uptake. Although adherence to a fasting protocol may vary, blood sugar must be checked and carefully controlled. However, there is a wide and unpredictable range of myocardial FDG uptake, even in fasting patients. That is, for any given blood sugar level determined in the setting of a fasting protocol, numerous factors may influence myocardial FDG localization, obscuring the effects of aging. This variability seems not to be directly related to blood sugar or insulin levels. Of course, the presence of diabetes, hypertension, LV hypertrophy, insulin resistance, and other factors that may influence myocardial glucose uptake must either be excluded or somehow taken into account. Even during fasting, there is

always a certain level of myocardial glucose metabolism and uptake in the normal myocardium. Evaluation of FDG uptake in myocardium or vascular walls requires exclusion of the possible contamination by the remnant blood pool activity, which cannot always be completely accomplished. Even when imaged late after FDG administration, significant activity frequently persists in the blood pool of the heart as well as in tumors. Techniques such as Patlak analysis can be used to correct for blood pool activity of fasting patients.[115] It will also be critical to separate blood pool and other background activity if and when FDG or other markers of inflammation are applied to study the coronary arteries, where myocardial activity itself will present a challenge with which to deal. Registered CT images may aid localization of a region of interest over the myocardium, but such a region would be blurred on nonrespiratory gated images further confounding such localization. Beyond this, there are roughly 25% of fasting patients who present with heterogeneous or intense myocardial uptake for unknown reasons.

Conclusion

Many of the developments discussed herine using CT, MRI, and PET imaging are quite new and have the potential to provide the means for noninvasive quantitation of cardiac and vascular changes with aging, as well as noninvasive detection, quantitation, and monitoring of atherosclerosis before and after therapeutic intervention. Such tools will be applied further to help understand the effects of aging on the cardiovascular system, and to benefit patients with atherosclerosis in the identification of the "vulnerable" plaque and the "vulnerable" patient. Their full potential has not yet been realized.

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