STRESS AND HYPERTENSION

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Introduction

Hypertension is a major cardiovascular risk factor that directly contributes to myocardial infarction, cerebrovascular accidents, congestive cardiac failure, peripheral vascular disease and premature mortality (1). In the great majority of cases, no cause can be found and this form of hypertension is termed 'primary' or 'essential' hypertension. Various theories have been put forward and the causes can be divided broadly into genetic and environmental factors. Based on twin studies, it was estimated that about 50 percent of blood pressure variance is genetic (2). The main environmental causes are dietary and psychosocial factors. In this review, we will concentrate on the latter while noting that there is still disagreement about the role of a dietary factor, sodium chloride, in causing hypertension. A meta-analysis of trials of sodium restriction concluded that sodium intake had no influence on blood pressure in normotensive subjects and in hypertensives below 45 years of age (3). We will also discuss an interesting phenomenon known as 'white coat hypertension'.

Evidence that stress causes hypertension

While psychological factors are suspected in the development of hypertension, conclusive evidence is still lacking. There are three ways in which the roles of environmental stress or blood pressure can be assessed: animal experiments, laboratory studies and field studies.

Henry and Stephens (4) pioneered the work on stress-induced hypertension in animals. They conducted a series of experiments in mice housed in colonies which were designed to promote social interaction and conflict. It was observed that the dominant mice developed higher pressures than the subordinates. The subdominant animals were thought to show a chronic defense reaction characterised by continuous sympathetic nervous system activation. The subordinates exhibited the defeat reaction in which there was pituitary-adrenocortical axis activation. Henry and Stephens proposed two distinct response types which they referred to as the defense and defeat reactions. While negative health consequences were postulated for both, they proposed that only the defense reaction is associated with the development of hypertension.

Not surprisingly, there are only a few comparable studies in humans. A situation somewhat similar to the social interaction of mice in population cages was reported by D'Atri and Ostfeld (5) who studied men confined to prison. The dormitory occupants had an average systolic pressure of 131 mmHg whereas that of those living in single-occupancy cells was only 115 mmHg. Furthermore, transfers from single cell to a dormitory caused the blood pressure to rise (6). These changes are not thought to be due to diet as all inmates ate the same food.

Blood pressure tends to rise with age. However, this is not an invariable phenomenon and studies have shown that blood pressure can remain low throughout life. The change of blood pressure with age appears to be determined culturally rather than genetically. A good example of this is reported by Timio *et al* (7). It is a 20-year observational study of Italian nuns living in a secluded order. The nuns were compared with a control group both at entry and after 20 years. Blood pressures were the same at entry but by the end of the study the systolic blood pressure was approximately 30 mmHg in the controls than in the nuns. The differences could not be explained by changes in body weight, by diet or by childbearing. It was concluded that the differences were due to the monastic and relatively stress-free environment.

Similar observations have been made in people who migrate from a stable traditional society to a Westernised one. Studies of the bushmen of the Kalahari (8) and the nomadic Samburo of Kenya (9) have shown no increase of blood pressure with age. Bushmen who abandoned their traditional lifestyle, however, and become farm labourers, or even prisoners, have blood pressures 15 mmHg higher than the nomads (10). Samburo warriors who joined the Kenyan army also showed an increase of blood pressure (11). Many other studies confirm the effect of acculturation from traditional societies to contemporary Western life but the primary problem with almost all of them is that it is difficult to know what factors were responsible for the rise of blood pressure. While stress may be one of them, there are also major dietary and other lifestyle changes associated with the transition between cultures. Nevertheless, these studies suggest that there is something about modern society that tends to elevate blood pressure. To investigate this further, Waldron *et al.* (12) collected data from 84 different societies and concluded that higher blood pressures were associated

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with increased emphasis on a market economy, increased economic competition and decreased family ties. These associations appeared to be independent of salt intake and, in men, of obesity; but again, the way in which such cultural factors might impact on individuals to alter their blood pressures remains unclear.

A number of epidemiological studies have shown that blood pressure is related to one's position in society, with people of lower socioeconomic status and less education having higher blood pressures (13,14). However, this relationship was dismissed in other major studies such as the United States Health and Nutrition Survey (HANES III) (15) and a Copenhagen County study (16).

Stress and disease models

A convenient model, as described by Pickering TG (17), for defining the roles of psychological factors is shown in Fig. 1. The magnitude of the response is thought to be determined by the interaction of three things:The degree of arousal in the central nervous system engendered by the stimulus, the individual's ability to cope with the stressor and the physiological susceptibility.

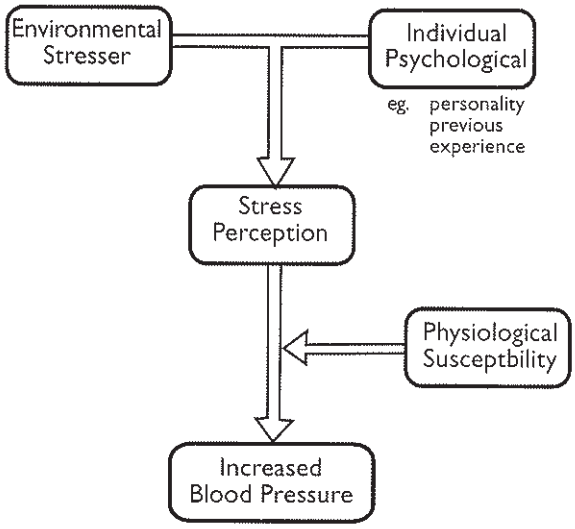

Fig. 1. A tripartite model of stress and disease

To qualify as a stressor, the stimulus must tax, exceed or threaten to exceed the adaptive capacity of the individual. The work setting is thought to be one of the most important sources of stressors in modern society. Others are the family, the site of marital discord and care-giving responsibilities. Various studies of blood pressure and specific occupations (with excessive demands) have been done (18-20) to see if there was a definite relationship but no clear picture has emerged. This is because of the difficulty in determining what characteristics of the work situation adversely affect incumbent's health either because specific characteristics are not assessed or because of a relative lack of variability within the occupation.

Karacek *et al.* (21) developed a job-strain model specifically to evaluate occupational stress. It has two orthogonal components which are psychological demands and decision latitude. The former is a measure of control while the latter is a measure of job control or autonomy. The most stressful jobs are those that are perceived to combine high demands and low decision latitude (Fig. 2). This combination is otherwise known as 'high-strain'. Studies (21-23) have shown the close association between job strain and the development of significant coronary heart disease leading to myocardial infarction. Hypertension is probably the most likely mechanism by which job strain might cause coronary heart disease (24).

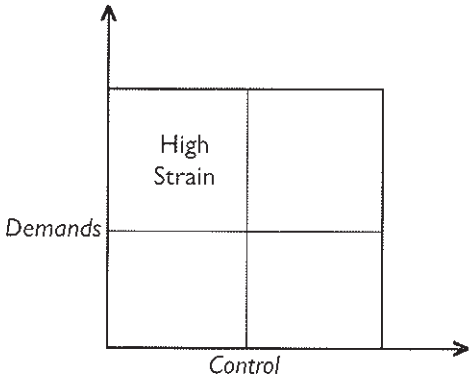

Fig. 2. The demand-control model

In a case-control study of men employed in a variety of jobs, it was found that hypertensive individuals were approximately three times as likely to be employed in high-strain jobs as the normotensive controls (25). Exposure to job strain was also associated with an increased left ventricular mass, which would be consistent with the effects of a sustained elevation of blood pressure from regularly occurring stress.

A closely related model is the effort-distress model of Frankenhaueser (26). This also has two orthogonal components (see Fig. 3), which are termed effort and distress. Effort is conceived as arousing the sympathetic

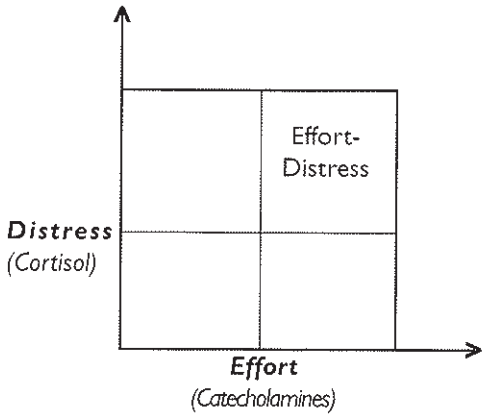

Fig. 3. The effort-distress model

nervous system, and distress is that of the adrenocortical system. While effort is needed to meet or respond to most demands, distress is experienced only when the demands are perceived as excessive, threatening or otherwise unpleasant.

Another model is the concept of lifestyle incongruity which was described by Dressler (27) as the extent to which a high-status lifestyle exceeds the norm for an individual's occupational class, which means to say living beyond one's means. It has been associated with increased blood pressure not only in developing countries (28,29), but also in American blacks (30).

Job strain and women

Pickering *et al.* (17) studied 80 women in their work site and showed that job strain had little effect on blood pressure in women. This is somewhat surprising as women are more likely than men to be employed in high-strain jobs. A study by James *et al.* (31), however, proved to the contrary. They made ambulatory blood pressure recordings in 50 normotensive working women doing technical and clerical jobs and they found that the blood pressures were elevated and were highest at work followed by at home and lowest during sleep. The most powerful behavioural predictor of systolic blood pressure was the perception that one's job is stressful, which was associated with higher pressures in all three situations: At work, at home and during sleep. An observation was made in the Framingham study that women employed in clerical jobs who also had children and were married to men with blue-collar jobs, had the highest incidence of coronary heart disease (32). A recent case-control study reported that women exposed to high job strain are at higher risk of developing preeclampsia and, to a lesser extent, gestational hypertension (33).

Pathophysiology of stress-induced hypertension

Evidence is amounting for the role of increased sympathetic nervous system activity in the early stages of essential hypertension (34,35). This raises the question of what is the main reason for this sympathetic overactivity. While it may be genetic, one has to look at the environmental aspects, and psychological stress is definitely a prime candidate, as discussed earlier. Stress can cause a transient rise of blood pressure. However, how does one explain its role in the pathogenesis of established hypertension since the latter is primarily a disorder of the tonic regulation of blood pressure rather than its short-term variability?

There are a number of theories and some of them are discussed below.

The adrenaline hypothesis

Studies have linked adrenaline with the development of stress-induced hypertension (36,37). It has been shown that infusion of adrenaline at low doses, which is equivalent to the levels seen during naturally occuring stress, can enhance noradrenaline release from sympathetic nerve terminals (38). This effect is thought to be mediated by prejunctional β2 receptors, since it can be blocked by β-blockers. Furthermore, circulating adrenaline may be taken up by sympathetic nerve terminals, stored with noradrenaline as a co-transmitter, and released with it during sympathetic nerve stimulation. There are two essential components to this mechanism. First, the release, re-uptake, and presynaptic facilitation of noradrenaline release acts as a positive feedback loop. Second, although the half-life of adrenaline in plasma is only a few minutes, if adrenaline is stored in sympathetic nerves, it may last for many hours. This is important in providing sustained effects. A schematic diagram is illustrated below (Fig. 4) .

Human studies have implicated this mechanism. An acute adrenaline infusion produces tachycardia with an increased systolic and slightly decreased diastolic pressure. When the infusion is terminated, the plasma adrenaline level returns to normal although the tachycardia and increased systolic pressure persist for an hour or two and diastolic pressure rises to above baseline levels (39). Adrenaline infusion can also enhance the pressor response to endogenous sympathetic stimulation, such as occurs during isometric exercise and the cold pressor test (40).

The delayed pressor effect of adrenaline was well demonstrated in a study conducted by Blankenstijn *et al.* (41) who infused adrenaline, noradrenaline, or dextrose for 6 hours (from 10am to 4pm) in normal volunteers, and monitored the effects on blood pressure over the next 16 hours using intra-arterial blood pressure monitoring. The pressure was first reduced by adrenaline but by the end of the infusion was above the baseline value and remained elevated throughout the night. Noradrenaline infusion produced an initial elevation of pressure but no sustained effects. The pressor effect of adrenaline was most marked during periods of increased sympathetic activity, ie. when the subject is active. This increased pressure effect was not accompanied by any changes of heart rate.

Structural changes in heart and resistance vessels

Peripheral resistance is increased in patients with sustained hypertension. This observation is thought to

be due to medial hypertrophy and can be regarded as an adaptive process in the presence of increased pressure and flow. It is unclear as to the extent to which stress can produce such changes but there is evidence that the growth of vascular smooth muscle can be influenced by a number of stress-related factors, including angiotensin, catecholamines and corticosteroids (42).

The role of glucocorticoids

The effects of glucocorticoids on blood pressure are complex and not well understood, although there is agreement that they tend to have a pressor effect (43). It plays a vital role in Frankenhaeuser's effort-distress model (26) where increased cortisol is found in the high-effort-high-distress situation. Whitworth *et al.* (44) gave four different synthetic glucocorticoids, with little or no mineralocorticoid effect, to normal subjects for five days. All four raised the blood pressure without any accompanying sodium retention.

White coat hypertension

"Doctor, why is my blood pressure always high whenever I visit you in clinic but is normal at home?"

This frequently asked question somewhat defines the phenomenon called 'white coat hypertension'. It is the finding of persistently raised blood pressure in the doctor's clinic but normal at other times. It is generally thought to be attributable to acute stress in the presence of a doctor and since the very basis for the initiation of treatment in hypertension are the clinic pressure readings, it requires more than a mere mention in this chapter. A few intriguing questions have been asked by clinicians through the years. Among others are: What is the aetiology? Is it a benign condition? Does it need to be treated?

Prevalence and demographic factors

The prevalence of white coat hypertension is perhaps higher than is generally thought. Pickering *et al.* (45) reported that 21 percent of patients with borderline hypertension (clinic diastolic pressures between 90 and 104 mmHg) studied had both systolic and diastolic pressures which were below this level during the ambulatory blood pressure monitoring. For patients with more advanced hypertension (clinic diastolic pressure above 105 mmHg), the prevalence was less at 5 percent. It has to be pointed out, however, that the criteria used to define white coat hypertension do vary between centres and as such will be a major determinant of its prevalence. Ambulatory blood pressure monitoring has been conventionally used to diagnose white coat hypertension. However, mental arithmetic is also a useful diagnostic evaluation in this condition (46).

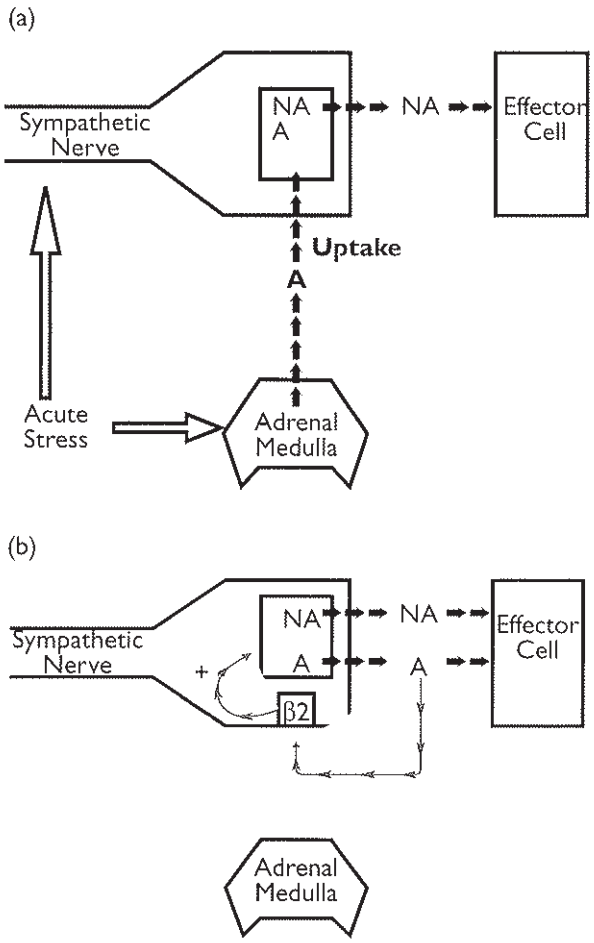

Fig. 4. Postulated mechanism for explaining the delayed pressor effects of adrenaline. **(a) Acute effect.** Adrenaline (A) is released by adrenal medulla in response to stress where it is taken up by sympathetic nerve terminals. **(b) Delayed effect.** There is gradual release of adrenaline as a co-transmitter, which enhances noradrenaline (NA) release via presynaptic β2-receptor stimulation

White coat hypertension has been found to be more common in women than men (45,47,48) although some studies have reported equal incidents in men and women (49,50).

White coat hypertension can occur at any age. It has been reported to be common in children (51) and in those over the age of 65 (52). Lerman *et al.* reported that their patients with white coat hypertension were on average nine years older than their sustained hypertensives (50). It was observed that women had white coat hypertension at a greater age than did men (53).

Psychological factors and white coat hypertension

It might be expected that white coat hypertensives would generally be more anxious but this is not necessarily the case. Laughlin *et al.* (54) reported no

correlation between the clinic and home differences. White coat hypertensives were found to have less anger than sustained hypertensives but did not differ on measures of anxiety, health worry or health stress (50).

The influence of a doctor's presence on the patient's blood pressure was well demonstrated by the study of Mancia's group (55) using continuous intraarterial pressure recording in hospitalised patients. There was an immediate rise of pressure when the doctor approached the patient and put a cuff around the arm. This lasted throughout the procedure of taking a reading and only returned to baseline over a period of several minutes. Repeat visits by the same doctor did not show any habituation of this response. In another similar study, the average change of pressure evoked by the doctor was 23/18 mmHg, approximately twice as high as when the pressure was taken by a nurse (56).

Sympathetic nervous activity in white coat hypertension

Evidence is growing that sympathetic nervous activity is normal in white coat hypertensives. Saito *et al.* (57) found that the patients with white coat hypertension had normal 24-hour urine noradrenaline and adrenaline, whereas the patients with sustained hypertension had elevated levels. This finding of whole-day sympathetic overactivity in sustained hypertension was recently replicated by Pierdomenico *et al.* (58). It can, therefore, be accepted that these two conditions differ in their pathophysiologic background.

Mechanism underlying white coat hypertension: The conditioned response

A number of mechanisms explaining white coat hypertension have been postulated. The first is the exaggerated or orienting response and therefore a generalised hyperreactivity to novel or stressful stimuli. However, the bulk of evidence does not support the view that it represents a generalised hyperreactivity (59,60). The second is that it is a precursor of sustained hypertension. While this cannot be excluded, the fact that it tends to be more, rather than less common in older patients would argue against this. The third mechanism is the learned or conditioned response.

In this third phenomenon, white coat hypertension is thought to originate as part of the defense reflex which later becomes perpetuated through classical conditioning (61). For example, after a patient is told by the doctor that his pressure is a matter of concern, the patient learns to associate the doctor as the harbinger of bad news, who then becomes a conditioned stimulus that continues to elicit the pressor effect response in this patient. This is in contrast to the normal habituation, which is the diminution of the alerting response to repeat visits.

Is white coat hypertension a benign condition?

Opinions vary as to the significance of white coat hypertension. The majority of investigators believe that it represents a benign entity whereas others have suggested that the risk in this condition is similar to that of patients with sustained hypertension. Since it has important prognostic and management implications, we will discuss the evidence for the two views.

Perloff *et al.* (62) conducted a prospective study of morbidity related to ambulatory pressures. They found that patients whose ambulatory pressure was low relative to their clinic pressure were at lower risk than those with higher ambulatory pressures. In a study of patients with borderline hypertension, cardiovascular morbid events was noted in 2.1 percent of patients with white coat hypertension and 4.4 percent in those with sustained hypertension (63). Floras *et al.* (64) reported an incidence of target organ damage in 64 percent of patients with sustained hypertension but only in 19 percent of white coat hypertensives.

However, a number of studies have since emerged that contradict the assumption that white coat hypertension is a harmless condition. Muldoon *et al.* (65) found that this subset of patients had evidence of carotid artery atherosclerosis and that the number was greater than the normotensives but equal to that of the subjects with sustained hypertension. White coat hypertension also a risk factor for left ventricular hypertrophy (66). Even in the absence of structural heart disease, in contrast to normotensives, white coat hypertensives are just as likely as sustained hypertensives to get diastolic dysfunction (67). Recently, Strandberg and Salomaa (68) reported a 21-year prospective data of 536 men with cardiovascular risk factors at baseline. Blood pressure was measured both by a nurse and a doctor. The men with a white coat effect (defined here as doctor minus nurse blood pressure) more than 30 mmHg had a significantly higher mortality than other men (relative risk 2.2). Mortality was also higher in the white coat hypertensives (33.3%) than in the normotensives (9.5%), with a p value less than 0.0005.

Treatment of white coat hypertension

Two studies, using calcium channel blockers (69,70) have shown that although the effects of the medication on clinic pressure were similar in patients with both high and normal ambulatory pressure, when ambulatory pressure was normal to begin with (ie., white coat hypertension), the drug did not lower it further. Another study compared nifedipine and enalapril and confirmed that nifedipine had little effect on ambulatory pressure if it was low to begin with (ie., white coat hypertension) while enalapril lowered it whether it started out

low or high (71). This finding suggests that there may be differences between the various classes of antihypertensives in the degree to which they affect white coat hypertension.

As shown above, there is conflicting evidence as to the clinical significance of white coat hypertension. If it is a truly benign condition, then is it justified to subject this group of people with white coat hypertension to drug therapy, which is potentially life long, and incurring the possible side effects along the way? Chrysant (72), in a recent article stated that white coat hypertension was a benign condition and suggested that pharmacologic treatment should be withheld. Instead, treatment should aim at lifestyle modification, moderate salt restriction, weight reduction, regular exercise, smoking cessation and correction of glucose and lipid abnormalities. However, if one chooses to ignore the body of evidence implicating white coat hypertension as a potentially hazardous condition, then would it be right to refrain from treating this condition?

Conclusions

In this review we discussed two distinct entities: Stress-induced hypertension and white coat hypertension. The primary candidate for the development of the former is chronic exposure to stress. Job strain, which focuses on the individual's perception of his or her working conditions, has the advantage over earlier concepts of work stress. It includes not only assessment of the demands of the job, but also how well these demands can be controlled. Job strain is well recognised as a risk factor for coronary heart disease, and it is thought to exert this effect by raising the blood pressure in men but not women. Why there is a sex difference is quite intriguing, and the answer may lie in a different need for control.

The issue of white coat hypertension remains unresolved. Is it a truly benign condition? Is withholding treatment a wishful thinking or is it fully justified? As the prevalence of white coat hypertension is high and as the prognosis and clinical implications are yet uncertain, more studies need to be done to help resolve these issues.

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