MECHANISMS LEADING TO HYPERTENSION AND CV MORBIDITY *by Joseph Schwartz, PhD, Karen Belkić, MD, PhD, Peter Schnall, MD, and Thomas Pickering, MD, DPhil*

The relationship between elevations in blood pressure (BP) and cardiovascular risk is "strong, continuous, graded, consistent, independent, predictive, and etiologically significant for those with and without CHD."[7] From the age of 20 on, in the U.S. and other industrialized settings, BP increases progressively with age for the population as a whole, so that by age 60 approximately 50% of the population has hypertension, according to the standard definition of BP > 140/90 mmHg.[392] It is now clear that an increase in BP, even for those at a far lower level of BP than the current definition of hypertension, is associated with an increase in CHD risk.[7] With heart disease and stroke representing the first and third leading causes of death in the U.S., respectively, the public health implications of the hypertension epidemic are clear.[263]

Essential hypertension is a chronic disease process defined by the presence of persistently elevated (not just acutely elevated) BP, without secondary causes. Epidemiologic evidence reveals that essential hypertension is a disease of industrialized society, as there is a minimal hypertension disease burden among hunter-gatherers, nonmarket agricultural communities, and other nonindustrialized societies.[329,387] Within industrial society, hypertension is socially patterned by class, race, and gender.[137,291,392]

Current evidence suggests that the "unidentified" cause(s) of essential hypertension most likely include one or more ubiquitous exposures. Thus, diet, lifestyle, work, and community should be examined. An adequate explanatory risk factor would also have to be consistent with the above-mentioned social patterning of the disease. Migration studies strongly suggest that genetic factors are not the primary determinants of hypertension. This is dramatically demonstrated by the fact that African-Americans have among the highest rates of hypertension in the world,[7] whereas in rural West Africa (from whence African-Americans underwent forced migration to the U.S.) the prevalence of hypertension is among the lowest in the world.[59]

The contemporary work environment is a ubiquitous environmental exposure. It is the locus in which adults now spend the majority of their waking time. The work environment is frequently the source of exposures to psychosocial, physical, and other cardionoxious factors.

We know that BP is higher during working hours, compared to leisure time, within a 24-hour period.[328] Furthermore, mean 24-hour BPs are lower on nonwork days compared to work days.[286] These observations have been made possible by the development of ambulatory blood pressure (AmBP) devices, and their use in working populations. In comparison to casual clinic BP, AmBP is a better reflection of "true blood pressure" and has been demonstrated to be superior to the former in predicting target organ damage (such as left ventricular hypertrophy) and clinical prognosis.[8,277,278,383] Thus, studies using AmBP provide indispensable insights into the link between environmental/situational factors and hypertension.

Whether, how, and when repeated acute rises in BP transform into the chronic process of essential hypertension are only partially understood. Clearly, longitudinal studies that follow this process over time are critical to our understanding of the mechanisms involved. Our goal is to present the current biological models and existing empirical evidence, to identify where the argument of biological plausibility is best substantiated.

Workplace Stressors and Hypertension

Occupations at High Risk

A number of the occupational groups that are at high risk for developing ischemic heart disease (IHD) also show an elevated risk for hypertension and/or elevated resting BP. These include professional drivers,[16,24,25,297,408] air traffic controllers,[57] and sea pilots.[90] These occupations can be characterized as predominantly threat-avoidant vigilant jobs, with a high total burden of occupational stressors. Cumulative exposure to this occupational stress burden emerges as a significant, independent predictor of hypertension among urban transit operators.[298] Among San Francisco urban transit operators aged 45–54 with over 20 years on the job, 52.2% had hypertension. In comparison, the prevalence of hypertension was 42.9% among those of the same age strata who had been on the job less than 10 years, and 48.8% among those with 10–20 years on the job. Prior to employment as an urban transport operator, the prevalence of hypertension among a group of the same age was 36.7%.

Elevations in AmBP have been found during working hours among urban transport operators, compared to workers whose overall occupational stress burden is much lower.[379] Acute rises in AmBP have been observed during emergency situations among healthy, middle-aged train drivers whose BP increased by +12.7/+9.4 mmHg compared to resting values.[194]

Chronic Exposure to Job Strain and Effort-Reward Imbalance

Of the psychosocial work stress models relevant to cardiovascular disease (CVD), the Job Strain Model has been one of the most intensively investigated in relation to hypertension. Strong empirical evidence links exposure to job strain with elevations in AmBP, greatest at work but also evident at home and during sleep. Besides the consistent body of cross-sectional data in men and women and the demonstration of a dose-response relationship, recent longitudinal studies reveal a significant cumulative effect, as well.[201,325] In the Cornell Work Site Blood Pressure Study, the adjusted worktime AmBP of men who were exposed to job strain at baseline as well as 3 years later was greater by 11.1/9.1 mmHg, compared to those without exposure at either time.[325] Exposure to high effort together with low rewards at work also has been demonstrated to predict hypertensive status prevalence in combination with hyperlipidemia.[341,343]

Physical and Chemical Exposures

Empirical evidence links exposures to certain physical and chemical agents with hypertension. With regard to noise, the literature is abundant, but not entirely consistent. However, several fairly recent studies were positive,[76,93,251,365] and three of these took into account length of exposure.[76,251,365] In the study of Talbott, et al., cumulative occupational noise exposure was a significant independent predictor of systolic BP in the two plants studied, while it predicted diastolic BP in only one of the plants.[365] The authors attribute this latter finding to a possible threshold effect. Among male industrial workers aged 25–44 with normal BP, Green and colleagues found a +3.2/+2.3 mmHg effect on work AmBP among those exposed to > 85 dB noise ($p < 0.001$), after controlling for potential confounders.[126] No significant effect was seen among those over 44 years of age. However, in another study from the same center in Israel, work AmBP was not significantly associated with noise intensity among male or female blue-collar workers.[196] Some evidence suggests that exposure to lead or to arsenic may be associated with an increased risk of hypertension.[52,143]

LONG WORK HOURS AND SHIFTWORK

Studies by Hayashi, et al.[136] and by Iwasaki, et al.[159] have shown that long working hours are associated with elevations in AmBP as well as casual BP. Shift workers appear to reverse the usual circadian BP pattern, showing peak levels at night while working. Chau and colleagues found that while the mean BP during the high pressure span was the same for three shift schedules, the duration of the high pressure span was longest during the night shift, and shortest during the afternoon shift.[50] There is also evidence that shift workers' BP during sleep fails to drop to the levels seen among day workers. In a study of approximately 100 nonhypertensive nurses, Yamasaki, et al. showed that those who worked evening/night shifts had higher BP during sleep than those who worked day shift.[404] As a result, shift workers exhibited less "nocturnal dipping," the lack of which has been associated with increased left ventricular mass according to Verdecchia, et al.,[384] although not according to Bhatt, et al.[30] A recent longitudinal study by Morikawa and colleagues indicates that among young (< 30 y.o.), initially normotensive, blue-collar working men in a single factory, the relative risk of developing hypertension during the 5-year followup was 3.6 for those who rotated shifts compared to those who worked day shift only, after adjusting for age, BMI, alcohol intake, and baseline systolic BP.[255] This effect was not seen among older workers, however.

Human Blood Pressure Responses to Simulated Work Stressors

ECOLOGICAL RELEVANCE

A large body of research examines human CV responses to various stressful paradigms. While acute elevations of BP and heart rate are achieved, these paradigms often bear little or no resemblance to real aspects of working life. Besides the artificiality of the laboratory environment itself, the tasks have not usually been chosen for their similarity to the cognitive exigencies of the subjects' jobs. Very few studies have, by design, examined between-subject responses to laboratory stressors that are similar to the subjects' workplace exposure. It is therefore not surprising that many of these studies have failed to find that BP reactions to laboratory stressors reflect real-life BPs during a workday.[121,287,352] Pickering concludes that "viewed as a whole, these studies suggest that if there is an association between reactivity measured in the laboratory and the BP variability or reactivity of daily life, it is rather weak, or is obscured by the problems of measurement error."[287]

Pickering notes, however, that when the laboratory stressors closely resemble task performance during real life, a significant correlation in BP responses has been found. He cites a study by Matthews, et al., in which BP changes during a laboratory speaking task were compared to a similar task in the classroom.[238] Concordantly, Steptoe and Vögele emphasize the importance of "ecological validity" of laboratory mental stress tests, which should be designed "to model processes that will be important to CV health only if they are repeated or sustained in everyday life over many years."[352]

BP response during an interview in which stressful workplace events are discussed can be informative, precisely because of the personal relevance of the subject. For example, among 22 young, healthy, mainly blue-collar, male workers, a short semi-structured laboratory interview about intensely stressful events related to work (e.g., work accidents, interpersonal conflicts) produced a greater pressor response (+12.4/+15.1 mmHg) than any of the standardized mental stress tests, (mental arithmetic, quiz, auditory and visual choice-reaction time tasks).[19]

Mental Stress

A body of laboratory-based cardiovascular research provides insight into some of the more generic aspects of workplace mental stress, most notably job strain. For example, external pacing, an important component of low control during performance of mental arithmetic is associated with increased systolic and diastolic BP responses.[34,120] Peters and colleagues found that both increasing effort in a mental task and lowered control provoked elevations in BP and plasma norepinephrine.[281] Uncontrollability also was associated with elevations in salivary cortisol. Furthermore, an effort-control interaction effect was observed with respect to diastolic BP response. Steptoe and colleagues found that BP reactions to an externally paced (low control) task were greater in teachers with high as compared to low job strain.[351] In contrast, BP responses to a self-paced (high control) task did not differ significantly between these two groups.

The ameliorating effects of social support also have been demonstrated in the laboratory setting. During performance of a speech task, BP reactivity was attenuated when an audience observer behaved in a supportive manner (nodding and smiling) as compared to acting neutrally.[54]

Physical Stress

One ecologically valid, laboratory-based model of a work-related physical stressor is the **glare pressor test** (GPT), in which a standardized stimulus mimics the commonly occurring circumstance of facing an oncoming headlight during night driving. Studies using the GPT were designed to compare exposed groups (professional drivers) to those with no driving experience whatsoever. Compared to matched working nondriver referents, young normotensive professional drivers showed diastolic hyperreactivity to the GPT, together with digital vasoconstriction and signs of central arousal (EEG desynchronization).[23] It has been postulated that BP reactivity to the GPT represents an early phase of sensitization (a conditioned defense response) to threatening stimuli in the driving environment which, with continued exposure, may lead to sustained hypertension.[26] Longitudinal study is needed to further test this hypothesis.

Some laboratory paradigms of **noise exposure** have provoked significant elevations in BP, while others have not. Among 18 healthy males, 95 dB of industrial noise induced significant elevation in diastolic BP, which persisted during the 20-minute exposure period. Total peripheral resistance (TPR) increased significantly, while stroke volume and cardiac output fell.[5] Sawada also found an increase in TPR, together with a reproducible, persistent elevation in BP, when a similar group of subjects was exposed to 100 dB of pink noise.[319] A significant elevation in systolic BP associated with noise exposure during performance of mental arithmetic has been reported by Linden,[218] but not by Tafalla and Evans.[359]

The **cold pressor test** (immersion of the hand into cold water for 1–3 minutes) induces significant increases in systolic and diastolic BP and marked elevations in norepinephrine and epinephrine levels.[14,19,27,146,262,304] Several studies applying the cold pressor test found no relation between reactivity and future level of BP.[287] The study of Menkes, et al., however, revealed that even after statistically controlling for other risk factors, including family history of hypertension, hyperreactivity to the cold pressor test was a significant predictor of hypertension among 1000 medical students followed for 20–36 years.[247]

Isometric handgrip is also an extremely potent pressor stimulus. Both systolic and diastolic BP rise out of phase with heart rate, and the baroreceptor set point is

changed such that a disproportionate pressure load is placed on the heart. Neurogenic mechanisms along with local factors such as afferent reflex stimulation and mechanical hindrance to blood flow, contribute strongly to these cardiovascular changes.[13,338] In normal subjects, isometric handgrip to one-third maximal capacity for 3 minutes evoked the greatest diastolic BP rise of a series of ten powerful cardiovascular stressors.[19] It also was associated with a significant rise in norepinephrine and epinephrine.[14] Among borderline hypertensive men, mean peak BP during isometric handgrip was 181.8/114.9 mmHg.[66] At 1-year followup BP reactivity while performing isometric handgrip and mental arithmetic was significantly correlated with the risk of developing established hypertension, but this association became nonsignificant after controlling for basal diastolic BP and mean ambulatory systolic BP during the day.

Among 33 post-MI patients, **carrying graded loads** of 20–50 lbs. while walking on a treadmill was associated with diastolic BP levels > 120 mmHg.[337] Hietanan reported that static exercise training (e.g., weight lifting, hammer throwing) was associated with increased ventricular wall thickness, and noted that increased afterload is the physiologic adaptation to static exercise (as opposed to increased pre-load for dynamic exercise).[144]

Thus, a number of physical stressors can provoke substantial acute rises in BP. However, the relationship between acute BP changes to these stimuli in the laboratory and tonic BP elevations brought about by chronic occupational exposure needs exploration.

Biological Mechanisms: I. The Defense Response

THE ACUTE REACTION: PREPARATION FOR "FIGHT OR FLIGHT"

The defense response comes into play when the organism is called upon to actively cope with a threat or challenge. The cardiovascular system is geared up for the anticipated physical activity (fighting or fleeing): cardiac output increases, with blood flow directed to the heart, brain, and skeletal muscle at the expense of the viscera. Skeletal muscle vasodilatation ensues, as a result of CNS inhibition of vasoconstrictor activity to skeletal muscle fibers and circulating epinephrine binding to beta-2 receptors in muscle resistance vessels. Higher CNS centers inhibit baroreceptor vagal activity, such that heart rate is simultaneously elevated. Efferent renal sympathetic nerves increase their firing, leading to diminished renal blood flow; the renin-angiotensin system activates; the glomerular filtration rate falls; sodimn retention is enhanced; and blood volume increases. The net hemodynamic result of activating the defense response is a rise in BP, with a hyperkinetic heart and with total peripheral resistance (TPR) usually within normal levels, although TPR is high relative to cardiac output.[78,97,166,287] The defense reaction to an acute threat is a rapid-acting, and arguably the best understood, biological mechanism for regulating BP and heart rate. The release of catecholamines triggered by the sympathetic nervous system produces nearly instantaneous increases in BP and heart rate, increasing the supply of oxygen and energy to the musculoskeletal system so as to facilitate active physical responses to enviromnental challenges.

RELATION OF THE DEFENSE RESPONSE TO SUSTAINED HYPERTENSION

The defense reaction is phylogenetically a very old response and is adaptive when the challenges faced by the organism are primarily direct, calling for a physical response. Levi notes that this reaction was "of practical value to Stone Age people confronted by a pack of wolves . . . (but that) we still prepare for bodily activity and muscular exertion when we encounter changes in our environment and the demands for adjustment that

they imply. Our environment—most of all, our work environment—however, has undergone drastic changes over the millennia. The demands placed on our adaptability have altered in character, while our genes have hardly changed."[212]

Gilmore in paraphrasing Charvat, Dell, Folkow, and Folkow[48] graphically illustrates this point as follows:

> *When a gazelle hears a predator approaching cardiovascular and humoral changes develop immediately, while the somatomotor or muscular response is perhaps only an alerting reaction. Later, as the predator comes closer, the gazelle explodes into an all-out flight response, with his cardiovascular system being already prepared.*
>
> *In contrast, civilized man is faced with stress-producing situations (which) seldom relate to physical danger, such that the defense response is no longer well coordinated, the autonomic-humoral component being dissociated from the somatotropic or muscular response. Since the cardiovascular or metabolic resources intended to support heavy or violent physical exertion will not be utilized in the natural way, the hormonally produced changes of the blood, and thus, the chemical environment of the blood vessels and the heart will be more long-lasting than when violent muscular activity occurs. In addition, since the neurogenically induced cardiovascular changes are not modified by the additional vasodilatation due to muscular activity itself, the pressure load on the heart and blood vessels will be greater than if muscular activity occurred.*[122]

The idea that intermittent elevations of BP, occurring in response to repeated exposure to environmental stressors and elicitation of the defense response, could result in sustained hypertension was first proposed by Folkow.[94,98] Folkow notes that when physical activity is suppressed, the magnitude of the pressor response to sympathetic activation becomes greater because there is no exercise-induced muscle vasodilatation. This is seen as a "forced dissociation of normal response patterns,"[97] which Eliot has described as a "constant state of visceral-vascular readiness,"[86] whereby the heart and blood vessels are activated irrespective of the actual metabolic needs of the organism. Thus, while the defense reaction, including the acute elevation in BP, is adaptive in the short run under certain circumstances, it may be maladaptive in the long run.

Still unknown are the precise dynamics by which repeated evocation of the defense reaction without physical fight-or-flight behavior translates into sustained hypertension. Elevations in BP do not necessarily lead to hypertension. As shown by Julius, et al., mechanical compression of the thighs in dogs can produce an acute increase of BP for as long as the compression is applied, but without causing any upward drift of the resting pressure.[169] Chronic instrumental CV conditioning in nonhuman primates provokes repeated elevations in BP, but does not consistently evolve into sustained hypertension after the conditioning paradigm is discontinued.[377] Henry and colleagues have found that long-term social disruption leads to hypertension in some but not all initially normotensive rats.[141] While heart and adrenal weights, adrenal catecholamine synthetic enzymes, and pathohistologic changes in the heart, aorta, and kidney in several rat strains generally paralleled the BP changes, the Wistar-Kyoto hyperactive strain showed stress-induced increases in heart and adrenal weights, but no BP changes. Thus, many questions are unanswered. The length and intensity of exposure to the stressor, and its nature, clearly are issues of importance.

THE ROLE OF ADRENERGIC ACTIVITY IN THE EARLY STAGES OF HYPERTENSION

BP changes occur over various time frames, and the factors that cause acute changes may not be the same as those that contribute to chronic changes. The fluctuations that occur throughout the day in response to environmental circumstances have been collectively called the "phasic" component of BP; the "tonic" (long-term resting level) component changes only gradually over time.[285] Essential hypertension is defined as an elevation of the tonic component.

There is evidence of a subtle increase in the level of sympathetic nervous system (SNS) activity in many patients during the early stages of hypertension, and this increase is primarily tonic rather than phasic. For example, several (but not all) studies have demonstrated that subjects with mild hypertension have increased resting catecholamine excretion, heart rate, and cardiac output,[124,165,283] as well as enhanced catecholamine responses to stressors.[123] Oparil and colleagues review a number of lines of evidence implicating SNS activity in essential hypertension. They state that "SNS activity is elevated in nearly every form of human and experimental hypertension, and reduction of this activity decreases arterial pressure" and note that "chemical or surgical lesions of the SNS lower arterial pressure in most hypertensive individuals."[270] Concordant conclusions are drawn by Mancia, particularly focusing on direct measurement of sympathetic nerve traffic to skeletal muscle circulation, which is found to increase with progressively more severe degrees of essential (but not secondary) hypertension.[231]

Pharmacologic studies, predominantly conducted by Majewski and Rand, have identified one potential mechanism by which adrenaline (epinephrine) might mediate stress-linked hypertension.[228] Both in vitro and in vivo studies have shown that infusion of epinephrine in low doses (equivalent to the levels seen during naturally occurring stress) can enhance norepinephrine release from sympathetic nerve terminals.[227] Although sustained experimental neurogenic hypertension has been quite hard to produce in practice, Majewski, et al. achieved it in rats using a slow-release depot implantation of epinephrine.[229] After the 8th week, when excess epinephrine could no longer be detected in the plasma, BP (but not heart rate) was still elevated.

Similarly, Blankenstijn, et al. showed that the arterial pressure of humans infused with epinephrine was at first reduced, but by the end of the infusion (6 hrs) was above the baseline value, and remained elevated throughout the night.[32] The pressor effect of epinephrine was most marked during periods of increased sympathetic activity—for example, when the subjects were active—and not when they were at rest. Infusion of norepinephrine produced an initial elevation of pressure, but no sustained effects.

STRUCTURAL CHANGES IN RESISTANCE VESSELS

Through repeated elicitation of the defense reaction—i.e., repeated pressor episodes—structural changes may gradually occur in the cardiovascular system, and these can result in a higher basal BP. Adrenergic neurotransmitters and other substances (e.g., angiotensin and insulin) that rise in association with the defense response act as "growth promoters" on vascular smooth muscle.[172] Prolonged exposure of resistance vessels to these substances can result in vascular structural changes (hypertrophy) and increased smooth muscle contractility. This is precisely what occurs during repeated exposure to mental stress, due to the lack of skeletal muscle vasodilatation. Furthermore, mechanical factors related to increased wall pressure, tension, or stress promote increased vessel wall thickness.[355]

According to Folkow and colleagues, activation of smooth muscle during repeated exposure to acute stress, even if only intermittent, can stimulate an increase in smooth muscle cell size (hypertrophy), thereby increasing the wall thickness of the resistance vessels and shrinking their internal radius.[98,98a] The net result is an increase in peripheral resistance. These hypertrophied vessels are rendered hyper-responsive to vasoconstrictive stimuli. This could explain why stress responses of hypertensive individuals are predominantly characterized by vasoconstriction with elevation of TPR, while the response of normotensive individuals is usually an increase in cardiac output.[38,123] Egan and colleagues have demonstrated increased forearm vascular resistance responses to norepinephrine and angiotensin II in patients with mild hypertension, compared to weight-matched normotensive controls.[83] The net outcome is a chronically increased TPR, usually with a down-regulation of beta-adrenergic receptors in the heart, leading to a normal cardiac output, as seen in established hypertension.[97,167,172]

Renal Mechanisms and Longer-Term Changes in Arterial BP

Besides structural changes in resistance vessels, longer-term changes in arterial BP appear to be strongly influenced by renal mechanisms. Guyton provides a possible explanation of how neurogenic mechanisms could contribute to chronic hypertension by their effects on the kidney.[129] With SNS activation, the renal vasculature becomes severely constricted, compromising renal blood flow. For example, chronic infusion of norepinephrine can permanently damage the renal arteries. Severe essential hypertension is characterized by approximately half the normal renal blood flow and a two- to fourfold increase in renal vascular resistance. In order to maintain an adequate glomerular filtration rate, the arterial pressure must be maintained at a high level. Furthermore, there is evidence that environmental stress can cause sodium retention, mediated via renal sympathetic nerve activity in animals[4,190] and in humans.[216] Hollenberg, et al. showed that the effects on renal blood flow of a behavioral challenge lasted much longer than the effects on BP.[152] This, in turn, can lead to sodium retention and a gradual increase in tonic BP.

Increased salt intake may exacerbate this process. Poulter and Sever present a model by which neurogenic pressor mechanisms (repeated elicitation of the defense response) combined with increased dietary sodium may together account for the elevated BP among persons migrating from environments with a low to those with a higher prevalence of hypertension.[291] However, Waldron and colleagues reported that the higher BPs that developed in the latter settings (e.g., those affected by the market economy, economic competition, breakdown of family ties) appeared to be independent of salt intake.[387]

Further Insights from Psychosocial Stress Models in Animals

Henry notes that in the early stages of psychosocial stimulation (continuing conflict resulting in social instability) in mice, adrenal catecholamine synthetic enzymes approximately double, and plasma renin is very high.[139] After about 3 weeks, however, although systolic BP is elevated, plasma renin levels have fallen. Subsequently, the renal and hindquarter vessels show greatly enhanced sensitivity to angiotensin. Induction of hypertension in experimental animals requires several months of repeated exposure to stressful situations.[101,142] These experimental results provide a biological rationale for the finding that an induction period appears to exist before exposure to job strain gives rise to an increased risk of established hypertension.

WORK STRESSORS, DEFENSE RESPONSES, AND HYPERTENSION: IS THERE A LINK?

The threats and challenges of working life are clearly capable of provoking arousal, as characterized by the defense response. Because these threats and challenges are often of a chronic nature, and are rarely, if ever, resolved by a physical fight-or-flight reaction, a prolonged state of "visceral-vascular readiness" is likely to emerge. Elevations in catecholamine excretion, typical of the defense response, have been associated with exposure to numerous acute and chronic work stressors. Furthermore, elevations in BP and catecholamine excretion during stressful work appear to be related. Among women who perceived work as the greatest source of stress, systolic BP at work was significantly higher compared to women who cited home as the greater stressor. In the former group, the percent changes in BP and catecholamine excretion during waking hours (relative to sleep) were significantly correlated. In contrast, among the women who cited home as more stressful, these waking BP changes were not correlated with changes in urinary catecholamines.[161]

Studies among professional drivers have demonstrated that laboratory stressors that are reminiscent of the threats and challenges of the work environment elicit signs of electrocortical arousal characteristic of the defense response, especially in hypertensive transport operators.[88] Other studies in which ecologically valid work stressors have been simulated in the laboratory indicate that these are capable of eliciting significant acute BP elevations.

However Schwartz, Pickering, and Landsbergis note that for work stress to contribute to a tonic elevation in BP, "the blood pressure of the exposed individuals would have to be elevated not only in the presence of a stressor but also during rest."[329] Thus, the focus should be on "exposure to chronic low- or moderate-grade stress rather than on discrete events that are widely acknowledged to produce brief spikes in the blood pressure profile."[329] The large, consistent body of data on AmBP and exposure to job strain indicates that these elevations are indeed persistent. They occur not only at work, but also at home and, in some studies, during sleep. Finally, and probably most compelling, are the data indicating that there may be a cumulative effect of chronic exposure to job strain on AmBP.

Biological Mechanisms: II. The Defeat Reaction and Glucocorticoids

Although most attention has been paid to the SNS as the prime mediator of stress-induced increases in BP, evidence also suggests that activation of the hypothalamic-pituitary-adrenocortical (HPA) axis may be involved. During exposure to some acute stressors, particularly those that are psychologically threatening (e.g., public speaking), cortisol is released over a period of about 15–20 minutes. This release is much more gradual, but also persists much longer after termination of the stress condition, than that of epinephrine and norepinephrine.[180]

Animal studies reveal that when repeatedly faced with noxious events that cannot be controlled, motivation becomes undermined, resulting in passive behavior and giving-up. In animals this pattern has been labeled the "defeat reaction,"[142] while in humans it is perhaps most closely linked to the construct of learned helplessness.[331] According to Folkow, defeat reactions, if prolonged, "may exert more harmful effects than strong and prolonged defense reactions."[97] Defeat reactions tend to activate the HPA axis to release glucocorticoids. Glucocorticoids have a likely pressor role, both singly and as potentiators of reactivity to adrenergic and angiotensin II stimulation.[258,270,318,394] They also have a weak mineralocorticoid effect, leading to renal sodium reabsorption at higher doses.[395] Thus, it is possible that glucocorticoids play a major role in mediating the effects of chronic stress.

Experimental studies have shown that strong control over an animal's behavior provokes hypertensive responses.[28] An integrated CNS-behavioral stress response pattern, distinct from the defense response and characterized by passive behavior (motoric immobilization, lying still, "playing dead"), generalized vasoconstriction, and vagally mediated bradycardia has been identified.[81,239] This "defeat-type" reaction pattern is typical of the "dive reflex,"[403] and can be activated under conditions of hopelessness, extreme fear, or exhaustion. A similar pattern also has been evoked by stimulation of the lateral hypothalamus in rabbits.[81] Finally, short-lived, repeated stimulation of the lateral hypothalamus for several days to weeks in rats leads to a progressive, sustained rise in arterial BP.[122,140] The role of the HPA axis in these processes needs to be further investigated.

Chronic Defeat Reactions and Hypertension

While pointing out the pitfalls of extrapolating from animal or human laboratory studies to real life, Lennerlöf hypothesized that "jobs that are characterized by little control, influence, learning and development entail risks of helplessness learning."[207] Some empirical support for this hypothesis comes from the Cornell Work Site Blood Pressure Study (WSBPS), in which Landsbergis and colleagues examined questionnaire responses of participants whose jobs were characterized as passive, i.e., low control, but also low demand.[202] These workers' responses to Seligman's Attributional Style Questionnaire indicated high levels of learned helplessness. Kohn and Schooler reported similar findings concerning the relationship between job characteristics and personality, both cross-sectionally and longitudinally.[191] However, contrary to expectation, the WSBPS participants in passive jobs did not show any elevation in BP compared to those in jobs with low demand and high control or high demand and high control.[327]

Empirical data links both acute (e.g., traffic peaks during bus driving) and chronic (e.g., heavy psychosocial job burden) exposure to work stressors with elevations in cortisol.[10,133] There is also some evidence that low job control is associated with elevated BP. For example, having undergone a forced job change was found to be a significant predictor, cross-sectionally, of hypertension among middle managers.[280] In a study by Härenstam and Theorell, low skill discretion predicted systolic AmBP among prison guards.[132] The meta-analysis of Pieper, et al. reported a significant association between low job decision-latitude and casual systolic BP.[288] However, there are also a number of studies in which low control, as a main effect, failed to show any association with BP. These include the AmBP studies of Light, et al.[217] and Schnall, et al.[327] as well as several casual BP studies, including the prospective investigation of Siegrist.[343] The outcome measure in the latter study was the co-occurrence of hypertension and hyperlipidemia (see Chapter 2 for further details). No single study has yet investigated each of the links in the hypothesized defeat reaction model as it applies to work stress and BP: low control → defeat reaction/learned helplessness → increased HPA axis activation → increased BP.

Biological Mechanisms: III. The Effort-Distress Model

Folkow states, "the ancient 'defense' and 'defeat' reactions, intended for quite different situations, are often activated by the artificial stimuli and symbolic threats inherent in today's hectic and competitive life . . . when intensely engaged over longer periods they can, indeed, profoundly disturb inner organ systems and metabolic events."[99] He notes that in stressful situations there often are shifts between the defense and defeat reactions.[97] Activation of both the sympathoadrenal medullary and the HPA cortical axes can be seen in such situations.[142] Frankenhaeuser observed

that the activation of these two axes could be evoked in human laboratory studies by paradigms that demanded effort while providing little or no opportunity for control over the task performance, a condition she hypothesized would engender distress.[104] This led to the Effort-Distress Model, which was described as follows:

> *Effort with distress is probably the state most typical of our daily hassles. It is accompanied by an increase in both catecholamine and cortisol secretion. Most of our studies concern this category. For instance, mental work carried out under conditions of either stimulus underload or overload will typically evoke feelings of effort, as well as distress and, consequently, both the catecholamine and the cortisol level will rise. . . . The key question is how to achieve the state of effort without distress. Our data point to personal control as an important modulating factor in this regard. A lack of control is almost invariably associated with feelings of distress, whereas being in control may prevent a person from experiencing distress. Hence, personal control tends to act as a buffer, reducing the negative arousal effects, and thereby changing the balance between sympathetic-adrenal and pituitary-adrenal activity.*[104]

One of the experimental paradigms applied in this context was performance of a monotonous vigilance task, as compared to a self-paced, reaction-time task. Both conditions required similar effort, but the former was associated with distress, while the latter was primarily enjoyable. During the vigilance task, both epinephrine and cortisol increased, whereas during the reaction-time task only epinephrine rose.[224] In a more recent study, Peters and colleagues applied a similar paradigm and registered BP as well as hormonal responses.[281] They found that when the effort involved in laboratory task performance increases and control is simultaneously diminished, not only do both catecholamines and cortisol rise together with BP, but an effort-control interaction effect is observed with respect to diastolic BP responses.

The Effort-Distress Model has not been tested as a predictor of sustained hypertension.[289a] It mainly has been applied in the human laboratory setting. However, neuroendocrine changes consistent with activation of both the sympathetic-adrenomedullary and the HPA axes have been demonstrated among metallurgists when performing paced assembly work with no control over the work pace.[374] These working conditions are clearly typical of job strain. The distress condition of the Effort-Distress Model is conceptually very similar to the high-strain condition of the Job Strain Model, though they are typically used to characterize laboratory versus actual workplace situations, respectively. While there is strong empirical evidence that chronic exposure to job strain is associated with the development of sustained hypertension, more investigation is needed to ascertain whether a combined catecholamine-glucocorticoid effect represents a major mechanism by which this process occurs.

Work Stress and Left Ventricular Hypertrophy

Schwartz, Pickering, and Landsbergis suggested that occupational stress may be of special etiologic importance in the progression from hypertension to IHD.[329] One of the mediating mechanisms may be increases in left ventricular mass (LVM), which is a major risk factor, independent of BP, for MI, cardiac electrical instability, and sudden cardiac death.[73,113,214,249,320]

Devereux and Roman contend that increased LVM occurs as a direct effect of chronic elevations in BP, due to increases in stroke volmne together with impairment of myocardial contractile performance.[75] In contrast, Mancia argues that SNS activation is also crucial,[231] citing data indicating that increased LVM can be induced by

sub-pressor doses of adrenergic agents,[272] and that lowering BP in spontaneously hypertensive rats prevents increased LVM only if not accompanied by high reflex sympathetic outflow to the heart.[333] Occupational stress can provoke both the hemodynamic and the adrenergic changes that promote increased LVM.

Ambulatory BP has been found to be more predictive of LVM or wall thickness than casual BP.[74,80,294,300,384] LVM is more highly correlated with average BP at work than at other periods, but a strong relation also has been observed between LVM and home BP measured on workdays.[15,74] Devereux and Roman interpret these findings as an indication of a "special impact on the heart of blood pressure responses to regularly recurring stress at work, with possible 'spillover' effect of home blood pressures on working days."[75] In addition, Schnall and colleagues found that exposure to job strain is associated with increased LVM index.[323] Synthesizing these results, we hypothesize that long-term exposure to job strain leads to a sustained elevation of BP that then causes structural changes in the left ventricle. Considering the strong, independent relation between increased LVM and cardiovascular morbidity, this pathophysiologic process may account for a substantial part of the reported association between job strain and CHD morbidity.[324]

MYOCARDIAL OXYGEN SUPPLY AND DEMAND: ENVIRONMENTAL TRIGGERS OF IMBALANCE

by Karen Belkić, MD, PhD

Whether or not accompanied by symptoms, myocardial ischemia has major prognostic importance. It is the consequence of an imbalance between the oxygen demand made by the myocardium and the available O_2 supply. Determinants of myocardial O_2 demand include: heart rate, blood pressure, myocardial contractility, size of the left ventricle (LV), and the duration of systole. Supply of O_2 to the myocardium is determined by coronary artery blood flow, the intraluminal size of the coronary arteries, the O_2 content of hemoglobin, the duration of diastole (during which approximately 85% of the coronary blood flow occurs), and coronary perfusion pressure (the difference between arterial pressure at the aortic root level and LV filling pressure).[49] Many of these determinants of myocardial O_2 supply and demand are affected by stress mechanisms and/or by chemical and other physical factors in the work environment. Exposure to these stressors has induced signs of myocardial ischemia among persons with various stable ischemic syndromes, and, in some instances, among apparently healthy workers.

Laboratory Studies of Mental Stress and Myocardial Ischemia

Laboratory studies have demonstrated that mental stress can trigger myocardial ischemia in 40–70% of patients with various stable ischemic syndromes. This is specifically associated with an adverse prognosis.[160,195] Among patients with single- or multiple-vessel coronary artery disease (CAD) LV ejection fraction assessed by radionuclide ventriculography as an indicator of myocardial ischemia was found to fall equally or more often in response to personally relevant mental stress as compared to exercise; this mental-stress induced ischemia was usually asymptomatic.[157,315] Patients with CAD who showed LV wall motion abnormalities during laboratory mental stress testing had a significantly increased likelihood of exhibiting myocardial ischemia during daily activities as assessed using ambulatory monitoring.[33,125] Laboratory mental stress–induced myocardial ischemia also is associated with a longer duration and increased frequency of ischemia during daily activity.[9]