Effects of positive-pressure ventilation on the spontaneous baroreflex in healthy subjects

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Fietze, Ingo, Dietrich Romberg, Martin Glos, Susanne Endres, Heinz Theres, Christian Witt, and Virend K. Somers. Effects of positive-pressure ventilation on the spontaneous baroreflex in healthy subjects. J Appl Physiol 96: 1155–1160, 2004. First published November 7, 2003; 10.1152/japplphysiol.00578.2003.—To determine the short-term effects of noninvasive positive-pressure ventilation (PPV) on spontaneous baroreflex sensitivity, we acquired time series of R-R interval and heart-to-beat blood pressure in 55 healthy volunteers (mean age 46.5 ± 10.5 yr) who performed breathing on four occasions at frequencies of 12 and 15 breaths/min without positive pressure (control) and also using PPV of 5 mbar. By using spectral and cross-spectral analysis, R-R interval variability and systolic blood pressure variability as well as the gain (α-index) of the baroreceptor reflex were estimated for the low-frequency and high-frequency (HF) bands. Compared with control breathing, PPV at 12 breaths/min and 15 breaths/min led to an increase in mean R-R (P < 0.001) and blood pressure (P < 0.05). The α-index of the HF band increased significantly for both respiratory frequencies (P < 0.05) due to PPV. These results indicate that short-term administration of PPV in normal subjects elicits a significant enhancement in the HF index of the baroreflex gain. These findings may contribute to understanding the mechanisms, indications, and effectiveness of positive pressure breathing strategies in treating cardiorespiratory and other disease conditions.

baroreflex sensitivity; heart rate variability; blood pressure variability

There is compelling evidence that phases of respiration have distinct and powerful effects on both vagal and sympathetic cardiovascular control. Changes in respiratory patterns, during hyperventilation for example, influence cardiac and vascular function not only by changes in blood gas chemistry, but also by modulating neural circulatory control mechanisms (42). The significance of these interactions in conditions of health and disease are being increasingly recognized (2, 12, 23, 44) and may be especially relevant to disease conditions affecting both the cardiovascular and respiratory systems, such as heart failure and obstructive sleep apnea (OSA).

Cessation of air exchange as occurs during sleep-disordered breathing also results in sympathetic activation and increases in blood pressure (46). Treatment of these sleep-related breathing disorders with noninvasive positive-pressure ventilation (PPV) as applied by a continuous positive airway pressure (CPAP) device has very significant effects on autonomic tone and baroreflex function (2, 5, 27). Both long-term and short-term applications of PPV have been shown to improve autonomic balance and baroreflex sensitivity in OSA patients with heart failure (28, 44). Autonomic circulatory control and baroreflex function are important in the pathophysiology and prognosis of cardiovascular diseases in patients with breathing disorders.

The baroreflex sensitivity (BRS) is usually quantified by vasoactive drug administration that raises or lowers systemic arterial pressure or by direct engagement of carotid baroreceptors with neck chamber devices (15). The need for intravenous infusions or neck chamber devices limits the use of these methods, especially in large populations, monitoring, or follow-up studies. Recent studies have suggested that transfer function analysis of spontaneous fluctuations of arterial blood pressure and R-R intervals offers a noninvasive and perhaps more “physiological” method for assessing BRS, especially in free living conditions (10, 31, 35, 38) with good BRS reproducibility (18).

Although noninvasive PPV is widely used in conditions of cardiovascular and respiratory dysfunction, the hemodynamic and reflex consequences of PPV application on cardiovascular control per se are poorly understood. Prior study examining the effects of PPV on the spontaneous baroreflex in humans was limited to the setting of deep slow patterned breathing at one breath every 10 s (45). We tested the hypothesis that the short-term application of PPV using a bilevel mode in healthy awake subjects, even in the absence of sleep-disordered breathing, would cause acute alterations in neural circulatory control mechanisms.

METHODS

Subjects. Fifty-five (26 women, 29 men) healthy volunteers (mean age 46.5 ± 10.5, range 28–64 yr) participated in the study. All gave their written, informed consent. The study was approved by the Institutional Human Subjects Review Committee. Sleep-related breathing disorders were excluded by two nights of standard polysomnography.

ECG, lung function test, blood analysis, and sleep and health questionnaires were performed before subjects entered the study. Subjects with heart rhythm disorders, obstructive or restrictive respiratory disturbances, and acute or chronic illness evident on these laboratory data were excluded from the study. None of the subjects was receiving acute or chronic medications.

Protocol. The study protocol was approved by the Institutional Ethics Committee. All recordings were performed between 9 and 11 AM during wakefulness in a quiet room. Subjects were studied in a...
45° head-up lying position. Each subject was trained in metronomecontrolled breathing at frequencies of 12 and 15 breaths/min. After an adaptation of ~10 min, data acquisition of ~6 min in each case was performed at each of the following low settings: 1) breathing at a frequency of 12 breaths/min without PPV (control) and with PPV of 5 mbar, and 2) breathing at a frequency of 15 breaths/min without PPV (control) and with PPV of 5 mbar. PPV was applied by use of a nasal bilevel positive airway pressure device with timed mode to control respiratory frequency under ventilated conditions and to make breathing more comfortable.

Signal acquisition. Heart rate was estimated from successive R-R intervals in ECG lead II. Continuous measurements of beat-to-beat blood pressure were obtained with the Portapres system (TNO-TPD, Amsterdam, The Netherlands). Noninvasive monitoring of the blood pressure has been shown to correspond closely to intra-arterial blood pressure measurements both at rest and during rapid changes in blood pressure (32) and to be adequate for more complex time and frequency domain analysis of blood pressure variability and baroreceptor sensitivity (14).

Respiratory effort was recorded by use of a thoracic belt containing a piezo-crystal transducer (Pro-Tech Services, Woodinville, WA). All signals were recorded simultaneously with an EMBLA digital polysonomographic recorder (Flaga, Reykjavik, Iceland). The sampling rate was 200 Hz for the ECG and blood pressure signals and 50 Hz for the respiration signal.

Signal analysis. All recordings were analyzed by use of a custom-made Matlab software package (version 5.3, The MathWorks, Natick, MA). After filtering (Butterworth band pass, 0.7–30 Hz) of the recordings, beat-to-beat time series of R-R intervals (R-R), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were determined. Artifacts were eliminated and corrected manually. Intervals of 180 consecutive beats were selected for R-R (ms), SBP (mmHg), and DBP (mmHg), interpolated with cubic splines, and resampled with 4 cycles/beat. After trend elimination and windowing (Hanning, n = 256), the fast Fourier transformation, based on Welch’s method (47), was calculated to obtain the power spectral density for R-R variability (HRV) and SBP variability (SBPV). Frequency unit dimensions were changed by means of the mean heart rate in the corresponding breathing protocol. The low-frequency (LF) and the high-frequency (HF) bands of HRV and SBPV were calculated by integration of the spectral components (LF: 0.04–0.15 Hz; HF: 0.15–0.4 Hz). In addition, the LF and HF components of HRV were measured in normalized units, which represent the relative value of each power component in proportion to the total power of the HF and LF bands (25). For further analysis of the autonomic balance, the ratio LF/HF was calculated.

The baroreflex function was described by the gain (α-index) between HRV and SBPV calculated separately for the LF (0.08–0.12 Hz) and HF (breathing frequency) band by using spectral and cross-spectral analysis (31, 37).

The α-index was obtained from the square root of the ratio between the low power spectral densities of HRV and SBPV for the HF and LF bands. Accordingly, αHF indicates the gain of the baroreflex loop in the HF band, whereas αLF indicates the gain of the reflex loop in the LF band (38). The overall gain (αTOT) was calculated as αTOT = 0.5(αHF + αLF) (24).

Statistics. Results are given as mean ± SE values. Mean values for R-R, SBP, and DBP were calculated as the average of the corresponding time series. Nonparametric Wilcoxon’s rank test was used to evaluate differences between control and PPV measurements at both respiratory frequencies. The squared coherence function K2(f), which ranges between zero and unity, was used to evaluate the statistical reliability of the cross-spectral analysis at each frequency. Estimations of the phase γ(f) were accepted if the squared coherence function K2 exceeded 0.56 (10, 37). Statistical analyses were performed by using the software package SPSS for Windows (version 10.0, SPSS, Chicago, IL). Differences were considered significant when a two-tailed P value of <0.05 was found.

RESULTS

Of the 55 subjects studied, results from five subjects were excluded from analysis because of extrasystolic activity or artifacts throughout the study.

Hemodynamic changes. Generally, similar changes in hemodynamic variables were observed during PPV for both respiratory frequencies. R-R intervals and DBP showed a significant increase, whereas SBP increased with PPV at 12 breaths/min, but the increase fell short of significance at 15 breaths/min respiratory frequency (Table 1).

Time series. A representative set of resampled time series of R-R intervals and SBP measured from one subject during all settings of the study protocol is demonstrated in Fig. 1. The presence of the breathing frequency is clearly visible in the R-R interval plots. It should be noted from the SBP waveforms that the larger amplitude LF fluctuations are not related directly to the breathing pattern.

Spectral analysis. Figure 2 shows the power density spectra of HRV and SBPV for the corresponding time series depicted in Fig. 1. The spectra for HRV show a dominant HF component at the respiratory frequency. Corresponding but smaller peaks can be also seen in the SBP spectra. In contrast, LF (less

### Table 1. Autonomic and baroreflex indexes during control breathing and PPV

<table>
<thead>
<tr>
<th>Variable</th>
<th>Respiratory Frequency (12 breaths/min)</th>
<th>Respiratory Frequency (15 breaths/min)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>PPV</td>
</tr>
<tr>
<td><strong>Time domain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR, ms</td>
<td>902.6 ± 15.4</td>
<td>957.1 ± 17.4†</td>
</tr>
<tr>
<td>RR-variance, ms²</td>
<td>38.94 ± 19.0</td>
<td>43.47 ± 21.0†</td>
</tr>
<tr>
<td>R-RMSD, ms</td>
<td>32.19 ± 22.6</td>
<td>37.30 ± 22.8†</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>129.6 ± 3.04</td>
<td>134.7 ± 2.79*</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>64.45 ± 1.91</td>
<td>68.63 ± 2.14*</td>
</tr>
<tr>
<td><strong>HRV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>0.657 ± 0.08</td>
<td>0.550 ± 0.07</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>16.32 ± 6.00</td>
<td>15.35 ± 1.41</td>
</tr>
<tr>
<td>LF-norm</td>
<td>0.375 ± 0.02</td>
<td>0.355 ± 0.03</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>34.08 ± 4.15</td>
<td>38.29 ± 5.85*</td>
</tr>
<tr>
<td>HF-norm</td>
<td>0.625 ± 0.02</td>
<td>0.645 ± 0.03</td>
</tr>
<tr>
<td><strong>SBPV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>3.442 ± 0.42</td>
<td>5.844 ± 1.26</td>
</tr>
<tr>
<td>LF, mmHg²</td>
<td>0.295 ± 0.02</td>
<td>0.283 ± 0.03</td>
</tr>
<tr>
<td>HF, mmHg²</td>
<td>0.168 ± 0.02</td>
<td>0.167 ± 0.03</td>
</tr>
<tr>
<td><strong>α-index</strong></td>
<td></td>
<td></td>
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<tr>
<td>αTOT, ms/mmHg</td>
<td>12.93 ± 6.45</td>
<td>13.90 ± 6.88†</td>
</tr>
<tr>
<td>αLF, ms/mmHg</td>
<td>7.743 ± 0.52</td>
<td>7.993 ± 0.64</td>
</tr>
<tr>
<td>αHF, ms/mmHg</td>
<td>18.58 ± 1.98</td>
<td>21.48 ± 2.35†</td>
</tr>
</tbody>
</table>

Values are means ± SE. Control, control breathing at 0 mbar; PPV, positive pressure ventilation at 5 mbar; RR, R-R intervals in ECG; RR-Var, variance of R-R intervals in ECG; RMSDD, root mean square of successive differences of R-R intervals in ECG; SBP, systolic blood pressure; DBP, diastolic blood pressure; HRV, heart rate variability; LF, low frequency; LF-norm, normalized LF units; HF, high frequency; HF-norm, normalized HF units; TOT, mean of LF and HF; SBPV, systolic blood pressure variability. PPV vs. Control: *P < 0.05, †P < 0.01, ‡P < 0.001.
than \(-0.05\) Hz) spectral power was more apparent for systolic blood pressure than R-R intervals.

Cross-spectral analysis. In Fig. 3, the frequency distribution of the \(\alpha\)-index is shown for the time series depicted in Fig. 1. For PPV, the spectra for the \(\alpha\)-index revealed a marked predominance of the respiratory frequency component. The reliability of the estimation of both measures was assessed by the coherence function. All breathing protocols yielded a significant relationship (coherence >0.56) between HRV and SBPV spectra in most of the 50 patients (at 12 breaths/min: 43 patients during control and 36 patients during PPV; at 15 breaths/min: 39 patients during control and 34 patients during PPV).

 Autonomic and baroreflex indexes. The mean values of the indexes of cardiovascular autonomic control and baroreflex function are summarized in Table 1. Significant differences between control breathing and PPV were present for the HF component of the HRV as well as for the \(\alpha\)-index at both respiratory frequencies. PPV did not cause any differences in SBPV characteristics.

DISCUSSION

The application of PPV is gaining increasing recognition as a potential therapeutic approach in OSA (48) and in central sleep apnea (41). Chronic nocturnal positive pressure therapy...
for heart failure patients with central sleep apnea improves cardiac hemodynamics (6, 28, 41). Important data from Sin et al. (41) show improvements even in quality of life and transplant-free survival. In patients with congestive heart failure, there is evidence that a reduction in the baroreflex sensitivity is associated with poorer prognosis (22, 26, 44). Interestingly, PPV has been shown to cause acute decreases of heart rate and blood pressure as well as acute increases of baroreflex sensitivity in congestive heart failure patients with OSA (19, 44). PPV also lowers blood pressure and increases baroreflex gain in patients with refractory hypertension and OSA (23). Hypertension, heart failure, and OSA are each associated with impaired neural circulatory control mechanisms. Thus short-term effects of PPV in disease conditions include an improvement in autonomic control of cardiovascular function, especially in baroreflex gain. Only very limited data (45) are available on the acute effects of PPV on neural circulatory control in healthy normal subjects.

Our study shows that in healthy awake normal subjects, administration of even modest levels of positive end expiratory pressure at 5 mbar results in significant changes in hemodynamics and in measurements of neural circulatory control with increases in blood pressure, decreases in heart rate, and an increase in the HF component of the α-index of baroreflex gain.

At breathing frequencies of both 12 and 15 breaths/min, application of PPV prolonged R-R interval and increased blood pressure. The increase in the R-R interval due to application of PPV may be caused by the reflex response to increased blood pressure, as well as by a decrease in sinoatrial stretch and an increase in parasympathetic control of heart rate (17). In addition, inhibition in sympathetic neural control of heart rate may be secondary to stimulation of pulmonary stretch receptors by PPV-induced increases of end-expiratory lung volume (39). Because of the increased time for filling associated with R-R prolongation, the subsequent stroke volume, and thus the pulse pressure, would increase in accordance with the Frank-Starling law. This is in line with the significant increase in the SBP and DBP during PPV (16, 36, 40) confirmed by our results. However, an additional mechanism for the blood pressure increase may be reflexive arteriolar constriction described as an early effect of baroreceptor stimulation (36).

Blood pressure responses to application of PPV in healthy awake subjects show striking differences to patients with OSA, in whom application of PPV results in very significant decreases in blood pressure levels, because of elimination of apneic events (1, 42). This may be caused, in part, by the different operating points and other characteristics of the baroreceptor reflex in both populations (2, 7, 44). We noted an increase in the α-index of the HF band, suggesting an enhanced HF component of baroreflex gain. To our knowledge, the only prior study investigating the effects of PPV application on spontaneous baroreflex function in healthy awake subjects was performed by Torok et al. (45). In a small group of subjects, effects of breathing were examined at a very LF (6 breaths/min) on baroreflex gain. They noted that whereas the slow breathing frequency enhanced baroreflex gain, application of PPV did not result in any further alteration. It is relevant that other studies have demonstrated a very significant effect of slow breathing on neural circulatory control, in particular, enhanced baroreflex gain (4, 13). Thus the profound effects of slow breathing on baroreflex gain may obscure the direct effects of PPV per se on neural circulatory control. Our study elicited a distinct increase in the HF α-index of the baroreflex due to PPV in the absence of slow breathing. The absence of further enhancement of baroreflex gain in the study by Torok et al. suggests that the ability of respiration to modulate the baroreflex is limited and that the increased gain induced by the LF breathing pattern cannot be extended further by the application of PPV. In addition, the sequence method used by Torok et al. does not take into account the confounding influences of respiration on heart rate and blood pressure (13, 37). By contrast, the present study employs more reliable and comprehensive methods for assessing baroreflex function by using spectral and cross-spectral analysis of HRV and SBV (9, 33, 35). In addition, controlled breathing frequencies of 12 and 15 breaths/min simulate more normal breathing patterns.

Mechanisms for the enhanced baroreflex gain may include a reduction in cardiac filling pressures and transmural pressure gradients and their consequence effects on the interactions between the cardiopulmonary and arterial baroreceptors (11, 12, 24, 29). PPV-mediated deactivation of cardiopulmonary receptors (as a consequence of reduced cardiac transmural pressure) may potentiate arterial baroreflex gain. The cardiopulmonary reflex deactivation may also help explain the increased blood pressure during PPV. PPV-mediated deactivation of those receptors registering filling pressure in the atria and great veins would elicit an increase in peripheral sympathetic vasocon-
striction traffic (16). This enhanced sympathetic vasoconstrictive action may contribute to the increase in blood pressure, which, acting via the arterial baroreflex, would slow the heart rate. We also cannot exclude that changes in reflex gain may in part be due to the higher blood pressure, with consequent increases in vagal tone on repositioning of the baroreflex with respect to gain characteristics on the sigmoid baroreflex curve.

The selective increase in the HF and not the LF α-index of baroreflex sensitivity speaks to a potential important role for enhanced vagal activity, as also suggested by the increase of the HF component of the HRV. As to the possible hemodynamic consequences of changes in baroreflex sensitivity, we could consider the importance of higher values of the HF α-index in promoting a buffering of the beat-by-beat variations in arterial pressure by way of changes in the R–R period when the system is operating toward stability (31).

The arterial baroreflex serves as a pressure buffer system against increases and decreases in arterial pressure. In this respect, the baroreflex has been thought to be the link between SBPV and HRV (31, 33). The increase in the HF component of R–R variability during PPV, in the absence of any change in respiratory frequency, supports the likelihood of a baroreflex-mediated contribution to the R–R prolongation (30). On the other hand, there is some evidence that heart rate changes related to respiration may contribute to SBPV, suggesting fundamental relationships between SBPV and HRV (21, 43).

Tidal volume was not controlled in this study, because the conscious mental effort to control both respiratory frequency and tidal volume may itself alter autonomic activity (13, 34). In addition, it has been previously found that changes in tidal volume are less important than breathing frequency (3, 20). However, we used a breathing protocol incorporating a stepwise change in respiratory frequency as recommended by Cooke et al. (8), who showed that subjects automatically (presumably with the aid of chemoreceptors) adjust their tidal volumes and maintain normal end-tidal CO2 levels during stepwise frequency breathing.

In conclusion, our data show that short-term administration of PPV in normal subjects elicits significant increases in R–R interval and blood pressure as well as an enhancement of the HF index of the baroreflex gain. Clinical studies of the effects of PPV have shown in patients with OSA and hypertension (23) and heart failure (42) that PPV induces increases in baroreflex gain in the context of a fall in blood pressure. These patients also have baseline impairment in baroreflex gain. Our data show that, even in healthy normal subjects, application of PPV still induces an increase in baroreflex gain, but in association with an increase in blood pressure. These findings may contribute to understanding the physiological effects of positive pressure breathing and its differential consequences when applied to treating cardiorespiratory and other disease conditions.

GRANTS

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