



INDIAN SOCIETY OF HYPERTENSION



CURRENT MEDICAL CONCEPTS

HTNJ



Review Article

Hypertension: New Facets

Prabhash Chand Manoria¹, Nidhi Mishra²

¹Director and Chief Cardiologist, Manoria Heart and Critical Care Hospital, Bhopal, Madhya Pradesh, India, ²Department of Biochemistry, Mahaveer Institute of Medical Sciences and Research, Bhopal, Madhya Pradesh, India

Abstract

The guidelines for hypertension provide all information regarding day-to-day management of hypertension. However, there are several issues such as mortality in a controlled hypertensive, fibrosis in cardiovascular system, vascular age, and target heterogeneity in response to decrease blood pressure which also require attention as they are clinically relevant.

Key words: J-Curve, BPV, fibrosis

Introduction

The numbers of blood pressure (BP) are very important and crucial in hypertension. The guidelines cover the number game with great precision and perfection in terms of diagnosis, initiation of treatment, and targets of BP control. However, there is panoply of facets beyond the number game which require refinements and are of interest to a clinician.

Mortality in Controlled Hypertensive

The mortality in a controlled hypertensive is at least 1½–2 times compared to a normal individual. There are two main reasons for it.

Atherosclerosis

This continues unabated even after control of BP and accounts for morbidity and mortality even in a controlled hypertensive. There is no doubt that lipids play a very important role in atherosclerosis, but when we look at the specimen of coarctation of the aorta, there are severe atheroscleroses in the segment above the coarctation and no atherosclerosis below the coarctation segment, indicating that hypertension alone can initiate atherosclerosis. It is important to remember that

most of the antihypertensive agents, no doubt, decreases the BP-related complications of hypertension such as cerebral hemorrhage, acute left ventricular failure, and aortic dissection but do not provide atheroprotection as shown the result of the hope-3 trial which showed that, in patients of intermediate risk, if only antihypertensive agents are used (Candesartan 60 mg + hydrochlorothiazide 12.5 mg), there is no decrease in the primary endpoint of cardiovascular death myocardial infarction (MI) and stroke, but when rosuvastatin 10 mg is added, there is a statistically significant decrease in the cardiovascular events by 24% (3.7% vs. 4.8%, hazard ratios 0.76, 95% confidence interval 0.64–0.91, $P = 0.002$).

Fibrosis in the cardiovascular system

This occurs in various parts of the cardiovascular system such as myocardium, left atrium (LA), big arteries, and small arteries. The fibrosis is beautifully delineated by late gadolinium enhancement on cardiac magnetic resonance (CMR).

Fibrosis in myocardium^[1]

This predisposes the individual to heart failure^[2] with preserved ejection fraction and also predisposes to ventricular arrhythmias^[3] which may culminate in sudden cardiac death.

Address for correspondence:

Dr. Prabhash Chand Manoria, E-5/103, Arera Colony, Bhopal - 462 016, Madhya Pradesh, India. Mobile: +91-98930 42229. Fax: 0755-4240999. E-mail: pmanoria@rediffmail.com

Received 07-07-2018; Accepted 11-08-2018



Fibrosis in the LA^[4,5]

This predisposes the individual to atrial fibrillation and thromboembolism. The electrophysiologist always looks at the AL fibrosis by CMR before doing radiofrequency ablation (RFA) for atrial fibrillation because, if there is marked fibrosis, the probability of sustaining sinus rhythm after RFA is remote.

Fibrosis in the large arteries such as the aorta

Normally, the aorta has elastic tissue and is compliant, but when fibrosis occurs in the aorta,^[6-8] the compliance decreases. Normally, the pulse wave velocity (PWV) is 8 m/s. When the impulse travels from the aorta to the periphery, it moves slowly, and when it is come back to the aorta, the diastole has already started. This results is increased in aortic diastolic pressure and produces augmentation of coronary blood flow. In aortopathy, there is fibrosis in the walls of the aorta and this results 12 m/sec in a decrease in compliance and an increase in the PWV about 12 m/s. Under such circumstances when the impulse travels rapidly from the aorta to the periphery and when it comes back to the aorta, the systolic is still ongoing [Figure 1].

This produces several adverse effects such as increase in central aortic pressure, increase in left ventricle afterload, increase in pulsatile strain with chances of plaque rupture, and no diastolic augmentation of coronary blood flow. The arterioles also undergo remodeling and capillaries also show changes such as increase in tone, remodeling, and rarefaction which results in increased resistance and decrease in blood supply to the tissues. Interestingly, certain drugs such as angiotensin-converting enzyme inhibitors (ACEI) (perindopril and ramipril), angiotensin receptor blockers (ARBs) (losartan and irbesartan), and calcium channel blockers (CCBs) (amlodipine) improve vascular remodeling while beta-blockers such as atenolol do not affect vascular remodeling. The question arises, is there any solution to minimize fibrosis? ACE inhibitors have shown to decrease myocardial fibrosis.^[9] Very interesting data emerged from the long-term follow of ALLHAT^[10] trial which showed that there was a significant reduction in conduction system disease with lisinopril compared to chlorthalidone and amlodipine after 5 years' follow-up. The effects were seen despite

higher BP in the lisinopril arm, and its seems that antifibrotic properties of renin–angiotensin–aldosterone–system inhibition could play a key role. Azilsartan due to its vasculoprotective and antifibrotic properties may be another possible solution to this difficult problem of preventing/minimizing fibrosis, but we do not have any trials at the moment.

Therefore, we should drift from a merely BP-centric approach to a disease-centric approach. This involves 24 h BP control including control of nocturnal BP, morning surges and BP variability (BPV), and small and large vessel remodeling.

Chronological Age and Vascular Age

Hypertension is a very important cause of premature vascular aging so that vascular age of an individual may be much higher than his chronological age. Early and good control of BP may improve vascular aging.

BPV

The BPV is the missing link in the current treatment of hypertension.^[11] In simplistic terms, it implies variation in BP over time. Although BPV is well known for several years, it is often not targeted. It is a threat to target organ damage, increase cardiovascular events, and has comparatively poor prognosis.^[12] CCBs such as amlodipine effectively decrease BPV. The various types of BPV^[13] are shown in Table 1. The normal values for BPVs are shown in Table 2.

Target Heterogeneity in Hypertension

The target organs of the body such as the heart, brain, and kidney do not respond in a similar way to decrease in BP. In brain lower is better applies both for systolic and diastolic BP. The action to control cardiovascular risk in diabetes BP study^[14] [Figure 2] was negative, but still, the stroke was significantly decreased in the arm of 120 versus 140 mmHg. Indicating lower systolic BP is better for the prevention of stroke. The INVEST trial^[15] showed that lower diastolic BP is also better for the prevention of stroke and there is no J-curve [Figure 3].

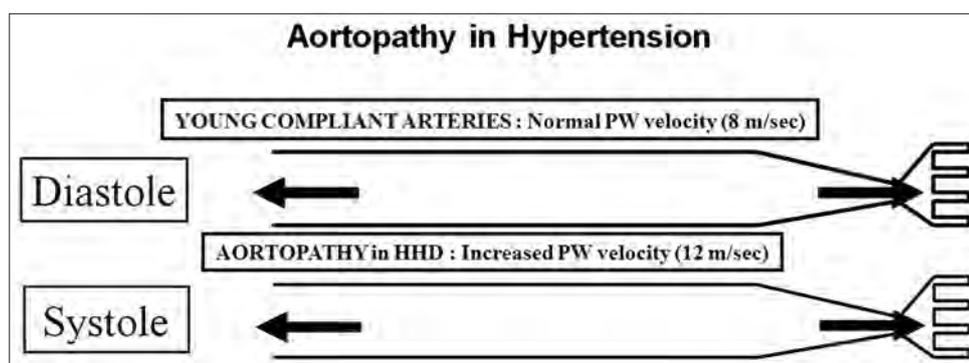


Figure 1: Pulse wave velocity in normal individual and aortopathy

Table 1: Types of BP variability

BPV	Oscillation of BP	Method	Indices of BPV
Very short term	Beat-to-beat variability	Continuous BP recordings in laboratory	ABPM SD, CV, Spectral analysis of 24 h BP fluctuations
Short term	Variation within 24 h	ABPM	SD, 24 h-weighted SD, CV, ARV
Mid term	Day-to-day variability	ABPM >48 h HBPM	SD, CV
Long term	Visit-to-visit variability <5 years	OBP, ABPM, HBPM	SD, CV
Very long term	Visit-to-visit variability >5 years	OBP, ABPM, HBPM	SD, CV

SD: Standard deviation, CV: Coefficient of variation, HBPM: Home blood pressure monitoring, OBP: Office blood pressure, ARV: Average real variability, ABPM: Ambulatory blood pressure monitoring, BP: Blood pressure

Table 2: BPV on the basis of 24 h ABPM in healthy persons

Mean SD SBP mmHg			Mean DBP mmHg		
24 h	Day time	Night time	24 h	Day time	Night time
15.2±3.5	13.6±3.8	11.2±4.1	13.0 ±2.6	12.1±2.8	9.8±3.0

BPV: Blood pressure variability, ABPM: Ambulatory blood pressure monitoring, SBP: Systolic blood pressure

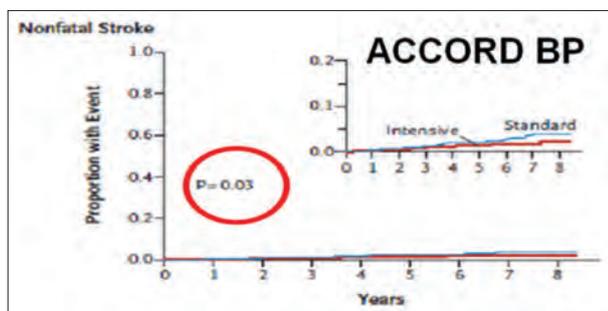


Figure 2: Action to control cardiovascular risk in diabetes blood pressure (BP) study showing decrease in stroke with lower BP

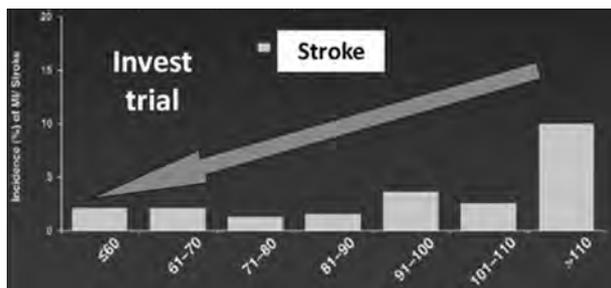


Figure 3: Invest study showing lower diastolic blood pressure is associated with lower incidence of stroke

In the heart, lower diastolic BP is not good because coronary arteries are filled during diastole, and if diastolic BP is decreased, it may increase coronary events. Even the hypertension optimal treatment study, when the data were analyzed on the basis of ischemic versus non-ischemic group, the MI was higher in the ischemic group when BP was lowered to <90/<85/<80, indicating that lower diastolic BP is not good for the heart [Figure 4]. The INVEST study [Figure 5] also showed that, when BP is decreased to <80, there is an increase in MI.

Thus, a J-Curve exists for the heart in hypertension, and in most studies, the J-shaped curve is found to be at the level

of DPB below 80–70 mm/Hg. Interestingly, when a DBP of 80–90 was compared with DBP below 60, there was more than doubled the odds of high sensitivity cardiac troponin-T levels equaling or exceeding 14 mg/ml and increased the risk of incident coronary heart disease by about 50%.^[16] Moreover, patients of coronary artery disease with coronary revascularization when compared to those without it tolerated lower diastolic BP better.^[17] In the kidneys, more important than the arterial BP is the intraglomerular pressure and an increase in it results in increased proteinuria and rapid progression of coronary kidney disease. ACEI/ARB are the preferred agents in CKD because, by dilating efferent arterioles, they decrease intraglomerular pressure which decreases proteinuria.

Why J-Curve is Present for the Heart and Not for the Brain or Kidneys

Coronary perfusion occurs in diastole, whereas cerebral perfusion and renal perfusion occur mainly in systole. Cerebral perfusion is capable of autoregulation in the range of 40–125 mmHg, so it is resistant to low BP. As a result, the J-curve phenomenon does not hold true for the incidence of stroke.

Quality of Life

It is important to remember that the treatment of hypertension is a long drawn out process for several years, and therefore, special attention must be paid on quality of life. We must never forget life is not merely being alive, but being well. Our hypertensive patient should not only live but also feel well. Hydrochlorothiazide, Chlorhexidine, and atenolol produce erectile dysfunction while indapamide, ACEI/ARB, and CCB do have this side effect.

Although we have a variety of powerful antihypertensive drugs to control BP, prevention should be our goal because the mortality in a controlled hypertensive is at least 1½ and 2 times that of normotensive. This is possible by adopting simple measures life eat less, eat right, eat in time walk more, sleep well, and smile.

Conclusion

We have conquered the number game of BP with non-pharmacological measures and drug treatment. However, several other areas in hypertension require attention for further improving its treatment.

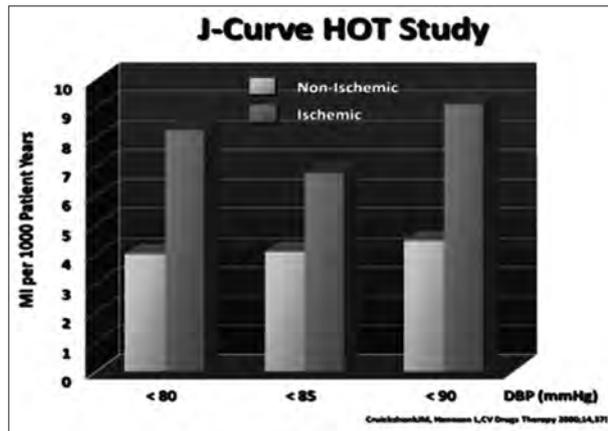


Figure 4: Hypertension optimal treatment study showing increase in myocardial infarction in the ischemic group at all levels of diastolic blood pressure compared to the non ischemic group

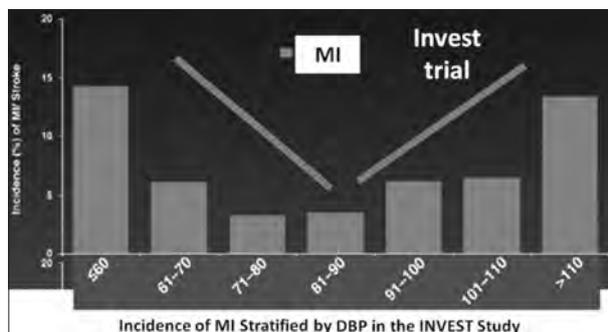


Figure 5: Inverse study showing increase in myocardial infarction when diastolic blood pressure is decreased below 80 mmHg

References

- Rudolph A, Abdel-Aty H, Bohl S, Boyé P, Zagrosek A, Dietz R, *et al.* Noninvasive detection of fibrosis applying contrast-enhanced cardiac magnetic resonance in different forms of left ventricular hypertrophy relation to remodeling. *J Am Coll Cardiol* 2009;53:284-91.
- Moreo A, Ambrosio G, De Chiara B, Pu M, Tran T, Mauri F, *et al.* Influence of myocardial fibrosis on left ventricular diastolic function: Noninvasive assessment by cardiac magnetic resonance and echo. *Circ Cardiovasc Imaging* 2009;2:437-43.
- Adabag AS, Maron BJ, Appelbaum E, Harrigan CJ, Buros JL, Gibson CM, *et al.* Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. *J Am Coll Cardiol* 2008;51:1369-74.
- Malcolme-Lawes LC, Juli C, Karim R, Bai W, Quest R, Lim PB, *et al.* Automated analysis of atrial late gadolinium enhancement imaging that correlates with endocardial voltage and clinical

- outcomes: A 2-center study. *Heart Rhythm* 2013;10:1184-91.
- Benito EM, Carlosena-Remirez A, Guasch E, Prat-González S, Perea RJ, Figueras R, *et al.* Left atrial fibrosis quantification by late gadolinium-enhanced magnetic resonance: A new method to standardize the thresholds for reproducibility. *Europace* 2017;19:1272-9.
- London GM, Guerin AP. Influence of arterial pulse and reflected waves on blood pressure and cardiac function. *Am Heart J* 1999;138:220-4.
- Ahimastos AA, Aggarwal A, D'Orsa KM, Formosa MF, White AJ, Savarirayan R, *et al.* Effect of perindopril on large artery stiffness and aortic root diameter in patients with Marfan syndrome: A randomized controlled trial. *JAMA* 2007;298:1539-47.
- Hundley WG, Kitzman DW, Morgan TM, Hamilton CA, Darty SN, Stewart KP, *et al.* Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance. *J Am Coll Cardiol* 2001;38:796-802.
- Brilla CG, Funck RC, Rupp H. Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. *Circulation* 2000;102:1388-93.
- Dewland TA, Soliman EZ, Davis BR, Magnani JW, Yamal JM, Piller LB, *et al.* Effect of the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) on conduction system disease. *JAMA Intern Med* 2016;176:1085-92.
- Stevens SL, Wood S, Koshiaris C, Law K, Glasziou P, Stevens RJ, *et al.* Blood pressure variability and cardiovascular disease: Systematic review and meta-analysis. *BMJ* 2016;354:i4098.
- Kumar A, Kalmath BC, Abraham G, Christopher J, Kaparthi P, Fischer L, *et al.* Role and relevance of blood pressure variability in hypertension related co-morbidities. *J Assoc Physicians India* 2017;65:83-92.
- Mancia G. Short- and long-term blood pressure variability: Present and future. *Hypertension* 2012;60:512-7.
- Accord Study Group, Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, *et al.* Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575-85.
- Cooper-DeHoff RM, Gong Y, Handberg EM, Bavry AA, Denardo SJ, Bakris GL, *et al.* Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA* 2010;304:61-8.
- McEvoy JW, Chen Y, Rawlings A, Hoogeveen RC, Ballantyne CM, Blumenthal RS, *et al.* Diastolic blood pressure, subclinical myocardial damage, and cardiac events: Implications for blood pressure control. *J Am Coll Cardiol* 2016;68:1713-22.
- Messerli FH, Panjath GS. The J-curve between blood pressure and coronary artery disease or essential hypertension: Exactly how essential? *J Am Coll Cardiol* 2009;54:1827-34.

How to cite this article: Manoria PC, Mishra N. Hypertension: New Facets. *Hypertens* 2018;4(4): 185-188.

Source of support: Nil, **Conflict of interest:** None

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/> © Chand Manoria P, Mishra N. 2019