

Chapter 13: Vascular Disease in the Elderly

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PHYSIOLOGIC EFFECTS OF AGING ON BLOOD VESSEL ELASTICITY AND COMPLIANCE

The aging process is commonly associated with increased vascular rigidity and decreased vascular compliance. This process reflects the accumulation of smooth muscle cells and connective tissue in the walls of major blood vessels. Endothelial cells and smooth muscle cells constitute most of vessel wall cellularity and the remainder of the wall is composed of extracellular matrix including collagen and elastin. Although aging has minimal effect on the muscular tunica media layer thickness, aging leads to profound progressive thickening of the tunica intima layer comprised of endothelial cells and an extracellular matrix. In addition, with aging, there is a thinning and separation of individual elastin lamellae, as well as an increase in the collagen matrix.¹

The age-related vascular rigidity and decreased arterial compliance leads to progressive increase in systolic BP, with 25% of patients over 75 yr of age suffering from isolated systolic hypertension.² Healthy elderly patients without hypertension also show a modest increase in peripheral vascular resistance and only a modest related increase in systolic BP.² Dilation and stiffening of the proximal aorta and its major branches including the brachiocephalic, carotid, and subclavian arteries occur to a greater extent than the peripheral arteries with aging. This also blunts the carotid baroreceptor sensitivity and increase the risk of end organ damage to the kidneys, heart, and brain.^{1,2} It is important to keep in mind that the presence of pre-existing hypertension and accelerated atherosclerosis intensify the vascular pathology discussed to a far greater extent.

EFFECTS OF ATHEROSCLEROSIS ON AGING

Atherosclerosis is characterized by the progressive

stiffening of medium and large arteries lined with atheromatous plaques. The progressive accumulation of atherosclerotic plaque continues with aging and often remains silent until lesions reach a critical stenotic threshold or rupture, leading to diminished organ perfusion. Arterial stiffening also leads to an increase in pulse wave velocity and an enhancement in central aortic systolic pressure.³ The increased waveform velocity allows the backward reflective wave to return earlier back to the heart. The resulting increases of the left ventricular myocardial load and the loss of coronary perfusion at the onset of diastole may potentiate myocardial ischemia.³

Common ailments in the elderly including diabetes, dyslipidemia, hypertension, obesity, and cigarette smoking can accelerate the process. Although the exact mechanisms have yet to be elucidated, multiple factors including genetics, advanced glycation endproducts, and oxidative stress likely contribute to the pathogenesis of accelerated atherosclerosis.

EFFECTS OF AGING, ATHEROSCLEROSIS, AND HYPERTENSION ON THE KIDNEYS

Renal blood flow declines with aging at a magnitude of 6 ml/min per year, with a proportionately larger reduction in cortical blood flow than medullary flow.² GFR also declines with aging albeit at a slower rate of 1 ml/min per year. It is unclear if this change is caused by the aging process alone or is also attributable to hypertension and arteriosclerosis. It is estimated that as much as 26% of all end-stage kidney disease (ESKD) in the United States is related to hypertensive arteriolar nephrosclerosis. This num-

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ber is expected to grow as the population of the United States continues to age.⁴ Furthermore, it is estimated that 10% of all ESKD is caused by renal artery stenosis.^{5,6} The ESKD incidence from renovascular disease has increased in parallel with the advancing age of the general population in the United States.⁶

Numerous causes of vascular insult to the kidneys exist as listed in Figure 1. When classified anatomically by arterial vessel size, the vascular diseases can be subdivided to those affecting (1) the microscopic vessels in the kidney, (2) arterioles, and (3) the main renal arteries. We will focus here on the predominant forms of vascular insult to the kidneys seen with aging: hypertensive nephrosclerosis, arteriolar hyalinosis, and atherosclerotic renal artery stenosis.

Microscopic Vascular Disease in the Kidney With Aging: Nephrosclerosis

As systemic hypertension worsens, an increase in renal vascular resistance and a progressive decrease in effective renal plasma flow are observed. Although the GFR is relatively maintained, serious renal impairment may occur in as many as 20% of essential hypertensive patients.

With aging, the total number of functioning glomeruli decrease by 30 to 50% as the percentage of sclerotic or abnormal glomeruli increases.⁴ Under ischemic insult from vascular disease, the glomeruli in renal cortex show wrinkling of the capillary basement membrane followed by thickening, collapse, and global sclerosis. The initial ischemic changes are reversible. However, with the appearance of hyaline in the capsular space, the process proceeds to complete glomerular obsolescence. In the deeper juxtamedullary areas, direct channels between afferent and efferent arterioles are formed that leads to the formation of aglomerular arterioles. These vascular lesions are usually distributed in a focal, irregular fashion throughout the renal cortex and result in ischemic changes that follow a similar pattern of distribution. However, if the vascular lesions are severe and generalized, the entire kidney may undergo ischemic atrophy.

There are several histologic changes seen with aging. Secondary tubular atrophy, thickening of tubular basement membranes, and interstitial fibrosis occur. Renal tubules decrease in number. Additionally, the proximal tubules decrease in volume and length, whereas the distal tubules form diverticula because of alterations in intrarenal vasculature.

Vascular Insult to Kidneys
Hypertensive nephrosclerosis
Atherosclerotic renal artery stenosis
Fibromuscular dysplasia induced renal artery stenosis
Renal artery thrombosis
Polyarteritis nodosa
Microscopic polyangiitis
Microangiopathic hemolytic anemia
Scleroderma
Atherosclerotic embolic disease to the kidneys

Figure 1. Causes of vascular injury to kidneys.

Intrarenal Arterioles and Interlobular Arteriolar Disease: Arterial Hyalinosis

Aging, hypertension, and arteriosclerosis all affect the arterioles in the kidney parenchyma causing afferent and efferent arteriolar atrophy.⁴ Microcirculatory adaptive changes to the glomerular mass also occur, including impaired autoregulation with preglomerular vasodilatation. This is associated with structural and functional hypertrophy of the intact nephrons leading to glomerular hypertension, albuminuria, and further glomerular sclerosis.⁴ The histologic changes include hyperplastic elastic arteriosclerosis present in the interlobular arteries, intimal thickening, reduplication of the lamina elastica interna, and mild hyalinization.⁴ The development of hyperplastic elastic and/or hyaline arteriosclerosis leads to a reduction in renal blood flow along with progressive ischemic changes observed in the cortical glomeruli and renal tubules.⁴

Main Renal Artery Disease: Atherosclerotic Renal Artery Stenosis

Renal artery stenosis (RAS) may be defined as the presence of cross-sectional arterial luminal narrowing, which may or may not have any significant hemodynamic effects. Atherosclerotic renal artery stenosis leads to an occlusion at the ostium and the proximal third of the renal arteries. Variability in criteria used to define RAS based on anatomical luminal narrowing exist but atherosclerotic RAS often becomes clinically significant only when the arterial cross-sectional luminal diameter is reduced by 70%.⁶ Hemodynamically significant stenosis leads to parenchymal ischemia, atrophy, and loss of kidney function.

The exact prevalence of atherosclerotic RAS is unclear, but it has been consistently shown that the risk increases with older age. Based on autopsy series estimates, when renal artery stenosis is defined as a 50% or greater reduction in luminal diameter, it is present in 27% of patients in their sixties and 62% of patients 70 years of age and older.⁶ The presence of aortic and peripheral arterial disease increases the chance of coexisting atherosclerotic renal arteries.

This ischemic insult leads to histologic changes in multiple levels. Patchy tubular necrosis and tubular atrophy are prominently seen, in addition to focal areas of collagenous filling of Bowman's space and patchy peritubular leukocyte and mononuclear infiltrates. Glomerular atrophy with wrinkling of glomerular capillary tuft and thickening and duplication of Bowman's capsule is also found. Of note, the often concurrent extension of atherosclerotic disease into the major branches of intrarenal arterioles can lead to the ischemic glomerular and tubular changes noted above even in the absence of hemodynamically significant main renal artery stenosis.

In response to the chronic vascular ischemic change, cortical blood flow is redistributed to the deeper corticomedullary circulation that further attenuates the GFR.⁶ Clinical correlate data suggest that approximately 30 to 60% of patients with atherosclerotic ischemic renal disease progressively worsen their stenosis and kidney function in a relatively short duration

of 6 months to 3 years.⁶ Total occlusion may take place in excess of 10% of patients during the same duration of follow-up.⁶

Diagnosis of Atherosclerotic Renal Artery Stenosis.

The presence of atherosclerotic RAS can lead to progressive renal insufficiency from ischemic nephropathy as outlined above. It also can lead to or exacerbate the underlying essential hypertension. No clinical signs are pathognomonic. However, such symptoms and signs as the onset of hypertension after the age 50 yr, abdominal bruit, the presence of atrophic kidney, recurrent flash pulmonary edema or the occurrence of acute renal failure after initiation of angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) may suggest the presence of renal artery stenosis. Additionally, progressive renal insufficiency in a patient with diffuse atherosclerosis may raise the level of clinical suspicion.

If adequate clinical suspicion warrants the work-up, the diagnosis must be confirmed by anatomical or functional correlation. Several diagnostic modalities with their respective benefits and limitations are listed in Figure 2. Although an angiogram of the renal arteries is still considered as the gold standard, it has low utility as a screening tool because of its invasive nature and the risks of cholesterol emboli. Renal artery Doppler and renal scintigraphy are limited by lower sensitivity. Computed tomographic (CT) angiogram requires the use of intravenous contrast, which has inherent risks of contrast nephropathy. Magnetic resonance arteriography (MRA) was once considered as the panacea to this diagnostic dilemma but recent concerns of nephrogenic systemic fibrosis in patients with CKD have diminished the enthusiasm for this modality.

Diagnosis of Intrarenal Arteriolar Disease and Ischemic Nephrosclerosis.

The aforementioned imaging modalities including MRA and

CT angiogram are poor in visualization of intrarenal arterioles. Renal Doppler ultrasound with concurrent measurement for resistive index (RI) can be used to indirectly assess the blood flow within the renal parenchyma. An RI reading of 0.8 or greater may signify the presence of intrarenal arteriolar disease. In patients with progressive CKD without a clear explanation, a renal biopsy may be required for definitive diagnosis of ischemic nephrosclerosis if the clinical situation warrants.

Treatment of Atherosclerotic Renal Artery Stenosis.

Not all cases of documented RAS need to be corrected because some patients will have no clinical sequela. However, RAS may lead to ischemic nephropathy with progressive CKD or it may exacerbate hypertension. Variable outcomes of percutaneous transluminal renal angioplasty (PTRA) with stents for the treatment of hypertension from RAS are reported depending on patient selection and the criteria used to show its efficacy. Nonetheless, it is rare for PTRA to cure hypertension.⁷ Better outcomes can be expected from treatment of ischemic nephropathy from atherosclerotic RAS with PTRA. Improvement and/or stabilization of progressive renal failure is seen in approximately two thirds of the patients undergoing this procedure.⁷ The elderly can benefit equally from PTRA, and age alone should not discourage the procedure.⁸ Ultimately, a decision to intervene must always be carefully weighed against the procedure related risks, including cholesterol emboli, renal arterial subintimal dissection, and renal artery thrombosis, because aggregate complication rates may be in excess of 9%.^{7,9}

THERAPEUTIC IMPLICATIONS

Elderly patients require a specialized approach in the management of vascular disease. Careful drug dosing is needed because of their often diminished GFR. The carotid baroreflex response is often blunted, and vasodilator antihypertensive

Imaging Modality	Benefits	Limitations
Doppler Ultrasound	<ul style="list-style-type: none"> • Non-invasive • No intravenous contrast 	<ul style="list-style-type: none"> • Operator dependent with potential compromised accuracy • Lower sensitivity than MRA
MRA with IV gadolinium	<ul style="list-style-type: none"> • High resolution near-angiogram 	<ul style="list-style-type: none"> • Risk of NSF • Not suitable with AICD/PPM
CT angiogram	<ul style="list-style-type: none"> • High sensitivity and specificity for RAS • 95% negative predictive value 	<ul style="list-style-type: none"> • Risk of CIN • Radiation exposure
Angiogram of Renal Arteries	<ul style="list-style-type: none"> • Gold standard • CO2 angiography may be used in patients with CKD 	<ul style="list-style-type: none"> • Invasive with potential risks of cholesterol emboli
Nuclear Renal Scan (ACEI Renal Scintigraphy)	<ul style="list-style-type: none"> • Positive predictive value as high as 92% under ideal conditions • Minimally invasive 	<ul style="list-style-type: none"> • Lower sensitivity, especially in patients with CKD • May need further confirmation by above modality

Figure 2. Imaging modalities available for evaluation of renal artery stenosis.¹⁰

medications may lead to dizziness and orthostatic hypotension. Physicians also must be aware of the manifestations of vascular disease when forming the differential diagnosis on hypertension and CKD. Additionally, clinicians must assess elderly patients for their understanding and ability to comply with the treatment regimen because older patients may not be taking the correct doses of medications because of cognitive impairment, visual challenges, swallowing difficulty, or inability to afford the medication.

CONCLUSIONS

Aging alters the physiology of arterial vasculature. Arterial circulation stiffens and becomes less compliant, proximal arteries dilate, and carotid baroreceptors become less sensitive. GFR also declines with aging. Coexisting hypertension and atherosclerotic disease exaggerate the normal vascular aging process, endangering the longevity of end organ function including the kidneys. Hypertensive and atherosclerotic renal diseases account for a large proportion of progressive CKD and ESKD in the United States. It is important for the nephrologists to focus on the preventative measures of atherosclerosis including an aggressive treatment of dyslipidemia, diabetes, and hypertension along with cigarette smoking cessation. Furthermore, a careful evaluation of suspected atherosclerotic disease may be warranted.

TAKE HOME POINTS

- Effect of aging on baroreceptor reflex may profoundly increase the orthostatic side effect profile of antihypertensive vasodilators
- As much as 26% of all ESKD in the United States is related to hypertensive arteriolar nephrosclerosis
- As much as 62% of patients over 70 may suffer from RAS and the risk increases with aging

- It is estimated that 10% of all ESKD is caused by renal artery stenosis
- Improvement and/or stabilization of progressive kidney disease is seen in approximately two thirds of the patients undergoing PTRAs; the elderly can benefit equally from PTRAs and age alone should not discourage the procedure

DISCLOSURES

None.

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REVIEW QUESTIONS: VASCULAR DISEASE IN THE ELDERLY

1. Age related changes in vasculature may lead to the following:
 - a. An increase in systolic BP and vascular rigidity only if there is an underlying history of hypertension
 - b. A continued decline in the total number of functional glomeruli, contributing to losses in GFR
 - c. Hypertensive arteriolar nephrosclerosis responsible for 75% of all end-stage kidney disease in the United States
 - d. Labile BP and increased orthostatic effects of vasodilators caused by carotid receptor hypersensitivity
2. In a patient with suspected renal artery stenosis, which of the following statements is considered true:
 - a. Renal artery stenosis should be identified on an imaging study and always be corrected by stents or surgery whenever present
 - b. Hypertension is usually curative after correction of renal artery stenosis with stents
 - c. All complication risks associated with renal artery stenting are trivial
 - d. Renal artery stenosis likely accounts for 10% of all end-stage kidney disease cases
 - e. Magnetic Resonance Imaging (MRI) with IV gadolinium is safe for patients with advanced chronic kidney disease and allows for high resolution imaging otherwise unavailable
3. Advancing age will:
 - a. Diminish the likelihood that renal artery stenting will be beneficial in the treatment of ischemic nephropathy and should be discouraged
 - b. Enhance the side-effect profile of vasodilator antihypertensive medications, such as dizziness and orthostatic hypotension
 - c. Often lead to increased risks of renal artery stenosis; the presence of abdominal bruit and acute pulmonary edema are pathognomonic for renal artery stenosis and should always be evaluated
 - d. Increase the risks for renal artery stenosis and hypertension from fibromuscular dysplasia