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Effect of PEEP, blood volume, and inspiratory hold maneuvers on venous return

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Running head: Venous Return, Blood Volume and Ventilatory Maneuvers

Abstract

According to Guyton's model of circulation, mean systemic filling pressure (MSFP), right atrial pressure (RAP), and resistance to venous return (RVR) determine venous return. MSFP has been estimated from inspiratory hold-induced changes in RAP and blood flow. We studied the impact of positive end expiratory pressure (PEEP) and blood volume on venous return and MSFP in pigs. $MSFP_{RAO}$ was measured by balloon occlusion of right atrium and $MSFP_{insp\_hold}$ extrapolated from RAP/pulmonary artery flow (Q_{PA}) relationships during inspiratory holds at PEEP 5 and 10 cmH_2O, after bleeding and in hypervolemia. $MSFP_{RAO}$ increased with PEEP [PEEP 5, mean (SD) 12.9 (2.5) mmHg; PEEP 10 14.0 (2.6) mmHg, p=.002] without change in Q_{PA} [2.75 (.43) *vs.* 2.56 (.45) L/min, p=.094]. $MSFP_{RAO}$ decreased after bleeding and increased in hypervolemia [10.8 (2.2) and 16.4 (3.0) mmHg respectively p<.001], with parallel changes in Q_{PA}. Neither PEEP nor volume state altered RVR (p=.489). $MSFP_{insp\_hold}$ overestimated $MSFP_{RAO}$ [16.5 (5.8) mmHg *vs.*13.6 (3.2) mmHg; p=.001; mean difference 3.0 (5.1) mmHg]. Inspiratory holds shifted the RAP/Q_{PA} relationship rightwards in euvolemia because inferior vena cava flow (Q_{IVC}) recovered early after an inspiratory hold nadir. The Q_{IVC} nadir was lowest after bleeding [36 % (24 %) of pre-inspiratory hold at 15 cmH_2O inspiratory pressure] and the Q_{IVC} recovery most complete at lowest inspiratory pressures independent of volume state [range from 80 (7) % after bleeding to 103 (8) % at PEEP 10 cmH_2O of Q_{IVC} before inspiratory hold]. The Q_{IVC} recovery thus defends venous return, possibly via hepatosplanchnic vascular waterfall.

New and Noteworthy:

Enhanced recovery of Q_{IVC} during inspiratory holds shifts the RAP/Q_{PA} relationship to the right. Hence, $MSFP_{insp\_hold}$ overestimates the $MSFP_{RAO}$. The preferential Q_{IVC} recovery helps to maintain venous return during sustained increased inspiratory airway pressure. The underlying mechanism is likely to be a hepatosplanchnic vascular waterfall.

Keywords: right atrial pressure, mean systemic filling pressure, mechanical ventilation, blood volume, cardiac output

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Introduction

Positive pressure ventilation has complex cardiovascular effects, which often necessitate administration of fluids or vasoactive drugs to support hemodynamics. Changes in hemodynamic measurements during the ventilator cycle have been proposed as a means to assess the potential response of cardiovascular system to fluids (45, 48, 49, 58).

The effects of positive pressure ventilation and application of positive end expiratory pressure on cardiac output can be explained by the interactions of the venous return function and cardiac function (19) – a concept proposed by Guyton more than 50 years ago (24). The effects of positive intrathoracic pressures on cardiac function have been well elucidated in patients with respiratory and circulatory failure (11, 59). In contrast, the effects of mechanical ventilation on the venous return function are more difficult to evaluate due to lack of clinically available methods to assess its variables.

The total blood volume consists of unstressed and stressed volume. The unstressed volume fills the vasculature without pressurizing, whereas the stressed volume causes elastic recoil pressure(47). The mean systemic filling pressure is the elastic recoil pressure caused by the stressed volume in the systemic circulation. It can be quantified during an acute no flow state (28). Venous return according to Guyton's model is driven by the gradient between MSFP and right atrial pressure. Thus, at zero blood flow the RAP equals the MSFP. When the rate of venous return is plotted as a function of RAP, it follows a linear function and the slope of the curve is the inverse of resistance to venous return, RVR (24, 27, 39, 60). The RVR reflects the

composite resistance of all systemic vascular beds for the blood flow returning to the heart(25, 68).

In Guyton's model, the working heart serves dual roles. It lowers RAP and thereby enables venous return and it provides the mechanical energy that maintains driving pressure for peripheral tissue perfusion (44, 46). Even though Guyton's model of the circulation is heavily criticized (2, 3, 36) and debated (6, 7, 44, 46, 56), approaches based on this concept have gained renewed interest for explaining hemodynamic instability and planning therapeutic interventions (19, 31, 43, 55, 70, 71). Specifically, changes in MSFP could help to assess changes in stressed volume.

Since MSFP cannot be directly measured in clinical practice, surrogate approaches have been proposed (42). These include extrapolation from pressure/flow relationships during inspiratory hold maneuvers (27, 39, 60), extrapolation from peripheral venous and arterial pressures during instantaneous vascular occlusion (21), and mathematical modeling (12, 54, 55). However, an important limitation of the interventional methods used to estimate MSFP is that they may trigger vascular reflexes and other adaptive responses that can alter MSFP and RVR. These approaches assume that Guyton's model for steady state conditions would be applicable in the presence of transient changes in pressures and flow – an assumption that has not been validated.

We used a porcine model to address the following questions: 1) Do changes in PEEP, volume status and tidal breaths alter MSFP and the slope of the venous return curve? 2) Does a measurement of MSFP obtained with inspiratory hold maneuvers correspond to MSFP measured by right atrial occlusion? 3) Do inspiratory hold

maneuvers modify the hemodynamic variables of the venous return function, and do PEEP and volume status modify these responses? The answers to these questions have important implications for the attempts by investigators to use respiratory maneuvers to assess MSFP.

Glossary

$C_{vascular}$	Compliance of the vascular system
F_IO_2	Fraction of inspired oxygen
HES	Hydroxyethyl starch
IVC	Inferior vena cava
MAP	Mean arterial pressure
MSFP	Mean systemic filling pressure
$MSFP_{insp\_hold}$	Mean systemic filling pressure obtained via extrapolation of pressure-flow relationships with airway occlusion
$MSFP_{RAO}$	mean systemic filling pressure; measured during right atrial balloon occlusion at end expiratory lung volume
PA	Pulmonary artery
P_{AW}	Airway pressure
PAP	Pulmonary artery pressure
P_{insp}	Inspiratory airway pressure
PEEP	Positive endexpiratory pressure
Q_{PA}	Pulmonary artery blood flow
Q_{IVC}	Inferior vena cava blood flow
Q_{SVC}	Superior vena cava blood flow
RA	Right atrium
RAP	Right atrial pressure

RAP_{tm}	Right atrial transmural pressure
RVR	Resistance to venous return
SVC	Superior vena cava
TV	Tidal ventilation
VRdP	Venous return driving pressure
V_s	Stressed volume
V_u	Unstressed volume

Materials and methods

The study complied with the Guide for the Care and Use of Laboratory Animals, National Academy of Sciences 1996, and Swiss National Guidelines and was approved by the Commission of Animal Experimentation of Canton Bern, Switzerland (approval number BE 71/14). Twelve domestic male pigs [body weight 39.1 (SD 1.7)] kg were fasted for 12 hours with free access to water. The first two pigs were used in pilot studies to establish the instrumentation and the feasibility of the study procedures. Ten pigs were included in the study. After premedication with intramuscular ketamine (20 mg/kg) and xylazine (2 mg/kg) anesthesia was induced with midazolam (0.5 mg/kg) and the pigs were orally intubated. Anesthesia was maintained with propofol (4 mg/kg/h) and fentanyl (5 µg/kg/h) and the depth controlled by repeatedly testing the response to nose pinch. Additional injections of fentanyl (50 µg) or midazolam (5 mg) were given as needed. Muscle relaxation was induced with rocuronium (0.5 mg/kg) for the study measurements. The pigs were mechanically ventilated in a volume controlled mode (Servo-I, Maquet Critical Care, Solna, Sweden) using positive end-expiratory pressure of 5 cm H_2O, a F_IO_2 of .30,

and a tidal volume of 300 mL [7.7 (0.3) mL/kg body weight]. Respiratory rate was adjusted to maintain an end-tidal pCO_2 of 40 mmHg.

Installations

The following catheters were surgically placed for the measurements of arterial and venous pressures: two double-lumen catheters in the superior vena cava via the right and left jugular vein, a catheter in the right carotid artery, an arterial and a venous catheter in the right hind limb, and introducer sheaths in the right and left femoral veins. A median sternotomy was used to enter the thoracic cavity. The pericardium was opened and appropriately sized transit time ultrasonic flow probes (Transonic Systems, Inc., Ithaca, NY, USA) were placed around the main pulmonary artery, the superior vena cava and the inferior vena cava. Another catheter was placed in the main trunk of the PA and a 12×20 mm balloon catheter for measurement of pericardial pressure (Tyshak II, Numed, Canada) was fixed in the pericardium at the level of the right atrium (35). All catheters and cables were guided outside the thoracic cavity. The pleural cavities were drained and placed under pressure of minus 20 cm H_2O until the measurements were started. The pericardium was closed by a continuous mattress suture, the sternum with figure of eight sutures, and the wound in layers. The urinary bladder was drained via a cystostomy. An esophageal balloon catheter (Sidam, Mirandola, Italy) was orally inserted to estimate changes in pleural pressure (14). The position of the pericardial and esophageal balloons was confirmed by chest compression during an expiratory hold (61). A catheter with a 50 mm×34 mm inflatable high compliance balloon (Amplatzer sizing balloon, St. Jude Medical, St. Paul, MN, USA) was introduced under fluoroscopy through the femoral vein sheath into the RA and a multilumen catheter was placed in the IVC. The position of the RA balloon and the catheters for measurement of pressure in the SVC and IVC

(both placed intrathoracically), as well as the location of the RA for zero reference of intravascular pressures were confirmed by fluoroscopy.

During surgery, Ringer's lactate was infused at a rate of 10 mL/kg/h, and in case of relevant blood loss supplemented by boluses of Ringer's lactate or hydroxyethyl starch (6% Voluven; Fresenius Kabi, Bad Homburg, Germany). After surgery the infusion rate was 3 mL/kg/h. Antibiotic prophylaxis was given as 1.5 g cefuroxime at skin incision and 4 hours later. Non-fractionated heparin was infused at a rate of 10'000 units/24 hours as thrombosis prophylaxis.

Data acquisition

Intravascular (carotid artery, PA, RA, SVC and IVC), esophageal, pericardial and airway pressures were measured using transducers (xtrans®, Codan Medical, Germany) and a multi-modular patient monitor (S/5 Critical Care Monitor®; Datex-Ohmeda, GE Healthcare, Helsinki, Finland), which also provided continuous ECG, end-tidal pCO_2 and body temperature. All pressure signals and the ultrasonic blood flow signals were recorded at 100 Hz in a data acquisition system (Labview™; National Instruments Corp., Austin, TX, USA), and processed off line using a customized analysis software (Soleasy, Alea Solutions, Zürich, Switzerland). The pressure transducers were calibrated using a water scale and the flow transducers zeroed and calibrated electronically before the study measurements. Baseline drift was checked, including zero flow in vivo, at the end of the experiment.

After surgery, 90 minutes were allowed for stabilization. Then, two 100 mL boluses of HES were given to replace any potential remaining perioperative volume deficit, and

214 in case of a stroke volume increase of >10 %, one further bolus was given. In the first
215 animal Ringer's lactate was given instead of HES. After the volume boluses, baseline
216 hemodynamics were recorded at PEEP 5 cm H_2O.
217
218 *Study protocol*
219
220 The protocol consisted of a series of five experimental conditions, at which the
221 variables of the venous return function were individually assessed. In the first two
222 conditions *PEEP 5 cm H_2O* and *PEEP 10 cm H_2O* were applied in random order.
223 Three volume states followed at PEEP 5 cm H_2O. The volume states started with
224 *euvolemia* followed by stepwise *bleeding* (6 and 3 mL/kg body weight) and
225 *hypervolemia* after rapid retransfusion of twice the bled volume with the shed
226 heparinized blood diluted in1:1 with HES.
227
228 In each condition, MSFP was assessed during a circulatory arrest induced by balloon
229 occlusion of the right atrium ($MSFP_{RAO}$) and extrapolated from inspiratory hold
230 maneuvers ($MSFP_{insp\_hold}$). Detailed descriptions are given below. The order of
231 $MSFP_{RAO}$ and $MSFP_{insp\_hold}$ maneuvers was randomized using opaque sealed
232 envelopes. A graphical summary of the protocol is given in Figure 1. As in steady
233 state conditions, pulmonary artery blood flow and cardiac output are essentially the
234 same, we use Q_{PA} and cardiac output interchangeably.
235
236 *$MSFP_{RAO}$*
237 To measure the $MSFP_{RAO}$ a right atrial balloon was rapidly filled under fluoroscopic
238 control with a mixture of radiocontrast and saline for 60 seconds at end expiratory
239 lung volume. PA pressure and flow tracings confirmed circulatory arrest. $MSFP_{RAO}$

was estimated as mean value of SVC and IVC pressure curves for 3 seconds as they approached a plateau at 9-12 seconds of RA occlusion before the onset of sympathetic reflex vasoconstriction, which was identified as a further increase in all intravascular pressures (Figure 2). The $MSFP_{RAO}$ was considered as the reference for true MSFP and was therefore used as the upstream pressure in all calculations of resistance to venous return unless indicated otherwise. Similar approaches have been used by others (51).

Total blood volume, stressed and unstressed volume and vascular compliance

Blood volume was measured using indocyanine green dye dilution (29) during baseline conditions at PEEP 5 cm H_2O, during *euvolemia* before *bleeding*, and in *hypervolemia* after retransfusion (Figure 1). The plasma dye concentration was measured by spectrophotometry. Ten blood samples were taken at 20 seconds intervals starting at 120 seconds after a bolus injection. The dye disappearance rate from plasma was extrapolated to time zero to calculate the plasma volume, and the blood volume using the mean hematocrit of an arterial and venous blood sample.

The blood volume measured at *euvolemia* before the bleeding and the rapid blood volume changes (*bleeding*, *hypervolemia* after retransfusion of blood and HES) were used to plot MSFP as a function of blood volume and to calculate the corresponding linear regression The intercept at zero MSFP represents the unstressed volume (V_u), and the slope of the linear regression line the inverse of vascular compliance ($C_{vascular}$). Assuming linear compliance (15, 40, 53, 67) across the blood volumes measured, the stressed volume corresponding to the $MSFP_{RAO}$ could be calculated (15, 40, 76) (Figure 3).

Reference function for venous return

The reference venous return function was constructed with the mean RAP and Q_{PA} of ten heart cycles during tidal ventilation immediately preceding the balloon occlusion, and the $MSFP_{RAO}$. VRdP was calculated for each pig and experimental condition as $MSFP_{RAO}$-RAP and RVR as ($MSFP_{RAO}$-RAP)/Q_{PA}. Thus, RVR is equal to the inverse of the slope of a line connecting Q_{PA} and RAP before the atrial balloon occlusion and the subsequent $MSFP_{RAO}$.

Extrapolation of $MSFP_{insp\_hold}$ with inspiratory hold maneuvers

Expiratory and inspiratory hold maneuvers at the respective PEEP and plateau pressures of 15, 20, 25 and 30 cm H_2O were done by adjusting tidal volume. Accordingly, the difference between inspiratory hold pressures and PEEP was smaller at PEEP 10 cm H_2O when compared to the other conditions.

Q_{PA} and RAP were taken as mean values over three cardiac cycles after 9 seconds of each expiratory and inspiratory hold. $MSFP_{insp\_hold}$ was defined as the zero flow intercept extrapolated from the plot of Q_{PA} as a function of RAP at these different airway pressures (Figure 4) (27, 38-42). A goodness of fit r^2>0.7 was considered as prerequisite for inclusion in analysis.

Effect of tidal breathing

The impact of changing from tidal ventilation to expiratory hold was assessed using the mean RAP and Q_{PA} of ten heart cycles during tidal ventilation preceding the expiratory hold and from the beginning of the expiratory hold.

Flow behavior in the thoracic veins

The impact of the inspiratory holds on SVC and IVC blood flows was evaluated. The relative decreases in SVC and IVC blood flows to the nadir beat of each flow during the inspiratory hold were compared to the values of a tidal breath preceding the respective inspiratory hold. Similarly, the three cardiac cycles used to calculate the $MSFP_{insp\_hold}$ during the inspiratory holds were compared to those during the tidal breath preceding the inspiratory holds in order to document flow recovery from the nadir during the inspiratory hold (Figure 4 Panel C).

Transmural pressures of the SVC and right atrium

Transmural pressure was calculated as intravascular minus esophageal pressure for the SVC and as RAP minus pericardial pressure for the right atrium (35), respectively. We report differences in transmural pressure between experimental conditions and changes from inspiration to expiration during the airway maneuvers. We have used this approach previously (5), as absolute esophageal pressures are less reliable than their changes from inspiration to expiration (22, 23).

Statistical analysis

Data were analyzed using SPSS software (Version 21; SPSS Inc., Chicago Illinois, USA). Paired t-test (for the two PEEP levels) and analysis of variance for repeated measures (for the three volume states) were used to analyze hemodynamics during tidal ventilation and at end expiratory lung volume. Analysis of variance for repeated measures was used to compare $MSFP_{RAO}$ and $MSFP_{insp\_hold}$ (within subject factor method, grouping factor experimental condition), venous return function during tidal ventilation and end expiratory hold (within subject factors breathing and PEEP). The effect of static inspiratory pressure on venous return function at the two PEEP levels

316 was assessed using analysis of variance for repeated measures (within subjects
317 factors P_{insp} and PEEP level). The effect of P_{insp} on venous return function was
318 assessed separately in each volume state, and compared between the volume states
319 at each P_{insp} using analysis of variance for repeated measures. The effect of
320 inspiratory holds on blood flow decrease and restoration was analyzed using
321 repeated measures analysis of variance (for vena cavas within subject factors vessel
322 and P_{insp}, for Q_{PA} flow pattern and P_{insp}; PEEP and volume state as grouping factors).
323 All data are shown as mean (SD).
324

RESULTS

Of the 10 animals studied, one died due to rupture of the right atrium and superior vena cava before the first set of measurements and a second animal developed prolonged ventricular fibrillation before measurements at *euvolemia* were completed. Hence, 42 of the planned 50 $MSFP_{RAO}$ measurements could be performed. The inflation of the right atrial balloon resulted in an abrupt cessation of PA blood flow, verified as disappearance of the PA pressure pulsatility (Figure 2). All 42 occlusions could be maintained for 60 seconds, and the hemodynamics were rapidly restored after deflation of the atrial balloon.

1) Do changes in PEEP, volume state and tidal breaths alter MSFP and the slope of the venous return curve?

At PEEP 10 cm H_2O as compared to PEEP 5 cm H_2O, both RAP and $MSFP_{RAO}$ increased, but RAP increased more than $MSFP_{RAO}$ so that VRdP decreased and RVR did not change. ΔRAP_{tm} did not change between PEEP levels. (Table 1, Figure 5a). Acute bleeding reduced $MSFP_{RAO}$ more than RAP, and hence, VRdP and Q_{PA} decreased. Hypervolemia increased $MSFP_{RAO}$ more than RAP, and VRdP and Q_{PA} increased relative to their euvolemia levels. The volume state had a significant effect on ΔRAP_{tm}. Bleeding and hypervolemia did not change RVR (Figure 5b). The relationship between VRdP and Q_{PA} over the volume states was highly linear (Figure 6).

RAP increased and Q_{PA} decreased with tidal breathing slightly but significantly in all study conditions when compared to an expiratory hold (Figure 7 a and b). There was a small decrease in RVR with tidal breathing in all volume states (Figure 7 b).

348 The $C_{vascular,}$ was 3.2 (.7) $mL \times mmHg^{-1} \times kg^{-1}$. The respective V_s before bleeding was 42
349 (9) $mL \times kg^{-1}$, or 43 (10) % of the total blood volume.

350 *2) Does $MSFP_{insp\_hold}$ correspond to $MSFP_{RAO}$?*

351 Three of the $MSFP_{insp\_hold}$ assessments had to be discontinued due to hemodynamic
352 instability (in two animals: one at PEEP 10 cm H_2O, two after bleeding), and two were
353 excluded due to lack of a sufficient linear fit. Paired comparisons - possible for 37
354 measurements of $MSFP_{RAO}$ - showed that $MSFP_{insp\_hold}$ was significantly higher than
355 $MSFP_{RAO}$ [16.5 (5.8) mmHg *vs.*13.6 (3.2) mmHg; p=.001; mean difference 3.0 (5.1)
356 mmHg for all paired measurements; Table 2]. The VRdP and RVR based on
357 $MSFP_{insp\_hold}$ were both higher than $MSFP_{RAO}$-based values (p<.001 and p=.003,
358 respectively).

359 *3) Do inspiratory hold maneuvers modify the hemodynamic variables of venous*
360 *return function, and does PEEP and volume status modify these responses?*

361 At both PEEP levels the Q_{PA} and RAP obtained during inspiratory holds shifted to the
362 right from the reference venous return curve based on the $MSFP_{RAO}$. This was not
363 the case after *bleeding* and in *hypervolemia* (Figure 8 a and b, Table 2).
364
365 The inspiratory hold maneuvers produced a rapid initial decrease of Q_{PA}, which
366 partially recovered during sustained hold (Figure 4 and Table 3). The Q_{PA} nadir was
367 reached during the first two cardiac cycles after starting the inspiratory hold, and the
368 respective nadirs of the vena cava flows occurred during the preceding cardiac cycle.
369 The maximum decrease in blood flow was different between the IVC and the SVC
370 and modified by the PEEP level and the P_{insp} (Table 4 and 5). Overall, the Q_{IVC}
371 decreased more than the Q_{SVC} and was lowest after *bleeding*. This difference

between the vessels was most prominent at *PEEP 5 cm H_2O* and *euvolemia* (Table 4 and 5).

The Q_{IVC} recovered most at lowest inspiratory pressures independent of volume state and more than the Q_{SVC} did (Table 4). The recovery occurred before the time point used to estimate $MSFP_{insp\_hold}$. There were no significant differences between the Q_{IVC} and Q_{SVC} in the maximum decrease or in the recovery from Q_{PA} nadir after bleeding and in hypervolemia.

The inspiratory hold maneuvers led to a progressive and linear increase in the inspiratory hold induced changes in transmural pressure of the SVC, indicating that transmural pressure became progressively lower with increasing plateau pressure (Figure 9).

DISCUSSION

The main findings of our study were

1) Increased PEEP during positive pressure ventilation with moderate tidal volumes produced an increase in MSFP, which almost completely compensated for the concomitant increase in RAP and did not change RVR. Consequently, cardiac output did not change. When blood volume was altered, MSFP and RAP changed in the same direction, but RAP was less affected. Accordingly, VRdP and cardiac output decreased and increased in parallel with blood volume, but again RVR did not change.

2) $MSFP_{insp\_hold}$ overestimated the $MSFP_{RAO}$ in euvolemic conditions, regardless of the PEEP level, whereas in *bleeding* and *hypervolemia* the observed values were very similar.

3) The inspiratory hold maneuvers shifted the venous return pressure/flow relationship to the right of the reference venous return curve in euvolemic conditions but did not do so in bleeding or hypervolemia.

In order to explain the shift of the pressure/flow relationship during the inspiratory holds and the consequent overestimation of $MSFP_{RAO}$ by $MSFP_{insp\_hold}$ during euvolemia but not with bleeding or hypervolemia, we analyzed the time course of changes in both caval and pulmonary artery flows. Q_{PA} decreased initially very rapidly but was then partially recovered (see Table 3). As expected, the nadir of vena cava flows preceded that of the Q_{PA} by one cardiac cycle but the patterns of decrease and recovery of blood flows differed between the IVC and the SVC in euvolemic

conditions. Although Q_{IVC} initially decreased more than Q_{SVC}, it recovered more completely in the euvolemic condition but not in bleeding or hypervolemia, and thus changes in caval flow during recovery patterns matched the shifts of the pressure/flow relationship in the three conditions. This recovery in Q_{IVC} occurred very rapidly within a few heartbeats, making reflex activation unlikely, and indicates that there must have been other adaptive mechanisms in the vascular compartments drained by the IVC. This flow recovery we observed cannot be explained by Guyton's model.

Two distinct mechanisms control hepatosplanchnic blood flow, when the outflow pressure is increased depending upon the venous pressure. The hepatic drainage has a vascular waterfall – or Starling resistor - that can be overcome when the outflow pressure is greater than 5 mmHg which will change the pressure/flow relationship (4, 9, 50). At higher outflow pressures, liver venous resistance decreases, consistent with passive distention of the venous system (9). In isolated porcine liver, distensibility appears to be maximal at outflow pressures above 10 mmHg (9). We have previously shown in intensive care patients that the venous driving pressure across the liver does not change in response to a 5 cm H_2O PEEP increase from 7-11 cm H_2O (range in individual patients) to 10-14 cm H_2O (34). Thus, these two mechanisms could act in concert to defend the hepatosplanchnic and IVC venous return. When RAP acutely increases, first the waterfall/Starling resistor is overcome and then there is distention of the vessels. These compensations would not occur in the hypervolemia condition because the higher RAP would have overcome the resistor and the drainage would already be maximally distended. Portal venous pressure equilibration with MSFP is delayed up to at least seven seconds in

hypovolemic conditions (20), and provides additional drainage of the splanchnic compartment. A waterfall with collapse in the IVC, as shown by Fessler in dogs (16), may provide an additional mechanism. Vessel compression has been shown to occur in the SVC during mechanical ventilation and it is accentuated in hypovolemia (74, 75). We show now indirect evidence of a progressive compression of the SVC with the inspiratory hold maneuver. The linear relationship between changes in vessel flow and transmural pressure in the studied range of airway pressures (Figure 9) suggests vessel closure if airway pressures would be further increased. Since the relationship between transmural pressure change and blood flow change may not be linear once the vessel is close to collapse (52), we cannot reliably estimate the critical closing pressures. For caval vein closure, higher transduction of airway or pleural pressure to the SVC than to the right atrium must be present. This has been shown by Fessler (16) and later in patients by Lansdorp (35). Our data show unchanged transmural atrial pressure between PEEP levels, which further supports this possibility.

A fourth mechanism that may contribute is the hepatic arterial buffer response. It increases the hepatic arterial flow acutely, when portal venous flow decreases. Low systemic blood flow reduces the hepatosplanchnic blood flow and partially abolishes these compensation mechanisms (30). In hypervolemia, the increased RAP would be expected to reduce the hepatic blood flow defense by exceeding the waterfall and by approaching the limits of the distensible system. Thus there was no shift in $MSFP_{insp\_hold}$. Since we did not measure hepatic blood flow, these proposed mechanisms need further confirmation. Venous return via the azygos vein directly into the right atrium was not accounted for, but may also have contributed to the flow recovery (26, 30). A fifth possible mechanism is an on-going shift of volume from the

458 arterial to venous compartments during the inspiratory hold. This seems unlikely as
459 the sole explanation, since the volume shift necessary to explain the mean difference
460 between $MSFP_{RAO}$ and $MSFP_{insp\_hold}$ would be in the range of 300 mL and would
461 have to occur within seconds. The volume transfer from the arterial to the venous
462 tree due to elastic recoil during circulatory standstill has been estimated to be around
463 4 mL/kg (64).

464 Regardless of the mechanism, volume status modified the shift of the Q_{PA}/RAP. The
465 main interest in estimation of MFSP in the clinical setting is to understand better the
466 complex hemodynamic problems and the response to therapeutic interventions. Our
467 results clearly demonstrate that $MSFP_{RAO}$ and $MSFP_{insp\_hold}$ are not interchangeable
468 and that $MSFP_{insp\_hold}$ overestimates the $MSFP_{RAO}$. The impact of volume status on
469 the Q_{PA}/RAP in our model of healthy anesthetized pigs was quantitatively moderate.
470 Overall, our values obtained with the balloon occlusion method are in the same range
471 as others have obtained in pigs (53) and dogs (51) with the same method, and are
472 also close to the MSFP of ICU patients promptly after death, as reported by Vieillard-
473 Baron and co-workers (62). In contrast, the MSFP values obtained with the
474 inspiratory hold method in postoperative and septic patients are considerably higher
475 (42, 57). Our results provide a possible mechanism for such unexpectedly high
476 MSFP values. Since considerably larger volume shifts than in our study are common
477 in patients with hemodynamic problems, shift of Q_{PA}/RAP during inspiratory holds
478 may be more pronounced. The $MSFP_{insp\_hold}$ values exceeding 30 mmHg reported in
479 septic patients (57) may at least in part be explained by the direct physiologic effects
480 of inspiratory holds.

481

Before criticizing our methodology, the conceptual issues related to the interpretation need to be discussed. The physiologic relevance and the actual existence of MSFP during on-going blood flow has been heavily debated. The MSFP is not located in any particular subdivision, but represents the stressed volume of the entire systemic vasculature. We consider it as the weighted mean of elastic recoil pressures in all systemic vascular beds, as measured after venous pressure equilibration during zero flow induced by RA occlusion. It will change if volume shifts alter the stressed volume, or if vascular elastance changes. When venous return is reduced during an inspiratory hold, volume will increase in the systemic vascular compartment due to reduced outflow and sustained inflow, until a new steady state has been reached(73). The low elastance compartment will receive most of this volume shift. Since the pulmonary circulation and the heart contribute to the volume shift, the stressed volume of the systemic circulation will increase, and consequently also the elastic recoil pressure caused by the stressed volume, i.e. the MSFP. The increase in MSFP due to such volume shifts in our experimental conditions would be very small - around 1-2 % (data not shown) and consistent with the result from other groups (73). Such volume shifts could therefore not account for the observed differences between $MSFP_{RAO}$ and $MSFP_{insp\_hold}$.

A second important issue is whether RA pressure acts as back pressure to venous return, or whether it only responds passively to volume shifts when flow changes, as proposed by Levy and Brengelmann (8, 36). Our study was not designed to solve this central point in the debate between proponents of Guyton and those of Levy. As discussed by Tyberg (69), "*It must be acknowledged that both interpretations are model-based and both are internally consistent. Thus, it is very difficult or perhaps impossible to 'prove' one at the expense of the other*".

507 The observed linearity of the RAP/Q_{PA} relationship during the inspiratory hold
508 maneuvers is compatible with both Levy's and Guyton's models, while neither would
509 *a priori* predict the occurrence of Starling resistors/waterfalls(73) or flow recovery
510 situations as we describe them.

511 There are some important methodological limitations to our study. Since we only
512 measured the $MSFP_{RAO}$ during expiratory holds, it is possible that MSFP changes
513 during the respiratory cycle. We tried to address this by plotting the Q_{PA}/RAP during
514 tidal breathing and end expiratory hold with the $MSFP_{RAO}$ (Figure 7). These venous
515 return curves were almost superimposed. However, we observed a very small but
516 significant decrease in RVR during tidal breathing as compared to expiratory hold –
517 i.e. the Q_{PA} and RAP during tidal breathing shifted slightly down and to the right
518 (Figure 7). It is unlikely that compliance changes could occur during one breath (60).
519 An alternative explanation for this apparent change in RVR is that tidal inflations may
520 enhance volume shifts from the pulmonary circulation, and therefore increase the
521 $MSFP_{RAO}$ without changing RVR (10). Volume shifts in pulmonary blood volume
522 during mechanical ventilation are small and depend on the zone conditions of the
523 lung (10). Given the large $C_{vascular}$ in our experiment, the effect on MSFP would be
524 negligible. To further assess the behavior of MSFP during mechanical ventilation,
525 $MSFP_{RAO}$ at expiratory hold and tidal breathing should be compared in future studies.

526 The balloon obstruction of the right atrium for determination of MSFP (51) is likely to
527 result in slightly higher values than those obtained using ventricular fibrillation, since
528 the beating heart shifts some volume from the pulmonary to systemic circulation(63).
529 $MSFP_{RAO}$ therefore dissociates from mean circulatory filling pressure obtained after
530 instantaneous cardiac arrest and full equilibration of all intravascular pressures. This

difference is likely to be marginal, since previous comparisons of balloon derived MSFP with potassium induced cardiac arrest showed no difference(53).

Furthermore, we did not use reflex blockade in our experiment, since it is not relevant for the clinical application of MSFP estimation. Anesthetic drugs may therefore have influenced the measurements.

Previous studies on the effects of increased intrathoracic pressure and positive pressure ventilation on venous return function have provided controversial results. Fessler et al. found that a PEEP of 15 cm H_2O *vs* no PEEP had no impact on VRdP in a ventricular fibrillation canine model, and since cardiac output decreased, the RVR had to increase (18). The increase in resistance to venous return with PEEP was confirmed with a venous bypass preparation (17). A brief change of airway pressure from 0 to 15 cm H_2O during apnea and ventricular fibrillation raised MSFP to the same extent as RAP was increased by apneic airway pressure. Since cardiac output decreased in response to higher airway pressure, the RVR must have increased (33). Nanas and Magder also found that increasing PEEP from 0 to 20 cm H_2O had no effect on VRdP, but increased RVR (51). Changing from spontaneous breathing to positive pressure ventilation in rats increased the MSFP and decreased the VRdP and cardiac output without an effect on RVR (13).

In contrast to previous studies, we found no change in RVR in response to PEEP. The differences in experimental setting and the measurement of variables of RVR, that is RAP, MSFP, and cardiac output, should be considered in interpreting the results. Most previous studies used much higher airway pressure changes and larger tidal volumes, 12-15 as compared to 7-8 mL/kg in the present study (13, 17, 18, 51). Furthermore, we used the same airway plateau pressures during the inspiratory hold

maneuvers with lower and higher PEEP. Accordingly, only PEEP and end expiratory lung volume were increased, resulting in lower airway driving pressure at the higher PEEP. This is likely to explain the modest effects of PEEP on cardiac output. In addition, we have previously shown in intensive care patients that a 5 cm H_2O PEEP increase from 7-11 cm H_2O (range in individual patients) to 10-14 cm H_2O has no effect on cardiac output (34). The mechanical effects of high PEEP with high tidal volumes on venous return, right heart function, and pulmonary vasculature are likely to be very different from our approach, and may explain much of the seemingly controversial results. On-going tidal positive pressure breathing (18), or turning ventilator off but not in a specific point of breath (51) may also modify the response. It is conceivable that on-going inflations during the assessment of MSFP may enhance volume shift from the pulmonary circulation (10), and therefore increase the MSFP to values higher than during normal circulation. This would result in an apparently higher RVR.

Our results on effects of PEEP cannot be extrapolated to conditions where higher PEEP levels are commonly used, such as acute lung injury. However, transmission of higher airway pressures to pleural pressures in acute lung injury may be attenuated due to impaired lung compliance (32).

Despite the higher MSFP estimates with the inspiratory hold method, the Q_{PA}/RAP response to the transient changes appeared remarkably linear, still consistent with Guyton's model. This suggests that despite the perturbations, a new steady state with a new resultant MSFP is achieved rapidly.

The further issue is the measurement of cardiac output as surrogate of venous return. Most previous studies on the effects of PEEP have used intermittent transcardiac thermodilution measurements (13, 18, 51), whereas we measured Q_{PA}

beat-by-beat, which allowed us to evaluate the $MSFP_{RAO}$ with the pressure and flow measurements right before the balloon occlusion. A similar approach was used in a landmark description of right ventricular heart lung interactions (59) and in the initial description of inspiratory holds for estimation of $MSFP_{insp\_hold}$ (73). The estimations of $MSFP_{RAO}$ in critical care patients have used arterial pulse contour analysis (37, 39-42, 57). Cardiac output measured by arterial pulse contour analysis does not track acute changes in venous return during brief periods because of the time delay between the change in outputs of the right and left ventricles. This is caused by buffering by the pulmonary vasculature and the transit time for rightsided changes to reach the left side during the respiratory cycle (10, 65, 72).

In conclusion, we found that during positive pressure ventilation with moderate levels of PEEP and low tidal volumes consistent with current recommended clinical practice (1, 66), PEEP produced modest changes in venous return, which were due to changes in VRdP and without alterations in RVR. This indicates that the concepts of mechanisms by which PEEP modifies hemodynamics should be revised when low tidal volumes and airway driving pressures are used. Furthermore, we conclude that inspiratory holds alter the venous pressure flow relationships, so that their use for bedside assessment of MSFP may be misleading and needs to be further studied.

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Authors Contributions

DB: conception of study and design of the protocol, preparation and performance of the experiment, data analysis and interpretation, drafting and revisions of the manuscript

PWM: contribution to the protocol design, performance of the experiment, data analysis and interpretation, drafting and revisions of the manuscript

AW: conducted the cardiac surgery, contribution to and revision of the manuscript

AB: performance of the experiment and revision of the manuscript

SB: preparation and performance of the experiment and revision of the manuscript

MH: protocol design, preparation and performance of the experiment, revision of the manuscript

SS: protocol design, data interpretation, revision of the manuscript

SMJ: conception of study, data interpretation, revision of the manuscript

SM: data analysis and interpretation, drafting and revision of the manuscript

JT: conception of study, data analysis including statistics and data interpretation, drafting and revising the manuscript. Study sponsor

All authors approved the final version of the manuscript

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Figure Captions

Figure 1: The course of the experimental protocol is depicted. The experiment was divided in two parts. Part A examined the effects of changes in positive end expiratory pressure on the venous return function. Part B assessed the effects of volume changes.

Figure 2. Time course of intravascular pressures after balloon occlusion (black arrow) of the right atrium. The mean of pressures from 9 to 12 seconds after occlusion were used to estimate the $MSFP_{RAO}$. Sympathetic activation is apparent as an increase in all pressures approximately 10 seconds later.

Figure 3: An exemplary extrapolation of stressed and unstressed volume is shown. Blood volume was measured at *Euvolemia* with ICG, see methods. After bleeding and retransfusion, $MSFP_{RAO}$ was measured. Stressed volume could be extrapolated with a linear regression (40, 51). The slope of the line equals the inverse of vascular compliance (elastance).Equation for the above graph, MSFP = -19.939 + (0.0077 × Blood Volume), r^2 = 0.988., $C_{vascular}$=129.9 mL/mmHg, 3.2 mL×mmHg^{-1}×kg^{-1}. V_u:unstressed volume, V_s:stressed volume.

Figure 4:

The figure describes the inspiratory hold maneuvers and their analysis. Expiratory holds at the given PEEP and inspiratory holds at plateau pressures of 15, 20 and 25 cm H_2O were performed over 30 seconds at all experimental conditions (Panel A).

Extrapolation of $MSFP_{insp\_hold}$: Mean values for Q_{PA} and RAP of the first three cardiac cycles occurring 9 seconds into the maneuver (green shade, Panel B and C) were taken and extrapolated to zero flow in order to estimate $MSFP_{insp\_hold}$ (Panel D).

Flow behavior in the thoracic veins: Inspiration causes an immediate drop in flow, visible as a single nadir beat for the caval veins (red shade in Panel B and C), transmitted to the pulmonary artery in the next heartbeat. Partial restoration of flow can be observed during the following beats. To assess these dynamic flow changes, the mean for all heartbeats during a full respiratory cycle preceding the inspiratory hold is used as *baseline* (blue shade Panel B and C). *Flow decrease* is presented as ratio of the nadir beat (red shade) to baseline (blue shade). *Flow restoration* is presented as the ratio of mean flow during the three beats at 9 seconds (green shade) to *baseline* (blue shade).

Figure 5: Effect of PEEP (Panel A) and acute alterations in blood volume (Panel B) on venous return function. Right atrial pressure and pulmonary artery blood flow were measured during tidal breathing for 10 cardiac cycles and the $MSFP_{RAO}$ as the mean of the caval pressures for 3 seconds at zero flow 9 seconds after right atrial balloon occlusion at end-expiratory lung volume. The expiratory hold was started immediately before the right atrial balloon was filled. The lines connect the mean values, while RVR was calculated in every individual animal, for details see Table 1. Effect of PEEP: $MSFP_{RAO}$ p=.002, RAP: p<.001, Q_{PA} p=.094; effect of volume: $MSFP_{RAO}$ p<.001; RAP: p<.001, Q_{PA} p<.001; Values are shown as means, error bars indicate one standard deviation.

Figure 6: Linear regressions were done over the three volume states for venous return driving pressure VRdP (=MSFP – RAP) and Q_{PA}. The relationship is highly linear with a median r^2 of 0.976 (range 0.726 - 1).

Figure 7. Effect of tidal ventilation on venous return function. Right atrial pressure and pulmonary artery blood flow was measured for 10 cardiac cycles during tidal breathing and during an expiratory hold immediately before the inspiratory hold maneuvers. The respective right atrial pressure and pulmonary artery blood flow values were plotted with the $MSFP_{RAO}$ to show the venous return during tidal breathing and at end-expiratory lung volume. Values are shown as means, error bars indicate one standard deviation. TV: tidal ventilation, exp: end expiration.

Solid line: end expiration; *dotted line*: tidal ventilation

a.) PEEP 5 cm H_2O and PEEP 10 cm H_2O

Effect of tidal ventilation: RAP p<.001, Q_{PA} p<.001, RVR p=.161

b.) euvolemia, bleeding, hypervolemia

effect of tidal ventilation RAP: p<.001, Q_{PA} p<.001, RVR p<.001

Figure 8: Venous return at end-expiratory lung volume and inspiratory holds. Right atrial pressure and pulmonary artery blood flow was measured over three cardiac cycles from 9 seconds into each expiratory and inspiratory hold and plotted with the $MSFP_{RAO}$ of each condition. The Q_{PA} and the corresponding RAP during inspiratory holds for each individual animal were used to construct individual linear regression lines. Their zero flow intercepts represent the $MSFP_{insp\_hold}$ for each animal and study condition, details see methods and figure 4. Values at expiratory hold values and the respective $MSFP_{RAO}$ were used as the reference venous return function. Values are shown as means, error bars indicate one standard deviation.

a.) PEEP 5 cm H_2O (triangle upwards) and PEEP 10 cm H_2O (triangle downwards), grey scale indicating increasing airway plateau pressure:

Statistics:

effect of PEEP: RAP p=.037, Q_{PA}=.713

effect of P_{insp}: RAP p<.001, Q_{PA} p<.001

P_{insp}*PEEP interaction: RAP p=.031, Q_{PA} p=.020

b.) Euvolemia (circle), bleeding (square), hypervolemia (diamonds), grey scale indicating increasing airway plateau pressure:

Statistics:

effect of P_{insp}: in all volume states, RAP p<.001, Q_{PA}: euvolemia p<.001, bleeding p= .001, hypervolemia p<.001

effect of volume state: at all pressure levels: RAP p<.001, Q_{PA} p<.001

Figure 9. Respiratory changes in transmural pressure of the SVC were analyzed over the inspiratory hold manoeuvers. With increasing plateau pressure, the change became progressively and linearly more negative, suggesting vessel compression. The linear regression equations are

for PEEP 5 cmH_2O: $\Delta P_{tm} = -2.352 + (0.00325 \times Q_{SVC})$, $r^2 = 0.98$

for PEEP 10 cm H_2O: $\Delta P_{tm} =$ = $-1.839 + (0.00331 \times Q_{SVC})$, $r^2 = 0.855$

Tables

Table 1. Effect of PEEP and blood volume on hemodynamics

	PEEP 5 cmH_2O (n=9)	PEEP 10 cmH_2O (n=9)	*p*	Euvolemia PEEP 5 cmH_2O (n=8)	Bleeding PEEP 5 cmH2O (n=8)	Hypervolemia PEEP 5 cmH_2O (n=8)	*p*
Heart rate; beats/min	100 (29)	96 (23)	.685	102 (21)	129 (31)	106 (20)	.001
MAP; mmHg	63 (7)	61 (12)	.609	60 (10)	50 (11)	63 (12)	.012
PAP; mmHg	18 (3)	20 (3)	.018	19 (3)	17 (3)	23 (3)	<.001
RAP; mmHg	5.9 (1.6)	7.5 (1.4)	<.001	5.9 (1.6)	5.1 (1.7)	8.2 (1.9)	<.001
$\Delta RAPtm_{exp}$; mmHg	.26 (1.02)		.496	-	.29 (.62)	.98 (1.26)	.033
Q_{PA}; L/min	2.75 (.43)	2.56 (.45)	.094	2.80 (.46)	2.20 (.42)	3.27 (.42)	<.001
$MSFP_{RAO}$; mmHg	12.9 (2.5)	14.0 (2.6)	.002	13.0 (2.8)	10.8 (2.2)	16.4 (3.0)	<.001
VRdP; mmHg	7.0 (2.2)	6.5 (2.3)	.033	7.0 (2.4)	5.7 (1.7)	8.2 (2.2)	<.001
RVR; mmHg/L/min	2.53 (.52)	2.53 (.63)	.945	2.49 (.59)	2.60 (.58)	2.50 (.52)	.489
	before PEEP changes			before bleeding	after bleeding	in hypervolemia	
Blood volume*; mL/kg	96 (14)			98 (16)	89 (15)	113 (21)	.008

MAP=mean arterial pressure; PAP=mean pulmonary artery pressure; RAP=right atrial pressure; $\Delta RAPtm_{exp}$= expiratory right atrial transmural pressure, Q_{PA}=pulmonary artery blood flow;
mean of 10 cardiac cycles before balloon occlusion during positive pressure ventilation with a tidal volume of 300 mL [7.7(.3) mL/kg]. Values for $\Delta RAPtm_{exp}$ are differences between experimental conditions of expiratory mean values of 5 respiratory cycles before balloon occlusion of 8 pigs (one pig excluded due to local hematoma around the pericardial balloon catheter).
$MSFP_{RAO}$=mean systemic filling pressure; measured during right atrial balloon occlusion at end expiratory lung volume
VRdP= venous return driving pressure; $VRdP=MSFP_{RAO} - RAP$, RVR=resistance to venous return; $RVR=VRdP/Q_{PA}$
*Blood volume after bleeding calculated as volume measured before bleeding – volume of shed blood
p-values: paired t-test for PEEP effect, repeated measures analysis of variance for effect of volume status, repeated measures analysis of variance for blood volume. Data shown for animals completing each series (PEEP n=9, volume n=8). Values are mean (SD).

Table 2. Comparison of $MSFP_{RAO}$ and $MSFP_{insp\_hold}$ at different PEEP-levels and blood volumes

	PEEP 5 cmH_2O (n=8)	PEEP 10 cmH_2O (n=7)	Euvolemia PEEP 5 cmH_2O (n=8)	Bleeding PEEP 5 cmH_2O (n=6)	Hypervolemia PEEP 5 cmH_2O (n=8)	*p**
$MSFP_{RAO}$; mmHg	12.9 (2.6)	14.1 (3.0)	13.0 (2.8)	10.9 (2.6)	16.4 (3.0)	.002
$MSFP_{insp\_hold}$; mmHg	15.7 (2.7)	18.7 (4.0)	15.9 (3.7)	11.9 (2.0)	19.7 (9.8)	

Comparison of all available paired measurements (n=37); * p-value for repeated measures analysis of variance for effect of measurement method; no interaction (p=.802) between method and underlying clinical condition (PEEP-level, volume status). Values are mean (SD).

Table 3. Blood flow decrease and restoration in pulmonary artery during inspiratory holds

	P_{insp} 15			P_{insp} 20			P_{insp} 25			
	Baseline [L/min]	minimum flow [L/min]	flow restoration [L/min]	Baseline [L/min]	minimum flow [L/min]	flow restoration [L/min]	Baseline [L/min]	minimum flow [L/min]	flow restoration [L/min]	interactions with flow pattern *p*
PEEP 5 cmH_2O	2.83 (.59)	2.08 (.56)	2.48 (.58)	2.77 (.53)	1.78 (.56)	2.21 (.53)	2.72 (.51)	1.37 (.59)	2.00 (.49)	PEEP <.001
										P_{insp} <.001
PEEP 10 cmH_2O	2.35 (.44)	2.02 (.50)	2.27 (.46)	2.44 (.53)	1.78 (.52)	2.13 (.50)	2.43 (.45)	1.56 (.47)	2.02 (.48)	
Euvolemia	2.60 (.58)	1.87 (.65)	2.30 (.56)	2.54 (.57)	1.41 (.62)	2.01 (.53)	2.60 (.67)	1.12 (.65)	1.82 (.50)	P_{insp} <.001
										P_{insp}*volume <.001
Bleeding	2.21 (.44)	1.44 (.39)	1.77 (.39)	2.27 (.43)	.73 (.46)	1.51 (.35)	1.51 (.57)	.60 (.09)	1.19 (.44)	
Hypervolemia	3.24 (.59)	2.63 (.76)	2.92 (.59)	3.12 (.50)	1.90 (.68)	2.56 (.67)	3.08 (.52)	1.63 (.69)	2.27 (.65)	

Statistics: **PEEP-levels**: repeated measures analysis of variance for Q_{PA} with flow pattern (baseline, nadir, restoration) and P_{insp} as within subject factors and PEEP as grouping factor. The p-values indicate interaction of PEEP and P_{insp} with flow pattern. **Volume status:** Repeated measures analysis of variance with flow pattern (baseline, nadir, restoration) and P_{insp} as within subject factors and volume state as grouping factor. The p-values indicate interaction of P_{insp} with flow pattern. Values are mean (SD).

Table 4. Blood flow decrease and restoration in caval veins during inspiratory holds at different levels of PEEP

		Maximum decrease in flow (fraction of baseline)			*p*			
		P_{insp} 15	P_{insp} 20	P_{insp} 25	vessel	P_{insp}	PEEP	interactions *
PEEP 5	IVC	0.47 (.22)	0.38 (.20)	0.04 (.21)	.002	<.001	.012	vessel*P_{insp}*PEEP 0.037
	SVC	0.65 (.25)	0.47 (.28)	0.37 (.18)				
PEEP 10	IVC	0.74 (.15)	0.57 (.14)	0.34 (.23)				
	SVC	0.74 (.15)	0.64 (.18)	0.40 (.19)				
		Flow restoration (fraction of baseline)						
PEEP 5	IVC	0.95 (.13)	0.86 (.07)	0.78 (.09)	.013	<.001	.028	--
	SVC	0.87 (.08)	0.81 (.10)	0.75 (.19)				
PEEP 10	IVC	1.03 (.08)	0.93 (.06)	0.90 (0.9)				
	SVC	0.94 (.05)	0.89 (.09)	0.84 (.13)				

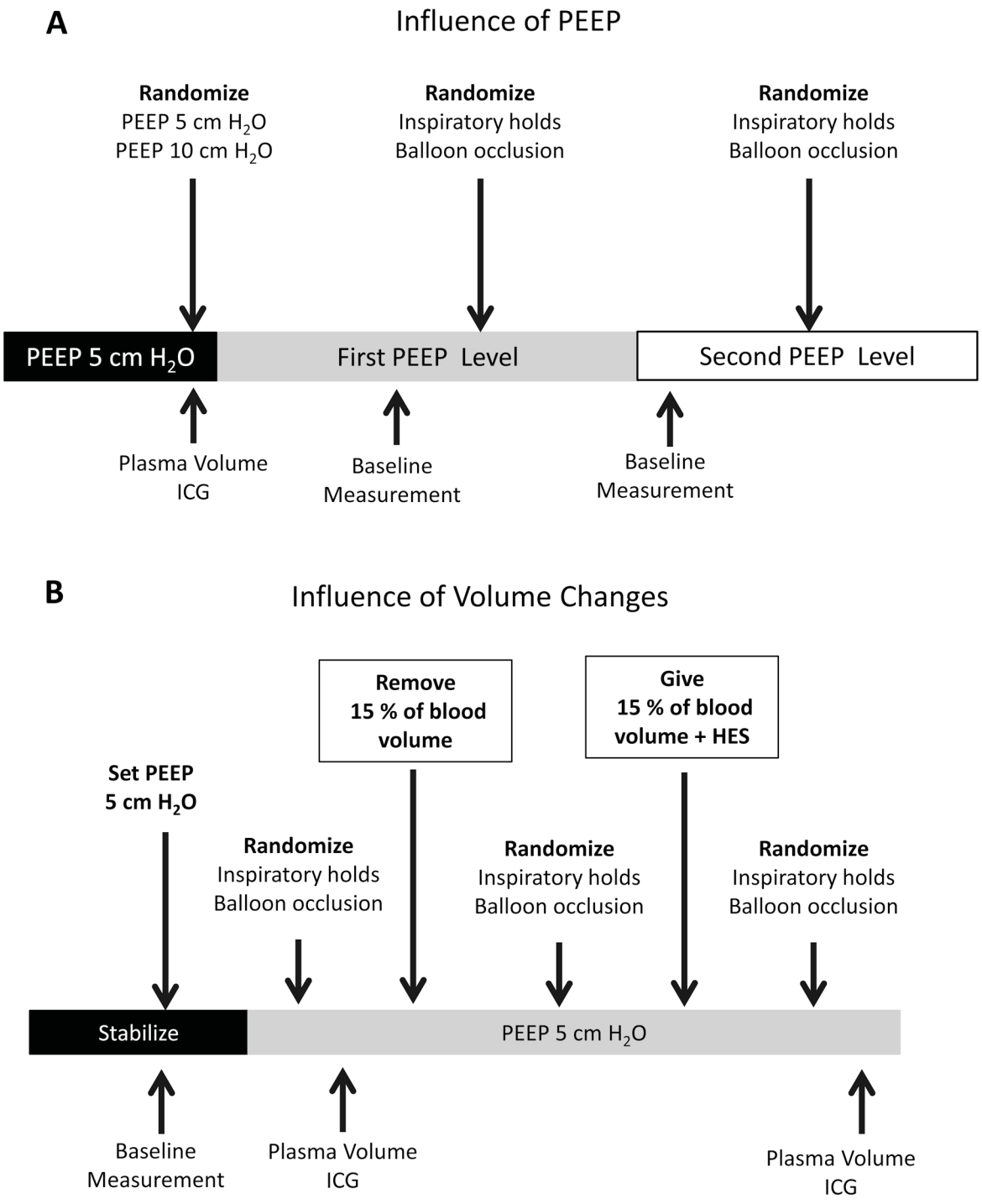
Blood flow changes as fraction of the respective flows during one breath cycle preceding the inflation (baseline). **The maximum decrease** is for the single nadir beat during the inspiratory hold; **the flow restoration** during the inspiratory hold is the fraction of the three beats used to extrapolate the $MSFP_{insp\_hold}$ of the baseline breath. Statistics: Repeated measures analysis of variance with vessel and P_{insp} as within subject factors and PEEP as a grouping factor. Post hoc tests within each PEEP level; repeated measures analysis of variance with vessel and P_{insp} as within subject factors. All values mean (SD); n=8

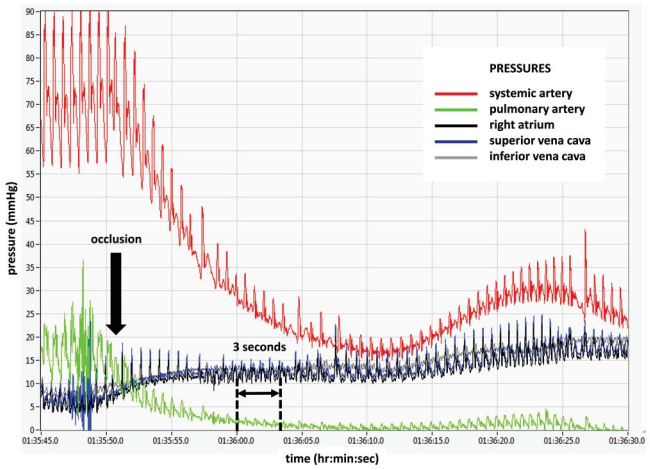
* significant interactions, if present, are reported with the highest number of interacting variables.

Table 5. Blood flow decrease and restoration in caval veins during inspiratory holds at different blood volumes

		Minimum flow (fraction of baseline)			
		P_{insp} 15	P_{insp} 20	P_{insp} 25	*p*
Euvolemia (n=9)	IVC	0.43 (.21)	0.19 (.19)	0.16 (.40)	vessel .003 P_{insp} <.001 vessel* P_{insp} <.001 volume .057
	SVC	0.64 (.23)	0.48 (.24)	0.48 (.22)	
Bleeding (n=6)	IVC	0.36 (.24)	0.07 (.22)	-0.11 (.32)	
	SVC	0.55 (.16)	0.33 (.16)	0.17 (.22)	
Hypervolemia (n=8)	IVC	0.58 (.10)	0.23 (.23)	0.14 (.33)	
	SVC	0.65 (.15)	0.48 (.28)	0.39 (.29)	
		Flow restoration (fraction of baseline)			
Euvolemia (n=9)	IVC	0.93 (.08)	0.79 (.12)	0.75 (.13)	vessel <.001 P_{insp} <.001 volume .003
	SVC	0.86 (.06)	0.77 (.10)	0.70 (.09)	
Bleeding (n=6)	IVC	0.80 (.07)	0.69 (.07)	0.55 (.12)	
	SVC	0.77 (.07)	0.62 (.12)	0.51 (.17)	
Hypervolemia (n=8)	IVC	0.91 (.06)	0.81 (.08)	0.75 (.14)	
	SVC	0.90 (.10)	0.85 (.16)	0.77 (.17)	

Blood flow changes as fraction of the respective flows during one breath cycle preceding the inflation (baseline). **The minimum flow** is for the single nadir beat during the inspiratory hold; **the flow restoration** during the inspiratory hold is the fraction of the three beats used to extrapolate the $MSFP_{insp\_hold}$ of the baseline breath. Statistics: repeated measures analysis of variance with vessel and P_{insp} as within subject factors and volume state as grouping factor. All values are mean (SD)


A
Influence of PEEP
Randomize
PEEP 5 cm H2O
PEEP 10 cm H2O
Randomize
Inspiratory holds
Balloon occlusion
Randomize
Inspiratory holds
Balloon occlusion
PEEP 5 cm H2O
First PEEP Level
Second PEEP Level
Plasma Volume
ICG
Baseline
Measurement
Baseline
Measurement
B
Influence of Volume Changes
Remove
15 % of blood
volume
Give
15 % of blood
volume + HES
Set PEEP
5 cm H2O
Randomize
Inspiratory holds
Balloon occlusion
Randomize
Inspiratory holds
Balloon occlusion
Randomize
Inspiratory holds
Balloon occlusion
Stabilize
PEEP 5 cm H2O
Baseline
Measurement
Plasma Volume
ICG
Plasma Volume
ICG


PRESSURES
systemic artery
pulmonary artery
right atrium
superior vena cava
inferior vena cava
occlusion
3 seconds
pressure (mmHg)
time (hr:min:sec)
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
01:35:45.0
01:35:50.0
01:35:55.0
01:36:00.0
01:36:05.0
01:36:10.0
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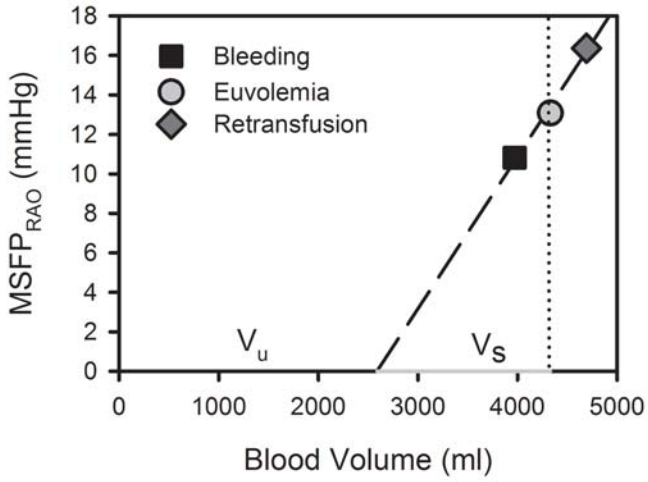
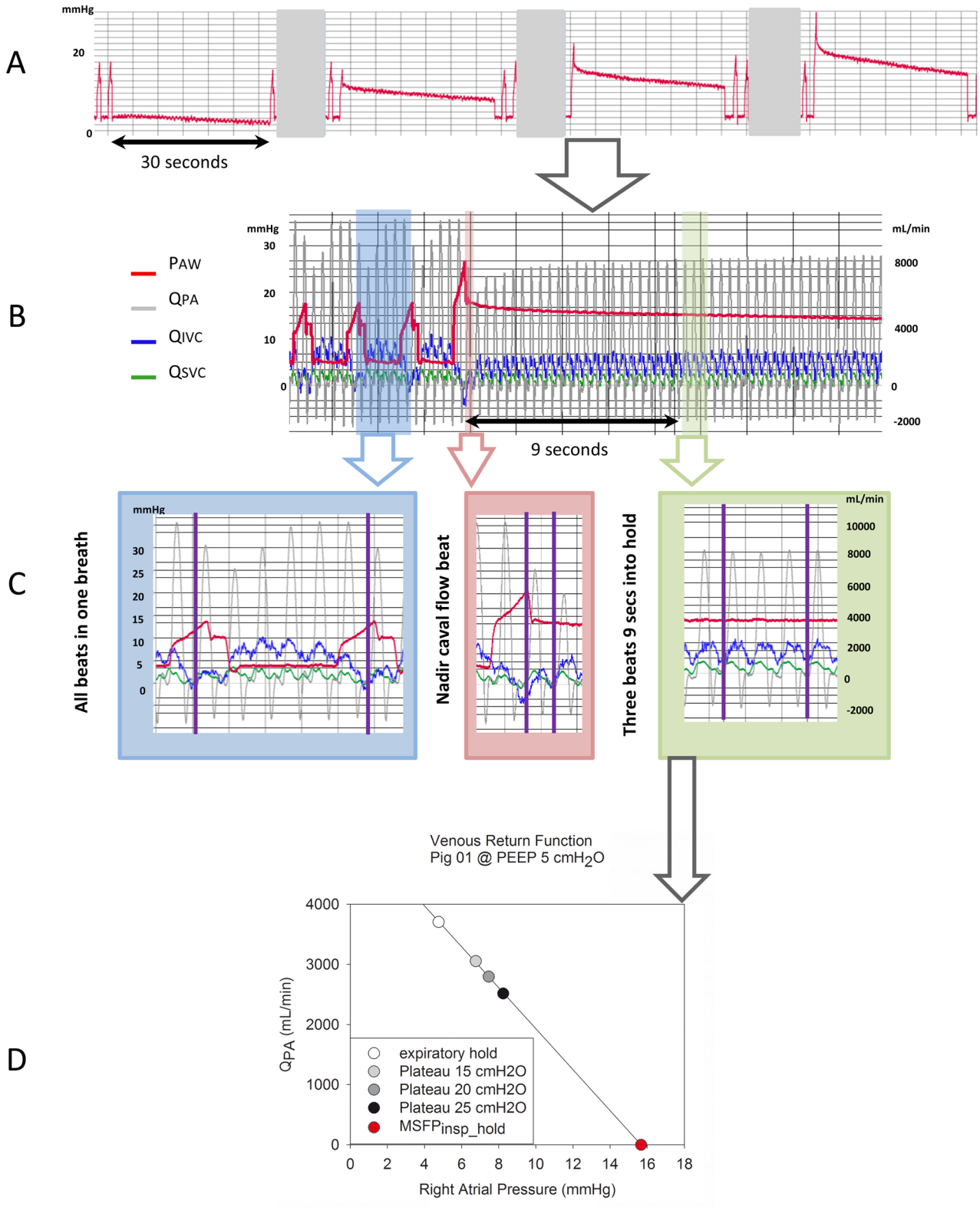
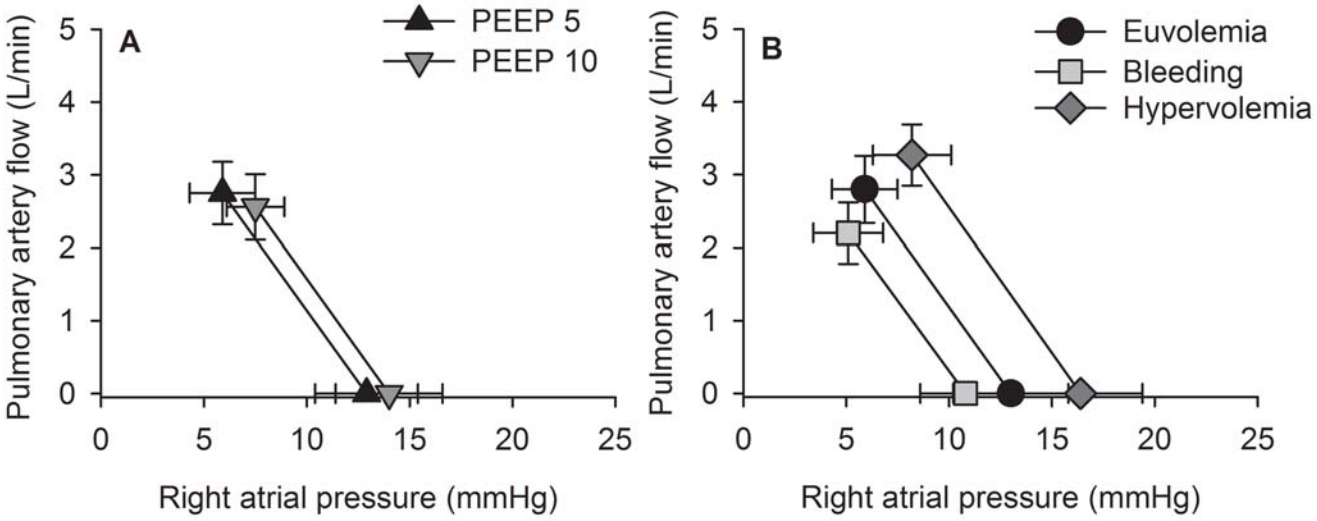
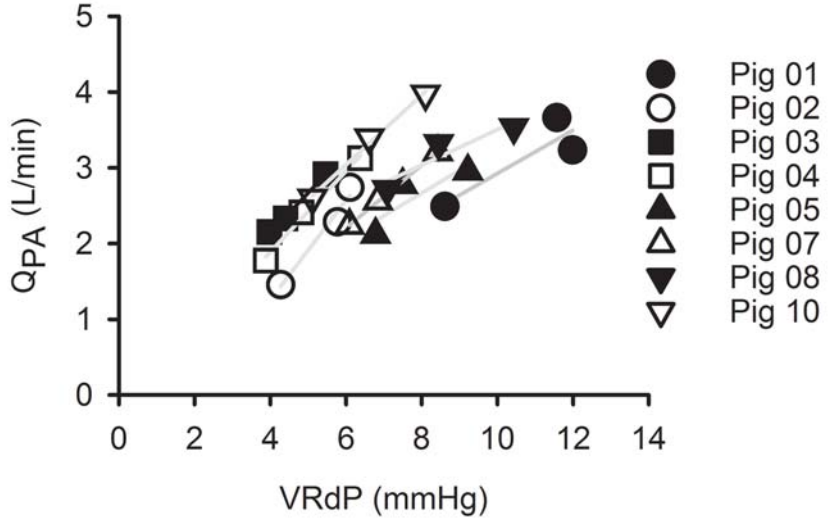
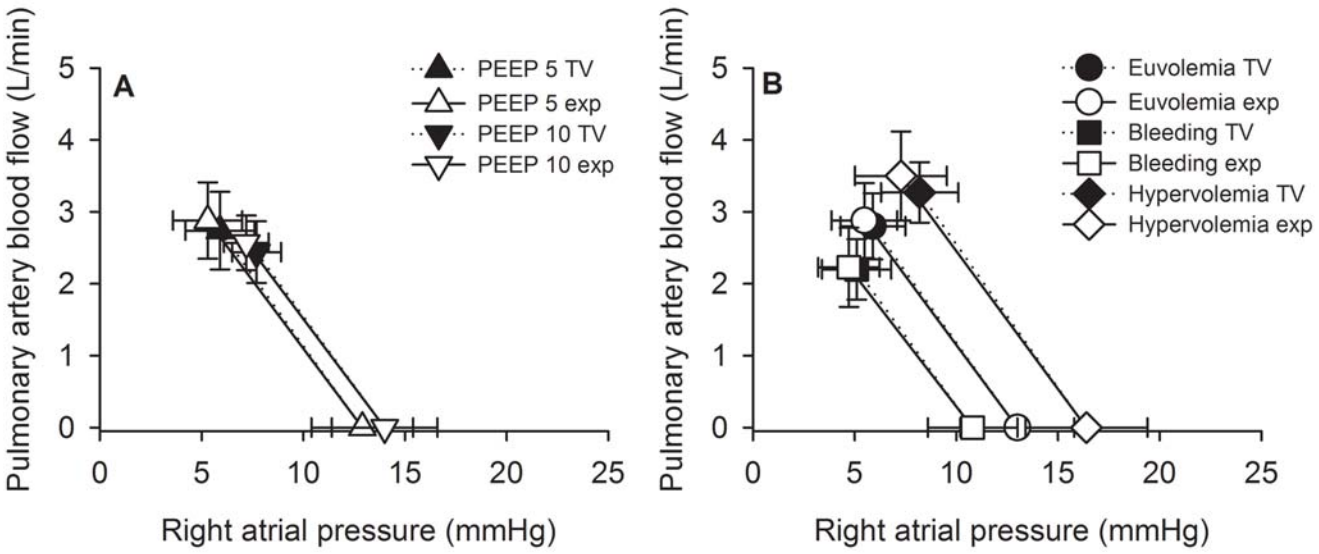
01:36:20.0
01:36:25.0
01:36:30.0

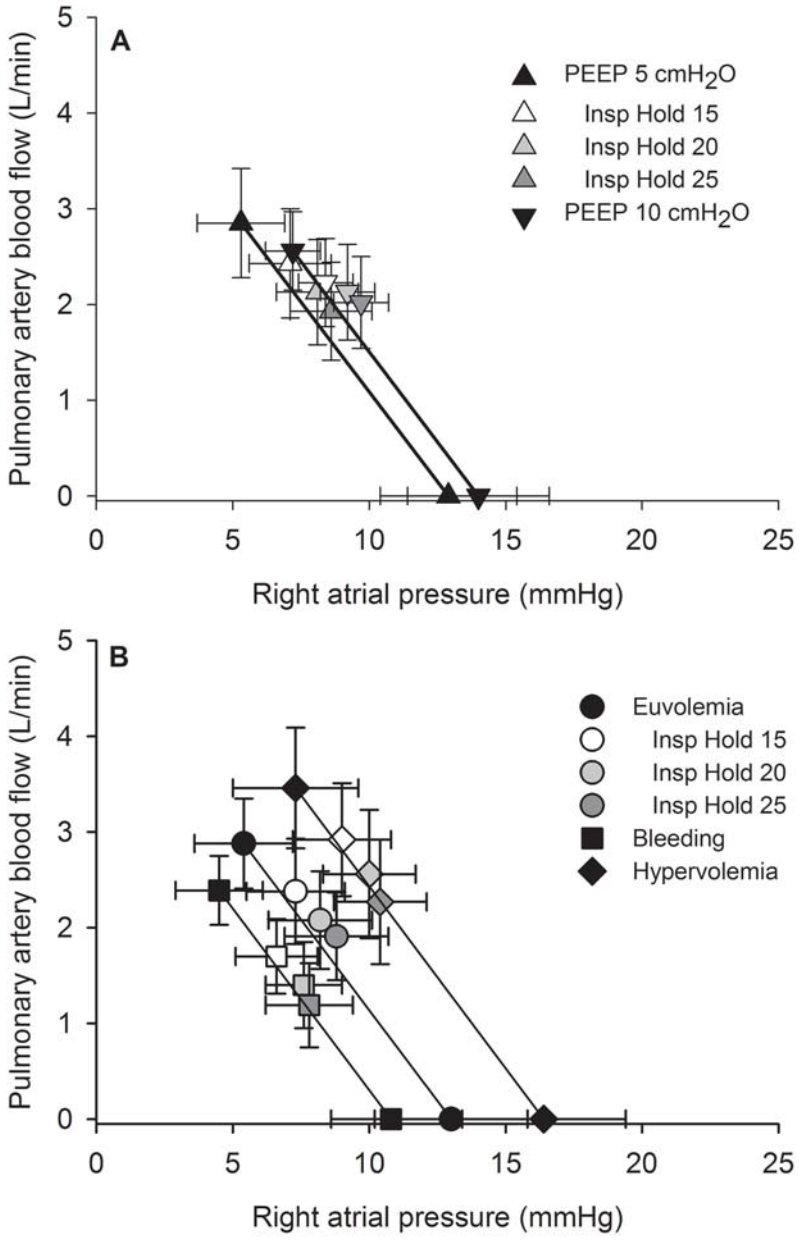

18
16
14
12
10
8
6
4
2
0
MSFP$_{RAO}$ (mmHg)
Bleeding
Euvolemia
Retransfusion
V_u
V_s
0
1000
2000
3000
4000
5000
Blood Volume (ml)

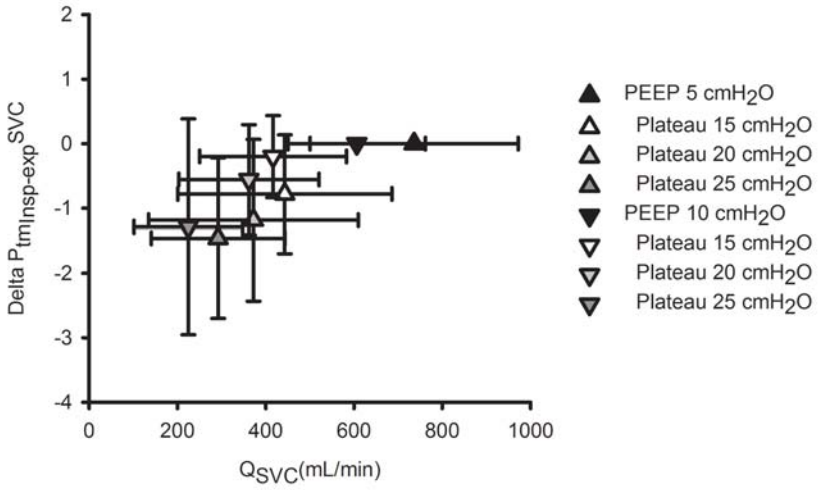

A
mmHg
20
0
30 seconds
B
PAW
QPA
QIVC
QSVC
mmHg
30
20
10
0
mL/min
8000
4000
0
-2000
9 seconds
C
All beats in one breath
mmHg
30
25
20
15
10
5
0
Nadir caval flow beat
Three beats 9 secs into hold
mL/min
10000
8000
6000
4000
2000
0
-2000
D
Venous Return Function
Pig 01 @ PEEP 5 cmH2O
QPA (mL/min)
4000
3000
2000
1000
0
expiratory hold
Plateau 15 cmH2O
Plateau 20 cmH2O
Plateau 25 cmH2O
MSFPinsp_hold
0
2
4
6
8
10
12
14
16
18
Right Atrial Pressure (mmHg)


A
PEEP 5
PEEP 10
Pulmonary artery flow (L/min)
Right atrial pressure (mmHg)
0
1
2
3
4
5
0
5
10
15
20
25
B
Euvolemia
Bleeding
Hypervolemia
Pulmonary artery flow (L/min)
Right atrial pressure (mmHg)


5
4
3
2
1
0
0
2
4
6
8
10
12
14
Q_{PA} (L/min)
VRdP (mmHg)
Pig 01
Pig 02
Pig 03
Pig 04
Pig 05
Pig 07
Pig 08
Pig 10


A
PEEP 5 TV
PEEP 5 exp
PEEP 10 TV
PEEP 10 exp
Pulmonary artery blood flow (L/min)
Right atrial pressure (mmHg)
0
1
2
3
4
5
0
5
10
15
20
25
B
Euvolemia TV
Euvolemia exp
Bleeding TV
Bleeding exp
Hypervolemia TV
Hypervolemia exp
Pulmonary artery blood flow (L/min)
Right atrial pressure (mmHg)


A
PEEP 5 cmH2O
Insp Hold 15
Insp Hold 20
Insp Hold 25
PEEP 10 cmH2O
Pulmonary artery blood flow (L/min)
Right atrial pressure (mmHg)
0
1
2
3
4
5
0
5
10
15
20
25
B
Euvolemia
Insp Hold 15
Insp Hold 20
Insp Hold 25
Bleeding
Hypervolemia
Pulmonary artery blood flow (L/min)
Right atrial pressure (mmHg)


2
1
0
-1
-2
-3
-4
0
200
400
600
800
1000
Delta $P_{tmInsp-exp}^{SVC}$
Q_{SVC}(mL/min)
PEEP 5 cmH2O
Plateau 15 cmH2O
Plateau 20 cmH2O
Plateau 25 cmH2O
PEEP 10 cmH2O
Plateau 15 cmH2O
Plateau 20 cmH2O
Plateau 25 cmH2O