INTERACTIONS OF STRESS, BREATING, AND SALT INTAKE IN BLOOD PRESSURE REGULATION

INTERAÇÃO ENTRE ESTRESS, RESPIRAÇÃO E CONSUMO DE SAL NA DETERMINAÇÃO DA PRESSÃO ARTERIAL

David E. ANDERSON
National Institute on Aging
National Institutes of Health

RESUMO

ANDERSON, D. E. Interactions of stress, Breathing, and salt intake in blood pressure regulation. **Estudos de Psicologia, 9(2)**: 54-79,1992

Este artigo faz uma revisão da evidência científica quanto à possibilidade de que o desenvolvimento da hipertensão arterial possa ser potencializado pelas interações sinergéticas entre eventos estressantes e dietas com alto nível de sódio. Uma visão popular quanto à contribuição do stress para a etiologia da hipertensão arterial focaliza o papel da excitação do sistema nervoso simpático (isto é, das reações de "defesa"). No entanto, estudos recentes com animais e com seres humanos indicam que outros mecanismos fisiológicos, que

estão envolvidos no manejo do sódio, também são de importância. Por exemplo, hipertensão experimental pode ser produzida, no laboratório, em cães que tenham recebido altas doses de sódio e que mostrem inibição respiratória entre sessões experimentais de esquiva, apresentadas de modo intermitente. Não é possível evitar tal hipertensão através do bloqueio adrenérgico. É possível que ela envolva mudanças no equilíbrio ácido-base as quais poderiam aumentar o nível total de sódio no corpo. Pesquisas se tornam necessárias para definir a gama de fatores comportamentais que possam influenciar a homeostase do sódio e a distribuição de sódio entre os compartimentos intra e extra celulares. Tais estudos poderiam elucidar o papel do stress no desenvolvimento da hipertensão arterial, e possibilitar intervenções não-farmacológicas mais eficazes no tratamento da hipertensão em seres humanos.

Interactions of Stress, Breathing, and Salt Intake in Blood Pressure Regulation

Primary hypertension is characterized by a sustained elevation in resting blood pressure. Although cardiac output of individuals with early hypertension may be increased, the essence of hypertension is an elevated resistance to blood flow due to thickening of the arterial wall (Folkow, 1982). Its origins have long remained a mystery, but intensive investigation over many years has led to the conclusion that environmental, as well as genetic, factors may be important to its etiology. The epidemiological literature has established significant correlations between high blood pressure and such environmental factors such as lifestyle and diet. However, experimental studies are required to prove cause and effect relationships, and clarify the mediating physiological mechanisms.

The present discussion begins with selected epidemiological studies which illustrate that lifestyle and

diet are both implicated in the development of hypertension. Then, research with laboratory animals is reviewed which supports the view that hypertension can develop as the result of interactions between these two factors. Specifically, it is suggested that environments which condition sustained respiratory depression may produce changes in blood chemistry which can activate cellular mechanisms to increase vasoconstriction and circulating plasma volume in response to high sodium intake. Thus, it will be suggested, not only may hypertension be environmental in origin, but sodium sensitivity may be a variable amenable to behavior modification, rather than a stable and invariant trait.

Sodium sensitivity and hypertension

That industrialized societies have an increased prevalence of hypertension has been known for decades (Henry & Cassel, 1969). Numerous studies have shown that the prevalence of hypertension is higher in cultures with a high sodium intake, and lower in those with a low sodium intake (MacGregor, 1985). However, demonstration that high sodium intake within a society is associated with an increased risk of hypertension has been much more difficult to document, and it is generally agreed that humans (and most genetically normotensive infrahuman species) do not develop hypertension in response to a high sodium diet (Sullivan & Ratts, 1983). Thus, the current consensus is that high sodium intake is a contributing, but not sufficient, cause of hypertension (Guyton, 1977). Dietary potassium has also been found to influence blood pressure (Parfrey et al., 1981), and a more accurate statement would be that the sodium/potassium ratio, rather than sodium, per se, is a critical dietary variable. In addition, considerable interest in an antihypertensive role of dietary calcium also exists (McCarron, 1975), even though, paradoxically, intracellular calcium increases vascular smooth muscle tone.

Because a small proportion of normotensive and a somewhat higher proportion of hypertensive individuals have been observed to respond to a high sodium diet with an increase in resting blood pressure (Mark et al., 1975), it is sometimes asserted that "sodium sensitivity" is an inherited trait, with some individuals having the required genes and others not. Thus, an interaction between genetic susceptibility and high sodium intake has been postulated as a cause of chronic hypertension. However, recent studies have shown clearly that the distribution of magnitudes of blood pressure to high sodium intake is not bimodal, but more nearly linear, in the sense that individuals within the group can show no, a little or much blood pressure increase during salt loading (Sharma, Kribben, Schattenfroh, Cetto, & Distler, 1990). In addition, the magnitude of individual sodium sensitivity may vary from one occasion to another (Weinberger & Fineberg, 1991).

Research with laboratory animals has shown that the effects of high sodium intake on blood pressure depend on concurrent endocrine factors. For example, administration of a synthetic hormone, deoxycorticosterone acetate (DOCA), to animals on a high sodium intake elevates blood pressure within days (Conway & Hatton, 1978). This form of experimental hypertension does not develop in animals who receive only the steroid or only the sodium loading, so that the hypertension is the product of a synergistic interaction between the two. DOCA-salt hypertension does not necessarily involve retention of fluid or increase in cardiac output, but may be mediated by an effect of the steroid on the permeability of the cell membrane to sodium, resulting in an increase in intracellular sodium levels in sodium-loaded animals (Onoyama, Bravo, & Tarazi, 1979). By processes which are as yet incompletely understood, increasing sodium in vascular smooth muscle cells increases vasoconstriction and blood pressure (Friedman, McIndoe, & Miyoshi, 1990). The changes in vascular function precede the increase in

blood pressure by several days (Berecek & Borh, 1978) and if the treatment is sustained, the hypertension becomes chronic (Morton, Kenyon, & Beattie, 1990). The DOCA-salt model of hypertension is instructive because it shows that a genetic predisposition is not required for the development of chronic hypertension.

Behavioral stress and hypertension

A separate epidemiological literature supports the view that the prevalence of hypertension is related to nondietary, life style factors, such as occupation. It has long been known that the prevalence of hypertension in bus drivers is higher than that of control groups (Morrison & Morris, 1959; Winkleby, Ragland, & Syme, 1988). Other studies have shown that the prevalence of hypertension in air traffic controllers is four times as great (Cobb & Rose, 1973), and in policemen, three times as great (Ely, 1985), as matched control groups. A recent study from Brazil reported that the prevalence of hypertension in factory workers was significantly greater than that of their supervisors (Costa et al., 1990). Similarly, the incidence of hypertension in men who had enlisted in the United States Navy was significantly greater than the prevalence of hypertension in Navy officers (Nice & Trent, 1979).

In addition to cross sectional studies, longitudinal studies have shown that the subsequent development of hypertension was predicted by a knowledge of early environmental circumstances and habitual behaviors. For example, medical students who reported decreases in activity level during periods of stress were far more likely to develop hypertension subsequently than other medical students who became more active under the same conditions (Thomas & Greenstreet, 1973). More recently, it has been found that nuns who lived a secluded existence for 20 years were far less likely to develop hypertension than controls, matched for diet and other factors (Timio et al., 1988). At least part of the

differences in the prevalence of hypertension observed between black and white Americans may reflect the effects of social influences (Anderson, 1989). For example, within the black population, the perceived disparity between life style (i.e. material possessions) and social class was a predictor of blood pressure levels (Dressler, 1990). Thus, a substantial body of evidence suggests that nondietary, behavioral factors may play a role in the development of at least some forms of human hypertension. Studies with animals have shown that genetic hypertension can be exacerbated by exposure to aversive stimuli (Folkow, 1987). Reviews of the experimental literature typically conclude, however, that aversive stimulation is, by itself, not sufficient to produce chronic hypertension in genetically normotensive animals (Anderson, 1987; Friedman, 1981; Lawler & Cox, 1985).

Behavioral Conditioning of sodium hypertension

In recent years, attention has focused on the possibility that the effects of high sodium intake and behavioral stress may be interactive. A series of studies with chronically instrumented laboratory dogs showed that an experimental hypertension, sustained 24 hours per day, could be produced over a period of days and weeks by concomitant exposure to avoidance conditioning schedules and high sodium intake (Anderson, 1986; Anderson, Kearns, & Better, 1983; Anderson, Dietz, & Murphy, 1987; Anderson, Kearns, & Worden, 1983). The avoidance schedule involved three, daily, 30 minute sessions of free operant avoidance behavior, with each session scheduled eight hours after the previous one. This schedule produces a cyclic cardiovascular pattern, characterized by elevations in heart rate, cardiac output and arterial pressure during each session, and a fall in blood pressure immediately following the session, followed by a gradual rise in blood pressure together with a fall in heart rate, during the hours between sessions. Previous research had

shown that the pre-avoidance blood pressure elevation was mediated by an increase in total peripheral resistance but not in cardiac output (Anderson & Tosheff, 1973).

When sodium intake of dogs maintained on the avoidance schedule was normal, the mean, 24-hour blood pressure level remained constant over days. However, when sodium intake was increased to the upper end of the human dietary range of sodium intake by constant infusion of isotonic saline, the mean 24-hour blood pressure increased progressively over days (Anderson, Kearns, & Better, 1983). Figure 1 shows this adaptation for a group of eight dogs whose heart rate, creatinine clearance, sodium balance, water intake and urine output were also measured (Anderson, Dietz, & Murphy, 1987). Mean 24-hour heart rate did not increase during the development of hypertension, but typically decreased, as did creatinine clearance. Sodium was retained for a day or two (before the increase in pressure had become substantial) and the higher level of sodium was then stably maintained for the next 10 days. Water intake during the development of hypertension was constant because saline infusion rate during the experimental period exceeded normal ad lib. water consumed. Water intake typically exceeds urine output because some water is lost in expired air. After the first few days on the schedule, the difference between water intake and output was decreased, showing the effects of breathing suppression, pressure diuresis, or some combination of these two. The hypertension was sustained as long as the experimental procedures remained in effect (up to 100 days).

The hypertension did not develop in response to saline infusion in dogs who had not been trained on the avoidance schedules. It could be reversed by either decreasing sodium intake or increasing potassium intake even though the avoidance schedules remained in effect (Anderson, Kearns, & Worden, 1983). Thus, the role of the behavioral conditioning procedures in producing the experimental hypertension involved effects on regulation of sodium and potassium ions.

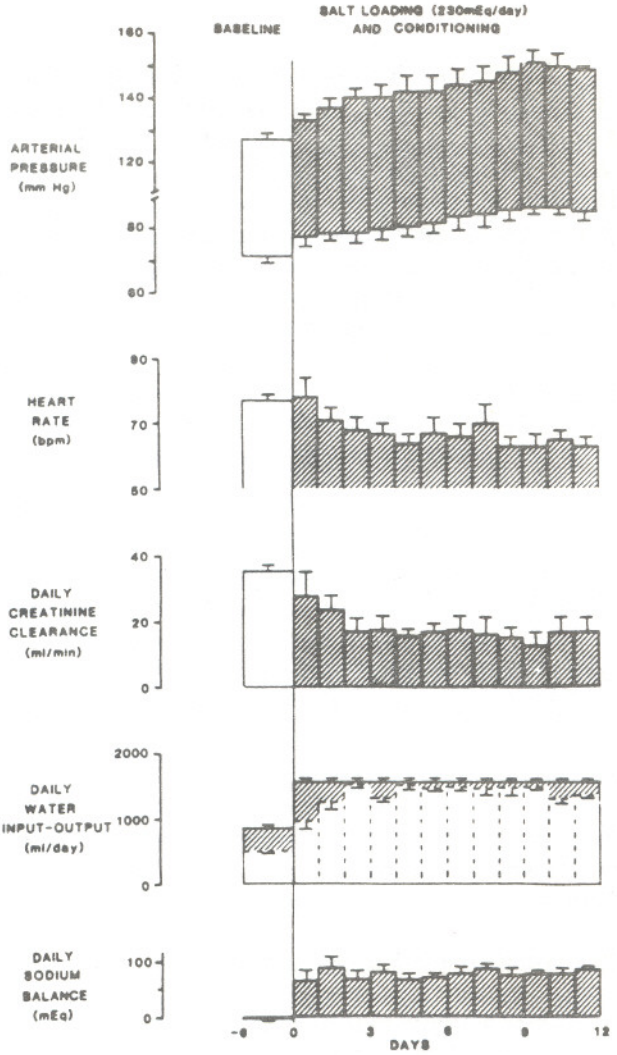

Figure 1. Twenty-four hour means of arterial pressure, heart rate, creatinine clearance, water intake and urinary output and sodium balance, averaged for eight dogs over six days of baseline monitoring, followed by 12 days of avoidance sessions and saline infusion.

Since the time of Cannon (Cannon, 1915), it has been hypothesized that aversive environmental conditions might contribute to the development of chronic hypertension via the sympathetic nervous system. Free operant avoidance conditioning is adequate to sustain sympathetic arousal during performance sessions. Avoidance performance has been associated with sympathetically-mediated effects on cardiac and renal functions which enhance plasma volume and cardiac output (Koepke, Light, Grignolo, & Obrist, 1983), and increases in activity of the renin-angiotensin-aldosterone (Blair, Feigl, & Smith, 1976; Mason, Jones, Ricketts, Brady, & Tolliver, 1968) axis, which further increase vasoconstriction and renal reabsorption of sodium and water.

However, the development of behavioral hypertension in sodium loaded dogs was not prevented by alpha or beta adrenergic blockade procedures or by bilateral renal denervation (Anderson, 1973).

Moreover, the hypertension was associated with a decrease in body weight, which would be consistent with a fall in circulating fluid volume. These facts suggest that sympathetic arousal during the avoidance sessions was not the principal factor in the sodium retention and development of 24-hour hypertension in sodium loaded dogs. Rather, physiological adaptations during the long intervals between avoidance sessions appear to have been of fundamental importance.

Cardiorespiratory inhibition and sodium regulation

Early studies in our laboratory showed not only that avoidance performance was associated with sympathetic arousal, but also that a pattern of progressive elevation in blood pressure mediated by increasing total peripheral resistance developed during baseline periods immediately preceding the onset of the avoidance task (Koepke et al., 1983). The vasoconstriction was accompanied by a decrease in heart rate and breathing frequency below levels

observed at rest. Unlike the cardiovascular pattern during avoidance sessions, however, administration of alpha and beta adrenergic blocking agents did not prevent the occurrence of the increases in blood pressure and decreases in heart rate during pre-avoidance periods (Anderson & Brady, 1976; Anderson, Yingling, & Brady, 1976). The pre-avoidance pattern could be observed to develop over long intervals (e. g. 15 hours) in animals who had learned to quietly await the onset of the avoidance task (Anderson & Brady, 1976). It was observed that 24-hour experimental hypertension in sodium-loaded dogs required not only an effective avoidance performance but also the repeated occurrence of this cardiorespiratory pattern between avoidance sessions. Apparently, sodium regulation is affected by some neuroendocrine concomitant of the **pre-avoidance** pattern.

Studies of adrenocortical activity in monkeys by Mason and Brady have shown that "anticipation" of a significant event (such as onset of an avoidance stimulus) is a particularly potent stimulus to secretion of cortisol and aldosterone (Mason, 1968; Mason & Brady, 1956). Thus, the adrenal cortex could be stimulated during pre-avoidance periods. Aldosterone levels are chiefly regulated by the renin-angiotensin system, but also by adrenocorticotrophic hormone (ACTH) from the pituitary, and by potassium (Williams & Dluhy, 1983). High sodium intake suppresses renin release, and stress-salt hypertensive dogs had very low levels of plasma renin activity (Anderson, Gomez-Sanchez, & Dietz, 1986). Aldosterone levels of stress-salt hypertensive dogs were also decreased, relative to normotensive baselines, but less so than renin (Anderson, Gomez-Sanchez, & Dietz, 1986). Thus, pre-avoidance periods may have been associated with increases in ACTH. ACTH is the principal stimulator of adrenal glucocorticoids which increase cell membrane permeability, and hence, influx of sodium (Kornel, Rafelson, Hyashi, Kanamarla-pudi, & Anderson, 1988).

Also of interest are the possible effects of respiratory depression on vascular functions. When ventilatory activity

decreases below metabolic activity, partial pressure of carbon dioxide in the circulatory system increases. Carbon dioxide diffuses freely into the cells. The increased carbon dioxide combines with water to form carbonic acid, which increases extracellular and intracellular pH, following partial dissociation of the hydrogen and bicarbonate ions (i. e. respiratory acidosis). Elevations in intracellular hydrogen stimulate molecules on the cell membrane to extrude them from the cell in exchange for sodium ions (Aalkjaer, 1990). Figure 2 shows a schematic diagram of this exchanger molecule. This process also occurs in epithelial cells in the kidney, resulting in increased reabsorption of sodium and water from the filtrate, to increase plasma volume. These processes are, of course, self limiting, and require continuing depression of respiration to maintain over time.

Maintenance of intracellular sodium homeostasis is normally accomplished by sodium-potassium-ATPase molecules on cell membranes (the sodium pump), which extrude sodium ions in exchange for potassium ions. Figure 2 also shows a schematic diagram of this molecule. However, activity of the sodium pump can be inhibited during expansion of plasma volume by increase in circulating levels of endogenous ouabain and digitalis-like factors, which attach to the potassium site on the molecule (Hamlyn et al., 1989). Significantly, increased concentrations of these sodium pump inhibitors are observed in hypertensive humans and laboratory animals (Haddy, 1987). Expansion of plasma volume by sodium-hydrogen exchange in the kidneys could increase circulating concentrations of sodium pump inhibitors and contribute to increased sodium in vascular smooth muscle cells in subjects during sustained respiratory depression. Finally, Figure 2 also shows a molecule that exchanges sodium ions for calcium ions (Blaustein, 1977). Increases in cell sodium engender increases in cell calcium levels via this mechanism, and contribute to increased vasoconstriction thereby. In addition, neuronal cell membranes also contain these exchanger molecules, so that, theoretically, at least, adrenergic transmission could be increased by respiratory depression and consequent increases in neuronal ions.

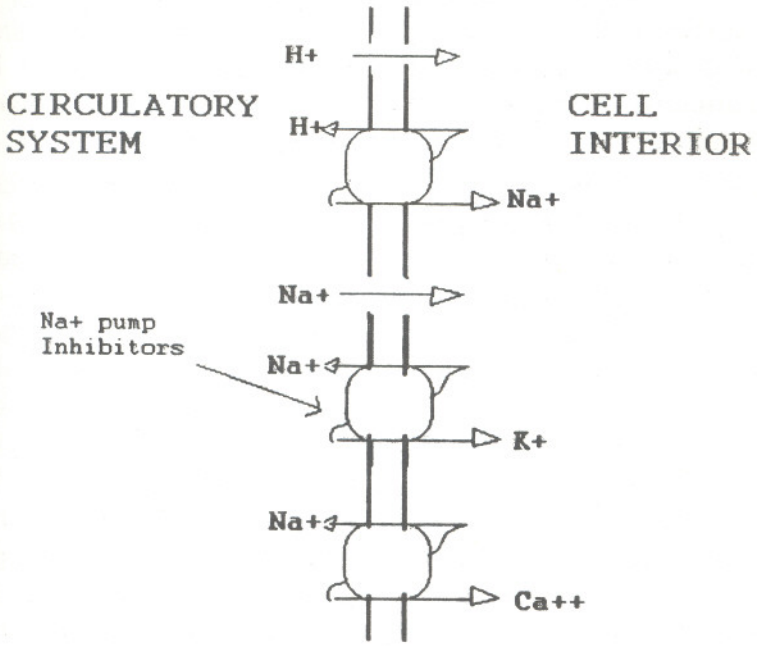

Figure 2. Mechanisms of intracellular ion homeostasis. Hydrogen (H+), sodium (Na+) and calcium (Ca++) leak in to the cell. Exchanger mechanisms extrude them for Na+, K+ and Na+ ions, respectively. Sodium pump inhibitors block Na+-K+ exchange.

Hypercapnic breathing and blood pressure

Recent studies have shown that episodes of a breathing pattern characterized by frequencies below resting levels and a normal tidal volume can be observed in normotensive ambulatory humans in the natural environment (Anderson, Coyle, & Haythornthwaite, in press). This breathing pattern is similar to that which occurs in dogs during pre-avoidance periods. Human inhibitory breathing is also accompanied by increased levels of systolic and mean blood pressure, with no consistent changes in heart rate (Anderson, Austin, & Haythornthwaite, in press). It has also been found that inhibitory breathing episodes are more likely to occur when subjects are at work than when they are at home, and more likely to occur in the presence of other people than when they are alone (Haythornthwaite, Moore, & Anderson, in press). The effects may be due to the content of verbal interactions, but not to the mechanics of speaking. Speaking increases the variability of breathing frequency, but does not decrease frequency to the extent observed in these studies.

Low frequency/normal tidal volume breathing is energetically inefficient, consuming more calories than the same level of ventilation maintained by a higher frequency and lower tidal volume (Otis, 1964). During nighttime sleep, a reduced level of ventilation is maintained by a comparable decrease in tidal volume, while breathing frequency is not significantly different from that observed in awake, resting individuals (Stradling, Chadwick, & Frew, 1985). Thus, inhibitory breathing must serve a behavioral function, such as increasing vigilance to the environment. Consistent with this concept is the observation that breath holding is associated

with an increase in blood flow to the brain and a decrease in blood flow to the skeletal muscle (Mithoefer, 1965).

The physiological effects of low frequency/normal tidal volume breathing are being investigated in normotensive humans in our laboratory. The basic procedure involves training the individual to maintain end-tidal carbon dioxide levels near the upper end of the normal range by maintaining a low frequency/normal tidal volume pattern, via a feedback display on a respiratory gas monitor. Subjects have learned to maintain this pattern comfortably over extended time periods (e. g. 30-60 minutes). Compared with normal breathing which maintains end tidal carbon dioxide in midrange, mild hypercapnic breathing is associated with higher systolic and diastolic arterial, and central venous pressure, which are mediated by an increased total peripheral resistance (Anderson, Somers, Clary, Sinkey, & Anderson, in press). Heart rate is slightly decreased, and stroke volume increased, so that cardiac output changes very little. The response is not due to small decreases in arterial oxygen saturation which develop under these conditions, because increasing oxygen content of the inspired air during task performance (which prevents the hypoxia) does not prevent the rise in blood pressure. Increases in blood pressure and decreases in heart rate have been reported previously during acute breath holding (Mithoefer, 1965). This study shows that the hemodynamic pattern can be sustained over time. There is no evidence to date that it is associated with any changes in emotional state.

Mild hypercapnic breathing is accompanied by no changes in sympathetic nerve activity in skeletal muscle in the leg (Anderson, Somers, Clary, Sinkey, & Anderson, in press). Although the role of sympathetic activity in other regions in the increase in total peripheral resistance has not yet been determined, the possibility that changes in acid-base balance might be involved in increasing vascular tone need to be evaluated because of the mechanisms described above. Preliminary data from an ongoing study in our laboratory show that, in fact, extracellular pH consistently decreases during mild hypercapnic breathing, compared with levels before and following task performance. Figure 3 shows changes in mean pressure, heart rate and blood pH for six subjects during successive 5-minute intervals of a 35 minute monitoring session, including a 15 minute period of hypercapnic breathing and 10 minute rest periods preceding and following. Whether these changes mediate the blood pressure increases is not known, but changes in blood pH of this magnitude have been associated with differences in blood pressure sensitivity to high dietary sodium intake in another study of normotensive humans (Sharma et al., 1990). Thus, breathing patterns during specific kinds of stress may impact on vascular function, increasing sensitivity to high sodium intake.

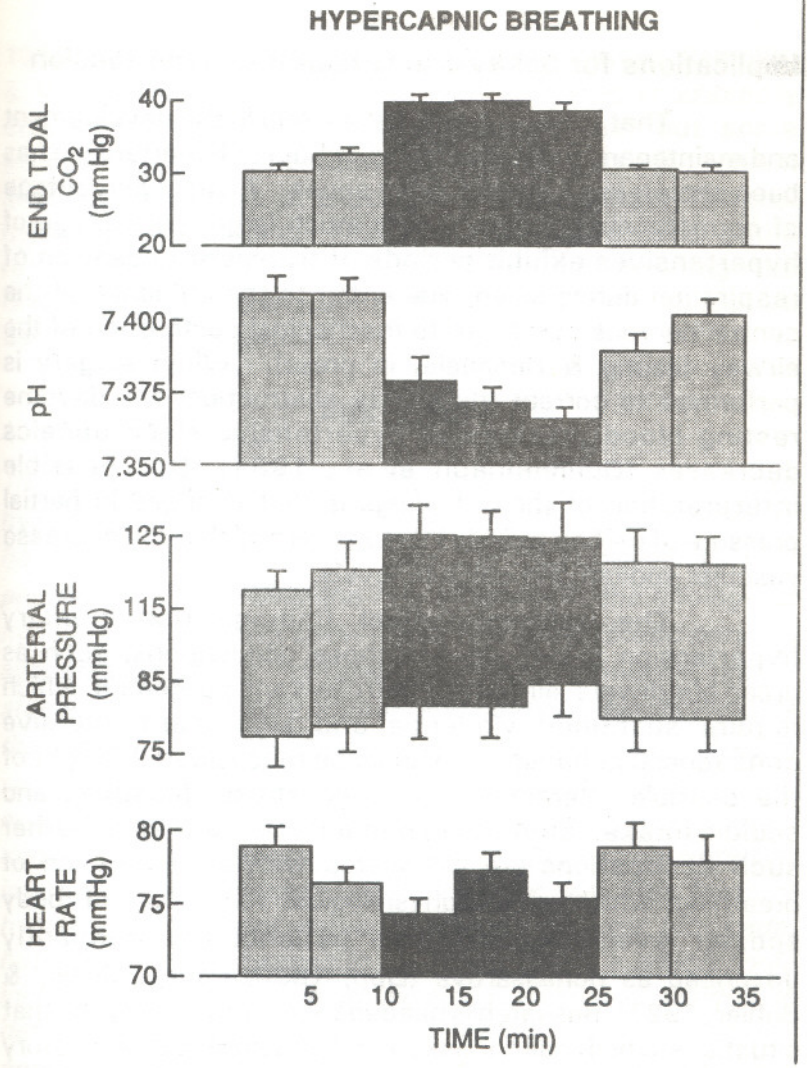

Figure 3. End tidal CO_2, ph, arterial pressure and heart rate over successive 5-min intervals of a 10 min baseline interval, a 15 min session of mild hypercapnic breathing and a 10 min post-performance recovery interval, averaged for six human subjects.

Implications for behavioral research in hypertension

That breathing may have a role in the development and maintenance of some forms of human hypertension has been shown in studies of sleep apnea. A small percentage of normotensive humans and a much larger percentage of hypertensives exhibit periods of transient cessation of respiration during sleep, due either to the influence of the central nervous system or to mechanical obstruction of the airway (Jeong & Dimsdale, in press). When surgery is performed to correct the airway obstruction, the daytime resting blood pressure of hypertensive sleep apneics decreases (Guilleminault et al., 1981). One possible interpretation of these findings is that changes in partial pressure of carbon dioxide increase pH and thereby decrease vascular sodium and calcium levels.

The epidemiological findings that primary hypertension is prevalent in those occupations, such as urban bus drivers, air traffic controllers and policemen, which require sustained vigilance and significant aversive consequences for lapses, should be reconsidered in light of the possible interactions between stress, breathing and sodium intake. Studies are needed to determine whether such occupations are associated with a suppression of breathing which alters physiological regulation of body sodium levels. Hypertensive patients are frequently described as nonassertive (Lipp, 1990; Perini, Muller, & Buhler, 1991). Research is needed to test the hypothesis that situations which call for assertive behavior elicit respiratory depression in nonassertive individuals. Assertive training might be therapeutic for some hypertensive individuals if it affected sodium regulation via alterations in breathing habits. In fact, breathing exercises are frequently prescribed in nonpharmacological interventions in hypertension (Benson,

1983; Lipp, 1991; Richter-Heinrich, Enderlein, Knust, Schmidt, & Wiedemann, 1989). Human hypertension is undoubtedly diverse in its origins and manifestations, but some proportion of individuals may be at risk for increased sodium sensitivity by virtue of experiences that condition habitual hypercapnic breathing. Test of these hypotheses could result in significant advances in understanding the origins of hypertension and in developing effective behavioral interventions.

ABSTRACT

This article reviews evidence that the development of hypertension is potentiated by synergistic interactions between stressful environments and high sodium diets. A popular view regarding the role of stress in the etiology of hypertension focuses upon the role of sympathetic nervous system arousal (i. e. "defense" reactions). However, recent studies with laboratory animals and human subjects indicate that other physiological mechanisms which are involved in sodium regulation may also be important. For example, experimental hypertension can be produced in sodium-loaded dogs who show sustained breathing depression between intermittently presented avoidance sessions. This form of hypertension is not prevented by adrenergic blockade, but may involve changes in acid-base balance which could increase total body sodium levels. Research is needed to define the range of behavioral factors which influence sodium homeostasis and sodium distribution between extracellular and intracellular compartments. Such studies may elucidate the role of stress in the development of hypertension, and lead to more effective nonpharmacological interventions in human hypertension.

REFERENCES

AALKJAER, C. (1990). Regulation of intracellular pH and its role in vascular smooth muscle function. **Journal of Hypertension, 8,** 197-206.

ANDERSON, D. E. (1987). Experimental behavioral hypertension in laboratory animals. In S. Julius & D. R. Bassett (Eds.), **Handbook of hypertension: Behavioral factors in hypertension** (pp. 226-245). Amsterdam: Elsevier Science Publishers.

ANDERSON, D. E. (1986). Operant conditioning, sodium loading, and experimental hypertension. **Journal of Cardiovascular Pharmacology, 8** (Suppl. 5), S23-S30.

ANDERSON, D. E., Austin, J., & Haythornthwaite, J. A. (in press). Blood pressure during inhibitory breathing in the natural environment. **Psychophysiology.**

ANDERSON, D. E., & Brady, J. V. (1973). Prolonged pre-avoidance effects upon blood pressure and heart rate in the dog. **Psychosomatic Medicine, 35,** 4-11.

ANDERSON, D. E., & Brady, J. V. (1976). Cardiovascular responses to avoidance conditioning in the dog: Effects of beta adrenergic blockade. **Psychosomatic Medicine, 38,** 181-188.

ANDERSON, D. E., Coyle, K., & Haythornthwaite, J. A. (in press). Ambulatory monitoring of respiration: Inhibitory breathing in the natural environment. **Psychophysiology.**

ANDERSON, D. E., Dietz, J. R., & Murphy, P. A. (1985). Behavioural hypertension in sodium-loaded dogs is accompanied by sustained sodium retention. **Journal of Hypertension, 5,** 99-105.

ANDERSON, D. E., Gomez-Sanchez, C., & Dietz, J. R. (1986). Suppression of renin and aldosterone in stress-salt hypertension in the dog. **American Journal of Physiology, 251**, R181-R186.

ANDERSON, D. E., Kearns, W. D., & Better, W. E. (1983). Progressive hypertension in dogs by avoidance conditioning and saline infusion. **Hypertension, 5,** 286-291.

ANDERSON, D. E., Kearns, W. D., & Worden, T. J. (1983). Potassium attenuates avoidance-saline hypertension in the dog. **Hypertension, 5,** 414-419.

ANDERSON, D. E., Somers, V. K., Clary, M., Sinkey, C. A., & Anderson, E. A. (in press). Muscle sympathetic nerve and hemodynamic responses during hypoventilation induced hypercapnia in humans. **Neuroscience.**

ANDERSON, D. E., & Tosheff, J. G. (1973). Cardiac output and total peripheral resistance changes during pre-avoidance periods in the dog. **Journal of Applied Physiology, 35**, 650-654.

ANDERSON, D. E., Yingling, J. E., & Brady, J. V. (1976). Cardiovascular responses to avoidance conditioning: Effects of alpha adrenergic blockade. **Pavlovian Journal of Biological Science, 11**, 150-161.

ANDERSON, N. B. (1989). Racial differences in stress induced cardiovascular reactivity and hypertension: Current status and substantive issues. **Psychological Bulletin, 105,** 89-105.

BENSON, H. (1983). The relaxation response: Physiologic basis, history and clinical usefulness. In T. M. Dembroski, T. H. Schmidt, & G. Blumchen (Eds.), **Biobehavioral bases of coronary heart disease** (pp. 539-547). Basel: Karger.

BERECEK, K. H., & Bohr, D. F. (1978). Whole body reactivity during the development of deoxycorticosterone acetate hypertension. **Circulation Research, 42**,764-771.

BLAIR, M. F., Feigl, E. O., & Smith, O. A. (1976). Elevations of plasma renin activity during avoidance performances by baboons. **American Journal of Physiology, 231,** 772-776.

BLAUSTEIN, M. P. (1977). Sodium ions, calcium ions, blood pressure regulation and hypertension: A reassessment of a hypothesis. **American Journal of Physiology, 323,** C165-C173.

CANNON, W. B. (1915). **Bodily changes in pain. hunger, fear and rage.** New York: Appleton-Century Crofts.

COBB, S., & Rose, R. M. (1973). Hypertension, peptic ulcer and diabetes in air traffic controllers. **Journal of the American Medical Association, 224,** 489-492.

CONWAY, J., & Hatton, R. (1978). Development of deoxycorticosterone acetate hypertension in the dog. **Hypertension, 43** (Suppl. 1), 82-86.

COSTA, E. A., Rose, G. A., Klein, C. H., Leal, M. D., Szarcwald, C. L., Bassanesi, S. L., Acxhutti, A. C., & Fischman, A. (1990). Salt and blood pressure in Rio Grande do Sul, Brazil. **Bulletin of PAHO, 24**(2), 159-176.

DRESSLER, W. W. (1990). Lifestyle, stress and blood pressure in a southern black community. **Psychosomatic Medicine, 52,** 182-198.

Ely, D. L. (1985). Behavioural and neuroendocrine aspects of stress in mice and humans. Satryck ur Stress i det kardiovasckulara perspekitvet. **Hassle Lakemedel, AB,** 50-70.

FOLKOW, B. (1982). Physiological aspects of primary hypertension. **Physiological Reviews, 62**(2), 347-504.

FRIEDMAN, R. (1990). Experimental psychogenic hypertension. In D. Wheatley (Ed.), **Stress and the heart** (pp. 209-228). New York: Raven Press.

FRIEDMAN, S., & McIndoe, R. A. Miyoshi T. (1990). The relation of blood sodium concentration to blood pressure in the rat. **Journal of Hypertension, 8,** 61-66.

GUILLEMINAULT, C., Simmons, F. B., Motta, J., Cummiskey, J., Rosekind, M., Schroeder, J. S., & Dement, W. C. (1981). Obstructive sleep apnea syndrome and tracheostomy: Long-term follow-up experience. **Archives of Internal Medicine, 141,** 985-988.

GUYTON, A. C. (1977). Personal views on mechanisms of hypertension. In J. Genest, E. Koiw & O. Kuchel (Eds.), **Hypertension** (pp. 566-575). New York: McGraw-Hill.

HADDY, F. J. (1987). Endogenous digitalis-like factor or factors. **New England Journal of Medicine, 316,** 621-623.

HAMLYN, J. M., Harris, D. W., Clark, M. A., Rogowski, A. C., White, R. J., & Ludens, J. H. (1989). Isolation and characterization of a sodium pump inhibitor from human plasma. **Hypertension, 13,** 681-689.

HAYTHORNTHWAITE, J. A., Moore, L., & Anderson, D. E. (in press). Social and behavioral factors in inhibitory breathing. **Behavioral Medicine.**

HENRY, J. P., & Cassel, J. (1969). Psychosocial factors in essential hypertension. **American Journal of Epidemiology, 90,** 171-185.

JEONG, D., & Dimsdale, J. (in press). Sleep apnea and essential hypertension: A critical review of the

epidemiological evidence for comorbidity. **Clinical Experimental Hypertension.**

KOEPKE, J. P., Light, K. C., Grignolo, A., & Obrist, P. A. (1983). Neural control of renal excretory function during behavioral stress of dogs. **American Journal of Physiology, 245,** R251-R258.

KORNEL, L., Rafelson, M. E., Hayashi, T., Kanamarlapudi, N., & Anderson, K. M. (1988). Arterial receptors for adrenal steroids and transport of electrolytes in vascular smooth muscle. **Clinical Physiology and Biochemistry, 6,** 188-200.

LAWLER, J. E., & Cox, R. H. (1985). The borderline hypertensive rat (BHR): A new model for the study of environmental factors in the development of hypertension. **Pavlovian Journal of Bioloqical Science, 20,** 101-115.

LIPP, M. N. (1990). Aspectos psicologicos do paciente hipertenso. In B. Lamosa (Ed.), **Psicologia aplicada a cardiologia** (pp. 35-250). Sao Paulo: Socesp.

LIPP, M. N. (l991). O valor do controle do stress no tratamento da hipertensão arterial. In M. Knobel (Ed.), **Psicossomática** (pp. 83-162). Campinas: NEP, UNICAMP.

MACCARRON, D. A. (1985). Is calcium more important than sodium in the pathogenesis of essential hypertension? **Hypertension, 7,** 607-627.

MacGregor, G. A. (1985). Sodium is more important than calcium in essential hypertension. **Hypertension, 7,** 628-637.

MARK, A., Lawton, W., Abbound, F., Fitz, A., Connor, W., & Heistad, D. (1975). Effects of high and low sodium intake on arterial pressure and forearm vascular resistance in borderline hypertension. **Circulation Research, 36,** 1-194.

MASON, J. W. (1968). A review of psychoendocrine research on the pituitary-adrenal cortical system. **Psychosomatic Medicine, 30,** 576-607.

MASON, J. W., & Brady, J. V. (1956). Plasma 17-hydroxycorticosteroid changes related to reserpine effects on emotional behavior. **Science, 124,** 983-984.

MASON, J. W., Jones, J. A., Ricketts, P. T., Brady, J. V., & Tolliver, G. A. (1968). Urinary aldosterone and urine volume responses to 72-hr. avoidance sessions in the monkey. **Psychosomatic Medicine, 30,** 733-746.

MITHOEFER, J. C. (1965). Breath Holding. In W. O. Fenn & H. Rahn (Eds.), **Handbook of physiology: Respiration II,** (pp. 1011-1025). Washington, DC: American Physiological Society.

MORRISON, S. L., & Morris, J. N. (1959). Epidemiological observations on high blood pressure without apparent cause. **Lancet, 2,** 864-870.

NICE, D. S., & Trent, L. K. (1979). **Prevalence of hypertension among active duty Navy personnel** (NHRC Technical Report N° 90-5). San Diego, CA: Naval Health Research Center.

ONOYAMA, K., Bravo, E. L. & Tarazi, R. C. (1979). Sodium, extracellular fluid volume and cardiac output changes in the genesis of mineralocorticoid hypertension in the intact dog. **Hypertension, 1,** 333-336.

OTIS, A. B. (1964). The work of breathing. In W. O. Fenn & H. Rahn (Eds.), **Handbook of Physiology: Respiration I** (pp. 463-476). Washington, DC: American Physiological Society.

PARFREY, P. S., Condon, K., Wright, P., Vandenburg, M. J., Holly, J. M. P., Goodwin, F. J., Evans, S. J. W., & Ledingham, J. M. (1981). Blood pressure and hormonal changes following alterations in sodium and potassium in young men with and without a familial predisposition to hypertension. **Lancet,** 113-117.

PERINI, C., Muller, F. B. & Buhler, F. R. (1991). Suppressed aggression accelerates early development of essential hypertension. **Journal of Hypertension, 9,** 499-503.

RICHTER-HEINRICH, E., Enderlein, J., Knust, U., Schmidt, K. H., & Wiedemann, R. (1989). Effects of a breath relaxation training. In K. V. Sudakov (Ed.), **Perspectives on research in emotional stress** (pp. 239-250). New York: Gordon & Breach.

STRADLING, J. R., Chadwick, G. A., & Frew, A. J. (1985). Changes in ventilation and its components during sleep. **Thorax, 40,** 364-370.

SULLIVAN, J. M., & Ratts, T. E. (1983). Hemodynamic mechanisms of adaptation to chronic high sodium intake in normal humans. **Hypertension, 5,** 814-820.

THOMAS, C. B., & Greenstreet, R. L. (1973). Psychobiological characteristics in youth as predictors of 5 disease states: Suicide, mental illness, hypertension, coronary artery disease and tumor. **Johns Hopkins Medical Journal, 132,** 16-43.

TIMIO, M., Verdecchia, P., Venanzi, S., Gentili, S., Ronconi, B., Francucci, B., Montanari, M., & Bichisao, E. (1988). Age and blood pressure changes: A 20-year follow-up study in nuns in a secluded order. **Hypertension, 12,** 457-461.

WILLIAMS, G. H., & Dluhy, R. G. (1983). Control of aldosterone secretion. In J. Genest, O. Kuchel, P. Hamet, & M. Cantin (Eds.), **Hypertension: Physiopathology and treatment (2nd Ed.)** (pp. 320-337). New York: McGraw-Hill.

WINKLEBY, M. A., Ragland, D. R., & Syme, L. (1988). Self-reported stressors and hypertension: Evidence of an inverse association. **American Journal of Epidemiology, 127,** 124-134.