Overview on Renovascular Hypertension: Review Article

Abstract:

Renovascular hypertension (RVH) is a prevalent cause of secondary hypertension that frequently develops to resistant hypertension. It is characterised as systemic hypertension that develops as a result of a restricted blood supply to the kidneys. Patients cannot be recognized clinically from those with essential hypertension; therefore, diagnosis requires arteriography, however urography and isotope renography may hint to the diagnosis. Atherosclerotic renal artery stenosis (ARAS) and fibromuscular dysplasia are the two most prevalent causes of RVH. The ultimate objective of controlling RVH, like with other kinds of hypertension, is to minimize the morbidity and mortality associated with high blood pressure The widespread use of effective antihypertensive medication treatment, statins, and other strategies to control vascular disease has resulted in remarkable improvements. In this review we will be looking at etiology, pathogenesis and treatment or RVH

Introduction:

In the United States, 75 million people have high blood pressure, which accounts for 8.6% of all primary care visits. Renovascular hypertension (RVH)is a prevalent cause of secondary hypertension that frequently develops to resistant hypertension. It is characterised as systemic hypertension that develops as a result of a restricted blood supply to the kidneys, which is generally caused by an occlusive lesion in the primary renal artery. [1] Renal artery lesions affecting the main renal artery or its branches can cause RVH. Excessive systemic vasoconstriction caused by increased renin production by one or part of one kidney is thought to be the cause of high blood pressure. Because of the constriction of the renal artery and the resulting intrarenal ischemia, renin production is increased. [2]

Patients cannot be recognized clinically from those with essential hypertension, therefore diagnosis requires arteriography, however urography and isotope renography may hint to the diagnosis. If differential renal vein renin ratios

lateralize, surgical cure can be anticipated, but a non-lateralizing study does not always suggest surgery will fail. Surgical outcomes are excellent in appropriately chosen individuals. [2] Vascular imaging has advanced to the point that it is now easier than ever to identify vascular abnormalities non-invasively. Simultaneously, the emergence of effective, well-tolerated antihypertensive medication treatment for renovascular hypertension enables for more successful medical care of this illness than has ever been possible before. While renovascular hypertension is listed as a "curable" sort hypertension, results from recent, small prospective trials have yet to show that revascularization, whether by endovascular techniques or surgery, has significant advantages. [3]

Different findings have left both patients and doctors unsure regarding the optimal way to manage renovascular hypertension, particularly in terms of whether endovascular or surgical intervention should be used. Because of this "equilibrium" between medical therapy and renal revascularization, the National Institutes of Health (NIH) in the United States is funding a large prospective, randomised trial comparing intensive medical therapy alone to intensive medical therapy plus renal revascularization for Renal Atherosclerotic Lesions. [3] The widespread use of effective antihypertensive medication treatment, statins, and other strategies to control vascular disease has resulted in remarkable developments. Surgical and endovascular treatment are no longer the exclusive choices for treating RVH. Major variations between patients participating in these trials and those met in practise with resistant hypertension and/or renal damage have impeded attempts to define the function of optimal medical treatment alone versus combining it with revascularization with randomised, prospective trials. [4] Renovascular disease has evolved dramatically in the last decade because to advancements in imaging, medicinal management, and renal revascularization procedures. This has proven especially true for renal artery stenosis (RAS) caused by atherosclerosis, which is still one of the most prevalent causes of hypertension and can be identified by chance. Regardless of, or maybe because of, these advancements, few clinical problems elicit greater debate and discussion than the best way to care patients with primary RAS. [5]

Renal damage, cardiovascular problems, and 'flash pulmonary edoema' are all possible outcomes of this illness. The most popular diagnostic procedures are duplex Doppler ultrasound, computed tomographic angiography, and magnetic

resonance angiography. Medical treatment, which includes renin-angiotensin-aldosterone system antagonists, lipid-lowering medicines, and antiplatelet medication, percutaneous angioplasty with or without stent implantation, and surgical revascularization are the three therapeutic options available. [6]

Magnetic Resonance Imaging
MRA is fast becoming a clinical standard for the safe and noninvasive detection of RAS, aneurysms, and occlusions. [22] A comprehensive examination includes 3D dynamic gadolinium-enhanced and 3D phase-contrast MRA techniques, which allow an evaluation of the renal arteries and other visceral arteries. The 3D phase-contrast technique is flow based and subject to dephasing in the presence of significant arterial stenosis. The 3D gadolinium-enhanced MRA method produces excellent contrast angiograms without the risk of iodinated compounds or radiation exposure.
(See the images below.)
Gadolinium-enhanced MRA has been proven to have high sensitivity for detecting stenosis in the main and accessory renal arteries. At presentation, MRA provides anatomic information regarding a vascular stenosis, but it provides little information about the functional significance of a stenosis. Studies have shown that 3D MRA with gadolinium-based contrast agents (which have a low potential for nephrotoxicity) has a sensitivity of 96-100% and a specificity of 71-96% for the detection of a main RAS greater than 50%. [23, 24, 25]
When combined with cardiac synchronization, 3D MRA can sharply delineate the entire length of the major renal arteries. However, MRA remains suboptimal for the detection of hemodynamically significant lesions of distal, intrarenal, and accessory renal arteries, which may cause physiologically significant RAS.
Limitations of MRA include its cost and lack of availability. Contraindications to MRA include claustrophobia and the presence of metallic implants, such as a pacemaker or surgical clip

Etiology:

Renovascular hypertension is caused by a number of factors, including: [1,7,8]

- Renal artery stenosis (RAS) caused by atherosclerosis.
- Fibromuscular dysplasia (FMD)

- Arteritides like Takayasu's, antiphospholipid antibody (APLA), and mid aortic syndrome
- Extrinsic renal artery compression
- Dissection or infarction of the renal artery
- Radiation fibrosis
- Aortic endovascular grafts that cause obstruction.

Atherosclerotic renal artery stenosis (ARAS) and fibromuscular dysplasia (FMD) are the two most prevalent causes of RVH. Obstruction can be caused by dissection, vasculitis, or neurofibromas in the renal artery wall, or it can be caused by extrinsic compression, such as a tumour. Embolism and blood flow diversion caused by arteriovenous malformations can potentially impair renal perfusion, resulting in RVH. ARAS is responsible for 90% of RVH cases. The lesion is seen in the ostium or proximal third of the renal artery as an extension of an aortic plaque, and it affects mostly older males. In almost one-third of instances, it is bilateral. [9] The data on ARAS progression is mixed, with progressive stenosis reported in 51% of patients 5 years after diagnosis and a yearly occlusion rate of 5% in the 1990s. In the DRASTIC (Dutch Renal Artery Stenosis Intervention Cooperative) research, 8/50 lesions (16%) in the drug cohort progressed to blockage within a year. 15 In contrast, disease progression occurred in 133 (11.1%) of 1189 patients who had cardiac catheterization, however only 4 (0.3%) of these patients advanced to complete blockage. 16 At an 8-year follow-up, ARAS advanced at 1.3 percent each year in 119 older people in the Cardiovascular Health Study, although none occluded. [5,10-14]

FMD is responsible for 10% of RVH cases. FMD is a group of noninflammatory vascular illnesses that affect the intima, media, and adventitia, the most common of which is medial fibroplasia. It is mostly prevalent in young women. Bilateral renal artery involvement is typical, with spread into the artery's distal part and branches. [9,15,16]

Pathophysiology:

Reduced perfusion to the kidney and stimulation of the renin-angiotensin-aldosterone (RAAS) pathway are the fundamental mechanisms in RVH. Goldblatt et al. were the first to explain this in the 1930s. His model looked at the effect of reduced blood flow to the kidneys in dogs and discovered that ischemia kidneys

contribute to chronic hypertension. He also suggested the presence of a chemical that "could influence a pressor effect similar to that of a hormone." The hormone he was referring to was 'renin' which is produced by the kidney's juxtaglomerular cells. [1] One of the most commonly researched models of hypertension are those in which a normal contralateral kidney is exposed to pressure natriuresis (2-kidney-1-clip) and those in which the full functioning renal mass is beyond a vascular blockage (1-kidney-1-clip). Hypertension is more reliably angiotensin-dependent in mice with a normal contralateral kidney. These models have been developed for a variety of animals, including the mouse, rat, dog, and pig.[3]

Renin secretion is triggered by three primary mechanisms: 1) renal baroreceptors that detect reduced kidney perfusion, 2) low sodium chloride levels sensed by the macula densa, and 3) beta-adrenergic stimulation. In a process known as 'JG recruitment,' prolonged ischemia increases the number of renin-expressing cells in the kidney. Renin works on angiotensinogen when it is released into the bloodstream (produced by the liver). Renin converts angiotensinogen to angiotensin I, which is subsequently converted to angiotensin II by angiotensin-converting enzyme (ACE), which is located largely in the endothelium of the lungs and kidneys. [1] The definition of a functionally substantial RAS that warrants revascularization is still not clear. RAS must create a severe enough pressure gradient between the aorta and afferent arterioles to upregulate renin production in order to generate hypertension; a peak systolic pressure gradient of >20 mmHg has been recommended. A 4-F catheter is routinely used to assess the gradient in the aorta and distal to the lesion. Because the catheter may restrict flow, a 0.014 in pressure wire is a more precise, but more expensive, option. In humans, a functionally meaningful RAS is defined by a 0.9 aorta to renal artery pressure gradient ratio, which equates to a systolic gradient of less than 25 mmHg. [5]

Angiotensin II elevates blood pressure through a variety of ways, including: [1]

- Vasoconstriction, which occurs mostly in the heart, kidneys, and vascular smooth muscle.
- Sympathetic nerve stimulation causes norepinephrine to be released presynaptically.
- Stimulates the adrenal cortex's release of aldosterone, which promotes salt and water retention, increasing blood pressure.

- It also induces an increase in collagen type I and III production in fibroblasts, resulting in fibrosis and thickening of the vascular wall and myocardium.
- It has been demonstrated to have a significant impact on renal cells, which has been linked to glomerulosclerosis and tubulointerstitial fibrosis development.

The efferent arterioles vasodilate when an angiotensin converting enzyme (ACE) inhibitor is administered. This may result in a drop in glomerular filtration rate (GFR) in the ischemic kidney, which is not evident in the contralateral kidney. In humans, unilateral RVH closely resembles the animal model of one-clip two-kidney hypertension. Converting enzyme inhibitors efficiently reduce blood pressure when plasma renin activity is high. The increased renin is attributed only to enhanced renin production by the ischemic kidney, while the contralateral kidney is fully inhibited. [17] The kidney is overperfused in comparison to its metabolic needs, which is consistent with its function as a filtering organ. As a result, blood flow and filtration may be reduced significantly without compromising tissue viability. Recent research suggests that while maintaining normal overall levels of cortical and medullary tissue oxygenation, a drop in renal blood flow sufficient to diminish kidney size and generate renin release can occur. These findings suggest that real renal "ischemia" is not required for RVH . [18,19]

Although it is unclear if bilateral RVH correlates to the one-clip one-kidney model, there is evidence that both renin and volume variables are involved. Atheroma, which is often bilateral, or fibromuscular dysplasia are the most prevalent causes of human RVH. The former is commonly linked to atheroma elsewhere in the arterial tree, and it can lead to total blockage and renal failure. The latter is more common in younger individuals and seldom leads to full blockage. [17]

Treatment:

The ultimate objective of controlling RVH, like with other kinds of hypertension, is to minimise the morbidity and mortality associated with high blood pressure. A secondary purpose is to safeguard the kidneys' circulation and function. As previously stated, several of the pressor pathways, including RAAS activation, are engaged when post-stenotic pressures and blood flows are reduced to levels that

the kidney can tolerate. As a result, antihypertensive medication treatment may often be used to effectively lower blood pressure while having minimal side effects on the post-stenotic kidney (s). [4] Antihypertensive medicines are used in pharmacological therapy to control blood pressure. Pharmacological therapy is recommended as the first-line treatment for renal artery stenosis by the American College of Cardiology and the American Heart Association (ACC/AHA). ACE-Is and angiotensin receptor blockers (ARBs) are the cornerstones of RVH management since RAAS is the most significant mechanism contributing to hypertension in these illnesses (Class 1a indication). [1] Effective blood pressure control became more practicable in the 1990s with the development of ACE inhibitors and later ARBs. For the majority of simple RVH patients, combining these medicines with calcium channel blocking agents, diuretics, and other classes has resulted in effective BP control with pharmacological treatment alone. Medical treatment produces acceptable BP control in many people with mild RVH (often undetected) and does not require additional diagnostic testing or intervention. [4]

Controlling blood pressure often necessitates the use of many medications. Calcium channel blockers, thiazides, beta-blockers, and hydralazine have all been found to help people with RAS regulate their blood pressure. To treat hypertension, direct renin inhibitors like aliskiren have been explored as monotherapy or in combination with ACEIs/ARBs. Despite the fact that it has been found to be useful in the treatment of hypertension, there is insufficient evidence to support its use in the treatment of renovascular hypertension. [1] It is important to note that removing the renin-angiotensin system has downsides. Initial agreement on the use of ACE inhibitors was difficult to come by, in part because of the well-known tendency for these drugs to impair glomerular filtration rate due to angiotensin II effects being lost at the efferent arteriole. Renin release can be seen when there is enough lumen blockage to provide a 10-20% pressure difference between the pre- and post-stenotic segments, as previously mentioned. This can happen even if there is just a little disruption in blood flow to the kidney, which only requires around 10% of its blood flow for metabolic processes. [3]

Because atherosclerotic disease is a systemic illness, RVH patients should get statin medication as well as lifestyle changes such as quitting smoking. Statins

have been proven in studies to alter the kidney's microvascular environment and reduce fibrosis and inflammatory damage. Statin-treated individuals with fully occluded kidneys who undergo nephrectomy had lower levels of transforming growth factor-beta activation and interstitial fibrosis than those who are not on statins. As a result, it should be routinely included in the medical treatment of ARAS patients. [4]

Percutaneous angioplasty is the preferred treatment for individuals with renovascular hypertension caused by FMD as well as those who have atherosclerotic renal artery stenosis that is not managed by medicines. Revascularization for renal artery disease is recommended by the ACC/AHA guidelines in the following situations: [1,20]

- Patients with RAS with recurring, unexplained congestive heart failure or abrupt, inexplicable pulmonary edoema (class Ia)
- RAS and accelerated hypertension, resistant hypertension, malignant hypertension or hypertension with an unexplained unilateral small kidney, and hypertension with drug intolerance are all examples of hemodynamically significant RAS and accelerated hypertension (Class IIa)
- Patients with a RAS to a single working kidney or a RAS to both kidneys with increasing chronic kidney disease (Class IIa)
- Patients with RAS that is hemodynamically severe and angina that is unstable (class IIa)
- Hemodynamically substantial RAS in asymptomatic bilateral or solitary viable kidney (Class IIb)
- Patients with unilateral RAS and chronic renal failure (class IIb)
- Patients with ostial atherosclerotic lesions may benefit from renal stent insertion in addition to angioplasty (Class I).

Three big studies failed to show that renal artery revascularization is more effective than pharmacological treatment at controlling blood pressure and maintaining renal function. As a result, revascularization is now only suggested for patients with gradually deteriorating renal function, recurring "flash pulmonary edoema," and a fast rise in antihypertensive demand in previously well-controlled hypertension. However, additional well-designed trials are required to determine which patient groups are likely to benefit from renal revascularization. [6] Recent

authors and guidelines highlight the importance of aggressive risk factor treatment for atherosclerotic disease, including blood pressure reduction, cholesterol management with statins, cigarette abstinence, and aspirin usage . In most individuals, antihypertensive medication treatment is now successful in reaching target blood pressure levels. [21]

Doppler ultrasonography can be used to measure the velocity of blood flow. It is a noninvasive technique, and it has high sensitivity in expert hands. Color-flow Doppler may demonstrate disorganized flow patterns and high-velocity flow stream associated with hemodynamically significant stenosis. [26] Radionuclide renography technetium (Tc)-mercaptoacetyltriglycine (MAG3)-captopril has a high sensitivity and specificity, and it adds a physiologic element to the diagnosis of RAS. [27, 28]
In a study by Cui et al, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of contrast-enhanced US (CEUS) in the diagnosis of renal artery stenosis were 88.9%, 87.8%, 88.5%, 93.5%, and 80.0%, respectively. [29]

Conclusion:

Renovascular hypertension is one of the common prevalent causes of secondary hypertension that frequently develops to resistant hypertension. Thankfully with emergence of ACEis and ARBs and other pharmacological and invasive methods there is significant improvement in managing of RVH, however an agreement on best way to approach the disease is not entirely clear therefore more research is required.

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