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Pathophysiology of Hypertension: A Review

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Abstract

Hypertension is a significant risk factor for heart disease, stroke and other cardiovascular diseases and an estimated 970 million people worldwide suffer from the disease resulting in significant morbidity, mortality and financial burden globally. Despite significant advances in pharmaceutical treatment only 53% achieve targeted blood pressure goals largely due to poor patient compliance compelling a structured and flexible yet, individually tailored approach for treatment of HTN.This review addresses the pathophysiology and diagnosis for the disease.

Keywords: *Hypertension; Sympathetic nervous system; Renin angiotensin-aldosterone system; Renal denervation*

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Introduction

Hypertension (HTN), defined as systolic blood pressure (SBP) > 120 mmHg or diastolic blood pressure (DBP) > 80 mmHg, is a major growing health problem across the globe (Hypertension 2014, World Heart Foundation) It is the most common risk factor for cardiovascular disease and affects nearly two-thirds of adults aged 60 years or older (GoA,S 2013). It is estimated that uncontrolled HTN is responsible for 7.5 million deaths per year worldwide. Despite various advances in the field it is projected that 1.56 billion people will suffer from HTN by 2025. Various randomized controlled trials have demonstrated that even slight blood pressure decreases such as 10mmHg reduces patients risk of death due to cardiovascular disease by 25% and, similarly decreases risk of stroke related mortality by 40%.

Our initial understanding of central aortic pressure and therefore blood pressure dates back to 1733 when Stephen Hales directly measured intra-arterial pressure in a horse (Hales S, 1733). Subsequently, it took almost a century to develop sphygmomanometric devices that could potentially measure blood pressure non-invasive and these devices were introduced into clinical practice in the late 1800s and early 1900s. Although the variability of blood pressure in response to various physical/emotional stimuli and sleep/wake periods gained attention even in the 1940s, it's significance became more evident towards the end of the 20th century when mercury manometers were replaced with electronic devices making blood pressure measurements safe and accessible. As early as 1906, insurance companies in the United States were the first to conduct initial studies identifying the risks associated with high blood pressure (Fisher J.W.1914) and in the 1920's several studies not only concurred with their findings but further identified that HTN is often associated with comorbidities such as insulin resistance and central obesity (Vague J., 1947).

Pathophysiology

HTN can be classified as primary (or essential) HTN and secondary HTN accounting for 95% and 5% of hypertensive patients respectively. Although the aetiology of essential HTN is unknown, it typically begins in the fifth or sixth decade of life, is often associated with increased salt intake and obesity and has a strong relationship with family history, underscoring the possibility of genetic predisposition for the disease (Weber M.A., et al. 2014). Conversely identifiable causes such as renal artery stenosis, chronic kidney disease, sleep apnoea and adrenal diseases accompany secondary HTN. The common phenomenon in both scenarios is the derangement of multiple mechanisms involved in the maintenance of normal blood pressures and as such, the sympathetic nervous system, renin-angiotensin-aldosterone system, endothelial function plus sodium and water retention have been extensively studied to

ascertain mechanisms involved in the development of the disease.

Cardiac Output and Peripheral Vascular Resistance (PVR)

Cardiac output and PVR are two important factors that maintain normal blood pressures and it has been suggested that increased cardiac output resulting from sympathetic dysfunction is the trigger for the development of HTN and increases in PVR is essentially the physiological response to accommodate change in pressure and maintain homeostasis (Carretro et al. 2000).

Systematic Nervous System

Over the last decade the role of SNS in the development and maintenance of blood pressure has been studied exhaustively and it has been identified that sympathetic stimulation of the heart, peripheral vasculature, and kidneys, resulting in increased cardiac output, increased vascular resistance, plus fluid retention is important in the development and maintenance of this disease. As evidenced in the Coronary Artery Risk Development in Young Adults (CARDIA) study, sympathetic overdrive is often accompanied by low parasympathetic tone, which further exacerbates the condition. Additionally, several studies have demonstrated evidence of sympathetic over activity by documenting increases in norepinephrine spill over in patients with HTN confirming that sympathetic over activity is a core component in the pathophysiology of this disease. The renal sympathetic nervous system is a major player in the development and maintenance of HTN affecting blood pressure via two pathways, namely, the efferent and afferent pathways.

Renin-Angiotensin-Aldosterone System (RAAS)

The RAAS system plays a major role in orchestrating the maintenance of normal blood pressures and is activated by dual mechanisms, stimulation of the SNS and glomerular under perfusion (Cain A.E. et al., 2002). These stimuli trigger the release of renin from the juxtaglomerular apparatus which converts angiotensinogen to inactive angiotensin I, the latter is further cleaved by endothelium bound angiotensin converting enzyme (ACE) into angiotensin II, the active component of this cascade and a potent vasoconstrictor. Although this conversion of angiotensin I to angiotensin II was initially believed to occur primarily in the lungs, it has since been established that the process occurs practically in all tissues. In response to decreased salt intake RAAS also triggers the release of aldosterone from the adrenal glands that increases salt reabsorption coupled with water retention resulting in further increase of blood pressure (Cody, R.J., 1997). Under these circumstances one would expect that patients with HTN would invariably have high circulating levels of renin and angiotensin II, however, studies have demonstrated that plasma renin activity is increased in 15 percent patients, normal in 60 percent patients, and reduced in approximately 25 percent patients. This can be reconciled by growing evidence for the

presence of local renin systems regulating regional blood flow that might play an essential part in the pathophysiology of HTN (Kobori, H. et al. 2007).

Endothelial Dysfunction

Whether endothelial dysfunction is a cause or an effect of hypertension is debatable, nonetheless there is substantial evidence linking endothelial dysfunction with hypertension. In fact, there is evidence of a positive association between the degree of endothelial dysfunction and the severity of hypertension (Benjamin E. et. al., 2007). The major underlying mechanism for endothelial dysfunction seen in HTN is the decrease in the availability of nitric oxide (NO), a consequence of increased oxidative stress in these patients.

Vasoactive Substances

Endothelin, a potent vasoconstrictor is one of the major substances involved in maintaining vascular tone. Identified by Hickey et al in 1985, it is secreted by endothelial cells and exerts its affects in a paracrine or autocrine manner on vascular smooth muscle cells and counteracts the relaxing activity of NO. Studies have demonstrated that both in animals and humans infusion of endothelin-1 (ET-1) results in increased blood pressures (Vierrhapper, H. 1990) and blocking the system using antagonists reverts the phenomenon. However, plasma levels of ET-1 are normal in patients with essential hypertension suggesting that activity of this system might not play a role in all types of HTN but rather in specific disease states such as salt-sensitive HTN and renal HTN. Large clinical trials aimed at determining both the importance of endothelin in the development and maintenance of HTN and, ascertaining necessity of treatments targeted towards maintenance of this system are warranted.

Bradykinin a vasodilatory peptide with autocrine and paracrine function has long and an indirect association with HTN since apart from its direct vasodilatory affects, bradykinin stimulates release of other vasoactive substances like prostaglandins. This peptide from the kinin-kallikrein system is shown to reduce blood pressures by vasodilation as well as enhanced natriuresis and diuresis both achieved via increased renal blood flow mediated by NO and prostaglandin release. Although vastly overlooked due to side effects of coughing and angioedema the hypotensive effects of ACE inhibitors is due to increased bradykinin levels owing to its reduced degradation therefore therapies targeted directly at bradykinin system are likely in the not so distant future.

Conclusion

Alterations in the sympathetic nervous system and the reninangiotensin-aldosterone system are key factors in the development and maintenance of hypertension. Changes in vascular tone and renal sodium excretion are a direct effect of this imbalance and these changes are often accompanied by alterations in baroreflexes and autoregulation, both set in place for

homeostasis of blood pressure. Therefore all treatment strategies for hypertension are directed at restoring the activity of the SNS and RAAS. Although pharmaceutical therapy of HTN is quintessential, life style interventions are equally important in conquering this preventable and easily diagnosed pathology.

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