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Chapter title: **Hypertension**

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Introduction

Essential hypertension is the chronic elevation in blood pressure of unknown origin, which is generally defined as systolic and diastolic blood pressure persistently above 140/90 mmHg, respectively. The condition is prevalent in 15-25% of the adult population in most countries (Mancia et al. 2013) and is estimated to cause 4.5% of current global disease burden. The use of pharmacological treatment alone to lower blood pressure may have adverse side effects and sometimes is not cost effective. Therefore, this has stimulated researchers to investigate lifestyle approaches for prevention and treatment of hypertension. Current recommendations emphasize weight loss in those who are overweight/obese, sodium reduction, increased physical activity, limited alcohol intake, and smoking cessation (Mancia et al 2013), although psychological risk factors are not widely recognised. Indeed, the fundamental question of whether psychosocial stress causes hypertension in humans has been difficult to evaluate using an experimental approach because of ethical constraints. Thus, evidence is mostly derived from observational studies, natural experiments, and laboratory studies to show whether stress modifies disease relevant biological processes. This chapter will focus on these lines of evidence and will specifically consider the role of subacute and chronic stressors, chronic psychological states, and interventions using psychological approaches. There has been a vast amount of animal research in this area, which has produced far from consistent findings, thus the present chapter will primarily focus on studies with human participants.

Sympathetic Nervous System

The sympathetic nervous system (SNS) is thought to play a pivotal role in many of the psychophysiological effects that will be described later. The peripheral SNS innervates tissues throughout the body, especially the heart, vasculature, and adrenal medulla. The adrenal medulla responds with systemic catecholamine release (predominantly epinephrine), whereas norepinephrine is released from terminals that line the vasculature. The SNS is primarily responsible for rapid, short term alterations in cardiovascular function during mental and physical stress, and also has metabolic effects (insulin resistance and lipolysis) and varied immunological effects (release of cytokines and acute phase proteins). A number of investigators have attempted to bring about chronic hypertension using neurogenic methods, such as direct stimulation of the defence area in the brain (Folkow and Rubinstein, 1966), exposing rats to noise (Rothlin et al, 1956), and operant conditioning of primates (Herd et al, 1969). However, only temporary elevations in blood pressure are generally observed, thus suggesting that the SNS is important in the short term regulation of cardiovascular function but not in long term control of arterial pressure. Other neuroeffector mechanisms, including the renal sympathetic nerves may influence the long term regulation of blood pressure by shifting the pressure natriuresis curve. The SNS can also exert long term trophic effects on vascular muscle (Bevan, 1984), that increase vascular resistance and the vasomotor response to vasoconstrictor stimuli.

Subacute and Chronic Stress

It is well known that acute stress results in elevated blood pressure. In the laboratory setting mental challenges such as unfamiliar hand-eye coordination tasks [**Figure 1**], public speech, or mental arithmetic can produce sizable increases in blood pressure, elevated cardiac output, increases in total peripheral resistance and local skeletal muscle vasodilatation. The reactivity hypothesis suggests that a recurrent pattern of exaggerated SNS activity may up-regulate basal blood pressure levels over time and also contribute to atherosclerotic processes. There is robust evidence demonstrating that individuals with greater cardiovascular responses to laboratory induced mental stressors subsequently have an increased risk of elevated blood pressure, hypertension, left ventricular mass, subclinical atherosclerosis, and clinical cardiac events (Chida and Steptoe, 2010). However, the majority of stress reactivity studies have been performed in middle- and older-aged adults in whom data interpretation is complicated by the problem of reverse causation. As such, it is unclear whether elevated reactivity indeed raises the risk of hypertension, or if heightened reactivity is simply a reflection of underlying disease pathophysiology. In an attempt to minimise such reverse causation bias we examined associations between stress reactivity in childhood with incident hypertension over an extended follow up into mid-life (Hamer et al 2016). Our findings showed that a higher pulse rate response to a stressor (a medical examination) in childhood was associated with a 30% increased risk of hypertension in adulthood some three decades later. A hyper-reactive disposition in childhood may be a marker for other underlying psychobiological processes across the life course relevant to disease. For example, acute stressors elicit transient endothelial dysfunction, greater fibrinogen and interleukin 6 responses that are positively associated with increased ambulatory blood pressure (Steptoe et al 2016), and increased cortisol responses that have been related to incident hypertension (Hamer and Steptoe, 2012). **[Figure 2]**

Acute psychological trauma has profound effects on blood pressure. For example, terrorist attacks and earth quakes have produced a substantial and sustained increase in resting blood pressure and blunted nocturnal blood pressure fall of participants from the local community (Gerin et al 2005; Parati et al. 2001). Individuals with posttraumatic stress disorder have higher levels of basal cardiovascular activity relative to age matched control groups, suggesting increased SNS activity (Buckley and Kaloupek 2001). Numerous studies have also demonstrated an association between work stress and increased risk of hypertension (Babu et al 2014).

Chronic Psychological States

Chronic psychological states refer to enduring mood states such as depression and anxiety, and personality traits such as type A behavior. In particular, depression has gained substantial attention as an independent predictor of cardiovascular disease and all cause mortality, and is often comorbid with chronic diseases that can worsen their associated health outcomes. The literature specifically relating depression and hypertension is,

however, inconsistent with overall pooled results demonstrating weak but statistically significant associations (Meng et al. 2012). In a study of British civil servants that examined longitudinal trajectories, the risk of hypertension increased with repeated experience of depressive episodes over time and became evident in later adulthood (Nabi et al 2011). Thus, the association between depression and hypertension is complex. Some have attributed the effects to hypertension 'labeling', whereby individuals 'labelled' as hypertensive might adopt a sick role that can impair quality of life. Indeed in a large population study we found that labelling individuals as hypertensive, rather than elevated blood pressure per se, may partially explain the greater levels of psychological distress (Hamer et al 2010). A number of mechanisms may underlie the cardiovascular risk associated with depression, which include inflammatory pathways, changes to sympatho-vagal balance, and alterations in hormone and catecholamine circadian rhythms. These adverse changes may partly develop through poor regulation and lack of adaptation to acute stressors. Health behaviors such as physical activity, diet, alcohol, and smoking may also partly mediate some of the health risks of depression, although the relevance of these mediators has not been well established.

Stress Reduction Interventions

There is an extensive literature on psychosocial interventions. Early animal work showed that treatment with the beta-blocker propranolol inhibited the development of coronary atherosclerosis in behaviourally stressed monkeys fed an atherogenic diet (Kaplan et al 1987). Stress management training has been used extensively in hospital based rehabilitation programs (Rozanski et al 2005) and is consistently associated with improved autonomic and hormonal regulation. The magnitude of the reduction in blood pressure obtained with multi-component, individualized cognitive behavioral intervention for stress management is comparable in some studies to that obtained with other lifestyle modification including weight loss, diet, and exercise, although single-component interventions such as biofeedback or relaxation are less effective **[Figure 3]**. Indeed, data on the blood pressure effects of relaxation therapies, such as guided breathing, are generally considered poor, largely because of methodological weaknesses in the published data (Mahtani et al. 2012). In a systematic review of 16 trials psychological and pharmacological interventions were shown to have only small effects on depression outcomes in coronary artery disease patients and this did not reduce the risk of mortality or cardiac events (Baumeister et al 2011). Thus, overall, evidence regarding the efficacy of stress reducing interventions on cardiovascular outcomes is inconsistent and further high quality and adequately powered trials are required.

Conclusion

There is consistent evidence for an association between psychosocial factors and hypertension, and biologically plausible mechanisms have been established. Acute and enduring stressors directly impact on blood pressure control. However, one intriguing

question that remains partly unanswered is why a similar level of stress exposure might lead to the development sustained hypertension in some individuals but not in others. This issue may be partly explained by genetic predisposition, personality style and the environment that determine how we react and adapt to life stressors, and ultimately determine individual susceptibility to hypertension. In addition, individual physiological responses and adaptation to stressors are likely to be influenced by health behaviors such as physical exercise, obesity, and diet. Lifestyle approaches that encompass all of these factors should therefore be considered in the treatment of hypertension and identifying those at high risk.

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Figure captions

Figure 1. The mirror tracing task can be used to elicit robust psychophysiological responses. Participants are requested to trace around the star using the mirror image as quickly and accurately as possible. Deviations from the black line are followed by a high pitch noise.

Figure 2. The cortisol stress response profile in relation to hypertension risk. Participants included 479 initially healthy men and women (mean age, 62.7 ± 5.6 yr), without history or objective signs of cardiovascular disease or hypertension at study entry. Solid line represents participants developing hypertension over 3 years follow up. Data are mean ± SEM adjusted for age. (See Hamer et al. 2012)

Figure 3. Comparative blood pressure lowering effects of weight loss, exercise, guided breathing, and diet. Mean effects extracted from Zomer et al (2016); Cornelissen and Smart (2013); Mahtani et al (2012); Gay et al. (2016).

Figure 1.

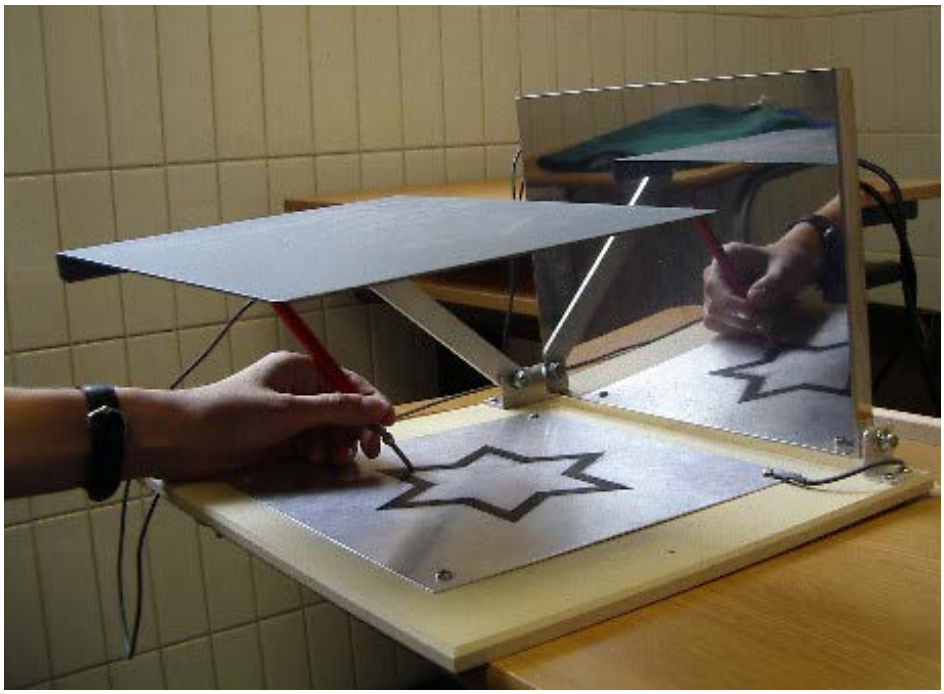


Figure 2

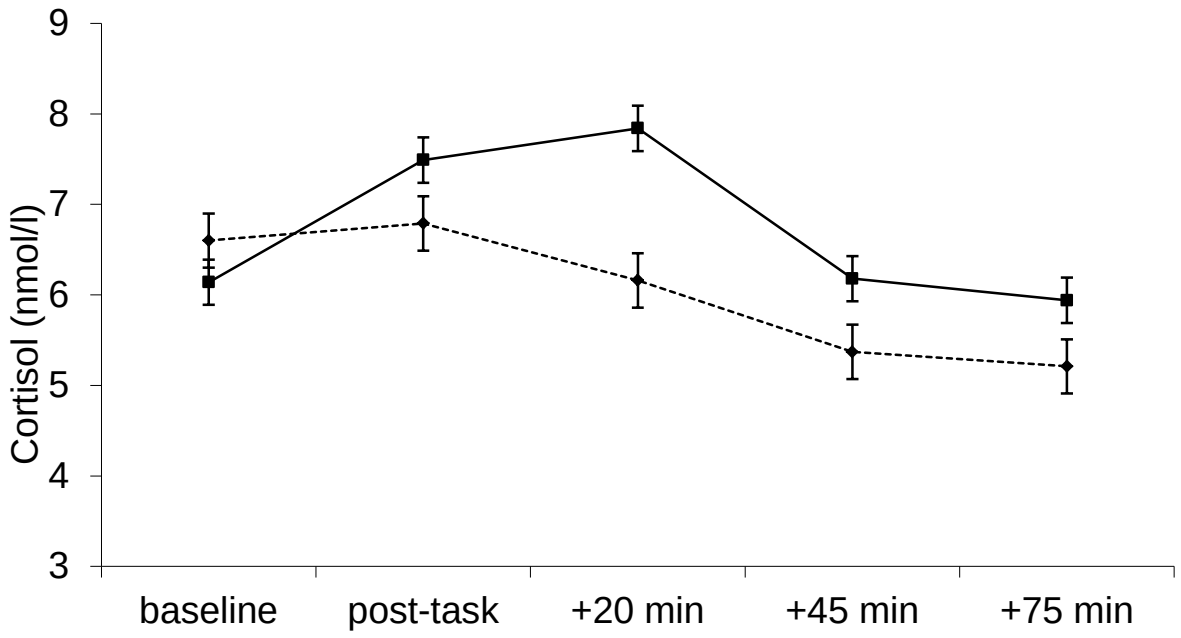
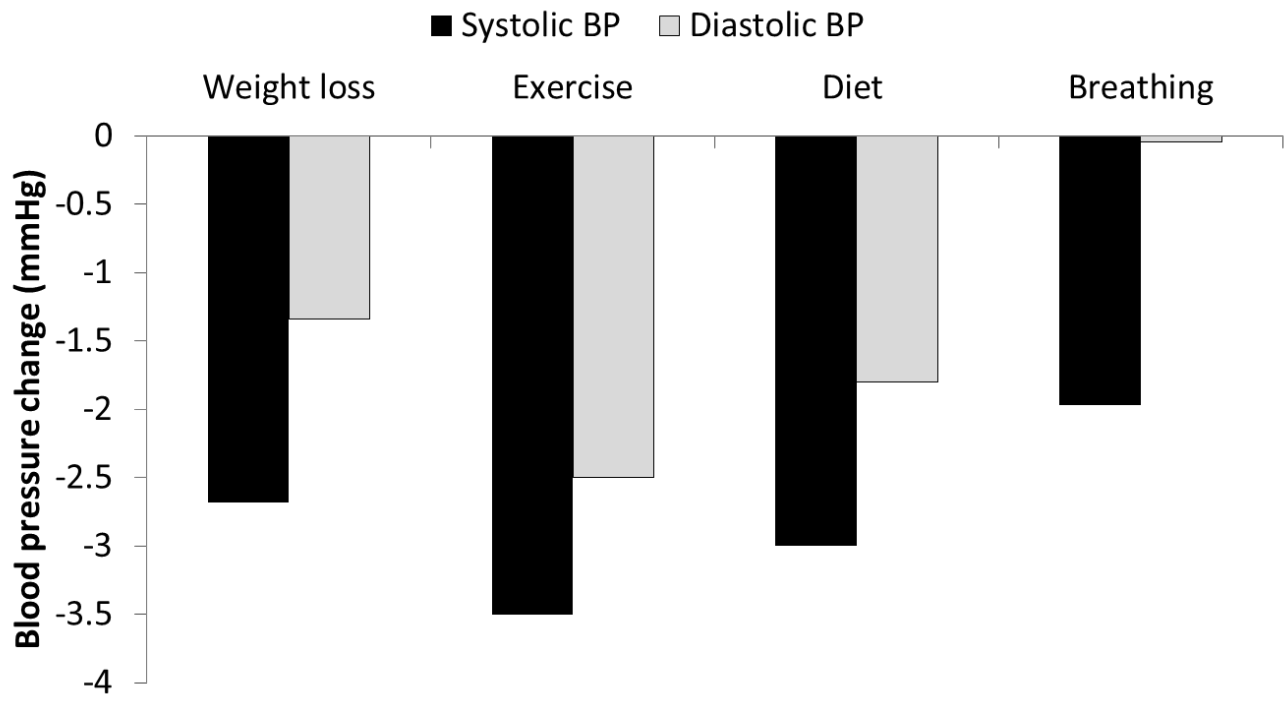

9
8
7
6
5
4
3
Cortisol (nmol/l)
baseline
post-task
+20 min
+45 min
+75 min

Figure 3


Systolic BP
Diastolic BP
Weight loss
Exercise
Diet
Breathing
Blood pressure change (mmHg)
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4