CHAPTER 7

Stress and Cardiovascular Disease

Cardiovascular disease ranks as the world's leading cause of morbidity and mortality. Globally in 2015, the total number of deaths from all causes was estimated to be 55.8 million people, of whom 17.9 million (32%) died from cardiovascular diseases. Approximately 50% of deaths from cardiovascular disease resulted from coronary artery disease, which increases the risk of a heart attack. Measures of the global burden of disease capture data on premature deaths (expressed as years of life lost) and years lived with a disability. These two measures are combined to yield disability-adjusted life years (DALYs), a measure of the burden of a given disease. Cardiovascular disease also ranks as the leading cause of DALYs globally (Joseph et al., 2017). In the United States, approximately 545,000 people died from coronary artery disease in 2016, a decrease of 15% from 1990. Not surprisingly, coronary artery disease was also the number one cause of years of life lost as well as DALYs in the United States in 2016 (Mokdad et al., 2018).

In this chapter, we will explore the role of stressful stimuli and allostatic load as contributors to the burden of cardiovascular diseases, with a focus on coronary artery disease and hypertension. What is the magnitude of the risk for coronary artery disease and hypertension associated with various stress-related stimuli? How do these risks associated with stressors compare to the more typical risk factors for cardiovascular disease, such as smoking, obesity, diet, and lack of exercise? Finally, are there effective interventions to reduce the effects of psychosocial stress on coronary artery disease and hypertension?

STRESS AND HEART DISEASE

By any measure, the heart is a remarkable organ. Assuming a resting heart rate of 70 beats per minute, the human heart beats about 100,000 times per day, pumping

approximately 2,000 gallons of blood throughout the body. Over the course of a lifetime, that comes out to 2.5 billion beats. Given the impressive capacities of the heart to work for so many years without fail, it is tempting to think that cardiac muscle cells are miniature superheroes that keep going through good times and bad. Unfortunately, for many people the heart becomes their weak link, especially in times of stress (Figure 7.1). In the sections that follow, we will look at the compelling evidence that psychosocial stressors can compromise normal cardiac function in at-risk individuals, and all too frequently, exposure to intense stressors may lead to premature death from negative effects on the cardiovascular system (Levine et al., 2021).

The Long Arc of Abuse and Neglect

Instances of abuse and neglect during early childhood and extending into adolescence may exert lifelong effects on risks for mental and substance use disorders (Cohen, Brown, & Smailes, 2001; Widom, White, Czaja, & Marmorstein, 2007). These same adverse childhood and adolescent experiences may also place individuals at greater lifetime risk of cardiovascular diseases, including coronary heart disease and heart attacks. In one large-scale meta-analysis of health risks of adverse childhood experiences, eight reports based on data from four countries were combined to yield more than 120,000 participants, some with no occurrence of early abuse and neglect and others with four or more instances of abuse or neglect. The results indicated that exposure to abuse and neglect was associated with a significant lifetime increase in incidence of cardiovascular disease (OR = 2.07, 95% CI = 1.66–2.59).

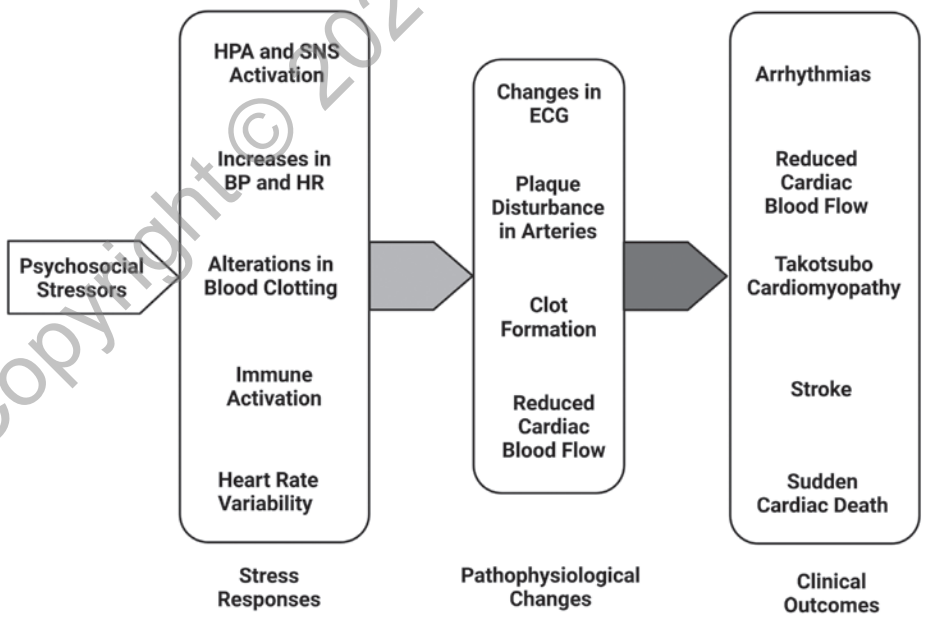

FIGURE 7.1. Pathways through which psychosocial stressors enhance the risk of cardiovascular disease.

Stress Cardiomyopathy

Stress cardiomyopathy, also known as takotsubo syndrome, broken heart syndrome, or even happy heart syndrome, was first described in Japan by Sato, Uchida, Dote, and Ishihara (1990) and typically involves symptoms similar to a heart attack, including pronounced left ventricular dysfunction, intense chest pains, and labored breathing. The Japanese word *takotsubo* ("octopus pot") refers to the characteristic ballooning of the apex of the left ventricle to resemble the shape of an octopus pot used by Japanese fishermen. The attack is often precipitated by an intense emotional or physical stressor, including death of a loved one, having a heated argument, experiencing a surprise birthday party, fearing a medical procedure, and being in a car accident. An increase in the incidence of stress cardiomyopathy was also reported during the COVID-19 pandemic in April and May 2020 compared to control periods prior to the pandemic (Jabri et al., 2020). A recent report from 26 medical centers in Europe and the United States provided an overview of 1,750 patients diagnosed with takotsubo cardiomyopathy and compared them to age- and sex-matched controls who experienced an acute coronary episode. Of the patients with takotsubo cardiomyopathy, 90% were female, with an average age of 67 years (Templin et al., 2015).

Self-reports indicated that 36% of patients with this syndrome experienced physical triggers before clinical symptoms occurred, 28% experienced emotional triggers, 8% experienced a combination of triggers, and 28% reported experiencing no triggers. Emotional triggers were more common among females, and physical triggers were more common among males. These patients also had a higher prevalence (56%) of prior neurologic and psychiatric diagnoses than controls with acute coronary syndrome, and 4% died while in hospital. Long-term follow-up of takotsubo patients revealed a death rate from any cause of 5.6% per patient-year and a rate of major adverse cardiac and cerebrovascular events of 9.9% per patient-year (Templin et al., 2015).

Physical and emotional triggers appear to precipitate takotsubo cardiomyopathy by activation of brain pathways involved in regulation of the sympathetic nervous system, resulting in excessive stimulation of the heart by catecholamines, especially epinephrine. During and after exposure to the physical or emotional triggering event, large quantities of epinephrine are released from the adrenal medulla into the circulation. In addition, norepinephrine and neuropeptide Y are co-released from postganglionic sympathetic nerve terminals in the heart. Activation of the sympathetic–adrenal medullary system in takotsubo cardiomyopathy patients was significantly greater than in patients experiencing an acute heart attack, and plasma catecholamine and neuropeptide Y levels remained elevated for up to 9 days after symptom onset (Wittstein et al., 2005). This significant and sustained stress-induced surge in peripheral catecholamines appears to lead to direct and indirect damage to the myocardium, including myocardial stunning, a reversible disruption in heart contraction. Lack of estrogen in postmenopausal women also plays an important role in the pathophysiology of takotsubo cardiomyopathy (Pelliccia, Kaski, Crea, & Camici, 2017).

Lau, Chiu, Nayak, Lin, and Lee (2021) reviewed the clinical records of 519 takotsubo patients who were treated between 2006 and 2016 and were followed for an average of 5.2 years at Kaiser Permanente Southern California Health System. During the follow-up period, 39 patients (7.5%) had a recurrence of takotsubo syndrome and 84 (16.2%) patients died. Treatment with beta-blockers was associated with a reduced risk of recurrence of takotsubo cardiomyopathy or death.

Stress Can Trigger Heart Attacks

John Hunter, (1728–1793) was one of 18th-century England's most distinguished surgeons and scientists. He was elected a fellow of the Royal Society in 1767, and he is buried in Westminster Abbey. One of his research assistants characterized him as "warm and impatient, readily provoked, and when irritated, not easily soothed" (Moore, 2005, p. 346). This vivid description of Hunter foreshadowed his death from a heart attack on October 16, 1793, following an intense argument with an administrator at a St. George's Hospital board meeting. Hunter's death has often been advanced as early evidence of the occurrence of sudden cardiac death following exposure to an intense psychosocial stressor.

More than two centuries later, anger was confirmed as a significant cross-cultural trigger for first heart attacks in the INTERHEART study, an international, multi-site research project in 52 countries using a case–control design. Of 12,461 participants with a first heart attack, 14.4% (N = 1,752) reported being angry or emotionally upset in the 1-hour period prior to the onset of cardiac symptoms. Anger or emotional upset in the prior 1-hour period was associated with an increased odds ratio of having a heart attack of 2.44 and a population-attributable risk of 8.5% (Smyth et al., 2016).

Living through catastrophic events such as earthquakes or missile attacks, or watching broadcasts of sports competitions offer present-day opportunities for researchers to examine the relationship between intensely stressful events and increased incidence of heart attacks. These situations are also unusual in that the exact time of the stressor can often be specified down to the minute and the affected population can be tracked through hospital admissions and death certificates. To provide baseline levels of various cardiac events, researchers have typically measured population-level cardiac events on the same date in previous and subsequent years or in the several days leading up to or following an event. Following are illustrative examples of some of these naturally occurring stressors.

Earthquakes

- *Athens, Greece, earthquake (6.7 Richter scale).* The earthquake occurred at 10:53 P.M. on February 24, 1981. In the 5 days following the earthquake, there was a 50% increase in deaths from acute cardiac events and a 100% increase in deaths from atherosclerotic heart disease (Trichopolous, Katsouyanni, Zavitsanos, Tzonou, & Dalla-Vorgia, 1983).

- *San Francisco, California, earthquake (7.0 Richter scale).* The earthquake occurred at 5:04 P.M. on October 17, 1989. No significant increase in the number of patients with heart attacks was reported for the day following the earthquake (Brown, 1999).

- *Northridge, California, earthquake (6.7 Richter scale).* The earthquake occurred at 4:31 A.M. on January 17, 1994, near Los Angeles, California. There was a significant increase in the number of sudden deaths from atherosclerotic cardiovascular disease, as well as an 80% increase in hospital admissions for heart attacks, on the day of the earthquake (Brown, 1999; Leor, Poole, & Kloner, 1996).

• *Kobe, Japan, earthquake (7.2 Richter scale).* The Hanshin–Awaji earthquake occurred at 5:46 A.M. on January 17, 1995. There was a 3.5-fold increase in patients with heart attacks and a significant increase in the number of deaths from heart attacks during the 8–12 weeks after the earthquake (Kario, Matsuo, Kobayashi, Yamamoto, & Shimada, 1997).

• *Ji-Ji, Taiwan, earthquake (7.3 Richter scale).* The Ji-Ji earthquake occurred at 1:47 A.M. on September 21, 1999. In the 6 weeks following the earthquake, there was a significant increase in the number of patients hospitalized due to heart attacks (Tsai, Llung, & Wang, 2004). In a separate report, 12 patients who were fitted with Holter ECG ambulatory monitors provided an opportunity to examine the beat-to-beat changes in heart rate before and after the earthquake. Analysis of heart rate variability immediately following the earthquake suggested a significant increase in sympathetic tone and/or a withdrawal of parasympathetic tone to the heart. The rapid increases in heart rate at the onset of the earthquake were blunted significantly in three patients who were taking a beta-blocker (Huang, Chiou, Ting, Chen, & Chin, 2001).

• *Great East Japan earthquake and tsunami (9.0 Richter scale).* The Great East Japan earthquake occurred at 2:46 P.M. on March 11, 2011. There was a significant increase in the number of patients seen in area emergency departments in the 3 weeks following the earthquake due to acute coronary syndrome and congestive heart failure but not because of out-of-hospital cardiac arrests (Nozaki et al., 2013).

Soccer

For most of the world, soccer (i.e., football) is *the* sport. Intense competitions within countries (such as the English Premier League) give way to national teams competing in regional championships and the World Cup. Committed football fans are never too far from their televisions during games, there is frequently consumption of rich food and alcoholic beverages leading up to and during the matches, and the level of success of favorite teams is a source of local and national pride. Even Pope Francis has his favorite team in Argentina, the San Lorenzo Crows. Given this context, let's explore studies that have examined cardiovascular morbidity and mortality during football championship matches.

• *1996 European Football Championship Quarterfinal Match, Netherlands versus France.* This match was played in Liverpool, England. The match ended in a 0–0 tie, after which France won in a penalty shoot-out. Mortality from heart attacks and stroke in the Dutch population aged 45 years and older was increased on the day of the match relative to several control periods. This finding was true for males but not females. This spike translated into 14 more deaths than expected on the day of the match from cardiovascular disease (Witte, Bots, Hoes, & Grobbee, 2000).

• *1998 FIFA (Fédération Internationale de Football Association) World Cup match, England versus Argentina.* Following England's loss to Argentina in a penalty shoot-out, there was a 25% increase in hospital admissions for heart attacks on the day of the match and for the 2 days after the match. There was no observed increase in

admissions for other diagnoses on these 3 days (Carroll, Ebrahim, Tilling, Macleod, & Smith, 2002).

- *2006 FIFA World Cup series*. Germany hosted this tournament. Cardiovascular events were studied in the Munich metropolitan area on days when the German team played and compared to various control periods. Cardiac emergencies increased 2.66-fold on days when the German team competed, with greater increases in males (3.26-fold) than females (1.82-fold). Among these patients, 47% had documented cardiovascular disease compared to 29% during control periods (Wilpert-Lampen et al., 2008).

War and Terror

- *Scud missile attacks in Israel*. From January 17 to January 25, 1991, a series of Scud missiles were launched from Iraq and aimed at locations in Israel during the initial phase of the first Gulf War. In a tertiary care hospital in a suburb of Tel Aviv, there was a significant increase in patients presenting with heart attacks and sudden death during the 8-day period of attacks compared to several control time periods (Meisel et al., 1991).

- *9/11 terrorist attacks in the United States*. A national probability sample of more than 2,700 adults was followed before and for 3 years after the series of terrorist attacks that occurred in the United States on September 11, 2001. There was a greater than 50% increase in the incidence of physician-diagnosed cardiovascular disease over the 3 years following the attacks (Holman et al., 2008).

Summary

Several key findings have emerged from studies of profoundly stressful events on the heart, such as earthquakes, national sporting events, and terrorist attacks as well as other events (e.g., job loss, intense anger, major holidays). Intense stressors can serve as emotional triggers for acute cardiac events in susceptible individuals by several mechanisms, including restriction of coronary blood flow due to vasoconstriction, rupture or disruption of an atherosclerotic plague in coronary vessels, increased cardiac electrical instability, increased blood clotting, and myocardial ischemia. These pathophysiological changes are driven in large part by stress-induced increases in sympathetic, HPA axis, and immune system activities (Kivimäki & Steptoe, 2018).

Some of the earthquake studies referenced above focused on the immediate effects of the natural disaster on cardiac events, while others demonstrated prolonged increases in heart-related morbidity and mortality due to extended periods of suffering in remote regions (e.g., Japan earthquake). A closer examination reveals that the timing of the earthquake was a critical variable, with late night–early morning earthquakes (e.g., Ji-Ji, Taiwan) having greater impact on cardiac morbidity and mortality than earthquakes occurring during the daytime (e.g., San Francisco). Imagine the extreme emotional reaction of being awakened from a sound sleep in total darkness with your home or apartment building violently shaking and your sympathetic nervous system increasing from a low level of activity to an extremely high one in a matter of seconds.

How might an emotionally triggering event lead to a heart attack? Strike et al. (2006) approached this question empirically by studying a group of 34 male patients an average of 15 months after they experienced a heart attack or unstable angina. At this time, patients were stable and medically well managed. Soon after the coronary event, 14 of the patients had reported that an emotionally charged (EC) event triggered their heart attack or chest pain, while the remaining 20 patients (nonemotionally charged—NEC) did not report having experienced an emotional event prior to their cardiac event. All patients were brought into the laboratory and exposed acutely to two stressors: a computer-based color–word interference task and a public speaking task. The color–word interference task typically involves rapid presentation on a computer screen of color words printed in an incongruous color of ink. For example, the word *red* is printed in yellow ink. The task is to say the color of the ink for each color word as quickly as possible. Blood samples and cardiovascular measures were obtained at rest and at timed intervals following exposure to the stressors. EC patients but not NEC patients displayed enhanced platelet–leukocyte aggregation during and after exposure to the stressors. EC patients also had greater increases in systolic blood pressure (BP) and cardiac output during and after stress testing compared to NEC patients. These results suggest that individuals who are vulnerable to emotional triggers may react to stressful situations with an increase in platelet activation and more prolonged BP changes that could lead to increased sheer stress on the walls of blood vessels, followed by potential rupture of atherosclerotic plaques.

STRESS-RELATED DISORDERS AND CARDIOVASCULAR DISEASES

Drawing upon the Swedish National Patient Register, Song, Fang, et al. (2019) identified patients who received a diagnosis of a stress-related disorder such as PTSD, acute stress reaction, adjustment disorder, and other stress reactions between 1987 and 2013 (N = 106,180). These investigators also constructed two control groups: unaffected full siblings of the patients with stress-related disorders (N = 171,314) and a group of unexposed individuals who were matched to the demographic characteristics of the patient group (N = 1,366,370). During the follow-up period that lasted as long as 27 years, the incidence of any cardiovascular disease (expressed as cases per 1,000 person-years) was 10.5, 8.4, and 6.9 in the stress-related disorder groups, the unaffected full sibling group, and the matched unexposed control group, respectively. Compared to unaffected siblings, those with stress-related disorders had an increased risk of developing any cardiovascular disorder during the year following the diagnosis (HR = 1.64, 95% CI = 1.45–1.84). A similar pattern was reported for patients with stress-related disorders compared to matched unexposed controls (HR = 1.71, 95% CI = 1.59–1.83). These results applied equally to males and females and were adjusted for family history of cardiovascular diseases and psychiatric comorbidities. These results demonstrate the profound effects of significant life stressors on the cardiovascular system and strongly suggest that patients should be carefully monitored for disorders of the cardiovascular system, especially in the first year following a stress-related diagnosis (Song, Fang, et al., 2019).

THE STRESS OF A CANCER DIAGNOSIS

Few things in life are more dreaded or more stressful than receiving news from a physician that you have cancer, especially an aggressive form of cancer with little chance of long-term survival. How will you prepare your loved ones, are your affairs in order, are there things you really want to do before you are no longer mobile?

To determine if receiving a cancer diagnosis is a stressful insult to the heart, Fang et al. (2017) conducted a study using Swedish national census and cancer and mortality databases that included slightly more than 6 million people who were born in Sweden and were at least 30 years of age between January 1, 1991 and December 31, 2006. Over the course of the study, more than 543,000 individuals who were cancer-free died from cardiovascular diseases, an incidence rate of 7.53 deaths per 1,000 participants. Following a diagnosis of cancer (excluding brain tumors), 48,991 individuals died from cardiovascular disease, an incidence rate of 23.1 deaths per 1,000 participants. The highest relative risk of cardiovascular deaths occurred during the first week following a cancer diagnosis, when the incidence rate increased to 116.8 deaths per 1,000 participants (OR = 5.6, 95% CI = 5.2–5.9). Extending out to the first 4 weeks after a cancer diagnosis, the incidence rate for cardiovascular deaths decreased to 65.8 deaths per 1,000 participants (OR = 3.3, 95% CI = 3.1–3.4). More than 1 year after a cancer diagnosis, there was no longer an elevated risk for cardiovascular deaths from most cancer diagnoses, with the exception of lung cancer.

To control for shared risk factors among cancer and cardiovascular disease, Fang et al. (2017) employed a case–crossover design such that participants who received a cancer diagnosis served as their own controls in the 17 4-week periods leading up to the diagnosis versus the 4-week period following the diagnosis. The results revealed that the risk of cardiovascular death was 3.7 times higher following a diagnosis compared to the control period prior to a cancer diagnosis. Deaths due to other disturbances of the cardiovascular system were also elevated (see Table 7.1).

These investigators took advantage of the excellent national census and health record systems in Sweden to address the question of how the elevated risk of cardiovascular

TABLE 7.1. Risk of Cardiovascular Death after a Cancer Diagnosis Using a Case–Crossover Design

	Number of patients who died with a cancer diagnosis		
Cause of death	Before diagnosis	After diagnosis	Odds ratio (95% CI)
Cardiovascular death	11,988	2,641	3.7 (3.6–3.9)
Heart attack	3,662	970	4.5 (4.2–4.8)
Other heart diseases	554	134	4.1 (3.4–5.0)
Embolism/thrombosis	477	159	5.7 (4.7–6.8)
Stroke	1,538	220	2.4 (2.1–2.8)

Note. Odds ratios were adjusted for seasonal variations in cancer diagnosis and cardiovascular deaths. Data are from Fang et al. (2017). Suicide and cardiovascular death after a cancer diagnosis. *New England Journal of Medicine, 366*, 1310–1318. Copyright © 2017 Massachusetts Medical Society. Used with permission of Massachusetts Medical Society.

disease plays out following a diagnosis of cancer. There can be little doubt that the period immediately following a cancer diagnosis is profoundly stressful and appears to serve as a trigger for heart attacks and other disturbances of the heart and circulation (Fang et al., 2017).

DEPRESSION AND THE HEART

As we discussed in Chapter 6, depression is the second leading cause of disability in the United States and globally. It has a 1-year prevalence of 10–12% and a lifetime prevalence of ~20%. Depression is also a major risk factor for the development of coronary heart disease, and those individuals with heart disease who are also depressed tend to have a much poorer long-term prognosis. Coronary heart disease, the other half of this dreaded 1–2 punch, remains the leading cause of mortality in the world and increases vulnerability for depression. In fact, the prevalence of depression increases to 15–30% in patients with coronary heart disease, and is two times higher in women than in men. This bidirectional relationship between depression and heart disease sets in motion a downward spiral of poor physical health and poor mental health (Whooley & Wong, 2013). Not surprisingly, when depression and heart disease co-occur, the prognosis for both worsens. One psychosocial factor that is shared in common between depression and heart disease is recurrent activation of stress-sensitive central and peripheral neural and endocrine pathways (Dhar & Barton, 2016; McCarty, 2020).

An immense literature on the comorbidity of depression and heart disease has developed, and many outstanding review articles and meta-analyses have been issued on this topic (see, for example, Carney & Freedland, 2017; Wholley & Wong, 2013). In the sections that follow, I have included several key studies to illustrate how depression is a prominent risk factor for the development of heart disease and how the occurrence of heart disease increases the risk for depression. Indeed, Dhar and Barton (2016) argued that major depressive disorder should be considered a modifiable risk factor for heart disease just like cigarette smoking, a sedentary life style, hypertension, and hyperlipidemia.

Is Depression a Risk Factor for Coronary Heart Disease?

Liu, Hernandez, Trout, Kleiman, and Bozzay (2017) reported on a prospective approach to exploring the toxic combination of depression and heart disease. These investigators analyzed data from the Americans' Changing Lives study led by the Survey Research Center of the University of Michigan and initiated in 1986 with a nationally representative sample of adults in the 48 contiguous United States. In 1989, 2,846 participants completed assessments of functional social support; body mass index; depressive symptoms over the previous 3-year period; and occurrence of heart disease, hypertension, and diabetes. Follow-up data were collected in 2001 and the remaining active participants (N = 1,642) were again asked about occurrence of heart disease over the previous year. Social support was found to be an important buffer between participants with depression and a later diagnosis of heart disease. Among participants with lower levels of social support (defined as 1 *SD* below the mean), depression was a significant risk factor for heart disease even after adjusting for demographic and health measures (OR = 2.07, 95% CI = 1.02–4.07, $p < .05$). In contrast, depression was not prospectively

associated with heart disease in participants with higher levels of social support (defined as 1 *SD* above the mean).

A strong system of social support may encourage health-related behaviors and dampen physiological responses to stress that have adverse effects on the heart and circulatory system. Although this study has many compelling aspects, all health-related data were based on participants' self-reports and no measures of perceived stress were taken. That a significant interaction between low levels of social support and later diagnosis of heart disease was determined makes the finding all the more remarkable (Liu et al., 2017).

Does Coronary Heart Disease Increase the Risk of Depression?

There is little doubt that experiencing a heart attack is about as stressful a situation as one can imagine. There is the rush to the hospital emergency room, perhaps by ambulance, and the team of doctors and nurses that descend upon the patient. If one is fortunate and survives the initial scare of the heart attack symptoms, the recovery can also present quite a few life stressors as the inevitable adjustments to a new way of life kick in with a changing diet and a new exercise plan. But what if all these changes become too much and symptoms of depression take hold. Are depressive symptoms to be expected, or do they pose a serious risk for longer-term survival from the heart attack?

Depression as a Risk Factor

A team of researchers in Montreal, led by Dr. Nancy Frasure-Smith, published an influential article that provided strong evidence that depression is a potent risk factor for death in the 6 months following a heart attack (Fraser-Smith et al., 1993). This team enrolled 222 patients who experienced heart attacks in a 6-month study relating depression to health outcomes. Interviews were conducted while patients were in hospital and included demographic information and a structured interview regarding symptoms of depression. Additional information on participants was obtained from hospital records. All participants were contacted 6 months after hospitalization to determine survival rates. Twelve patients had died of cardiac complications by the 6-month follow-up. Strikingly, depression was a significant predictor of mortality, even after controlling for demographic and cardiac-related variables (HR = 4.29, 95% CI = 3.14–5.44, $p < .02$).

Large-Scale Study of Depression as a Risk Factor

The prospective report by Frasure-Smith, Lespérance, and Talajic (1993) was the first to demonstrate that depression has an adverse impact on survival in patients following a heart attack. A more recent large-scale study has extended these initial findings and explored mortality rates among treated and untreated depressed patients following a heart attack. The TRIUMPH study (Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status) enrolled more than 4,000 patients who experienced heart attacks at 24 medical centers across the United States (Smolderen et al., 2017). Three groups of patients were established based on reviews of medical records and screening with the Patient Health Questionnaire–9

(PHQ-9, scores range from 0 to 27) during admission: (1) no depression evident (PHQ-9 score < 10), (2) untreated depression (PHQ-9 score ≥ 10), and (3) depression treated with antidepressants or counseling (PHQ-9 score ≥ 10). Mortality rates 1 year after the heart attack were tracked for all patients.

Patients with untreated depression had significantly higher mortality rates 1 year after a heart attack compared to patients who received treatment for depression and patients without depression, even after adjusting for demographic and clinical variables in the three patient groups ($p < .001$). These findings emphasize the importance of screening for depression and instituting treatment options (drugs, psychotherapy, exercise regimen, stress management) to increase survival in heart attack patients following discharge from the hospital. These observational data are compelling, but definitive evidence of a connection between effective treatment of depression and enhanced survival following a heart attack awaits large-scale, multi-center randomized clinical trials.

Several review articles have emphasized stress-induced sympathetic nervous system, HPA axis, and immune activation as shared mechanisms relating to the onset of depression and the occurrence of a heart attack. In particular, the role played by heightened levels of inflammation in both diseases provides new therapeutic targets for treatment of depression and heart disease (Rohleder, 2014; Shao et al., 2020; Whooley & Wong, 2013).

Coronary Heart Disease Leads to Persistent Psychological Distress

One criticism that could be leveled at the preceding studies was their complete dependence on a single measure of depression in probing the onset of coronary heart disease or the response to a coronary event. Persistence of depressive symptoms over time may be a critical variable that has been overlooked in many previous studies that explored the links between depression and coronary heart disease. Stewart et al. (2017) tackled this problem head-on by taking a longer view of this critical relationship. In their study, 950 participants from a larger sample of individuals who were enrolled in a study of the effectiveness of a statin on coronary heart disease completed at least four general health questionnaires (GHQ-30) at the start of the study and after 6 months and 1, 2, and 4 years. All individuals were then followed for a median of 12.5 additional years, and mortality from coronary heart disease and other causes was tracked.

Over the 4-year assessment period, participants were ranked for levels of distress relating to anxiety and depression based on their scores on the GHQ-30. Participants were categorized as follows: never distressed to mildly distressed (5 < GHQ score < 10), moderately to severely distressed (GHQ score > 10). Persistent distress was defined as a GHQ score > 10 on at least three of the five assessments. Participants with persistent moderate to severe levels of distress over the 4-year assessment period had higher risks of cardiovascular deaths and all-cause mortality (two- to fourfold increase) over the 14-year follow-up period compared to participants with no distress (ps < .001). These findings point clearly to the persistence of distress over a long period of time as a key contributor to mortality, and they are consistent with long-term distress contributing to allostatic load (Stewart et al., 2017). Persistent levels of distress should be measured and considered in designing behavioral interventions to improve well-being in patients at high risk of mortality from coronary heart disease.

Summary

For the past 30 years, compelling evidence suggests that symptoms of depression result in reduced survival from a heart attack. In addition, treatment of depression reduces the risk of death from a heart attack. Finally, long-term, persistent levels of distress lead to increases in allostatic load and an increased risk of death from coronary heart disease as well as other causes of mortality. Taken together, these findings emphasize the need to address levels of psychosocial stress in patients diagnosed with coronary heart disease and in patients recovering from heart attacks (Vaccarino et al., 2020).

WORK-RELATED STRESSORS AND THE HEART

Adults throughout the world spend a great deal of time spanning many decades in work-related activities, including commuting from their homes to places of employment. In addition, with increased access to smartphones and wireless technology, many individuals are involved in work projects through texts, emails, and teleconferences during evenings and weekends and even during vacations. During the COVID-19 pandemic, many individuals worked from home, and the challenges associated with telecommuting have been widely discussed. Work-related stressors comport nicely with the concept of allostatic load, as summarized in Chapter 1.

To combat the intrusion of work-related activities on leisure time, in 2017 the French government passed a law that introduced the right of employees to disconnect from all digital devices during their personal time. The details of implementation were vague, but the intent was clear: to reduce levels of stress on workers. On top of time demands, add a tendency for workers to have less job security while dealing with stagnant wages. It's easy to see how the contemporary pressures and insecurities associated with work might increase levels of allostatic load and in turn place individuals at greater risk for development of coronary heart disease.

Demand–Control Imbalance

Demand–control imbalance (DCI; better known as job strain) refers to the stress associated with a job that places significant psychological demands on an employee but allows that person little or no control over task assignments or input on work-related decisions. Many differences of opinion exist on the impact of work stress on cardiovascular disease, with some researchers favoring significant adverse effects of work stress, and others suggesting the impact of work stress is negligible (Kivimäki & Kawachi, 2015). To tackle this important issue, Kivimäki et al. (2012) combined individual data from 13 European cohort studies initiated between 1985 and 2006 that were part of what is known as the Individual-Participant Data Meta-Analysis of Working Populations (IPD-Work) consortium. Some of the findings were previously published, and some were unpublished. The combined dataset included 197,473 participants, with approximately equal numbers of men and women with an average age of 42 years. Fifteen percent of participants (30,214) reported significant job strain on an initial questionnaire. After a follow-up period that averaged 7.5 years, there were 2,358 diagnoses of coronary heart disease. After adjusting for sex and age, the hazard ratio for participants with job strain

versus no job strain was 1.23 (95% CI = 1.10–1.37). These findings point to a modest but consistent effect of job strain on elevated risk for coronary heart disease.

Effort–Reward Imbalance

Imagine a job where you are expected to work long hours, the workload never lets up, and the pace of work expected is unreasonably high. Now combine these measures of effort with an absence of rewards or incentives such as salary increases, special recognition, opportunities for promotion, or increased job security. These characteristics are the essential features of the effort–reward imbalance (ERI) model of work stress. The literature suggests that jobs that have high effort but low rewards are associated with increased risk of coronary heart disease and cardiovascular-related mortality.

One major prospective study has tackled this important question by establishing a consortium across 11 cohort studies in six European countries (Denmark, France, Finland, Germany, Sweden, and United Kingdom) to explore associations between work-related psychosocial measures and disease outcomes (IDP-Work consortium) (Dragano et al., 2017). The study population included 90,164 participants (mean age = 45 years, 61% female) without coronary heart disease at the start of the individual studies (beginning in 1985–2005). All participants completed questionnaires relating to job strain and ERI at baseline and were followed for an average of 9 years, 8 months, with data collected on heart attacks and mortality from coronary heart disease.

At the beginning of the study, 32% of participants reported ERI associated with their jobs, 16% reported job strain but not ERI, 10% reported both, and 62% reported neither. Over the course of the study, there were 1,078 coronary events. After adjusting for demographic variables and coronary heart disease risk factors, the results indicated that the effects of ERI or job strain on coronary heart disease were modest (HR = 1.16, 95% CI = 1.01–1.34) and that the combined effects of both stressors on coronary heart disease were additive (HR = 1.41, 95% CI = 1.12–1.76). These findings of a significant association between work stress and risk of coronary heart disease are all the more remarkable given that all study participants worked in European countries where occupational safety and health standards are at high levels, attention is given to reducing workplace stress levels, and strong social welfare policies have been put in place to protect workers. It remains to be seen whether the impact of ERI and/or work stress on coronary heart disease risks are of greater impact in countries that lack these well-established labor protection and social welfare policies (Dragano et al., 2017).

Shift Work

Shift work places significant demands on workers and their loved ones given the constantly changing schedules and the alterations in sleep–wake cycles. In some instances, shift work also includes weekend work hours. In many sectors of our nation, work-related activities continue nonstop 24 hours per day, 7 days per week. Consider hospital workers, first responders, fulfillment center and call center staff members, manufacturing plants, and transportation workers as a few of the many areas that almost never shut down.

In a meta-analysis of 21 studies that included over 170,000 participants, Torquati et al. (2018) reported that shift workers had a 17% greater risk of any cardiovascular

disease event compared to controls who worked standard day shifts. Further, the risk of coronary heart disease morbidity (HR = 1.26, 95% CI = 1.10–1.43) and coronary heart disease mortality (HR = 1.18, 95% CI = 1.06–1.32) were both elevated in shift workers compared to day workers. The longer an individual continued with shift work beyond the first 5 years, the greater the risk of experiencing cardiovascular disease-related events.

Loss of Job

Economic downturns, which seem to come out of nowhere, can place job security at risk for even the most valuable employees. Organizations in many sectors of national economies have operating budgets that are largely connected to employee pay and benefits. Thus, during a steep economic downturn, the quickest way to cut operating costs is unfortunately to furlough or terminate employees. Think back to the rapid economic downturn that occurred during the COVID-19 pandemic in early 2020. Tens of thousands of employees were furloughed or terminated from businesses large and small, including colleges and universities, as quarantine orders and travel restrictions were issued. Clearly, loss of one's job is not a remote possibility: it is all too real even under the best of economic circumstances.

To address these important issues, Virtanen et al. (2013) combined data from four published studies and 13 IDP-Work studies conducted in the United States and six European countries to yield a meta-analysis dataset of almost 175,000 participants. Participants completed an assessment of job insecurity (one question or a series of questions, depending on the study methodology) and were followed for an average of 9.7 years, with records made of fatal and nonfatal heart attacks. Across these 17 studies, job insecurity was reported by 16% of participants, many of whom were in low-paying jobs and tended to be less physically active, with more cases of hypertension and hypercholesterolemia. There were 1,892 cases of coronary heart disease over the course of the studies, and high job insecurity was associated with a higher incidence of coronary heart disease among men and women combined (HR = 1.32, 95% CI = 1.09–1.59), with women being at slightly higher risk than men.

Summary

Work can be a blessing or a curse. For many, work is rewarding, challenging, and exciting, and it offers opportunities to enhance the success of one's employer and to benefit personally from that success. For others, work is a means to an end—a way to earn a modest salary in a job that is a dead-end with no hope of promotion, little job security, no on-the-job training, and no prospects for assuming responsibilities or benefiting from the success of the employer. As we have seen, job strain, effort–reward imbalance, shift work, and job insecurity contribute modestly to risk of an acute heart attack. These risks do have consequences, and some companies and national governments have taken steps to reduce workplace stressors, address effort–reward imbalances in creative ways, enhance opportunities for training and advancement, and enhance the quality of life for their employees. Employers receive returns on these investments by having a more dedicated and productive workforce that is committed to the long-term success of the company (Marmot, 2004).

BELIEFS ABOUT STRESS AND THE HEART

Nabi et al. (2013) were interested in the long-term impact of beliefs that stress affects one's health. To address this important research question, these investigators made use of data from the Whitehall II study of British civil servants. Begun in 1985 with more than 10,000 participants aged 35–55 years old, this prospective study included periodic data collection via mailed questionnaires and clinic visits. In Phase 3 (1991–1993), the following question was added to the larger mailed questionnaire: "To what extent do you feel that the stress or pressure you have experienced in your life has affected your health?" Responses included (1) not at all, (2) slightly, (3) moderately, (4) a lot, or (5) extremely. Participants were followed until Phase 9 (2007–2009), for a maximum period of 18.3 years. A complete dataset was available for 7,268 participants, of whom 8% (N = 584) responded "a lot" or "extremely" to the question about stress affecting health. There were 352 coronary deaths or nonfatal heart attacks over the course of the study. After adjusting for biological and behavioral risk factors (including perceived levels of stress), there was an increased risk of coronary heart disease among those individuals who responded a lot or extremely to the key question regarding stress effects on health (HR = 1.49, 95% CI = 1.01–2.22). Nabi et al. (2013) concluded that behavioral interventions designed to alter the belief that stress has a significant impact on personal health could be an effective strategy for reducing the risk of coronary heart disease in this cohort of patients. Perhaps a more effective intervention would be to provide strategies for managing life stressors more effectively.

BRAIN RESPONSES TO STRESS

Psychosocial stressors exert deleterious effects on the cardiovascular system via activation of brain circuits that control autonomic, endocrine, and immune activities (McCarty, 2020). In an elegant prospective study, Tawakol et al. (2017) enrolled 293 participants from a larger group of more than 6,000 patients who were screened for cancer over a 3-year period (2005–2008). All participants were at least 30 years old, had been cancer free for at least 1 year, and had no history of immune dysfunction. Individuals were included in a functional magnetic resonance imaging (fMRI) study and an ^{18}F-fluorodeoxyglucose (^{18}F-FDG) study to measure brain neuronal activity and tissue metabolic activity, respectively. Over the follow-up period (median = 3.7 years), 22 participants experienced 39 cardiovascular disease events (e.g., heart attack, unstable angina, stroke, heart failure). Interestingly, fMRI-based activity in the amygdala under resting conditions, an important component of the brain's stress circuitry, was significantly associated with cardiovascular disease events even after adjusting for other standard risk factors (HR = 1.61, 95% CI = 1.21–2.14). This relationship was not apparent for other brain areas, including the cerebellum and the cerebral cortex. Amygdala activity also correlated with metabolic activity in bone marrow and spleen and uptake of ^{18}F-FDG in arteries, an index of inflammation. Activation of the amygdala also increases sympathetic nervous system activity, which directly affects levels of arterial inflammation and atherosclerosis. These investigators suggested that efforts to reduce levels of psychosocial stress might dampen the negative effects of the amygdala–sympathetic–immune axis and reduce cardiovascular disease risk (Tawakol et al., 2017).

THE PROTECTIVE EFFECT OF SOCIAL NETWORKS

The Nurses' Health Study was launched in 1976 with more than 120,000 female nurses who were 30–55 years of age at the time. Women were followed every 2 years with a mailed questionnaire regarding health risks and outcomes. Beginning in 1992 and continuing every 4 years, new information was collected on social networks and their impact on coronary heart disease, and 1992 served as the baseline year for a study by Chang et al. (2017). There were 76,362 participants (mean age = 58 years) after exclusions for preexisting conditions and advanced age, and they were followed for fatal and nonfatal heart attacks until May 2014. After adjusting for demographic and health-related behaviors, participants with the highest social integration scores were less likely to develop a fatal heart attack compared to those participants with the lowest social integration scores (HR = 0.68, 95% CI = 0.51–0.92). For nonfatal heart attacks, those participants with higher social integration scores also had higher levels of health-promoting behaviors (nonsmoking and regular exercise) that reduced their risk compared to participants with the lowest scores for social integration. This study emphasized the importance of psychosocial well-being as an important contributor to physical health and as an inhibitor of biological pathways that promote coronary heart disease (Chang et al., 2017).

STRESS-TARGETED INTERVENTIONS FOLLOWING A HEART ATTACK

If psychosocial stressors play a critical role in the occurrence of acute heart attacks, is it a good idea to have post-heart attack patients return to dealing with this plethora of stressors in the weeks and months following discharge from the hospital? If post-heart attack patients continue to experience high levels of stress, there is an increased risk of readmission to the hospital (de Albuquerque et al., 2020). As we will see in the next several studies, behavioral interventions have been developed to supplement standard cardiac rehabilitation programs, with an emphasis on developing strategies to aid patients in more effectively managing psychosocial stressors (Chauvet-Galinier & Bonin, 2017).

Karolinska University Intervention

In this study, 237 women (mean age = 62 years) who were treated at the Karolinska University Clinics for acute heart attacks, coronary artery bypass surgery, or placement of a stent(s) to open partially occluded coronary vessels were recruited to participate in a psychosocial intervention program to improve recovery. Four months after discharge from the hospital, participants were randomly assigned to the group-based psychosocial intervention (N = 112) or to a control group receiving usual care (CON, N = 125). The psychosocial intervention involved groups of four to eight women who met 20 times over a 1-year period to discuss cardiovascular risk factors, relaxation techniques, cognitive restructuring, coping with stress at home and at work, self-care, and medical compliance. The group members benefited from social bonding and mutual support and encouragement over the 1-year period of meetings. All participants were followed for an average of just over 7 years from the start of the intervention. During this time,

25 control participants (20%) but only 8 psychosocial intervention participants (7%) died, pointing to a significant protective effect of the intervention even after controlling for use of medications ($p < .01$). These results could not be explained by differences between groups in demographic factors, acuity of initial diagnosis, risk profiles, or drug regimens. In addition, women in the two groups exhibited similar levels of life stressors at the start of the intervention. The mechanisms to explain this dramatic increase in survival in women in the psychosocial intervention group remain to be explored, but might include reduced levels of inflammation, sympathetic nerve activity, coagulation, and atherosclerosis (Orth-Gomér et al., 2009).

Duke University Intervention

We have already seen that stressors can serve as triggers to increase the probability of an acute heart attack in susceptible individuals. What can be done to improve health outcomes for individuals who have experienced a significant cardiac event? A remarkable intervention study led by James A. Blumenthal of Duke University addressed this issue by incorporating a well-developed stress management module within a standard cardiac rehabilitation program for patients with coronary heart disease. As we will see, a focus on stress management during cardiac rehabilitation enhanced survival significantly following an initial diagnosis of coronary heart disease (Blumenthal et al., 2016).

Participants in this study were evaluated for levels of stress, traditional cardiovascular risk factors, and coronary heart disease biomarkers, and they were then randomly assigned to either comprehensive cardiac rehabilitation ($N = 75$) or cardiac rehabilitation plus stress management training ($N = 76$). A third group declined to participate in cardiac rehabilitation; individuals were randomly selected from this larger group ($N = 75$) and followed clinically. Cardiac rehabilitation was delivered over a 12-week period and involved aerobic exercise three times per week, education about coronary heart disease and nutrition, and two classes on stress. Stress management sessions were presented in 12 weekly 1.5-hour sessions in small groups of four to eight participants. The stress management sessions were structured based on a cognitive-behavioral model, with life stressors presented as an imbalance between high demands and low coping resources. Emphasis was also placed on cognitive appraisal processes, anger management, effective problem solving, and related topics. Patients were followed for a median of 3 years, 2 months, and a maximum of 5 years, 3 months.

The results clearly indicated that the cardiac rehabilitation plus stress management group had greater reductions in self-reported stress levels compared to the cardiac rehabilitation only group, indicating the effectiveness of the stress management intervention. Reductions in stress levels in this group were attended by significant reductions in adverse cardiac-related events compared to the cardiac rehabilitation group, including heart attacks, cardiac or peripheral vascular treatment, strokes, or unstable angina. Both groups receiving cardiac rehabilitation had significantly lower adverse event rates compared to the group that refused all treatment.

As impressive as these results are, the sample sizes were quite small and were drawn from only two sites. In addition, the participants volunteered to be involved in the study and may have been more motivated to engage in the program than typical recovering patients. The stress measure was a composite of several other measures, and this aspect

of the study could definitely be improved. In spite of these concerns, these results are sufficiently promising to warrant a multi-center study with significantly larger sample sizes (Blumenthal et al., 2016).

Summary

Nearly 50% of American adults have some form of cardiovascular disease, including coronary heart disease, heart failure, stroke, and hypertension. The majority of affected adults have hypertension, with cutoff values recently set at lower levels (Table 8.1) (Benjamin et al., 2019). Many adults with cardiovascular disease deal with psychosocial stressors on a daily basis. Given these extremely large numbers of affected individuals, small-group stress management workshops simply cannot handle this level of demand. When a physician is concerned about an individual patient's stress levels or when someone feels the need for support in dealing with life stressors, web-based stress management programs offer an affordable and scalable solution (Chinnaiyan, 2019). In addition, when policymakers recognize the critical role of psychosocial stressors in the etiology of cardiovascular disease and other chronic conditions, changes may be made in areas that directly contribute to levels of stress for many adults (e.g., working hours and conditions, availability of childcare, opportunities for training and advancement, better public transportation, affordable housing) (Marmot, 2004).

STRESS AND HYPERTENSION

One of the most frequently measured physiological variables in all of medical practice is blood pressure (BP). The first documented measurement of BP was reported by the English clergyman and scientist Stephen Hales (1677–1761), who built on the earlier findings of William Harvey regarding the heart and its role in the recirculation of blood (refer to Chapter 1). Noninvasive methods for measuring BP were first introduced in the mid-19th century and employed mercury manometers. The modern-day sphygmomanometer for measuring BP noninvasively in humans is a relatively recent invention, appearing in various forms at the end of the 19th and the beginning of the 20th centuries (Booth, 1977).

BP reflects the pressure of blood being forced through arteries by the contraction of the heart. Systolic BP (SBP) is the pressure in arteries when the heart contracts, and diastolic BP (DBP) is the pressure in arteries when the heart relaxes. The units of BP measurement are in mm of mercury (mmHg) and are reported as SBP/DBP.

In 2018, the American College of Cardiology and the American Heart Association published major changes in clinical practice guidelines regarding resting BPs of adults (Whelton & Carey, 2018). As summarized in Table 7.2, normal adult BPs were set at an SBP of less than 120 mm Hg together with a DBP of less than 80 mm Hg. There are also categories for elevated BP and two levels of hypertension. These new guidelines will quickly be incorporated into clinical research protocols for studying risk factors for elevated BP and for hypertension. However, much of the existing literature will have prior thresholds for hypertension; this should be kept in mind as you consider the next series of studies of psychosocial effects on BP regulation.

TABLE 7.2. American Heart Association Guidelines for Normal and Elevated Blood Pressure and for Hypertension

BP category	SBP		DBP
Normal	< 120 mm Hg	*and*	< 80 mm Hg
Elevated	120–129 mm Hg	*and*	< 80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	*or*	80–89 mm Hg
Stage 2	≥ 140 mm Hg	*or*	≥ 90 mm Hg

Note. Values are presented for systolic (SBP) and diastolic blood pressure (DBP) in mm Hg for adults based on two or more BP determinations on two or more occasions. Details are provided in Whelton and Carey (2018).

A recent meta-analysis of 48 randomized clinical trials of pharmacological BP-lowering medications versus placebo or other classes of BP-lowering medications revealed that a 5-mmHg reduction in basal BP resulted in a 10% reduction in risk of cardiovascular events, even when starting BPs were in what would have been considered the normal or high-normal range. These findings were true for patients without a history of cardiovascular disease and for patients with a prior history of cardiovascular disease (Blood Pressure Lowering Treatment Trialists' Collaboration, 2021).

The World Health Organization estimates that more than 1.1 billion people in the world have hypertension (World Health Organization, 2021). In the United States alone, 50% of adults (108 million people) have hypertension. Although BP is easily measured, many people with hypertension remain undiagnosed, and as a result, their health status is placed at significant risk. There are several highly effective drugs for the treatment of hypertension, but many individuals who would benefit from these drugs are unaware that they need them or cannot afford them due to lack of prescription drug benefits or high co-pays.

Hypertension develops over many years, and there are no overt signs that signal that BP is gradually increasing—these are the *slow* and *silent* features of hypertension. As BP increases, the elasticity of blood vessels is diminished and may reduce the delivery of oxygenated blood to various tissues, including the heart. Elevated BP is a significant risk factor for heart and kidney disease and stroke; this is the *deadly* feature of hypertension. There are several risk factors for hypertension, including tobacco use, elevated intake of salt and fat in the diet, lack of regular exercise, and being overweight. Another important risk factor that is the focus of this section is psychosocial stress.

Baseline BP Measurements

Imagine you are a single mother with two children and you have your yearly medical check-up scheduled for today at 10:00 A.M. You have canceled two previous visits because one of your children was sick, you have used up all of your personal time off from work, and it is only October. You are successful in getting your children out of bed, dressed, and fed in record time. You take them into their school, and they are happy to be back with their friends. You return to your car and turn the key and nothing

happens—dead battery. You remain calm and order an Uber, but there is a delay due to a major traffic jam leading into the city center. You arrive for your doctor's appointment 20 minutes late, and the receptionist is less than welcoming. You are finally taken into an examining room, and you notice a text from your coworker: "Where are you? Our meeting starts in 10 minutes." You realize you did not request time off for your appointment. At that moment, your nurse comes in to measure your BP and heart rate. You feel as if your head is going to explode as the cuff is inflated around your arm.

This is one of many scenarios that plays out each day when adults go for clinic appointments with their doctors. Not all of these appointments are accompanied by racing around at home and traffic jams and sick children. But this level of chaos can affect baseline BP measurements at the point of care.

White-Coat Hypertension

Pickering et al. (1988) coined the term *white-coat hypertension* to describe individuals who have elevated BPs in a clinical setting but normal BPs at other times as measured by continuous ambulatory BP monitoring for 1 day. The white coat phenomenon was most evident when male physicians measured BPs and much less so when nurses or technicians measured BP. Of 292 patients with untreated borderline hypertension included in the report by Pickering et al. (1988), 21% had ambulatory daytime BPs that were within the normotensive range. Patients with white coat hypertension tended to be younger females who weighed less and had been diagnosed with hypertension for a shorter period of time than patients with stable hypertension. Patients with white coat hypertension did not appear to have greater levels of anxiety when they came into the clinic, and their BPs were consistently elevated over multiple clinic visits and did not display habituation. The authors suggested that the elevated BP levels may be explained by a classically conditioned response to stimuli associated with the first clinic visit that activates a pressor response on subsequent clinic visits.

Masked Hypertension

The flip side of white coat hypertension is masked hypertension, which occurs when a patient has normal BP in the clinic setting but elevated BP based on ambulatory daytime BP monitoring or home BP monitoring. Anstey et al. (2017), in a review of the literature on masked hypertension, estimated that the prevalence of this phenomenon in population-based studies ranged from 15–30% of adults with normal clinic BPs. In the United States, masked hypertension has a prevalence of 11–16%, with some variations among racial groups. Prior studies have documented that target organ damage (e.g., left ventricular hypertrophy and carotid artery arteriosclerosis) is as severe in patients with masked hypertension as in patients with hypertension based on clinic and ambulatory BP measurements.

Given the millions of normotensive individuals in the United States, it is simply impractical to measure ambulatory or home BPs to screen for masked hypertension. Masked hypertension does tend to be more common in individuals who have poor scores on many of the standard risk factors for hypertension (history of smoking, higher BMI, less healthy diet, lower activity levels, etc.). It is possible that patients with masked hypertension are more relaxed in the clinic setting but more consistently reactive to the

day-to-day stressors that they encounter in their lives. One way to identify such individuals is through wearable devices (e.g., smartwatches) that measure BP during the day and night.

Impact of Psychosocial Stressors on BP

So many studies have examined the effects of psychosocial variables on BP regulation that it would be impossible to provide a summary of even a significant percentage of them (Sparrenberger et al., 2009; Spruill, 2010). Instead, in the sections that follow, I will provide overviews of some important and well-designed studies to illustrate the effects of various psychosocial stressors on BP levels in adults.

Hostile and Impatient

The Coronary Risk Development in Young Adults (CARDIA) study was a multi-center prospective study of 3,308 young adults (18–30 years of age at the start of the study in 1985–1986), with five follow-up data collections through 2001. Efforts were made at each data collection site to recruit and retain up to year 15 a participant sample balanced by sex (56% female) and race (44% African American). Five psychosocial measures were taken: (1) hostile attitudes in Years 0 and 5, (2) time urgency/impatience and achievement striving/competitiveness in Year 0, and (3) depression and anxiety in Year 5. The incidence of hypertension in year 15 (defined as SBP ≥ 140 mm Hg, DBP ≥ 90 mm Hg or taking antihypertensive medication) was 15%, up slightly from 13.6% in Year 5. After adjusting for standard risk factors for hypertension, both hostility and time urgency/impatience were significantly associated with development of hypertension in Year 15. Those scoring highest for hostility had an adjusted odds ratio of 1.84 (95% CI = 1.33–2.54) compared to the lowest scoring group. Those scoring highest for time urgency/impatience had an adjusted odds ratio of 1.84 (95% CI = 1.29–2.62) compared to the lowest scoring group. In addition, there was a dose–response relationship for hostility and time urgency/impatience on hypertension, with incidence of hypertension increasing with each quartile increase in the two behavioral measures. Measures of achievement striving/competitiveness, depression, and anxiety did not have significant effects on the development of hypertension in Year 15.

There are several limitations in the design of this study. Behavioral measures were taken at different times, and there were inconsistencies across measures. In addition, measures of BP were a single time for each follow-up data collection rather than multiple measures at each follow-up or ambulatory monitoring of BP. Finally, the study was underpowered to determine race- and sex-specific risk estimates. In spite of these limitations, this important study demonstrated a clear impact of psychosocial factors on the development of hypertension (Yan et al., 2003).

Job Strain

A quantitative meta-analysis of 22 cross-sectional studies of job strain and ambulatory SBP and DBP was reported by Landsbergis, Dobson, Koutsouras, and Schnall (2013). Their findings indicated that job strain was associated with increases in SBP (3.43 mm Hg) and DBP (2.07 mm Hg). In men, there were significant associations between job

strain and ambulatory BPs measured at work, at home, and while asleep. In women, however, the only significant association was between job strain and SBP at work. All data for men and women were adjusted for standard risk factors for hypertension. There was also evidence in support of a dose–response relationship between increasing levels of job strain and increasing levels of ambulatory BP. Interventions to address the adverse effects of job strain on workers would require large-scale interventions by workplace managers and by regulatory authorities, and these efforts are unlikely to occur (Landsbergis et al., 2013).

Social Isolation and Loneliness

Individuals who are socially isolated have few relationships with others and infrequent social contacts. In contrast, loneliness reflects a subjective feeling of being alone due to a mismatch between one's desired level of social contacts versus the actual level. Loneliness can have serious negative effects of overall physical and mental health and increases the risk of all-cause mortality (Holt-Lunstad, 2021). In a prospective study of a diverse group of male and female adults who were 50–68 years old, Hawkley, Thisted, Masi, and Cacioppo (2010) reported that those participants with the highest starting levels of loneliness as measured by the revised UCLA Loneliness Scale displayed the greatest increases in SBP over the 4-year study period ($p < .05$). Importantly, the effects of loneliness on SBP persisted after adjusting for previous health conditions; levels of depression, hostility, social support, and perceived stress; medications; and cardiovascular risk factors.

Depression

In the report by Yan et al. (2003) summarized above, depression scores did not exert a significant influence on BP levels in the CARDIA study. A more detailed study of the effects of depression on BP was summarized by Patten et al. (2009) based on their analyses of data from the Canadian National Population Health Survey of 12,270 individuals who did not report a diagnosis of high BP or the use of antihypertensive medications at the initiation of the study in 1994. Over a 10-year follow-up period with assessments at 2-year intervals, participants with and without major depression (based on the Composite International Diagnostic Interview Short Form) were compared for incidence of elevated BPs. After adjusting for age and other risk factors, the chance of developing high BP was increased in participants with major depression (HR = 1.6, 95% CI = 1.2–2.1). An obvious concern in the clinical management of patients is that depression may exacerbate some risk factors for hypertension, including perceived levels of stress, weight gain, reduced exercise, increased tobacco use, and increased intake of alcohol (Patten et al., 2009).

Summary

In this brief overview of psychosocial factors and hypertension, an individual psychosocial factor was the focus of each study. In reality, individuals face a shifting tide of psychosocial stressors over time, and some periods are worse than others. What is clear from these and many other studies is that a range of life stressors can impact

BP regulatory systems and lead to progressive increases in resting BPs that approach or exceed levels that meet the criteria for hypertension. Hypertension is a significant risk factor for heart attacks, stroke, kidney disease, and other medical conditions that increase morbidity and mortality. Providing at-risk individuals with strategies to manage psychosocial stressors more effectively could increase quality of life for many adults.

STRESS-TARGETED INTERVENTIONS AND HYPERTENSION

Given the impact of psychosocial stressors on BP levels, it would appear that behavioral interventions to enhance stress management skills in patients with elevated BPs would be an effective therapeutic approach to manage hypertension. Following are the results of two stress management interventions that demonstrate the promise of this approach.

Not Quite Personalized Stress Management

Linden, Lenz, and Con (2001) conducted a small intervention trial with 60 male and female participants (mean age = 55 years) whose BPs exceeded 140/90 mm Hg. Participants were randomly assigned to an immediate stress management program or to a wait-list control group. Eventually, participants in the wait-list control group were offered entry into the stress management program. To the extent possible, the stress management program was delivered in 10 weekly 1-hour sessions and was somewhat tailored to the needs of each participant based on an intake interview with a therapist. BP was measured by an ambulatory BP monitoring device prior to and at the end of the stress management program and at a 6-month follow-up. A total of 36 participants in the stress management program were available for the 6-month follow-up.

Compared to wait-list controls, participants immediately following completion of the stress management program had greater reductions in ambulatory SBP (–6.1 vs. +0.9 mm Hg) and DBP (–4.3 vs. 0.0 mm Hg). A similar pattern was true at the 6-month follow-up for ambulatory SBP (–12.5 mm Hg) and DBP (–9.9 mm Hg) in participants who completed the stress management program. The results of this study are intriguing, but the sample sizes were quite small and precluded detecting meaningful changes in psychosocial measures. The sustained decreases in ambulatory BPs were substantial given the modest level of stress management training and warrant follow-up studies with larger numbers of participants (Linden et al., 2001).

Stress Management in the Workplace

Stress reduction interventions may be ideally suited for implementation in a workplace setting because of greater access by employees during normal working hours. Employers have placed greater emphasis on wellness programs in workplace settings in recent years; adding a stress management program would be consistent with this emphasis on employee well-being. Clemow et al. (2018) presented the effects on BP of 10 weekly 1-hour cognitive-behavioral coping skills training sessions for groups of 8–10 participants per site. Controls received information about the management of hypertension, but they did not meet in small groups. Following initial BP screening of employees at an academic medical center, individuals were identified with SBPs/DBPs in the following

range: ≥ 140/90 mm Hg and < 180/110 mm Hg. Forty-one controls and 40 participants in the intervention group completed the 10-week program. The mean age of all participants was approximately 48 years, and more than 70% were female. The mean number of intervention sessions completed was 8.1 out of 10.

Two months after the final intervention sessions, mean SBP in controls decreased modestly (–1.7 mm Hg), while in the intervention group, SBP decreased significantly (–9.1 mm Hg). DBP changes were similar in controls and intervention group participants. Although this study included a relatively small sample size and automated BP measures were not confirmed with ambulatory BP measures, the results are encouraging and point to workplace interventions for delivering a standardized cognitive-behavioral intervention as a promising avenue for behavioral modification of elevated BP (Clemow et al., 2018).

CONCLUSIONS

Cardiovascular diseases, especially heart attacks and hypertension, have retained their ranking as the number one cause of morbidity and mortality in the world. In this chapter, we have explored multiple connections between real-life stressors and disability and death, with a focus on heart attacks and high BP. Intense stressors can precipitate the onset of a heart attack, as has been documented in many studies, ranging from experiencing an earthquake, a terror attack, or a disappointing defeat of a favorite sports team as well as being diagnosed with cancer and/or depression. Hypertension tends to affect individuals over a longer timescale, and many individuals are unaware that they have sustained elevations in BP for many years.

An encouraging aspect of the research on psychosocial stressors and cardiovascular diseases is the apparent effectiveness of interventions to reduce perceived levels of stress in patients. These interventions have been tested in patients following a heart attack as well as in patients with sustained elevations in BP. A future challenge is to develop scalable interventions through web-based or smartwatch platforms, given the overwhelming number of individuals who have been diagnosed with coronary heart disease or hypertension (Hughes, Serber, & Kuhn, 2022).

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