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Respiratory induced heart rate and blood pressure variability during mechanical ventilation in critically ill and brain death patients *

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Abstract — **We analysed respiratory induced heart rate and blood pressure variability in mechanically ventilated patients with different levels of sedation and central nervous system activity. Our aim was to determine whether it is possible to distinguish different levels of sedation or human brain activity from heart rate and blood pressure. We measured 19 critically ill and 15 brain death patients ventilated at various respiratory frequencies – 15, 12, 8 and 6 breaths per minute. Basal and deeper sedation was performed in the critically ill patients. We detected and analysed heart rate and blood pressure parameters induced by ventilation.**

Results: Respiratory induced heart rate variability is the unique parameter that can differentiate between brain death patients and sedated critically ill patients. Significant differences exist, especially during slow deep breathing with a mean period of 10 seconds. The limit values reflecting brain death are: baroreflex lower than 0.5 ms/mmHg and tidal volume normalised heart rate variability lower than 0.5 ms/ml. Reduced heart rate variability parameters of brain death patients remain unchanged even after normalisation to respiration volume. However, differences between basal and deep sedation do not appear significant on any parameter.

I. Introduction

The measurement of anaesthetic depth and brain activity is an important procedure during mechanical ventilation in unconscious patients. It is well known that heart rate variability (HRV) is profoundly affected and strongly reduced by general anaesthesia [1, 2]. HRV has been shown [3] to fall with sedation, and is significantly reduced in a state of full unconsciousness. However, changes in HRV are minimal on any further increase in sedation during unconsciousness. There is, therefore, a serious limitation to the utilisation of the HRV parameter and it has not yet been commonly used in clinical practice.

Further decrease in HRV can be expected only in the case of brain death [4]. F Conci [4] has shown that there are differences in blood pressure, heart rate variability and baroreflex sensitivity before and after brain death – general reduction in power spectra.

In our work we attempted to analyse the influence of basal and deeper sedation and brain death on HRV and blood pressure variability (BPV). We used several frequencies and depths of breathing for HRV and BPV excitation.

In comparison with previous papers, we used a different method for respiratory induced HRV and BPV estimation. Normally these parameters are calculated in two frequency bands (LF and HF) with mechanical ventilation in one frequency within the HF band. Unfortunately, in most studies no respiratory parameters are reported.

Oscillations in the LF band are mainly mediated by the parasympathetic system [2] and reflect spontaneous blood pressure oscillations translated into heart rate fluctuations by the baroreflex. Oscillations in the HF band reflect respiratory activity and are almost exclusively mediated by the sympathetic system. In the case of general anaesthesia, the mechanical ventilation is the dominant oscillation in the HF band.

Our approach is rather different. We chose 4 respiratory rates – 15, 12, 8 and 6 breaths per minute. We computed respiratory induced HRV and BPV directly on the breathing frequency and ignore HF and LF differentiation. Nevertheless, for the sake of comparison with the common terminology, frequencies 15 and 12 breaths per minute are 0.25 and 0.2 Hz and belong to the HF band (0.15–0.40 Hz), frequencies 8 and 6 breaths per minute are 0.13 and 0.1 Hz and belong to the LF band (0.05–0.15 Hz).

II. Methods

As part of a pilot study, we measured 19 critically ill adult ICU patients and 15 all brain dead patients with sinus rhythm mechanical ventilation mode. We excluded those with acute respiratory distress syndrome or with significant hypercapnia, as well as patients with shock, defined as both norepinephrine >0.2 ug/kg/min and higher lactate level.

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Patients were ventilated in the pressure control mode. Inspiration to expiration time was maintained at a ratio of 1:1. Respiratory frequency was changed at 5-minute intervals, and inspiratory pressure was adjusted on each frequency to maintain the end tidal CO_2 equal to baseline. The sequence of frequencies was 15, 6, 8, 12, 15 breaths per minute. This set of frequency/pressure changes was performed twice during basal and deeper sedation. The respiratory rate 15 breaths per minute was used as the initial and final frequency. The dual record at this frequency allows for stability in the monitoring of measurement conditions. The brain dead patients had no sedation and relaxation.

The deeper sedation was generally applied after lighter – basal sedation and was managed by increasing the dose of propofol and sufentanil to achieve a decrease of at least 5 points in the Bispectral index (BIS index). The mean BIS index decreased after sedation from 38 (34–47) to 29 (23–35) ($p<0.001$). The BIS index was zero in most of the brain dead patients.

Invasive arterial blood pressure and ECG were measured on a BP monitor (Datex Ohmeda S/5, Instrumentarium corp., Finland). To quantify sedation, the BIS index was recorded and analysed with a BIS VISTA^{TM} Monitoring System (Norwood, MA, USA). The respiratory monitor was assembled from two pressure transducers (Validyne DP45, Validyne Engineering, Northridge, CA, USA) and a flow meter. The data was displayed in real time and saved at a frequency of 500 samples/sec using ScopeWin (ISI Brno, CZ) software for data measurement and analysis.

RR intervals, systolic (SBP), diastolic (DBP), mean (MBP) blood pressure and pulse pressure (PP) calculated as SBP-DBP were detected from ECG and arterial blood pressure signals. Detected haemodynamic data was filtered in the 0–3 Hz pass band, respiration in the 0.2–3 Hz pass band.

Intervals with irregularities were manually de-selected, i.e. we discarded the parts of data with an unstable respiratory frequency, tidal volume or heart rate and blood pressure irregularities. Intervals with the same respiratory frequency and depth were further divided into short segments of a length of two respiratory cycles. All segments were checked again and artificial segments were removed. Artificial segments mainly included abnormal heart rhythm, extrasystoles or erroneously detected R waves in ECG or blood pressure parameters. Artefact-free segments were then averaged with expiration start trigger. The expiration trigger was detected from the respiratory volume curve at the time of a rapid decline at the beginning of exhalation. Using this averaging procedure, we can achieve the highest possible quality of waveforms of blood pressure and heart rate connected with respiration. This processing yielded averaged signals (time course) of respiratory volume and haemodynamic signals. The averaging technique was chosen because it makes it possible to minimise the influence of irregularities and refine the results. Though they may not seem important, artefacts significantly affect processing using a continuous signal, for example frequency analysis. We have devoted great effort to the issue of artefacts. We have achieved the best results by a procedure providing correct separated respiratory cycles.

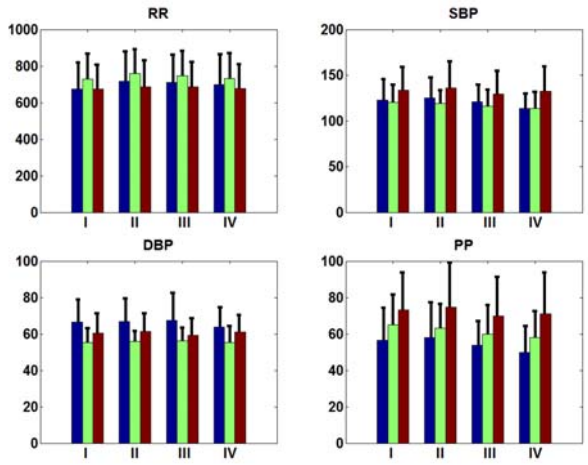

Figure 1. Mean values of RR (ms), SBP, DBP and PP (mmHg). The left blue bar represent brain death patients, the middle green bar deeper sedation and the right red bar basal sedation. I, II, III, IV mean respiratory frequency 15, 12, 8 and 6 breaths per minute.

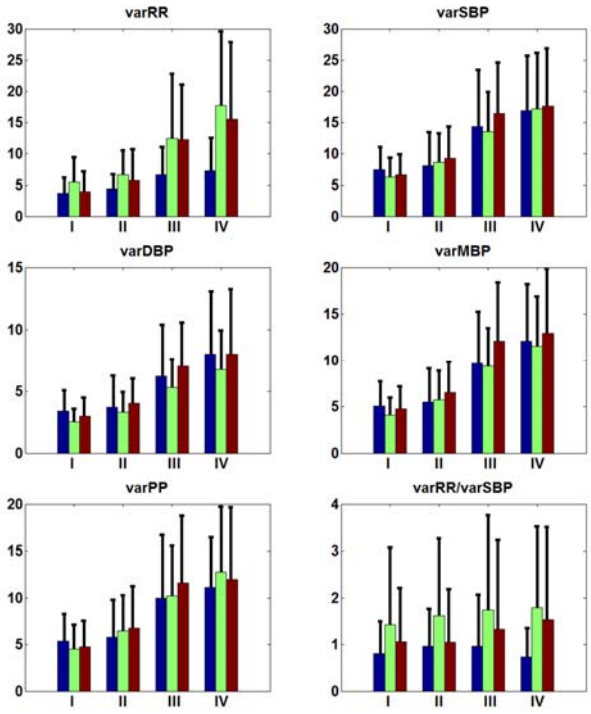

Figure 2. Respiratory induced variability varRR (ms), varSBP, varMBP, varDBP, varPP (mmHg), RR variability normalised to systolic blood pressure variability – baroreflex varRR/varSBP (ms/mmHg).

Analysed parameters were automatically detected and calculated from averaged signals within one respiratory period: mean values – RR, SBP, DBP, MPB and PP; differences between maximal and minimal values within an averaged respiratory cycle – Tidal volume (TV), varRR,

varSBP, varDBP, varMBP and varPP (maximal PP minus minimal PP). varXX parameters represent respiratory induced variability. We computed normalised parameters to eliminate the effect of different respiratory volumes – parameter value divided by tidal volume – gain to TV.

III. Results

All data is presented as mean and standard deviations over three groups – brain death, deeper sedation and basal sedation at four different respiratory frequencies.

The results are demonstrated in common figures – bar graphs: the left blue bar represent brain death patients, the middle green bar deeper sedation and the right red bar basal sedation; I, II, III, IV mean respiratory frequency 15, 12, 8 and 6 breaths per minute.

The statistical significance of differences between groups at different respiratory frequencies or between frequencies in a specific group was tested by paired and unpaired t-tests and ANOVA. For all comparisons and interpretation in text as significant differences, p-values smaller than 0.05 were considered statistically significant.

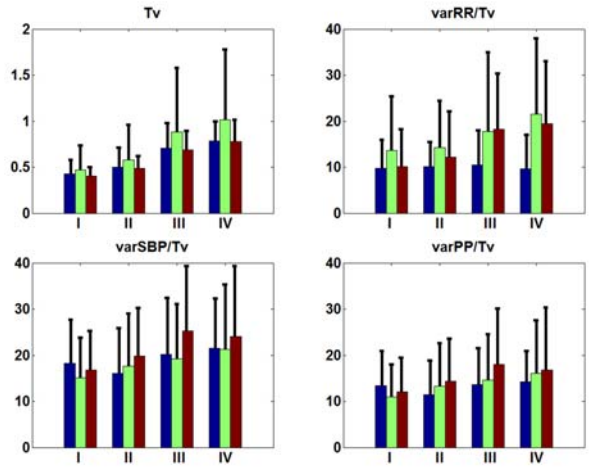

Figure 3. Tidal volume TV (litre), normalised RR variability to tidal volume varRR/Tv in ms/litre, normalised SBP and PP variability to tidal volume varSBP/Tv and varPP/Tv in mmHg/litre

IV. Discussion

Breathing frequency and depth do not affect mean values of RR intervals and arterial blood pressure parameters – Fig 1. There are weak differences between basal sedation, deep sedation and brain death. However, significant differences can be detected only in pulse pressure between brain death and other groups. Lower pulse pressure most likely indicates lower stroke volume in brain death subjects.

The respiratory induced variability of all parameters strongly depends on respiration frequency/depth – Fig. 2. This is the expected result. Significant differences between groups can be found only in HRV (varRR) in brain death subjects versus general anaesthesia subjects. The HRV is significantly reduced during slow breathing in brain death patients. There is no significant difference between basal and deeper sedation.

HRV normalised to SBP variability (varRR/varSBP) can be interpreted as baroreflex. Baroreflex depends on the transfer between SBP and RR variability. Our results demonstrate that baroreflex predominantly reflects RR variability, the contribution of SBP variability is negligible. So, similarly as with the varRR parameter, there is a significant baroreflex reduction in brain death patients during slow deep breathing. However, differences between basal and deep sedation do not appear significant on any parameter. This fact can be explained by the small effect of basal and deep sedation on haemodynamic change. In healthy volunteers, slow 0.1 Hz paced spontaneous breathing increases baroreflex up to 20 ms/mmHg and around 7 ms/mmHg in older healthy volunteers and patients with chronic heart failure [5]. However, respiratory induced baroreflex is extremely reduced in sedated subjects to a mean value of around 1.5 ms/mmHg. This small baroreflex value most likely does not allow more variability induced by respiration. We can conclude that it would not be possible with slow respiration to differentiate between levels of sedation based on baroreflex or heart rate variability in general anaesthesia.

To eliminate differences in breathing depth in subjects, we normalised the varRR, varSBP and varPP parameters to respiratory tidal volume Tv – varRR/Tv, varSBP/Tv and varPP/Tv. This normalisation was computed in each subject separately. Normalised blood pressure parameters (varSBP/Tv, varPP/Tv) lost their dependency on respiration, but normalised HRV (varRR/Tv) keeps the same character as varRR. There remains a significant difference between brain death and others, especially during slow deep breathing 8 (III) and 6 (IV) breathes per minute.

This confirms that differences in respiratory induced HRV in subjects are not caused by different breathing depth. While normalised heart rate variability in non brain death patients increases with slower breathing, it remains the same in brain death patients. We can speculate that reduced heart rate variability is affected by absent central nervous system activity in brain death subjects.

V. Conclusion

Respiratory induced HRV is the only parameter that can differentiate between brain death patients and sedated critically ill patients. Significant differences between groups can be detected especially during slow deep breathing with a mean period of 10 seconds. Differences in the HRV

parameter remain unchanged even after normalisation to respiration volume. This is an important finding that shows that HRV is independent and is not affected by different respiratory parameters.

The following recommendation may be made for clinical utilisation. During a short simple test with 0.1 Hz deep mechanical ventilation, the critical values reflecting brain death are: baroreflex lower than 0.5 ms/mmHg and tidal volume normalised HRV lower than 0.5 ms/ml.

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