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COMMENTARY

Towards understanding the aetiology and pathophysiology of human hypertension: where are we now?

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As one of the earliest recorded medical conditions, hypertension and its consequences contribute significantly to worldwide morbidity and mortality. In spite of its widespread prevalence and intense research into its pathophysiology, only 5% of hypertensive patients have an identifiable cause. While our understanding of the 'cause' of hypertension is ever increasing, we now know that hypertension is the product of dynamic interaction between various diverse genetic, physiological, environmental and psychosocial factors. Of considerable interest is the fact that we have not yet fully determined the extent to which each of these factors contributes to the hypertensive status of an individual. While traditional teaching has associated hypertension with 'tangible' risk factors, such as obesity and smoking, our understanding of the underlying pathophysiology of human hypertension has grown tremendously in the past few years.

Where shall we start? The original 'foetal origins hypothesis' of hypertension (the so-called 'Barker hypothesis') generated considerable interest and controversy in assessing the significance of low birth weight and other prenatal antecedents of adult cardiovascular diseases, including hypertension. Indeed, initial nutritional experiments in animals using low-protein diets in gestation to produce hypertensive offspring appeared to validate the above hypothesis. More recently, further evidence has extended this hypothesis in human populations. For example, Pearce and Sullivan[1] found a significant inverse association of birth weight and pulse pressure of schoolchildren in a cross-sectional analysis. A longitudinal analysis by Li *et al.*[2] also showed a strong prepubertal association between low birth weight and systolic blood pressure. However, Koupil *et al.*[3] could not find any significant association between birth weight and high blood pressure (as measured by 24 h ambulatory readings). Clearly, the debates and uncertainties will remain over the foetal origins hypothesis, and its applicability to diverse populations worldwide.

Perhaps the environment is an important consideration. For example, hypertension and socioeconomic levels have been long-recognized to be inversely associated. Indeed, varying degrees of hypertension are noted in different socio-economic groups within similar populations. Most studies carried out in the developed countries have found an inverse relationship between hypertension and socioeconomic status, which is thought to be more consistent in women than in men. Nonetheless, the relationship between hypertension and socioeconomic status in developing countries is less clearly defined. An interesting theory relates to developing countries being placed at an 'earlier' epidemiological transitory phase in developing hypertension, as compared to the more developed countries, thereby questioning the role of primary intervention.[4] However, some inconsistencies exist in the available studies that assess the role of socioeconomic status and hypertension in developing countries due to a number of other factors (e.g. obesity, salt intake, diet, exercise, education, alcohol consumption, etc) which may have a significant interplay with low socioeconomic status and also with hypertension.[5] Recently, Van Minh *et al.*[4] demonstrated a higher prevalence of hypertension in lower socioeconomic classes in both men and women (although affluent men of lower socioeconomic class were more likely to be affected) in a Vietnamese population. In a Trinidadian cohort, Gulliford *et al.*[6] found no association of hypertension and education or income in the case of men, and perhaps even a consistent negative association amongst women. In a Qatari population, a low educational level was found to be an independent risk factor for developing hypertension.[7]

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Perhaps one of the most interesting mechanistic (or pathophysiological) insights into development of hypertension is the recent recognition of an association between hypertension and inflammation.[8] The possibility of an inflammatory state leading to the initiation and sustenance of hypertension raises relevant questions and has implications for novel therapeutic strategies. Of many inflammatory markers, high sensitive C-reactive protein (CRP) has been shown to have a strong, independent relationship to cardiovascular disease and future cardiovascular events. Also, a prospective analyses from the Women's Health Study showed that CRP levels were associated with an increased risk of developing hypertension in all subgroups, including those with no traditional coronary risk factors.[9] More importantly, the modulation of inflammation in cardiovascular disease may be a potential mechanism for the benefits of statins and drugs affecting the renin–angiotensin–aldosterone system. This is most evident for the common conditions that complicate hypertension, such as heart failure and atrial fibrillation.[10,11]

If hypertension is indeed caused by, or causes a proinflammatory state, then other inflammatory markers apart from the CRP must also have a role in the pathogenesis of hypertension. Recently, Orakzai *et al.*[12] showed a linear relationship between higher while blood cell counts (WCC) and systolic blood pressures in a Brazilian population. Whether elevated WCC contributes to hypertension by translating into increased adherence, capillary leucocytosis and increased vascular resistance – or whether increased cytokines secondary to a high WCC results in endothelial damage/dysfunction, leading to development of hypertension – remains uncertain.

What is the evidence for this relationship? A relation between monocyte-derived reactive oxygen species (ROS) and increased intima media thickness has been demonstrated.[13] ROS has also been proved to be associated with early morning surges of blood pressure in patients with pre-existing hypertension. Other inflammatory markers and cytokines have also been studied in hypertension. For example, Bautista *et al.*[14] demonstrated a significant relationship between elevated blood pressures and TNF-α and IL-6 levels. Interestingly, Manabe *et al.*[15] reported carotid haemodynamic parameters, such as the pulsatility index (PI) and resistive index (RI) (both markers of peripheral vascular resistance were associated with atherosclerosis and inflammation in hypertensive patients. This intriguing study raises the hypothesis that inflammation and hypertension may be linked via abnormal arterial stiffness.[16] In diabetic patients with hypertension, inflammation can be linked to urinary albumin excretion, as well as endothelial dysfunction.[17] Of note, aggressive antihypertensive therapy can significantly improve urinary albumin excretion, endothelial function and inflammatory activity, regardless of the drug class of antihypertensive therapy used.[18]

Another pathophysiological risk factor under scrutiny is plasma total homocysteine, which has a long association with cardiovascular disease. The mechanisms through which homocysteine levels are related to hypertension are thought to be related to smooth muscle proliferation, collagen synthesis, increased oxidative stress and endothelial dysfunction – all of which contribute to increased arterial stiffness. Ustundag *et al.*[19] recently reported elevated homocysteine levels in hypertension; indeed, patients with elevated homocysteine levels had higher mean systolic and diastolic blood pressures. Mayer *et al.*[20] have reported an independent link between raised homocysteine levels and 'central artery' (i.e. aortic) stiffness, which may also have a role in contributing to hypertension.

Hypertension rarely occurs in isolation and is often coexistent as a cluster of symptoms with dyslipidemia, obesity and glucose intolerance. Whether this so-called 'metabolic syndrome' has its origins in 'insulin resistance' or whether it is simply a euphemism for an underlying proinflammatory state is an ongoing debate. Certainly, we know that obesity by itself is one of the most important risk factors in the development of hypertension, but yet it remains difficult to assess the precise contribution (and mechanisms) of obesity to hypertension. Elevated adipocytokines, such as leptin, may have a role. Indeed, leptin levels have been independently linked to an increased intima media thickness and sympathetic systemic activation, leading to increased vascular tone, impaired arterial distensibilty and consequently, hypertension.[21] For example, Schutte *et al.*[21] recently investigated the effects of leptin in African subjects and found a positive association of leptin with pulse pressure and systolic blood pressure, and a negative association with arterial compliance, which was independent of the effects of obesity, hyperinsulinemia and age.

The endothelium has attracted great interest as a pathophysiological feature of hypertension. Endothelial damage/dysfunction is closely associated to abnormal thrombogenesis and atherogenesis in cardiovascular disease. Another related pathophysiological process – abnormal angiogenesis – is also linked to many cardiovascular disorders, including hypertension. For example, Karter *et al.*[20] recently found elevated Vascular Endothelial Growth Factor levels (one of many indices of angiogenesis) in cohorts of patients with established hypertension, as well as in white coat hypertension. Circulating endothelial progenitor cells (EPCs), which have also attracted great interest in relation to cardiovascular disease or its risk factors, also seems to be related to endothelial damage/dysfunction, contributing to impaired arterial elasticity.[22,23] Indeed, an age-related fall in EPCs may contribute to impaired arterial elasticity, thus contributing to hypertension.[22] Karter *et al.*[20] also found decreased Nitric Oxide levels and increased Endothelin-1, which are

both involved in a functional regulatory role for arterial stiffness and endothelial (dys)function.[24]

The renin–angiotensin–aldosterone system is central to the pathophysiology of cardiovascular disease. The atherogenic effects of Angiotensin II have been attributed to its ability to cause endothelial dysfunction and vascular hypertrophy. Normally, there is a fine balance between intrinsic NO production and Angiotensin II and when this balance is upset, endothelial dysfunction occurs. For this reason, it is thought that the beneficial effects of the angiotensin receptor blockers extend beyond the lowering of blood pressure.[25] While the role of angiotensin receptor blockers is well established in treating hypertension, further research is underway to evaluate the role of these agents in primary prevention of hypertension by suppressing the inflammatory state or by prevent endothelial dysfunction.[26] Finally, oxidation of low-density lipoproteins by oxygen-free radicals may increase hypertension-related atherogenesis – perhaps via endothelial damage/dysfunction – and antioxidants may be beneficial in this regard.[27]

A discussion on new insights into the pathogenesis of hypertension cannot fail to mention genes. The hope for the discovery of genes for common human diseases, such as hypertension and diabetes mellitus was the justification behind the ambitious human genome project. Apart from the rare monogenetic forms of secondary hypertension, there is relatively limited evidence for genes that determine the majority of essential hypertension, and even less so for the existence of causative alleles within these genes. The difficulty in identifying a genetic *cause* for hypertension *per se* could be due to numerous alleles, small individual impact(s) and unequal distributions between populations. In a comprehensive review by Tanira *et al.*,[28] a summary of genetic variations potentially implicated in hypertension have been highlighted in association with the renin–angiotensin system, G protein signal transduction, ion channel defects, noradrenergic system and the immune system and inflammation. However, the clinical implications of these variants needs to be further evaluated. The Medical Research Council BRItish Genetics of HyperTension (BRIGHT) study, for example, concluded that human essential hypertension may have an oligogenic element (i.e. a few genes may be involved in determination of the trait) possibly superimposed on more minor genetic effects, and that several genes may be tractable to a positional cloning strategy.[29] Other researchers have demonstrated many further genetic associations but consensus is lacking.[30–39] Clearly, the availability of data from diverse populations, including Chinese,[31] Hispanics[32,33] and African-Americans[34] cohorts, is encouraging, gene variants may influence target organ damage[35] in hypertension and blood pressure variation,[36] but again, more data from diverse populations are needed. Although in the current environment, the cynics would argue that the genetic basis for essential hypertension is tenuous and far from conclusive, the hope still remains to locate specific genes for hypertension that could provide for novel targeted therapy, which would improve our current management of this condition. Some day, pharmacogenetics may even feature more prominently in future hypertension treatment guidelines.

This brief (and selective) overview provides a flavour of the wide diversity in our progress towards understanding the aetiology and pathophysiology of hypertension. Clearly, exciting times lie ahead.

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