Examining the Role of Psychosocial Stressors in Hypertension

Komal Marwaha

Department of Medical Education, Paul L Foster School of Medicine, Texas Tech University Health Science Center, El Paso, TX, USA

Despite advances in medicine and preventive strategies, fewer than 1 in 5 people with hypertension have the problem under control. This could partly be due to gaps in fully elucidating the etiology of hypertension. Genetics and conventional lifestyle risk factors, such as the lack of exercise, unhealthy diet, excess salt intake, and alcohol consumption, do not fully explain the pathogenesis of hypertension. Thus, it is necessary to revisit other suggested risk factors that have not been paid due attention. One such factor is psychosocial stress. This paper explores the evidence for the association of psychosocial stressors with hypertension and shows that robust evidence supports the role of a chronic stressful environment at work or in marriage, low socioeconomic status, lack of social support, depression, anxiety, post-traumatic stress, childhood psychological trauma, and racial discrimination in the development or progression of hypertension. Furthermore, the potential pathophysiological mechanisms that link psychosocial stress to hypertension are explained to address the ambiguity in this area and set the stage for further research.

Key words: Psychosocial stress, Hypertension, Depression, Anxiety, Racial discrimination, Lifestyle risk factors

INTRODUCTION

Hypertension is a major risk factor for cardiovascular disease (CVD) and premature mortality worldwide, accounting for more CVD deaths than any other modifiable risk factor [1]. Globally, 1.13 billion people have hypertension. From 2003 to 2013, the number of deaths attributable to hypertension increased by 34.7% [2].

At present, 45.6% of adults in the United States have hypertension. The total burden of hypertension has consistently increased, from 87.0 million in 1999-2000 to 108.2 million in 2015-2016, in the United States. It is estimated that by 2035, the total direct costs of high blood pressure could increase to US$220.9 billion [3].

Despite advances in medicine and preventive strategies, fewer than 1 in 5 people with hypertension have the problem under control [1]. This could partly be due to gaps in fully elucidating the etiology of hypertension. Genetics and conventional lifestyle risk factors, such as the lack of exercise, unhealthy diet, excess salt intake, and alcohol consumption, do not fully explain the pathogenesis of hypertension, indicating the need to revisit other suggested risk factors that have not been given due attention. Psychosocial stress is one such factor. It not only increases the incidence of hypertension, but is also associated with poor hypertension control [4], unhealthy lifestyle behaviors [5], and non-compliance with treatment regimens [6]. Although there are many psychosocial stressors, this paper will focus on those with substantial scientific evidence supporting their role in hypertension.

A few studies in the past have explored the associations of various stressors with hypertension, but there is a scarcity of studies that have attempted to explain these associations. Thus, this study will also offer potential underlying processes that connect psychological stress with hypertension. The aim is to close the knowledge gap so that this information can be used to further research in this field.

PSYCHOSOCIAL RISK FACTORS ASSOCIATED WITH HYPERTENSION

Psychological stress is said to occur if an event or environmental demands are perceived as challenging enough to surpass an individual's capacity to cope. The challenging event or environmental demands are termed stressors, and the physiological or psychological response to exposure to the stressor is termed a stress response. It is worth noting that stress may predispose some individuals to short-term or long-term effects that include disruptions in neuroendocrine and immunological mechanisms, resulting in the development or progression of psychological, autoimmune, respiratory, or CVD, including hypertension. Below is the evidence for psychosocial factors associated with the onset and progression of hypertension.

Occupational Stress

According to World Health Organization, stress, especially work-related, is the second most frequent health problem impacting employed people in the European Union [7]. Approximately 25% of European workers experience work-related stress that negatively affects their health [8]. High job strain (i.e., low control or decision leeway) is especially reported to increase the incidence of hypertension [9]. Landsbergis et al. [10] conducted a meta-analysis of 22 cross-sectional studies and found that exposure to job strain was associated with higher systolic blood pressure (3.43 mmHg; 95% confidence interval [CI], 2.02 to 4.84; $p<0.001$) and diastolic blood pressure (2.07 mmHg; 95% CI, 1.17 to 2.97; $p<0.001$) compared to no exposure. Higher workload or work demands [11], increased working hours [10], job insecurity [12], and low wages are other occupation-related factors that lead to chronic stress and have been found to increase the incidence of hypertension.

Social Integration/Social Isolation

Social integration is the degree to which an individual feels connected to others in their group or community. Individuals with poor social integration have an increased risk of developing hypertension. Having fewer social ties across 5 areas of social activities—namely, marital status, contact with parents, children, neighbors, and volunteer activities increases the odds of developing hypertension [13]. Notably, one's perceived sense of isolation, or having fewer social ties than desired, also increases the reactivity to laboratory stress (stress response upon exposure to a stressor in a laboratory setting) and causes a cumulative increase in blood pressure over the years [14,15].

Marital Status and Quality of the Marital Relationship

Studies have consistently demonstrated the effect of marital status and marriage quality on blood pressure. High marital quality is found to be associated with lower stress and lower ambulatory blood pressure (ABP) at home and work compared to low or intermediate marital relationship quality or not having a partner [16]. Increased spousal contact in low-quality marriages was found to increase ABP over 3 years. Although married individuals had a greater nocturnal drop in blood pressure than single individuals, singles fared better than people in low-quality marriages [16]. Usually, there is a 10% to 15% decrease in blood pressure at night, and the absence of a nocturnal dip is associated with target organ damage [17]. Interestingly, no other forms of social support fully compensated for the effects of being single or in an unhappy marriage [16].

Racial Discrimination

Actual or perceived racial discrimination has been identified as an adverse psychosocial stressor for cardiovascular health [18]. A systemic review and meta-analysis of 44 articles (n=32 651) found an association between perceived racial discrimination and hypertensive status (Z=0.048; 95% CI, 0.013 to 0.087) [19]. Racial discrimination contributes to psychological stress and low self-esteem that negatively affect blood pressure levels [18]. Racial discrimination is associated with higher daytime ABP and nocturnal ABP, decreased nocturnal blood pressure dipping, and an increased risk of developing hypertension [20]. Even after adjusting for age, gender, and socioeconomic status (SES), the lifetime level of discrimination is associated with greater hypertension prevalence [21]. Both African Americans and Latinos report experiencing discrimination. African Americans report the highest rates of major lifetime discrimination (48.9%), with 91.2% experiencing minor day-to-day

discrimination. Furthermore, 47% of Latinos born in the United States report minor day-to-day experiences of discrimination [19]. Exposure to racial/ethnic discrimination across the life course has been found to be associated with elevated blood pressure in middle-aged to older Black and Latino adults [22]. African Americans demonstrate high cardiovascular reactivity to race-related laboratory stressors (e.g., recall of personally relevant experiences of discrimination or exposure to audio or videotapes of racist scenarios) compared to neutral tasks or non-race-related stressors [21]. Stress associated with racism has been proposed to contribute to higher blood pressure levels and disproportionately higher rates of hypertension and CVD in African Americans compared to Whites in the United States [23]. Institutional-type discrimination has been suggested to be more clearly associated with hypertension incidence in population-based studies using contextual-level indicators of neighborhood segregation [20].

Low Socioeconomic Status

A meta-analysis of 51 studies found an increased risk of hypertension with low SES across all 3 indicators: income (pooled odds ratio [OR], 1.19; 95% CI, 0.96 to 1.48), occupation (pooled OR, 1.31; 95% CI, 1.04 to 1.64), and education (pooled OR, 2.02; 95% CI, 1.55 to 2.63) [24]. SES is inversely related to the risk of hypertension, CVD, and mortality [25]. Several studies have evaluated the associations between various SES indices (educational level, occupational status, income, social class, social status, and neighborhood characteristics) and hypertension. Matthews et al. [26] studied changes in several socioeconomic indicators as predictors of incident hypertension in the 10-year follow-up of Coronary Artery Risk Development in Young Adults (CARDIA) study participants. They found that difficulties paying for basic needs at baseline and during the follow-up period predicted hypertension incidence. There was also a trend for association between a decline in income and incident hypertension. Low SES was also related to hypertension-related blood pressure patterns, including reduced nocturnal blood pressure dipping [27] and delayed blood pressure recovery following laboratory stress [28]. Low SES may augment the stress response to other stressors. Landsbergis et al. [10] found that individuals with low SES showed a more robust response to high job strain than those with high SES, suggesting a potentiating role of low SES in exacerbating the effects of other chronic stressors that increase the incidence of hypertension. It is hypothesized that individuals with lower SES are exposed to multiple sources of stress and have lower resources to cope with it. This is often accompanied by poor health behavior that increases the risk for hypertension [29].

Negative Affective States

Negative affective states such as anxiety and depression may develop as downstream consequences of psychological stress and contribute to the onset and progress of high blood pressure [29]. The first episode of depression often occurs after exposure to stressful life events such as divorce, unemployment, or the suicide of a relative [30]. Depression is associated with blood pressure progression and increased cardiovascular morbidity and mortality risk. A meta-analysis of 9 studies found that depression increased the risk of hypertension by 1.42-fold, and the risk was correlated with the length of follow-up [31]. Data from the CARDIA study found that individuals with high depression scores had a 2.8-fold increased risk of hypertension after 5 years of follow-up [32].

Individuals with anxiety are also reported to have a higher risk of hypertension than those without anxiety [33]. This association was found to hold across the spectrum of anxiety disorders, namely generalized anxiety, post-traumatic stress disorder, panic disorder, and obsessive-compulsive disorder, and also when controlling for comorbid conditions such as depression and physical ailments [34]. Childhood psychological trauma has also been found to be associated with the development of anxiety, depression, and hypertension later in life [35].

Psychosocial Stress and Disease Susceptibility

It has been suggested that an individual's physiological and psychological resilience determines the predisposition to stress-induced disease. Neuroendocrine reactivity, genetics, environment, nutrition, and sleep are important mediators of physiological stability. An individual's coping abilities, sense of control, optimism, social support, early life experiences, learning, genetics, and sleep determine his psychological resilience [36].

PATHWAYS LINKING PSYCHOLOGICAL STRESSORS TO HYPERTENSION

Though several studies in the past 4 decades have shown an association between psychosocial stress with hypertension, the underlying mechanisms are still a matter of debate. This

paper presents a theoretical model that explains the stress-hypertension association based on the 3 widely accepted theories of the stress response. These include cardiovascular reactivity to stress, activation of the psycho-neuroendocrine and immune systems, and a predisposition to high-risk behavioral characteristics (e.g., poor diet, lack of exercise, smoking, and alcohol abuse, among others).

The physiological and psychological response to an acute stressor is adaptive, but repeated or prolonged exposure to a stressor in predisposed individuals produces an inadequate stress response that does not match the demands. This becomes maladaptive and causes more damage than protection [37]. Cardiac over-reactivity is an example of a maladaptive stress response to stressors and results in an acute increase in blood pressure after exposure to the stressor and a prolonged recovery time to return to the baseline blood pressure after exposure to the stressor is over.

Repeated acute or chronic stress also activates the endocrine and immune systems, resulting in endothelial damage, vascular inflammation, and hypertension. At the center of mechanisms involved in the pathogenesis of stress-associated hypertension are the overactivation of the sympathetic nervous system and the hypothalamic-pituitary-adrenocortical axis, which in turn influence several physiological processes involved in blood pressure regulation [38]. In individuals with physiological and psychological predispositions, psychosocial stressor-induced episodes of blood pressure cause and exacerbate structural changes in the heart and blood vessels that produce inflammation and sustained vasoconstriction, leading to increased blood pressure and hypertension. This paper presents a model explaining the physiological mechanisms most likely involved in the development of hypertension.

Psycho-neuroendocrine and Immune Mechanisms Underlying Stress-induced Hypertension

Chronic exposure or repeated acute exposure to psychosocial stressors causes hyperactivation of the sympathetic nervous system and subsequently increased levels of catecholamines, resulting in renal, splanchnic, and cutaneous vasoconstriction. Decreased organ perfusion due to widespread vasoconstriction activates the renin-angiotensin-aldosterone system in the kidneys [39], and elevated catecholamine levels cause endothelial dysfunction [39], leading to blood pressure increase and hypertension. In addition, stress-induced depression in the baroreceptor reflex response results in "adjusting"

blood pressure to a higher level [38], which also contributes to hypertension [40] and raises the risk for premature coronary atherosclerosis.

Activation of the renin-angiotensin-aldosterone system results in vasoconstriction and sodium retention due to elevated levels of angiotensin-II (Ang II) and aldosterone [41]. Both aldosterone and Ang II potentiate the effect of catecholamines on blood vessels by increasing the expression of norepinephrine and inhibiting the uptake of norepinephrine from nerve endings [42].

Stress results in endothelial inflammation and damage. Stress-induced repeated episodes of acute sympathetic stimulation cause sharp increases in blood pressure, which may damage the vascular endothelium and impair the release of nitric oxide (NO), which under normal conditions causes vasodilatation and counteracts the effects of vasoconstrictors such as Ang II and endothelin-1 [43]. Acute elevations in blood pressure are also associated with increased activation of circulating T cells that infiltrate blood vessels. These cells release pro-inflammatory cytokines that promote vasoconstriction and sodium retention, leading to hypertension [44]. Stress-induced increased Ang II levels cause increased production of endothelin-1 and reactive oxygen species (ROS), causing vasoconstriction, endothelial dysfunction, and upregulation of transcription factors (such as nuclear factor κB), promoting vascular inflammation and hypertension. In addition, the ROS generated after stress reduce NO production and bioavailability [45]. It has been suggested that elevated levels of circulating Ang II also contribute to increased glucocorticoids in the circulation by stimulating the physiologically active central angiotensin-1 receptors. These receptors play a role in the formation and release of glucocorticoids, aldosterone, and catecholamines [46], all of which are involved in the pathogenesis of hypertension and mediate other cardiovascular effects [38].

Stress-induced activation of the hypothalamic-pituitary-adrenal axis increases glucocorticoid and aldosterone levels [40]. Aldosterone increases sodium and water retention and inhibits norepinephrine reuptake [47], thus supporting the peripheral effects of catecholamines [38], including vasoconstriction and endothelial dysfunction, by triggering the secretion of endothelial endothelin-1, cytokines, and the production of ROS [48], leading to vascular damage and increased blood pressure. It is worth noting that stress also predisposes individuals to unhealthy behaviors such as smoking, alcohol consumption, lack of exercise, unhealthy diet, and noncompliance to

medication, which may also lead to endothelial damage by activating neuro-immune/endocrine mechanisms.

Modifying the Stress-hypertension Association

In the past 2 years, the world has been going through a pandemic; the resulting economic shutdown and social interaction restrictions were implemented for months, raising many health concerns, including increases in anxiety and depression, social isolation, and loss of income. These have the potential to promote the development or progression of hypertension. Although completely removing psychosocial stressors from an individual's life may not be practically possible, physicians can nonetheless recommend evidence-based strategies to help vulnerable patients cope with the stressors. Published studies provide robust evidence of the efficacy of behavioral stress reduction modalities, such as transcendental meditation, mindfulness-based stress reduction, progressive muscle relaxation, biofeedback, yoga, and exercise in reducing stress and related CVD, especially hypertension [49].

CONCLUSION

A chronic stressful environment at work or in marriage, low SES, lack of social support, depression, anxiety, post-traumatic stress, childhood psychological trauma, and racial discrimination are psychosocial risk factors that have significant evidence for their role in hypertension. Evidence shows that stress causes dysregulation of the sympathetic nervous system, the hypothalamic-pituitary-adrenal axis, and the immune system through repeated acute reactivity or chronic overactivity, thus resulting in vascular damage, vasoconstriction, and hypertension. Since hypertension is the most important modifiable risk factor for cardiovascular mortality, it is pertinent to address psychosocial risk factors to control or prevent hypertension and cardiovascular mortality. This review has summarized the psychosocial stressors responsible for causing hypertension with the anticipation that researchers and clinicians would consider approaches to modify these risk factors to improve the management and prevention of hypertension and thus cardiovascular morbidity and mortality.

Ethics Statement

This study is exempt from institutional review board approval as it is a review of previously conducted studies.

CONFLICT OF INTEREST

The author has no conflicts of interest associated with the material presented in this paper.

FUNDING

None.

ACKNOWLEDGEMENTS

None.

AUTHOR CONTRIBUTIONS

All work was done by KM.

ORCID

Komal Marwaha   *https://orcid.org/0000-0002-8131-3898*

REFERENCES

1. World Health Organization. The atlas of heart disease and stroke. Part two: risk factors; 2019 [cited 2021 May 1]. Available from: https://www.who.int/news-room/fact-sheets/detail/hypertension.

2. Writing Group Members, Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation 2016;133(4):e38-e360.

3. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation 2019;139(10):e56-e528.

4. Sanz J, García-Vera MP, Espinosa R, Fortún M, Magán I, Segura J. Psychological factors associated with poor hypertension control: differences in personality and stress between patients with controlled and uncontrolled hypertension. Psychol Rep 2010;107(3):923-938.

5. George ES, Davidson I, El Masri A, Meade T, Kolt GS. Unhealthy lifestyle behaviours and psychological distress: a longitudinal study of Australian adults aged 45 years and older. Int J Environ Res Public Health 2022;19(7):4399.

6. Roohafza H, Kabir A, Sadeghi M, Shokouh P, Ahmadzad-Asl M,

Khadem-Maboudi AA, et al. Stress as a risk factor for noncompliance with treatment regimens in patients with diabetes and hypertension. ARYA Atheroscler 2016;12(4):166-171.

7. World Health Organization. Mental health: facing the challenges, building solutions: report from the WHO European Ministerial Conference; 2005 [cited 2021 May 1]. Available from: http://apps.who.int/iris/handle/10665/326566.

8. Eurofound, European Agency for Safety and Health at Work (EU-OSHA). Psychosocial risks in Europe: prevalence and strategies for prevention; 2014 [cited 2021 May 1]. Available from: http://irep.ntu.ac.uk/id/eprint/31136/1/PubSub8692_Hassard.pdf.

9. Smith PM, Mustard CA, Lu H, Glazier RH. Comparing the risk associated with psychosocial work conditions and health behaviours on incident hypertension over a nine-year period in Ontario, Canada. Can J Public Health 2013;104(1):e82-e86.

10. Landsbergis PA, Janevic T, Rothenberg L, Adamu MT, Johnson S, Mirer FE. Disability rates for cardiovascular and psychological disorders among autoworkers by job category, facility type, and facility overtime hours. Am J Ind Med 2013;56(7): 755-764.

11. Trudel X, Brisson C, Milot A, Masse B, Vézina M. Adverse psychosocial work factors, blood pressure and hypertension incidence: repeated exposure in a 5-year prospective cohort study. J Epidemiol Community Health 2016;70(4):402-408.

12. Modrek S, Cullen MR. Health consequences of the 'Great Recession' on the employed: evidence from an industrial cohort in aluminum manufacturing. Soc Sci Med 2013;92:105-113.

13. Yang YC, Li T, Ji Y. Impact of social integration on metabolic functions: evidence from a nationally representative longitudinal study of US older adults. BMC Public Health 2013;13:1210.

14. Hawkley LC, Masi CM, Berry JD, Cacioppo JT. Loneliness is a unique predictor of age-related differences in systolic blood pressure. Psychol Aging 2006;21(1):152-164.

15. Steptoe A, Owen N, Kunz-Ebrecht SR, Brydon L. Loneliness and neuroendocrine, cardiovascular, and inflammatory stress responses in middle-aged men and women. Psychoneuroendocrinology 2004;29(5):593-611.

16. Holt-Lunstad J, Birmingham W, Jones BQ. Is there something unique about marriage? The relative impact of marital status, relationship quality, and network social support on ambulatory blood pressure and mental health. Ann Behav Med 2008; 35(2):239-244.

17. Bankir L, Bochud M, Maillard M, Bovet P, Gabriel A, Burnier M. Nighttime blood pressure and nocturnal dipping are associated with daytime urinary sodium excretion in African subjects. Hypertension 2008;51(4):891-898.

18. Davis SK, Liu Y, Quarells RC, Din-Dzietharn R; Metro Atlanta Heart Disease Study Group. Stress-related racial discrimination and hypertension likelihood in a population-based sample of African Americans: the Metro Atlanta Heart Disease Study. Ethn Dis 2005;15(4):585-593.

19. Pérez DJ, Fortuna L, Alegria M. Prevalence and correlates of everyday discrimination among U.S. Latinos. J Community Psychol 2008;36(4):421-433.

20. Brondolo E, Hausmann LR, Jhalani J, Pencille M, Atencio-Bacayon J, Kumar A, et al. Dimensions of perceived racism and self-reported health: examination of racial/ethnic differences and potential mediators. Ann Behav Med 2011;42(1):14-28.

21. Sims M, Diez-Roux AV, Dudley A, Gebreab S, Wyatt SB, Bruce MA, et al. Perceived discrimination and hypertension among African Americans in the Jackson Heart Study. Am J Public Health 2012;102(Suppl 2):S258-S265.

22. Beatty Moody DL, Waldstein SR, Tobin JN, Cassells A, Schwartz JC, Brondolo E. Lifetime racial/ethnic discrimination and ambulatory blood pressure: the moderating effect of age. Health Psychol 2016;35(4):333-342.

23. Carnethon MR, Pu J, Howard G, Albert MA, Anderson CA, Bertoni AG, et al. Cardiovascular health in African Americans: a scientific statement from the American Heart Association. Circulation 2017;136(21):e393-e423.

24. Leng B, Jin Y, Li G, Chen L, Jin N. Socioeconomic status and hypertension: a meta-analysis. J Hypertens 2015;33(2):221-229.

25. Conen D, Glynn RJ, Ridker PM, Buring JE, Albert MA. Socioeconomic status, blood pressure progression, and incident hypertension in a prospective cohort of female health professionals. Eur Heart J 2009;30(11):1378-1384.

26. Matthews KA, Kiefe CI, Lewis CE, Liu K, Sidney S, Yunis C, et al. Socioeconomic trajectories and incident hypertension in a biracial cohort of young adults. Hypertension 2002;39(3):772-776.

27. Spruill TM, Gerin W, Ogedegbe G, Burg M, Schwartz JE, Pickering TG. Socioeconomic and psychosocial factors mediate race differences in nocturnal blood pressure dipping. Am J Hypertens 2009;22(6):637-642.

28. Steptoe A, Marmot M. Psychosocial, hemostatic, and inflammatory correlates of delayed poststress blood pressure recovery. Psychosom Med 2006;68(4):531-537.

29. Spruill TM. Chronic psychosocial stress and hypertension. Curr Hypertens Rep 2010;12(1):10-16.

30. Hammen C. Stress and depression. Annu Rev Clin Psychol 2005; 1:293-319.

31. Meng L, Chen D, Yang Y, Zheng Y, Hui R. Depression increases the risk of hypertension incidence: a meta-analysis of prospective cohort studies. J Hypertens 2012;30(5):842-851.

32. Davidson K, Jonas BS, Dixon KE, Markovitz JH. Do depression symptoms predict early hypertension incidence in young adults in the CARDIA study? Coronary Artery Risk Development in Young Adults. Arch Intern Med 2000;160(10):1495-1500.

33. Pan Y, Cai W, Cheng Q, Dong W, An T, Yan J. Association between anxiety and hypertension: a systematic review and meta-analysis of epidemiological studies. Neuropsychiatr Dis Treat 2015;11:1121-1130.

34. Player MS, Peterson LE. Anxiety disorders, hypertension, and cardiovascular risk: a review. Int J Psychiatry Med 2011;41(4): 365-377.

35. Stein DJ, Scott K, Haro Abad JM, Aguilar-Gaxiola S, Alonso J, Angermeyer M, et al. Early childhood adversity and later hypertension: data from the World Mental Health Survey. Ann Clin Psychiatry 2010;22(1):19-28.

36. Dhabhar FS. Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology. Neuroimmunomodulation 2009;16(5): 300-317.

37. McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 2007;87(3):873-904.

38. Ayada C, Toru Ü, Korkut Y. The relationship of stress and blood pressure effectors. Hippokratia 2015;19(2):99-108.

39. Zhang DY, Anderson AS. The sympathetic nervous system and heart failure. Cardiol Clin 2014;32(1):33-45.

40. Golbidi S, Frisbee JC, Laher I. Chronic stress impacts the cardiovascular system: animal models and clinical outcomes. Am J Physiol Heart Circ Physiol 2015;308(12):H1476-H1498.

41. Givertz MM. Manipulation of the renin-angiotensin system. Circulation 2001;104(5):E14-E18.

42. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. J Am Coll Cardiol 2009;54(19):1747-1762.

43. Toda N, Nakanishi-Toda M. How mental stress affects endothelial function. Pflugers Arch 2011;462(6):779-794.

44. Crowley SD, Song YS, Lin EE, Griffiths R, Kim HS, Ruiz P. Lymphocyte responses exacerbate angiotensin II-dependent hypertension. Am J Physiol Regul Integr Comp Physiol 2010; 298(4):R1089-R1097.

45. Neves VJ, Moura MJ, Almeida BS, Costa R, Sanches A, Ferreira R, et al. Chronic stress, but not hypercaloric diet, impairs vascular function in rats. Stress 2012;15(2):138-148.

46. Yang G, Wan Y, Zhu Y. Angiotensin II--an important stress hormone. Biol Signals 1996;5(1):1-8.

47. Adams KF Jr. Pathophysiologic role of the renin-angiotensin-aldosterone and sympathetic nervous systems in heart failure. Am J Health Syst Pharm 2004;61 Suppl 2:S4-S13.

48. Goodwin JE, Geller DS. Glucocorticoid-induced hypertension. Pediatr Nephrol 2012;27(7):1059-1066.

49. Rainforth MV, Schneider RH, Nidich SI, Gaylord-King C, Salerno JW, Anderson JW. Stress reduction programs in patients with elevated blood pressure: a systematic review and meta-analysis. Curr Hypertens Rep 2007;9(6):520-528.