Respiratory-related arterial pressure variability as an indicator of graded blood loss: involvement of the autonomic nervous system

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ABSTRACT

During positive pressure mechanical ventilation, percentile systolic pressure variation (%SPV) or respiratory-related arterial pressure variability (RAPV) have both been used in assessment of graded haemorrhage. We aimed to investigate whether changes in %SPV and RAPV are correlated during graded haemorrhage (by 5, 10 or 20% of the estimated blood volume) in anaesthetized positive pressure ventilated rats and to investigate the involvement of autonomic regulation. Saline vehicle or atropine produced no discernible effect on baseline %SPV or RAPV but, thereafter, %SPV and RAPV increased progressively with graded haemorrhage. Propranolol significantly decreased baseline %SPV and RAPV and changes induced in %SPV and RAPV by graded haemorrhage. Phentolamine significantly enhanced baseline %SPV and RAPV, and further enhancement of %SPV and RAPV by graded haemorrhage did not occur until 20% of the estimated blood volume was removed. RAPV was significantly correlated with %SPV in all experimental groups. We conclude that RAPV is comparable with %SPV as an indicator of graded haemorrhage and that, in anaesthetized and positive pressure ventilated rats, both are dependent on autonomic function, especially β-adrenoceptors.

INTRODUCTION

It has been reported [1–4] that, during positive pressure mechanical ventilation, variations in systolic pressure arterial waveform (SPV) allow assessment of cardiac preload. Such an idea has provided an opportunity to detect blood volume status non-invasively and is potentially of great clinical importance. Although SPV can be manually approximated from the arterial waveform, an accurate calculation is difficult to achieve and there are still no automatic real-time analyses. In addition, the mechanism underlying the relationship between SPV and blood volume status is still unclear and very little is known about the involvement of the autonomic nervous system (ANS) in haemorrhage-induced SPV changes. These issues warrant further investigation.

The use of SPV for detecting blood volume status has been recommended, but the technique calls for a special mechanical ventilation pattern and is not easily applied in a continuous and automatic way. A more accurate method for assessment of preload is based on measuring the left ventricle end-diastolic area using a transoesophageal echocardiogram [4]. However, its...
application is limited to a small number of patients and it cannot be used continuously for long periods of time. The recently introduced PiCCO (PULSION, Munich, Germany) monitor is another choice for the continuous estimation of the effects of mechanical ventilation on cardiac function [5], but this method requires that a special catheter be inserted via the jugular or subclavian veins and the cost is very high.

Using fast-Fourier transform, power spectrum analyses of heart rate variability and arterial pressure variability (APV) have provided much information for basic research and clinical applications [6,7]. The high-frequency power of APV has been correlated with respiration and is also known as respiratory-related APV (RAPV) [8]. A previous study from our laboratory [9] demonstrated that, in rats under positive pressure ventilation, the magnitude of RAPV increased with higher tidal volumes or lower respiratory frequency. Since RAPV can be dose-dependently suppressed by β-adrenoceptor blocking agents, we have suggested that RAPV may provide a valid assessment of cardiac sympathetic regulation, which is independent of parasympathetic and vascular sympathetic influences [8,10]. Some studies have reported the relationship between RAPV and haemorrhage. In conscious spontaneously breathing rats [11,12] and anaesthetized mechanically ventilated dogs [13], RAPV increases during haemorrhage.

Given these findings, it is reasonable to hypothesize that, in rats under positive pressure ventilation, RAPV in the frequency domain is equivalent to SPV in the time domain as an indicator of graded haemorrhage and that both variables are dependent on the functioning of the ANS.

METHODS

Anaesthetic technique

The animals and procedures used in this study were approved by the Animal Research Committee of the Tzu Chi University, Hualien, Taiwan. Sixty-one adult male Spraque–Dawley rats, weighting 300–320 g, were randomly divided into four groups. Anaesthesia was induced with an intraperitoneal injection of sodium pentobarbital (50 mg/kg of body weight). Bilateral femoral arteries and veins were catheterized. After a tracheostomy, respiration was controlled with a mechanical ventilator at a constant tidal volume (10 ml/kg of body weight) and a fixed ventilation frequency (80 breaths/min). Anaesthesia was maintained with a continuous intravenous (i.v.) infusion of pancuronium bromide (2 mg·h⁻¹·kg of body weight⁻¹) and sodium pentobarbital (15 mg·h⁻¹·kg of body weight⁻¹). This anaesthetic management offered maintained anaesthesia while preserving the capacity of cardiovascular regulation [14]. The adequacy of anaesthesia was continuously assessed by on-line monitoring of the power spectrum of arterial pressure and heart rate signals [7,14].

Haemodynamic monitoring

A right-side femoral arterial catheter was connected to a pressure transducer (P23ID; Gulton-Statham Transducers, Amherst, NY, U.S.A.) and, in turn, to a universal amplifier (G-20-4615-58; Gould Instruments, Valley View, OH, U.S.A.). The arterial pressure signals were acquired with a 12-bit analogue-to-digital converter (PCL1800; Advantech, Taipei, Taiwan) at a sampling rate of 1024 Hz, which satisfied the requirement of the Nyquist theorem. Lead II of the ECG was also amplified and filtered. The computer used was a general purpose personal computer (IBM PC compatible). All data were analysed on-line and were also simultaneously stored on a hard disk for subsequent off-line verification.

Detailed procedures for the RAPV analysis were as described previously [8–10]. In brief, the raw arterial pressure signals were first normalized to their mean value and then expressed as a percentage variation from the mean arterial pressure (unit). This normalization procedure rendered the subsequent spectral analysis independent of an absolute mean value [8]. Signals to be analysed were first subjected to an eight-point average algorithm, which essentially reduced the sampling rate to 128 Hz. These were subsequently truncated into 16 s (2048 point) epochs with 50 % overlap. For each epoch, the linear trend was removed to avoid its contribution to the power of lower frequencies. A Hamming window in the time domain was used to attenuate the leakage effect. Power spectral analysis of arterial pressure signals was accomplished by fast-Fourier transform. Power spectra of the systemic arterial pressure (SAP) were quantified by determining the areas of the spectra. Because the respiratory rate was at a constant condition (80 breaths/min; 1.32 Hz), the high-frequency component (0.8–2.4 Hz) was then taken as the RAPV.

Magnitudes of the SPV were measured as the mean difference between the maximal and minimal values of the systolic blood pressure (SBP) over five consecutive breaths at each step of the experiment [2,3]. %SPV is defined as (SPV/mean SBP) × 100 %, where mean SBP is the mean value of SBP over these same breaths. Since %SPV relates the SPV to the absolute level of the SBP, it was applied in later studies [2].

Experimental protocol

Rats were randomly divided into the following four groups: a saline group, a β-adrenoceptor blockade group (propranolol, 1 mg/kg of body weight), an α-adrenoceptor blockade group (phentolamine, 2.5 mg/kg of body weight) and a muscarinic blockade group (atropine, 0.3 mg/kg of body weight). To avoid the confounding effect of drug interaction, only one pretreatment schedule
Arterial pressure variability and graded blood loss

was performed in each animal. Nonetheless, the efficacy of each blocker was ascertained by the lack of discernible changes in SAP and heart rate in response to i.v. administration of the respective agonists, phenylephrine (5 µg/kg of body weight), isoprenaline (1 µg/kg of body weight) or metacholine (0.1 µg/kg of body weight), at the end of the recording session. All rats were given 1 ml of a saline solution by i.v. infusion after preparation to avoid unrecognized hypovolaemia before the experiment and were maintained with 1 ml·h⁻¹·kg⁻¹ of an i.v. saline solution during the experiment. The estimated blood volume (EBV) of rats in this study was calculated as 6.5 % of the body weight [15].

Stable blood pressure and heart rate data were collected initially for 5 min. The pretreatment drug dissolved in 1 ml of saline or vehicle was given by i.v. infusion. After 10 min, three steps of consecutive haemorrhage (5, 10 and 20 % EBV) were performed by manual withdrawal of arterial blood from the left-side femoral artery catheter. Five experimental phases were defined as follows: baseline phase, pretreatment phase (2 min after giving vehicle or drugs), 5 % EBV haemorrhage, 10 % EBV haemorrhage and 20 % EBV haemorrhage. Each phase was maintained for at least 10 min with stabilization of blood pressure and heart rate.

**Statistical analysis**

All values are expressed as the means ± S.E.M. Data between groups were compared using one-way ANOVA with repeated measures, followed by Fisher’s least significant difference test for a posteriori comparison of individual means. Differences were considered statistically significant at *P* < 0.05. Relationships between %SPV and RAPV were compared using a linear regression method.

**RESULTS**

The magnitudes of RAPV were automatically analysed on-line with a computer, but the magnitudes of %SPV were manually calculated off-line. Figure 1 demonstrates the continuous on-line and real-time spectral analysis of SAP before, during and after haemorrhage of 5 % EBV in the saline group. A typical example of the changes in %SPV and RAPV in the saline group is shown in Figure 2. Both %SPV and RAPV were elevated after mild haemorrhage (5 % EBV haemorrhage), and the degree of elevation was proportional to the severity of the haemorrhage. Significant elevations in %SPV and RAPV during graded haemorrhage were also identified in the group data (Table 1).

Figure 3 shows a typical example of changes in %SPV and RAPV under β-adrenoceptor blockade. After propranolol administration, both %SPV and RAPV significantly decreased to a very low level. Following propranolol administration, %SPV and RAPV showed slight responses to graded haemorrhage, but were still statistically significant (Table 1). After phentolamine treatment, the magnitude of %SPV and RAPV was
Figure 2  Typical example of changes in %SPV and RAPV amplitudes in the saline group
Five experimental phases revealed significant elevations of %SPV and RAPV during graded haemorrhage. Bas, baseline phase; Sal, pretreatment with saline (1 ml, i.v.); 5 %, 5 % EBV haemorrhage; 10 %, 10 % EBV haemorrhage; 20 %, 20 % EBV haemorrhage; BPSDn, normalized power spectral density of SAP.

Figure 3  Typical example of changes in %SPV and RAPV amplitudes in the β-adrenoceptor blockade group
After propranolol (Pro; 1 mg/kg of body weight, i.v.) pretreatment, both %SPV and RAPV amplitudes significantly decreased. In the following three phases of graded haemorrhage (5, 10 and 20 % EBV), the increases in %SPV and RAPV were less prominent than those found in the saline group.

markedly elevated, but further elevation induced by haemorrhage was not evident until the haemorrhaging was severe (20 % EBV; Table 1). Atropine itself had no significant effect on %SPV and RAPV. Following atropine administration, elevation of %SPV and RAPV in response to graded haemorrhage was similar to those of the saline group (Table 1). Linear regression analysis revealed significant correlations ($r > 0.87$; $P < 0.001$) between %SPV and RAPV in all groups of our experiment (Figure 4). It is noteworthy that, although RAPV of 5 % EBV haemorrhage did not exhibit significant difference compared with baseline, %SPV of 5 % EBV haemorrhage did (Table 1), implying that the sensitivity of %SPV to haemorrhage was greater than that of RAPV.

DISCUSSION

Frequency domain analysis of cardiovascular variability has increased in popularity with broader applications in recent years. Since it is easily accessible, increasing numbers of clinical and basic investigators are using the technique to monitor ANS function in humans and experimental animals [14,16–18]. Research on frequency domain analysis of RAPV as an indicator of blood volume is, however, relatively rare. The present study demonstrates a high correlation ($r = 0.89$; $P < 0.001$) between the magnitudes of %SPV and RAPV during graded haemorrhage. This phenomenon persists even in the presence of autonomic blocking agents. Such observations offer direct evidence that %SPV in time domain analyses and RAPV in frequency domain analyses may assess the same physiological phenomenon when they are applied to evaluating blood volume or preload. Since assessment of respiratory variations in arterial pressure can be analysed by %SPV or RAPV, frequency domain analysis of RAPV may have the advantage of being an automatic real-time operation. Such an advantage is especially important if RAPV is to be applied to routine cardiorespiratory management in hospitals.

In our previous studies, RAPV magnitude was dose-dependently suppressed by 0.01–1 mg of propranolol/kg.
Haemodynamic changes in SAP, heart rate, RAPV and %SPV during graded haemorrhage in rats under positive pressure ventilation

Linear regression analysis of %SPV and RAPV for the saline, propranolol, phentolamine and atropine groups

Values are expressed as means ± S.E.M. PreTx, after i.v. pretreatment with 1 ml of saline or pharmacological antagonist dissolved in 1 ml of vehicle. *P < 0.05 compared with baseline; †P < 0.05 compared with PreTx; ‡P < 0.05 compared with 5 % EBV; §P < 0.05 compared with 10 % EBV.

<table>
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<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>PreTx</th>
<th>5 %</th>
<th>10 %</th>
<th>20 %</th>
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<td>Static SAP (mmHg)</td>
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<td>Saline group</td>
<td>124.0 ± 2.2</td>
<td>125.4 ± 2.5</td>
<td>91.5 ± 5.0†</td>
<td>79.8 ± 4.1‡</td>
<td>50.6 ± 3.3§§</td>
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<td>124.0 ± 2.0</td>
<td>107.8 ± 6.6*</td>
<td>93.8 ± 5.6†</td>
<td>81.4 ± 4.7‡</td>
<td>51.1 ± 2.9§§</td>
</tr>
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<td>Phentolamine group</td>
<td>125.2 ± 2.3</td>
<td>85.8 ± 3.0*</td>
<td>70.3 ± 3.8†</td>
<td>61.9 ± 4.2‡</td>
<td>52.6 ± 3.8§§</td>
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<td>Atropine group</td>
<td>127.9 ± 3.5</td>
<td>124.3 ± 2.8</td>
<td>96.1 ± 5.6†</td>
<td>81.4 ± 4.3‡</td>
<td>61.5 ± 5.1§§</td>
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<td>Saline group</td>
<td>467.5 ± 9.6</td>
<td>466.1 ± 9.2</td>
<td>455.5 ± 11.0</td>
<td>450.4 ± 11.3</td>
<td>407.2 ± 14.7§§</td>
</tr>
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<td>Propranolol group</td>
<td>468.3 ± 6.1</td>
<td>354.9 ± 7.0*</td>
<td>357.2 ± 5.4*</td>
<td>354.4 ± 5.3*</td>
<td>322.4 ± 8.0§§</td>
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<td>Phentolamine group</td>
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<td>464.4 ± 9.9</td>
<td>453.8 ± 16.0</td>
<td>433.1 ± 18.8*</td>
<td>433.7 ± 16.6*</td>
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<td>473.1 ± 9.2</td>
<td>447.1 ± 12.1§§</td>
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<tr>
<td>Saline group</td>
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<td>1.8 ± 0.3</td>
<td>4.3 ± 0.7</td>
<td>6.0 ± 0.9†</td>
<td>7.9 ± 2.3‡‡</td>
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<td>Propranolol group</td>
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<td>0.9 ± 0.1*</td>
<td>1.4 ± 0.2‡</td>
<td>3.2 ± 0.7§§</td>
</tr>
<tr>
<td>Phentolamine group</td>
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<td>8.0 ± 1.1*</td>
<td>6.7 ± 1.0*</td>
<td>5.9 ± 1.1*</td>
<td>10.3 ± 1.8§§</td>
</tr>
<tr>
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<td>2.8 ± 0.4</td>
<td>2.4 ± 0.4</td>
<td>5.0 ± 1.0</td>
<td>6.5 ± 0.9*</td>
<td>9.6 ± 1.7§§</td>
</tr>
<tr>
<td>%SPV (%)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Saline group</td>
<td>6.2 ± 0.5</td>
<td>5.8 ± 0.4</td>
<td>9.9 ± 0.8†</td>
<td>12.6 ± 1.2†</td>
<td>16.4 ± 2.1§§</td>
</tr>
<tr>
<td>Propranolol group</td>
<td>5.8 ± 0.5</td>
<td>2.4 ± 0.2*</td>
<td>4.8 ± 0.5†</td>
<td>6.3 ± 0.6‡</td>
<td>11.2 ± 1.2§§</td>
</tr>
<tr>
<td>Phentolamine group</td>
<td>6.8 ± 0.6</td>
<td>13.2 ± 1.1*</td>
<td>12.6 ± 1.2*</td>
<td>13.0 ± 1.0*</td>
<td>20.9 ± 1.9§§</td>
</tr>
<tr>
<td>Atropine group</td>
<td>7.5 ± 0.8</td>
<td>6.9 ± 0.8</td>
<td>10.2 ± 1.2†</td>
<td>12.2 ± 1.1†</td>
<td>16.8 ± 1.4§§</td>
</tr>
</tbody>
</table>

Figure 4 Linear regression analysis of %SPV and RAPV for the saline, propranolol, phentolamine and atropine groups

Values were obtained from all phases of the experiments including the baseline, pretreatment and 5, 10 and 20 % EBV haemorrhage. The correlation coefficients (r) were 0.87 for the saline (Sal) group, 0.92 for the propranolol (Pro) group, 0.87 for the phentolamine (Phe) group and 0.89 for the atropine (Atr) group. All correlations were statistically significant (P < 0.001).

of body weight i.v. [8] and stroke volume variability exhibited a similar pattern of suppression [10]. In the present study, it is especially noteworthy that the magnitude of both %SPV and RAPV was coincidentally suppressed by propranolol administration. Under β-blockade, increases in the two indices in response to haemorrhaging were not pronounced. This may possibly be clinically relevant if a patient has a history of long-term β-blocker administration or has received a β-blocker perioperatively; the blood volume deficit reflected by RAPV and %SPV may be less prominent and, thus, may possibly be overlooked. The use of β-adrenergic blocking agents to treat perioperative hypertension or induce deliberate hypotension in some surgical conditions is very
common practice for anaesthetists. In such conditions, evaluation of the blood volume status by %SPV or RAPV would result in an underestimation and thus great care must be taken.

The magnitude of %SPV and RAPV dramatically increased after i.v. phentolamine administration. We suggest that suppression of the influence of sympathetic activity on α-adrenoceptors in the peripheral circulation induced a compensatory increase in the action of cardiac sympathetic activity and circulating catecholamines on cardiac β-adrenoceptors, which led to increases in both %SPV and RAPV. Since %SPV and RAPV were increased to high values under baseline conditions before haemorrhage, they were not increased further until blood loss was severe (20% EBV). Results from the atropine group resembled patterns in the saline group and showed no significant differences. This suggests that parasympathetic activity acting on muscarinic receptors does not play a major role in the response of RAPV or %SPV to graded haemorrhage in the anaesthetized rat.

Although RAPV and %SPV are both increased under graded haemorrhage, %SPV showed a higher sensitivity to graded haemorrhage than RAPV. It should be noted that %SPV was calculated manually by averaging five consecutive breaths (around 3.8 s) and RAPV was analysed automatically from 16 s signals. Thus differences in data sampling and analysis may have caused apparent differences in the sensitivity of RAPV and %SPV to haemorrhage.

In addition to body fluid status, it has been well documented that the magnitude of SPV and RAPV is also affected by respiratory factors, including lung and chest wall compliance, tidal volume and respiratory frequency [19]. Lower chest wall compliance, higher tidal volume, lower respiratory frequency, increased positive end-expiratory pressure and pneumoperitoneum all cause the intrathoracic pressure to increase and ultimately elevate the magnitude of SPV and RAPV [19–22]. Therefore in non-sedated or spontaneously breathing patients, the use of SPV and RAPV for detecting body fluid status remains to be evaluated.

The interactions between respiration and circulation are rather complex. Factors that may influence changes in RAPV include respiratory conditions [23], blood volume status [1], cardiac function [24] and autonomic function [8,10]. Our previous studies [8–10] have demonstrated that at least two mechanisms jointly constitute RAPV. The autonomic mechanism may produce its effects via pulse pressure variability. We have demonstrated that the β-adrenergetic system has a tonic facilitating effect on pulse pressure variability and thus enhances RAPV. Transmitted intrathoracic pressure, on the other hand, contributes to the non-autonomic mechanism. It has a generalized effect on pulse pressure, systolic pressure, mean pressure and diastolic pressure and thus an RAPV due to such a mechanism would be synchronized with intrathoracic pressure. The autonomic mechanism contributes a significant part of RAPV in the anaesthetized rat. Therefore the augmentation of RAPV by haemorrhage may be explained, at least in part, by the baroreceptor response of the sympathetic system.

The present study establishes relationships between the time domain parameter of %SPV and the frequency domain parameter of RAPV and demonstrates the involvement of autonomic nerve activities in the modulation of %SPV and RAPV in response to graded haemorrhage in rats under positive-pressure ventilation. Our present data also suggest that %SPV and RAPV may not be reliable indices of circulating blood volume when autonomic nerve activities, especially sympathetic activity, are unstable or changing. We expect that future investigations will clarify the applicability and limitations of these potential techniques in humans.

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