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Evaluation of Target Organ Damage from Hypertension

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Abstract

Hypertension is not just a leading and treatable cause of cardiovascular morbidity & mortality, but also a major causative factor behind cerebrovascular, renal, retinal and peripheral vascular diseases. Cardiac failure and End Stage Renal Disease are the two major cause of death from hypertension. Complications of hypertension are usually associated with other risk factors which can exacerbate the end organ damage from hypertension. Effective, timely and aggressive treatment of hypertension can prevent or reverse these end organ damages and prevent significant morbidity and mortality in hypertensive patients. This review briefly outlines evaluation of target organ damage from hypertension & its associated risk factors.

Key Words : Hypertension, target organ damage, cardia failure, end stage renal disease, hypertensive nephropathy, hypertensive heart disease, hypertensive retinopathy

Introduction

Hypertension is a leading risk factor for coronary heart disease (CHD), heart failure, stroke, renal failure, retinopathy and peripheral vascular disease (PVD). The cutoff for defining hypertension is ideally defined as the level of arterial Blood Pressure (BP) at which benefits of intervention exceed those of inaction.

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However, a prehypertensive group was classified in the JNC 7 guidelines on hypertension as, patients with BP ranging from 120-139 mm Hg systolic (SBP) and 80-89 mm Hg diastolic (DBP), due to the increased cardiovascular risk and risk of developing hypertension. Data from observational studies involving more than a million individuals have indicated that the death from ischemic heart diseases and stroke increases progressively and linearly from SBP as low as 115 mm Hg and DBP as low as 75 mm Hg (1). The increased risk is present in all age groups ranging from 40-89 years old. For every 20 mmHg systolic and 10 mm Hg diastolic increase in BP, the mortality due to stroke and ischemic heart disease doubles (1). An increase in SBP alone has been well documented to be associated with increased risk of renal failure (RR >2.8), stroke (RR> 2.7), heart failure (RR> 1.5) , peripheral vascular disease (RR> 1.8) and coronary artery disease (RR> 1.5) (2-6). In the MRFIT study (3), those with highest SBP had highest risk of CHD mortality, a particular risk observed for those with higher SBP (>160) along with lower DBP (<70).

Hypertension is usually associated with other cardiovascular risk factors like dyslipidemia, glucose intolerance, abdominal obesity, etc., and only around 20% of the time does hypertension occur in isolation. The relationship between BP and risk of cardiovascular events is continuous, consistent and independent of other risk factors. Although the risk of death and disability associated with hypertension is increased in a statistical sense but the majority of patients with hypertension have normal longevity. This suggests that there are multiple factors operative in predicting complications from hypertension in an individual and the risks are concentrated in a subgroup rather than being randomly distributed. Thus assessment of complications from hypertension must be done with consideration of other known risk factors and timely evaluation of target organ damage. Figure 1 emphasizes the significance of silent effects of hypertension leading to overt target organ damage. This article briefly describes the approach to evaluate the target organ damage from hypertension.

Hypertensive Nephropathy

Hypertension is regarded as a cause and consequences of chronic kidney disease (CKD) which is defined in term of reduced GFR (<60ml/min/ $1.73m^2$) which corresponds to a

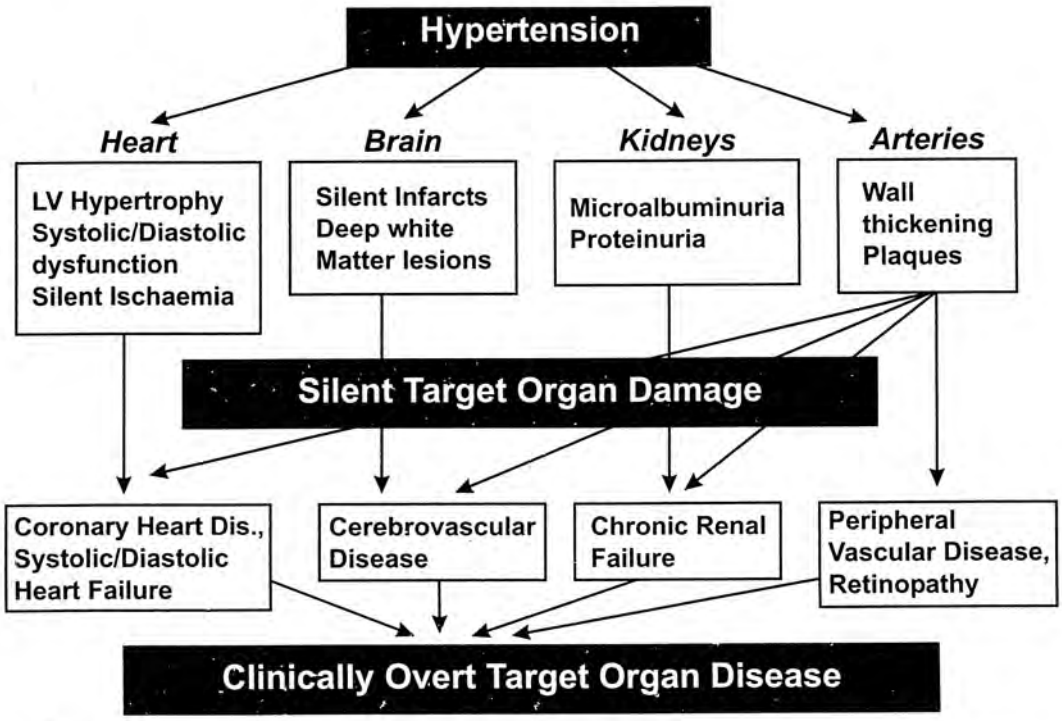

Figure 1 : Clinical significance of recognizing silent target organ damage from hypertension

creatinine level of > 1.5mg/dl in men or >1.3mg/ml in women or the presence of micro albuminuria (urine albumin >300 mg/day or 200mg/g of creatinine). Predictors for chronic kidney disease (CKD) in hypertensive patients are simple clinical parameters like age >65 years, female gender, atherogenic dyslipidemia and clinical manifestations of atherosclerosis. Black patients have an approximate eight-fold elevation in the risk of hypertension-induced end-stage renal disease (7).

The renal execretory function deteriorates with age beginning in third or fourth decade of life. This age related deterioration of glomerular filtration rate can accelerate at a rate of 4-8ml/min per year if SBP remains uncontrolled (8). Higher BP values at baseline have been significantly associated with a graded increase of the risk of end-stage renal disease. At times when antihypertensive medication had not yet become available, a large proportion of patients with essential hypertension

wound up in renal failure. This was often ascribed to the occurrence of malignant hypertension. Now with the advent of effective antihypertensive medication, malignant hypertension has become much rarer but still around 10 % of deaths caused by hypertension result from renal failure.

Patients with nephrosclerosis typically present with a long history of hypertension, slowly progressive elevations in the blood urea nitrogen (BUN) and plasma creatinine concentration and mild proteinuria. Renal damage can be assessed by looking for:

a. **Microalbuminuria:** has been defined as urine albumin >300 mg/day or 200mg/gm of creatinine. Spot urine samples may be used to calculate albumin creatinine ratio which when between 30-200mg albumin/gm creatinine denotes presence of microalbuminuria. The prevalence of microalbuinuria increases with increasing age and duration of hypertension. In a longitudinal study involving more than 4500 American Indians, microalbuminuria was associated with a significantly greater risk of developing hypertension (9). Microalbuminuria was also associated with significantly higher prevalence of LVH, coronary artery disease, Myocardial Infarction, hyperlipidemia and peripheral vascular disease (10). Measurement of microalbuminuria is a specific, cost-effective way to identify patients at higher risk, for whom additional preventive and therapeutic measures can be instituted.

b. **Proteinuria:** Protein excretion is usually mildly elevated (less than 1 g/day) in nephrosclerosis and this reflects the generally focal nature of the glomerular involvement.

c. **Microscopic Hematuria** : may occur because of glomerular lesions.

d. **Hyperuricemia:** (independent of diuretic therapy) is a relatively early finding in benign nephrosclerosis and appears to reflect the reduction in renal blood flow induced by the vascular disease.

e. **Imaging** Abdominal ultrasound, CT, MRI or other imaging modalities are not much helpful in early stages of hypertensive nephropathy but can show advanced renal damage.

Risk of renal failure in hypertension

In MRFIT study (3) a strong correlation between both SBP and DBP and end-stage renal disease was identified, independent of the association between the disease and age, race, use of medication for diabetes, history of myocardial infarction, serum cholesterol concentration and cigarette smoking. Even in patient with moderate hypertension with mean SBP 127 mm Hg and mean DBP 82 mm Hg the relative risk of renal damage is significantly increased. Interventions to prevent the disease need to emphasize the prevention and control of high as well as high-normal blood pressure (2).

Treatment

The cornerstone in management of Hypertension with CKD is optimal control of BP and inhibition of Renin Angiotensin System (RAS).

Whether hypertension is a cause or consequences of CKD, achieving an optimal blood pressure is one of the most important strategies to preserve remaining renal function. A metanalysis has shown that SBP of 110 to 129 mm Hg and urine protein excretion less than 2.0 g/d were associated with the lowest risk for kidney disease progression (11). Another metanlysis has shown Antihypertensive regimens that include ACE inhibitors are more effective than regimens without ACE inhibitors in slowing the progression of non diabetic renal disease (12). The beneficial effect of ACE inhibitors is mediated by factors in addition to those decreasing blood pressure and urinary protein excretion and is greater in patients with proteinuria.

Hypertensive Heart Disease

Hypertensive heart disease is a result of complex interaction between various hemodynamic and genetic factors. All these factors cause many pathological changes in heart leading to increase risk of coronary artery disease, congestive cardiac failure, stroke and sudden death. Most deaths due to hypertension result from MI or CHF. Key factors in determining the effect of hypertension on the heart are level of the pressure and time of exposure to increased pressures.

There are changes in various myocardial compositions in response to increased after load. The myocytes constitutes 75% of heart mass and 25% is interstitum that is composed of coronary vasculature, fibroblasts, macrophages and mast cells. Hypertensive heart disease causes

increase in myocyte hypertrophy and remodeling. Excess collagen deposition also causes increase in total interstitial and perivascular fibrosis which decreases ventricular systolic as well as diastolic performance.

Evaluation :

a. **Clinical:** Hypertensive patient can have dyspnea or frank heart failure secondary to diastolic dysfunction of the heart. Clinical findings in hypertensive heart disease can be enlarged heart with prominent LV impulse, accentuated aortic closure sound, frequent S4, occasional S3 or a faint murmur of aortic regurgitation.

b. **ECG:** Investigations should begin with an ECG. Various criteria are used for detection of LVH in ECG. The relative diagnostic accuracy of these methods has been tested using autopsy, radiographic, echocardiographic, and most recently MRI evaluation. The sensitivity is lower and specificity is higher for all the criteria. Repolarisation abnormalities associated with ECG findings increase the correlation with anatomical LVH.

c. **Echocardiography:** Echocardiography can be a useful tool in assessment of LVH. Accurate measurement of LV wall thickness although useful, involves a degree of subjective variation. Septal and posterior wall thickness is used for assessment of LVH but eccentric hypertrophy (characterized by chamber enlargement with normal left ventricular thickeness) is usually missed, in spite of increased LV mass.

LVH can be estimated more accurately by measuring LV mass which can be measured by calculating LV volume and multiplying it with specific gravity of myocardium (1.04g/ml). Devereux and associates derived a formula for calculating LV mass

[1.04{(LVID+PWT+IVST)3 - LVID 3} x 0.8 + 0.6] (13). Tracing of endocardial and epicardial border provides a more accurate quantification of LV mass. Three dimensional echocardiography is even more accurate to estimate LV mass. Taking MRI as a standard, inter-observer variability of measured LV mass is 37±19% with 2D echocardiography and 7±10% with 3D echocardiography (14).

Other features that can be assessed by echocardiography are

diastolic and systolic functions, valvular functions and regional wall motion abnormalities.

d. **MRI:** MRI is probably the most accurate, noninvasive method for assessment of left ventricular mass. It also gives information about myocardial structure and functions and valve diseases, but MRI may not be routinely available or feasible for evaluation of hypertension.

e. **Others:** Stress Electrocardiography has a high incidence of false positive reports in patients with LVH. Stress Myocardial Perfusion Imaging is also useful to evaluate coronary artery disease in hypertensive patients. Coronary angiography and LV angiography should be undertaken when significant coronary artery diseases is suspected.

Importance of LVH

The presence of LVH (on ECG or echocardiography) is important clinically because it is associated with increase in the incidence of systolic and diastolic heart failure, ventricular arrhythmias and sudden death following myocardial infarction and cerebrovascular events. In a prospective study, 1033 subjects over the age of 50 with essential hypertension and no previous cardiovascular events were followed for a median of three years (15). The rate of major cardiovascular events (fatal and nonfatal MI; all-cause, sudden, or cardiovascular mortality; severe heart failure; or severe renal failure requiring dialysis) was significantly higher in patients with an increased LV mass, defined as $\geq$ 125 g/m^2 body surface area (3.2 versus 1.3 per 100 patient years with normal mass). After adjustment for other risk factors, LVH was associated with an increase in cardiovascular events (relative risk 2.08). For each 39 g/m^2 increase in left ventricular mass there was a 40% increased risk of a major cardiovascular event. A report from the Framingham Heart Study examined the relationship between left ventricular mass and hypertrophy and sudden death in 3661 subjects over the age of 40 who were followed for 14 years (16). The prevalence of left ventricular hypertrophy was 22 percent and the risk factor adjusted hazard ratio for sudden death was 2.16 ($p = 0.008$). For each 50 g/m increment in left ventricular mass, the risk-factor adjusted hazard ratio for sudden death was 1.45 ($p = 0.008$) (16).

LVH is also associated with an increased risk of cerebrovascular events (stroke or transient ischemic attack), presumably because it is a marker for more severe and/or prolonged hypertension. This was illustrated by one study of 2363 hypertensive patients without cardiovascular disease who were followed for up to 14 years (17). The presence of LVH on ECG (18 percent of the group) or echocardiography (24 percent) increased the risk of a cerebrovascular event (relative risk 1.79 and 1.64, respectively). For each increase in LV mass of one standard deviation on echocardiography, the relative risk of an event was 1.31 (17).

Patients with repolarization abnormalities have more severe degree of LVH and more commonly have symptoms of left ventricular dysfunction and greater risk of cardiovascular events. In LIFE study hypertensive patients with LVH related ST-T changes were 1.8 times more likely to develop congestive cardiac failure and 2.8 times more likely to experience heart failure related death than were patients without ST-T changes (18).

Treatment and Regression of LVH:

LVH regression is associated with lower overall CVD risk. Control of BP rather than choice of drug is important. A meta analysis of fifty trials has shown that the predictors of LV mass regression are higher pretreatment LV mass, greater fall in SBP and DBP, and longer duration of treatment. The most consistent reduction in LV mass was achieved with ACEIs and least with BBs, and intermediate benefit occurred for diuretics and calcium channel blockers (19). LIFE study found that greater reduction in LV mass was with lorsatan based therapy than atenolol based therapy despite equal BP lowering effect (20).

Hypertensive Retinopathy

On the basis of the JNC criteria, the presence of retinopathy may be an indication for initiating antihypertensive treatment, even in people with stage 1 hypertension (BP:140-159/90-99 mm Hg) who have no other evidence of target-organ damage. Strong association is seen between the presence of signs of hypertensive retinopathy and elevated blood pressure. The detection of hypertensive retinopathy with the use of an ophthalmoscope has long been regarded as part of the standard evaluation of persons with hypertension. Generalized narrowing and arteriovenous nicking are markers

of vascular damage from chronic hypertension. In contrast, other signs (focal arteriolar narrowing, retinal hemorrhages, microaneurysms, and cotton-wool spots) are related to current but not previous blood-pressure levels (21, 22). Furthermore, the observation of signs of retinopathy in people without a known history of hypertension suggests that these signs may be markers of a prehypertensive state.

A quantitative way of assessing one of the microvascular changes-generalised arteriolar narrowing in the retina - has been developed and used in population based studies (23). The photographs were digitised and the diameters of individual arterioles and venules coursing through a zone located ½ –1 disc diameter from the optic disc margin were measured with a dedicated software and summarized as an arteriole-venule ratio (AVR).

Independent associations exist between signs of hypertensive retinopathy, as defined by the findings on retinal photographs, and the risk of stroke. Some signs of retinopathy (e.g., retinal hemorrhages, microaneurysms, and cotton-wool spots) were associated with a risk of newly diagnosed clinical stroke that was two to four times as high as that for patients who did not have these signs (24). Signs of retinopathy are associated with reduced cognitive performance on standardized neuropsychological tests (25), cerebral white-matter lesions (26), and cerebral atrophy as defined on the basis of findings on magnetic resonance imaging (MRI) (27). These findings also support the concept that an assessment of specific signs, rather than the presence or absence of hypertensive retinopathy, may be important for risk stratification.

Persons with retinal arteriolar narrowing are two to six times as likely to have preexisting coronary heart disease as those without these changes (28).

Signs of hypertensive retinopathy regress with the control of blood pressure, although spontaneous resolution of these signs in the presence of high blood pressure has also been reported. It is unclear whether antihypertensive medications that are thought to have direct beneficial effects on the microvascular structure (e.g., ACE inhibitors) would reduce the damage of retinopathy beyond the reduction effected by lowered blood pressure. No data from prospective, controlled trials demonstrate that the specific reduction

of hypertensive retinopathy also reduces the morbidity and mortality associated with cardiovascular disease.

Peripheral Vascular Disease (PVD)

In addition to contributing to the pathogenesis of hypertension, blood vessels may be a target organ for atherosclerotic disease secondary to long-standing elevated blood pressure. Hypertensive patients with arterial disease of the lower extremities are at increased risk for future cardiovascular disease. Patients with abnormal Ankle Brachial Index (ABIs) are two to four fold more likely to have a history of myocardial infarction, CCF or cerebrovascular diseases (29). Coronary calcium score and carotid intimal thickness are greater in patients with PVD. The risk of death from cardiovascular causes increases 2.5-6 fold in patients with PVD and their annual mortality is 4.3-4.9% (30).

Assessment of PVD includes clinical assessment by measuring ABI and radiologic evaluation. An ABI ratio less than 0.9 is considered abnormal. The risk of death inversely correlates with ABI (31). Radiological evaluation includes detail evaluation using ultrasound Doppler, CT scan and MRI. The gold standard is invasive angiography.

It is not clear whether antihypertensive therapy reduces progression of PVD but intensive antihypertensive therapy does reduce cardiovascular events in patients with PVD.

Cerbrovascular Diseases

Hypertension increases the risk of both ischemic and hemorrhagic stroke. The incidence of stroke rises progressively with increasing blood pressure levels, particularly SBP, in individuals >65 years. Hypertension is a cause of multiple lacunar infarcts in subcortical white matter which results in impaired cognitive function.

Doppler imaging of the carotid arteries for carotid intimal thickness gives an idea of extent of associated atherosclerosis and luminal stenosis of carotids indicates risk of future stroke. CT scan is helpful in evaluation of acute ischemic or hemorrhagic stroke. MRI studies in patients with chronic hypertension have revealed greater number of subcortical white matter lesions and micro infarcts, astrogliosis, ventricular enlargements and extracellular fluid accumulation (32). MR angiography is often performed to look for intracranial aneurysms which have a high risk of rupture in hypertensive patients.

Effective antihypertensive therapy reduces the risk of developing significant white matter changes in MRI. However white matter changes once develop, don't appear to be reversible (33). There are no comparative data available regarding whether certain classes of antihypertensives are superior to others in prevention of cognition decline. The stroke risk also decreases by control of blood pressure. No specific agents have been found to be superior in stroke prevention. In LIFE study fewer stroke occurred in losartan group than atenolol group (20). ALLHAT study has shown that stroke incidence was greater in lisinopril group than diuretics or CCB group (34). The PROGRESS trials have shown that addition of indapamide to peridopril decreases the stroke recurrence (35).

Conclusion

The message from the above discussion is that the end points from hypertensive diseases like cerebrovascular disease, CHD and hypertensive emergencies are preventable. Therapies targeted to hypertension can reverse these end organ damages if treated early and aggressively. Cardiac failure and ESRD are the two major cause of death from hypertension. Complications of hypertension are usually associated with other risk factors which can exacerbate the end organ damage from hypertension. So along with evaluation of target organ damage and control of hypertension, other risk factors should also be modified simultaneously to achieve effective benefit.

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