Altered Cardiorespiratory Transfer in Hypertension

Vera Novak, Peter Novak, Jacques de Champlain, Reginald Nadeau

Abstract The effect of continuously slowing respiration (from 0.46 to 0.05 Hz, eg, from 30 to 3 breaths per minute) on cardiovascular variables was studied in 14 hypertensive patients and 16 normotensive subjects. Beat-to-beat time-frequency (Wigner) distributions were used for dynamic analysis of RR interval and systolic and diastolic pressures. Dominant breathing frequency at rest did not differ in hypertensive patients from the control group (0.21 versus 0.19 Hz). However, in the hypertensive group it was disturbed 34.4% of the time by slow breathing and apneas, which evoked transient blood pressure instability and increased spectral powers at low frequencies (range, 0.01 to 0.1 Hz). The nonrespiratory fluctuations (NONRFs) and respiratory fluctuations (RFs) in RR interval and NONRFs in systolic pressure were smaller in hypertensive patients than in normotensive subjects. Respiratory fluctuations (RFs) in RR interval and NONRFs in systolic pressure increased higher at maximum, corresponding to breathing frequencies from 0.07 to 0.09 Hz (P < .001). A dynamic cardiorespiratory index (ratio of RFs in RR interval and systolic pressure) was smaller (P < .01) in hypertensive patients than in normotensive subjects. Irregular breathing at rest was found in hypertensive patients. The transfer from respiration into RR interval was diminished, suggesting an impaired parasympathetic responsiveness in mild hypertension. (Hypertension. 1994;23:104-113.)

Key Words • spectrum analysis • cardiovascular system • respiration • hypertension, essential

The problem of hyperreactivity of the sympathetic nervous system in essential hypertension has been studied frequently in the last two decades. An exaggerated sympathetic tone in mild hypertension can result from an increased intrinsic activity of the brain stem vasomotor neurons or can be secondary to a reduction of the inhibitory potency of baroreceptors and pulmonary volume receptors. An augmentation of sympathetic tone was considered a primary mechanism of hypertension in a subgroup of patients in which elevated levels of plasma norepinephrine and epinephrine were found. High RR interval fluctuations from 0.05 to 0.1 Hz were reported and attributed to the augmentation of sympathetic efferent activity. However, these oscillations are under combined parasympathetic and sympathetic influences. Only the parasympathetic muscarinic blockade consistently suppresses RR interval fluctuations over the range of 0.01 to 0.4 Hz, and the effect of sympathetic blockade is ambiguous. Moreover, direct recordings of sympathetic efferent activity did not show exaggerated resting levels of sympathetic tone.

Heart rate fluctuations at respiratory frequencies are recognized as a noninvasive measure of cardiovagal activity and reflect more modulation of the firing of baroreceptors and of cardiac and pulmonary volume receptors than an absolute measure of vagal tone. Diminished respiratory fluctuations (RFs) in the RR interval associated with higher resting heart rate and faster breathing have been reported in mildly hypertensive patients.

Baroreceptor reflex sensitivity is commonly evaluated by maneuvers that increase or decrease blood pressure either pharmacologically or by neck suction. In mild hypertension, baroreceptor reflex resetting and diminished baroreceptor reflex gain were proposed as indirect mechanisms for increased sympathetic neural traffic. In contrast, direct neural recordings did not reveal significant differences between normotensive subjects and hypertensive patients in baroreceptor reflex responsiveness. It was suggested that greater increases of sympathetic efferent activity during orthostatic stress were due to a withdrawal of an exaggerated resting sympathoinhibitory effect from cardiopulmonary receptors.

In the present study the respiratory pattern in mildly hypertensive patients at rest was evaluated. The effect of breathing on RR interval variability was tested using methods of dynamic spectral analysis. The cardiorespiratory interaction was studied by paced respiration in which breathing frequency slowed from 0.46 to 0.05 Hz.

Methods

Subjects

Fourteen male and 2 female (aged 23 to 45 years) healthy subjects participated in the study. Fifteen subjects participated in a previous study with synchronized respiration. Twelve male and 2 female patients (aged 35 to 53 years) with mild sustained hypertension qualified for the study after elevated blood pressure levels were determined in three successive sessions by cuff measurements and 24-hour ambulatory blood pressure monitoring. Two patients had chronic hypertension for more than 10 years. Fourteen patients had hypertension diagnosed for the first time, and they were not being treated.

None of the patients received cardiovascularly active medication at the time of study. Two patients were previously...
treated by β-blocking agents but stopped using all medications 3 weeks before the study. None of the hypertensive patients or control subjects suffered from cardiopulmonary disease or obesity. Sleeping disturbances and sleep apnea syndrome were screened by detailed history and blood pressure profile during night hours. All experiments were done in a light-attenuated room between 9 AM and noon. Subjects lay in a supine position during recording. The study protocol was approved by the Ethics Committee of Sacré-Coeur Hospital, and written informed consent was obtained before the study.

Data Acquisition

The respiration signal was recorded with a nasal thermistor; electrocardiogram (ECG) (lead II) and noninvasive beat-to-beat blood pressure from the third finger (based on the combination of photoplethysmographic and volume-clamp methods [Ohmeda Finapres]) also were recorded. Continuous data acquisition for each experimental condition was done with a sampling rate of 200 samples per second. This sampling rate was good enough for the accuracy of the R wave and systolic and diastolic pressure detection algorithms. RR intervals were detected as intervals between consecutive R waves of the ECG. Signals were acquired and stored on a PC-based system equipped with an eight-channel A/D acquisition card (model DT 2801, Data Translation Inc).

Technique of Respiration

All subjects were instructed to inhale and exhale with tones in a sequence of 100-millisecond-long beeps recorded on a cassette tape. The cassette was played back for each recording session. Respiratory period prolonged from 30 to 3 breaths per minute over a period of 8.5 minutes to achieve a continuous sampling of 200 samples per second. This sampling rate is based on the discrete Wigner distribution and decomposes the signal as a function of time into a function of time and frequency. Time-frequency mapping gives beat-to-beat spectral estimations, and it was shown to be a good method for short nonstationary time series. High resolution was achieved by independent time and frequency smoothing using a moving 128 events data window. Time-frequency distributions were computed with the same parameter set for all signals.

The actual breathing frequency was first detected from the respiratory time-frequency distribution. This frequency then was used as the template for detection of RFs in the RR interval and blood pressure. Cross time-frequency distributions were computed between respiration and the signal of interest, eg, RR interval. RFs were defined as the local maxima at actual respiratory frequency on the respiratory, RR interval, and systolic and diastolic pressure time-frequency distributions. Nonrespiratory fluctuations (NONRFs) were identified as the local maxima at frequencies ranging from the respiratory frequency down to 0.01 Hz. A classical periodogram was computed from whole time series.

ANOVA with repeated measures and a paired t test were applied for group comparisons. Results are presented as the mean and SEM.
TABLE 1. Group Characteristics at Rest

<table>
<thead>
<tr>
<th></th>
<th>Normoten(\text{ve})</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, No.</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Women, No.</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Age, y</td>
<td>23-45</td>
<td>35-53</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168.6</td>
<td>171.6</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72.3</td>
<td>70.2</td>
</tr>
<tr>
<td>RR Interval, ms</td>
<td>903.2±3.6</td>
<td>1002.5±1.1</td>
</tr>
<tr>
<td>Finapres</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>127.6±0.3</td>
<td>152.4±0.4</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>64.6±0.2</td>
<td>85.4±0.2</td>
</tr>
<tr>
<td>Cuff</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>123.3±2.3</td>
<td>158.3±3.7</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>62.3±0.3</td>
<td>94.4±2.0</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

Hypertensive Group

RR intervals, blood pressure values, and patient characteristics are provided in Table 1. Unlike the control group at rest, breathing in hypertensive patients was irregular (Fig 1, right). Distribution of breathing frequencies was binomial, although the mean frequency (0.21±0.4 Hz) did not differ from the control group. The patients were breathing at frequencies from 0.15 to 0.3 Hz (8 to 20 breaths per minute) only 65.6% of the time during resting recordings. For 34.4% of the time, the dominant breathing frequency was interrupted by slower breaths or short apneas of 15- to 20-seconds' duration. Apneas occurred mainly after expiration. These slow breaths evoked a transient elevation of RF in all cardiovascular variables at corresponding low frequencies, eg, from 0.15 down to 0.01 Hz (Figs 2B and 3B). Cross time-frequency distributions between respiratory and systolic pressure showed in detail how slow breathing cycles were reflected in blood pressure and contributed to greater signal variability (Fig 5).

The global spectra (Fig 4B) represent the sum of powers in a given range over an evaluated period. Therefore, it is difficult to distinguish the RFs from NONRFs if they are present in the same frequency band but at a different time. In the global respiratory spectrum, irregularities of the respiratory frequency represented only an elevated noise at slow frequencies. However, in blood pressure the corresponding spectral powers at low frequencies were greater. In this approach, it is not possible to quantify which portion of low-frequency powers corresponds to RFs or NONRFs. When RFs were carefully separated from NONRFs, both RFs and NONRFs in the RR interval and systolic pressures were significantly

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![Graphs](http://hyper.ahajournals.org/)

**Fig 2.** Tracings show respiratory, RR interval, systolic (Syst.) pressure, and diastolic (Diast.) pressure signals during spontaneous respiration at rest (control subject No. 1 [A] and hypertensive patient No. 1 [B]) with irregularities in breathing pattern noted.
smaller in the hypertensive than the normotensive group (Table 2). The NONRF-RF ratio did not differ between groups.

**Paced Respiration**

**Control Group**

Slowing of respiration from 0.46 to 0.05 Hz paced the RFs in the RR interval and systolic and diastolic pressures over this whole range (Figs 6A and 7A). The RF amplitudes in all variables followed the trend of spectral powers in respiration and nonlinearly increased to a maximum at 0.07 to 0.09 Hz (Fig 7A). RF amplitudes were averaged across the population. Their dynamic profile showed a nonlinear trend, which increased toward slow breathing frequencies (Fig 8). The profile of NONRFs (0.02 to 0.03 Hz) remained unchanged and did not differ from values at rest in either of the variables.

**Hypertensive Group**

As in the control group, the slowing of breathing frequency from 0.46 to 0.05 Hz paced the RFs in the RR interval and blood pressure (Figs 6B and 7B) over this range. When respiration was synchronized, the RFs in the RR interval were greater than at rest and achieved a maximum at breathing frequencies of 0.07 to 0.09 Hz. However, they remained significantly smaller ($P<.001$) than in the control group. RF amplitude in systolic...
pressure was similar to the control group at faster breathing frequencies, but at slower frequencies (at maximum) it increased more \( (P<.01) \). The RFs in diastolic pressure were not different (Fig 8) from the control group. At maximum (at breathing frequency between 0.07 and 0.09 Hz), RFs in all variables were significantly greater \( (P<.01) \) than at a breathing frequency of 0.2 Hz (average breathing frequency during rest). This suggests that even a short-lasting slowing of breathing frequency to 0.07 to 0.09 Hz causes a sudden and significant elevation of RF in all variables.

Linear regressions between RR intervals and RFs in the RR interval were used for evaluation of the effect of actual RR interval on the amplitude of RFs (Fig 9). On average, the RR intervals were longer by 100±5.8 milliseconds in hypertensive patients than in the control group. In contrast, the increment of RFs in the RR interval was significantly \( (P<.01) \) smaller in hypertensive patients. This suggests that in hypertensive patients, slowing of breathing frequency has a greater chronotropic effect but affects the RR interval variability less.

Spectral content of NONRFs in the RR interval and blood pressure did not differ from rest in either group. NONRFs remained lower in the RR interval (1316±52.4 versus 6891.8±70.6 ms²/Hz) \( (P<.001) \) in hypertensive patients. NONRFs in systolic \( (25.7±0.6 \text{ versus } 30.3±0.5 \text{ mm Hg}²/\text{Hz}) \) and diastolic \( (8.2±0.2 \text{ versus } 7.9±1.4 \text{ mm Hg}²/\text{Hz}) \) pressures were similar in hypertensive patients and normotensive subjects.

Cardiorespiratory Index

We propose the cardiorespiratory index (CRI) as a dynamic measure of interaction between respiration, systolic pressure, and RR interval. CRI index was evaluated over the respiratory frequency range from 0.46 to 0.05 Hz, when the RFs in the RR interval and
systolic pressure were synchronized by controlled breathing. The RR intervals prolonged and systolic pressure increased in the early phase of expiration, whereas RR intervals shortened and systolic pressure decreased in the early phase of inspiration. In this approach the actual transfer from respiration to systolic pressure and RR interval can be evaluated beat-to-beat and adjusted for RR interval and systolic pressure values in a given heart period.

\[ \text{CRI} = \frac{[\text{RR at RF}/\text{RR}][\text{SBP at RF}/\text{SBP}]}{2} \]

where RR at RF is respiratory fluctuations in the RR interval, RR is the given RR interval, SBP at RF is respiratory fluctuations in systolic pressure, and SBP is systolic pressure in a given RR interval.

CRI at rest did not differ significantly between the normotensive and hypertensive groups (6.6±0.05 versus 4.9±0.04 ms/mm Hg). However, CRI was lower in hypertensive patients during the paced respiration over the range of 0.46 to 0.05 Hz (P<.01) (Fig 10). CRI tended to increase as respiration slowed to 0.1 Hz in the control subjects; however, CRI declined in hypertensive patients when breathing was paced at frequencies from 0.3 to 0.1 Hz.

Discussion

An impairment of the breathing pattern at rest was found in hypertensive patients. Frequent slow breaths and apneas that interfered with spontaneous breathing suggested an impaired regulation of respiration. The relation between daytime breathing irregularities and hypertension has not been systematically studied. Abnormalities in respiratory pattern in hypertensive disease have been described only in association with the obstructive sleep apnea syndrome. A greater prevalence of hypertension has been reported in this population of hypertensive patients during the paced respiration over the range of 0.46 to 0.05 Hz (P<.01) (Fig 10). CRI tended to increase as respiration slowed to 0.1 Hz in the control subjects; however, CRI declined in hypertensive patients when breathing was paced at frequencies from 0.3 to 0.1 Hz.

**Table 2. Averaged Spectral Powers at Rest at Respiratory and Nonrespiratory Frequencies**

<table>
<thead>
<tr>
<th>Spectral Powers</th>
<th>Normotensive Subjects</th>
<th>Hypertensive Patients</th>
<th>RF</th>
<th>NONRF</th>
<th>NONRF/RF</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR interval, ms⁻²/Hz</td>
<td>2293.6±23.5</td>
<td>2736.1±47.6</td>
<td>1.2</td>
<td>681.3±9.9*</td>
<td>1466.9±25.9*</td>
</tr>
<tr>
<td>SBP, mm Hg²/Hz</td>
<td>7.7±0.1</td>
<td>34.3±0.9</td>
<td>4.5</td>
<td>4.68±0.11†</td>
<td>22.11±0.49*</td>
</tr>
<tr>
<td>DBP, mm Hg²/Hz</td>
<td>2.9±0.2</td>
<td>10.3±0.6</td>
<td>3.4</td>
<td>4.32±1.71†</td>
<td>12.56±0.28</td>
</tr>
</tbody>
</table>

RF indicates respiratory fluctuations; NONRF, nonrespiratory fluctuations; SBP, systolic blood pressure; and DBP, diastolic blood pressure. Values are mean±SEM.

*P<.001, †P<.01, normotensive vs hypertensive.
patients, and a relation between nighttime hypoxemia and daytime hypertension was suggested. Even in healthy young subjects, the sequence of voluntary apneas evoked blood pressure elevation, which persisted into the resting period. In an elderly population, periodical breathing with subsequent hypoxemia is more common. It has been suggested that an underlying defect of chemoreceptor sensitivity can lead to an unstable feedback control of respiration and contribute to abnormal blood pressure regulation.

In our study, both RFs and NONRFs in the RR interval and systolic pressure, but not in diastolic pressure, were diminished at rest in hypertensive patients. As breathing rate gradually shifted from faster to slower frequencies, compensatory increases of tidal volumes could be expected. Differences in tidal volumes affect filling of the right ventricle, stroke volume, and activity of cardiac volume receptors. Consequently, the irregular breathing patterns imposed a variable input and instability into the baroreceptor reflex feedback loop. The smaller and irregular RFs and NONRFs in systolic pressure represented a noisy stimulus for the sinoaortic reflex loop. Consequently, the RFs and NONRFs in the RR interval decreased.

When respiration was synchronized, the RFs in the RR interval were greater compared with at rest. They were augmented proportionally to the decreasing respiratory frequency, and their temporal profile was similar to normotensive subjects. However, the absolute values of RFs in the RR interval and CRI remained diminished in the hypertensive group. We presume that there were no significant differences in actual tidal volumes between the normotensive and hypertensive groups, because the RF amplitudes in systolic and diastolic pressures were not generally different between groups. These data suggest that a transfer from intrathoracic pressure changes via venous return into blood pressure was preserved. However, diminished RR interval variability suggests an altered responsiveness of baroreceptors. Respiratory abnormalities at rest also support the hypothesis of impairment of the baroreceptor reflex feedback loop. Similarly, removing baroreceptors in animals resulted in abnormal breathing characterized by deep breaths concomitant with increased blood pressure lability.

Time-frequency mapping showed that RFs in cardiovascular signals mimic any change in breathing frequency. Thus, the RFs can appear at slow frequencies in the RR interval and blood pressure, where they usually are not expected, and indexes based on the ratio of low to high frequencies can give falsely positive results. Our method enabled instantaneous separation of the respiratory and nonrespiratory components, and thus a bias caused by the effect of respiration on spectral powers in the low-frequency band was effectively excluded. In contrast to previous studies, which used global Fourier transform or autoregressive models, in our study the NONRF powers were not elevated in the hypertensive

Fig 6. Tracings show respiratory and cardiovascular signals during synchronized slowing of respiration control in normotensive subject No. 2 (A) and hypertensive patient No. 2 (B). Syst. indicates systolic; Diast., diastolic.
FIG 7. Plots show time-frequency distributions of respiration, RR interval, systolic (Syst.) pressure, and diastolic (Diast.) pressure in normotensive subject (A) and hypertensive patient (B) during paced respiration (signals from Fig 6). Note lower RR interval fluctuations in hypertensive patient.

compared with the control group. The NONRFs reflect sympathetically mediated feedback modulation in blood pressure, which did not seem exaggerated in our hypertensive patients.

In addition to classic techniques, baroreceptor reflex sensitivity can be estimated noninvasively in either the time or frequency domain. The almost complete disappearance of hypertension/bradycardia and hypotension/tachycardia sequences after sinoaortic denervation in rats strongly supports a theory of baroreceptor reflex involvement in these phenomena. Spectral analysis methods such as a modulus function at the middle frequencies or as an “alpha index,” e.g., a ratio between RR interval and systolic pressure powers at the low and higher frequencies over a coherent portion of spectra. The “alpha index” was found to be invariably lower in hypertensive patients than in normotensive subjects. However, these global spectral indexes of baroreceptor reflex function are in fact limited by the basic properties of the spectral estimation. Secondly, the respiratory influence on both high and low frequencies cannot be well distinguished by these methods.

The CRI confirmed previous findings that transfer from respiration into RR intervals is diminished in hypertensive patients. Its major advantage is that it combines both the time and frequency domain approaches and enabled us to dynamically analyze cardiorespiratory interaction over a wide range of breathing frequencies. Although in normotensive subjects the CRI
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