Pulse rate variability is not a surrogate for heart rate variability

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ABSTRACT

To investigate the differences between heart rate (HR) variability and pulse rate (PR) variability, short-term variability of finger pulse wave and ECG signals were studied in 10 children with a fixed ventricular pacemaker rhythm (80 beats/min). Ten healthy children in sinus rhythm served as a reference population. Distal PR and HR were measured continuously using a Finapres device and an ECG respectively. Power spectra for HR and PR were calculated in both the supine and orthostatic positions. In paced subjects, PR spectra exhibited the characteristic respiratory peak, although the HR spectra were flat. Similarly, in healthy children the respiratory fluctuations were more pronounced when calculated from the finger pulse wave signal compared with the ECG signal. The overestimation of HR respiratory fluctuation resulting from distal PR measurement was more pronounced in the standing position; however, this postural effect was demonstrated only in healthy subjects. We observed mechanical respiratory modulation of distal PR independent of classical HR modulations. Our results suggest a mechanical respiratory influence via cardiac output and aortic transmural pressure changes on pulse wave velocity. We conclude that respiratory PR variability does not precisely reflect respiratory HR variability in standing healthy subjects and in patients with low HR variability. Consequently, HR modulation should be studied using the ECG signal rather than the distal pulse wave signal. However, when ECG recording is not available, the distal pulse wave is an acceptable alternative.

INTRODUCTION

Heart rate (HR) is usually calculated from the time elapsed between two ventricular contractions; in other words, the time between two consecutive R-waves on the ECG (R–R interval). This time period is strongly regulated and depends mainly on neural factors such as autonomic control on the sinus node, on hormonal factors such as the renin–angiotensin peptides, and on mechanical factors such as right auricular wall stretch. Given that HR is a determinant of stroke volume and cardiac output, it plays a major role in the regulation of arterial blood pressure.

Continuous recording of HR shows regular fluctuations that reflect parasympathetic and sympathetic neural control on the sinus node. Spectral analysis of the short-term variability of HR allows quantitative assessment of these neurogenic oscillations, and therefore provides indices of neural regulation of HR [1,2]. This non-invasive methodology has numerous clinical applications, specifically in physiology, in cardiology and in pharmacology.

Key words: autonomic nervous system, blood pressure, children, heart rate, pacemaker, pulse rate, respiration, variability, velocity.

Abbreviations: HF, high-frequency; HR, heart rate; LF, low-frequency; PR, pulse rate; PW, pulse wave; ΔR, beat-to-beat difference between HR and PR.

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In clinical practice, HR is routinely obtained from the distal pulse. Indeed, HR is commonly approximated from the pulse rate (PR), estimated from the time between two systolic peaks of pulse wave (PW), i.e. at a radial or digital level. This use of PR as a surrogate for HR requires identity of HR and PR fluctuations. Indeed, HR is closely correlated with PR, but small periodic deviations around an accurate mean cannot be excluded. HR-independent PR fluctuations are poorly documented. The ideal way to investigate the specific modulation of PR is to suppress HR modulation. In humans, the lack of an influence of HR on PR can be investigated in a variety of ways: after pharmacological blockade (although drugs may modify the vascular physiological responses); after cardiac transplantation (although a small cardiac intrinsic variability may still persist); and in patients with fixed pacemaker rhythm. Unfortunately, most patients in this final category have cardiovascular diseases and are undergoing treatment which may interact with the physiological process. To avoid this bias, we studied young subjects with normal cardiac performance, in whom a pacemaker was implanted because of congenital impairment of atrioventricular conduction. To test the hypothesis that PR fluctuates independently of HR modulation, we compared HR fluctuations with PR fluctuations in these paced subjects with fixed ventricular rhythm. In addition, we studied age-matched healthy children, in order to evaluate in healthy subjects the relative contribution of this HR-independent modulation of PR.

HR was derived simultaneously from the R-wave of the ECG, and from the systolic peak of the digital blood pressure curve (Finapres). These parameters were subjected to spectral analysis as described previously [3]. The study was performed in both the supine and orthostatic positions in order to examine the effects of postural variations on these parameters.

Previously we evaluated the consequences of withdrawal of HR fluctuations on the short-term regulation of blood pressure in a group of young children with fixed ventricular pacemaker rhythm [4]. The study reported herein represents our continued investigations into the consequences of withdrawal of HR fluctuations on short-term blood pressure regulation.

**METHODS**

**Study population**

Results from 10 children with an implanted bipolar DDD pacemaker [age 8.7 ± 2.2 years (mean ± S.D.), range 6–13 years; weight 27.6 ± 10.8 kg] and 10 healthy children with sinus rhythm (age 8.6 ± 2.5 years, range 6–13.5 years; weight 28.8 ± 6.0 kg) form the basis of this study. The indication for pacemaker implantation was isolated congenital complete heart block. All paced children had normal cardiac anatomy and left ventricular function, as assessed by echocardiography. None of the patients was taking medication of any type. At 1 h before recordings, the paced children (PM group) were programmed to the VVI mode (fixed ventricular rate) at a pacing rate of 80 beats/min.

**Study protocol**

Children were studied in the morning in a quiet room at 22 °C. Electrocardiograph measurements were taken with disposable electrodes attached to the thorax, placed to provide clear R-waves, and connected to a Datex cardiocap II monitor (Instrumentation Corp, Helsinki, Finland). Finger arterial pressure was monitored non-invasively by a Finapres device (model 2300; Ohmeda, Trappes, France). In this study, all children had a finger circumference of between 42 and 60 mm. To ensure optimal Finapres blood pressure measurement, we used appropriate cuff sizes (S or M) according to the manufacturer’s instructions. The cuff was fitted to the third finger of the right hand, which was passively maintained at heart level during the manoeuvres. Two recordings of 5 min duration were obtained; the first recording was obtained during 5 min in the supine position after a 10-min rest, and the second was taken when the subjects were in orthostatic posture.

Breathing was quantified by respiratory inductance plethysmography with a Respitrace device (Ardley, New York, NY, U.S.A.). During recordings obtained in the supine and standing positions, children breathed spontaneously during the first 1 min and were then asked to control their breathing frequency using an auditory signal from an electronic metronome. The controlled respiratory rate was determined from the spontaneous breathing rate of each child during the first 1 min of recording. HR variability studies were performed during controlled breathing.

The investigation conformed to the principles outlined in the Declaration of Helsinki (1989) of the World Medical Association, and was approved by the local Ethical Committee. The nature of the research was explained to the children’s parents, and informed consent was obtained.

**Data processing and spectral analysis**

The details of data sampling and analysis have been described previously [2]. The analogue output of the Datex monitor and of the Finapres device was connected to an analogue-to-digital converter to permit data acquisition, storage and analysis using a microcomputer. The blood pressure and ECG signals were digitized (500 Hz) and processed by an algorithm based on feature extraction to detect and measure the characteristics of a blood pressure cycle and an R-wave (Anapres 3.0; Notocord Systems, Croissy/Seine, France). According to the sample rate (500 Hz), the precision of signal
detection was 0.002 s, which represents the limits of resolution of the methodology. HR was estimated simultaneously from both finger blood pressure and ECG signals, as 60000 divided by the pulse or heart period in ms, measured from the corresponding systolic peak and the preceding one, and from the corresponding R-wave and the preceding one, respectively. A resampling rate of 10 Hz was chosen without interpolation, i.e., HR values were replicated every 0.1 s until a new blood pressure cycle or R-wave occurred within a 0.1 s window.

The evenly spaced sampling allowed direct spectral analysis using a fast Fourier transform (FFT) algorithm on a 2048-point stationary time series. This corresponded to a period of 3 min 25 s. Thus each spectral band corresponded to a harmonic of 5/1024 Hz, or 0.00488 Hz. The power of the HR shown in the Figures had units of (beats min$^{-1}$). Modulus (square root of the power) was used for calculations and statistical analysis.

The integration of the values of consecutive bands was computed in order to estimate the various components of the variability. As breathing frequency was controlled, the high-frequency (HF) oscillation was easily detected within the 0.2–0.5 Hz range, and we summed the value of the band corresponding to the respiration and the four values of higher and lower frequency (i.e., nine values) to integrate the HF component of HR. The low-frequency (LF) component was obtained by integration of the values of the consecutive bands from 0.0635 to 0.127 Hz of the HR spectrum, in order to include the 10-s rhythm (0.1 Hz) [5]. We also calculated descriptive statistics (means, S.D.) of the distribution of the HR of each stationary period of 205 s used for spectral analysis. In addition, to analyse further the difference between HR and PR variability, the beat-to-beat difference between HR and PR was re-calculated. Spectral analysis of this parameter was performed after equidistant resampling (10 Hz).

**Statistical analysis**

Data are expressed as means $\pm$ S.E.M. Significant differences between PR and HR, and between postures, were determined by one-way analysis of variance for repeated measures. When the F-value of the analysis of variance was significant, differences between groups and postures were tested using the modified t-statistics based on the Bonferroni method. Differences were considered to be statistically significant when the P value was $< 0.05$.

**RESULTS**

**Blood pressure data**

Average levels of systolic blood pressure and spectral profiles of systolic blood pressure were comparable in the paced subjects and in the healthy children in both postures (Table 1).

**Comparisons between HR variability and PR variability**

**Paced subjects**

As expected, HR variability was greatly reduced and the corresponding spectra were dramatically flat in paced subjects; accordingly, PR variability was markedly reduced. However, PR exhibited small fluctuations with respiration; indeed, the corresponding spectra showed a respiratory peak significantly more pronounced than in the HR spectra ($P < 0.001$) (Table 2).

**Control subjects**

Healthy children exhibited a high degree of HR variability and PR variability, as estimated by the S.D. of the distribution ranging between 4 and 10 beats/min (Table 2). Frequency domain analysis of these variabilities revealed classical components, mainly assessed by the LF and the respiratory (HF) peak of the power spectra. The respiratory peak (HF) of PR variability was more pronounced compared with the respiratory peak of HR variability ($P < 0.001$), while the LF components of HR variability and PR variability were similar.

**Variability of the beat-to-beat difference between HR and PR ($\Delta R$)**

In all subjects, $\Delta R$ displayed respiratory fluctuations (Table 3). Spectral analysis of beat-to-beat calculation of $\Delta R$ led to characteristic spectra with a single peak located at the respiratory frequency (HF) (Figure 1). In the control group, overall variability (S.D.) and the HF peak were increased in the standing position (respectively $P = 0.001$ and $P = 0.024$), while in the PM group this postural effect was not significant.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Average systolic blood pressure (SBP) values in the supine and standing positions, obtained in healthy controls (group C) and in paced children (group PM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP</td>
</tr>
<tr>
<td>Supine</td>
<td></td>
</tr>
<tr>
<td>Group PM</td>
<td>84.3</td>
</tr>
<tr>
<td>Group C</td>
<td>76.2</td>
</tr>
<tr>
<td>Standing</td>
<td></td>
</tr>
<tr>
<td>Group PM</td>
<td>94.8</td>
</tr>
<tr>
<td>Group C</td>
<td>99.8</td>
</tr>
</tbody>
</table>
Table 2  Average HR and PR values in the supine and standing positions, obtained in healthy controls (group C) and in paced children (group PM)

Included are the S.D.s of HR and PR, and the LF and HF components of the HR and PR spectra in absolute values (beats/min). Data are means ± S.E.M. Statistical significance of differences between HR and PR: 

<table>
<thead>
<tr>
<th>Rate (beats/min)</th>
<th>Group C</th>
<th></th>
<th>Group PM</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HR S.D. of HR</td>
<td>04.5 ± 4.2</td>
<td>7.4 ± 0.5</td>
<td>04.4 ± 4.2</td>
<td>04.1 ± 0.4</td>
</tr>
<tr>
<td>PR S.D. of PR</td>
<td>04.5 ± 4.2</td>
<td>7.4 ± 0.5</td>
<td>04.1 ± 0.4</td>
<td>04.0 ± 0.4</td>
</tr>
<tr>
<td>HR LF</td>
<td>2.6 ± 0.3</td>
<td>2.7 ± 0.3</td>
<td>2.6 ± 0.3</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td>PR LF</td>
<td>2.6 ± 0.3</td>
<td>2.7 ± 0.3</td>
<td>2.6 ± 0.3</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td>HR HF</td>
<td>3.1 ± 0.4**</td>
<td>3.1 ± 0.4**</td>
<td>3.1 ± 0.4**</td>
<td>3.1 ± 0.4**</td>
</tr>
<tr>
<td>PR HF</td>
<td>3.1 ± 0.4**</td>
<td>3.1 ± 0.4**</td>
<td>3.1 ± 0.4**</td>
<td>3.1 ± 0.4**</td>
</tr>
</tbody>
</table>

Table 3  Average ΔR values in the supine and standing positions, calculated in healthy controls (group C) and in paced children (group PM)

Included is the S.D. of ΔR, and the LF and HF components of the ΔR spectra in absolute values (beats/min). Data are means ± S.E.M. Statistical significance of differences between standing and supine: 

<table>
<thead>
<tr>
<th>Difference (beats/min)</th>
<th>ΔR</th>
<th>S.D. of ΔR</th>
<th>ΔR LF</th>
<th>ΔR HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>0.05 ± 0.01</td>
<td>0.82 ± 0.38</td>
<td>0.09 ± 0.01</td>
<td>0.41 ± 0.04</td>
</tr>
<tr>
<td>Standing</td>
<td>0.04 ± 0.01</td>
<td>1.19 ± 0.47**</td>
<td>0.09 ± 0.01</td>
<td>0.60 ± 0.07**</td>
</tr>
<tr>
<td>Group PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>0.02 ± 0.00</td>
<td>0.81 ± 0.30</td>
<td>0.07 ± 0.00</td>
<td>0.44 ± 0.05</td>
</tr>
<tr>
<td>Standing</td>
<td>0.02 ± 0.00</td>
<td>0.80 ± 0.34</td>
<td>0.06 ± 0.01</td>
<td>0.35 ± 0.03</td>
</tr>
</tbody>
</table>

DISCUSSION

Young subjects implanted with a cardiac pacemaker for the alleviation of a congenital impairment of atrioventricular conduction, but with no other clinical indications, provide a clinical model whereby the fluctuations of PR can be assessed independently of those of HR. In the present study we provide evidence documenting respiratory fluctuations of PR independent of fluctuations of HR, and an increase in the magnitude of these fluctuations in the standing position in healthy subjects only.

Therefore assessment of HR variability from PR may lead to an overestimation of the HF component of HR variability, by as much as 25% in standing healthy subjects and by 300% in subjects with fixed ventricular rhythm. The present study supports the results published by Karrakchou et al. [6] suggesting that the spectra of HR calculated from the ECG and finger blood pressure signals differ for high frequencies.

The respiratory fluctuations of PR independent of fluctuations of HR were demonstrated using the finger PW signal. Our results might be specific to measurement of PR at a distal site. The detection of the systolic peak from the blood pressure signal was processed by a complex algorithm including a sequence of mathematical validations based on derivative processes. A minimal respiratory-induced change in the shape of the blood pressure waveform peak cannot be excluded as making a possible contribution to the differences observed.

In paced subjects programmed in the VVI mode, the cardiac electrical impulse is regularly generated at the level of the right ventricle, and if we assume that variations of electromechanical coupling are negligible, HR does not fluctuate. Hence the time interval between two consecutive systolic ejections may be considered as constant. Under these conditions, the existence of periodic fluctuations of distal PR must be due to periodic fluctuations in the time taken for the arterial pulse pressure wave (shock wave) to be generated from the electrical impulse and to travel from the aortic valve to a peripheral site. While the pre-ejection time (left ventricular isometric contraction) depends mainly on left ventricular contractility, the duration of propagation of the PW depends on PW velocity [7]. Hence periodic variations in distal PR might result from periodic changes in isometric contraction time or in PW velocity, or both. In healthy adults the pre-ejection time is usually of the order of 50 ms, while the propagation time of the PW is approx. 250 ms [8]. Respiratory-induced changes in ventricular loading conditions may result in respiratory-dependent variability of the pre-ejection time via modulation of the mechano–electric feedback [9]. However, the difficulty in detecting the exact moment of opening of the aortic valve non-invasively, along with the relatively small contribution of the pre-ejection time, led us to only discuss the involvement of periodic changes in the PW propagation time in the genesis of distal PR fluctuations.

We hypothesized that periodic fluctuations in distal PR result mainly from periodic fluctuations of PW velocity. Given that stiffness and tension in the arterial wall are the main factors determining the speed of
Figure 1 Examples of HR, PR, ΔR and respiration recordings in one 10-year-old normal child (left) and in one 10-year-old child with a fixed ventricular rhythm (right).
Recordings were obtained in the standing position, and the corresponding power spectra are shown. Note that the scales for the spectral analysis of HR and PR differ by a factor of 500 between the healthy child and the paced child.
transmission of the PW, several mechanisms may be suggested to explain our results. Periodic fluctuations of PW velocity may be related to active changes in arterial compliance resulting from a central modulation, such as sympathetic baroreflex-mediated oscillations, or from local modulation, such as spontaneous oscillations of small arteries. It may also be hypothesized that periodic fluctuations of PW velocity result from passive changes in cardiovascular loading conditions via a mechanical influence of respiration, such as variations in intrathoracic vessel transpapertial pressure and in systolic ejection volume.

PW velocity varies inversely with the arterial compliance. As such, any increase in vessel stiffness (decreased compliance) increases PW velocity. Changes in PW velocity might be the consequence of sympathetic vasomotor fluctuations. Direct measurements of efferent muscle sympathetic nerve activity have demonstrated that the sympathetic nervous activity consists of rhythmic oscillations \[10\]. In human, both LF (around 0.1 Hz) and HF (respiratory frequency) components have been detected \[11\]. The oscillation characteristics of muscle sympathetic nerve activity were closely mirrored by oscillations of systolic blood pressure \[12\]. Respiratory fluctuations in PR might be due to sympathetic-mediated and respiratory-induced changes in vascular compliance; however, we failed to demonstrate any LF fluctuation of PR in our study. The respiratory specificity of PR fluctuations seems to rule out the involvement of sympathetic-mediated alterations in vascular compliance.

The site of measurement might be taken into consideration as a potential factor involved in the genesis of the unexplained periodicity of the PR. Indeed, the PW signal was recorded using a digital photoplethysmographic device. The digital arteries under the cuff may be subject to rhythmic contractions. Several rhythms have been demonstrated in smooth muscle tone in human arteries \[13, 14\]. Cyclic vasomotor oscillations observed at frequencies ranging between 0.02 and 0.15 Hz may act independently as local spontaneous oscillations, or synchronously as a driving sympathetic rhythm. However, these peripheral vasomotor rhythms seem to predominate at lower frequencies (\(<0.15\) Hz) \[15\], and consequently are probably not involved in the mechanism accountable for the PR respiratory variability.

Respiration strongly influences arterial pressure. Respiration-induced changes in blood pressure result from changes in cardiac output, probably via respiration-induced changes in HR and ventricular filling \[16, 17\]. Jurgen and co-workers \[18–20\] have extensively studied the normal decreases in both arterial pressure and left ventricular stroke volume that occur with an inspiratory decrease in intrathoracic pressure. They concluded that the phenomenon is due to independent effects of negative intrathoracic pressure on both left ventricular preload and afterload \[18\]. They suggested that the decreases in peripheral arterial flow and pressure (pulsus paradoxus) with negative intrathoracic pressure are associated with a diminished left ventricular output, together with retained blood within the intra-arterial compartment \[19\]. They also demonstrated that the negative intrathoracic pressure led to an increase in aortic cross-sectional area, a decrease in thoracic aortic pressure and a decrease in anterograde flow (or even retrograde flow) in the descending aorta \[20\]. These findings, which Olsen et al. referred to as a ‘reverse thoracic pump’ \[21\] may support a mechanism for a decrease in PW velocity on inspiration. With differences between HR and PR apparently strongly and specifically related to respiratory fluctuations in systolic blood pressure, we hypothesize that changes in intrathoracic pressure, and subsequent fluctuations in cardiac output and aortic loading conditions, are involved in the genesis of the differences between HR variability and PR variability. In agreement with our findings, Pitson and co-workers \[22, 23\] demonstrated that the inspiratory rise in pulse transit time (measured from the R-wave to the finger PW) correlates well with the degree of inspiratory effort.

The mechanical coupling between respiratory activity and vasculature within the thorax is stronger in the standing than in the supine position \[4\]. In agreement with this finding, we demonstrated an orthostatic accentuation of the difference between respiratory HR variability and respiratory PR variability. However, this postural effect was evident only in healthy children. We have found previously that, in paced children, the lack of autonomic control on the sinus node was associated with a reduction in the magnitude of the differences in systolic blood pressure variability induced by the standing position \[4\]. We hypothesized that the orthostatic accentuation of systolic blood pressure in control subjects might be due to marked variations in HR, resulting in cardiac output and subsequent blood pressure variations, and we concluded that, in normal children, HR fluctuations increase the systolic blood pressure variability rather than buffering it. These findings are consistent with the involvement of variations in HR, via cardiac output changes, in the magnitude of the difference between HR and PR respiratory variability. However, as HR itself is a major determinant of PW velocity, we cannot eliminate a potential influence of the posture-related increase in average HR levels on the orthostatic accentuation of the difference between respiratory HR variability and respiratory PR variability.

In conclusion, we have observed a mechanical respiratory modulation of PR, which acts independently of classical HR modulations. Our results might testify to a mechanical respiratory influence, via cardiac output and aortic transmural pressure changes, on PW velocity. Consequently, PR variability does not exactly reflect HR variability, especially in standing healthy subjects and in patients with low HR variability. However, under several
conditions, PR may represent an acceptable surrogate signal for HR, provided that care is taken to avoid subjects that show either very high or very low HR variability.

REFERENCES


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