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Special issue of the journal from PRS Hospital, Trivandrum, Kerela, India

AIMS & SCOPE

Hypertension Journal is a peer-reviewed journal which highlights epidemiology, health implications and cardiovascular risk from hypertension in India/South-Asia. Hypertension is much more common than diabetes. It is vastly under diagnosed and poorly treated in India/South-Asia. There are excellent therapeutic options to treat hypertension, but the available resources are not fully utilized by doctors therefore neglecting this disorder. The journal will hereby promote the significance of hypertension and the urgent need to bring it under control. The medical community should be educated on hypertension evaluation, diagnosis, workup and management simultaneously bringing up the literature, research, guidelines and scientific advances related to hypertension and its disorders. We are hereby starting a high-quality journal dedicated solely to hypertension and thus promoting the awareness, evaluation and effective management in India/South-Asia. Dr C Venkata S Ram is a world authority on hypertension with lifelong work (research, clinical and publications).

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𝓔ditorial

Greetings from PRS Hospital, Trivandrum, Kerala, India

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Occupying only a small percentage of Indian landmass, Kerala has an exemplary record of quality health care, comparable to the "western" standards! Life expectancy is the highest and infant mortality is lowest in the country. While this "special" standing separates Kerala from other states and is laudable, we at the PRS Hospital continue to explore newer and technology-based solutions to further reduce the burden from cardiovascular disease (CVD). Thanks to the visionary mission of the founders of PRS Hospital, we are able to implement and show improvements in the care of individuals at risk for CVD. The founder of our hospital (Mr. P. Ratnaswamy) envisioned a small pilot project in 1986 to provide quality care through "Mother and Child Hospital" at affordable costs to the patients. The logo "care like only a mother can give" reflected his vision then, and today, PRS Hospital has grown into one of the best health-care providers not only in Kerala but also in the country. It is now a highly respected multispecialty hospital covering all aspects of disease detection and treatment. For example, the cardiovascular services at PRS can be considered as an anchor, evidenced by National Accreditation Board for Hospitals & Healthcare Providers (NABH) and ISO accreditations. Not only clinical medicine but we also have a dedicated dimension for academic advancement – medical education, research, professional and publications, etc.

This dedicated issue of the Hypertension Journal is one example of the contribution of our staff and the hospital to disseminate scientific developments for the ultimate benefits of the society and to protect and preserve public health in South Asia.

Dr. Prakash Nair addresses the importance of the left ventricular hypertrophy (LVH) in the evaluation of patients with hypertension. His narrative reminds us how a simple procedure like echocardiography can be instantly useful in detecting LVH in the clinical setting; his article reminds the reader about the value of early detection of target organ damage in clinical practice. Dr. Vijayan's article on white coat hypertension (WCH) helps the reader to understand in depth about the manifestations of WCH and its prognosis. Dr. Santosh *et al.* brought to the readership an old technique angiotensin-converting enzyme inhibitor radionuclide renography in the modern diagnosis of renovascular hypertension. It should be readily evident to the readers that when used "properly," renography still has a diagnostic role. Dr. Krishnakumar in his review elucidates the mechanisms and management of resistant hypertension; he provides simple steps on tackling resistant hypertension in the community. Dr. Geetha's article describes to us that secondary hypertension, while not so common should not be missed by busy practitioners; she describes the features of secondary hypertension which may help the reader in considering diagnostic work-up in certain patients with hypertension. The reviews written by the senior consultants from the world-famous Baylor University Medical Center, Dallas, USA, provide the latest scientific information on the statin use and on the important critical adverse relationship between chronic kidney disease and CVD. And finally, I have reviewed the subsets of hypertension in India which are missed and not documented. I hope that the description will be helpful to the readers.

I expect the readers to enjoy and experience, as much as I did, the public health significance of the varied articles in this issue of the Hypertension Journal.

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Review Article

Statin Update: Intolerance, Benefit, and Beyond

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Abstract

Statins (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors) comprise a class of lipid-lowering therapy (LLT) with demonstrated effects on reducing cholesterol synthesis so that less very low-density lipoprotein cholesterol (LDL-C) are secreted into plasma by the liver, ultimately reducing the concentration of plasma LDL-C. An additional effect of statins is upregulation of sterol regulatory element-binding protein 2, upregulation of this protein increases the density of LDL-receptors on the cell surface of hepatocytes and causes greater clearance of LDL-C. Therefore, because statins reduce the creation and increase the clearance of a family of atherogenic particles (particularly LDL-C), there is a clear biologic rationale for the reduction in atherosclerotic cardiovascular disease (ASCVD) events shown in multiple large-scale clinical trials. This makes statins well-suited as the base of therapy in the prevention and treatment of ASCVD. Real and perceived intolerance is the greatest detractor of statins from the potential public health benefits of broad-scale use. Up to one-third of patients who are prescribed statins fail to take them over the long-term and thus derive no benefit. About half of these patients have "perceived statin intolerance," in which they believe they have stain intolerance due to conflated chronic symptoms or concern for adverse effects. Randomized, placebo-controlled blinded trials including such patients demonstrate that approximately 85% can, in fact, tolerate a statin during the blinded period. The other half of the statin-intolerant population is believed to have "real statin-intolerance" due to reproducible legitimate adverse effects such as myalgias, increases in hepatic transaminases, and malaise; there is a pharmacoepidemiologic explanation for this 15% of the patient population. The full public health benefit of statins can only be accomplished through improved patient education and public awareness. This paper will provide an update on statins and their position in clinical lipidology, especially given advances in other forms of LLT.

Key words: Cardiovascular death, intolerance, lipids, low-density lipoprotein cholesterol, myalgia, myocardial infarction, statin, stroke

Introduction

Statins, also known as 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are a class of lipid-lowering therapy (LLT) that has proven effects in reducing the synthesis of cholesterol and as a result, less very low-density lipoprotein cholesterol (VLDL-C) is secreted by the liver into plasma.[1] With less VLDL, there is less conversion to intermediate density lipoprotein (IDL) cholesterol and ultimately LDL-C. Thus, on average, administration of moderate intensity statins can result in a 30–50% reduction in LDL-C; similarly, high-intensity statins can result in a >50% reduction.[2] In addition, statins upregulate

sterol-regulatory element binding protein-2 transcription factors, increasing the density of LDL receptors (LDL-R) on the cell surface of hepatocytes allowing for greater clearance of LDL-C.[3]

There are several explanations for why some patients may have a lower than expected reduction in LDL-C. First and foremost, high intake of dietary saturated fat, which stimulates the production of VLDL can partially negate the statin effect on LDL-C.[4] There are known gain-of-function mutations of HMG-CoA-reductase which render statins less effective.[5-8] Patients with normal alleles for LDL-R stand to have the greatest LDL-C reduction and conversely, those with polymorphisms for this complex 839 amino acid protein receptor are likely to have less LDL-C clearance and less of a statin

benefit. This form of familial hypercholesterolemia (FH) is an important clinical condition to consider when the treated LDL-C remains >145 mg/dl. Other forms of heterozygous FH (HeFH) can result in defects in the production of apoprotein B-100 (apoB), the signal protein on VLDL, IDL, and LDL.[9] Rarely, HeFH can result from a gain-of-function mutation for proprotein convertase subtilisin kexin-9 (PCSK-9), which regulates the density of LDL-R on the hepatocyte surface.

Thus, by reducing the production of a family of atherogenic particles – particularly LDL-C – and increasing its clearance, statins have a strong biologic rationale for the reduction in atherosclerotic cardiovascular disease (ASCVD) events demonstrated in a multitude of large-scale clinical trials. This supports statins as the base of therapy in the prevention and treatment of ASCVD as well as additional therapy as indicated.

Statin Intolerance

The single greatest detractor to statin use and its observed benefit is statin-intolerance. A unified definition of statin intolerance has been proposed: The inability to tolerate at least two different statins – one statin at the lowest starting average daily dose and the other statin at any dose.[10,11] In addition, this statin intolerance should meet these additional conditions: (1) Characterized by inability to use statins due to significant symptoms and/or biomarker abnormalities which can be temporally attributed to the initiation or dose escalation of statins, supported with appropriate drug withdrawal and rechallenge; (2) either "complete" (intolerant to any statin at any dose) or "partial" (intolerant to some statins at some doses); and (3) not attributable to established predispositions such as drug-drug interactions and untreated chronic disease (hypothyroidism, fibromyalgia, and osteoarthritis). Up to one-third of patients who are prescribed statins do not take them over the long-term and hence derive no benefit. Approximately half of such individuals have "perceived statin intolerance" in which conflated chronic symptoms or concern for adverse effects cause them to believe they have statin intolerance. When these individuals participate in randomized, placebo-controlled blinded trials, approximately 85% can tolerate a statin during the blinded period. The other half of the statin-intolerant population is believed to have "real statin intolerance" due to reproducible bona fide adverse effects; most commonly myalgias, increases in hepatic transaminases, and malaise. Data from the Statin Response Examined by Genetic Haplotype Markers study and the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine study found that polymorphisms for the organic anion transporter 1, which is responsible for clearance of statins and stain alcohols by the liver, were associated with statin intolerance as defined by a composite adverse event of discontinuation for any side effect, myalgia, or a creatine phosphokinase >3× upper limit of normal during follow-up (occurred in 19%).[12] The SLCO1B1*5 mutation was associated with intolerance of pravastatin and more so with simvastatin, which requires cytochrome P450 3A4

detoxification before the OATP1 step. Furthermore, there was evidence supporting a gene-dose effect (rates of statin intolerance in those with 0, 1, or 2 alleles were 19%, 27%, and 50%, respectively, *P* = 0.01). When these data are considered together with what is known about statin clearance with glucuronidation, cytochrome P450, and now OATP1 systems, it is reasonable to infer that impaired drug clearance and high drug levels (genetically and/or due to drug-drug interactions) play a role in the pathogenesis of statin intolerance in at least half of those who are unwilling to take this class of agents.[13] Importantly, Vitamin D deficiency, ubiquinone depletion, coenzyme Q10, and low lipid levels are unlikely to play pathogenic roles in statin toxicity.[14] In summary, there is a pharmacoepidemiologic explanation for this 15% of the population and only through improved patient education and public awareness can the maximal public health benefit of statins be realized.[15,16]

Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) Trial as a Working Example of CV Benefit

There have been many analyses of the CV benefits of statins. In general, the higher the LDL-C and greater risk, the greater the benefit of statins on coronary heart disease (CHD) events. The most striking example is the JUPITER trial [Table 1].[17] This trial recruited *n* = 18,702 statin-naïve men >50 years and women >60 years without diabetes, LDL-C <130 mg/dl, and high sensitivity C-reactive protein (hs-CRP) >2.0 mg/L (present in 2/3 who were screened) and randomized them to rosuvastatin 20 mg daily versus placebo. Rosuvastatin reduced LDL-C from 108 to 55 mg/dl (48% reduction), and this was associated with a 44% reduction in the primary endpoint of myocardial infarction, stroke, revascularization, hospitalization for unstable angina, and cardiac death, *P* < 0.00001. There was a 47% risk reduction in the traditional tripartite endpoint of nonfatal myocardial infarction, stroke, or CV death, *P* < 0.00001. Finally, there was a 20% reduction in all-cause death, *P* = 0.02. From a relative risk reduction standpoint, the JUPITER trial stands as the most successful primary prevention study of statins. The success of this trial is partly ascribed to the use of a high-potency statin and recruiting statin-naïve patients, with the results of patients with hs-CRP > 2.0 mg/dl implying that multiple confounding risk factors that raise hs-CRP were present (adiposity, metabolic syndrome, hypertension, smoking, etc.).

Beyond Statins

In the United States, the entry of generic ezetimibe into the marketplace will allow much greater use of this adjunctive medication. Ezetimibe (when used in addition to a statin) lowers LDL-C by an additional ~18% by impairing enterohepatic reabsorption of cholesterol.[18] This is roughly 3 times greater efficacy than a strategy of doubling the statin dose.[19] The Improved Reduction of Outcomes: Vytorin Efficacy

Table 1: Comparison of three contemporary seminal trials of LLT: The JUPITER, IMPROVE-IT, and further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk (FOURIER) trials

Clinical trial	JUPITER	IMPROVE-IT	FOURIER
Baseline characteristics (averaged between treatment and control groups)	Median age 66.0 years Male sex 61.5% White race 61.8% Diabetes 0% History of MI 0%	Mean age 63.6 years Male sex 75.7% White race 83.8% Diabetes 27.2% History of MI 21.5%	Mean age 62.5 years Male sex 75.5% White race 85.1% Diabetes 36.7% History of MI 80.9%
Study population	17,802 patients, assigned in a 1:1 ratio to rosuvastatin (20 mg daily) (n=8901) or placebo (n=8901)	18,114 patients, assigned in a 1:1 ratio to simvastatin (40 mg) + ezetimibe (10 mg) (n=9067) or simvastatin monotherapy (40 mg) (n=9077) daily	27,564 patients, assigned in a 1:1 ratio to evolocumab (either 140 mg every 2 weeks or 420 mg monthly) (n=13,784) or placebo (n=13,780)
Primary and composite secondary end points	Primary: MACE (nonfatal MI, nonfatal stroke, unstable angina, revascularization, CV death) Secondary: MI, stroke, CV death	Primary: MACE (CV death, major coronary event [MI, unstable angina, revascularization], stroke) Secondary: (1) Death, major coronary event, stroke. (2) Death (coronary heart disease), MI, urgent revascularization. (3) CV death, MI, unstable angina, revascularization, stroke	Primary: MACE (CV death, MI, stroke, unstable angina, revascularization) Secondary: CV death, MI, stroke
Baseline LDL-C	Median level 108 mg/dl (2.8 mmol/L)	Mean level 93.8 mg/dl (2.4 mmol/L)	Median level 92 mg/dl (2.4 mmol/L)
LDL-C reduction in the treatment group	50%	24%	59%
Primary and composite secondary endpoint RRR	MACE−0.44 (HR 0.56, 95% CI 0.46–0.69, *P*<0.0001) MI, stroke, CV death−0.47 (HR 0.53, 95% CI 0.40–0.69, *P*<0.00001)	MACE−0.064 (HR 0.936, 95% CI 0.89–0.99, *P*=0.016) Death, major coronary event, stroke−0.05 (HR 0.95, 95% CI 0.90–1.0, *P*=0.03) Death (coronary heart disease), urgent revascularization -0.09 (HR 0.91, 95% CI 0.85–0.98, *P*=0.02) CV death, MI, unstable angina, revascularization, stroke−0.05 (HR 0.95, 95% CI 0.90–1.0, *P*=0.04)	MACE−0.15 (HR 0.85, 95% CI 0.79–0.92, *P*<0.001) CV death, MI, stroke−0.20 (HR 0.80, 95% CI 0.73–0.88, *P*<0.001)
All-cause mortality RRR	−0.20 (HR 0.80, 95% CI 0.67–0.97, *P*=0.02)	−0.01 (HR 0.99, 95% CI 0.91–1.07, *P*=0.78)	N/A (HR 1.04, 95% CI 0.91–1.19, *P*=0.54)
Efficacy and safety of LLT	Rosuvastatin significantly reduced the incidence of major cardiovascular events, without significant increase of myopathy, hepatic injury or cancer but with a high incidence of physician-reported diabetes	Ezetimibe added to simvastatin lowered LDL-C levels and improved cardiovascular events. No significant differences in adverse effects were found between statin and placebo groups	Evolocumab lowered LDL-C levels and reduced the risk of cardiovascular events. No significant differences in adverse effects were found between evolocumab and placebo groups.

MI: Myocardial infarction, MACE: Major adverse cardiovascular event, CV: Cardiovascular, LDL-C: Low-density lipoprotein cholesterol, RRR: Relative risk reduction, HR: Hazard ratio, CI: Confidence interval, N/A: Not available. LLT: Lipid-lowering therapies, JUPITER: Justification for the use of statins in prevention: An intervention trial evaluating rosuvastatin, IMPROVE-IT: Improved reduction of outcomes: Vytorin efficacy international trial

International (IMPROVE-IT) Trial [Table 1] randomized 18,144 participants with acute coronary syndromes to ezetimibe 10 mg daily in addition to simvastatin 40 mg p.o. q.d. or simvastatin alone. The combination therapy produced an achieved LDL-C of 53.7 mg/dl as compared to 69.5 mg/dl in the simvastatin-only group.[20] This additional 22.7% reduction in LDL-C attributable to ezetimibe was associated with a 2.0% absolute risk reduction in the primary endpoint of a major coronary event (nonfatal myocardial infarction, hospitalization for unstable angina, or coronary revascularization), stroke, or CV death, P = 0.016. IMPROVE-IT – considering JUPITER – suggests that (1) the larger relative benefit is due to the statin and (2) the addition of ezetimibe to statin is associated with further LDL-C lowering. The modest relative benefit in the reduction of events in IMPROVE-IT may be partly due to the limited percent LDL-C lowering and the patient population post-acute coronary syndromes where other factors including prothrombotic and procedural may have introduced variation in the natural occurrence of CHD events.[21]

The advent of PCSK-9 inhibitors has raised an entirely new set of issues with respect to lipid management and reduction in CHD events. These monoclonal antibodies to PCSK-9 allow LDL-R to recycle to the cell surface and clear LDL-C with greater efficiency and have been associated with an additional 60% reduction in LDL-C. The further CV Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial [Table 1] randomized 27,564 patients with stable coronary disease on maximally tolerated statin therapy and LDL-C of 92 mg/dl to evolocumab in standard doses or placebo and the resultant LDL-C values were 30 mg/dl (59% reduction).[22] This was associated with a 15% relative risk reduction in the primary endpoint of nonfatal myocardial infarction, ischemic stroke, coronary revascularization, hospitalization for unstable angina, or CV death, P < 0.001.

Thus, when a statin is used at baseline, the addition of ezetimibe (22.7% additional lowering LDL-C and 2.0% absolute risk reduction in CHD) and monoclonal antibodies against PCSK-9 (59% additional LDL-C lowering and 15% relative risk in CHD) improve outcomes significantly. The largest relative benefit appears to be with the statin positioned as the foundation of therapy (up to ~50% reduction in CHD risk), likely due to its mechanism of action in reducing the production of all the atherogenic particles while upregulating LDL-R at the same time. It is entirely possible that whichever drug is positioned as the first form of LLT may have the largest role in reducing CHD events; however, given the mechanism of action and the results of recent clinical trials, it is unlikely there will be a departure from statins as first-line LLT in patients at risk for and with CHD.

Mechanism of Action for Statins, Ezetimibe, and Monoclonal Antibodies Against PCSK-9

While statins, ezetimibe, and monoclonal antibodies against PCSK9 all contribute to the reduction of LDL-C levels, the mechanism of action for each LLT is different [Figure 1].[17,19,20]

Thus, the use of these agents is complementary to one another and is attractive both mechanistically and clinically.

Statins reduce cholesterol biosynthesis in the liver; this is associated with a reduction in LDL cholesterol and decreasing the incidence of CV events. These beneficial effects make it possible for statins to act as primary and secondary prevention of CV events.[1] The mechanism of action for statins is dependent on the inhibition of HMG-CoA reductase, an enzyme that converts HMG-CoA into mevalonic acid, a cholesterol precursor that catalyzes the rate-limiting step in cholesterol production.[1,23,24] Statins reduce serum cholesterol by reducing the synthesis of cholesterol in the liver through HMG-CoA inhibition.[24] The reduction of cholesterol in hepatocytes leads to the increase of hepatic LDL-R (these determine the reduction of circulating LDL and its precursors, IDL, and VLDL), leading to LDL-C being taken from the blood into the liver.[1,24] Interestingly, cholesterol reduction by statins leads to a significant increase in endothelial function.[1] In addition, statins inhibit transendothelial migration and chemotaxis of neutrophils, producing an anti-inflammatory effect.[1]

Ezetimibe is an intestinal and biliary cholesterol absorption inhibitor. Its primary target of action is to inhibit the delivery of intestinal cholesterol to the liver through the transport protein Niemann–pick C1 like 1 protein (NPC1L1). Therefore, the mechanism of action for ezetimibe is dependent on the inhibition of NPC1L1. By binding to the NPC1L1 receptor, ezetimibe prevents uptake of intestinal luminal micelles – which contain cholesterol – into enterocytes.[24,25]

Because cholesterol uptake is reduced and hepatic cholesterol is decreased, ezetimibe causes a depletion of hepatic LDL-C stores, leading to upregulation of hepatic LDL-R, thereby causing LDL-C to be taken up by the liver from the blood.[24,25] In addition to inhibition of intestinal cholesterol absorption, ezetimibe is also able to interact with hepatic NPC1L1, and thus reduces biliary cholesterol absorption. The dual absorption further reduces serum cholesterol levels.[25] As demonstrated in IMPROVE-IT, combining ezetimibe with simvastatin provides greater reductions in LDL-C levels than those achieved with either agent used as monotherapy; this incremental CV benefit is presumably due to reductions of both intestinal and hepatic sources of cholesterol.[17,26,27]

This benefit is consistent with the LDL hypothesis in that lowering LDL acts as a primary target of therapy for the primary and secondary prevention of CV events.[25,28] It is noteworthy that the NPC1L1 receptor (the target of ezetimibe) and HMG-CoA reductase (the target of statins) are roughly the same by polymorphisms, indicating that the efficacy of LDL-C lowering through the NPC1L1 receptor is comparable to that through the HMG-CoA reductase.[28]

PCSK9 plays an important role in LDL-C/LDL-R metabolism.[29] Therefore, anti-PCSK9 monoclonal antibody-induced reduction of LDL-C is dependent on the inhibition of PCSK9, which increases LDL-C metabolism by recycling LDL-R on the surface of hepatocytes. Under conditions of high levels of PCSK9, the degradation of the PCSK9-LDL-R complex in lysosomes is increased. In contrast, when PCSK9 levels are low, hepatic surface LDL-R levels become high because LDL-R
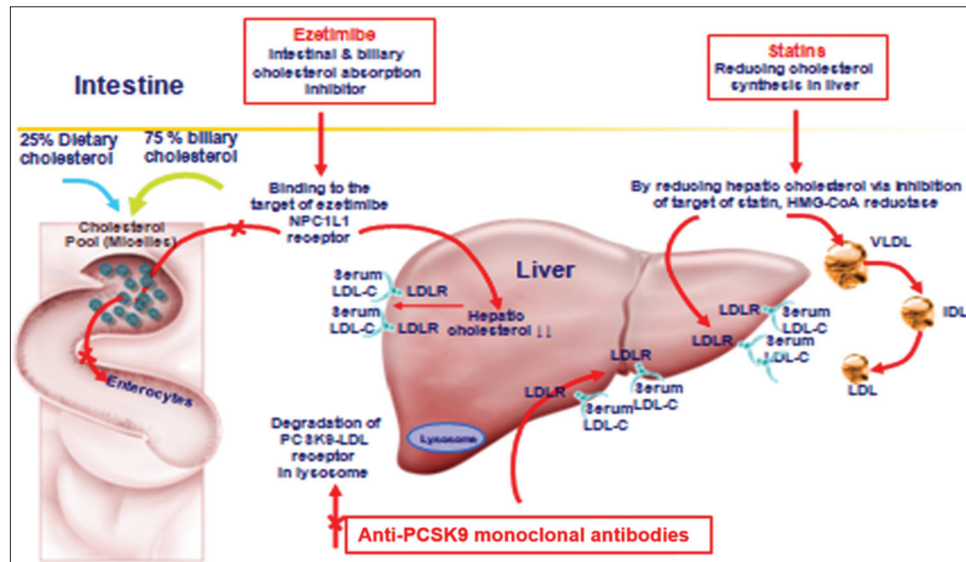
Figure 1: Mechanisms of action for statins, ezetimibe, and monoclonal antibodies against PCSK-9

can be recycled to the hepatic surface after delivery of LDL-C particles to endosomes, thus resulting in lower circulating LDL-C levels.[29] PCSK9 activity can be inhibited by monoclonal antibodies against PCSK9 through the extracellular pathway.[29]

Data from the JUPITER trial demonstrate that rosuvastatin-treated patients achieved both LDL-C and hs-CRP reduction, thereby leading to a reduction in ASCVD events.[20] The results indicate that the direct linkage between cholesterol and inflammation in the atherosclerotic plaque exists, and the beneficial impact of statins on inflammation is proportional to the reduction of levels of LDL-C.[22] Recently, it has become clear that hs-CRP is not a causal factor for atherosclerosis, but rather a powerful risk biomarker for ASCVD events. In fact, both rosuvastatin and ezetimibe have the ability to decrease CRP and improve CV outcomes.[22] However, the relationship between the reduction of LDL-C and CRP has not been observed in clinical trials of anti-PCSK9 monoclonal antibodies, perhaps due to the exclusion of patients with systemic inflammation.[22] Another postulated mechanism of action by which statins and ezetimibe decrease CV risk is by improving vascular endothelial dysfunction and by reducing pro-inflammatory cytokines, CRP, and damage of the arterial wall.[22] A recent clinical trial comparing simvastatin at a high dose of 80 mg to simvastatin 10 mg/ezetimibe 10 mg found that the decrease in LDL-C and improvement of endothelial function (assessed by flow-mediated vasodilation) were similar between the groups.[30] The results suggest that the improvement in endothelial function with statins is likely dependent on a reduction in LDL-C, independent of the dose of statin administered, without evidence of a pleiotropic action.[30]

Conclusions

There remains a large opportunity to improve CHD event rates across the globe with the use of statins in primary and secondary care. Approximately half of "statin intolerance" is perceived and is amenable to another trial of statin therapy in the well-prepared patient. The other half of statin intolerance has a genetic basis in impaired clearance of statins and their metabolic breakdown products which are toxic to skeletal myocytes when they remain in high concentrations in plasma over time. The use of rosuvastatin in a primary prevention population at risk for CHD resulted in a 48% reduction in LDL-C and a corresponding 44% reduction of CHD, conferring a 20% reduction in mortality. The addition of ezetimibe or PCSK-9 inhibition therapy to maximally tolerated statins further lowers LDL-C by 24% and 50%, respectively. However, this corresponds to a much smaller relative risk reduction of CHD events (6% and 15%, respectively) and neither ezetimibe nor PCSK-9 inhibitors have demonstrated a mortality benefit. Therefore, at this time, statins should remain foundational LLT in the prevention of CHD events.

- The mechanism of action for statins: By reducing the synthesis of cholesterol in the liver through the HMG-CoA inhibition, statin-reduced cholesterol in hepatocytes converts VLDL to IDL to LDL, and results in the increase of hepatic LDL-R, thereby leading to LDL-C being up taken from blood into the liver (upper left corner of figure).
- The mechanism of action for ezetimibe: By binding to the NPC1L1 receptor, ezetimibe prevents uptake of intestinal luminal micelles, which contain cholesterol, into enterocytes. Due to reduced cholesterol uptake and decreased hepatic cholesterol, ezetimibe leads to upregulation of hepatic LDL-R, causing LDL-C to be taken up by the liver from the blood (upper right corner of figure).
- The mechanism of action for anti-PCSK9 monoclonal antibodies: By inhibition of PCSK9 on the surface of hepatocytes, anti-PCSK9 monoclonal antibodies interrupt the degradation of the PCSK9-LDL receptor complex in lysosomes, and recycle LDL-R on the hepatic cell surface,

thus resulting in lower circulating LDL-C levels (bottom of figure).

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Review Article

Echocardiography in Hypertension

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Abstract

Hypertension (HTN) is a treatable risk factor for cardiovascular diseases. Accurate diagnosis of HTN along with the assessment of cardiovascular risk is essential for proper treatment in hypertensive patients. Echocardiography provides prognostic factors in HTN including left ventricular mass, systolic function, diastolic function, left atrial function, and size. Apart from routine echo methods, tissue Doppler, three-dimensional echo, and strain imaging are newer echo techniques in the evaluation of hypertensive patients. Familiarity with routine and newer echo parameters is helpful for risk stratification in HTN.

Key words: Left ventricular mass, echo parameters, cardiovascular risk

Introduction

Echocardiography is the simple routine investigation which provides information regarding pathophysiology and complications of hypertension (HTN). Anatomical and physiological changes in heart can be detected with this reproducible imaging technique [Figure 1]. Early target organ dysfunction can be detected by echo as a predictor of risk.

Indications of Echocardiography in HTN[1]

- In patients with mid-diastolic HTN (90–94 mmHg) with no other cardiovascular risk factors or evidence of end-organ damage (including lack of or equivocal signs of the left ventricular hypertrophy [LVH] on electrocardiography [ECG])
- The demonstration of LVH by echo is generally an indication for medical therapy, while non-pharmacological modalities alone can be used if the left ventricle (LV) mass is normal
- In patients who have no evidence of end-organ damage, who have either severe or refractory HTN or HTN that is present in the doctor's office, but not at home or work. The absence of LVH in this setting suggests either HTN of recent onset or white coat HTN. The presence of the latter can be confirmed by ambulatory blood pressure (BP) monitoring
- Similarly, the presence of significant LVH on echocardiography, with normal clinical BP recordings, mandates ambulatory BP monitoring, to detect masked HTN
- In patients with known or suspected concomitant heart disease in whom the heart disease itself needs further evaluation or in whom the type of heart disease might suggest a particular form of antihypertensive therapy. As an example, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker would be preferred in a patient with systolic dysfunction or mitral regurgitation
- In patients who have a bundle branch block on ECG.

In contrast, performance of an echocardiography for the purpose of measuring LV mass is not recommended for the selection of antihypertensive therapy or for the assessment of LV mass in patients without adequate BP control.[1]

The European Society of Cardiology HTN guidelines in 2013 mention echocardiography as the second approach after routine history, clinical examination, and laboratory tests. Echocardiography detects LVH, left atrial (LA) dilatation, or associated heart diseases (Class IIb). Canadian HTN Education Programme in 2014 suggested echo evaluation in selected patients with HTN. Echo is not routinely indicated in all hypertensive patients [Table 1 and Figure 2]. If cardiac failure or coronary disease is suspected clinically, LV mass, systolic and diastolic function should be assessed by echo.[2]

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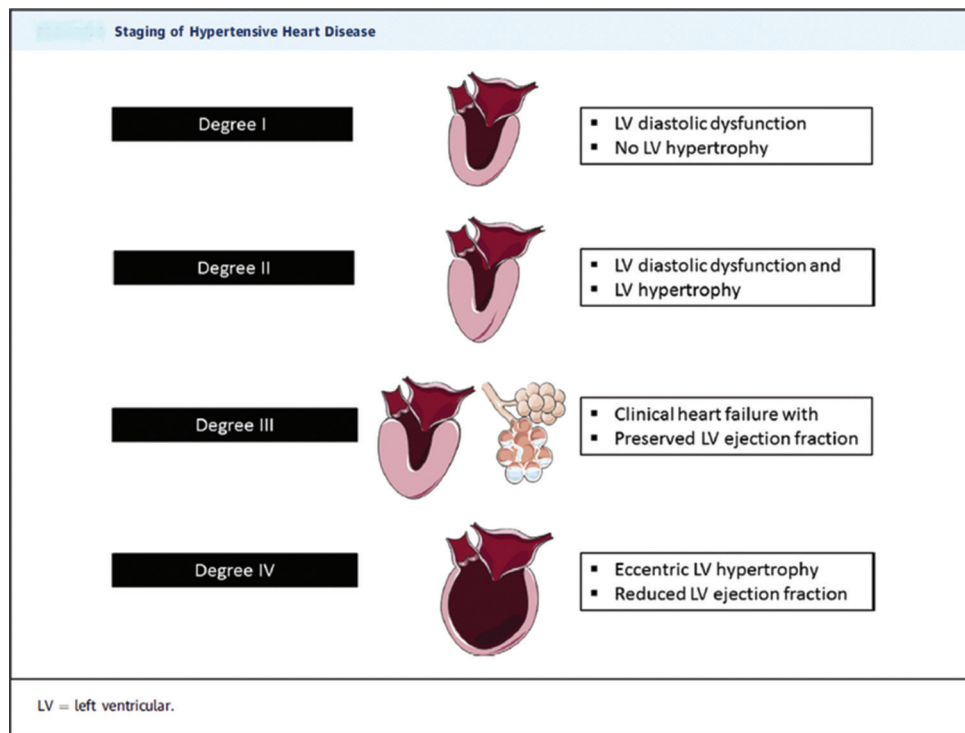
Figure 1: Staging of hypertensive heart disease
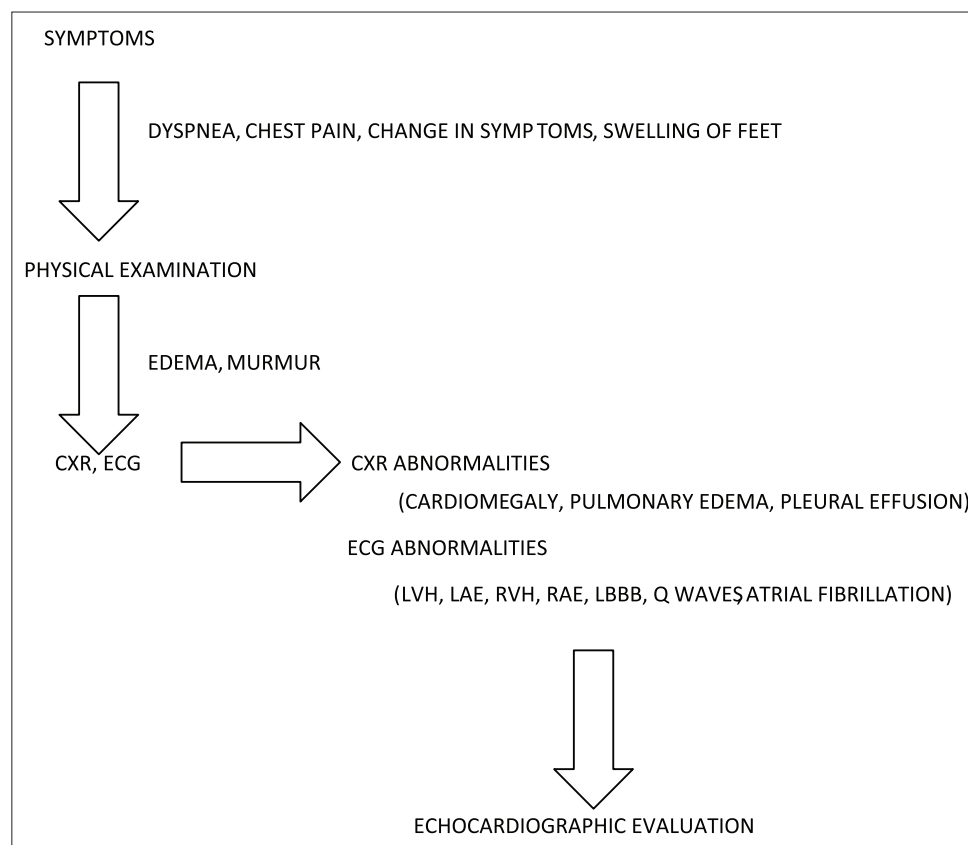
Figure 2: Clinical flow chart for echocardiographic evaluation in hypertension

Echocardiographic Evaluations

LV Mass[3]

Echo is more sensitive than ECG for the assessment of LVH. Echo helps in cardiovascular risk assessment and in selection of proper antihypertensive treatment [Figures 3-5]. LV mass can be measured with the equation from the American Society of Echocardiography, using two-dimensional (2D) linear LV measurements [Figure 6].

LV mass = 0.8 × 1.04 × ([LVIDd + PWTd + SWTd] 3– LVIDd 3) + 0.6

(LVID-LV internal diameter - end diastole, PWTd posterior wall thickness - end diastole, and SWTd Interventricular septal wall thickness - end diastole). Small variations in calculation can cause significant changes in values. Relative wall thickness (RWT), measured as (2 × PWTd)/LVIDd, classifies LVH into concentric

Table 1: Clinical indications for echocardiography in hypertension

Management of hypertension	Indications for echocardiography
Suspected heart failure	Symptoms – dyspnea, edema
	Clinical findings – edema, murmur
	ECG findings – LVH, LAE, LBBB, pathological Q waves, poor R wave progression, atrial fibrillation
	X-ray chest abnormalities – cardiomegaly, pulmonary edema, pleural effusion
Suspected structural heart disease	Symptoms – dyspnea
	Clinical findings – edema, murmur
	ECG – LVH, RVH, LAE, RAE
	CXR – cardiomegaly, pulmonary edema, pleural effusion
Suspected coronary artery disease	Symptoms – chest pain, dyspnea
	ECG abnormalities – ST T Changes
Assessing cardiovascular risk	

RAE: Right atrial enlargement, LAE: Left atrial enlargement, LVH: Left ventricular hypertrophy, RVH: Right ventricular hypertrophy, ECG: Electrocardiogram, LBBB: Left bundle branch block
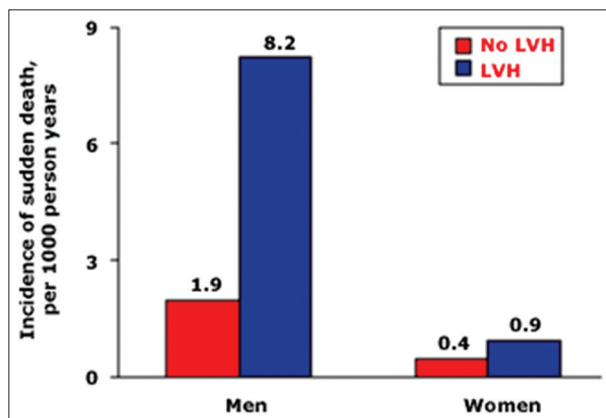
Figure 3: Effect of LVH on incidence of sudden cardiac death

type (RWT > 0.42) or eccentric type (RWT< 0.42). Cutoff levels of LV mass, suggesting LVH – are 125 g/m^2 in men and 110 g/m^2 in women.[2] Concentric hypertrophy correlated with mortality risk for patients with suspicion of coronary artery disease (CAD). Three-dimensional (3D) echocardiographic assessment of LV mass correlated well with magnetic resonance imaging (MRI).

LV Systolic Function

Ejection fraction (EF) can be assessed with modified Simpson's method. Normal EF is >55%. Echo suggests evidence of CAD along with the assessment of LV function. 3D echo measurement has advantages for calculation of LV volumes in patients with regional wall motion abnormalities (RWMA) or LV aneurysms. 3D echo correlates well with MRI assessment. 3D echo has significant reproducibility. Tissue Doppler imaging (TDI) assesses mitral annular movement. Mitral annular velocity is less in HTN with normal EF. Hence, it predicts subclinical LV systolic dysfunction. Myocardial function assessment by strain echo has advantages over routine LVEF measurement by echo. Global and regional myocardial functions are well assessed. 2D speckle tracking echo assesses myocardial deformation by tracking of natural acoustic markers formed between ultrasound and myocardium. These markers are described as speckles. Angle independent and multidirectional (longitudinal, radial, and circumferential) strain values can be derived. Inter- and intra-observer variability with 2D strain echo is much less than
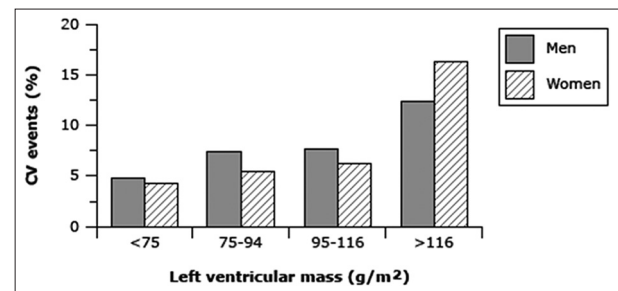
Figure 4: Effect of LV mass on cardiovascular events
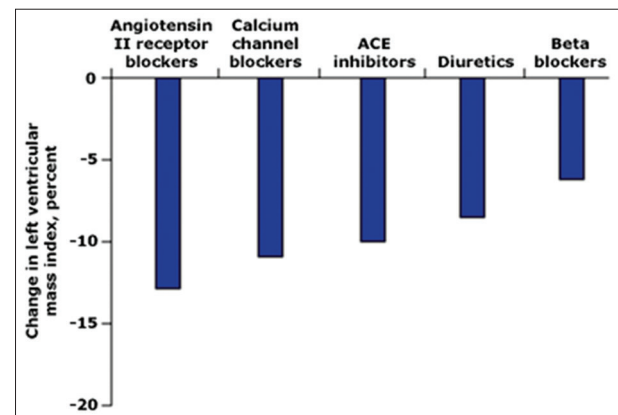
Figure 5: Comparative efficacy of antihypertensive drugs to reduce LV mass
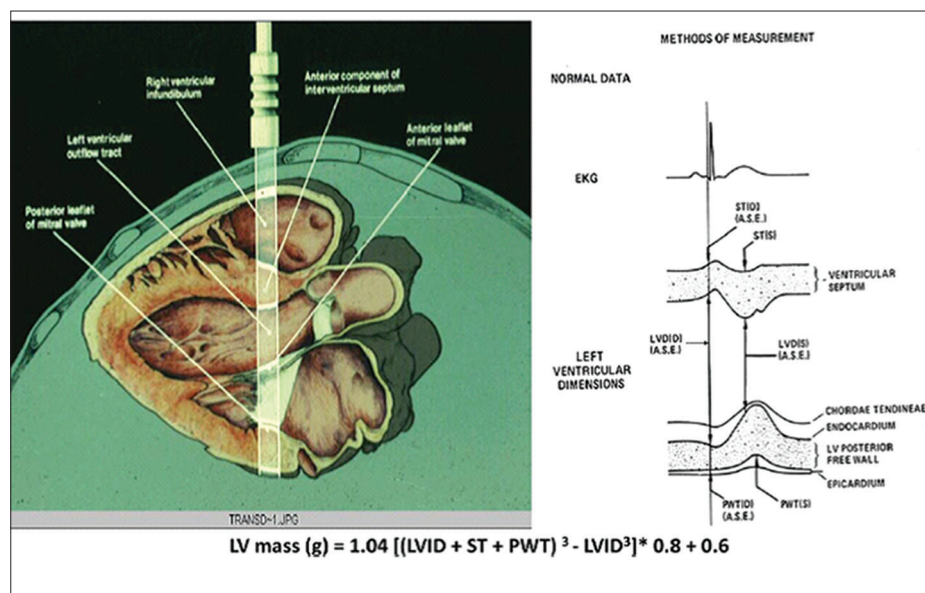
Figure 6: Calculation of LV mass

tissue Doppler assessment. Subclinical target organ damage can be assessed early. Longitudinal strain is less in patients with HTN, having normal LV systolic function, and it correlates with serum tissue inhibitor of matrix metalloproteinase-1 value, a biomarker for myocardial fibrosis.

3D strain echocardiography can assess the motion of myocardial speckles. Assessment of the whole LV from a single volume data can be done with 3D strain echocardiography.[2]

LV Diastolic Function [Table 2][2]

Echocardiography assesses LV diastolic function. LV filling pressure is estimated. Increased LA size and volume suggest increased LV filling pressure. Increased LA diameter was seen in 20% of hypertensive patients. Enlarged LA indicates elevated LV filling pressure and increased LA size and volume correlate with morbidity and mortality.

Mitral inflow pattern assessed by pulsed-wave Doppler technique estimates diastolic dysfunction. Isovolumetric relaxation time, ratio of E and A velocities, deceleration time of E velocity, and duration of A wave can be used to assess diastolic dysfunction. However, these velocities can be influenced by multiple factors including age, heart rate and rhythm, cardiac output, mitral annular size, and LA function.

Mitral annular velocity can be assessed by pulsed-wave Doppler of mitral annulus from TDI [Figure 7].

The ratio E/e' can be a good indicator of LA pressure and it is the most feasible marker for estimation of LA filling pressure. This ratio correlates well with LA filling pressure. If E/e' is <8 correlation is better. Ratio >15 indicates elevated LA filling pressure.

E/e' ratio may not always correlate with LA filling pressure. In patients with systolic heart failure, there is poor correlation. In patients with tachycardia, valvular heart disease, and left bundle branch block, the ratio may be inaccurate.

Diastolic stress echo with exercise stress identifies hemodynamic effects of exercise-induced rise in diastolic filling pressure, as a non-invasive method. Subclinical diastolic dysfunction can be diagnosed in patients having dyspnea.

LA Assessment

LA enlargement is seen in systemic HTN, in the absence of valvular heart disease, and it is usually seen along with obesity, LVH, and metabolic syndrome. The LA size is measured with parasternal long axis view – end systole at its maximum dimension, avoiding foreshortening. Normal value is 2.7–3.8 cm in female and 3.0–4.0 cm in male.[2]

LA volume is measured by 2D echo [Figure 8]. Normal value is <28 ml/m² and enlarged LA predicts prognosis. Rise in LA size and volume indicates diastolic dysfunction in HTN and suggests morbidity and mortality. Volume >34 ml/m² marks poor prognosis predicting death, heart failure, atrial fibrillation (AF), and ischemic stroke. LA volume does not change fast with treatment, it is not a good marker of treatment response.

LA strain with strain rate identifies subclinical dysfunction of atria in HTN.

LA appendage function provides clue of LA function. Reduced function is seen in non-dipper than dipper patients with HTN. 3D echo also measures size and function of LA.

Associated EchoCharacteristics in HTN[4]

Secondary pulmonary artery pressure (PAH) occurs due to raised LA pressure being transmitted into pulmonary vasculature. Heart failure with preserved left ventricular ejection fraction leads to PAH. Echo measures pulmonary artery pressure
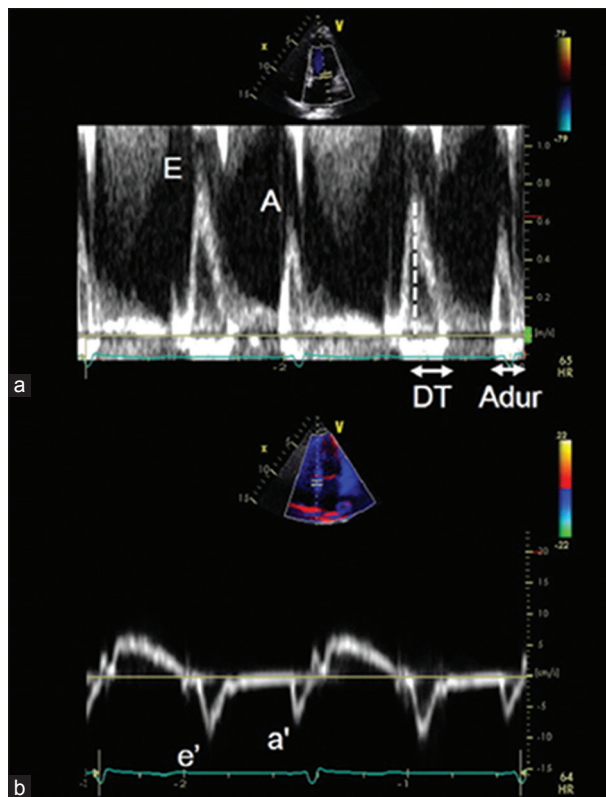
Figure 7: Left ventricular diastolic function assessment
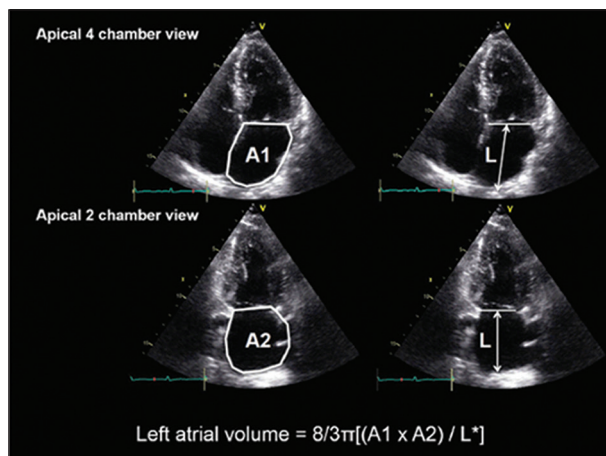
Figure 8: Left atrial volume measurement

with tricuspid regurgitation (TR) velocity or right ventricular outflow tract (RVOT) velocity.[2]

PASP=RVSP=RAP + 4 X TR V max^2

RVOT acceleration denotes the time from beginning of RV ejection to maximum systolic flow velocity. Normal value is 140 ms and is reduced in PAH (near 80 ms).

HTN acts as risk factor causing atherosclerosis. Atherosclerotic cardiac involvement is seen during echo evaluation. CAD, ascending aorta dilatation, and aortic valve

Table 2: Echo parameters for LV Diastolic function (Based on European Society of Cardiology guidelines)[5]

Measurement	Abnormal value
LV mass index (g/m^2)	>95 in women, >115 in men
Relative wall thickness (RWT)	>0.42
Diastolic function	
Septal e' velocity (cm/s)	<8
Lateral e' velocity (cm/s)	<10
LA volume index (ml/m^2)	≥34
LV filling pressures	
E/e' (averaged) ratio	>13

LA: Left atrium, LV: Left ventricle, RWS: Relative wall thickness

stenosis or sclerosis may be found. RWMA or LV aneurysm may be found in CAD patients. Stress echo by dobutamine or exercise is more sensitive for CAD. Ascending aorta dilatation is seen along with increased arterial stiffness and LV mass, in about 17 % of patients with HTN. Aortic valve calcification is a common finding, suggesting atherosclerosis. Aortic valve sclerosis predicts clinical events.

Dipper and Non-dipper BP

BP reduction at night time <10% suggests non-dipper pattern of BP. Non-dipper BP pattern is usually seen with high LV mass, reduced LV and RV function. Hence, it predicts cardiovascular events.

Stress Echocardiography

LVH leads to false-positive results in exercise tests by ECG or single-photon emission computed tomography. It does not change the results of stress echo. Exercise echo is thus a better method to diagnose CAD in patients with HTN.[6]

Acute Chest Pain and HTN[6]

In the setting of equivocal ECG changes and negative biomarker, echo evidence of RWMA indicates acute coronary syndrome (ACS). No RWMA by echo rules out significant ACS and points toward HTN as a cause of chest pain. HTN raises intracavitary end-diastolic pressures, which compresses the subendocardial region, inducing ischemia resulting in chest pain, an effect exaggerated by the presence of LVH. Normalizing BP will lead to relief of chest pain and save unnecessary diagnostic workup for ACS in emergency. Bedside echo easily diagnoses aortic stenosis in the presence of chest pain and high BP may reveal dissection of aorta involving ascending aorta and its extent. In young hypertensive patients, echo can reveal coarctation of aorta or aortoarteritis.

Arrhythmias and HTN[6]

Slow progression of HTN results in dilatation of LA. Large LA provides ripe situation for looping sinus rhythm within itself resulting in AF. The LV is increasingly dependent on atrial

contraction for adequate filling. Sudden onset of AF offsets this filling, leading not only to inadequate LV filling but also elevated LA pressure which transmits to pulmonary vasculature. Fibrotic area can act as a substrate for ectopic rhythm generation which results in chronic intractable AF and lead to clot formation with the risk of systemic embolization.

Excessive LVH causes smaller LV cavity with low stroke volume. It also leads to disorganization of the LV contraction of different layers. This can be measured by strain imaging. Excessive LVH results in different areas achieving peak contractions at different times. This mechanical dispersion can be measured by strain imaging. Evidence is emerging that dispersion beyond standard deviation can cause ventricular arrhythmias and sudden cardiac death (SCD). Prediction of subsets of such patients likely to develop ventricular fibrillation and SCD may be possible in future by the use of strain imaging echo technology.[6]

Conclusion

According to the most recent guidelines, initiation and monitoring of the response to the treatment of HTN are based on clinical findings. Echocardiography is the second-line approach in evaluating selected patients. It provides valuable assessment of cardiovascular risk at clinical and subclinical levels. Standard 2D and 3D echo techniques detect end-organ damage at clinical level. New techniques like strain imaging help to diagnose dysfunction at subclinical level. Early detection and treatment can prevent progression of hypertensive heart disease.

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Review Article

White-coat Hypertension

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Abstract

The term white-coat hypertension (WCHT) comes from the reference to the white coats traditionally worn by the doctors. It is also called "isolated office or clinic hypertension." Thomas Pickering coined the term WCHT to denote individuals who were not on the treatment for hypertension but who had elevated office blood pressure and normal blood pressure measured at home or with ambulatory blood pressure monitor. When your blood pressure is taken at home, the systolic value can be 10 mmHg lower than it would be if taken by a doctor and 5 mm lower on the diastolic blood pressure value. For some people, the difference can be even greater. The traditional definition of WCHT is based, therefore, on an elevated office blood pressure with a normal blood pressure during the awake period with ambulatory blood pressure monitoring. The most recent European guidelines propose an alternative definition of WCHT, which encompasses subjects with office systolic/diastolic blood pressure readings of >140/90 mmHg and 24 h blood pressure <130/80 mmHg. This condition cannot be considered as innocent since it is associated with metabolic abnormalities as well as cardiac and vascular end-organ damage. Evidence has been provided that WCHT state is characterized by an increased risk of fatal and non-fatal cardiovascular (CV) events as compared to normotensive individuals. People with WCHT were more likely to be female young less obese and more recently diagnosed with hypertension. The purpose of the review is to provide new insights into the definition, characteristics, CV risk assessment, therapeutic implications, and all-cause mortality in patients with WCHT.

Key words: Ambulatory blood pressure monitoring, white-coat hypertension, sustained HTN

Introduction

The term white-coat hypertension (WCHT) describes a subgroup of untreated individuals with persistently elevated office blood pressure but normal ambulatory blood pressure values. This isolated clinic hypertension is frequently diagnosed in current clinical practice. The prevalence of WCHT depends mainly on the demographic and clinical characteristics of the subjects as well as on the methods (including ambulatory or home blood pressures measurement) and the blood pressure cutoffs used to define normal out-of-office values. Majority of the clinical studies have reported that WCHT accounts for 25–30% of individuals and the phenomenon is reasonably reproducible; however, whether WCHT is a benign phenomenon is still under debate. Failure to identify the condition results in a large expenditure on necessary drugs. Years of investigation have shown that this condition cannot be regarded as "innocent"

nature but with a greater CV risk and, hence, retains important clinical implications.

The task force of the eighth international consensus conference on blood pressure monitoring recommends ambulatory blood pressure monitoring to exclude WCHT in untreated patients when

- Office blood pressure > 140/90 mmHg on >3 separate office visits.
- >2 Blood pressure measurements taken outside the office are <140/90 mmHg frequently using home blood pressure monitoring and
- There is no evidence of hypertensive end-organ damage.

The National Institute for Health and Clinical Excellence guidelines advocate that every person with elevated office blood pressure aged >18 years undergo ambulatory blood pressure monitoring to rule out a diagnosis of WCHT with the potential

for savings in health costs by virtue of unnecessary treatment with antihypertensive drugs.

Once ambulatory blood pressure has confirmed the diagnosis of WCHT, the European Society of Hypertension Working Group on blood pressure monitoring recommends that the diagnosis be reconfigured in 3–6 months and followed up yearly with ambulatory blood pressure monitoring to detect any evidence of progression to sustained hypertension.[1-6]

Etiology

Emotional factors such as anxiety or stress may be responsible for the microneurographic response in which pronounced activation of skin nerves and associated sympathetic inhibition of muscle nerve traffic when physicians take the blood pressure. This anxious emotional response may act as a mechanism in the development of WCHT.[2,3]

Implications

The studies have shown that there is greater risk of future sustained hypertension, high associated metabolic risk, and end-organ damage.[4]

Future Hypertension Risk

There is a greater risk of developing hypertension in white coat subjects based on in-office blood pressure and out-of-office blood pressure values. The condition of sustained blood pressure >140/90 mmHg and mean 24 h blood pressure values <125/79 mmHg or home blood pressure <132/82 mmHg are white-coat hypertensives. 10-year follow-up study showed that 43% of them had progressed to sustained hypertension. Hence, sustained hypertension was 2.5-fold higher for WCHT, even after adjusted for age.

Metabolic Risk

Evidence has supported the association between WCHT and metabolic derangements which may precipitate CV events. When compared to the normotensive individuals, subjects with WCHT may have high triglycerides, uric acid, and glucose values. These subjects with increased waist circumference and body mass index show high blood pressure variability which all contributes to cardiac vascular and renal involvement. The persistent impairment in glucose metabolism has been reported in white-coat hypertensive subjects, and hence, the development of new-onset diabetes mellitus is much more high in white-coat hypertensive patients than in normotensives.

End-organ Damage

Studies show that the development of target organ damage in white-coat hypertensive subjects is intermediate between normotensives and sustained hypertensives. At CV level, there may be an increase in the left ventricular (LV) mass index, a

reduction in early to late mitral flow ratio (an index of the LV distensibility) and greater values of the left atrial diameter. Untreated white-coat hypertensive subjects show the high-risk development of intima-media thickness. Early renal damage may be assessed by urine microalbumin.

Treatment Strategies[4-6]

Maintain a Good Patient-health-care Professional Relationship

WCHT may be addressed through the development of a therapeutic relationship between physician and patient. Effective communication and relationship building can reduce the patient's anxiety about their illness and about their interaction with a physician. Communication between physician and patient is often considered the cornerstone of good medical care.

Relaxation Techniques

Some relaxation techniques such as breathing exercises or meditation may help the patient to calm down before blood pressure checking.

Supportive Management

It mainly includes lifestyle modification, weight reduction, and proper management of other risk factors such as diabetes mellitus, dyslipidemia, and renal dysfunction.

Drug Treatment

Antihypertensive medications may be considered in addition to the lifestyle modifications if there are any associated risk factors including the end-organ damage. In unstable white-coat hypertensive patients, the CV risk has been noted to be low than a stable white-coat hypertensive patient. No any antihypertensive medication is recommended for a stable white-coat hypertensive patient with no additional risk factors and also for an unstable white-coat hypertensive patient.

Conclusion

WCHT is not considered as an innocent condition as it can be associated with metabolic derangements, high CV risks, and other target organ damages, it has to be diagnosed earlier to prevent further complications. Even though there is no evidence-based data regarding treatment of WCHT, the European Society of Hypertension/European Society of Cardiology guidelines suggest that antihypertensive medications to be restricted to high-risk patients.

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Review Article

Angiotensin-converting Enzyme Inhibitor Radionuclide Renogram – A Non-invasive Tool to Suspect Renovascular Hypertension

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Abstract

Renal hypoperfusion due to renal artery stenosis (RAS) activates the renin–angiotensin–aldosterone system, leading to an elevated blood pressure (BP) that constitutes renovascular hypertension (RVH). Differentiation between RVH and RAS is essential because RAS is quiet in many non-hypertensive elderly persons. Furthermore, RAS is an associated but non-causative finding in a number of hypertensive patients. Angiotensin-converting enzyme inhibitors (ACEIs) renogram helps to detect RAS as the cause of hypertension and predicts curability or improvement in hypertension after intervention. ACEI renogram is most cost effective if used primarily in patients with moderate-to-high risk of RVH that includes abrupt or severe hypertension, hypertension resistant to three-drug therapy, bruits in the abdomen or flank, unexplained azotemia or recurrent pulmonary edema in an elderly hypertensive patient, or worsening renal function during therapy with ACEIs. In this report, we describe how ACEI renogram helped in the management of a patient with refractory hypertension due to RAS.

Key words: ACE inhibitor, renogram, DTPA, renal artery stenosis, renovascular hypertension

Introduction

A 42-year-old male who is a known smoker and alcoholic presented to the vascular surgery department with complaints of gripping pain in both lower limbs over the past 6 months. He is undergoing treatment for refractory hypertension (BP 200/130 mmHg) despite optimum medication comprising calcium channel blocker, beta-blocker, and diuretics over 6 years. His serum creatinine was 1.6 mg/dl while the blood sugar, electrolytes, cholesterol, and liver function tests were within normal limits. He is also being treated for chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] = 27 ml/min/1.73m² at diagnosis) and possible bilateral renal artery stenosis (RAS) was considered. Contrast-enhanced computed tomography showed complete occlusion of the right renal artery with contracted right kidney and 70–80% occlusion at the origin of the left renal artery [Figure 1a and b]. Pan angiogram showed a significant peripheral vascular disease of both iliac arteries while

the subclavian, carotid, and upper limb vessels were normal. He was treated for one episode of flash pulmonary edema 9 months ago. At that time, his echocardiography showed concentric LVH and global LVEF of 58%. There was no regional wall motion abnormality. ECG showed ST depression in II, III, and aVF, and therefore, he was started on statins also, along with aspirin. At the time of referral to our institution, his global LVEF was 43%.

We received him in our department to study the functional significance of RAS with 99mTechnetium-DTPA renogram with angiotensin-converting enzyme inhibitors (ACEIs). The patient was prepared as per the Society of Nuclear Medicine and Molecular Imaging guidelines for baseline and ACEI renogram (2 days protocol).[1] He was allowed to continue his medication during the study period. On day 1, baseline renogram was performed by giving intravenous injection of 100 MBq of 99mTc-DTPA in 1.0 ml saline through an intravenous cannula. Sequential dynamic and periodic static images of the abdomen

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were acquired in posterior view (patient in supine position) using a dual-headed gamma camera (GE-Discovery NM 670, USA). Similar study was repeated the next day 1 h after oral administration of 10 mg Enalapril. Blood pressure (BP) in the right upper limb was continuously monitored with the patient in supine position and was found to maintain around
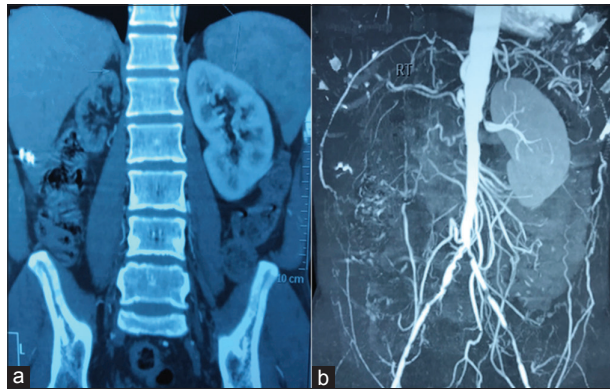
Figure 1: Coronal section of contrast-enhanced computed tomography KUB showing smaller right kidney (a). Digital subtraction angiogram showing narrowing at the origin of the left renal artery with post-stenotic dilatation and complete occlusion with non-visualization of the right renal artery (b)

200/130 mmHg. There was no change in BP 1 h after enalapril administration.

The left kidney showed adequate cortical function with timely tracer transit into pelvis and unobstructed subrenal drainage at baseline study. During ACE inhibition (ACEI), it showed marked parenchymal retention and prolonged intraparenchymal tracer transit, suggesting a high probability of renovascular hypertension (RVH) [Figure 2a and b]. The right kidney did not show any tracer uptake, suggesting non-functional status. The left kidney renogram showed an upsloping pattern of time activity curve during ACEI [Figure 3a and b]. Six different patterns of renogram curves have been described in literature, based on the renal excretory function.[1] They are as follows: 0 normal; 1 minor abnormalities, but with Tmax >5 min and a 20-min/max cortical ratio >0.3; 2 a marked delay in excretion rate with preserved washout phase; 3 delayed excretion rate without washout phase (accumulation curve); 4 renal failure pattern with measurable kidney uptake; and 5 renal failure pattern without measurable kidney uptake.[1] Our patient's baseline renogram showed Type 1 curve which changed to Type 3 during ACEI which represents a high probability for RVH.[1] Quantitative estimates also confirmed the impairment in renal function and prolongation of tracer transit time after ACEI by demonstrating >10% reduction in GFR and >0.15 increase in the 30-min/peak
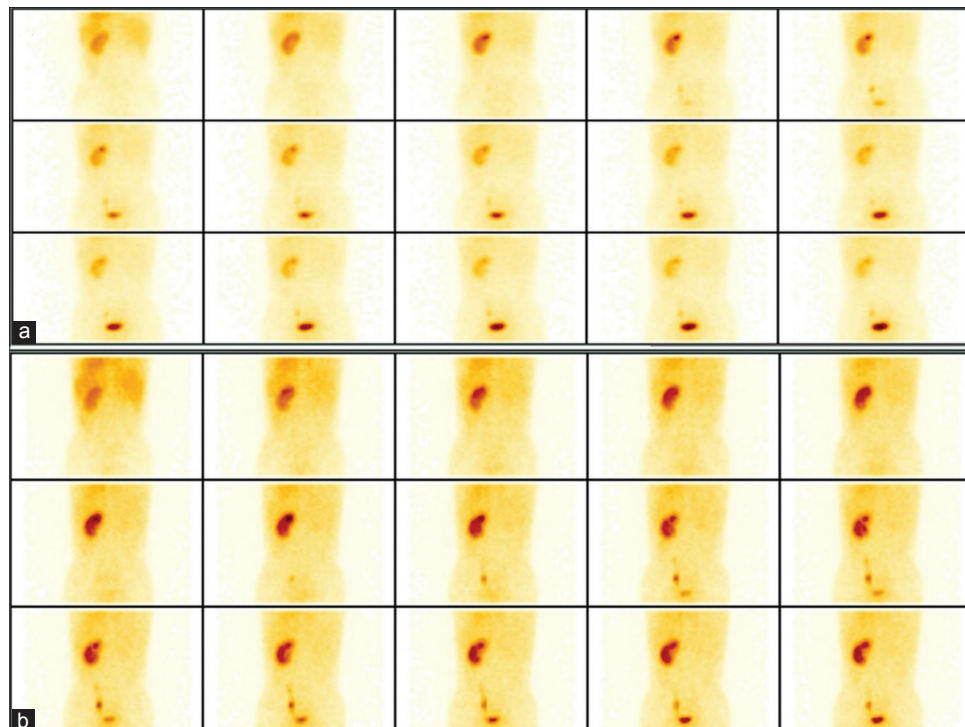
Figure 2: 2 min/frame images of renogram at baseline (a) and during angiotensin-converting enzyme inhibitors (ACEIs) (b). The left kidney shows adequate tracer uptake followed by timely transit into pelvis and excretion into the bladder by 8th min (a). After ACEI, there is a continuous accumulation of tracer in the left kidney with delayed transit into the pelvis and delayed excretion into the bladder by 16th min. An increase in background activity is also seen suggesting impaired tracer clearance by the left kidney. After ACEI, significant tracer retention can be noted in the left kidney at the end of dynamic study (the last frame corresponding to 30th min) compared to baseline study
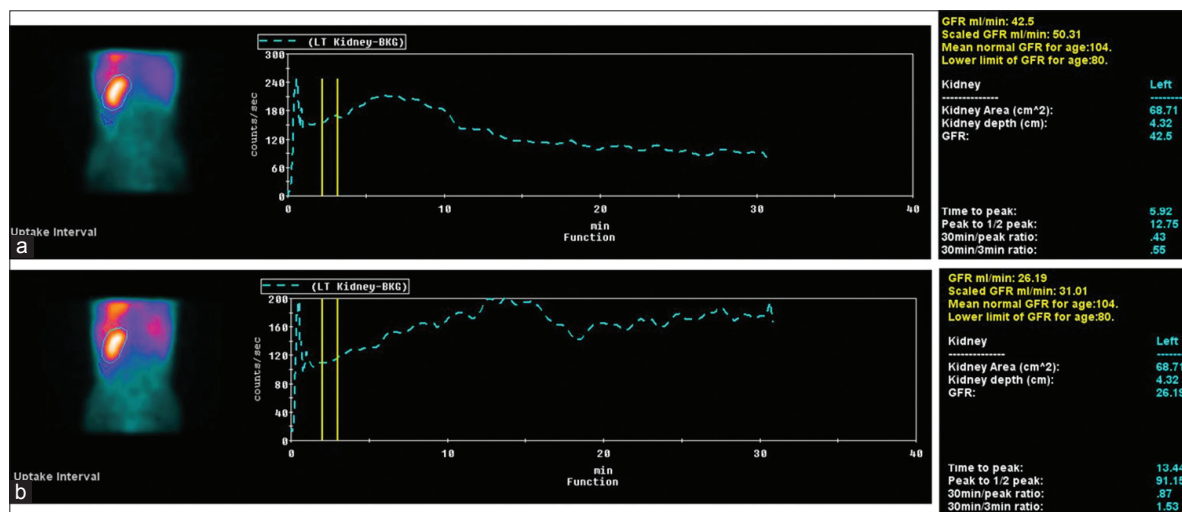
Figure 3: Renogram curve-time activity curve of counts in the kidneys (Y-axis) versus time (X-axis) after i.v administration of 99mTc-DTPA at baseline (a) and during angiotensin-converting enzyme inhibitors (ACEIs) (b). An upsloping of the curve during ACEI suggests delayed time to peak activity, prolonged renal tracer transit, and excretion as given the corresponding quantitative parameters in the right panel

Table 1: Renogram parameters of the left kidney at baseline and during ACEI study

Renogram parameters	Left kidney	
	Baseline	ACEI
Time to peak, Tmax (min)	5.92	13.44
Peak to ½ peak	12.75	91.15
30 min/peak ratio	0.43	0.87
30 min/3 min ratio	0.55	1.53
GFR (ml/min/1.73 m²)	50.31	31.01

ACEI: Angiotensin-converting enzyme inhibitors, GFR: Glomerular filtration rate

ratio and 3 min increase in the T_{max} from the baseline study, respectively [Table 1].

Renal hypoperfusion due to RAS activates the renin–angiotensin–aldosterone system (RAAS), leading to an elevated BP that constitutes RVH. Differentiation between RVH and RAS is essential because RAS is quiet in many non-hypertensive elderly persons. Furthermore, RAS is an associated but non-causative finding in a number of hypertensive patients. ACEI renogram helps to detect RAS as the cause of hypertension and predicts curability or improvement in hypertension after intervention. The principle of this study is that ACEI decreases glomerular filtration by inhibiting the compensatory increase in vascular tone at the postglomerular arteriole, mediated by high intrarenal activity of the RAAS in the setting of RAS (perfusion pressure, and hence, the filtration across the glomerulus decreases following ACEI administration). ACEI renogram is most cost effective if used primarily in patients with moderate-to-high risk of RVH that includes abrupt or severe hypertension, hypertension resistant to 3-drug therapy, bruits in the abdomen or flank, unexplained azotemia or recurrent pulmonary edema in an elderly hypertensive patient, or worsening renal function

during therapy with ACEIs.[1-4] In patients with normal or minimally reduced renal function (creatinine <1.7 mg/dL), ACEI renography has a sensitivity and specificity of about 90% for diagnosis of RVH,[1] as seen in this case.

The Society for Cardiovascular Angiography and Interventions has issued Expert Consensus Statement on the appropriateness criteria for Renal Artery Stenting.[5] Our patient's clinical presentation of flash pulmonary edema, resistant hypertension, and CKD with eGFR <45 cc/min with bilateral significant RAS meets the appropriateness criteria for revascularization of his left RAS.[5] Demonstration of the hemodynamic significance in moderate RAS (50%–70%) by invasive angiography (IA) with measures such as fractional flow reserve and translesional gradient is required before planning stenting. IA has its own potential complications like contrast-induced nephropathy in patients with ischemic nephropathy and procedure-related complications such as pseudoaneurysm and hematoma. ACEI renogram could be considered as a safe non-invasive procedure that can demonstrate the contribution of RAAS to hypertension and the potential complications with IA can be avoided. IA could be averted with negative ACEI renogram, while a therapeutic IA can be planned following a positive ACEI renogram.

Conclusion

a) In our patient with CKD due to bilateral RAS, ACEI renogram diagnosed RVH due to the left RAS and confers a high probability of recovery following successful revascularization.

b) In young patients with refractory hypertension, ACEI renogram could be considered as one of the first-line investigations to identify a potentially curable cause of secondary hypertension, i.e., RAS.

c) ACEI renogram can be safely performed in CKD patients since it uses only micromolar quantity of

radiopharmaceutical (i.e., 99mTc-DTPA) that causes no functional overload to the kidneys unlike angiogram, which carries a risk of contrast-induced nephropathy/nephrogenic systemic fibrosis.

d) DTPA renogram can be used to assess the differential renal function in patients with bilateral significant RAS to guide optimal therapeutic strategy.

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Review Article

Common but Underrated – Are we Neglecting these Hypertensive Subsets in India?

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Abstract

Unusual subsets of hypertension need different strategies for detection, treatment and follow up. Isolated systolic hypertension of the young (ISH-Y), metabolic nocturnal hypertension (MNH) and white coat 'Alarm' are subsets which are found in India, but often go undetected. A detailed review of such unusual subsets.

Key words: Isolated Systolic hypertension, nocturnal hypertension, white coat hypertension

Introduction

The detection, awareness, treatment, and control rates of hypertension are poor in Indian subcontinent; the huge 1.3 billion population posing a substantial challenge to health providers. The new data analysis in JAMA estimates that a systolic blood pressure (SBP) between 110 and 115 mmHg accounts for 212 million disability-adjusted life year worldwide; of which, 39 million (around 20%) are from India.[1] The scenario of hypertension detection management in India is challenging; as per the National Capital Region cross-sectional database, there is a progressive increase in prevalence – from 23% in urban areas and 11% rural areas in 1991–1994 period to 42.2% urban and 29.9% rural in 2012–2014. More concerning is the fact that these cross-sectional data show that there has been no substantial change in terms of awareness, treatment, and control rates of hypertension in the tested population between the two time periods.[2]

The data from Jaipur (Jaipur Heart watch), in contrast, show progressive rise in awareness (13–56%), treatment (95–36%), and control (2–21%) from 1991 to 1994 compared to 2012–2014 period, despite the point that the numbers fell short of the WHO global monitoring framework and UN sustainable development goal.[3]

Why Bother about Subsets?

The availability of an array of drugs has made drug choice confusing among general practitioners (GPs), the group who tend to see the hypertensives in the first place. Clear demarcation of some of these hypertensives into distinct subsets would give a distinct advantage in choosing out the target population, defining their outcome, and treating them with guideline-recommended therapy.

This review aims at looking at some of the subsets unique in the Indian population.

Are they Common?

Despite the fact that epidemiological data are not available, most GPs and specialists tend to see such patients of hypertension off and on. A clear knowledge about such subset would enable them to better document such subsets making it possible to organize a database of such distinct subsets.

Why are these Subsets Unusual?

Several subsets of hypertension are described depending on etiology, pathophysiology, and associated comorbidities. Classification depending on elevation of systolic, diastolic, or both parameters also helping subclassification. We describe three new subsets of hypertension which are seen in clinical practice which need to be defined as subsets since they need different diagnostic criteria, different outcome, as well as different modality of treatment. These subsets are unusual in that they differ in presentation, outcome, and treatment.

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Unusual subsets
Isolated systolic hypertension in the young (ISH-Y)
Metabolic nocturnal hypertension (MNH)
White Coat "Alarm"

Subset 1

ISH-Y

With increase in age, SBP tends to increase, while diastolic blood pressure (DBP) tends to decrease.[4]
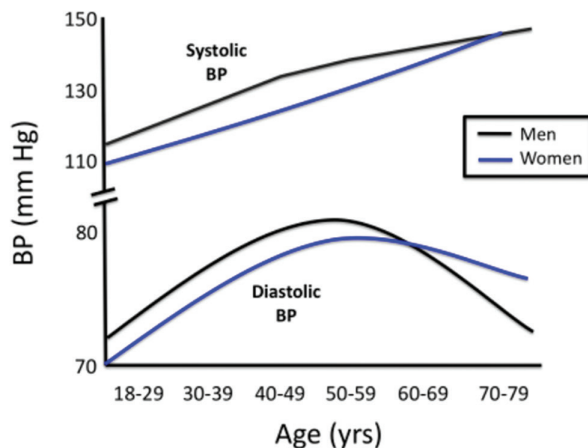
(Adapted from JNC 7 and Burt *et al.*, 1995, Hypertension 23: 305-313)

Isolated elevation of SBP Isolated systolic hypertension (ISH) is generally seen in elderly population with increased peripheral resistance and stiff arteries. The diastolic pressure is typically normal or low.

An almost similar blood pressure (BP) reading with isolated elevation of SBP may be seen in stress prone, young people who are generally anxious and exhibit features of sympathetic overdrive.

In ISH-Y, the BP elevation is driven entirely by sympathetic overstimulation. Clinical signs of sympathetic overdrive include sinus tachycardia, tremor, sweating, and features of anxiety [Box 1]. They are generally <40 years of age, working in high-stress jobs (IT sector) and handling time-bound projects with their corporate future at stake.

Salient features
ISH-Y
Age < 40
ISH
Sinus tachycardia
Fine tremor
Job stress
Absence of family history of hypertension
Good response to beta-blockers

Data from a large French cohort of 19,386 hypertensives were classified into three categories; those with heart rate (HR) between 60 and 80, 80 and 100, and >100. There was progressive increase in mortality (coronary heart disease, cardiovascular disease, and all-cause mortality) with increase in HR, proving the relationship between HR and outcome in hypertension.[5]

Julius *et al.* analyzed the data of 15,193 patients enrolled in the valsartan antihypertensive long-term use evaluation trial. It showed that, even those with well-controlled BP, a faster HR increases cardiovascular (CV) event rate, compared to those with controlled HR, indicating the important and pivotal role of sympathetic nervous system activity in determining the outcome of hypertensive patients.[6] The national health service (NHS) guideline also recommends the use of beta-blockers in this subgroup of patients with ISH and sinus tachycardia, driven by an excess of sympathetic outflow.

Among the array of beta-blockers available in the market, these young patients of ISH-Y tend to have better compliance with highly selective beta-blockers, in view of the absence of side effects such as fatigue, bronchospasm, and erectile dysfunction. This makes cardioselective ß-blocker such as bisoprolol and nebivolol as preferred agent for the treatment of ISH-Y.

Subset 2

Metabolic Nocturnal Hypertension (Metabolic Owl)

There are middle-aged patients with a typical clinical picture of obesity, impaired fasting glucose (IFG)/Frank diabetes, and metabolic syndrome with host of metabolic derangement including increase triglycerides and uric acid levels. They often have features of obstructive sleep apnea (OSA). Their echocardiogram and Echo tend to show evidence of the left ventricular hypertrophy (LVH), but more often, the office BP is not severely elevated. In fact, a dichotomy between office measures BP (mismatch) and LVH is given a clue to the diagnosis. Many patients can have classical Class 2 effort angina [Box 2].

Salient features
Metabolic nocturnal hypertension
Middle age
Mild "office" hypertension
Metabolic derangement (IFG, diabetes mellitus, hypertriglyceridemia, and uric acid elevation)
OSA
Ambulatory blood pressure monitoring (ABPM) – High nocturnal BP load
Good response to renin–angiotensin–aldosterone system inhibitors.

Ambulatory BP in these patients shows a typical pattern of mild daytime hypertension with severely elevated nocturnal BP. This pattern was previously confused with masked hypertension. Isolated nocturnal hypertension tends to increase total mortality and cardiovascular events for more than isolated daytime hypertension.

Chart 1: Difference between morning blood pressure (BP) and pre-awake BP in ABPM

Chart 2: Difference between morning blood pressure (BP) and lowest nocturnal BP
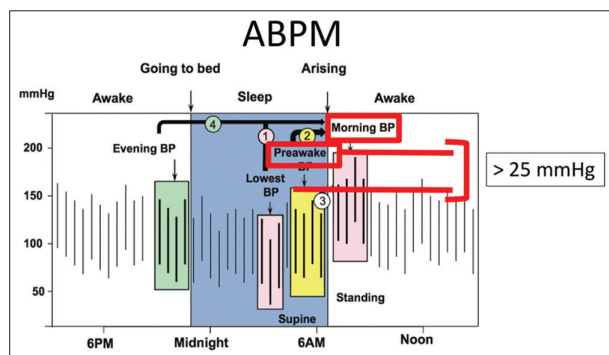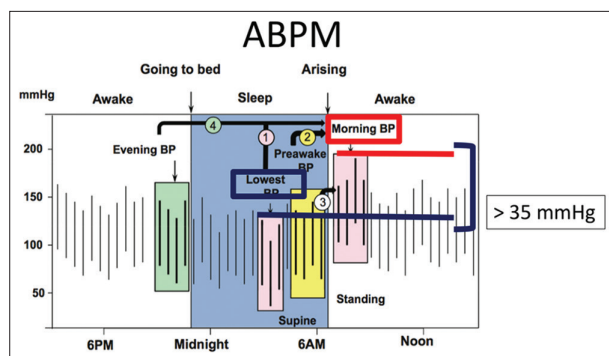
In a review of data on nocturnal hypertension, Li *et al.*[7] clearly showed that isolated nocturnal hypertension is seen more often in Chinese (10.9%) and Japanese (10.5%) population as well as South African people (10.2%) in comparison to lower rates among West European population (6%). This might account for the lack of data and clinical importance of nocturnal hypertension in literature and guidelines since majority of data and guideline emanate out of the western world.

Angina in these patients can result from decreased coronary blood flow as a result of decreased coronary flow reserve.

An increase in intake of high fructose corn syrup, which is used as a sweetening agent in packaged food and sweetened beverages (cola) can exacerbate the metabolic derangement by increasing uric acid and triglycerides in this subset.

Subset 3

White Coat Alarm

White-coat hypertension (WCH) is a stress response of the patient resulting in elevation of BP during interaction with a medical personal. In general, this condition is thought to be benign. An ambulatory BP shows normal BP values as the patient goes outside the area of medical consultation (hospital). WCH is defined as an office BP >140/90 with 24-h ambulatory

BP average of < 130/80. It is estimated that 15–30% of people with elevated office BP has WCH. It is estimated that, generally, the BP of any patient tends to progressively drop by 15/7 mmHg during the third office visit compared to the first visit even in the absence of intervention of lifestyle or pharmacologic agents. Persistently, elevated office BP of > 140/90, measured out of office BP < 130/80, normal ABPM average BP < 130/80, and absence of target organ damage are thought to be clues to suspect the diagnosis of WCH.[8]

The long-term outcome of WCH is unclear. While most studies agree that patients of WCH have a higher chance of progression to sustained hypertension; and the risk of WCH is more than normotensive patients while less than those with sustained hypertension, the actual natural history is unclear since studies have looked into different groups of patients.

The analysis of IDACO database shows that International Database on ABPM in relation to CV Outcomes shows that compared to normotensives, WCH with low baseline risk has similar outcomes, while those with high baseline risk (ISH, age, and diabetes) have a higher CV risk with WCH in comparison to normotensives.[9]

The subgroup that we find a high risk is the one with WCH with an early morning rise of BP. Studies have shown that those with early morning BP rise have a higher chance of plaque rupture (connected to protein misfolding and the inappropriate activation of proteasome-ubiquitin pathway). Careful interpretation of the ABPM tends to give a clue to the warning signals of this subset.

In addition to the WCH in the ABPM, a difference of morning BP in comparison to pre-awake BP of more than 25 mmHg or a difference between morning BP and lowest nocturnal BP of more than 35 mmHg points to the possible presence of this subset. Since the BP rise tends to be triggered by sympathetic system and the overall nocturnal BP is normal, beta-blockers are likely to be more effective in this subset. The presence of sinus tachycardia also points to this diagnosis.

Conclusion

The three subsets of hypertension discussed above are unique in nature pertaining to their diagnosis, prognosis, and treatment. Understanding their clinical presentation would help the clinician in targeting their therapy more precisely for a better outcome.

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Review Article

Cardiovascular Disease in Patients with Chronic Kidney Disease

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Abstract

Kidney and cardiovascular diseases are strongly associated due to the connections between the heart and the kidneys; kidney disease may even be seen as a cardiovascular risk. The Chronic Kidney Disease (CKD) Prognosis Consortium showed that CKD severity was related to cardiovascular death risk, among other factors. When reduced estimated glomerular filtration rate and albuminuria – both biomarkers for declining renal function – are present in a patient, the rate of cardiovascular events increases significantly. Kidney and heart diseases are linked with regard to coronary atherosclerosis, myocardial disease, valvular calcification, and atrial and ventricular arrhythmias. CKD and end-stage renal disease (ESRD) patients with coronary atherosclerosis frequently have accentuated calcification; many CKD-related factors accelerate the calcification process. These may include traditional risk factors such as hypertension or diabetes, as well as non-traditional risk factors such as uremia, anemia, and increased coagulation proteins. This is also associated with more stable lesions, often leading to episodes of silent and symptomatic coronary ischemia in these patients. CKD is linked to heart failure by accentuating pressure overload, volume overload, and cardiomyopathy, the three major pathophysiologic mechanisms causing left ventricle failure. Hemodialysis itself may lead to myocardial disease through "myocardial stunning," in which episodes of hypotension during hemodialysis cause transient wall motion abnormalities, worsening survival overtime. Short daily hemodialysis in the home setting may be associated with improved outcomes. CKD and ESRD patients often experience accelerated aortic valvular and mitral annular calcification and fibrosis. These patients should receive echocardiography during care, to evaluate for valve disease severity as well as the left ventricular systolic and diastolic function. Finally, CKD patients have many of the myocardial and hemodynamic factors of arrhythmia. 62% of cardiac deaths in the United States Renal Data System database are due to arrhythmias. CKD and ESRD patients should receive individualized treatment and frequent monitoring due to the increased risk of adverse events and iatrogenic death in this patient population. One option is to form hybrid "cardionephrology" teams comprised cardiologists and nephrologists. This will optimize care for cardiorenal patients and boost interest in the nephrology field, which is presently lagging.

Key words: Chronic kidney disease, atherosclerosis, heart failure, aortic valve, mitral valve, arrhythmia, sudden death

Introduction

The heart and the kidneys are inextricably linked through vascular, neurological, hormonal, and cellular signaling systems. The kidneys are the most vascular organ in the body, receiving a quarter of cardiac output at rest. Thus, kidney disease is strongly associated with cardiovascular illness and, in fact, may be considered as a cardiovascular risk state. In addition, when either organ sustains injury or begins to fail, there appears to be a consequential effect on the other organs in either an adaptive or maladaptive response that we now recognize as a "cardiorenal syndrome(s)."[1] This chapter will review the connections between the heart and the kidneys from epidemiological, biological, and clinical perspectives with the aim of gaining greater appreciation for this important interface in both acute and chronic care.

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Why Does Ckd Convey Increased Cardiovascular Risk?

The CKD Prognosis Consortium (CKD-PC) was established in 2009 by the Kidney Disease: Improving Global Outcomes (KDIGO) organization in an attempt to understand the risks of declining renal filtration function represented by the estimated glomerular filtration rate (eGFR) and the presence of albumin in the urine indexed to the filtered creatinine concentration (urine albumin: creatinine ratio [ACR]). In a series of manuscripts, this group used a very large, pooled database (1,555,332 subjects in 45 cohorts) to demonstrate that the severity of CKD was related to the risks of all-cause mortality, cardiovascular death, acute kidney injury, progressive CKD, and end-stage renal disease (ESRD) as shown in Figure 1.[2] These relationships can also be shown in a "heat map" of risk as demonstrated in Figure 2. It is important to understand that when both eGFR and elevated ACR overlap, there appears to be magnified risk for all outcomes. Data from the National Kidney Foundation Kidney Early Evaluation Program (KEEP) and the National Health and Nutrition Examination Survey suggest that the majority of individuals with CKD in the younger age groups are identified by albuminuria while those in the older age strata have reduced eGFR (<60 ml/min/1.73 m²) as the CKD marker [Figure 3].[3] Importantly, the overlap between the two markers is less common than one alone in these large populations. However, when both reduced eGFR and albuminuria are present in the same patient, the predicted and observed rates of cardiovascular events are markedly increased over a relatively short (<5 years) duration. Thus, it is critical that in every patient, the eGFR is calculated from

the patient's age, gender, race, and serum creatinine using standardized equations and the urine ACR is checked on a first morning voided specimen. Structural kidney disease (including polycystic kidney disease) detected by imaging studies is also characterized as CKD in the absence of eGFR and ACR abnormalities. The CKD-PC was limited in terms of non-fatal cardiovascular outcomes; therefore, we must turn our attention to other sources of information to understand the connections to coronary atherosclerosis, myocardial disease, valvular disease, and arrhythmias.

The term "reverse epidemiology" has been applied to patients with ESRD for many risk factors, particularly body weight. This means that in the general population, increased adiposity, as expressed with the body mass index, is consistently associated with cardiovascular events and reduced survival. However, in ESRD, increased BMI confers improved survival. This suggests that increased adiposity is the inverse of cachexia. That is, as chronic disease progresses, cachexia and reduction in weight are common observations on the pathway towards death. Thus, retention of adiposity is associated with survival. Reverse epidemiology has also been observed with total cholesterol and albumin which are proxies for nutritional intake which again is inversely related to the degree of cachexia.

Kidney Disease and Coronary Atherosclerotic Calcification

Data from many studies suggest that the CKD milieu promotes the early initiation and accelerated course of coronary atherosclerosis. Since CKD is strongly associated with traditional coronary risk factors including hypertension,
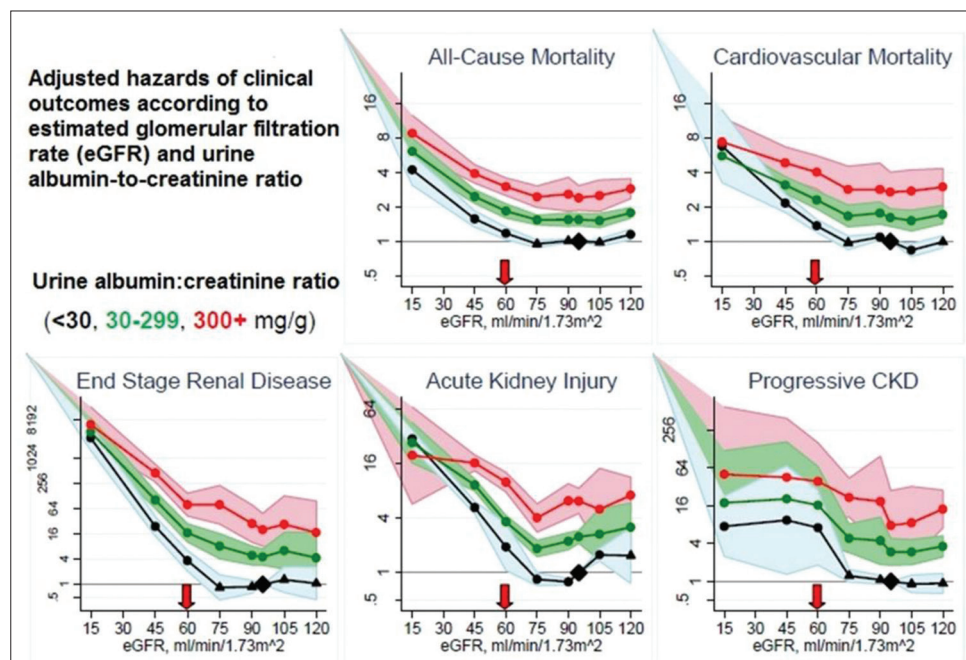
Figure 1: Risks of fatal and non-fatal kidney outcomes from the chronic kidney disease prognosis consortium stratified by baseline urine albumin: creatinine ratio across a spectrum of eGFR. The red arrows denote an inflection point at eGFR < 60 ml/min/1.73 m². Adapted from reference[2]

Figure 2: Adjusted risk of outcomes according to eGFR and urine ACR. Adapted from reference[2]
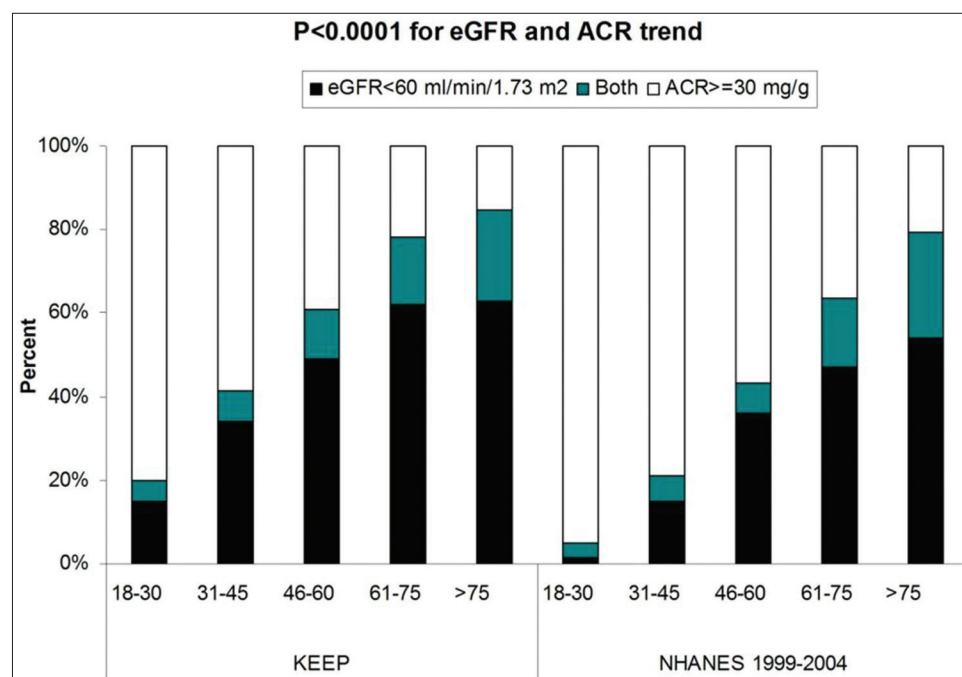
Figure 3: Identification of CKD by eGFR and urine ACR in KEEP, *N* = 40,013 and NHANES, *N* = 10,486. Adapted from reference.[3]

diabetes, dyslipidemia, and smoking, the combination of these factors may be reflected by CKD, and thus, its relationship is amplified by positive confounding. However, when adjusting for these factors, CKD has been consistently associated with non-fatal myocardial infarction and cardiovascular death.[3] A prominent feature of coronary atherosclerosis in patients with

CKD and ESRD is accentuated calcification which occurs in all cases of atherosclerosis when reviewed at necropsy. Initially, calcium deposits on cholesterol crystals in the subendothelial space.[4] However, the progression of atherosclerosis involves a multitude of local and systemic factors which stimulate vascular smooth muscle cells to undergo osteoblastic transformation into

osteocyte-like cells which deposit calcium hydroxyapatite crystals into both the subendothelial and medial compartments of blood vessels. Many factors have been implicated in CKD to accelerate this process including low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, vascular calcification factor, osteoprotegerin, and most notably phosphorus.[5] As eGFR falls, there is retention of phosphate which can stimulate the Pit-1 receptor on vascular smooth muscle cells, thereby facilitating the osteoblastic transformation.[6] Of note, neither dietary calcium nor the plasma concentration of calcium has been independently associated with calcific deposits in the coronary arteries. As CKD progresses, coronary artery disease is commonly identified on a variety of clinical studies, frequently as longer lesions and in more proximal vessels.[7] Fortunately, more extensive calcification – while related to the burden of coronary disease – is also associated with more stable lesions; thus, CKD patients often have stable but extensive CAD leading to episodes of both silent and symptomatic coronary ischemia.

It has been suggested that there are both traditional and non-traditional risk factors that may contribute to more accelerated atherosclerosis in persons with CKD. The traditional risk factors include elevated LDL-C, hypertension, diabetes mellitus, smoking, and family history of premature coronary disease (first-degree relative female before age 55 and male before age 45 years). Non-traditional risk factors in CKD have been variously mentioned in literature and include blood markers of mineral and bone disorder (hyperphosphatemia, elevated calcium-phosphorus product, osteopontin, and hyperparathyroidism), C-reactive protein, uremia, asymmetric dimethylarginine and reduced nitric oxide availability, anemia, increased unbound iron (catalytic or poorly liganded iron), homocysteine, fibrinogen, and increased coagulation proteins. None of these factors have been sufficiently tested in prospective studies to be considered a therapeutic target for prevention in CKD patients with atherosclerosis.

Heart Failure in Ckd

CKD promotes the three major pathophysiologic mechanisms by which the left ventricle can fail: Pressure overload, volume overload, and cardiomyopathy. Since hypertension is both a determinant and a consequent of CKD, the vast majority of CKD patients have longstanding histories of elevated blood pressure and increased cardiac afterload resulting in left ventricular hypertrophy and increased left ventricular mass.[8] Salt and water retention result in chronic volume overload. Nephrotic syndrome and loss of oncotic forces result in worsened fluid retention and edema. Uremia and retention of many substances (indoxyl sulfate and p-cresol) result in impaired myocyte function in both systole and diastole. It has become recently understood that the production of fibroblast growth factor-23 from bone in response to CKD phosphate retention has off-target effects on the left ventricular myocardium, resulting in increased left ventricular mass and cardiac fibrosis. The resultant
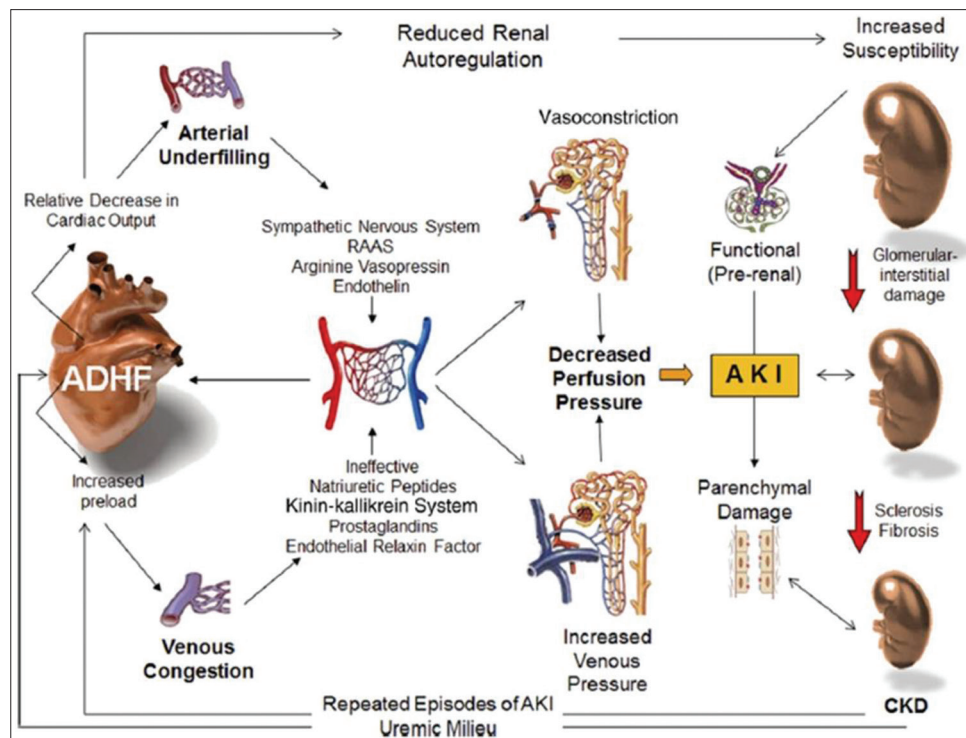
Figure 4: Pathophysiology of cardiorenal syndrome type 1. ADHF = acutely decompensated heart failure. AKI = acute kidney injury. Reproduced with permission from reference.[10]

myocardial tissue has a reduced capillary density compared to that of persons with normal renal function. Considerable evidence is accumulating that "CKD cardiomyopathy" is manifest by impaired systole and diastole with biomarker and imaging evidence of cardiac fibrosis. The observation that galectin-3 levels correlate with type III aminoterminal propeptide of procollagen, matrix metalloproteinase-2, and tissue inhibitor of metalloproteinase-1 suggests that myocardial macrophage infiltration enhances turnover of extracellular matrix proteins in patients with CKD.[9] Thus, patients with CKD are at very high risk for the development of heart failure associated with markedly impaired cardiorespiratory function and the cardinal features of fatigue, effort intolerance, edema, and clinical findings including pulmonary congestion and elevation of B-type natriuretic peptides (BNP and NT-proBNP).[10] When acutely decompensated heart failure is present, then a vicious cycle of worsened renal filtration function, venous and renal congestion, and further retention of salt and water can occur. This is commonly termed cardiorenal syndrome type 1 [Figure 4].[11]
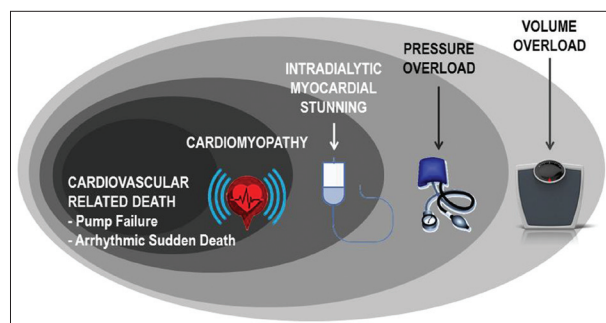
Figure 5: Pathophysiologic rationale for myocardial stunning in ESRD on hemodialysis

It has become increasingly recognized that hemodialysis itself may contribute to myocardial disease through the process of "myocardial stunning," in which there are transient wall motion abnormalities that are related to episodes of hypotension during hemodialysis. The greater the number of segmental wall motion abnormalities, the worse the survival overtime [Figure 5]. Recent analyses suggest that short daily hemodialysis in the home setting is associated with fewer episodes of intradialytic hypotension, regression of left ventricular hypertrophy, and a 41% lower risk of heart failure, fluid overload, and cardiomyopathy.[12]

Valvular Calcification

Accelerated aortic valvular and mitral annular calcification and fibrosis are common in patients with CKD and nearly universally present in patients with ESRD. The murmur of aortic valve sclerosis is found in the majority of patients while the mitral annular disease is usually silent and detected only by echocardiography or other forms of imaging. The aortic valve sclerosis and calcification can progress to symptomatic aortic stenosis while the mitral annular disease can result in very mild functional stenoses or regurgitation by Doppler but rarely requires surgical attention. Both valvular lesions can be the substrate for acute infective endocarditis in ESRD patients with temporary dialysis catheters, which occurs at the rate of 6–8% per year. *Staphylococcus aureus* is the main cause (75%) of vascular access-related bacteremia among patients receiving long-term hemodialysis. When endocarditis occurs in this setting, the operative mortality rate can be in excess of 50%.[13] Most patients with CKD should undergo echocardiography at some point in their care not only to evaluate for the extent of valve disease but also to assess the left ventricular systolic and diastolic function.
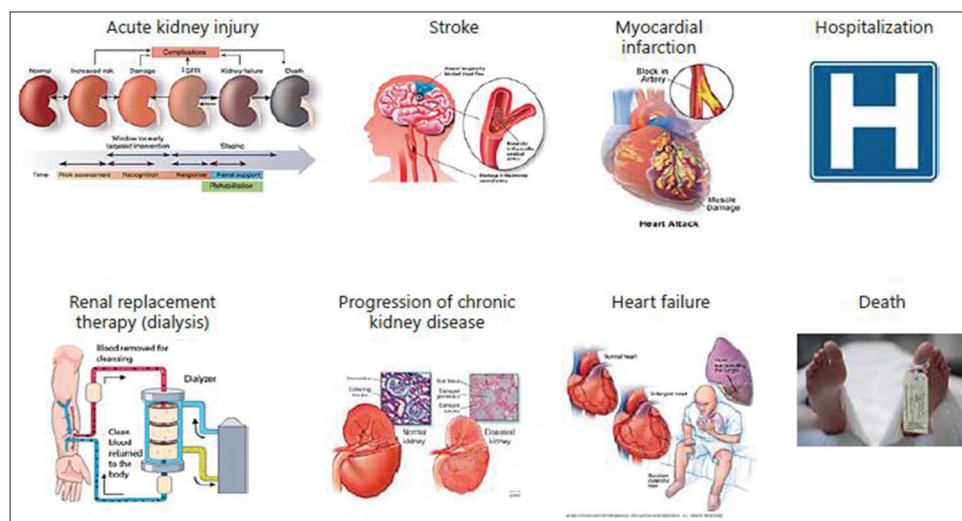
Figure 6: Major adverse renal and cardiac events (MARCE) are strongly associated with AKI and raise the possibility of strategies that reduce AKI, translating into improved clinical outcomes as measured by the time to first MARCE event in clinical trials. Reproduced with permission from reference[18]

Atrial and Ventricular Arrhythmias

Patients with CKD have the myocardial and hemodynamic determinants of all forms of arrhythmias. In the United States Renal Data System database, 62% of cardiac deaths (27% of all deaths) are attributable to lethal arrhythmias.[14] Atrial fibrillation occurs at an elevated rate in patients with CKD and is associated with an increased risk of cardioembolic stroke compared to those with normal renal function at all levels of the CHA_2DS_2-VASc score. Recent data are supportive of apixaban (either 2.5 mg or 5 mg p. o. bid) potentially in place of warfarin for CKD patients with non-valvular atrial fibrillation at high risk of stroke or systemic embolism.[15] Due to accelerated myocardial fibrosis and the presences of both macrovascular and microvascular disease, reentrant ventricular tachycardia is believed to be the prelude to ventricular fibrillation followed by asystole and sudden death. Increased premature atrial and ventricular beats, when seen on monitoring, can be harbingers of atrial fibrillation and ventricular tachycardia, respectively. Electrolyte shifts – particularly changes in potassium concentration that occurs in CKD and are accentuated with forms of dialysis – are also believed to play a role in ventricular arrhythmias and sudden death, most likely due to ventricular fibrillation. The role of implantable cardio-defibrillators is controversial at the time of this writing, given the associated shortened survival and the risks of device and lead infection in ESRD.[16] Each guidelines-based approach in the population of patients with heart disease and normal renal function is complicated by increased adverse events and even iatrogenic death in patients with CKD and ESRD. Thus, therapy must be individualized and very frequent monitoring is required.

Cardionephrology Collaboration

In light of the strong link between kidney disease and heart disease, there is a great need for collaboration between cardiologists and nephrologists. This is becoming increasingly relevant with the growing use of mechanical devices such as left ventricular assist devices and novel cardiorenal therapies.[17] Rangaswami *et al.* advocated the formation of hybrid "cardionephrology" teams for the treatment of cardiorenal syndromes.[17] One possibility is a dedicated cardionephrology training track for fellows, involving nephrology/cardiology fellow cross rotations.[17,18] This would revive the currently declining interest in the nephrology field as well as optimize care for cardiorenal patients [Figure 6].[17]

Summary

The connection between kidney and heart disease can be viewed in four domains: Coronary atherosclerosis, myocardial disease, valvular abnormalities, and arrhythmias. CKD plays a role in the pathogenesis, presentation, outcomes, and management of each manifestation of CVD. Future research is needed to better understand the unique mechanisms at work in patients with CKD that promotes and worsens CVD outcomes. Practical strategies, such as the formation of dedicated cardionephrology teams, are needed to guide clinicians in the appropriate management of this high-risk population.

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Review Article

Resistant Hypertension: Overview

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Abstract

Resistant hypertension (RH) is defined as office blood pressures (BP) which is uncontrolled on ≥3 or controlled on ≥4 different classes of antihypertensive medications at optimal doses and preferably including a diuretic.
- RH is important as many patients in this subgroup have secondary causes of hypertension.
- Most important aspect of treatment in RH is to divide RH into true RH and pseudo-RH.
- Three factors, namely patient adherence, optimal dosing of antihypertensive medications, and out-of-office BP recordings, are important in classifying RH to true RH and pseudo-RH.
- Many RH patients are volume expanded and respond to intensified diuretic therapy, sodium restriction, dual calcium-channel blocker, or α-adrenoreceptor blocker. Plasma renin activity can be used for personalized therapy in RH.

Key words: Resistant hypertension, insulin resistance, artifacts, adherence, secondary hypertension, indapamide, valsartan, escalating diuretics, renin guided therapy

Introduction

Resistant hypertension (RH) is defined as blood pressures (BP) uncontrolled on ≥3 or controlled on ≥4 different classes of antihypertensive medications at optimal doses and preferably including a diuretic.
- Insulin resistance and obstructive sleep apnea are two common associations of RH.
- True RH and pseudo-RH are two subsets of RH which have to be identified and treated.

BP measurement artifacts

- It is important to obtain accurate BP values before labeling as RH. Standard BP measurement protocols are required to segregate true RH from apparent RH.
- To minimize measurement artifacts.
- To get a BP value which represents true out-of-office BP.
- BP has to be measured accurately in office setting by trained individuals to avoid problem of white-coat effect.
- Automated office BP in which a series of BP measurements are made in office usually mimicks daytime recordings.[1]

Optimal therapy

- It is important to define what is optimal therapy before classifying patients as true RH.

What medications and what dose ?
Patient should be on three different classes of antihypertensive medications including a diuretic.[2]

Antihypertensive dose should be ≥50% of maximum recommended dose.

Patient adherence

Can be assessed by direct questions – Are you regularly taking medications?
- Indirect question: Regarding concern for cost or side effects.
- In apparent RH, clinicians appear to have opportunities to improve BP control by optimizing antihypertensive medication dosing.
- Once a diagnosis of true RH is made, one has to evaluate for the cause of secondary hypertension (HTN).

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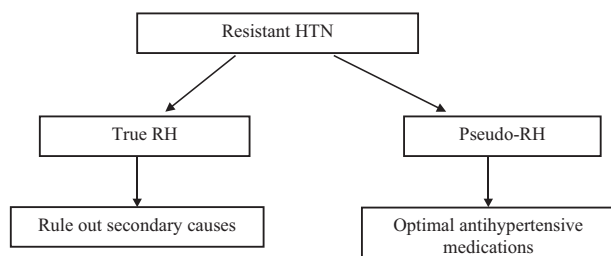
Prognosis

In patients with apparent-resistant HTN based on the measurement of office BP, the subject with nonhypertensive out-of-office BP values has a favorable prognosis. This is where ambulatory BP recordings are useful. Both self-monitored BP and ambulatory BP recordings provide prognostically important information beyond office BP, in this group of patients.[1]

Pharmacotherapy of RH

Commonly prescribed three drugs regimen for RH include ARB + CCB + thiazide diuretic. Beta blockers could be added for specific indications.[3]

Drugs and Dosing for RH

Diuretic	ACE/ARB	CCB[4]	Aldo Receptor blocker	Beta blocker
Indapamide 1.25 to 2.5 mg daily	Lisinopril 20-40 mg	Amlodipine 5-10 mg	Sprinolactone 25-50 mg	Bisoprolol 10-20 mg
Hydrochlorothiazide 12.5-25 mg	Perindopril 4-8 mg		Eplerenone 25-50 mg	Metoprolol 100-200 mg
Chlorthalidone 6.25-25 mg Torsamide 20-40 mg	Valsartan 160-320 mg			

Rationale

Low-dose aldosterone antagonist, spironolactone 12.5–50 mg, lowers BP in RH. Spironolactone at a dose of 25 mg daily lowered BP by 25–50 mmHg (systolic)/10–15 mmHg (diastolic). Eplerenone is an alternative aldosterone antagonist devoid of sex steroid effects.

Beta Blockers

Aldosterone is projected to play a major role in BP regulation in long term than renin–angiotensin system.[5] Aldosterone raises BP by increasing number and activity of epithelial sodium channels. Amiloride which is epithelial sodium channel blocker has similar effect as Aldosterone antagonist.

However target organ protection is seen only with Aldosterone antagonist Patients with serum K+ value >4.5 and eGFR <45 ml/min are not ideal candidates for spironolactone. Target organ protection is a major advantage of Aldosterone antagonists.

Diuretics

Escalating diuretic potency from hydrochlorothiazide to chlorthalidone to torsemide as GFR decline from >45 to <30 ml/1.7 m²/min helps to reduce fluid retention and helps in BP control.

Diuretics	EGFR
HCTZ	>50 ml/1.73m²/min
Chlorthalidone	45-50 ml/1.73m²/min
Torsemide	<45 ml/1.73m²/min

Personalized Therapy for RH

Renin-guided therapy, i.e. Plasma renin activity (PRA), can be used to guide antihypertensive therapy without increasing number of medications.[6]

Low PRA-better response	High PRA-better response
Diuretics	Renin/Angiotensin blocker
CCB	β Blockers
α Blockers	
Aldosterone antagonist	

Control of other cardiovascular risk factors is important
- Diabetes
- Dyslipidemia – statins have shown 36% reduction of coronary events.
- Choose antihypertensive medication depening on other compelling indications like CAD, CKD, CHF, Diabetes.

Summary

RH should be clearly defined into true RH and pseudo-RH. Screening for secondary causes is important in true resistant HTN.

Clinicans should identify and address psuedoresistance, screen for secondary hypertension, initiate changes to lifestyle and pharmacotherapy to improve BP control.

Personalized drug therapy depending on PRA may be a choice for truly RH.

Device-based therapy may evolve in future for the treatment of RH.

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Review Article

Select Considerations for Secondary Hypertension

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Abstract

Hypertension assumes a dominant position among chronic non-communicable diseases worldwide. Of this, secondary hypertension constitutes only 5–10% of the total disease burden. In routine clinical practice, physicians come across hypertensive cases which are difficult to control despite optimal therapy. In this backdrop, the present paper reviews the less frequently encountered etiologies of hypertension which can pose difficulties to both the patient and treating clinician. This is classified as secondary hypertension and the major entities include renal parenchymal diseases, renovascular diseases, primary hyperaldosteronism, and sleep-disordered breathing. Among patients with resistant hypertension, investigations such as urine analysis, renal function tests, electrolytes, sonogram for kidneys, duplex ultrasound for renal artery stenosis, plasma aldosterone concentration/plasma renin activity (PAC/PRA) ratio, and sleep study may be done in serial manner depending on the individual patient to identify a secondary cause. Drug-induced high blood pressure should also be addressed, especially in young ladies due to oral contraceptives pills and in chronic obstructive pulmonary disease patients on long-term steroids. Many a time, a proper evaluation and diagnosis can reduce the pill burden and long-term consequences of resistant hypertension.

Key words: Endocrine, renovascular, secondary hypertension, sleep disorder

Introduction

Increasing prevalence of hypertension is a global epidemiological concern, as the disease already tops the burden of chronic diseases across the world. Indian scenario turns out to be more worrying due to several reasons; specifically, the growing size of the urban population and economic burdens leading to stressed lifestyles. Hypertension has been marked as the most common single diagnosis by the primary care providers.[1-3] An overriding majority of these hypertension cases (90–95%) fall under essential or idiopathic hypertension category.

Secondary hypertension is the effect of a definite, identifiable predisposing cause and accounts for approximately 5–10% of cases. Secondary hypertension often goes underdiagnosed, leading to lifelong medications. End-organ damage is earlier and more prevalent due to the resistant nature of hypertension in these patients. This deems important, particularly in countries such as India, where the likelihood of obesity is increasing at an alarming rate due to change in lifestyle patterns, consumerism, and related factors.[4-6] Unlike patients with primary or essential hypertension those with secondary hypertension need extensive investigations, resulting in greater psychological distress and financial burden which leads to a vicious cycle of irregular follow-up and poor compliance. However, proper case selection, evaluation, and focused treatment strategies lead to complete or partial cure in good proportion of patients.[7]

Evidence reveals an array of causes for secondary hypertension which broadly could be classified into renal, endocrine, cardiovascular/pulmonary, and drug induced. The present review makes an attempt to focus on, the major etiologies of secondary hypertension such as renovascular hypertension (RVHTN), endocrine hypertension due to primary hyperaldosteronism, and hypertension due to sleep-disordered breathing.

An Updated Overview of Management Protocols for Secondary Hypertension

Secondary hypertension is strongly suspected in the following situations:

1. Persistent hypertension in spite of concurrent use of optimal doses of at least three antihypertensive drugs belonging to three different classes, of which one is a diuretic. This is termed as resistant hypertension.
2. Labile hypertension or acute rise in blood pressure in a person with previous optimal control.
3. Sudden onset of hypertension in persons with no family history or risk factors, who are <30 years of age and are non-obese or in patients more than 55 years of age.
4. Malignant or accelerated hypertension accompanying a target organ damage such as heart failure, acute kidney injury, retinal hemorrhage, papilledema, or neurological disturbances.
5. Hypertension with dyselectrolytemia – hypokalemia and metabolic alkalosis.
6. Well-documented age of onset before puberty.

Major Causes of Secondary Hypertension

Renal causes

- Renal parenchymal hypertension
- RVHTN.

Endocrine causes

   Primary hyperaldosteronism
- Cushing's syndrome
- Pheochromocytoma
- Hypothyroidism
- Hyperparathyroidism.

Cardiovascular or cardiopulmonary causes

- Coarctation of aorta
- Obstructive sleep apnea (OSA).

Drugs

- Glucocorticoids, NSAIDs, combined oral contraceptive pills, calcineurin inhibitors, caffeine, phenyl ephedrine, and erythropoietin.
- Inherited rare causes such as Liddle's syndrome and Gordon's syndrome.

Renal parenchymal diseases

Primary renal disease is the most common cause of secondary hypertension and can happen in acute as well as chronic kidney disease (CKD). Hypertension is present in more than 80% of patients with CKD. Out of this, glomerular diseases cause more severe hypertension than tubulointerstitial diseases. Clues for diagnosis are the presence of proteinuria, especially more than 1000 mg/day, active urine sediment (with RBCs, WBCs, and casts) and other sonological and histological features favoring a renal pathology. On the other hand, long-standing uncontrolled blood pressure can also cause nephrosclerosis and then many a time, clinicians find it difficult to identify whether hypertension or renal disease was the initial problem. The etiology of hypertension in CKD could be clinically discernible from the occurrence of one or more of such symptoms as extracellular volume overload, increased renin–angiotensin–aldosterone activity, endothelial cell dysfunction, oxidative stress, increased vasopressin release, and hypertensinogenic drugs such as erythropoietin and steroids.

Detailed evaluation of primary renal disease with appropriate tests (sonogram, urinalysis, histopathology, etc.) is required. Uncontrolled hypertension adds on to significant morbidity and mortality in CKD, across all stages, by causing rapid progression of renal failure and its associated huge cardiovascular risk. The target blood pressure recommends in patients with significant proteinuria (500–1000 mg/day) is 130/80 mmHg. Angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) are preferred agents in CKD, but periodic monitoring of creatinine and serum potassium is advised.[8,9]

RVHTN

It caused by occlusive lesion of a renal artery resulting in reduction of renal artery perfusion pressure. It is most often a potentially curable cause of hypertension. RVHTN is relatively uncommon in patients with mild hypertension but quite common in patients with severe or refractory hypertension, especially in patients with other atherosclerotic diseases such as aortic disease, peripheral occlusive arterial disease, and coronary disease. Renal artery disease if progressive can cause decline in glomerular filtration rate (GFR) and such resultant CKD is called as ischemic nephropathy.[7,10] Atherosclerosis affecting the renal artery, mostly at its origin accounts for 85% of cases. Fibromuscular dysplasia (FMD) which is a non-inflammatory, non-atherosclerotic disorder affecting young ladies is the second most common cause of RVHTN.[11,12]

Table 1: Clinical features of renal artery stenosis due to atherosclerosis and fibromuscular dysplasia

Patient factor	ARAS	FMD
Prevalence	2/3	1/3
Age	15–50	>50 years
Sex	(More in) Males	(More in) Females
Renal failure	Common	Uncommon
Site	Ostium, first 1–2 cm of renal arteries	Distal part of main renal artery
Association	Other risk factors of atherosclerosis	Familial in 10%, carotid vertebral artery disease
Progression	Fast involving other arteries	Slow progression
Angiography	Bilateral in 20–40%, high-grade diffuse	String of beads appearance
Response to treatment	Case-to-case variation	Curative in 50% with angioplasty, if indicated

ARAS: Atherosclerotic renal artery stenosis, FMD: Fibromuscular dysplasia

Clinical characteristics of these two pathologies are detailed in Table 1.

Clinical Clues to RVHTN[10,11]

- Late-onset severe hypertension – more than 180/120 blood pressure after the age of 55 years.
- Episodes of flash pulmonary edema with normal ventricular function.
- Unexplained acute kidney injury (AKI) within 1–2 weeks of starting ACEI or ARB.
- Asymmetric kidney size with more than 1.5 cm difference.
- Severe hypertension with features of diffuse atherosclerosis, especially in >50 years.
- Presence of unilateral systolic-diastolic bruit.

Establishing the Diagnosis of RVHTN

Detailed diagnostic testing is advocated only in those patients with high clinical suspicion and those who have high likelihood of benefiting from the procedure. Compelling indications for extensive evaluation include as follows:
- A short duration of accelerated hypertension
- Failure or intolerance to optimal medical therapy
- Progressive renal failure in the absence of another etiology for CKD
- High clinical suspicion of FMD in young hypertensives.
- Recurrent flash pulmonary edema.[11,12]

The gold standard for diagnosing renal artery stenosis is renal arteriography. However, a variety of less invasive tests is available for initial evaluation. They are renal artery duplex ultrasonography (RADUS), CT angiography, and MR angiography. The choice of the test depends on patient factors and institutional expertise. Testing for RVHTN is associated with potential risks, particularly in patients with impaired renal function who are at risk for contrast-induced nephropathy and nephrogenic systemic fibrosis associated with gadolinium exposure during MR angiogram. Invasive testing is done if the screening tests are inconclusive with highly suggestive clinical setting.

RADUS is an important diagnostic test in assessing RAS. It is relatively easier non-invasive test which can be repeated and it provides functional assessment of the renal arteries along with certain anatomical information.

Peak systolic velocity 180 cm/s and/or a relative velocity above 3.5 as compared to the adjacent aortic flow are useful. This has a sensitivity and specificity of 90 and 96%, respectively, in lesions having more than 60% stenosis determined angiographically. As with many diagnostic procedures, a positive test is more informative than a negative test. Disadvantages of Doppler study of renal arteries in diagnosing RVHTN are its operator dependence, failure to identify accessory, distal branch stenosis, and inability to predict outcome after revascularization.[13]

Spiral CT scan with CT angiography is highly accurate for atherosclerotic RAS but less useful for FMD.

Magnetic Resonance Angiography

It provides excellent vascular images of RAS, especially gadolinium contrast-enhanced images. The risk of nephrogenic systemic fibrosis is avoided by technical improvements in MRA like breath-hold MRA with paramagnetic less nephrotoxic contrast material.

Invasive imaging

Intra-arterial angiography is the gold standard for diagnosing RAS . More than 70% stenosis in angiography, resting translesional mean pressure gradient of more than 10 mmHg, and renal fractional flow reserve ≤0.8 are features to suggest a hemodynamically significant stenosis. However, most centers do not proceed directly to arteriography due to the risk of contrast nephropathy and cholesterol embolization. If there is huge suspicion of RVHTN both clinically and by way of screening tests like Doppler, CTA, or MRA, one can proceed with invasive arteriography. This is particularly useful in young FMD patients where non-invasive tests might miss the lesion.[14,15]

Carbon dioxide angiography – CO_2 is useful as an alternative contrast agent either alone or in combination with smaller doses of iodinated contrast. It is the only known contrast agent which is non-nephrotoxic. CO_2 is also of help in people with hypersensitivity to iodine-containing contrast medium. It is worth mentioning here that though CO_2 is regarded as a useful contrast agent, it should not be used in coronary, cerebral, and thoracic imaging due to its potential neurotoxicity. Lack of familiarity restricts its use in day-to-day practice.[15]

In patients without renal failure Doppler study, CT angiography and MR angiography are safe and useful tests before proceeding with intrarenal arteriography. However, in patients with renal failure, both invasive and non-invasive tests using contrast agents carry risk of nephrotoxicity. In patients with GFR <30 ml/mt, CT angiogram is preferred over MR angiogram due to higher risk of gadolinium-induced nephrogenic systemic fibrosis.

Treatment of Unilateral Renal Artery Stenosis – Three Options are Available[16-20]

1. Medical management – Medical management should be essentially offered to all patients. Addition of ACE inhibitors and ARBs has markedly improved blood pressure control. If adequate blood pressure control is not achieved, diuretics, long-acting calcium channel blockers, beta-blockers, etc., may be added as in primary hypertension. Progressive stenosis resulting in long-term ischemic changes in the kidneys and resultant renal failure is potential concerns with medical management.
2. Revascularization by percutaneous transluminal renal angioplasty with stenting is advised in patients who have a high likelihood of benefiting from the procedure and in patients who fail to tolerate or achieve optimal

blood pressure control with medical management. This includes patients who have a short duration of refractory hypertension, young ladies on multiple drugs in whom the chances of FMD are high and in those with refractory heart failure with resistant hypertension and repeated occurrence of flash pulmonary edema. Observational outcome studies of atherosclerotic renal artery stenosis from 14 series of trials comprising 678 patients showed hypertension cure defined as BP <140/90 with no antihypertensive medications were seen in 12%. In 73% BP level improved with lesser number of drugs and in 41%, the renal function also improved. Proper selection of patient who is best suited for this treatment is important rather than performing angioplasty in all innocent incidental lesions.

3. Surgical treatment – Splenorenal and hepatorenal bypass surgeries are less commonly performed in selected category of patients with complex anatomical lesions and with severe aortoiliac occlusive disease.

Treatment of Bilateral Renal Artery Stenosis

All management options discussed with unilateral renal artery stenosis are applicable in the case of bilateral disease also. Additional concerns here are high chances of chronic ischemic nephropathy, progressive renal failure, and hemodynamically mediated AKI while on ARB or ACE inhibitors.

Endocrine Hypertension

Primary hyperaldosteronism[21-23]

It is the most common but often underdiagnosed cause of hypertension due to an endocrinopathy. Among patients with resistant hypertension, the prevalence is around 11–20%. It may be caused by bilateral adrenal hyperplasia (65% of cases), aldosterone-producing adenoma (30%), or rarely secretory adrenal carcinoma or inherited endocrinopathies. Other than features of resistant hypertension, patients can present with episodic paralysis secondary to hypokalemia and alkalosis.

Screening for hyperaldosteronism is recommended for the following groups:

1. Sustained BP >150/100 on three different occasions, resistant hypertension despite three drugs, or controlled hypertension on four or more drugs.
2. Hypertension with spontaneous or diuretic-induced hypokalemia.
3. Hypertension with adrenal incidentaloma.
4. Hypertension with OSA.
5. Hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age of <40 years.
6. All hypertensive first-degree relatives of patients with PA.

Measurement of the ratio of plasma aldosterone concentration (PAC) to plasma renin activity (PRA) is the screening test of choice. Although at present, there are no firm recommendations for aldosterone to renin ratio cutoffs, due to

variability of assays, a PAC/PRA >20 in combination with a PAC >15 ng/dl or 416 pmol/L is considered as a positive screening test result. Many factors such as GFR, diet, drugs, potassium level, and menstruationetc affect the value and hence should be appropriately addressed before screening.

How to Confirm?

The hallmark of primary aldosteronism is non-suppressible aldosterone secretion with non-stimulable renin secretion. Therefore, aldosterone suppression tests with fludrocortisone, saline suppression test, and oral salt loading are suggested. Since their tests are cumbersome, time consuming, and with risks attached, radiological methods are preferred. CT and MRI are used to differentiate between a unilateral and bilateral adenoma. Adrenal vein renin sampling is theoretically useful but difficult to put in practice.

Treatment

Medical management is best with aldosterone antagonists such as eplerenone, spironolactone, or amiloride. Additional antihypertensives like ARBs are most often needed. Surgical removal and ethanol embolization are done for unilateral adenomas. If no discrete nodules are identified in the CT scan with negative adrenal vein renin lateralization, it is advisable to do follow-up under medical management.

Sleep Apnea Syndrome

Sleep apnea syndrome has emerged as an independent risk factor for hypertension irrespective of the associated metabolic factors such as diabetes, dyslipidemia, and obesity. Around 50% of patients with OSA are estimated to be having hypertension. Although OSA has been linked to high risk for cardiovascular disease, stroke, pulmonary hypertension, and arrhythmias, the association with hypertension is very much obvious in all longitudinal and cross-sectional studies. The observed risk factors are male sex, ethnicity, and high apnea–hypopnea index (more than 30/h). Increased sympathetic nervous system activity and abnormal vascular functional and structural changes resulting from oxidant stress are supposed to be contributory factors for hypertension. Sleep study is diagnostic. Weight reduction and continuous positive airway pressure are beneficial in most of the patients and surgical intervention is rarely needed.[24,25]

Conclusion

Secondary hypertension being rare often goes underdiagnosed.0 It is not cost effective to evaluate extensively every hypertensive person for a secondary cause. Young hypertensives, those who develop early target organ damage and patients on multiple drugs, should be screened for a treatable cause, in these patients if investigations are carefully selected, it is an extremely fruitful exercise because in a good proportion of patients, hypertension can either be cured or at least better controlled. The common

causes of secondary hypertension are renal parenchymal diseases, renovascular diseases, primary hyperaldosteronism, and sleep-disordered breathing. Among patients with resistant hypertension, investigations such as urine analysis, renal function tests, electrolytes, sonogram for kidneys, duplex Doppler ultrasound for renal artery stenosis, PAC/PRA ratio, and sleep study can be done serially to rule out a secondary cause. Drug-induced hypertension should always be addressed in young ladies on oral contraceptives pills and in chronic obstructive pulmonary disease patients on long-term steroids. Rarer causes include pheochromocytoma, Cushing's syndrome, and coarctation of aorta which should be excluded in appropriate clinical settings. With the background of fast-growing economy, unhealthy lifestyle practices, and progressive urbanization, we have a growing epidemic of obesity and metabolic syndrome and therefore of OSA. More studies should be directed to identify hypertension in relation to OSA and sleep-disordered breathing.

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