Effect of esmolol on positive-pressure ventilation-induced variations of arterial pressure in anaesthetized humans

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ABSTRACT

Positive-pressure ventilation-induced variations in arterial pressure have been related to cardiac sympathetic activity in animals. However, the effect of β-adrenoceptor blockade on these variations in anaesthetized humans under positive-pressure ventilation has not yet been investigated. In the present study, RAPV (respiratory-related arterial pressure variability) and %SPV (percentile systolic pressure variation) were determined before and after esmolol treatment in ten mechanically ventilated patients. RAPV and %SPV decreased significantly after intravenous esmolol (1 mg/kg of body weight) treatment (maximal decrease of RAPV, 50% and %SPV, 35%). Linear regression analysis of RAPV and %SPV before and after esmolol treatment both revealed high correlation (r = 0.93 and 0.91 respectively). The amplitudes of RAPV and %SPV also significantly increased in a graded way with higher tidal volumes. Thus we propose that esmolol suppresses the variations in arterial pressure induced by positive-pressure mechanical ventilation, and we suggest that RAPV and %SPV may be alternative choices for monitoring cardiac sympathetic regulation in anaesthetized patients under positive-pressure ventilation.

INTRODUCTION

The regulation of the ANS (autonomic nervous system) is very important in clinical anaesthesia, but the assessment of autonomic activity is frequently a challenging clinical task. Unfortunately, as McCance [1] suggested, many of the current approaches, including measuring the level of circulating stress hormones, are off-line techniques representing the “overall sympathetic activity” instead of being real-time and organ-specific ones.

The fact that arterial pressure fluctuates about a mean value has long been known: this is termed APV (arterial pressure variability). In recent years, APV has been extensively explored and found to be closely related to the functioning of the ANS [2–5]. Using Fast Fourier transformation, power spectral analyses of APV and HRV [HR (heart rate) variability] provide much information for basic research and clinical applications [6–8]. Although not as popular as HRV, frequency domain analyses of APV have revealed that it also carries important information.

Key words: adrenergic receptor, arterial pressure, autonomic nervous system, positive-pressure ventilation, systolic pressure.

Abbreviations: ANS, autonomic nervous system; APV, arterial pressure variability; BP, blood pressure; BHF, BP high-frequency power; BLF, BP low-frequency power; BTP, BP total power; HR, heart rate; HRV, HR variability; HHF, HR high-frequency power; HLF, HR low-frequency power; HTP, HR total power; PI, pulse interval; SAP, systemic arterial pressure; BPSDn, three-dimensional power spectral density of normalized SAP; RAPV, respiratory-related arterial pressure variability; SBP, systolic BP; SPV, systolic pressure variation; %SPV, percentile systolic pressure variation.

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about autonomic regulation [4,9]. The low-frequency component of APV has been correlated with vasomotor activity [4,5,10]. The high-frequency component of APV has been correlated with respiration and is also known as RAPV (respiratory-related arterial pressure variability) [3,11,12]. Our previous study [3] demonstrated that the magnitude of RAPV increases with higher tidal volumes or lower respiratory frequencies in rats. We also demonstrated [11] that RAPV can be dose-dependently suppressed by β-adrenoceptor blocking agents in rats. Therefore these results suggested that RAPV might provide a valid assessment of cardiac sympathetic regulation, which is independent of parasympathetic and vascular sympathetic influences in rats [11,12].

Other studies have documented the usefulness of time domain analyses of the arterial pressure waveform as an indicator of cardiac preload or blood volume. They include SPV (systolic pressure variation) and its derivative %SPV (percentile SPV). SPV and %SPV have been shown in animals [13] and humans [14] to correlate with blood volume status and specifically to be more pronounced in hypovolaemia. Previous studies have focused primarily on the response to graded haemorrhage and the optimization of fluid challenge [15], but few investigations concerning the involvement of autonomic regulation in the function of SPV have been reported [16]. As RAPV is dose-dependently suppressed by β-adrenoceptor blockade in rats, the issue of whether this physiological phenomenon can also be demonstrated in clinically anaesthetized patients is of interest, but has not yet been investigated. Esmolol is a synthetic short-acting selective β1 antagonist, which has been widely used in clinical anaesthesia to decrease the sympathetic response to endotracheal intubation [17], and this action is associated with concomitant increase of plasma catecholamines [18]. Thus the first aim of the present study was to investigate whether RAPV and %SPV are suppressed simultaneously by esmolol in anaesthetized patients under positive-pressure ventilation.

A more recent study [16] has demonstrated that RAPV in the frequency domain and %SPV in the time domain are well correlated during graded haemorrhage in mechanically ventilated rats, but this correlation has not been proven in humans. Therefore the second aim of the present study was to analyse the correlation between RAPV and %SPV before and after esmolol administration in anaesthetized patients under positive-pressure ventilation. Finally, we investigated the effects of changes in tidal volume on RAPV and %SPV.

METHODS

Anaesthetic technique

With approval of the Human Research Committee of our hospital and after obtaining written informed consent, ten female patients (age, 48 ± 6 years; weight, 54.3 ± 8.7 kg; height, 155.0 ± 10.8 cm), ASA (American Society of Anesthesiologists) class I–II, scheduled to receive elective surgery under general anaesthesia that was expected to last at least 3 h, were asked to participate in the study. We excluded subjects with conditions that affect cardiovascular fluctuations, including hypotension, hypertension, diabetic neuropathy, an implanted cardiac pacemaker, abnormal thyroid function, frequent occurrence of atrial fibrillation, premature atrial or ventricular contractions, or other forms of arrhythmia [4,16]. Furthermore, no patients were receiving medication reported to influence cardiovascular fluctuations, such as hypnotics or autonomic blockers. Anaesthesia was induced with an intravenous injection of fentanyl (3 µg/kg of body weight), sodium thiopental (5 mg/kg of body weight), and rocuronium (1 mg/kg of body weight) following pre-oxygenation (2 min) by mask. After tracheal intubation, patients were ventilated with a mechanical ventilator at a tidal volume of 12 ml/kg of body weight; the ventilation rate was 10 breaths/min. The anaesthesia was maintained with nitrous oxide in oxygen (1:1), sevoflurane (3 %), rocuronium (0.2 mg/kg of body weight · h⁻¹), and fentanyl (1 µg · kg⁻¹ · body weight · h⁻¹). The recordings made during anaesthesia included ECGs, pulse oximetry, capnography (end-tidal CO₂), central venous pressure, body temperature and urine output. Continuous arterial BP (blood pressure) was measured by direct radial arterial cannulation. The patient was then positioned for surgical preparation. An adequate anaesthetic depth was carefully maintained to ensure that the BP and HR would increase to an extent less than 10 % of their baseline values after skin incision. Intravenous fluid supplements were kept at a constant rate of 4 ml · kg⁻¹ · h⁻¹ of body weight · h⁻¹ by infusion pump and were also monitored closely by continuous central venous pressure to avoid inadvertent hypovolaemia status during the operation. The operative time was from 3 h and 10 min to 5 h, and the average total blood loss during operation was less than 50 ml.

Haemodynamic monitoring

The arterial catheter was connected to a pressure transducer (Abbott transpac iv monitoring kit) and, in turn, to a universal amplifier (Hewlett Packard M1006A). The arterial pressure signals were acquired by a 12-bit analogue-to-digital converter (Advantech PCL1800) at a sampling rate of 256 Hz, which satisfied the requirement of the Nyquist theorem [8]. The computer was a general-purpose personal computer (IBM PC compatible). The computer program was written in Pascal (Borland Pascal 7.0, Borland). All data were analysed on-line, but were simultaneously stored on a hard disk for subsequent off-line verification.
**Autospectral analysis of cardiovascular signals**

The arterial pressure and PI (pulse interval) signals were simultaneously analysed and displayed in an on-line and real-time manner throughout the experiment [8,19,20]. In brief, PI was estimated continuously and instantaneously from the digitized arterial pressure signals by a process of sample and hold at a refreshing rate of 16 Hz. The sampling rate of arterial pressure signals was reduced to 16 Hz by a 16-point average algorithm. The arterial pressure and PI signals to be analysed were truncated into successive 64-s (1024 points) time segments (window) with 50% overlapping [8]. For each time segment, the linear trend was removed and a Hamming window in the time domain was used to attenuate the leakage effect [8]. Our algorithm then estimated the means of arterial pressure and PI as well as the total power [BTP (BP total power) and HTP (HR total power), 0–8 Hz], low-frequency power [BLF (BP low-frequency power) and HLF (HR low-frequency power), 0.04–0.12 Hz] and high-frequency power [BHF (BP high-frequency power) and HHF (HR high-frequency power), 0.12–10.4 Hz] of the arterial pressure and PI autospectra. The BLF/BHF and HLF/HHF ratios were also calculated.

**RAPV and %SPV estimation**

We evaluated further RAPV based on a method developed previously [3,11,12]. The raw arterial pressure signals were first normalized to their mean value and were expressed as the percentage variation from the mean arterial pressure. This normalization procedure made the subsequent spectral analysis independent of an absolute mean value [11]. The normalized arterial pressure signals were subjected to autospectral analysis as described above. Since the respiratory rate was maintained at a constant rate (10 breaths/min; 0.167 Hz), the high-frequency power (0.12–10.4 Hz) was then taken as RAPV.

The magnitudes of SPV were measured as the mean difference between the maximal and minimal values of the SBP (systolic BP) over five consecutive breaths at each step of the experiment [14,21]. %SPV was defined as (SPV/mean SBP) × 100 %, where mean SBP is the mean value of SBP over these same breaths. Since %SPV relates SPV to the absolute level of SBP [14], it was applied in the present studies.

**Experimental protocol**

After skin incision and stable BP and HR had been maintained for more than 10 min, three sets of different tidal volumes (8, 10, and 12 ml/kg of body weight) were applied randomly to the patients via a constant ventilator; the interval of each period persisted for 10 min. After evaluating the effects of tidal volumes, the tidal volume was switched back to 12 ml/kg of body weight for at least 10 min, intravenous injections of 0.9 % saline (0.1 ml/kg of body weight) were given 10 min later as a volume control. Intravenous injection of esmolol hydrochloride (1 mg/kg of body weight) was administered, and the analyses were made for 20 min thereafter. RAPV was calculated on-line, and %SPV calculations were performed manually off-line after completion of the study protocol.

**Statistical analysis**

All values are expressed as means ± S.E.M. Data between groups were compared by Student's t test or ANOVA, followed by Fisher's least significant difference test for a posteriori comparison of individual means. Relationships between RAPV and %SPV were determined using a linear regression method. Differences were considered statistically significant at P < 0.05.

**RESULTS**

The effect of esmolol on haemodynamic variables, including SAP (systemic arterial pressure), BPSDn (three-dimensional power spectral density of normalized SAP), RAPV and PI, are shown in Figure 1. After esmolol treatment, BP decreased transiently and then returned to baseline. PI increased and there was a pronounced decrease in RAPV. A typical example indicating that both %SPV and RAPV were significantly suppressed after esmolol treatment is shown in Figure 2. The suppressive effects of esmolol on the mean value and maximal change of RAPV and %SPV were significantly suppressed after esmolol treatment is shown in Figure 2. The suppressive effects of esmolol on the mean value and maximal change of RAPV and %SPV are shown on Figure 3. The maximal decrease of RAPV and %SPV were 50 % and 35 % respectively, after intravenous esmolol administration.

Figure 4 shows the effects of esmolol on standard APV and HRV parameters. For the APV parameters, only the BLF/BHF ratio revealed a significant elevation. For the PI signals, only the mean static value and HHF was significant elevated.

Figure 5 shows the relationship between %SPV and RAPV under saline and esmolol treatment. Esmolol
not significantly change the correlation between %SPV and RAPV (r = 0.93 after saline treatment, and r = 0.91 after esmolol treatment), although the amplitudes of both values decreased with esmolol.

The effects of changes in tidal volume on RAPV and %SPV are shown in Figure 6. Both RAPV and %SPV were significantly and proportionally increased as the tidal volume increased. No significant changes in the endtidal CO₂ levels of the different tidal volumes were revealed (29.9 ± 1.6 mmHg in 8 ml/kg of body weight group; 29.4 ± 1.7 mmHg in 10 ml·kg⁻¹ of body weight group; 29.0 ± 1.6 mmHg in 12 ml/kg of body weight group; P > 0.05).
Effects of tidal volumes on RAPV and %SPV of body weight; † suppressed significantly by β-adrenoceptor blockade. Our laboratory has developed a stable and reproducible rodent model to investigate the phenomenon of RAPV and %SPV under positive-pressure ventilation [3,11,16]. In the present study, we extended these investigations to humans under constant positive-pressure ventilation. This is important and worthy of further investigation, since the assessment of autonomic activity, especially the cardiac sympathetic regulation, is frequently difficult in clinical situations.

It has been demonstrated in anaesthetic and critical care fields that %SPV allows the assessment of cardiac preload in humans [13,14,21]. However, positive-pressure ventilation is known to influence cardiovascular function due to the intermittent increases in the intrathoracic pressure it produces. A previous study [23] reported that %SPV was affected by the magnitude of the tidal volume, with higher tidal volumes causing corresponding to higher %SPV values under the same blood volume status. Thus the use of %SPV in detecting blood volume changes during spontaneous ventilation appears problematic, simply because respiration is not controlled [24]. Many other factors also affect the magnitude of %SPV, including intravascular volume status [21], cardiac function, chest wall compliance [25,26] and lung compliance [2].

On the other hand, RAPV derived from the frequency domain analysis has been investigated in basic physiological and neuroscience fields, and RAPV has been shown to be an indicator of cardiac sympathetic regulation in rats [11]. However, our previous studies demonstrated that at least two mechanisms contribute to RAPV [12]. The ANS may produce its effects via pulse pressure variability. Thus β-adrenergic receptor stimulation may have a tonic facilitating effect on pulse pressure variability and thus enhance RAPV [3,11,12]. On the other hand, transmitted intrathoracic pressure contributes a non-autonomic influence on RAPV. Comparing RAPV in the frequency domain and %SPV in the time domain, it is reasonable to hypothesize that they may represent the same physiological phenomenon. Indeed, our previous study [16] demonstrated that RAPV and %SPV are correlated well in mechanically ventilated rats. The present study confirmed this for the first time in anaesthetized humans under positive-pressure ventilation. Clearly, since both RAPV and %SPV are affected by tidal volume, they cannot be used to indicate changes in cardiac sympathetic activity in a spontaneously breathing individual, particularly if respiration is not being monitored.

The effects of esmolol on arterial pressure and HR spectra were also investigated in present study. For the PI values, the increase in the static value after esmolol treatment is probably explained by its negative chronotropic effect. The explanation for the increase of HLF/HHF has been regarded as an index of cardiac sympathetic activity [6], this ratio showed no discernible change after esmolol administration. The reason for this is that, together with the significant increase in HLF, there was a trend for HLF to increase. Since HLF is contributed jointly by the vagal and sympathetic activities [6], it may be that the increase in vagal activity proposed above explains why HLF tended to increase. In the arterial pressure spectrum, BHF tended to decrease after esmolol administration, but this did not reach statistical significance. In fact, RAPV was the only frequency domain parameter to reflect the suppression of cardiac sympathetic function produced by esmolol.

Arterial pressure is a complex product of interactions among various systems. Thus adequate analyses of this basic signal may deliver much functional information. In many animal studies, arterial cannulation and the recording of arterial pressure are routine procedures. In the hospital, arterial pressure is also recorded in many critical care units and operating theatres. Furthermore, recent techniques such as servo-controlled infra-red finger plethysmography and finapres tonometry have

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**Figure 6 Effects of tidal volumes on RAPV and %SPV**

Values are means ± S.E.M. * P < 0.05 compared with the group receiving 8 ml/kg of body weight; † P < 0.05 compared with the group receiving 10 ml/kg of body weight. P values determined using Fisher’s least significant difference test (n = 10).
enabled the non-invasive recording of the human arterial waveform in less critical situations. Therefore analyses of the arterial pressure signals, either RAPV in the frequency domain or %SPV in the time domain, may hold advantages in the further development of diagnostic techniques. In the present study, we combined an investigation of the frequency domain with the time domain analyses of APV and demonstrated that cardiac sympathetic function is involved in the regulation of both RAPV and %SPV in anaesthetized humans. RAPV can be automatically calculated in real time with the aid of a personal computer and can reveal dynamic changes during surgical operations. Thus we suggest that RAPV and %SPV may be alternative choices for monitoring cardiac sympathetic regulation in anaesthetized patients under positive-pressure ventilation.

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