Detection of Right Ventricular Insufficiency and Guidance of Volume Therapy Are Facilitated by Simultaneous Monitoring of Static and Functional Preload Parameters

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Objective: **Acute right ventricular failure (RVF) is a life-threatening condition. This study investigated whether the combination of central venous pressure (CVP) and left ventricular functional preload parameters, such as stroke volume variation (SVV) and pulse pressure variation (PPV), can be used for the detection of acute RVF and for guidance of volume therapy.**

Design and Setting: **Experimental study in a university laboratory.**

Participants: **Fifteen anesthetized and ventilated pigs.**

Measurements and Main Results: **For the induction of RVF, mean pulmonary artery pressure (MPAP) was increased by 50% with a continuous infusion of a thromboxane-A_2 analog (U46619). Then, blood removal (300 mL) and retransfusion (blood 200 mL + colloid solution 200 mL) were performed. An analysis of volume responders and nonresponders was implemented. Increasing MPAP (25.1 to 37.4 mmHg) led to decreases in mean arterial pressure (72.2 to 60.1 mmHg) and cardiac output (2.8 to 2.3 L/min, $p < 0.05$). CVP (11.3 to 12.6 mmHg), PPV (13% to 17%), and SVV (11 to 14%) increased significantly ($p < 0.05$). During volume removal, MPAP (37.4 to 34.1 mmHg), mean arterial pressure (60.1 to 53.2 mmHg), and cardiac output (2.3 to 2.1 L/min) decreased ($p < 0.05$), whereas PPV and SVV remained unchanged. During volume loading, CVP increased in volume responders and nonresponders; however, PPV decreased in responders only.**

Conclusions: **Increases of CVP and SVV or PPV are suspicious for RVF. However, SVV and PPV fail to predict volume responsiveness in RVF. Changes in SVV and PPV during a volume-loading maneuver can be used to assess volume responsiveness.**

KEY WORDS: acute right ventricular insufficiency, functional preload parameters, central venous pressure, stroke volume variation, ventricular interdependence, volume therapy

ACUTE RIGHT VENTRICULAR (RV) insufficiency or failure is a potentially life-threatening condition. Diagnosis and appropriate therapy often are delayed or missed.[1] In critically ill patients, the incidence of RV failure (RVF) is believed to be similar to that of left ventricular (LV) failure.[2] A sudden increase in RV afterload is one possible cause of acute RV insufficiency or RVF. The optimization of cardiac preload, treatment of the underlying disease, and pharmacologic circulatory support constitute the cornerstones of successful therapy.

For the left ventricle, functional preload parameters, such as stroke volume variation (SVV) and pulse pressure variation (PPV), have been investigated extensively in the past decade. They have been found useful to assess volume responsiveness in mechanically ventilated patients. These parameters may help to determine the preload condition of ventilated patients and to monitor continuously the effects of volume administered as part of hemodynamic management. Increases of PPV and SVV by >12% to 14% represent the possibility to increase cardiac output (CO) by volume administration.[3-5] It is well established that they are superior to static preload parameters, such as cardiac filling pressures and volumetric preload parameters, for assessing volume responsiveness and guiding volume therapy in most mechanically ventilated, critically ill patients. Functional preload parameters can reflect the individual LV function curve, whereas static preload parameters reflect only one determinant of cardiac preload: pressure or volume.

SVV and PPV reflect the LV, but not the RV, function curve. They have been reported to falsely suggest volume responsiveness in patients with altered RV function during mechanical ventilation.[6-9] However, RV function is the limiting force for overall CO in RVF and is highly sensitive to sudden changes in ventricular filling. In clinical practice, RV filling usually is assessed with static preload parameters, such as central venous pressure (CVP), RV end-diastolic pressure (RVEDP), or RV end-diastolic volume (RVEDV)[1] or by echocardiography. RV dilatation is a consequence of RV pressure overload but also is part of the compensation mechanism.[2] Early in compensation, an increasing RVEDV supports contractility and maintenance of a sufficient SV. RV ejection fraction (RVEF) decreases, resulting in RV dysfunction. However, volume overloading occurs very rapidly and SV suddenly is no longer sufficient (RVF).[10,11]

This experimental study investigated the combination of continuous RV (CVP) and LV (SVV/PPV) preload monitoring for the detection of RVF and guidance of volume therapy. If the right ventricle fails, RV filling increases and LV filling decreases because of the decreased RV output. Therefore, the authors intended to demonstrate that CVP and SVV or PPV increase in acute RVF and that, during a volume challenge in RVF, a decrease in SVV or PPV indicates RV volume responsiveness.

METHODS

The study was approved by the local governmental ethical commission, with consent issued on April 20, 2006. The animals received care in compliance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health publication number 86-23, revised 1996). Fifteen pigs (29 ± 0.8 kg) were enrolled in this study.

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After intramuscular premedication with ketamine (250 mg), midazolam (15 mg), and azaperone (280 mg), pigs were anesthetized with fentanyl (0.02 mg/kg/h) and sevoflurane (1.8% to 2.5% end tidal). For the surgical preparation, relaxation was achieved by administering pancuronium (0.3 mg/kg). After intubation, controlled mechanical ventilation was initiated at a tidal volume of 10 mL/kg, an inspiration-to-expiration ratio of 1:2, and a positive end-expiratory pressure of 5 cmH_2O (Zeus, Draeger Medical, Lübeck, Germany). Respiratory rate (20 to 25 breaths/min) was adjusted to maintain normocapnia (partial pressure of carbon dioxide 35 to 40 mmHg). After sternotomy and pericardiotomy, an ultrasonic flow probe (Medi-Stim ASA, Oslo, Norway) was implanted surgically around the pulmonary artery for the determination of CO. Subsequently, the chest and pericardium were readapted and closed in 4 layers. During surgical preparation and in the baseline condition, the animals were kept normovolemic (SVV $\leq$12%) by a continuous infusion of normal saline at a rate of 10 to 14 mL/kg/h. No catecholamines were administered throughout the study.

All hemodynamic measurements were recorded as raw data with 500-Hz sensing by the acquisition software IOX 2.2.17.17 (EMKA, Paris, France). Postprocessing was performed with the analyzing software Datanalyst 2.3.4.1 (EMKA). CVP was recorded by a microtip catheter placed in the superior central vein (SPC 350, Millar Instruments, Houston, TX). Another microtip catheter was positioned into the right ventricle to measure RVEDP, RVEDV, and the peak rate of maximum of RV pressure increase (RVdP/dTmax). Microtip catheters were positioned through 5F introducer sheaths through the jugular veins. Correct positioning was assured by typical waveform signals and radiography. Mean pulmonary artery pressure (MPAP) and RVEF were measured by pulmonary artery thermodilution (VoLEF catheter PV 2047, PACC 947, Pulsion, Munich, Germany). Mean arterial pressure (MAP), PPV, SVV, and global end-diastolic volume (GEDV) were obtained from a femoral artery catheter and by transcardiopulmonary thermodilution (Picco PV2015L20N, Pulsion). PPV was calculated as $PPV\ (\%) = ([PP_{max} - PP_{min}]/[\{PP_{max} + PP_{min}\}]/2) \times 100$, where PP_{max} is the maximum pulse pressure and PP_{min} the minimum pulse pressure during the respiratory cycle. SVV was calculated as $SVV\ (\%) = ([SV_{max} - SV_{min}]/[\{SV_{max} + SV_{min}\}/2]) \times 100$. The GEDV, which reflects the end-diastolic volume of the four heart chambers, was derived from transpulmonary thermodilution as described previously.[12] Three boluses of cold saline solution (10 mL, <8°C) were injected into the central vein. CO was derived continuously from the ultrasonic flow probe placed around the pulmonary artery. RVSV was calculated by CO divided by heart rate. Subsequently, the computed SV was used to calculate the SVV.

After the baseline measurement of all hemodynamic parameters, RV insufficiency was induced by increasing MPAP by 50% using a continuous infusion of the thromboxane-A_2 analog U46619 (Sigma Aldrich, St Louis, MO) as described previously.[13,14] RVF was characterized by a concomitant decrease in CO. Acute RV insufficiency was initiated over a period of approximately 60 minutes. When MPAP and RVdP/dTmax remained stable at the elevated target level for $\geq$10 minutes, a subsequent set of measurements was acquired.

During the RV insufficiency condition, two volume maneuvers were performed. First, 300 mL of whole blood were removed over a period of 30 minutes. The blood volume removed was collected in heparinized retransfusion bags. Second, volume loading with 400 mL was performed using 200 mL of blood and 200 mL of a colloidal solution (Voluven, Hydroxyethylstarch 6%, 130/0.4, Fresenius Kabi, Germany). The volume was retransfused over 30 minutes and hemodynamic data were acquired. Post hoc analysis was performed and the study group was divided into two groups: volume responders (with an increase of CO >5%) and volume nonresponders (with no increase or an increase <5%).

Statistical analysis was performed using SigmaStat 3.5 (SYSTAT Software, Inc, Erkrath, Germany). Normally distributed data (Kolmogorov-Smirnov test) were analyzed with a one-way analysis of variance for repeated measurements, and non-normally distributed parameters were analyzed with Friedman repeated measures analysis of variance on ranks. Post hoc testing was performed using the Tukey test. Results are presented as mean (standard deviation) if normally distributed and as median (25th and 75th percentiles) for non-normally distributed data. A p value <0.05 was considered statistically significant.

RESULTS

After the surgical preparation, the induction of acute RV insufficiency and volume removal could be performed in all animals (n = 15). Volume retransfusion was survived by 11 of 15 pigs. Four animals died because of low CO syndrome during the volume retransfusion. All changes in hemodynamic data are presented in Table 1.

In all animals, MPAP was augmented by 50%, which led to significant decreases of CO ($p < 0.001$), RVEF, and MAP ($p < 0.05$). In contrast, RVdP/dTmax, CVP, SVV, and PPV increased significantly ($p < 0.05$). The volumetric parameter GEDV showed a significant decrease, whereas heart rate, and RVEDP increased slightly but resulted in statistical significance. RVEDV remained unchanged.

The removal of 300 mL of blood during acute RV insufficiency led to significant decreases of CO, MAP, MPAP, and RV filling pressures (CVP, and RVEDP) and of GEDV ($p < 0.05$). No significant changes in PPV or SVV, RVEF, RVEDV, and RVdP/dTmax were observed.

After the retransfusion of 400 mL of blood, MAP, MPAP, CVP, RVEDP, and RVEDV ($p < 0.05$) increased significantly compared with volume removal. CO increased slightly but not significantly. PPV and SVV remained unchanged, as did RVEF and RVdP/dTmax. The separate analysis of volume responders (CO >5%, n = 5; Fig 1) and volume nonresponders (CO <5%, n = 6; Fig 1) during retransfusion showed an increase in CVP in the two groups. However, in the responder group, the increases in CVP and CO were accompanied by decreases in PPV (25% [14, 30] to 17% [8, 21]) and SVV (16% [11, 22] to 12% [9, 22]), whereas in the nonresponder group, PPV (12% [7, 20] to 16% [10, 24]) increased and SVV (13% [12, 14] to 13% [11,16]) remained. A significant increase in MPAP occurred in the nonresponder group (from 34.4 $\pm$ 6.5 to 44.5 $\pm$ 7.7, $p = 0.015$) but not in the responder group (from 33.4 $\pm$ 3.9 to 36.9 $\pm$ 8.0).

DISCUSSION

This study prospectively investigated the combination of RV filling pressures (CVP) and LV functional preload indices (SVV, PPV) in a frequently used experimental model of acute pulmonary hypertension.[13,14] Increases in CVP and SVV or PPV seem indicative for RV dysfunction or failure. During the volume challenge, PPV and SVV decreased in volume responders but increased in nonresponders.

A sudden increase in RV afterload, which can occur for vascular (such as lung embolism) or extravascular (such as lung edema, mechanical ventilation) reasons,[11] usually decreases the ejection fraction and thus CO because of forward RVF. The elevation of RV afterload led to decreases in RVEF and CO in the present model. At the same time, RVdP/dTmax increased,