Breathing cardiovascular variability and baroreflex in mechanically ventilated patients

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Van de Louw A, Médigue C, Papelier Y, Cottin F. Breathing cardiovascular variability and baroreflex in mechanically ventilated patients. Am J Physiol Regul Integr Comp Physiol 295: R1934–R1940, 2008. First published October 15, 2008; doi:10.1152/ajpregu.90475.2008.—Heart rate and blood pressure variations during spontaneous ventilation are related to the negative airway pressure during inspiration. Inspiratory airway pressure is positive during mechanical ventilation, suggesting that reversal of the normal baroreflex-mediated pattern of variability may occur. We investigated heart rate and blood pressure variability and baroreflex sensitivity in 17 mechanically ventilated patients. ECG (RR intervals), invasive systolic blood pressure (SBP), and respiratory flow signals were recorded. High-frequency (HF) amplitude of RR and SBP time series and HF phase differences between RR, SBP, and ventilatory signals were continuously computed by Complex DeModulation (CDM). Cross-spectral analysis was used to assess the coherence and the gain functions between RR and SBP, yielding baroreflex sensitivity indices. The HF phase difference between SBP and ventilatory signals was nearly constant in all patients with inversion of SBP variability during the ventilator cycle compared with cycling with negative inspiratory pressure to replicate spontaneous breathing. In 12 patients (group 1), the phase difference between RR and ventilatory signals changed over time and the HF-RR amplitude varied. In the remaining five patients (group 2), RR-ventilatory signal phase and HF-RR amplitude showed little change; however, only one of these patients exhibited a RR-ventilatory signal phase difference mimicking the normal pattern of respiratory sinus arrhythmia. Spectral coherence between RR and SBP was lower in the group with phase difference changes. Positive pressure ventilation exerts mainly a mechanical effect on SBP, whereas its influence on HR variability seems more complex, suggesting a role for neural influences.

Heart rate; blood pressure; baroreflex gain; hypoxemia; complex demodulation

In healthy individuals, respiratory sinus arrhythmia (RSA) reflects a physiological interaction between ventilation and circulation. The heart rate (HR) increases during inspiration and slows during expiration (3). This HR variability, synchronous with breathing, is related to both peripheral and central mechanisms. The intrathoracic pressure becomes negative during inspiration, leading to an increase in right ventricular stroke volume and to a decrease in left ventricular stroke volume (13). The resulting blood pressure (BP) decrease activates the arterial baroreceptors, which in turn inhibit vagal activity, leading to an increase in HR (6). During expiration, BP increases, leading to vagal stimulation with a decrease in HR. Central mechanisms that contribute to RSA include direct vagal tone modulation by the central respiratory drive (7).

Inspiratory airway pressure is negative during spontaneous breathing and positive during mechanical ventilation. The negative inspiratory pressure seems to be a key factor in the normal pattern of BP variability with breathing. Therefore, positive inspiratory pressure related to mechanical ventilation would be expected to reverse this pattern of BP variability. Provided arterial baroreflex sensitivity is preserved and predominates over the central mechanisms of HR variability, HR would be expected to slow during inspiration and to accelerate during expiration. This reversed pattern of RSA was seen in a study of anaesthetized rats receiving mechanical ventilation (33).

Few data are available about the effect of mechanical ventilation on RSA in humans. In two studies of low-risk patients under general anesthesia (American Society of Anesthesiologists class 1), reversal of the RSA pattern was noted in 26 of 28 (37) and 3 of 10 patients (19), respectively. In neither study was arterial pressure recorded continuously or baroreceptor sensitivity evaluated. Neither study used a signal-processing method that allowed determination of the instantaneous phase difference between ventilation signal and beat-to-beat RR or BP signals throughout the recordings.

The objective of this study was to investigate HR and BP variability synchronous with breathing as well as baroreceptor sensitivity in patients receiving mechanical ventilation. We hypothesized that positive pressure ventilation would reverse the pattern of BP variability, causing BP to increase during inspiration and to decrease during expiration. We also hypothesized that, provided the baroreflex remained efficient and predominated over the central mechanisms of RSA, the RSA pattern would also be reversed.

METHODS

This prospective observational study was conducted between January and September 2007 in the 14-bed medical-surgical intensive care unit (ICU) of the Sud-Francilien General Hospital (Evry, France). The study protocol was approved by the ethics committee of the Francophone Society for Critical Care, who waived the need for written informed consent, because of the noninterventional nature of the study. Nevertheless, an information letter was given to the patients and/or close relatives, indicating the possibility for the patients to refuse the use of their data.

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Inclusion Criteria

According to the definition of the American-European Consensus Conference on acute respiratory distress syndrome (2), all patients with acute lung injury (ALI) were included. Inclusion criteria were 1) acute hypoxemia with a ratio of the partial pressure of arterial oxygen over the fraction of inspired oxygen (PaO2/FIO2) no greater than 300 mmHg, 2) bilateral infiltrates consistent with pulmonary edema on a frontal chest radiograph, and 3) either no clinical evidence of left atrial hypertension or (if measured) a pulmonary-artery wedge pressure no greater than 18 mmHg. All the study patients required full sedation and/or neuromuscular blockade to tolerate mechanical ventilation. In addition, all were equipped with a radial or femoral artery catheter for continuous monitoring of arterial pressure.

Exclusion Criteria

Patients who had preexisting or new-onset cardiac arrhythmias, treatment with antiarrhythmic drugs, incomplete adaptation to the ventilator, or no arterial catheter were not included.

Protocol

Patients were kept in a semirecumbent position and left undisturbed with no changes in ventilator parameters or medications during data collection. Ventilator settings were as follows: volume assist-control mode; tidal volume (Vt), 6 ml/kg ideal body wt; breathing rate, 20 cycles/min; inspiratory/expiratory ratio, 1/2; and positive end-expiratory pressure, 5 cmH2O. FIO2 was adjusted to maintain transcutaneous oxygen saturation in blood ≥ 94%. All the patients were sedated with midazolam and fentanyl in dosages that were titrated to achieve adequate adaptation to the ventilator settings. Age, gender, etiology of ALI, the SAPS II severity-of-illness score (20), administration of vasoactive drugs, the PaO2/FIO2 ratio, and ICU mortality were collected.

Signal Acquisition

One-lead ECG, arterial pressure, and respiratory flow signals were recorded during a 15-min period using a Biopac 100 System (Biopac Systems, Goleta, CA). The respiratory flow was measured with a Hans-Rudolph pneumotachograph (Hans Rudolph, Shawnee, KS) connected with a differential pressure transducer (model MP-45; Validyne, Northridge, CA) and an electronic flow integrator (model MC1-3; Validyne). All the data were sampled at 1,000 Hz and stored on a hard-disk. The data were acquired for all the patients at the same time of the day to ensure comparable circadian influence.

Signal analysis

Raw data processing. Signal processing was performed using the Scicos-Scilab and Matlab environments at the French National Institute for Research in Computer Science and Automation (INRIA-Sisyph team). For each 15-min recording, the first and last 100 s were removed to avoid border effects. As very few extra-systolic beats or artifacts periods were observed, they were not corrected but discarded from the analysis. Thus, 700-s artifact-free periods were available in most of the patients. RR and systolic BP (SBP) time series were extracted from ECG and BP raw signals; ECG and BP were multiplied by a parabolic signal, adapted to the QRS/systolic pressure width, along successive windowing epochs. This parabolic fitting enhances their maximal values and minimizes their lower values, improving the detection of the R peak from the ECG and of the systolic value from the BP signal (38). Vt was computed with Chart5 soft (Chart5, version 5.5, ADInstruments) by integration of the respiratory flow signal after calibration, as previously described (24). All series (RR, SBP, and Vt) were resampled at 4 Hz, by interpolation of a third-order spline function to obtain equidistant data and were then analyzed by the following time and frequency methods.

Assessment of the Phase Difference Between Cardiovascular and Respiratory Signals and the Instantaneous Breathing Amplitude of RR and SBP Series

Complex DeModulation (CDM), a time local version of harmonic analysis, has been used to measure cardiovascular and respiratory interactions (5, 15, 23, 25). CDM provides an instantaneous and continuous assessment of the amplitude (HF-CDM), frequency, and phase of RR and SBP variabilities with breathing. To reduce noise and to obtain a monocomponent signal, cardiovascular series were first filtered through a narrow band-pass filter centered on the breathing frequency (0.30–0.36 Hz). This narrow band differed from the conventional HF band (0.15–0.4 Hz) defined by the Task Force (30). In healthy individuals breathing spontaneously, breathing frequency can change and the HF range was defined from 0.15 to 0.4 Hz to ensure that the breathing cardiovascular variability peak is contained in the HF range. In our study, Vt was delivered by the ventilator at a strictly regular frequency (0.33 Hz). This allows us to determine a narrow band around this central frequency, which contains nearly all the RSA and only the RSA, avoiding noise or spectral activity different from RSA, and providing more accurate data than the classical range (25).

The instantaneous delay between cardiovascular and respiratory phases was assessed based on the actual modulating breathing frequency (23, 25). CDM provided the following indices for RR and SBP: mean HF-CDM amplitude, minimal HF-CDM amplitude, percentage of time spent with HF-CDM amplitude under a predefined threshold (50% of the mean HF amplitude for the total period), standard deviation (SD) of the delay between cardiovascular and respiratory phases, and amplitude of its maximum drift.

Assessment of Baroreflex Sensitivity

The smoothed power spectral density (SPSD) was used to quantify local SBP and RR variabilities, which served to assess baroreflex sensitivity. SPSD has been already described (23, 25). SPSD was applied to a 256-point Hannan window (64 s) for each cardiovascular series.

Spectral power was computed in the low-frequency (LF) and HF ranges (spectral components) by integrating the power spectral density in the RR and SBP spectra. The LF band was set between 0.04 and 0.15 Hz, as recommended by the European Task Force (30). The HF band was the same as for CDM analysis.

A cross-spectral analysis was applied to HR and SBP spectra to compute the coherence and transfer functions (23, 25). The spectral baroreflex sensitivity (BRS) is supported by the hypothesis of a linear relation between the input (BP) and output (RR) of the model. The degree of linearity between the two signals is estimated by the value of the coherence function. It was accepted that RR and SBP spectra had a reliable linear relationship when the coherence index was higher than 0.5 (6, 31).

The averaged spectral gain in HF and LF bands was the modulus of the transfer function between RR and SBP spectra (21, 22).

Statistical Analysis

All the results are presented as means ± SE of the parameters over the recording periods. The normality of the data was checked with a Kolmogorov-Smirnov test. A paired t-test was used to compare RR vs. SBP phase indices in the same period of the same subject, as normality passed, a parametric test was applied. As normality failed for comparison of RR and SBP indices and clinical data between the two groups of patients, a nonparametric test, the Mann-Whitney rank sum test, was applied.

RESULTS

Patients

We included 17 patients (12 men and 5 women). ALI was due to community-acquired or ventilator-associated pneumo-
nia (12 patients), peritonitis (2 patients), severe acute pancreatitis (1 patient), cellulitis (1 patient), or massive blood transfusion (1 patient). The median values (range; SD) were 55 years (30–76; 9.4) for age, 59 (28–107; 21.4) for the SAPS II score, 10 (4–16; 3.8) for the SOFA score, and 240 (79–300; 73.7) for the PaO2/FIO2 ratio. Ten patients received vasoactive drugs, and 10 patients died in the ICU.

**Phase Between Arterial Pressure and Respiratory Signals**

SBP (mean ± SE) value for the 17 patients was 124 ± 11 mmHg. In all patients, the HF phase difference between SBP and respiratory signals was nearly constant (Fig. 1A). SBP increased during inspiration and decreased during expiration (Fig. 1B).

**Phase Between RR and Respiratory Signals**

The HF phase difference between RR and respiratory signals differed across patients and varied over time in some of the patients (Figs. 1, C and D). Two patterns of cardiorespiratory phase difference were individualized by CDM. In 12 of the 17 patients (group 1), the phase difference changed continuously, so that neither normal nor reversed RSA occurred. Furthermore, abrupt dephasings coexisted with gradual variations in the phase difference. The abrupt dephasings were associated with disappearance of the HF amplitude of the RR signal, whereas HF amplitude persisted at a decreased value during gradual dephasing (Fig. 2, G1-a and G1-b). In the five remaining patients (group 2), the phase difference between RR and respiratory signals showed little change (Fig. 2, G2-a and G2-b). Individual RR and ventilatory signals of these five patients are shown in Fig. 3, as well as the individual values of the phase difference between RR and ventilation. Only one patient exhibited a RR-ventilation phase difference suggesting a preserved RSA (120°), as previously described in healthy humans breathing spontaneously (18).

**Comparison of the Phase Difference with Ventilation Between RR and SBP**

The SD of the phase difference with ventilation was significantly higher for RR than SBP (0.94 ± 0.25 radians vs. 0.27 ± 0.19 radians; P = 0.006), as well as the amplitude of the maximum drift of the phase difference (3.10 ± 0.71 radians vs. 0.78 ± 0.47 radians; P = 0.01).

**Comparison of the RR-Ventilation and SBP-Ventilation Interactions Between the Two Groups**

Table 1 compares RR-CMD indices between the two patient groups. Although the two groups did not differ significantly by their mean HR and mean HF-RR amplitude, they differed by the different dynamics of RR-ventilation phase differences and HF-RR amplitude, which together presented a greater variability in group 1.

For the HF phase difference, this greater variability was quantified by SD and by the maximal drift values. For the HF-RR amplitude, this greater variability was quantified by SD and by the percentage of time spent with an HF-RR amplitude < 50% of the mean value. No significant differences in the indices of SBP-ventilation interaction were found between the two groups.

**Cross-Spectral Analysis of Baroreflex Gain**

In the HF band, spectral coherence (for periods with coherence ≥ 0.5) was greater in the group 2 than in the group 1 (0.95 ± 0.02 vs. 0.77 ± 0.02, P = 0.05). In addition, the percentage of time (periods of 64 s) with coherence < 0.5 was significantly smaller in the group 2 (0% vs. 16.9 ± 5.5%, P = 0.003). This
percentage correlated strongly with HF-CDM amplitude variability, assessed based on the percentage of time spent < 50% of the mean amplitude ($r = 0.625; P < 0.01$). Spectral gain was not significantly different (Table 2). No differences in LF parameters were found between the two groups.

**Comparison of Clinical Data Between the Two Groups of Patients**

No significant differences were found between the two groups for ICU mortality, $\text{PaO}_2$-to-$\text{FiO}_2$ ratio, SAPS II, SOFA, or use of vasoactive drugs.

**DISCUSSION**

**Physiopathology**

We investigated SBP and HR variability and baroreflex sensitivity in relation to the respiratory cycle in mechanically ventilated patients with ALI. In contrast to the pattern associated with spontaneous breathing, SBP increased during inspiration and decreased during expiration in all patients. The phase difference between SBP and respiratory signals was constant (Fig. 1), indicating that the direct mechanical effect of breathing on SBP was the main determinant of SBP variability.

**Fig. 2.** RR-ventilation interactions expressed in terms of instantaneous amplitude and phase (CDM) in patients with great changes in the RR-ventilation phase difference (group 1, examples in G1-a and G1-b) and in patients with little changes in the RR-ventilation phase difference (group 2, examples in G2-a and G2-b). The 4 patients exhibited different mean heart rates and Vt, whereas the breathing frequency was constant (0.33 Hz). Regarding high-frequency (HF) variability, the patients mainly differed by the dynamics of HF amplitude and phase: unstable in (G1-a and G1-b), evidenced by disappearance/diminution of HF amplitude associated with sudden shifts and drifts of the phase difference, and, conversely, stable HF phase and amplitude in (G2-a and G2-b). The dashed line indicates the threshold equal to 50% of the mean HF-CDM RR amplitude. Periods below this threshold occurred in G1-a and G1-b (group 1 patients) but not in G2-a and G2-b (group 2 patients).

**Fig. 3.** Individual high-pass-filtered RR (solid line) and Vt (dashed line) of the 5 patients of group 2 over 10 s. This group is characterized by a nearly constant RR-ventilation phase difference. Arrows represent the RR-ventilation phase difference for each patient, in radians and degrees. Only 1 patient (patient 5) exhibited a RR-ventilation phase difference (120°), suggesting a preserved RSA.
HR exhibited no constant phase difference with the respiratory cycle (Fig. 1). Mechanical considerations indicate that, compared with spontaneous breathing, the reverse airway pressure regimen during mechanical ventilation should result in reversal of the normal RSA pattern. The results of a study showing RSA reversal during positive-pressure ventilation in 15 anaesthetized rats support this hypothesis (33). However, of 28 human patients undergoing elective surgery, two did not exhibit reversal of the RSA pattern (37). In another study, positive-pressure ventilation was associated with a reverse RSA pattern in only three of 10 low-risk surgical patients under general anesthesia (19). No explanation to these discrepancies was suggested by the authors of either study. However, neither study involved invasive BP recording to investigate the mechanical effect of positive-pressure ventilation on BP variability. Furthermore, the phase difference between respiratory and RR signals was not assessed continuously. In keeping with these two studies, the phase difference between RR and ventilation differed across patients in our population. In addition, by using CDM to assess the instantaneous phase of signals, we were able to detect within-patient changes in the phase difference between RR and ventilation. Based on the phase difference between RR series and respiratory signals and the correlated HF-RR amplitude, we identified two groups of patients. SBP-ventilation interactions were not significantly different between these two groups, indicating that the mechanical effect of positive-pressure ventilation on arterial pressure variability was constant. Conversely, RR-ventilation interactions significantly differed between the two groups, cardiorespiratory dephasing and variations in HF-CDM amplitude being greater in the group 1. Patients of group 2 exhibited lower mean RR and mean HF-CDM amplitudes, but the difference did not reach statistical significance. It would be interesting to further evaluate in a larger study whether mean RR value and mean HF-CDM amplitude are correlated with the variability of both cardiorespiratory phase difference and HF amplitude.

The reasons underlying the highly variable behavior of HR in relation to ventilation remain unclear. An effect of sedative drugs on HR variability has been described (8). However, all of our patients received the same regimen of sedation, and no medication changes occurred during data recording so that sedation cannot account for the considerable variability found in our study. Patients were left undisturbed, and every effort was made to keep the environmental conditions stable throughout data acquisition, suggesting a limited role for environmental factors. All the patients were hemodynamically stable, even those treated with vasoactive drugs; vasoactive-drug use and dosages did not differ between the two groups, and the dosages were not changed during data acquisition. Therefore, our results cannot be ascribed to differences or variations in hemodynamic status. A reduction in HR variability with aging was well described, but the key point of our study was the phase difference between RR and ventilation and not the HR variability itself. To our knowledge, an effect of age on the phase difference between RR and ventilation was not previously reported. Considering the small number of patients included, the comparison of patients grouped by age was difficult in the present study. Moreover, the large range of age was largely attributable to two patients. The range of age of the 15 remaining patients was 44–62 yr, which constitutes a more homogeneous group. Finally, no difference of age was observed between the two groups of patients. Thus, an effect of age on our main results seems unlikely.

Within-patient variability of cardiorespiratory phase differences probably indicates that the mechanical effect of positive-pressure ventilation on HR variability is counteracted by neural influences that render the RSA pattern unpredictable. Thus, the baroreflex alone cannot fully explain the occurrence of RSA (7). There is growing evidence that central mechanisms play a key role in the genesis of RSA that can persist in humans (16) and dogs (17) in the absence of respiratory movements. Conceivably, conflicts between mechanical and neural influences may explain the functional uncoupling between RR and respiratory signals seen in many of our patients. Why this uncou-
pling occurred in some patients and not others remains to be determined.

We found no significant correlations linking RR-ventilation interactions, SBP-ventilation interactions, or baroreflex sensitivity and various markers of severity (PaO2/FiO2, SAPS II, SOFA, catecholamine use, and mortality). However, our main objective was to assess the persistence of RSA in ALI patients receiving mechanical ventilation. Our study was not designed to investigate correlations between RSA or baroreflex sensitivity and clinical data. The number of patients may have been too small to detect such correlations. Further studies in larger populations would be of interest.

The relatively constant phase between BP and respiratory signals and the stable HF-BP amplitude, combined with the variable phase between RR and ventilation and the variable HF-RR amplitude, suggest altered baroreflex sensitivity in the group 1. An important finding from our study was the lesser coherence between RR and BP spectra in the HF band in this group, which probably indicated lower baroreflex efficiency compared with the other group. These results suggest uncoupling of HR, BP, and ventilation in critically ill patients. Uncoupling of biological oscillators has been suggested as a pathogenic mechanism in multiple organ dysfunction syndrome (10). Several studies provided convincing evidence of uncoupling in various situations, such as acute brain injury and brain death (11) or critical pediatric illnesses (12). Reduced HR variability was also found in patients with sepsis (1), trauma (26), or complicated abdominal aortic surgery (29), as well as in healthy volunteers exposed to endotoxin (28). In pediatric patients with sepsis or septic shock, recovery was associated with the restoration of several HR variability indices (32). Nevertheless, none of these studies investigated the effect of mechanical ventilation on RSA by recording respiratory signals in critically ill, mechanically ventilated patients. Thus, our study showing a constant phase between BP and ventilation contrasting with a variable phase between HR and ventilation supports the uncoupling hypothesis.

A major finding from our study is that RSA was usually absent in mechanically ventilated, critically ill patients. A clear definition of preserved or reversed RSA is lacking in the absence in mechanically ventilated, critically ill patients. A clear definition of preserved or reversed RSA is lacking in the absent in mechanically ventilated, critically ill patients. A clear definition of preserved or reversed RSA is lacking in the.

Supporting the uncoupling hypothesis.

Contrasting with a variable phase between HR and ventilation a study showing a constant phase between BP and ventilation in critically ill patients.

The normal pattern of RSA was preserved or reversed in hypoxemic, mechanically ventilated patients. The normal pattern of RSA was preserved or reversed in hypoxemic, mechanically ventilated patients. The normal pattern of RSA was preserved or reversed in hypoxemic, mechanically ventilated patients. The normal pattern of RSA was preserved or reversed in hypoxemic, mechanically ventilated patients.

Signal Processing Methodology

In this study, two methods, the CDM and the spectral BRS, were conjointly used to reinforce the assessment of the cardiovascular and respiratory interactions, from two different points of view. The CDM is a temporal analysis, well adapted for following the dynamics of time series, particularly their sudden transitions. On the contrary, the BRS assessment is based on a spectral analysis, which assumes the hypothesis of linearity between HF-RR and HF-SBP, estimated by the values of the coherence function. The patients of group 1 presented more instability in HF-RR phase difference and amplitude than the patients of group 2, with RSA disappearance or diminution (evidenced by the CDM). Group 1 presented less epochs with a linear relationship between HR-RR and HF-SBP and a lower relationship when this linearity was assumed (evidenced by the spectral gain method). So, the periods of RSA diminution, expressed in a temporal way, correspond to epochs with a lower BRS efficiency, expressed in a spectral way. These results were so mutually reinforced.

Moreover, about the CDM, the two groups were not significantly separated by their mean HR and mean HF amplitude, but by the different dynamics of their HF amplitude and phase. Indeed, CDM allows the quantification of temporal indices: minimal HF amplitude value, percentage of time spent with HF amplitude lower than a fixed threshold, standard-deviation, and maximum drift of HF phase difference between RR and Vt. About the two methods, the determination of a narrow band around the central respiratory frequency, which contains all the RSA and only the RSA, allows a more accurate estimation of the HF variables. Indeed, it largely reduces noise effects on the instantaneous frequency and amplitude and gives better time and frequency resolution, mainly in noisy environments.

Perspectives and Significance

During positive pressure ventilation, we observed a constant phase between arterial pressure and respiratory signals. Compared with the spontaneous ventilation with negative inspiratory airway pressure, this phase is reversed, suggesting a preponderant mechanical effect of positive pressure ventilation on arterial pressure variability. Its effect on RSA appears more complex: although some patients have a preserved RSA, the majority of them have a variable phase between RR and ventilation, associated with an altered BRS. This suggests determinant neural influences overwhelming the mechanical effect of positive pressure ventilation. Future works needs to evaluate the prognostic significance of a preserved or disrupted RSA in critical care, mechanically ventilated patients, and to
explore the effect of therapeutic interventions (sedation, ventilator settings) on the RR-ventilation interactions.

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