

## The relationship between cardiac output and posthyperventilation hyperpnoea in patients with essential hypertension

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**ABSTRACT:** Posthyperventilation hyperpnoea (PHVH) is the progressive decline in minute ventilation ( $V'E$ ) that follows abrupt cessation of voluntary hyperventilation. It has been hypothesized that the increase in cardiac output (CO) during hyperventilation could contribute to the duration of PHVH.

This hypothesis was tested by measuring the duration of PHVH in patients with essential hypertension, in whom the increase in CO as a result of various stimuli is less pronounced. Twenty male hypertensives (mean arterial blood pressure  $\pm$  SEM: 178/107  $\pm$  3/1 mmHg), and 12 age-matched male healthy subjects were studied. The study consisted of three periods: control (5 min), voluntary hyperventilation (2 min), and recovery (3 min).  $V'E$ , CO, end-tidal  $CO_2$  and  $O_2$  tensions were measured, and the time constant ( $\tau$ ) of the  $V'E$  decay during recovery calculated.

The  $V'E$  decay was faster in hypertensives ( $\tau$ : 0–8.4 s) than in healthy subjects ( $\tau$ : 12–59 s;  $p < 0.01$ ). During voluntary hyperventilation, CO increased to a lesser extent in hypertensives (6.8  $\pm$  0.7 L  $\cdot$  min<sup>-1</sup>) than in healthy subjects (12.9  $\pm$  1.1 L  $\cdot$  min<sup>-1</sup>;  $p < 0.01$ ). In hypertensives, changes in CO during voluntary hyperventilation were significantly related to  $\tau$  ( $r = 0.646$ ;  $n = 20$ ;  $p = 0.002$ ).

The less pronounced rise in cardiac output during hyperventilation in hypertensives could account for the shorter duration of posthyperventilation hyperpnoea.

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Following abrupt cessation of voluntary hyperventilation, ventilation declines gradually towards the baseline. This phenomenon has been called posthyperventilation hyperpnoea (PHVH), and it is believed to be due to the activation of a reverberating circuit of neurons in the respiratory centre area [1]. This reverberating circuit is activated along with the respiratory neurons and provides sufficient input to the respiratory centres to maintain ventilation after the decrease in chemoreceptor activity [1]. It has been demonstrated that different factors, such as the changes in arterial pH and  $CO_2$  tension [2, 3], blood progesterone levels [4], and respiratory frequency during hyperventilation [3], can affect the duration of PHVH.

It is well known that increases in cardiac output (CO) are followed by an increase in respiratory frequency and minute ventilation ( $V'E$ ) in dogs [5, 6]. However, there is evidence that during voluntary hyperventilation CO is substantially raised in healthy subjects [7, 8]. Thus, it has been suggested that the increase in CO occurring during voluntary hyperventilation may affect the duration of PHVH [2]. It is also known that, in hypertensive patients, the increase of CO in response to exercise is less pronounced [9]. Therefore, if PHVH is influenced by the rise in CO during voluntary hyperventilation, hypertensive patients are expected to have a shorter duration of PHVH, thus providing a model to study the determinants of the PHVH phenomenon in humans. To test this hypothesis,

the duration of PHVH and the changes in CO during voluntary hyperventilation in patients with essential hypertension and in healthy subjects were assessed.

### Materials and methods

We studied 20 male patients with essential hypertension (age range: 29–62 yrs) and 12 age-matched male healthy subjects (controls). Four hypertensives and two controls were current smokers. The mean values ( $\pm$  SEM) of arterial blood pressure were 178/107  $\pm$  3/1 and 121/71  $\pm$  2/2 mmHg in hypertensives and controls, respectively. Hypertensive patients belonged to stage I or II of the World Health Organization (WHO) classification and showed no concurrent illness, including respiratory tract disorders. Antihypertensive drugs were withdrawn  $\geq$  4 weeks before the study. Subjects were not allowed to drink beverages containing xanthines for  $\geq$  24 h before the study. The study was approved by the Ethics Committee of the University of Catania, and each subject gave informed consent to participation in the study.

Subjects were seated and breathing through a face mask to which was attached a turbine flow head to measure airflow. A sampling line for the collection of end-expiratory gases was also connected to the face mask. After 10 min of quiet breathing, subjects were asked to perform sustained

hyperventilation for a 2-min period. The two-minute voluntary-hyperventilation period was started and stopped by verbal command. Subjects were free to regulate both tidal volume and respiratory frequency during the hyperventilation period. However, during the very beginning of the hyperventilation period, verbal instructions were given to adjust the level of hyperventilation in order to maintain end-tidal  $\text{CO}_2$  tension ( $P_{\text{ET},\text{CO}_2}$ ) as close as possible to 2.7 kPa. This target was obtained within the first minute of voluntary hyperventilation in all study subjects.  $V_{\text{E}}$ ,  $P_{\text{ET},\text{CO}_2}$  and end-tidal oxygen tension were measured on a breath-by-breath basis with a computerized system (MMC 4400tc; SensorMedics, Yorba Linda, CA, USA). Measurements were performed during quiet breathing (5 min; control), during the two-minute voluntary-hyperventilation period and in the first 3 min of the recovery period. Measurements of CO were performed during control quiet breathing and during the last 30 s of voluntary hyperventilation. CO was measured noninvasively by the  $\text{CO}_2$ -rebreathing method [10]. Briefly, subjects inhaled at end-expiration a gas mixture containing 5%  $\text{CO}_2$  and 21%  $\text{O}_2$  in  $\text{N}_2$  and then rebreathed that gas mixture for 30 s in a two-litre bag.  $\text{CO}_2$  and  $\text{O}_2$  concentrations during the rebreathing were measured breath-by-breath by fast-response (<200 ms) infra-red and zirconium analysers, respectively. Arterial blood pressure was recorded noninvasively (Dynamap 845; Dynamap, Tampa, FL, USA) at baseline, during hyperventilation and during the recovery; the mean of three values obtained at each time interval was used for analysis.

The reproducibility of the PHVH was assessed by repeating the study after a two-hour interval in a subgroup of eight hypertensives and eight controls. The values for  $V_{\text{E}}$  and of  $P_{\text{ET},\text{CO}_2}$  were averaged for the control period and during the two-minute voluntary-hyperventilation period. During the recovery period, for each subject,  $V_{\text{E}}$  was averaged every 10 s. The first breath of recovery was calculated separately, but it was also included in the 0–10-s average. The time constant ( $\tau$ ) of the  $V_{\text{E}}$  decay over time ( $t$ ) during the recovery was calculated by fitting an exponential curve to the  $V_{\text{E}}$  data:  $V_{\text{E}}(t) = g \exp(-t/\tau)$ , where  $g$  is the magnitude of the first breath in the recovery period. The exponential equation was calculated by the least-squares method. Data are reported as mean  $\pm$  SEM. Differences in the two study groups were assessed by a two-sample  $t$ -test. Statistical significance was accepted for  $p < 0.05$ .

## Results

Figure 1 shows the mean ( $\pm$ SEM)  $V_{\text{E}}$  measured at rest, during voluntary hyperventilation and in the recovery period in the two groups. The mean baseline value ( $\pm$ SEM) of  $V_{\text{E}}$  in hypertensive patients was  $9.9 \pm 0.9 \text{ L}\cdot\text{min}^{-1}$ , and did not differ from the corresponding values in normal subjects:  $9.8 \pm 0.7 \text{ L}\cdot\text{min}^{-1}$  ( $p = 0.56$ ). During the two-minute voluntary hyperventilation period, the average  $V_{\text{E}}$  was also similar in hypertensive patients and controls ( $74.7 \pm 2.6$  and  $76.8 \pm 3.1 \text{ L}\cdot\text{min}^{-1}$ , respectively). The respiratory frequency achieved during the last minute of voluntary hyperventilation did not differ in the two groups ( $55.4 \pm 3.2$  and  $56.9 \pm 3.7 \text{ breaths}\cdot\text{min}^{-1}$ , in hypertensives and controls, respectively). Resting  $P_{\text{ET},\text{CO}_2}$  was  $5.20 \pm 0.028$  and  $5.17 \pm 0.023 \text{ kPa}$  in hypertensive patients and controls, respectively. During voluntary hyperventilation,  $P_{\text{ET},\text{CO}_2}$  fell to  $2.80 \pm$

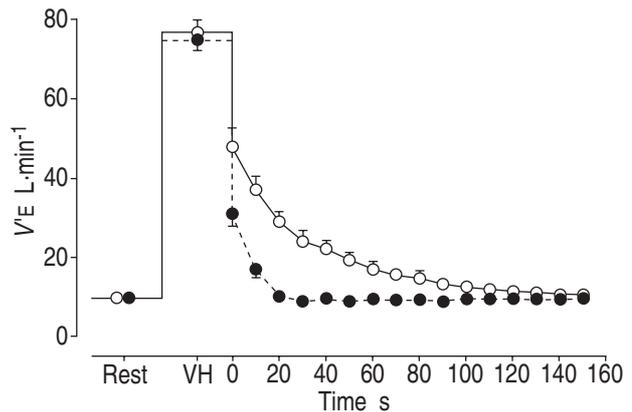


Fig. 1. – Mean ( $\pm$ SEM) minute ventilation ( $V_{\text{E}}$ ) measured at rest, during voluntary hyperventilation (VH) and during the 150 s following cessation of voluntary hyperventilation in 20 hypertensive patients ( $\bullet$ ) and in 12 healthy subjects ( $\circ$ ).

$0.016$  and  $2.79 \pm 0.021 \text{ kPa}$  in hypertensive patients and controls, respectively. At the end of the hyperventilation period, during the CO measurement,  $P_{\text{ET},\text{CO}_2}$  rose to similar values in both groups ( $4.50 \pm 0.055$  and  $4.55 \pm 0.082 \text{ kPa}$ , in hypertensives and controls, respectively).

After voluntary hyperventilation,  $V_{\text{E}}$  fell immediately to basal values in seven out of 20 hypertensives; in the remaining 13 patients, the decay of  $V_{\text{E}}$  ( $\tau$  range: 0.2–8.4 s) was faster than in the controls ( $\tau$  range: 12–59 s). The mean  $\pm$  SEM of  $\tau$  obtained in the whole group of hypertensive patients ( $n = 20$ ) was significantly lower than in the controls

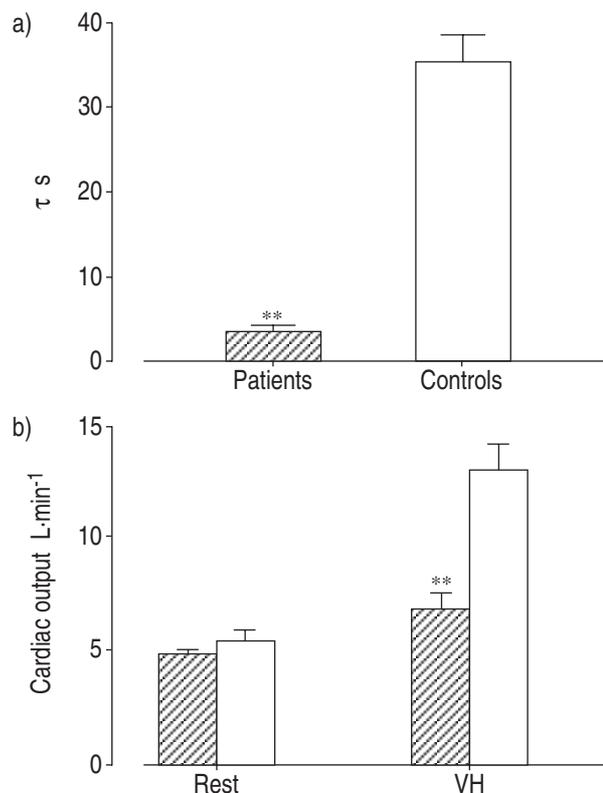


Fig. 2. – a) Mean ( $\pm$ SEM) time constant ( $\tau$ ) of decay of posthyperventilation hyperpnoea obtained in hypertensive patients ( $\square$ ;  $n = 20$ ) and in healthy subjects ( $\square$ ;  $n = 12$ ). b) Mean ( $\pm$ SEM) cardiac output at rest and during voluntary hyperventilation (VH) in hypertensive patients ( $n = 20$ ) and in healthy subjects ( $n = 12$ ). \*\*:  $p < 0.01$ .

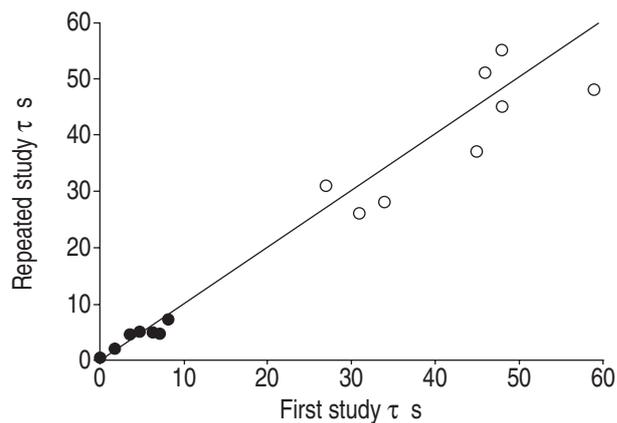


Fig. 3. – Identity plot of the time constant ( $\tau$ ) of decay of posthyperventilation hyperpnoea measured in the first study and after a two-hour interval (repeated study) in eight hypertensive patients ( $\bullet$ ) and in eight healthy subjects ( $\circ$ ).

( $p < 0.01$ ; fig. 2). Basal CO was not significantly different in hypertensives as compared with controls ( $4.8 \pm 0.5$  versus  $5.4 \pm 0.2$  L $\cdot$ min $^{-1}$ , respectively), whereas during hyperventilation, it rose to a lesser extent in hypertensives as compared with controls ( $6.8 \pm 0.7$  versus  $12.9 \pm 1.1$  L $\cdot$ min $^{-1}$ , respectively;  $p < 0.01$ ; fig. 2). In hypertensive patients, there was a significant linear relationship between changes in CO during voluntary hyperventilation and  $\tau$  ( $r = 0.646$ ;  $n = 20$ ;  $p = 0.002$ ).

Identity plots of  $\tau$ , measured in both hypertensives and healthy subjects, in the first study and after a two-hour interval are reported in figure 3. The duration of the PHVH was reproducible in both groups, the intra-individual coefficient of variation of  $\tau$  ranging from 2.4–11.7%.

During voluntary hyperventilation, the arterial blood pressure fell slightly from  $175/106 \pm 10/8$  to  $168/93 \pm 9/5$  mmHg, nonsignificant (ns) in hypertensive patients and from  $124/78 \pm 8/4$  to  $118/74 \pm 7/4$  mmHg (ns) in controls. The heart rate during voluntary hyperventilation rose significantly from  $78.4 \pm 6.5$  to  $94.7 \pm 7.2$  beats $\cdot$ min $^{-1}$  in hypertensives ( $p < 0.01$ ), and from  $74.9 \pm 5.3$  to  $98.6 \pm 6.7$  beats $\cdot$ min $^{-1}$  ( $p < 0.01$ ) in controls. The differences between the groups for blood pressure and heart rate changes were not significant.

### Discussion

In this study, it was demonstrated that hypertensive patients have a shorter duration of PHVH as compared to control healthy subjects. This phenomenon was reproducible and was associated with a lesser increase in CO during voluntary hyperventilation.

PHVH is a well-known phenomenon occurring in healthy subjects after a short period of sustained voluntary hyperventilation. The activation of reverberating circuits of neurons in the respiratory centre area has been hypothesized to be a major determinant of the progressive decay of  $\dot{V}_E$  occurring after cessation of voluntary hyperventilation [11]. It is conceivable that this neural mechanism, associated with active hyperventilation, supplies sufficient neural input to the respiratory centres in order to prevent apnoea caused by the decrease in chemoreceptor activity

due to the decreased levels of arterial carbon dioxide tension that occur during hyperventilation [11].

It is well established that in healthy subjects, voluntary hyperventilation is associated with a substantial increase in CO [8]. Indeed, the respiratory alkalosis caused by hyperventilation induces a decrease in pulmonary vascular resistance, yielding, in turn, an increase in CO [12, 13]. Another mechanism contributing to this increase in CO is the rise in venous return along with the improvement in left ventricular function due to rapid swings in intrathoracic pressure associated with hyperventilation. A second aspect of the integration between  $\dot{V}_E$  and CO should be taken into account. It has been pointed out that the increase in CO is followed by a rise in resting  $\dot{V}_E$  as well as in respiratory frequency in dogs [5, 6], thus indicating that changes in CO can affect the ventilatory output. In addition, it has been postulated that the increase in CO occurring during voluntary hyperventilation could be partially responsible for the occurrence of PHVH [2]. Our results, showing that the smaller increase in CO during hyperventilation is followed by a shorter duration of PHVH in patients with essential hypertension, and that there was a significant correlation between changes in CO and duration of PHVH in hypertensives, substantially support this hypothesis and suggest a causal relationship between these two phenomena. The small increase in CO in hypertensive patients observed in our study is in agreement with previous observations showing that hypertensive patients have a less pronounced increase in CO during exercise as a consequence of the poor functional reserve of the left ventricle [9, 14]. In our study CO, was measured noninvasively by the indirect Fick method because a more invasive procedure would not have been justified for the purpose of the study. In addition, the indirect Fick method is widely accepted for the assessment of CO [10, 15, 16], and it has been used for measuring CO during voluntary hyperventilation in healthy subjects [8].

Mechanisms other than CO changes may be involved in the regulation of PHVH. For example,  $P_{ET,CO_2}$  levels as well as respiratory frequency during voluntary hyperventilation are two important factors affecting the duration of PHVH [2, 3]. In our study, however, both hypertensives and controls showed similar levels of  $P_{ET,CO_2}$ ,  $\dot{V}_E$ , and respiratory frequency during hyperventilation, thus implying that these factors can be ruled out as determinants of the different durations of PHVH in the two groups. Furthermore,  $P_{ET,CO_2}$  at the end of hyperventilation during the CO measurements was similar in hypertensives and controls. It should also be emphasized that the pattern of the decay of  $\dot{V}_E$  after voluntary hyperventilation was highly reproducible, as assessed by the  $\tau$  values obtained at two-hour intervals, both in healthy subjects and in hypertensive patients. Finally, the possibility that cerebrovascular damage associated with hypertension can affect the activity of neural centres responsible for the after discharge cannot be excluded. We have previously demonstrated that hypertensive patients exhibit a faster recovery from cerebral vasoconstriction caused by hyperventilation-induced hypocapnia, indicating an alteration in cerebrovascular reactivity [17]. However, the possibility that these or other cerebrovascular alterations can affect the respiratory centres remains purely speculative.

This study represents the first observation that hypertensive patients exhibit alterations in the control of breathing

characterized by a shorter duration of posthyperventilation hyperpnoea after voluntary hyperventilation. Furthermore, our results support the notion that cardiac output and minute ventilation are strongly integrated and indicate that the alteration in cardiac function has important consequences on the control of breathing in essential hypertension. Our findings that hypertensive patients, who have a less pronounced rise in cardiac output, have a much shorter posthyperventilation hyperpnoea are in agreement with previous observations showing that spontaneous hyperventilation during sleep is followed by central sleep apnoea or periodic breathing in patients with congestive heart failure [18]. Our data indicate that patients with essential hypertension are more prone to alterations of the mechanisms involved in the control of breathing. We suggest that these alterations could be responsible for changes in breathing pattern during sleep and central apnoea episodes occurring in hypertensive patients during sleep.

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