Slow Breathing Improves Arterial Baroreflex Sensitivity and Decreases Blood Pressure in Essential Hypertension

Chacko N. Joseph, Cesare Porta, Gaia Casucci, Nadia Casiraghi, Mara Maffeis,
Marco Rossi, Luciano Bernardi

Abstract—Sympathetic hyperactivity and parasympathetic withdrawal may cause and sustain hypertension. This autonomic imbalance is in turn related to a reduced or reset arterial baroreflex sensitivity and chemoreflex-induced hyperventilation. Slow breathing at 6 breaths/min increases baroreflex sensitivity and reduces sympathetic activity and chemoreflex activation, suggesting a potentially beneficial effect in hypertension. We tested whether slow breathing was capable of modifying blood pressure in hypertensive and control subjects and improving baroreflex sensitivity. Continuous noninvasive blood pressure, RR interval, respiration, and end-tidal CO_2 (CO_2-et) were monitored in 20 subjects with essential hypertension (56.4 ± 1.9 years) and in 26 controls (52.3 ± 1.4 years) in sitting position during spontaneous breathing and controlled breathing at slower (6/min) and faster (15/min) breathing rate. Baroreflex sensitivity was measured by autoregressive spectral analysis and "alpha angle" method. Slow breathing decreased systolic and diastolic pressures in hypertensive subjects (from 149.7 ± 3.7 to 141.1 ± 4 mm Hg, $P<0.05$; and from 82.7 ± 3 to 77.8 ± 3.7 mm Hg, $P<0.01$, respectively). Controlled breathing (15/min) decreased systolic (to 142.8 ± 3.9 mm Hg; $P<0.05$) but not diastolic blood pressure and decreased RR interval ($P<0.05$) without altering the baroreflex. Similar findings were seen in controls for RR interval. Slow breathing increased baroreflex sensitivity in hypertensives (from 5.8 ± 0.7 to 10.3 ± 2.0 ms/mm Hg; $P<0.01$) and controls (from 10.9 ± 1.0 to 16.0 ± 1.5 ms/mm Hg; $P<0.001$) without inducing hyperventilation. During spontaneous breathing, hypertensive subjects showed lower CO_2 and faster breathing rate, suggesting hyperventilation and reduced baroreflex sensitivity ($P<0.001$ versus controls). Slow breathing reduces blood pressure and enhances baroreflex sensitivity in hypertensive patients. These effects appear potentially beneficial in the management of hypertension. (*Hypertension*. 2005;46:714-718.)

Key Words: baroreceptors ■ blood pressure ■ heart rate ■ hypertension ■ nervous system, autonomic ■ respiration

---

Autonomic imbalance has a major role in the etiology of hypertension.[1–4] Such imbalance, characterized by an increase in sympathetic activity (with a possible reduction in parasympathetic activity), is present not only in early and borderline hypertension but also contributes to the maintenance of sustained hypertension.[2] Moreover, several cardiovascular risk factors frequently associated with hypertension are etiologically linked to sympathetic activation.[2,5] At least one of the mechanisms associated with this autonomic imbalance is the reduced baroreflex sensitivity. The baroreflex is reduced or reset toward elevated blood pressure values in hypertension, blunting its ability to suppress the increased sympathetic activity.[6] An impairment of the baroreflex has a direct relation to increased 24-hour blood pressure variability, which in turn correlates with the increase in target-organ damage.[7] Furthermore, there are reports indicating a chemoreflex activation in essential hypertension, which can be

an additional mechanism responsible for the increase in sympathetic activity.[8]

Given the clinical and prognostic value of reducing sympathetic activation and increasing baroreflex sensitivity in hypertension, it is interesting to note that slow breathing at 6 cycles/min increases baroreflex sensitivity in normal subjects and patients with chronic heart failure[9,10] and also reduces muscle nerve sympathetic activity[11] and chemoreflex activation,[12] thus suggesting a potentially beneficial effect in hypertension. However, there is little evidence about the effect of slow breathing on arterial baroreflex in hypertensive patients, although a few recent studies have shown that device-guided breathing exercise may reduce blood pressure in hypertensive patients.[13] This study aims to test whether slow breathing at 6 cycles/min reduces blood pressure in hypertensive and normal subjects, and if this effect is linked to a modification in cardiovascular control mechanisms.

Hypertension is available at http://www.hypertensionaha.org DOI: 10.1161/01.HYP.0000179581.68566.7d

Baseline Characteristics of Hypertensive and Control Subjects

Variable	Hypertensives	Controls	P*
N	20	26	
Male/female	10/10	14/12	NS†
Age, years	56.4±1.9	52.3±1.4	NS
Weight, kg	75.4±3.4	64.5±2.3	<0.05
Height, cm	170.4±1.9	165.3±1.9	NS
Body mass index, kg/m^2	25.7±0.9	23.5±0.5	NS
Total cholesterol, mg/dL	191.3±8.1	184.8±7.3	NS
HDL cholesterol, mg/dL	57.2±4.3	55.1±4.2	NS
Triglycerides, mg/dL	154.3±11.3	142.2±12.0	NS
Fasting glucose, mg/dL	82.3±4.4	80.5±6.8	NS
Creatinine, mg/dL	0.94±0.06	0.91±0.04	NS
Uric acid, mg/dL	5.4±0.8	5.5±0.6	NS
K+, mEq/L	4.4±0.1	4.2±0.3	NS
Aldosterone, pg/mL	85.2±19.2	78.1±13.4	NS
Renin, ng/mL	1.64±0.21	1.33±0.23	NS

Values are mean±SEM or No.

*Differences between hypertensives and controls by unpaired t test; †difference between the groups by χ^2 test.

Methods

Subjects

The protocol of the study was approved by the local ethics committee, and all subjects gave informed consent to participate in the study. We studied 20 patients with essential hypertension (untreated or after 2-week pharmacological washout) and 26 healthy controls. Secondary causes of hypertension were excluded on the basis of negative history and absence of clinical signs, normal renal function, normal serum electrolytes, and normal aldosterone and renin plasma levels. We excluded from the study subjects drinking >60 g of ethanol per day or consuming licorice, smokers, and women taking oral contraceptives. We avoided testing women during menstrual and premenstrual phases.[14,15] The Table shows the main anthropometric and laboratory test data.

Protocol

Subjects were examined in the late morning. Light breakfast was permitted during the early morning, but coffee or tea was not admitted on the day of the study. After 30 minutes of quiet rest and familiarization with the laboratory, we obtained recordings of ECG, respiration (by inductive belts), end-tidal CO_2 (side stream capnograph; COSMO, Novametrix), and blood pressure (Pilot model, Colin tonometry) during 5 minutes of spontaneous breathing, 2 minutes of controlled breathing at 6 cycle/min, and 2 minutes of controlled breathing at 15 cycle/min to verify the effect of simple regularization of breathing rate at a frequency in the same range of the spontaneous one. The breathing was controlled by visual instructions and under continuous monitoring of breathing rate by the capnograph. All recordings were obtained with the subject in sitting position and were made in random order.

All signals were acquired continuously on a personal computer (Apple Macintosh G3) at 300 samples per channel and stored on optical disks. From these data, the time series of RR interval and systolic and diastolic blood pressures were obtained. Mean values for these signals were obtained during the various recordings. Breath-by-breath end-tidal CO_2 (CO_2-et), breathing rate, and relative changes in minute ventilation (Vm) and tidal volume (Vt) were also obtained by interactive software written by one of us (L.B.) by the analysis of inductive belt signals and by analysis of the capnograms. The changes in Vm and Vt were calculated as percent increase or decrease from the recordings obtained during spontaneous breathing.

To validate this indirect method, we recorded in each subject the expiratory flow by a heated pneumotachograph (Fleish; Metabo) connected to a mouthpiece, together with the inductive belts, during various respiratory rates and depths. We then compared the amplitude of the inductive signal during each breath with the Vt obtained by electronic integration of the pneumotachographic signal. The correlation coefficient between the Vt or Vm measured with the 2 methods ranged from 0.984 to 0.822 (P always <0.0001). Thus, the inductive belts could successfully track changes in ventilation in relative terms. Instead, the use of a pneumotachograph during the entire procedure could have altered the spontaneous breathing pattern, as shown previously.[16]

The arterial baroreflex sensitivity was measured by spectral analysis using the "alpha-angle" method.[4,10] This approach is an accepted method for measuring the baroreflex sensitivity.[17]

Statistical Analysis

Data are presented as mean±SEM. Comparison of variables was done by ANOVA for mixed design (factorial model for differences between groups; repeated measures for differences between breathing rates). If overall significance ($P<0.05$) was observed, then Sheffe' test was used to assess differences between different breathing patterns.

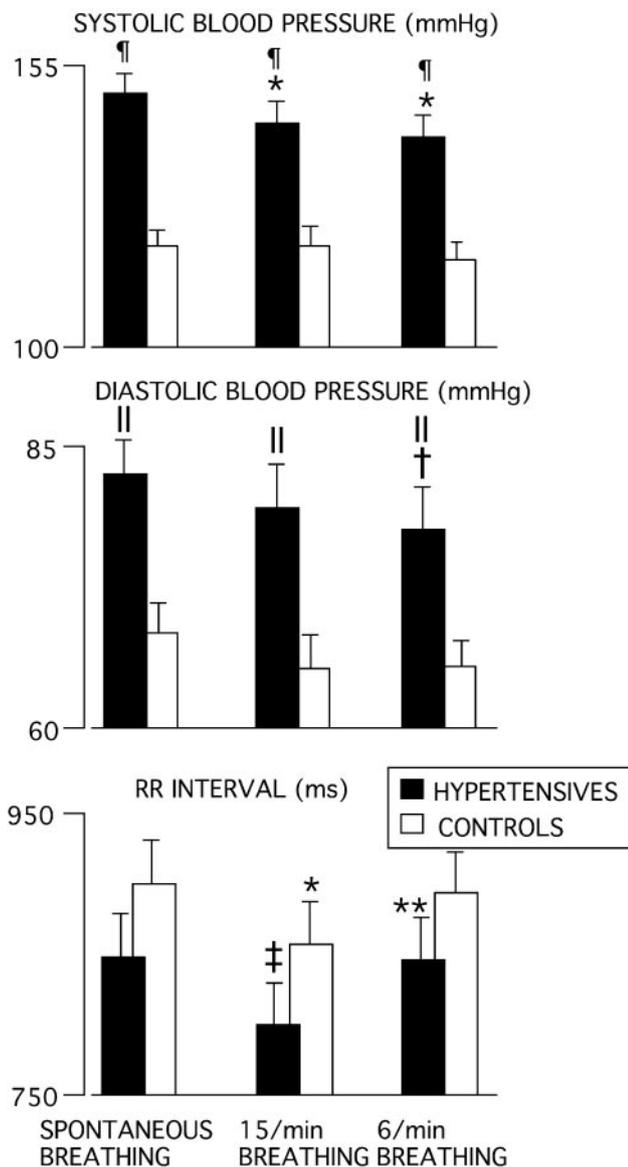## Results

Effects of Slow Breathing on Blood Pressure

In hypertensive subjects, the slow breathing significantly decreased systolic and diastolic blood pressures (from 149.7±3.7 to 141.1±4 mm Hg, $P<0.05$, and from 82.7±3 to 77.8±3.7 mm Hg, $P<0.01$, respectively; Figure 1), with no significant changes in RR interval. During controlled breathing at 15/min, we also found a significant decrease in systolic blood pressure (from 149.7±3.7 to 142.8±3.9 mm Hg, $P<0.05$; Figure 1); however, diastolic blood pressure did not change significantly, and the RR interval showed a significant shortening ($P<0.05$; Figure 1). Controls showed the same trends for RR interval but without significant differences.

Effects of Slow Breathing on Baroreflex Sensitivity

During spontaneous breathing, baroreflex sensitivity was depressed in the hypertensives compared with the controls ($P<0.001$; Figure 2). However, breathing at 6 breaths/min significantly increased the baroreflex sensitivity in hypertensive (from 5.8±0.7 to 10.3±2.0 ms/mm Hg; $P<0.01$) and control subjects (from 10.9±1.0 to 16.0±1.5 ms/mm Hg; $P<0.001$; Figure 2). In hypertensive patients, baroreflex sensitivity increased to values similar to those of the controls during spontaneous breathing. Therefore, slow breathing had the effect of acutely normalizing the baroreflex sensitivity in these patients. Conversely, the controlled breathing at 15/min induced only minor and nonsignificant changes in baroreflex sensitivity (from 5.8±0.7 to 5.4±0.9 ms/mm Hg; $P=$NS) in hypertensive subjects and in controls (from 10.9±1.0 to 11.4±1.0 ms/mm Hg; $P=$NS).

Respiratory Changes Induced by Hypertension and by Slow Breathing

Hypertensive subjects showed a significantly higher resting respiratory rate (14.55±0.82 versus 11.76±1.00; $P<0.05$) and a significantly lower CO_2-et values compared with control subjects (Figure 3). During controlled breathing at 6/min, there were no significant changes in CO_2-et

SYSTOLIC BLOOD PRESSURE (mmHg)

DIASTOLIC BLOOD PRESSURE (mmHg)

RR INTERVAL (ms)

Figure 1. Effect of breathing rate on RR interval and blood pressure. $*P<0.05$, $†P<0.01$, and $‡P<0.001$ vs spontaneous breathing; $§P<0.05$, $\|P<0.01$, and $¶P<0.001$ versus controls; $\#P<0.05$, $**P<0.01$, and $††P<0.001$ vs 15/min controlled breathing
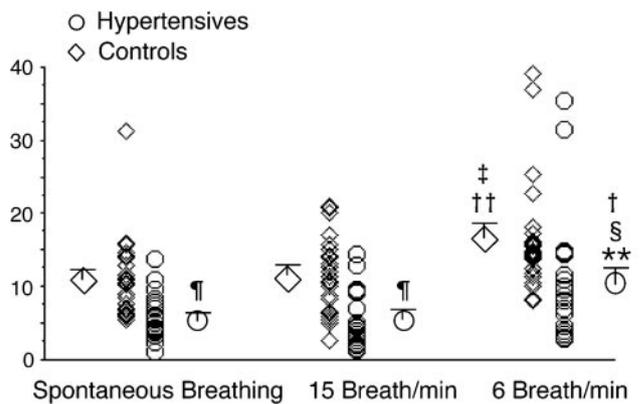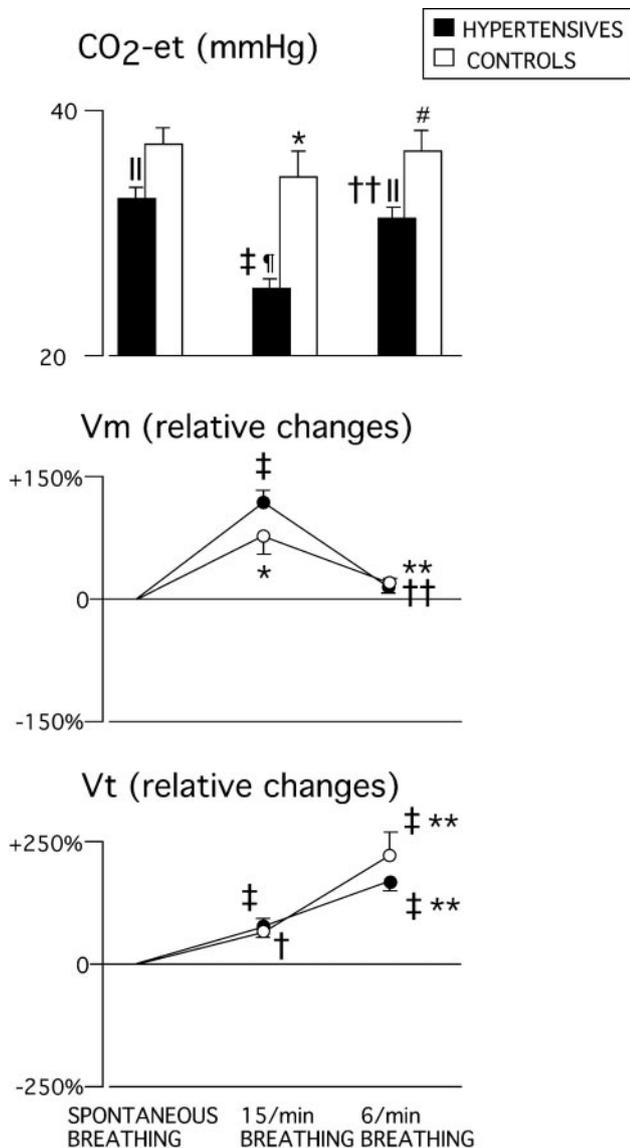
BAROREFLEX SENSITIVITY (ms/mmHg)

Figure 2. Effect of breathing rate on baroreflex sensitivity. Symbols as in Figure 1.

sympathetic activity. Finally, hypertensive subjects showed signs of spontaneous hyperventilation, suggesting that the cardiovascular and the respiratory abnormalities could be linked by a common pattern of excitation that can be, at least in part, modified by adoption of a specific breathing pattern.

Effect of Slow Breathing on Cardiovascular Modulation

There are many possible explanations for the present findings. Slow breathing at 6 cycle/min has the effect of entraining all RR interval fluctuations, thereby causing them to merge at the rate of respiration and to increase greatly in amplitude. This increase in RR interval fluctuations (relative to blood pressure changes) has the effect of enhancing the baroreflex efficiency,[10,18] and, in turn, might have contributed to lower blood pressure. Additionally, slow breathing may reduce sympathetic activity by enhancing central inhibitory rhythms[19] and, consequently, may also decrease the blood pressure while enhancing the baroreflex. Furthermore, the increase in Vt (deriving from the slowing in breathing rate) activates the Hering–Breuer reflex,[9] which in turn reduces the chemoreflex sensitivity and thus might enhance the baroreflex, with an additional effect on reducing blood pressure and sympathetic activity.[9–12,20] Whatever the mechanism, it is reasonable to assume that changes in sympathetic activity and in baroreflex sensitivity are interrelated.[20–22]

The increase in baroreflex sensitivity depends on the slow breathing rate and not on the regularization obtained by controlling the breathing because controlled breathing at a fixed and faster frequency (15/min) did not produce such effect. However, it is intriguing to note that controlled breathing at 15/min decreased blood pressure despite a decrease in RR interval and no change in baroreflex sensitivity. A possible speculation is that conscious control of breathing at the faster rate, by markedly increasing Vm, caused sympathetic-induced tachycardia, whereas at the same time, the inspiration-induced stimulation of the intrathoracic stretch receptors might have counteraffected the baroreflex.[23] Alternatively or in addition, a regularization of rhythm during controlled breathing may have entrained central inhibitory rhythms.[19]

and in Vm. The lack of change in Vm, despite lower breathing rate, was attributable to a significant increase in Vt in hypertensives and controls. Controlled breathing at 15/min induced a marked decrease in CO_2-et, particularly in hypertensive subjects, and a marked relative increase in Vm and Vt (Figure 3).

Discussion

Main Findings

We found that paced breathing, and particularly slow breathing at 6 cycle/min, reduces blood pressure in hypertensive patients. The reduction in blood pressure during slow breathing is associated with an increase in the vagal arm of baroreflex sensitivity, indicating a change in autonomic balance, related to an absolute or relative reduction in

CO₂-et (mmHg)

Figure 3. Effect of breathing rate on respiratory variables. Symbols as in Figure 1.

Interaction Between Cardiovascular and Respiratory Control

Taking together this and previous studies,[9–12,19] it seems that slow breathing induces a generalized decrease in the excitatory pathways regulating respiratory and cardiovascular systems. It is important to consider that respiratory and cardiovascular systems share similar control mechanisms, thus alterations in one system will modify the functioning of the other.[20,21] For example, in essential hypertension, the sympathetic hyperactivity has been found associated with a generalized enhancement of the excitatory pathways, leading not only to sympathetic vasoconstriction, but also chemoreflex activation.[8,24] Therefore, one can expect that a modification in the respiratory control would affect also the control of the cardiovascular system. Because the breathing is also under voluntary control, it is theoretically possible to induce such changes by voluntary modification of breathing. In turn, this practice might induce with time long-term cardiovascular and

respiratory effects, ultimately independent of volitional control. To what extent this is to be expected?

We have shown previously that slow breathing reduces chemoreflex activation; this was shown to occur almost immediately, even in untrained subjects,[9] thus suggesting a reflex origin, but also to persist in subjects with long-term training in slow breathing and even when breathing rate was forced to increase.[12] Furthermore, this was associated with a reduction of sympathetic activation and with an enhancement of the inhibitory pathways, such as the arterial baroreflex.[9,10]

This demonstrated that slow breathing is indeed capable of inducing a modification in respiratory and cardiovascular control, and that appropriate training could induce a long-term effect. In subjects with chronic congestive heart failure, a condition known to induce sympathetic and chemoreflex activation, slow breathing induced a reduction in chemoreflexes and an increase in baroreflex.[10,25] We have also shown that in these patients, 1-month training in slow breathing could induce prolonged benefits, even in terms of exercise capacity.[25]

Respiratory Modifications in Essential Hypertension

Our data showed that subjects with essential hypertension have a tendency to hyperventilate. Although absolute values of ventilation were not measured in the present study, the higher respiratory rate and the lower values of CO₂-et clearly point to this conclusion. Our findings are also consistent with previous reports of an enhanced chemoreflex in essential hypertension.[8,20,24] This may have important consequences because it is well known that an enhanced chemoreflex can increase sympathetic activity and, in turn, increase blood pressure.[20,26,27] Therefore, manipulation of the breathing pattern bears a logical rationale because by using a voluntary stimulus on respiration, we can induce reflex changes on the cardiovascular system.

Our data show that slowing breathing rate does not induce hyperventilation because neither Vm nor CO₂-et were changed despite the necessary increase in Vt. At the opposite, we found that subjects with long-term practice in slow breathing have higher CO₂-et levels and lower Vm.[12] Previous studies show that individuals who regularly practice yogic breath control techniques that involve slow breathing, such as yoga[12] and Zazen meditation, tend to have slower baseline respiratory rate.[18] Because the CO₂ is maintained within resting values, the slow breathing is well tolerated by the patients, and therefore it can be maintained for longer time with adequate training.

Study Limitations

In the present study, we did not find a decrease in heart rate during slow breathing (unlike in our previous study of patients with congestive heart failure[9]). This could have been because of some difficulty in performing the test without any previous training. Data obtained in trained subjects indicate that slow breathing is also associated with a decrease in heart rate and a decrease in ventilation, together with an increase in CO₂-et. This allows speculation that repetition of the tests

after specific training would further enhance these positive effects.

Although we observed clear short-term effects of slow breathing, it remains to be assessed whether these changes persist after resuming normal respiration and whether longer-term practice will lead to stable modifications of blood pressure and of cardiovascular and respiratory control. Further studies are needed to assess the long-term effect on this practice in subjects with essential hypertension in terms of modifications in blood pressure and in terms of the possibility of correction of this respiratory control abnormality.

Conclusions

Several previous studies have reported the increase in sympathetic activity in essential hypertension[1–4] and underlined its relevance to etiology,[2] progression, and connection with cardiovascular risk.[2,5] Many pharmacological and nonpharmachological interventions effective in treating essential hypertension, such as β-blocking agents, angiotensin-converting enzyme, angiotensin inhibitors, and physical exercise,[4] tend to reduce sympathetic activity. We presented new data indicating that slow breathing acutely reduces blood pressure in hypertension and improves baroreflex sensitivity. We have also shown that hypertensive subjects have a tendency to hyperventilate; and on the basis of our present findings, we suggest that correction of hyperventilation could improve not only cardiovascular but also respiratory control abnormalities.

Perspectives

Slow breathing showed the potential to be a simple and inexpensive method to improve autonomic balance and respiratory control and reduce blood pressure in hypertensive patients. However, the present study only reports acute modifications, and whether an acute effect of respiration on blood pressure and baroreflex sensitivity could be maintained chronically remains to be assessed. Further research is required to establish the long-term reliability of these short-term findings.

Acknowledgments

References

1. Malliani A, Pagani M, Lombardi F, Furlan R, Guzzetti S, Cerutti S. Spectral analysis to assess increased sympathetic tone in arterial hypertension. *Hypertension.* 1991;17:III36–III42.
2. Brook RD, Julius S. Autonomic imbalance, hypertension, and cardiovascular risk. *Am J Hypertens.* 2000;13:112S–122S.
3. Mancia G. Bjorn Folkow Award Lecture. The sympathetic nervous system in hypertension. *J Hypertens.* 1997;15:1553–1565.
4. Pagani M, Somers V, Furlan R, Dell'Orto S, Conway J, Baselli G, Cerutti S, Sleight P, Malliani A. Changes in autonomic regulation induced by physical training in mild hypertension. *Hypertension.* 1988;12:600–610.
5. Mancia G, Grassi G, Giannattasio C, Seravalle G. Sympathetic activation in the pathogenesis of hypertension and progression of organ damage. *Hypertension.* 1999;34:724–728.
6. Radaelli A, Bernardi L, Valle F, Leuzzi S, Salvucci F, Pedrotti L, Marchesi E, Finardi G, Sleight P. Cardiovascular autonomic modulation in essential hypertension: effect of tilting. *Hypertension.* 1994;24:556–563.
7. Mancia G, Grassi G. Mechanisms and clinical implications of blood pressure variability. *J Cardiovasc Pharmacol.* 2000;35(suppl 4):S15–S19.
8. Somers VK, Mark AL, Abboud FM. Potentiation of sympathetic nerve responses to hypoxia in borderline hypertensive subjects. *Hypertension.* 1988;11:608–612.
9. Bernardi L, Gabutti A, Porta C, Spicuzza L. Slow breathing reduces chemoreflex response to hypoxia and hypercapnia, and increases baroreflex sensitivity. *J Hypertens.* 2001;19:2221–2229.
10. Bernardi L, Porta C, Spicuzza L, Bellwon J, Spadacini G, Frey AW, Yeung LY, Sanderson JE, Pedretti R, Tramarin R. Slow breathing increases arterial baroreflex sensitivity in patients with chronic heart failure. *Circulation.* 2002;105:143–145.
11. Goso Y, Asanoi H, Ishise H, Kameyama T, Hirai T, Nozawa T, Takashima S, Umeno K, Inoue H. Respiratory modulation of muscle sympathetic nerve activity in patients with chronic heart failure. *Circulation.* 2001;104:418–423.
12. Spicuzza L, Gabutti A, Porta C, Montano N, Bernardi L. Yoga and chemoreflex response to hypoxia and hypercapnia. *Lancet.* 2000;356:1495–1496.
13. Rosenthal T, Alter A, Peleg E, Gavish B. Device-guided breathing exercises reduce blood pressure: ambulatory and home measurements. *Am J Hypertens.* 2001;14:74–76.
14. Minson CT, Halliwill JR, Young TM, Joyner MJ. Sympathetic activity and baroreflex sensitivity in young women taking oral contraceptives. *Circulation.* 2000;102:1473–1476.
15. Guasti L, Grimoldi P, Mainardi LT, Petrozzino MR, Piantanida E, Garganico D, Diolisi A, Zanotta D, Bertolini A, Ageno W, Grandi AM, Cerutti S, Venco A. Autonomic function and baroreflex sensitivity during a normal ovulatory cycle in humans. *Acta Cardiol.* 1999;54:209–213.
16. Askanazi J, Silverberg PA, Foster RJ, Hyman AI, Milic-Emili J, Kinney JM. Effects of respiratory apparatus on breathing pattern. *J Appl Physiol.* 1980;48:577–580.
17. Davies LC, Francis D, Jurak P, Kara T, Piepoli M, Coats AJ. Reproducibility of methods for assessing baroreflex sensitivity in normal controls and in patients with chronic heart failure. *Clin Sci (Lond).* 1999;97:515–522.
18. Lehrer P, Sasaki Y, Saito Y. Zazen and cardiac variability. *Psychosom Med.* 1999;61:812–821.
19. Montano N, Cogliati C, Porta A, Pagani M, Malliani A, Narkiewicz K, Abboud FM, Birkett C, Somers VK. Central vagotonic effects of atropine modulate spectral oscillations of sympathetic nerve activity. *Circulation.* 1998;98:1394–1399.
20. Francis DP, Ponikowski P, Coats AJS. Chemoreflex-baroreflex interactions in cardiovascular disease. In: Bradley DT, Floras JS, eds. *Sleep Apnea. Implications in Cardiovascular and Cerebrovascular Disease.* New York, NY: Dekker; 2000:33–56.
21. Somers VK, Mark AL, Abboud FM. Interaction of baroreceptor and chemoreceptor reflex control of sympathetic nerve activity in normal humans. *J Clin Invest.* 1991;87:1953–1975.
22. Pagani M, Pizzinelli P, Bergamaschi M, Malliani A. A positive feedback sympathetic pressor reflex during stretch of the thoracic aorta in conscious dogs. *Circ Res.* 1982;50:125–132.
23. Narkiewicz K, Somers VK. The sympathetic nervous system and obstructive sleep apnea: implications for hypertension. *J Hypertens.* 1997;15:1613–1619.
24. Trzebski A, Tafil M, Zoltowski M, Przybylski J. Increased sensitivity of the arterial chemoreceptor drive in young men with mild hypertension. *Cardiovasc Res.* 1982;16:163–172.
25. Bernardi L, Spadacini G, Bellwon J, Hajiric R, Roskamm H, Frey AW. Effect of breathing rate on oxygen saturation and exercise performance in chronic heart failure. *Lancet.* 1998;351:1308–1311.
26. Narkiewicz K, van de Borne PJ, Montano N, Dyken ME, Phillips BG, Somers VK. Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea. *Circulation.* 1998;97:943–945.
27. Van De Borne P, Mezzetti S, Montano N, Narkiewicz K, Degaute JP, Somers VK. Hyperventilation alters arterial baroreflex control of heart rate and muscle sympathetic nerve activity. *Am J Physiol.* 2000;279:H536–H541.

Hypertension

American Heart Association®

Slow Breathing Improves Arterial Baroreflex Sensitivity and Decreases Blood Pressure in Essential Hypertension

Chacko N. Joseph, Cesare Porta, Gaia Casucci, Nadia Casiraghi, Mara Maffeis, Marco Rossi and Luciano Bernardi

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/46/4/714