Intensive Care Med (2011) 37:118–123
DOI 10.1007/s00134-010-2046-7

PEDIATRIC ORIGINAL

Eva Kühlwein
Christian Balmer
Vincenzo Cannizzaro
Bernhard Frey

Determinants of arterial and central venous blood pressure variation in ventilated critically ill children

Received: 14 July 2009
Accepted: 25 July 2010
Published online: 15 October 2010

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-010-2046-7) contains supplementary material, which is available to authorized users.

E. Kühlwein (✉) · V. Cannizzaro · B. Frey
Department of Paediatric Intensive Care and Neonatology, University Children's Hospital, Steinwiesstr. 75,
8032 Zurich, Switzerland
e-mail: eva.kuehlwein@kispi.uzh.ch

C. Balmer
Department of Cardiology, University Children's Hospital, Steinwiesstr. 75,
8032 Zurich, Switzerland

Abstract *Purpose:* Ventilation-induced arterial pressure variation predicts volume responsiveness in adults. Several factors are known to influence the interpretability of these variations. We analysed ventilation-induced variations in critically ill children with reference to ventilatory and circulatory parameters. *Methods:* We prospectively included 20 paediatric patients. Variation of systolic pressure (SPV), pulse pressure (PPV) and central venous pressure (CVP) were assessed during pressure-controlled ventilation with inspiratory pressures (P_{insp}) of 20 and 28 cmH_2O. Blood gases were analysed and echocardiography was performed. *Results:* SPV, PPV and CVP variation significantly increased with elevated P_{insp} ($p < 0.001$, $p = 0.008$ and $p = 0.003$). Baseline CVP and shortening fraction were significant negative predictors of PPV and SPV. *Conclusion:* This preliminary study identified P_{insp} as a determinant of SPV, PPV and CVP variation in children. Further independent determinants of SPV and PPV were baseline CVP and ventricular performance, both of which must be considered when interpreting pressure variations.

Keywords Pulse pressure variation · Systolic pressure variation · Children · Central venous pressure · Volume responsiveness · Mechanical ventilation

Introduction

The phenomenon of pulsus paradoxus has been known for decades. Ventilation-induced variations have been intensively investigated in the past years to further understand their nature and useful interpretation [1].

Three decades ago McGregor [2] explained the interaction between the heart and lungs by two mechanisms. One encompasses the changes in intra-thoracic pressure causing alterations in the pressure gradient between the heart cavities and the extra-thoracic blood vessels. The other follows the interdependence of cardiac ventricles, as the filling of one may compromise the compliance of the other. Thus, following the curvilinear Frank–Starling relationship between preload and stroke volume, the stroke volume will change in the course of one respiratory cycle.

In 1987 Perel [3] showed increased systolic pressure variation (SPV) in hypovolaemic ventilated dogs. Consecutively, the same phenomenon was found in mechanically ventilated patients. Ventilation-induced SPV or pulse pressure variation (PPV) was used to determine volume responsiveness, i.e. enhancement of cardiac output following volume loading, in different patient groups [4–6].

Two studies looked at ventilation-induced variation predicting volume responsiveness in children. Tibby et al. [7] investigated central venous pressure (CVP) and

transoesophageal Doppler measurements to predict stroke volume increase after volume expansion. Durand et al. [8] showed that stroke volume variations (SVV) but not PPV predicted volume responsiveness in children. In a paediatric animal model SVV but not PPV predicted volume responsiveness [9].

To our knowledge no study has looked at modifying circulatory and ventilatory parameters of blood pressure variation in children yet. The aim of this study was to analyse ventilatory and circulatory determinants of ventilation-induced variation in arterial pressure and CVP in children.

Patients and methods

With the approval of the institutional ethics committee and the parental written informed consent, we recruited 20 critically ill children in a prospective interventional study. Children were intubated and ventilated without spontaneous respiratory activity. They were in sinus rhythm and already equipped with a radial arterial and central venous catheter and an open nasogastric tube. Central catheter position was radiologically confirmed to be in the superior vena cava. Bedside monitoring comprised continuous ECG, pulse oximetry, arterial and CVP curve (Solar 8000 M Modular Patient Monitor, GE Medical Systems, Freiburg, Germany). We excluded preterm babies and children with intracardial right-to-left-shunt, single ventricle, cardiac rhythm disorders, and inspiratory pressures (P_{insp}) of 24 cmH_2O or higher.

The intervention included pressure-controlled ventilation (Evita 4, Dräger, Lübeck, Germany) at two different plateaus. For baseline measurements patients were ventilated with P_{insp} of 20 cmH_2O, positive end-expiratory pressure (PEEP) 5 cmH_2O, respiratory frequency of 20/min and inspiratory time of 0.6 s, which was followed by an increase of P_{insp} to 28 cmH_2O with all other ventilation parameters unchanged including inspiratory oxygen fraction and pharmacological support. After each 5 min of ventilation the arterial pressure and CVP curve were printed out over ten respiratory cycles. Ventilatory and circulatory parameters as measured by the ventilator and/or displayed on the monitor were recorded. Central venous and arterial blood gases were analysed (ABL700, Radiometer, Copenhagen, Denmark). Within 3 h of the intervention the ejection fraction (EF) and the shortening fraction (SF) were determined by echocardiography.

Pressure variations were determined as follows. SPV is calculated as the difference between maximal and minimal systolic pressure (SP) in one respiratory cycle [10]:

$$\mathrm{SPV}\ [\%] = 100 \times \frac{\mathrm{SP_{max}} - \mathrm{SP_{min}}}{(\mathrm{SP_{max}} + \mathrm{SP_{min}})/2}$$

The pulse pressure (PP) is the difference between the systolic and the diastolic pressure. PPV is calculated as the difference between maximal and minimal PP in one respiratory cycle [11]:

$$\mathrm{PPV}\ [\%] = 100 \times \frac{\mathrm{PP_{max}} - \mathrm{PP_{min}}}{(\mathrm{PP_{max}} + \mathrm{PP_{min}})/2}$$

The CVP variation was calculated from maximal and minimal trough values after the a-wave in one respiratory cycle as described by Magder [12]. SPV, PPV and CVP variation were averaged over ten respiratory cycles. An example curve can be found in the "Electronic supplementary material".

Paired Student's t tests, repeated-measure ANOVA and multiple linear regression analysis were used for statistical analysis (SPSS 13 for Mac OS X, SPSS Inc., Chicago, USA).

Results

Except for two patients, admitted after fronto-orbital advancement and for a cerebello-vascular malformation, we primarily recruited patients after cardiac surgery. Their age ranged from 2 months to 17 years (median 2 years 2 months). Mean weight was 10.95 kg (range 3.8–82 kg). All patients remained haemodynamically stable during the intervention. Two data sets were incomplete due to incorrect position of the arterial (no curve) or of the central venous catheter (in the axillary vein).

Measured patient data are presented in Table 1. When P_{insp} was elevated to 28 cmH_2O, SPV, PPV and CVP variation increased significantly by 0.2% ($p < 0.001$), 1.94% ($p = 0.008$) and 0.36 mmHg ($p = 0.003$), respectively.

Repeated-measure ANOVA confirmed this time effect of inspiratory pressure on pressure variation but could not identify tidal volume as a covariate. Nor did arterial pH and central venous oxygen saturation influence pressure variation.

With muliple regression we identified SF and baseline CVP as significant predictors of SPV and PPV independent of inspiratory pressure by using a forward stepwise approach including baseline CVP, baseline SP, dynamic lung compliance, and SF. Figure 1 shows statistical details.

Discussion

In this preliminary study we identified P_{insp} as a major determinant of ventilation-induced SPV, PPV and CVP variation in children. These results are in accordance with

studies in adult patients [5, 6, 11, 13–15]. Moreover, baseline CVP and SF inversely predicted SPV and PPV in this study. No other circulatory or ventilatory parameter could be identified as determinants of ventilation-induced arterial or venous pressure variation.

In adults several confounding factors in the interpretation of respiratory variation in the arterial pressure curve have been identified. In adults SVV and SPV are a function of the tidal volume [14, 16]. Equally, the respiratory systolic variation test described by Perel et al. [13, 17], where the minimal SPs of consecutive respiratory cycles decrease with elevation of P_{insp} as indication of volume responsiveness, shows that tidal volume influences SPV [13, 17]. In our study the higher the inspiratory pressure was, the more variation was induced. The amount of variation i.e. 8–10% in PPV was comparable, whereas for SPV it was lower than previous results in adults [14] and children [8]. Although tidal volumes were in the recommended range (about 8 ml/kg) [1] and also increased significantly with elevation of P_{insp}, we could not identify tidal volume as a determinant of SPV or PPV. However, it is conceivable that the measurement of tidal volume, as provided by the ventilator, was not accurate enough to emerge as a determinant of SPV and PPV.

In heart failure or hypervolaemia, left ventricular stroke volume increases in early mechanical inspiration explaining parts of SPV [13] as increased intrathoracic pressure squeezes blood out of the lungs and reduces left ventricular afterload [1, 15]. PPV is not directly influenced by intrathoracic pressure [11]. However, in our study, lower SF as a measure of ventricular performance was associated with greater SPV and PPV. There was no interaction with the effect caused by elevating the inspiratory pressure (data not shown). This may lend support to what Perel et al. [13, 17] showed: With increasing P_{insp} in sequential steps the decrease of the minimal SP correlates with volume responsiveness independently of the pre-operative left ventricular EF [13]. The confounding factor of ventricular performance could thus be avoided. It is conceivable that volume responsiveness can be determined despite various confounding parameters by analysing the increase of variation between two inspiratory pressures. For example in patients with heart failure requiring volume repletion the heart functions on the steeper end of an overall flatter Frank–Starling curve. Thus, the P_{insp}-enhanced SPV and PPV may point to low volume status irrespective of the heart function as found in our subjects.

Hypovolaemia causes increased pressure variations in adults [4–6]. This is used for prediction of volume responsiveness in critically ill patients. In our study low CVP correlated with increased SPV and PPV. CVP has repeatedly been shown not to be a reliable indicator of volume status [18], but rather a marker of the right ventricular function. If at all, the lower CVP in our study might indicate a steeper Frank–Starling curve in these patients. There was also ventilation-induced CVP variation. However, no other circulatory variables were associated with CVP variation, which is in accordance with adult data [13, 19].

Little is known about the confounding factors of pressure variations in children. It is conceivable that other

Table 1 Measured patient data (mean, SD)

	Inspiratory pressure	
	20 cmH_2O	28 cmH_2O
Systolic blood pressure variation (%)	1.1 (±0.6)	1.3 (±0.6)**
Pulse pressure variation (%)	8.3 (±3.6)	10.3 (±4.4)**
Central venous pressure variation (mmHg)	1.6 (±0.7)	1.9 (±1.0)**
Systolic blood pressure (mmHg)	91.7 (±22.9)	93.2 (±22.7)
Central venous pressure (mmHg)	9.2 (±2.2)	8.4 (±2.7)
Mean airway pressure (cmH_2O)	7.8 (±0.7)	9.0 (±0.2)**
Inspiratory tidal volume per weight (ml/kg)	8.6 (±5.1)	10.7 (±2.9)
Expiratory tidal volume per weight (ml/kg)	7.7 (±4.7)	10.1 (±3.1)*
Dynamic lung compliance per weight (ml/cmH_2O/kg)	1.4 (±0.9)	1.4 (±1.4)
Central venous oxygen saturation (%)	72.9 (±10.1)	70.4 (±11.2)
Transcutaneous oxygen saturation (%)	98.6 (±2.1)	99.2 (±1.3)
Arterial oxygen saturation (%)	98.1 (±1.1)	98.6 (±1.0)**
O_2 − extraction (%)	25.2 (±9.7)	28.3 (±11.1)*
O_2 arterial partial pressure (kPa)	16.8 (±5.3)	18.2 (±6.1)**
CO_2 arterial partial pressure (kPa)	5.5 (±1.3)	4.8 (±1.0)**
Arterial pH	7.35 (±0.07)	7.40 (±0.07)**
Base excess (mmol/l)	−2.8 (±2.1)	−2.8 (±2.2)
Bicarbonate (mmol/l)	21.8 (±1.5)	21.8 (±1.7)
Lactate (mmol/l)	1.1 (±0.4)	1.0 (±0.3)
Heart rate (beats/min)	123.0 (±26.4)	122.4 (±26.6)
Ejection fraction (%)	54.2 (±9.2)	
Shortening fraction (%)	34.4 (±6.9)	

Paired Student's t test (20 vs. 28 cmH_2O): * $p < 0.05$, ** $p < 0.01$

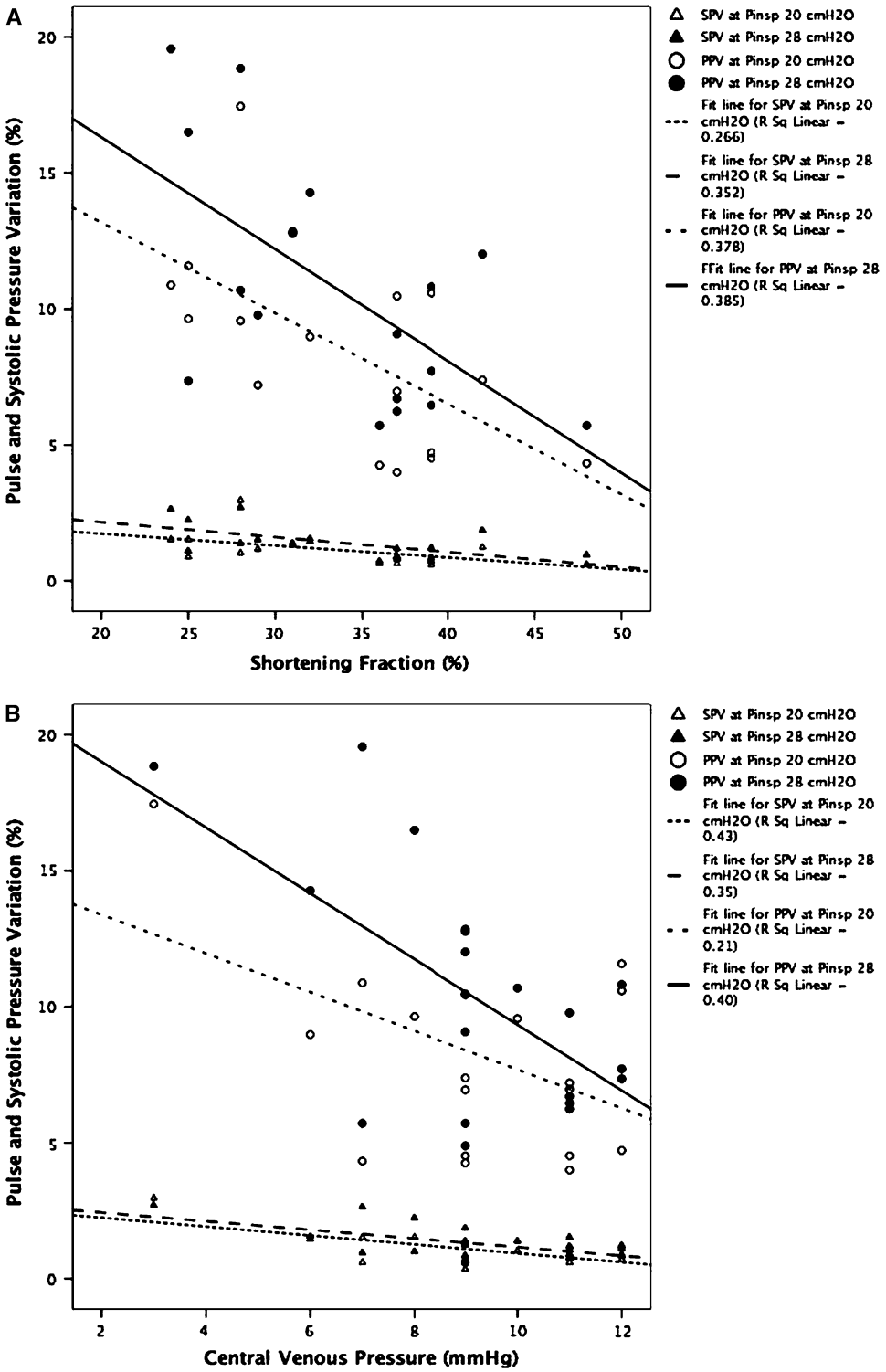

Fig. 1 **a** Pulse and systolic pressure variation dependent on SF. Regression coefficient $b = -0.04$, $p = 0.034$, 95% confidence interval (CI) -0.08 to -0.01 for SPV at 20 cmH_2O; $b = -0.06$, $p = 0.008$, 95% CI -0.09 to -0.02 for SPV at 28 cmH_2O; $b = -0.32$, $p = 0.009$, 95% CI -0.55 to -0.09 for PPV at 20 cmH_2O; $b = -0.40$, $p = 0.008$, 95% CI -0.67 to -0.12 for PPV at 28 cmH_2O. **b** Pulse and systolic pressure variation dependent on CVP. Regression coefficient $b = -0.17$, $p = 0.002$, 95% CI -0.27 to -0.07 for SPV at 20 cmH_2O; $b = -0.16$, $p = 0.008$, 95% CI -0.27 to -0.05 for SPV at 28 cmH_2O; $b = -0.73$, $p = 0.048$, 95% CI -1.44 to -0.01 for PPV at 20 cmH_2O; $b = -1.23$, $p = 0.004$, 95% CI -2.01 to -0.46 for PPV at 28 cmH_2O

factors than in adults play a role. In contrast to adult data Durand et al. [8] did not find PPV and SPV to predict volume responsiveness in children, findings they attributed to the low tidal volume used in their study. Renner et al. [9] showed that SVV predicted volume responsiveness at tidal volumes of 10 ml/kg. However, PPV, although correlating with stroke volume index, did not accurately predict volume responsiveness.

Other variables, which we did not assess in this study, may influence SPV and PPV. Elevated intra-abdominal pressure augments SPV [20] but reduces the interpretability of SVV and PPV with respect to volume responsiveness [21] in animals. It probably modifies venous return and chest wall compliance. Chest wall compliance as an independent confounder of blood pressure variation varies with age and is higher in small children than adults [22]. Respiratory rate also influences PPV in adults. Respiratory rates above 30/min, which are commonly found in ventilated neonates and infants, can dampen PPV [23]. Moreover, arterial compliance, which changes with age, is one of the major determinants of PP [24]. Another influential factor may be partial pressure of CO_2 by changing pulmonary and systemic vascular resistance through pH changes.

Several limitations of our study have to be taken into account. In this preliminary study we only included 20 children. This number may be too low to identify confounding parameters, especially with the wide range of ages and body weights in this study. In adults several functional parameters like SVV, PPV and SPV have been investigated. PPV and the distinct SPV component Δdown have been shown to be most accurate in predicting volume responsiveness [13]. However, an end-expiratory ventilation pause of about 10 s is necessary to determine the reference SP for Δdown. This was not part of the intervention. Furthermore, EF and SF, the parameters which we used as surrogates for heart function in this study, are influenced by loading conditions and thus cannot be equated with myocardial contractility. Therefore, the influence of the SF on arterial pressure variation is not easily interpretable. Finally, we did not include a volume loading intervention, which is indispensable for any conclusion on fluid responsiveness in children.

In summary, we have shown that P_{insp} interacts with SPV, PPV and CVP variation in children. CVP and SF are also determinants of SPV and PPV. These factors may all affect pressure variations as observed on the monitor and should therefore be taken into account by paediatric clinicians interpreting SPV and PPV in mechanically ventilated children. Further studies will have to elucidate other factors that influence pressure variation in children, and identify child-specific thresholds for interpretation of pressure variation especially with respect to volume responsiveness.

References

1. Feihl F, Broccard AF (2009) Interactions between respiration and systemic hemodynamics. Part II: practical implications in critical care. Intensive Care Med 35:198–205
2. McGregor M (1979) Current concepts: pulsus paradoxus. N Engl J Med 301:480–482
3. Perel A, Pizov R, Cotev S (1987) Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. Anesthesiology 67:498–502
4. Perel A (1998) Assessing fluid responsiveness by the systolic pressure variation in mechanically ventilated patients. Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. Anesthesiology 89:1309–1310
5. Tavernier B, Makhotine O, Lebuffe G, Dupont J, Scherpereel P (1998) Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. Anesthesiology 89:1313–1321
6. Solus-Biguenet H, Fleyfel M, Tavernier B, Kipnis E, Onimus J, Robin E, Lebuffe G, Decoene C, Pruvot FR, Vallet B (2006) Non-invasive prediction of fluid responsiveness during major hepatic surgery. Br J Anaesth 97:808–816
7. Tibby SM, Hatherill M, Durward A, Murdoch IA (2001) Are transoesophageal Doppler parameters a reliable guide to paediatric haemodynamic status and fluid management? Intensive Care Med 27:201–205
8. Durand P, Chevret L, Essouri S, Haas V, Devictor D (2008) Respiratory variations in aortic blood flow predict fluid responsiveness in ventilated children. Intensive Care Med 34:888–894
9. Renner J, Cavus E, Meybohm P, Gruenewald M, Steinfath M, Scholz J, Boening A, Bein B (2008) Pulse pressure variation and stroke volume variation during different loading conditions in a paediatric animal model. Acta Anaesthesiol Scand 52:374–380
10. Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, Richard C, Pinsky MR, Teboul JL (2000) Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 162:134–138
11. Michard F, Teboul JL (2000) Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. Crit Care 4:282–289
12. Magder S (2006) Central venous pressure: a useful but not so simple measurement. Crit Care Med 34:2224–2227
13. Preisman S, Kogan S, Berkenstadt H, Perel A (2005) Predicting fluid responsiveness in patients undergoing cardiac surgery: functional haemodynamic parameters including the respiratory systolic variation test and static preload indicators. Br J Anaesth 95:746–755
14. Reuter DA, Bayerlein J, Goepfert MS, Weis FC, Kilger E, Lamm P, Goetz AE (2003) Influence of tidal volume on left ventricular stroke volume variation measured by pulse contour analysis in mechanically ventilated patients. Intensive Care Med 29:476–480
15. Vieillard-Baron A, Chergui K, Augarde R, Prin S, Page B, Beauchet A, Jardin F (2003) Cyclic changes in arterial pulse during respiratory support revisited by Doppler echocardiography. Am J Respir Crit Care Med 168:671–676
16. De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL (2005) Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. Intensive Care Med 31:517–523

17. Perel A, Minkovich L, Preisman S, Abiad M, Segal E, Coriat P (2005) Assessing fluid-responsiveness by a standardized ventilatory maneuver: the respiratory systolic variation test. Anesth Analg 100:942–945
18. Marik PE, Baram M, Vahid B (2008) Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest 134:172–178
19. Reuter DA, Kirchner A, Felbinger TW, Weis FC, Kilger E, Lamm P, Goetz AE (2003) Usefulness of left ventricular stroke volume variation to assess fluid responsiveness in patients with reduced cardiac function. Crit Care Med 31:1399–1404
20. Duperret S, Lhuillier F, Piriou V, Vivier E, Metton O, Branche P, Annat G, Bendjelid K, Viale JP (2007) Increased intra-abdominal pressure affects respiratory variations in arterial pressure in normovolaemic and hypovolaemic mechanically ventilated healthy pigs. Intensive Care Med 33:163–171
21. Renner J, Gruenewald M, Quaden R, Hanss R, Meybohm P, Steinfath M, Scholz J, Bein B (2009) Influence of increased intra-abdominal pressure on fluid responsiveness predicted by pulse pressure variation and stroke volume variation in a porcine model. Crit Care Med 37:650–658
22. Papastamelos C, Panitch HB, England SE, Allen JL (1995) Developmental changes in chest wall compliance in infancy and early childhood. J Appl Physiol 78:179–184
23. De Backer D, Taccone FS, Holsten R, Ibrahimi F, Vincent JL (2009) Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. Anesthesiology 110:1092–1097
24. Lamia B, Teboul JL, Monnet X, Osman D, Maizel J, Richard C, Chemla D (2007) Contribution of arterial stiffness and stroke volume to peripheral pulse pressure in ICU patients: an arterial tonometry study. Intensive Care Med 33:1931–1937