The pathogenesis of hypertension results from an interaction of genetic and environmental factors. Behavioral factors might participate in sodium sensitive forms of hypertension via a cascade of physiological responses triggered by conditioned inhibition of breathing. When an individual decreases ventilation sufficient to increase pCO_2 but not sufficient to activate chemoreceptor reflexes, plasma pH decreases transiently to stimulate a renal mechanism that can expand plasma volume via sodium retention. The combination of high resting pCO_2 and high sodium intake elevates resting blood pressure in laboratory animals and healthy human participants. In the natural environment, this mechanism seems to be more important for the development of hypertension in women than in men, perhaps due to differential expression of anger and aggression. Studies are needed to clarify the role of breathing pattern in individual differences in resting pCO_2 and the effects of breathing interventions on salt sensitivity and sodium sensitive forms of hypertension.

Respiratory Psychophysiology in Hypertension Research

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Accumulating evidence suggests that disordered breathing can play a role in some forms of high blood pressure. For example, studies have linked sleep apnea to an increased incidence of hypertension (Silverberg, Oksenberg, & Iaina, 1997) and the regular practice of meditative breathing to the reversal of hypertension (Barnes, Schneider, Alexander, & Staggers, 1997). The physiological pathways through which breathing pattern might affect blood pressure regulation remain to be clarified. Traditional accounts of the role of behavioral stress in the pathogenesis of hypertension have traditionally focused on the fight-or-flight reaction, in which breathing activation increases oxygen consumption. In contrast, studies in our laboratory have indicated that conditioned decreases in anticipation of aversive events can play a role in blood pressure via effects on blood gases, acid-base balance, and renal sodium regulation. Specifically, we have

BEHAVIOR MODIFICATION, Vol. 25 No. 4, September 2001 606-620

observed that increases in pCO_2 within the normal range accompanying behaviorally induced suppression of breathing decrease plasma pH and result in increased plasma volume as an autoregulatory reflex that restores pH levels. Individuals who engage in habitual mild hypercapnic breathing might, therefore, manifest increased vulnerability to the hypertensive effects of a high-sodium diet because of a decreased capacitance of the cardiovascular system.

This hypothesis emerged originally in a series of experimental studies with chronically instrumented laboratory animals, which showed that periods of quiet anticipation of the onset of a familiar avoidance task were accompanied by progressive decreases in heart rate and breathing frequency (BF). When the preavoidance setting was combined with continuous intravenous infusion of isotonic saline for 10 days, renal sodium retention occurred, and 24-hour resting blood pressure increased to hypertensive levels (Anderson, 1987). That the suppression of breathing was a necessary component of this outcome was indicated by the finding that no changes in sodium balance or blood pressure were observed when saline was infused in the absence of behavioral stress.

Whether the breathing suppression (from a normal resting rate of approximately 14 breaths per minute to 8 to 10 breaths per minute at a comparable tidal volume) was an integral part of the hypertensive response or merely an epiphenomenon was initially unclear. However, hypercapnia is known to decrease renal sodium excretion and expand plasma volume, due to acidification of the plasma and increased renal sodium-hydrogen exchange. That plasma volume is expanded by breathing suppression is suggested by studies showing that preavoidance periods evoke increases in circulating natriuretic compounds that are elicited by increases in plasma volume (Fedorova, French, & Anderson, 1995). Thus, laboratory studies show that the combination of (a) contingencies on behavior that suppress breathing and expand plasma volume and (b) increased dietary sodium intake is sufficient to elevate resting blood pressure.

Over the past decade, we have investigated whether the suppressed breathing pattern observed in laboratory animals can also be observed in ambulatory humans in their natural environments. We have attempted to identify social conditions that elicit this breathing pattern

and to investigate physiological effects of slowed breathing in humans. In these studies, we found large individual differences in resting end tidal CO_2 ($PetCO_2$) (which in humans with healthy lungs estimates pCO_2), and we found that high resting $PetCO_2$ is a marker for blood pressure sensitivity to high sodium intake. Finally, we have observed that women with high resting $PetCO_2$ tend to develop thicker arteries and higher resting blood pressure as they age. The current review summarizes these findings and concludes with implications for behavioral interventions in sodium sensitive hypertension.

AMBULATORY MONITORING OF BREATHING IN HUMANS

Accurate measurement of breathing in humans is, of course, one of the more formidable challenges in all of psychophysiology, because methods that involve mouth tubes can alter breathing dynamics and systems that use chest bands are vulnerable to artifact from postural change. Tidal volume (TV) can be estimated by summing the expansion of the chest and abdomen during inspiration (Kono & Mead, 1967). Sackner, Nixon, Davis, Atkins, and Sackner (1980) used this principle to develop and refine the Respitrace® system, which passes a small electrical inductance through a sinusoidal arrangement of electrical wires sewn into elasticized bands worn around the torso, under the armpits, and over the umbilicus. The system is calibrated by breathing into a respiratory gas monitor in seated and recumbent postures. This system was shown to be effective for measurement of BF, TV, and minute ventilation (MV) during standing exercise and sleep, as well as during seated rest (Tobin et al., 1983).

We combined the Respitrace® system with a lightweight, portable microprocessor, which was custom-designed for our research by Kent Laboratories (Palm Harbor, Florida) (Anderson & Frank, 1990). The microprocessor monitored the breathing cycle and recorded averaged BF and TV over successive 1- or 10-minute intervals for 24 hours. The system had two electronic filters for eliminating postural artifact. BF almost never exceeds 30 breaths per minute (or 1 breath every 2 seconds). Therefore, the microprocessor was made insensitive to band

expansions for 2 seconds following a breath, which eliminated approximately half of all possible artifact. The other filter was based on the observation that band stretch rarely exceeds (or is less than) a range of values during inspiration. Thus, any postural change that stretched the bands beyond this value was also eliminated. This left as remaining artifact only postural shifts equal to or less than maximal TV occurring more than 2 seconds after the preceding breath. The system was not suitable for fine-grained analyses of the breathing cycle but was adequate for investigating episodic breathing pattern changes in the natural environment and for characterizing differences between participants.

With this system, we were able to confirm that the "energetic" aspects of breathing are regulated via TV at a relatively constant BF (Anderson, Coyle, & Haythornthwaite, 1992). In mild exercise, for example, mean TV and MV increase proportionally, while mean BF remains unchanged (although during more strenuous exercise, BF also increases). Conversely, during sleep, mean TV and MV decrease proportionally from resting daytime levels, again with little or no change in mean BF. Mean daytime and nighttime BF were comparable, as illustrated in previous studies with nonambulatory participants (e.g., White, Weil, & Zwillich, 1985)

BF during the day consisted of a relatively normal distribution around a modal value, averaging approximately 14 ± 1.4 breaths per minute for the group. An approximately equal number of daily episodes of decreased and increased BF were observed; that is, there were as many occasions when participants breathed more slowly than they did at rest as there were occasions when they breathed more rapidly than at rest. Mean TV of those decreased and increased BF episodes were not significantly different from that at modal BF breathing, so that MV decreased or increased in parallel with the changes in BF. Because the energetically efficient way to change MV is by varying TV (Otis, 1964), changes in MV mediated by BF must have served another, overriding function. Breath holding is known to increase cerebral blood flow (Irving, 1938), which could enhance vigilant attention to the external environment. That behavioral interactions had a significant influence on breathing pattern was shown in the findings that the episodic decreases in BF occurred more frequently in par-

ticipants when they were at work than when they were at home and more frequently when they were with other people than when they were alone (Haythornthwaite, Anderson, & Moore, 1992). In addition, BF-mediated breathing inhibition was typically accompanied by acute increases in systolic blood pressure (SBP) but not heart rate (Anderson, Austin, & Haythornthwaite, 1993). The changes in MV mediated by changes in BF, with no mean changes in TV, would appear to be of psychological significance, because they are energetically inefficient. Thus, evidence exists that socially significant environmental conditions could elicit sustained inhibitory changes in breathing pattern, accompanied by physiological arousal.

ACUTE HYPERCAPNIC BREATHING IN HUMANS

Resting pCO_2 is difficult to assess accurately due to the variable effects of venipuncture on breathing itself. In participants with healthy lungs, however, the amount of CO_2 at the end of the expiratory phase of the breathing cycle, $PetCO_2$, is highly correlated with pCO_2 (although 2 to 3 mmHg lower). $PetCO_2$ is a more convenient measure, because it can be recorded non-intrusively and continuously. Others have investigated hyperventilatory breathing and decreases in $PetCO_2$ in experimentally induced (e.g., Ley & Yelich, 1998) or naturally occurring (Martinez et al., 1996; Roth, Wilhelm, & Trabert, 1998) anxiety states. We were interested in whether $PetCO_2$ could be experimentally increased by paced breathing and whether the physiological effects would be comparable to those observed in previous studies with aversively conditioned animals (Anderson, 1987). Specifically, we trained individuals to maintain BF at 6 breaths per minute at the lowest TV that was comfortable for them, by breathing into a respiratory gas monitor that provided breath-to-breath digital feedback of $PetCO_2$ for periods of up to 15 minutes. Task performance required practice and concentration, but virtually all participants learned to sustain increases in $PetCO_2$ of at least a few mmHg, with the magnitude of change being an inverse function of resting level of $PetCO_2$. The levels of pCO_2 attained were not sufficient to stimulate pH-sensi-

tive chemoreceptors but were sufficient to produce transient decreases in plasma pH and sustained increases in plasma bicarbonate concentrations (Anderson, Austin, & Coyle, 1993).

These physiological effects were rapidly reversed by restoration of normative breathing. The same patterns were elicited whether $PetCO_2$ was elevated by low BF at normal TV or by low TV at normal BF. In another study (Anderson, Bagrov, & Austin, 1995), participants were hydrated to increase urine flow via a standardized water-drinking procedure (Light, Koepke, Obrist, & Willis, 1983) and trained to elevate $PetCO_2$ for 30-minute intervals. Urine volume and urinary sodium excretion were decreased by performance of the task, and post-task urinary excretion of plasma volume-sensitive compounds was increased. Thus, these experiments showed that the changes in acid-base balance and renal sodium regulation that had been observed in laboratory animals under anticipatory stress could also be produced in humans by voluntary inhibition of breathing.

AGE, GENDER, AND RACIAL DIFFERENCES IN END TIDAL CO_2

The range of individual differences in resting levels of $PetCO_2$ observed in these experimental studies was also observed in a study of more than 600 participants, the Baltimore Longitudinal Study on Aging. Each of the participants breathed into a nasal cannula connected to a respiratory gas monitor during 20 minutes of seated rest. Intra-individual resting $PetCO_2$ showed little variation and no significant trends within the monitoring session. Figure 1 shows a histogram of the range of individual mean resting $PetCO_2$ of 323 men and 383 women, aged 20 to 79 years. When participants returned to the laboratory days or weeks later, resting levels tended to be similar to those observed during the first session (Dhokalia, Parsons, & Anderson, 1998). Even after 2 years between measurements, the test-retest correlation coefficient was +.69 ($p < .001$). These findings confirm earlier reports (Schaefer, 1979) of intraparticipant consistency in breathing pattern at rest, with some individuals showing faster BF with more shallow TV, while others showed slower BF with deeper

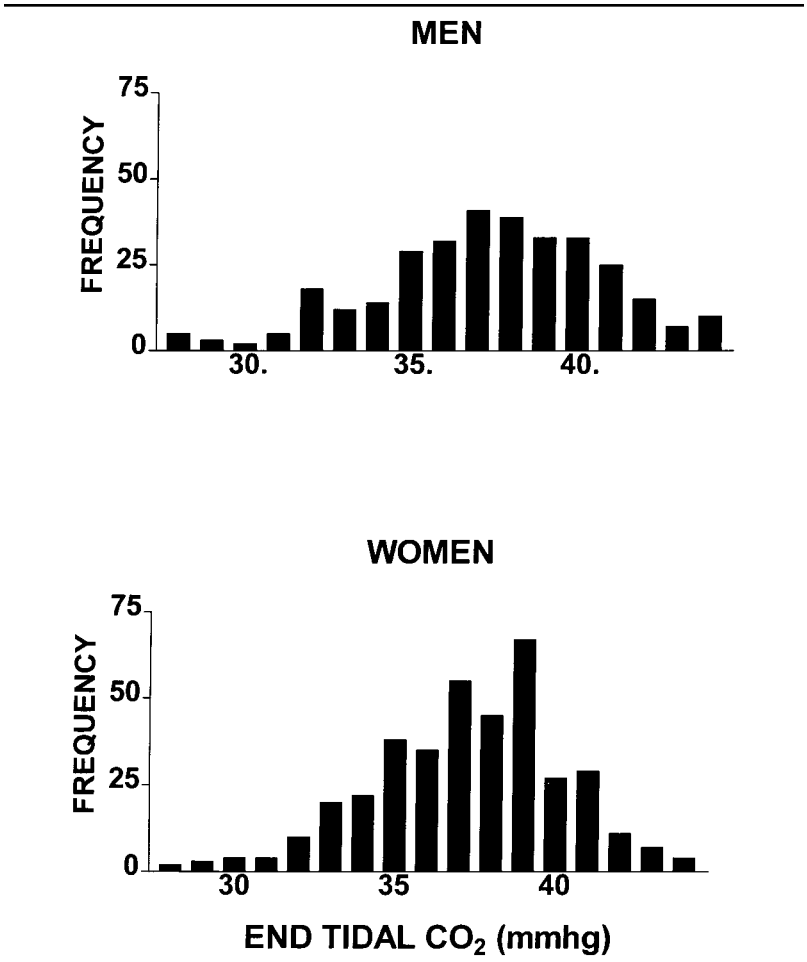

Figure 1. Frequency distribution of individual mean resting end tidal CO_2 in 322 male and 383 female participants in the Baltimore Longitudinal Study on Aging.

TV. The former group tended to maintain lower resting $PetCO_2$ and to report more trait anxiety than the latter group.

Mean $PetCO_2$ for men averaged over the life span was not significantly different from that of women. However, as shown in Figure 2, significant gender differences in age-associated changes were observed. Although $PetCO_2$ of women remained relatively constant

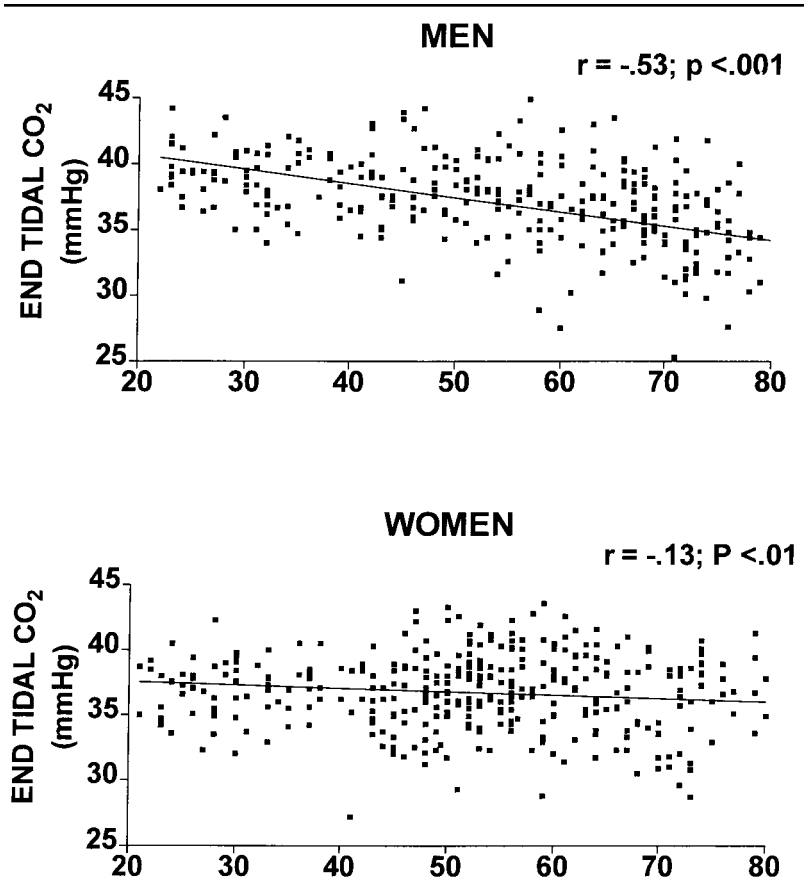

Figure 2. Gender differences in age-associated changes in end tidal CO_2 in 322 male and 383 female participants in the Baltimore Longitudinal Study on Aging.

over the life span, that of men decreased markedly (Dhokalia et al., 1998). Mean resting $PetCO_2$ of men in their 20s was significantly higher than that of women in their 20s but, by age 70, was significantly lower than that of women. The age-associated decline in $PetCO_2$ of men was independent of changes in forced vital capacity. Other studies have also found that pCO_2 of men decreases progressively over the life span, whereas no studies of age-associated changes in pCO_2 in women have been found (Frassetto & Sebastian, 1996). Estrogen

administration is known to decrease resting $PetCO_2$ (Regensteiner et al., 1989), so higher estrogen levels in younger women might contribute to their lower resting $PetCO_2$ in early life and the loss of estrogen to higher levels in later life.

African Americans show a greater prevalence of hypertension than Caucasian Americans (Gillum, 1996), are also slower to excrete a salt load (Luft, Grim, Fineberg, & Weinberger, 1979), and show greater blood pressure sensitivity to high sodium intake (Morris, Sebastian, Forman, Tanaka, & Schmidlin, 1999), but the reasons for these differences remain to be clarified. It is of interest, therefore, that resting $PetCO_2$ was found to be higher in African Americans than in Caucasian Americans (Anderson, Scuteri, Agalakova, Parsons, & Bagrov, in press). This difference was not manifested before age 50 in either men or women but was observed after that age in both men and women, accompanied by differences in plasma volume-sensitive compounds. That the racial differences are observed only in later life is consistent with the view that psychosocial factors might contribute to the differential time course of age-associated changes in $PetCO_2$.

END TIDAL CO_2 AND BLOOD PRESSURE SENSITIVITY TO HIGH SODIUM INTAKE

In the aforementioned animal studies, increased pCO_2 during sustained behavioral stress was found to potentiate blood pressure sensitivity to high sodium intake (Anderson, Dhokalia, Parsons & Bagrov, 1996, 1998). This raises the question of whether high resting $PetCO_2$ might be a risk factor for blood pressure sensitivity to high sodium intake in humans, as well. We tested this hypothesis in a study with normotensive men and women, ages 40 to 70, who were placed on a low-sodium diet for 4 days followed by a high-sodium diet for 7 days. Dietary intake of sodium was standardized by avoidance of high-sodium foods (fast foods, frozen commercial dinners, processed meats, salted snack foods, canned soups and pasta, and table and cooking salt) and increased by ingestion of enteric-coated sodium chloride capsules. Two servings of fruits or vegetables were scheduled daily to standardize intake of potassium. Adherence to the diet was determined by monitoring overnight urinary sodium and potassium

excretion. Urinary excretion of endogenous digitalis-like factors was also measured before and after high sodium intake. The high-sodium diet increased urinary sodium excretion and body weight and produced significant increases in resting and 24-hour ambulatory SBP and diastolic blood pressure (DBP) in the highest $PetCO_2$ quartile. Increases in 24-hour SBP were observed in the second highest quartile. Neither of the two lower $PetCO_2$ quartiles showed any changes in blood pressure in response to changes in sodium intake.

A second study was conducted with younger normotensive men and women, who tend to be much less salt sensitive (Anderson et al., 1998). No significant effects of sodium loading on SBP or DBP were observed for the younger group, as a whole. However, significant positive associations were found between individual mean resting $PetCO_2$ and the changes in individual resting SBP and DBP. High-$PetCO_2$ participants showed no significant changes in resting blood pressure, whereas low-$PetCO_2$ participants actually showed significant decreases in resting blood pressure. High-$PetCO_2$ participants showed a significant increase in ambulatory SBP, whereas no change was observed in the low-$PetCO_2$ group. These studies showed that high resting $PetCO_2$ is a risk factor for blood pressure sensitivity to high sodium intake.

END TIDAL CO_2 ASSOCIATION WITH ARTERIAL STRUCTURE AND BLOOD PRESSURE IN WOMEN

If high resting $PetCO_2$ is accompanied by expanded plasma volume, individuals with high resting $PetCO_2$ might also develop thicker arteries to accommodate the chronic volume load. Intima-media thickness (IMT) of the common carotid artery can be measured noninvasively and quantitatively via high-frequency ultrasound technology (Poli et al., 1998). We measured left and right carotid IMT in 188 Baltimore Longitudinal Study on Aging participants via this technique and analyzed the relative influence of resting $PetCO_2$, age, race, body mass index, SBP, and DBP to carotid IMT (Anderson, Scuteri, Metter, & Chesney, 2001). High resting $PetCO_2$ was found to be an independent determinant of carotid IMT and of wall to lumen ratio in women but not in men. It is interesting, therefore, that occupa-

tional stress has also been shown previously to predict increased carotid IMT in women but not in men (Rosvall et al., 2000). Moreover, women with high anger also showed increased carotid IMT (Matthews, Owens, Kuller, Sutton-Tyrell, & Jansen-McWilliams, 1998). In another study (Anderson, Parsons, & Scuteri, 1999) with 314 Baltimore Longitudinal Study on Aging participants, multiple regression analyses revealed that resting $PetCO_2$ was an independent predictor of resting SBP (but not DBP). Again, this association was specific to women but not to men and specific to women older than age 50. These findings provide support for the hypothesis that behaviorally induced alterations in breathing pattern can mediate structural cardiovascular changes in women that contribute to the development of hypertension.

SUMMARY AND DIRECTIONS FOR FUTURE RESEARCH

Figure 3 shows a schematic diagram of how breathing pattern could combine with high sodium intake to elevate blood pressure. As shown, sustained inhibition of breathing decreases plasma pH via increased formation of carbonic acid. Restoration of normal pH could involve not only increases in buffer compounds but also expansion of plasma volume via transfer of fluid from the interstitial space and decreased renal sodium excretion. The enhanced plasma volume in participants who maintain the breathing pattern would render these individuals more vulnerable to the effects of high dietary sodium intake. Whether habitual breathing suppression can cause an upward resetting of the set point for resting $PetCO_2$ remains to be determined, but if individual differences in resting $PetCO_2$ are due to behavioral histories rather than to inherent constitutional differences, behavioral interventions that restore homeostatic levels of pCO_2 may be useful in prevention or delay of onset of sodium sensitive forms of hypertension.

Additional research is needed to clarify the incidence of episodic or characteristic breathing suppression in the natural environment and the extent to which it is gender specific and to elucidate its pro-hypertensive effects. One recent review proposed that although men tend to react to stress with a fight-or-flight response, women tend to

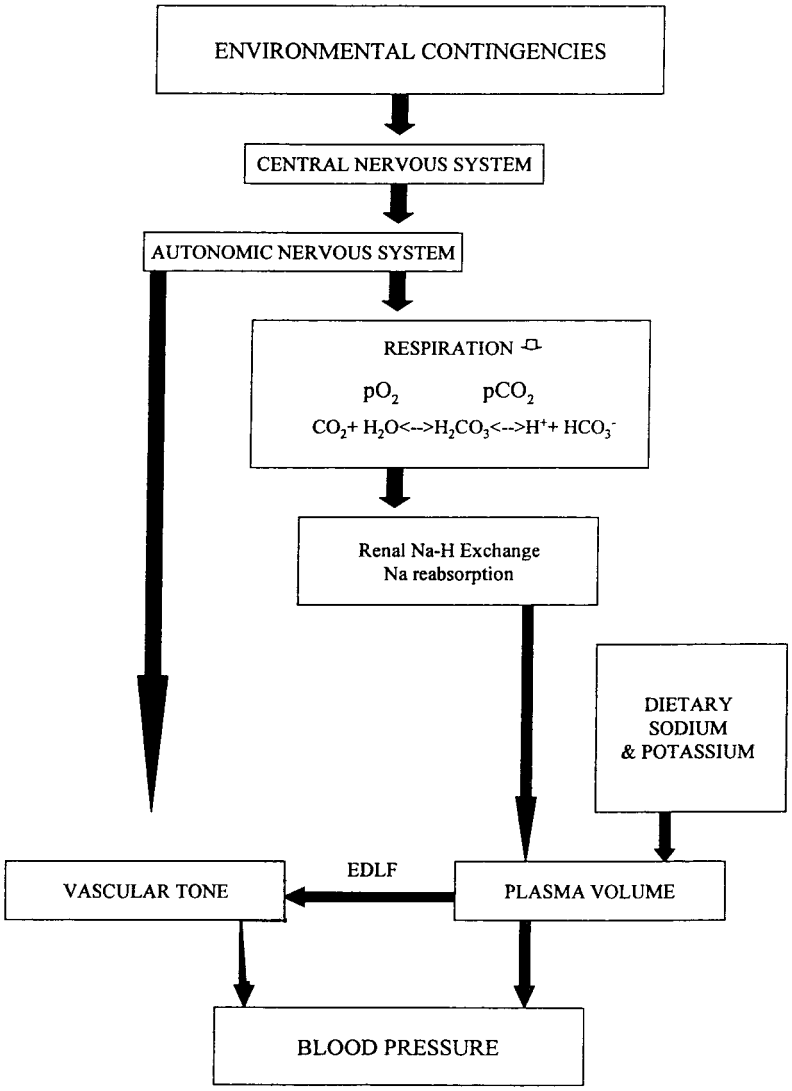

Figure 3. Schematic diagram of hypothesized role of behaviorally induced breathing suppression in cardiovascular regulation and the development of sodium sensitive hypertension.

react with a response that involves avoidance of aggressive behavior (Taylor et al., 2000). Whether characteristic breathing adaptations of

men and women under stress differ remains to be clarified. However, a tendency to hold anger in during social stress was associated in one study with acute increases in blood pressure in women but not men (Helmers, Baker, O'Kelly, & Tobe, 2000). The emerging field of respiratory psychophysiology can make a significant contribution to the understanding of cardiovascular disease pathogenesis and intervention by devising improved methods for carrying out laboratory and field studies of acute and chronic effects of behavioral and social stress on breathing adaptations, blood gases, and renal sodium regulation.

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