Effect of volume status on the estimation of mean systemic filling pressure

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Abstract

Various methods for indirect assessment of mean systemic filling pressure (MSFP) produce controversial results as compared to MSFP at zero blood flow. We recently reported that the difference between MSFP at zero flow, measured by right atrial balloon occlusion ($MSFP_{RAO}$) and MSFP estimated using inspiratory holds depends on the volume status. We now compare three indirect estimates of MSFP with $MSFP_{RAO}$ in *Euvolemia*, *Bleeding*, and *Hypervolemia*, in a model of anesthetized pigs (n=9) with intact circulation. MSFP was estimated using instantaneous beat-to-beat venous return during tidal ventilation ($MSFP_{inst\_VR}$), right atrial pressure-flow data-pairs at flow nadir during inspiratory holds ($MSFP_{nadir\_hold}$), and using a dynamic model analog adapted to pigs ($MSFP_a$). $MSFP_{RAO}$ was underestimated by $MSFP_{nadir\_hold}$ and $MSFP_a$ in all volume states. Volume status modified the difference between $MSFP_{RAO}$ and all indirect methods (method*volume state interaction; $p \leq 0.020$). All methods tracked changes in $MSFP_{RAO}$ concordantly, with the lowest bias seen for $MSFP_a$ [bias (CI): -0.4 (-0.7 to -0.0) mmHg]. We conclude that indirect estimates of MSFP are unreliable in this experimental setup.

New and Noteworthy:

For indirect estimations of MSFP using either inspiratory hold maneuvers, instantaneous beat-to-beat venous return or a dynamic model analog, the accuracy was affected by the underlying volume state. All methods investigated tracked changes in $MSFP_{RAO}$ concordantly.

Keywords: hemodynamics, mean systemic filling pressure, venous return, cardiac output, positive pressure ventilation

Introduction

Mean systemic filling pressure (MSFP) is the equilibrated pressure of the systemic vasculature measured at circulatory arrest. In the running circulation, venous return (VR) is driven by the pressure gradient (VRdP) between MSFP and right atrial pressure (RAP), against the resistance to VR (12). Volume expansion and use of vasoactive drugs are the most common interventions to support circulation in the perioperative and intensive care setting. Such interventions often fail to produce the expected response: approximately 50% of intensive care patients receiving volume expansion fail to respond, and despite this often receive repeated interventions (6). Assessment of MSFP and VRdP may help to reveal the underlying pathophysiology and guide the clinical management with volume, and vasoactive, and inotropic drugs (3, 5, 27, 29). Various indirect methods have been suggested to estimate MSFP during ongoing circulation (9, 20, 27, 30): Instantaneous venous return MSFP from beat-to-beat right ventricular stroke volume during tidal ventilation agreed well with zero-flow MSFP obtained during ventricular fibrillation and open arterio-venous fistula (30). For clinical use, zero-flow extrapolation of RAP-flow data-pairs during various levels of airway pressure (17, 20, 37), exclusion of the circulation in the arm with a high-pressure cuff (1) and a dynamic analog of MSFP ($MSFP_a$) based on a two-compartment model of the circulation have been proposed (27, 28). It has been assumed that tidal breathing has little or no effect on MSFP (30). This assumption has been recently challenged (2, 31). Tidal volume and PEEP both cause acute changes in RAP and thereby also in VR. Temporary imbalances between atrial and venous in- and outflow may lead to underestimation of steady state VR (9). A new steady state MSFP is reached only after transient changes in blood flow and volume shifts have settled (2, 22).

Zero-flow extrapolation of MSFP from inspiratory occlusion maneuvers in patients have led to unexpectedly high MSFP values (16, 18-20, 29) in comparison to measurements during testing of implantable cardioverter defibrillators (14) or just after death (31) and may further be influenced by the underlying volume state (2). The acute changes in MSFP following increased airway pressure are likely to contribute to these findings.

The clinically used indirect methods for MSFP estimation have been evaluated against each other (20), but not against a zero-flow reference method over changing volume states. Further, if estimations of MSFP should be used for therapeutic decision-making, they need to be highly accurate since the normal VRdP may be ≤ 5 mmHg (14, 33). The aim of this study was to compare indirect estimations of MSFP with MSFP obtained during right atrial balloon occlusion ($MSFP_{RAO}$) in three volume states (*Euvolemia*, *Hypovolemia*, and *Hypervolemia*). For each indirect method, the absolute agreement *vs*. $MSFP_{RAO}$ and the tracking ability of changes in the method *vs*. changes in $MSFP_{RAO}$ was determined. Part of the data on the reference method $MSFP_{RAO}$ presented here has been published previously (2). In this study, MSFP was estimated with three methods; first, using instantaneous venous return curves ($MSFP_{inst\_VR}$) (30); second - in order to minimize the influence of volume state dependent flow restoration (2) - as the zero-flow extrapolation of MSFP from single beat nadir pulmonary artery flow (Q_{PA}) matched with RAP of the preceding beat during inspiratory holds ($MSFP_{nadir\_hold}$); third, by using the non-interventional approach of calculating a dynamic analog ($MSFP_a$) with the original formula (26) adapted for pigs.

Glossary

CO	cardiac output

95	F_IO_2	fraction of inspired oxygen
96	HES	hydroxyethyl starch
97	IVC	inferior vena cava
98	MAP	mean arterial pressure
99	MSFP	mean systemic filling pressure
100	$MSFP_a$	dynamic analog of static MSFP calculated using mean values of
101		RAP, MAP and Q_{PA} from 10 beats during tidal ventilation
102	$MSFP_{inst\_VR}$	mean systemic filling pressure estimated as the zero-flow
103		extrapolation of beat-to-beat instantaneous venous return during
104		tidal ventilation
105	$MSFP_{nadir\_hold}$	mean systemic filling pressure estimated as the zero-flow
106		extrapolation of nadir flow caused by inspiratory hold maneuvers
107	$MSFP_{RAO}$	MSFP measured at zero-flow caused by right atrial balloon
108		occlusion at PEEP 5 cm H_2O
109	PA	pulmonary artery
110	P_{AW}	airway-pressure
111	PEEP	positive end-expiratory pressure
112	$P_{pericard}$	pericardial pressure
113	Q_{PA}	pulmonary artery blood flow
114	Q_{IVC}	inferior vena cava blood flow

115	Q_{SVC}	superior vena cava blood flow
116	RA	right atrium
117	RAP	right atrial pressure
118	RAP_{tm}	right atrial transmural pressure
119	R_v	resistance in the venous compartment
120	RVR	resistance to venous return
121	SVC	superior vena cava
122	VR	venous return
123	VRdP	venous return driving pressure

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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 (Commission of Animal Experimentation of Canton Bern, approval number BE 71/14). We used data collected during a previous study that evaluated the effects of PEEP, tidal airway pressures, and blood volume, on venous return (2). As described in detail previously (2), 10 male pigs [*Sus scrofa domesticus*; ES breed (Schweizer Edelschwein); body weight (mean ± SD) 39.1 ± 1.7] kg were included in the study. After premedication (intramuscular ketamine and xylazine, 20 and 2 $mg \times kg^{-1}$ respectively), anesthesia was induced (intravenous midazolam 0.5 $mg \times kg^{-1}$) and maintained with propofol and fentanyl (4 $mg \times kg^{-1} \times h^{-1}$ and 5 $\mu g \times kg^{-1} \times h^{-1}$), with intermittent muscle relaxation induced with rocuronium (0.5 $mg \times kg^{-1}$). Adequate depth of anesthesia was checked by repeatedly testing the response to nose pinch, with bolus injections of fentanyl (50 µg) or midazolam (5 mg) added as needed. The pigs were mechanically ventilated at PEEP 5 cm H_2O, F_IO_2 of 0.3, and a tidal volume of 300 mL (7.7 ± 0.3 $mL \times kg^{-1}$) with I:E-ratio 1:2, using a volume-controlled mode.

Installations

By cut-down, catheters for vascular access and pressure measurement were placed in the superior and inferior vena cava (SVC and IVC), right atrium (RA) and carotid artery, and introducer sheaths in both femoral veins. Ultrasonic transit time flow probes (Transonic Systems, Inc., Ithaca, NY) were placed around the pulmonary artery (PA), SVC and IVC. A catheter was placed in the PA and a 12×20 mm balloon catheter was fixed in the pericardium at the level of the RA (15). Pressures were measured using transducers (xtrans®, Codan Medical, Germany). Pleural drains were placed and exposed to negative pressure until the start of measurements.

Catheters and cables were guided outside the thorax, which was closed in an airtight fashion. An esophageal balloon catheter was inserted to estimate changes in pleural pressure. Through the femoral vein sheaths, a catheter with a 34×50 mm high compliance balloon was introduced into the RA. The positions of the RA balloon and catheters for measurement of SVC and IVC pressures were confirmed by fluoroscopy and the level of the RA was marked on the external aspect of the chest wall for zero reference of intravascular pressures.

Ringer's lactate was infused at a rate of 10 $mL \times kg^{-1} \times h^{-1}$ during surgery and at 3 $mL \times kg^{-1} \times h^{-1}$ thereafter. Blood loss was replaced by boluses of Ringer's lactate or hydroxyethyl starch (HES). After surgery, 90 minutes were allowed for stabilization. Two 100 mL boluses of HES were given to replace any potential remaining perioperative volume loss - in case Q_{PA} increased >10 %, one further bolus was given.

Data acquisition

Pressure and ultrasonic blood flow signals were recorded at 100 Hz in a data acquisition system (LabVIEW™; National Instruments Corp., Austin, TX) and processed off-line using a customized analysis software (Soleasy, Alea Solutions, Zürich, Switzerland).

Study protocol

The three estimates of MSFP obtained with a running circulation ($MSFP_{inst\_VR}$, $MSFP_{nadir\_hold}$, and $MSFP_a$) were compared to $MSFP_{RAO}$ as the reference method. Baseline measurements (*Euvolemia*) were followed by bleeding 9 $mL \times kg^{-1}$ (*Hypovolemia*) and retransfusion of the shed heparinized blood and an equal amount

of HES (*Hypervolemia*). We performed all measurements at PEEP 5 cm H_2O, in conjunction with evaluation of the effect of changing blood volume in the original study (2). The order of zero-flow and inspiratory hold maneuvers was randomly assigned using opaque sealed envelopes. Adequate level of anesthesia was confirmed before each set of maneuvers. When the study measurements were completed, the animals were killed in deep anesthesia by injection of potassium chloride.

$MSFP_{RAO}$

Circulatory arrest was induced in expiratory hold (at PEEP 5 cmH_2O) by rapidly filling the RA balloon with a mixture of saline and radiocontrast dye. $MSFP_{RAO}$ was taken as the mean value of SVC and IVC pressures during three seconds of venous pressure plateau, before the onset of reflex-mediated vasoconstriction, which was seen as a secondary increase in all intravascular pressures. After restoring flow, the animals were allowed at least three minutes for arterial blood pressure and heart rate to return to pre-arrest levels before any following measurements were made (2).

$MSFP_{inst\_VR}$

$MSFP_{inst\_VR}$ was calculated as the zero-flow extrapolation of the linear regression from beat-to-beat data-pairs consisting of mean values from single beat Q_{PA} matched with mean RAP from the preceding beat over three respiratory cycles of undisturbed tidal ventilation preceding RA balloon inflation (30) (Figure 1).

$MSFP_{nadir\_hold}$

$MSFP_{nadir\_hold}$ was calculated as the zero-flow extrapolation of the linear regression from data-pairs consisting of the mean values from nadir single beat Q_{PA} matched

with mean RAP from the preceding beat, caused by inspiratory hold to four levels of airway pressure (Figures 1 and 4). Tidal volume was adjusted to reach plateau pressures of 15, 20, 25 and 30 cm H_2O in maneuvers lasting 30 seconds, separated by at least 1 min in order for ABP and heart rate to return to pre-inspiratory levels.

$MSFP_a$

The $MSFP_a$ calculation used mean values of steady-state RAP, MAP and Q_{PA} from 10 beats during tidal ventilation before RA balloon occlusion, with the originally published equation adapted to pigs (see Appendix I) (28).

Calculation of the components of venous return

Venous return driving pressure was calculated as $VRdP = MSFP_{RAO} – RAP$. The resistance to venous return for the reference method was calculated as $RVR_{RAO} = (MSFP_{RAO}-RAP) / Q_{PA}$. RVR_{inst_VR} was calculated as 1 / [slope of the individual regression lines].

Statistical analysis

Data were analyzed using SPSS software (Version 25; SPSS Inc., Chicago Illinois). The null-hypothesis was rejected at $p < 0.05$, if not stated otherwise. Paired t-test or Wilcoxon signed ranks test as appropriate, were used to compare methods of MSFP estimation for all volume states combined. Repeated measurements ANOVA (within-subject factor volume state) was used to analyze the effect of changing volume state on MSFP and a repeated measurements ANOVA (within-subject factors method and volume state) was used to compare methods of MSFP estimates and derived variables over volume states. Mauchly's test of sphericity was used with Greenhouse-Geisser correction as appropriate. Bonferroni correction of *p*-values was

used for multiple comparisons. In case of significant method*volume state interaction, *post hoc* paired t-tests, or Wilcoxon signed ranks test as appropriate, were used to compare methods of MSFP estimation for separate volume states (as a consequence of Bonferroni correction, significance should then only be accepted at a *p*-level ≤0.017). Data is presented as mean ± SD unless indicated otherwise. Assumptions of equal variance and normality were assessed as studentized residuals <±3, visually by Q-Q plots and histograms, and by Kolmogorov-Smirnov testing. The linear regressions for the zero-flow extrapolations were done using the least square method. For both inspiratory-hold derived MSFP estimates, a cut-off value of the proportion of variance (r^2) >0.7 was required for inclusion in the analysis (2). Paired comparisons of absolute values (test method *vs*. reference method on data from *Euvolemia*, *Bleeding* and *Hypervole*mia) and changes (∆test method *vs*. ∆reference method on changes between *Euvolemia-Bleeding* and *Bleeding-Hypervolemia*) were performed with the Bland-Altman method accounting for multiple paired comparisons from each subject using a web-based resource (https://sec.lumc.nl/method_agreement_analysis/index.html) (24). An *a priori* desired agreement between ∆test method *vs*. ∆reference method was set to ≤10% of venous return driving pressure in *Euvolemia* (8).

RESULTS

Of the 10 animals studied, one died from RA/SVC rupture before any measurements were taken and a second one developed prolonged ventricular fibrillation at *Bleeding*. At the end of the stabilization period, the coefficients of variation for heart rate, MAP, PAP, RAP, and Q_{PA} for end-expiratory beats over 10 consecutive respiratory cycles, were ≤ 6%. Hemodynamics were stable at repeated baseline conditions and changed

252 significantly with bleeding (bled volume 331 ± 38 mL) and retransfusion (Table I) (2).
253 The remaining arterio-venous pressure difference at time of best equilibrium was
254 [n=25, mean (range)] 12 (0-25) mmHg. MSFP measured with the reference method
255 and estimated by the indirect methods over changing volume states, is presented in
256 Table II. Venous return driving pressure was 6.8 ± 2.4 mmHg in *Euvolemia*, thereby
257 corresponding to a desired method agreement for changes in MSFP of ≤0.7 mmHg.
258 Results of the derivation of the factor 'c' adapted for pigs and the impact of changing
259 R_v on $MSFP_a$ are shown in Appendix II.

260 *Method comparisons*

261 When all volume states were lumped together, no difference was detectable between
262 $MSFP_{inst\_VR}$ and $MSFP_{RAO}$, but $MSFP_{nadir\_hold}$ and $MSFP_a$ underestimated $MSFP_{RAO}$
263 (Table III). The underlying volume state influenced the relationships between the
264 indirect estimates ($MSFP_{inst\_VR}$, $MSFP_{nadir\_hold}$, and $MSFP_a$) and the reference method
265 $MSFP_{RAO}$ (method*volume state interaction $p \leq 0.020$) (Table IV). *Post hoc* paired
266 comparisons between methods in respective volume state showed a trend of
267 $MSFP_{inst\_VR}$ underestimating $MSFP_{RAO}$ in *Bleeding* (Table V). RVR_{RAO} did not change
268 over volume states and was (n=8) 2.49 ± 0.60, 2.60 ± 0.58, and 2.50 ± 0.52
269 $mmHg \times min \times L^{-1}$ in *Euvolemia, Bleeding* and *Hypervolemia* respectively (p=0.489). In
270 contrast, RVR_{inst_VR} (n=8) decreased in *Bleeding* and was 2.25 ± 0.48, 1.46 ± 0.40,
271 and 2.96 ± 1.28 $mmHg \times min \times L^{-1}$ respectively (p=0.009; pairwise comparisons
272 significant between Bleeding-Euvolemia at p=0.019 and Bleeding-Hypervolemia at
273 p=0.031).

274 *Method comparisons – Bland-Altman analysis and 4-quadrant plots*

The lowest bias for absolute values, compared to the reference method of $MSFP_{RAO}$, was seen for $MSFP_{inst\_VR}$ [bias (95% CI): -0.6 (-2.3 to 1.0)] with wide limits of agreement (LoA) and CIs (Table VI, Figure 2). Four-quadrant plots showed that all methods tracked changes in $MSFP_{RAO}$ concordantly with high correlations, close to the line of identity (Figure 3). Bland-Altman analysis for changes in methods showed lowest bias between $\Delta MSFP_a$ and $\Delta MSFP_{RAO}$ [bias (95% CI): -0.4 (-0.7 to -0.0) mmHg]. Limits of agreement were still wide (-2.9 to 2.1) mmHg, and exceeded 10% of VRdP in *Euvolemia* (0.7 mmHg) (Table VII, Figure 2).

DISCUSSION

The main findings of this study were that:

The underlying volume state influenced the relationships between the inspiratory hold estimates of MSFP and the reference method $MSFP_{RAO}$. We have previously shown that the inspiratory hold technique (using pressure-flow data 9-12 s into the hold) was influenced by the volume state, due to alterations in restoration of venous return during the hold (2). In the clinical setting, estimation of MSFP should help to assess changes in stressed volume and venous return driving pressure in response to therapeutic interventions. Our results demonstrate that the accuracy of the estimate is modified by acute changes in stressed volume. Despite modifications to limit acute volume shifts the inspiratory hold maneuvers were still associated with considerable dynamic change in venous return.

The underlying volume state also influenced the relationship between the dynamic analog of static filling pressure $MSFP_a$ (26), adapted here for pigs, and $MSFP_{RAO}$. The clinical relevance of this is uncertain, as $MSFP_a$ tracked changes in $MSFP_{RAO}$

with a low bias, but with wide limits of agreement, exceeding the desired 0.7 mmHg. As the within-method variability is unknown, (see further under Limitations) we cannot assess the relative contributions of variance in $MSFP_{RAO}$ and $MSFP_a$ to the LoA.

Optimal fluid management improves patient outcome (4). A detailed framework for therapeutic control of the circulation based on MSFP has been developed by Parkin (27), although its clinical benefit has been questioned (25, 34, 35). In clinical studies including patients post-surgery and with septic shock, estimations of MSFP have been used to characterize the volume state (18), to assess the response to passive leg raising (7), to fluid challenges (3, 11), and to vasopressor therapy (19, 29). To justify further clinical research based on estimations of MSFP, including the *use for therapeutic decision-making*, it is of paramount importance to establish the accuracy *vs*. a zero-flow reference method.

The rationale for studying the three indirect methods was based on the following physiological arguments. $MSFP_{nadir\_hold}$: Nadir flow data-pairs occur early in the inspiratory hold maneuver and are unaffected by flow restoration (2), which eliminates one mechanism behind a possible volume-state dependent bias *vs*. the reference method $MSFP_{RAO}$. However, as acute increase in airway-pressure will lead to volume loading of upstream venous vessels, the RA inflow will be lower than steady state VR (9, 36). Consequently, $MSFP_{nadir\_hold}$ is expected to underestimate $MSFP_{RAO}$. $MSFP_{inst\_VR}$: Apart from the cyclically changing airway-pressure, this method of MSFP estimation does not *per se* involve an intervention with the potential of disturbing the cardiovascular system, and $MSFP_{inst\_VR}$ is conceptually unaffected by the volume-state dependent flow recovery seen in static hold maneuvers in our previous study (2). Furthermore, since acute changes in airway-pressure have been shown to affect zero-flow MSFP (14, 22, 32), a measurement obtained during

ongoing tidal ventilation would represent the net effect on stressed vascular volume exerted by the average airway-pressure over the respiratory cycle. Regarding $MSFP_a$, the method is non-interventional and data sampled during ongoing ventilation should integrate airway-pressure related effects (representing the average over the respiratory cycle) on stressed vascular volume and zero-flow MSFP.

Estimates of MSFP from simple airway-pressure maneuvers have attracted a lot of interest (13), but are associated with considerable physiological complexity. We have previously shown that MSFP could not be reliably estimated from data-pairs obtained 9-12 seconds into inspiratory hold maneuvers, since the degree of flow restoration was related to the underlying volume state (2). For the inspiratory hold estimates of MSFP studied here ($MSFP_{inst\_VR}$ as proposed by Pinsky (30) and $MSFP_{nadir\_hold}$ as a new method), the volume state influenced the accuracy of the method. This was manifested as a significant bias for *changes* between methods – i.e. poor tracking ability of changing volume state, where measurement of MSFP would be clinically most useful (Table VII). A constant bias over changing volume state would be less problematic.

A recent review of clinical studies reported values of 19-33 mmHg for MSFP from inspiratory hold maneuvers (42). This is well above the range of what could be expected from animal data. It is also considerably higher than reported in the two clinical studies that asses MSFP at zero-flow during testing of implantable cardioverter defibrillators (14, 33). To the best of our knowledge, the inspiratory hold method has not been properly evaluated against a zero-flow measure *over changing volume status* – except in our study, and the unexpectedly high values of MSFP and range may be related to the method itself, questioning further its clinical utility.

Reliability of the reference method

From the time of RA balloon occlusion to the time of best pressure equilibrium, the beating heart will shift some volume from the cardio-pulmonary to the systemic compartment. Due to the large average compliance of the latter, the pressure effect of this volume is small. In a porcine study $MSFP_{RAO}$ overestimated the equilibrated vascular pressure at ventricular fibrillation induced by potassium chloride by only 0.3 mmHg (<3%) (23). An elegant canine study using a right-heart bypass preparation found no difference in MSFP obtained with and without pump-assisted arterio-venous volume transfer (10). Compared to animal and patient data, the present study had a very low remaining A-V pressure difference at time of best equilibrium (14, 23, 33), and a mathematical correction would only lead to minor increase in MSFP. Taken together, the values of $MSFP_{RAO}$ reported here are *unlikely to underestimate* the true zero-flow pressure.

Stability of experimental conditions

The full protocol, as presented in the original paper (2), also included study measurements performed in euvolemia at PEEP 5 and 10 cm H_2O (in randomized order). PEEP level 5 (as presented in the original paper) and volume state *Euvolemia* (presented here) thereby represent repeated experimental conditions. As an indication of the stability of the preparation, there was no significant difference (data not shown) in any of the hemodynamics heart rate, MAP, PA pressure, RAP, blood volume, $MSFP_{RAO}$ or Q_{PA} between these conditions (2).

$MSFP_{nadir\_hold}$

We have recently shown that flow restoration during inspiratory holds influences the estimated MSFP values. Pressure-flow data-pairs obtained at nadir flow, early in the

inspiratory hold maneuver, are conceptually unaffected by *flow restoration*. However, the increasing RAP from positive pressure inspiration will not only impede venous return [immediate “back pressure” effect (22)], but also leads to volume loading of upstream venous vessels [demonstrated in slow inflation procedures (9)]. Flow measured early in the inspiratory hold therefore underestimates steady state VR, as represented by the reference method $MSFP_{RAO}$. Data-points are shifted downwards, and the zero-flow extrapolation is shifted to the left, underestimating true MSFP. In this study, we showed that $MSFP_{nadir\_hold}$ underestimated $MSFP_{RAO}$ (Figure 1, Tables III-IV). In addition to upstream volume loading, three additional mechanisms might add to the underestimation; first, airway-pressure induced vessel collapse upstream from the RA would lead to pressure-flow dissociation, shifting the zero-flow estimate to the left (2); second, venous vessel compliance and factors governing vessel collapse could vary over changing volume state (2, 39, 40), thereby partly explaining that volume state changed the relationship *vs*. $MSFP_{RAO}$; third, transmural right atrial pressure increased between the beat preceding nadir Q_{PA} beat, and nadir Q_{PA} beat ($\Delta RAP_{tm}=\Delta RAP-\Delta P_{pericard}$), in 62 of 93 cases (67%) (data not shown). This suggests that tidal inflation was associated with an increase in afterload and possible right ventricular distention (15, 38, 41), adding to the discrepancy between measured flow and steady state VR.

$MSFP_{inst\_VR}$

The volume loaded in upstream veins as a consequence of increasing RAP during inspiration will be released into the RA as vessels recoil during expiration (9, 22). However, the effects of vessel distention and recoil *on the zero-flow estimate* do not cancel, but act additively. Increasing airway-pressure will create high RAP with low flow, and decreasing airway-pressure will create low RAP with high flow (Figure 1).

Compared to the reference VR plot unaffected by volume shifts, vessel distention will displace high RAP-low flow data-pairs downwards, and vessel recoil will displace low RAP-high flow data-pairs upwards *with a clockwise rotation of the regression line* and leftward shift of the zero flow intercept (Figure 1)

$MSFP_{inst\_VR}$ showed a trend of underestimating $MSFP_{RAO}$ in *Bleeding*. The original study by Pinsky compared $MSFP_{inst\_VR}$ to MSFP measured at zero-flow induced by ventricular fibrillation and reported no interaction between volume state and method (30). In contrast, we found that the volume state influenced the accuracy of $MSFP_{inst\_VR}$ as compared to $MSFP_{RAO.}$ Calculation of RVR using $MSFP_{inst\_VR}$ resulted in a reduction of RVR in *Bleeding.* Such a finding is physiologically highly unlikely and was not seen for RVR_{RAO}. However, the finding that $MSFP_{inst\_VR}$ underestimated $MSFP_{RAO}$, and led to a reduced RVR in *Bleeding*, could be explained by factors that enhance the rotation of the regression line. Hypovolemia promotes transient vessel collapse during inspiration (39), which leads to a dissociation of the pressure-flow relation where dynamically measured flow does not represent steady state VR. As major vessels close, venous inflow into the RA ceases, and volume is loaded in upstream areas. Inspiratory pressure-flow data-pairs would deviate even further from the VR reference line. During expiration, vessels would open and release the pooled venous blood, causing data-pairs to be elevated above the VR reference line. Regardless of the underlying explanations, flow variation during the respiratory cycle was largest in *Bleeding* whereas the ventilator-induced change in RAP was constant over volume states (data not shown), which enhanced the rotation of the regression line.

$MSFP_a$

To our knowledge, the Parkin dynamic analog has never been compared to zero-flow measurements of MSFP. As the original authors note, the dynamic analog would differ from systemic static filling pressure if the actual veno-arterial compliance and/or resistance ratios deviate from the assumptions (28). A derived variable like $MSFP_a$ is mathematically coupled to the precision of the entering signals RAP, MAP and CO. Our data come from a well controlled setting, with careful zeroing and levelling and a highly invasive ultrasonic flow probe with an accuracy of ±10%. In *Euvolemia* this error was equal to ±0.28 L/min. The average value of 'c'= 0.78 ± 0.18 $mmHg \times min \times L^{-1}$ in the equation translates into an error in the pressure signal of ±0.2 mmHg in $MSFP_a$. A bias (CI) for $\Delta MSFP_a$ *vs*. $\Delta MSFP_{RAO}$ = -0.4 (-0.7 to -0.0) mmHg, is impressive, but may not reflect clinical reaility. In the clinical setting, the absolute values of MSFP estimates are likely to be less relevant than the changes in MSFP. Any indirect estimates of MSFP will be limited by the accuracy of the cardiac output measurements, typically in the range of 6-10 %.

Method comparisons

For all indirect methods, the accuracy *vs*. the reference method was dependent on the underlying volume state. Hence, comparison *between* indirect methods was not performed. The volume-state dependent inaccuracy of the indirect methods *vs*. the reference method was evident as method*volume state interaction (Table IV) and very wide LoA in the Bland-Altman over volume states (Table V). Consequently, when comparing the *relative* performances of the indirect methods, the most relevant information is the ability of each individual method to track changes in MSFP as measured with the reference method (Table VII). The bias of $MSFP_{inst\_VR}$ against $MSFP_{RAO}$ was higher (non-overlapping 95% confidence intervals) than the biases of $MSFP_{nadir\_hold}$ and $MSFP_a$ respectively. No statistical differences in bias or LoA were

found in the performance between $MSFP_{nadir\_hold}$ and $MSFP_a$. However, there is an obvious practical advantage of the non-interventional method of $MSFP_a$ as compared to $MSFP_{nadir\_hold}$, which requires a series of inspiratory hold maneuvers.

Limitations of the study

The main limitation comes from the small sample size of the experiment. That said, the effect sizes of all findings supporting the presented conclusions were robust. Our study demonstrated effects of dynamic changes in flow related to tidal ventilation and inspiratory hold maneuvers. The possible impact of static airway pressure on true MSFP, would be that of an *increase* (32). Our zero-flow MSFP measurements were all taken in expiratory hold. However, the indirect estimates $MSFP_{inst\_VR}$, $MSFP_{nadir\_hold}$ and $MSFP_a$ reflect conditions where the average airway pressure exceeded that of expiration, and still they *underestimated* the reference method. If we had determined $MSFP_{RAO}$ at elevated airway pressures, the observed differences in respect to the estimates would likely have been even more pronounced. Any future study addressing the effects of acute changes in airway pressure on MSFP would need to compare zero-flow measurements taken at varying levels of airway pressure. In this study, in order to determine the respective within-method precision, ideally both the reference method $MSFP_{RAO}$ and the tested estimates should have been assessed repeatedly in each condition. We did not consider this feasible due to the complexity of the experiment, and the added physiological stress. The unknown variability of the reference method thereby affects the interpretation of the limits of agreement. This study, using a highly instrumented and invasive experimental model, demonstrates accuracy problems of current less invasive methods for the estimation of MSFP in clinically relevant scenarios. The use of systemic arterial pulse contour analysis as a surrogate of Q_{PA} may cause additional, device-dependent problems,

and should be evaluated in future studies. For $MSFP_a$, the correct measurement of RAP is crucial, but susceptible to errors in the clinical setting (21).

Conclusions

Although respiratory maneuvers provide valuable insights into the physiology of circuit-heart-lung interactions, they are unsuitable for the estimation of MSFP, since the accuracy is affected by the underlying volume state. However, all indirect methods investigated tracked changes in $MSFP_{RAO}$ concordantly, with the lowest bias seen for $MSFP_a$ and $MSFP_{nadir\_hold}$. Of these methods, the high tracking ability and non-interventional nature of the dynamic analog $MSFP_a$ favors its application in the clinical setting.

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502

503 **Author's contributions**

504

505 PWM: study design, performed the experiment, data analysis and interpretation,
506 drafting and revision of the manuscript

507 SS: data analysis and interpretation, revision of the manuscript

508 SMJ: revision of the manuscript

509 JT: data interpretation, revision of the manuscript

510 DB: study design, performed the experiment, data interpretation, revision of the
511 manuscript

512 All authors approved the final version of the manuscript.

513

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Figure legends

Figure 1: Venous return plots for animal 5 in *Bleeding*. The VR reference line connects the RAP-Q_{PA} data-point (square; representing mean values of 10 beats during tidal ventilation before RA balloon occlusion) with $MSFP_{RAO}$. Filled circles represent individual beat mean Q_{PA} matched with mean RAP from the preceding beat obtained during three respiratory cycles of tidal breathing. Green and red circle data-points, representing inspiration and expiration, are displaced downwards and upwards in respect to the reference VR line because of distention and recoil of compliant vessels upstream from the RA. The dashed regression line extrapolates to $MSFP_{inst\_VR}$. Blue triangle data-points represent the mean values of individual beat nadir Q_{PA}, matched with mean RAP from the preceding beat, caused by inspiratory hold to increasing levels of airway pressure. They are displaced downwards in respect to the reference VR line because of upstream vessel distention, and the dotted regression line extrapolates to $MSFP_{nadir\_hold}$. The data on the reference method $MSFP_{RAO}$ has been previously published (2).

Figure 2: Bland-Altman plots. Left hand panels represent [difference between test method and reference method] *vs*. absolute values of $MSFP_{RAO}$ (*Euvolemia* – circles; *Bleeding* – downward pointing triangles; *Hypervolemia* – upward pointing triangles). Right hand panels represent [difference between Δtest method and $\Delta MSFP_{RAO}$] *vs*. $\Delta MSFP_{RAO}$. Method bias in red, upper and lower LoA in green and blue, dashed lines CIs. Part of the data on the reference method $MSFP_{RAO}$ has been previously published (2).

Figure 3: Four-quadrant plots for Δtest method *vs*. $\Delta MSFP_{RAO}$. Part of the data on the reference method $MSFP_{RAO}$ has been previously published (2).

Figure 4: Flow dynamics in response to changing airway pressure.

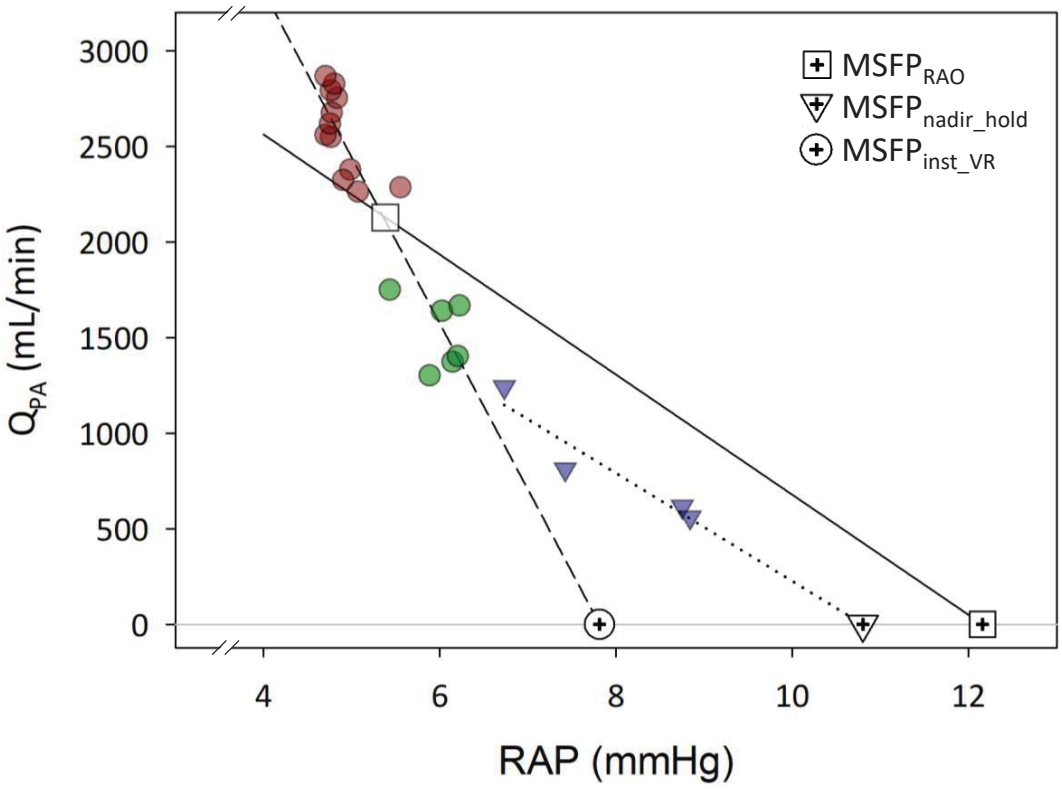
The upper panel shows three tidal inflations followed by an inspiratory hold maneuver to a plateau pressure of 15 cm H_2O (animal 5 in *Euvolemia*). The lower panel focus on the hold breath. RAP and flow in all vessels change in opposite directions. In response to the inspiratory hold maneuver, caval vein flows drop immediately. In this particular case, Q_{PA} nadir beat follows two beats later and flow gradually restores over the next eight beats towards a new steady state. Part of the data has been previously published (2).

669 **Appendix I: Adapting the Parkin equation to pigs**

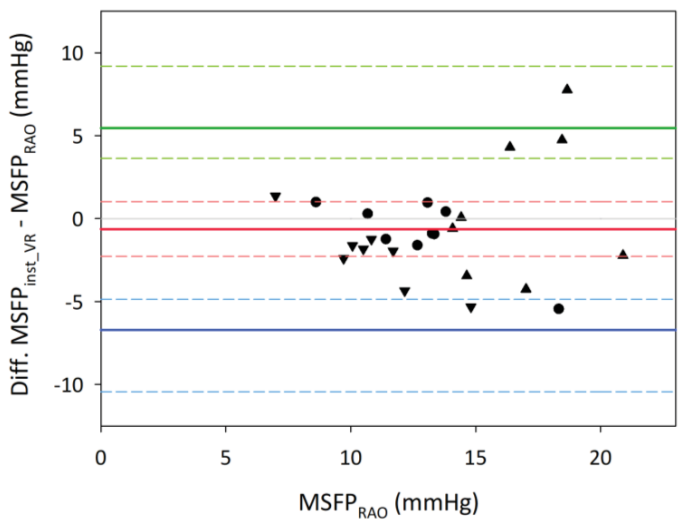
670 Assuming a veno-arterial compliance ratio of 24:1, the $MSFP_a$ was calculated as
671 $0.96 \times RAP + 0.04 \times MAP + c \times CO$. All data entering calculations of $MSFP_a$ came from
672 steady-state conditions where Q_{PA} could be assumed to equal CO. 'c' is 0.96×venous
673 compartment resistance (R_v) and scales the flow component of $MSFP_a$ to fit the
674 subject. Assuming an arterio-venous resistance ratio of 25:1, R_v can be calculated as
675 SVR / (25+1), where SVR = (MAP-RAP) / Q_{PA}. To derive a valid 'c' for each individual
676 animal, we used the SVR at *Euvolemia* calculated from mean values of 10 beats
677 during tidal ventilation preceding RA balloon inflation. At each experimental condition,
678 $MSFP_a$ was then calculated using the 'c' from *Euvolemia*. As changing experimental
679 conditions might affect R_v and/or the arteriovenous resistance ratio, we also
680 assessed the impact of *changing* R_v on $MSFP_a$ (in absolute and relative terms), by
681 comparing the value calculated at *Euvolemia* to a 'c' calculated anew from the current
682 SVR at each time point.

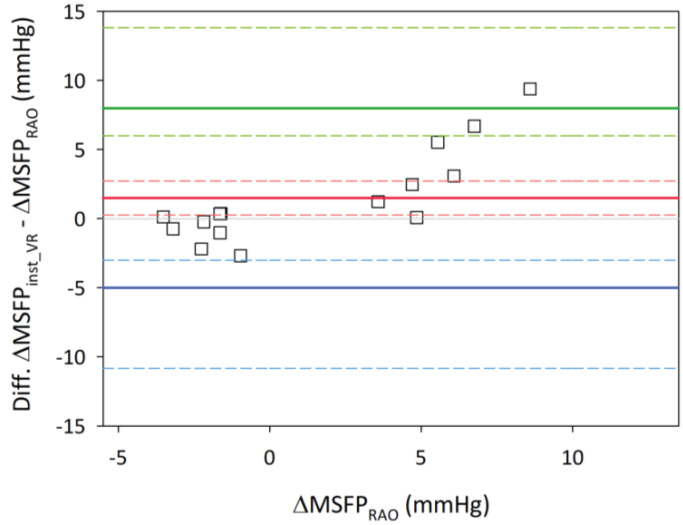
683 **Appendix II: Impact of changing venous resistance on $MSFP_a$**

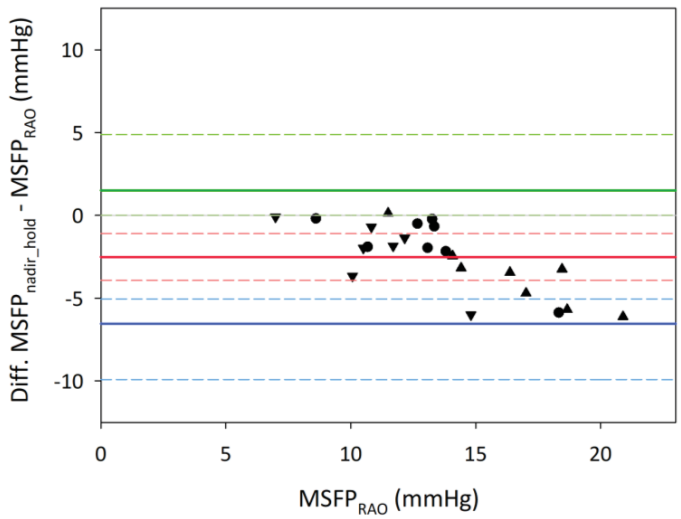
684 Factor 'c' derived from SVR at *Euvolemia* was 0.78 ± 0.18 $mmHg \times min \times L^{-1}$ (range
685 0.51-1.02). The corresponding values calculated from SVR at *Bleeding* and
686 *Hypervolemia* were (n=8) 0.77 ± 0.22 and 0.63 ± 0.19 $mmHg \times min \times L^{-1}$ respectively
687 (main effect of volume state p=0.002; pairwise comparisons significant between
688 *Euvolemia-Hypervolemia* and *Bleeding-Hypervolemia* at $p \leq 0.017$). The impact of per-
689 condition-updated values for 'c' on calculated values for $MSFP_a$ was -0.02 ± 0.26 and
690 -0.48 ± 0.30 mmHg in *Bleeding* and *Hypervolemia*, respectively – i.e. the model
691 assumption of a non-changing R_v overestimated the dynamic filling analog with 0.48
692 mmHg (or 3.8 ± 2.3%) in *Hypervolemia*.

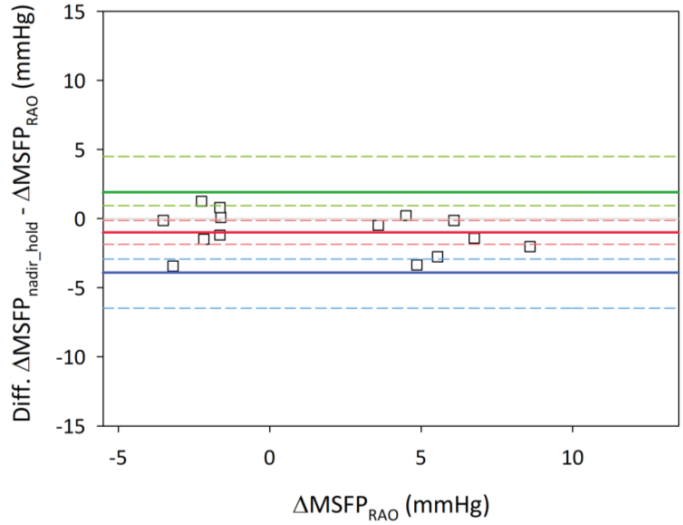


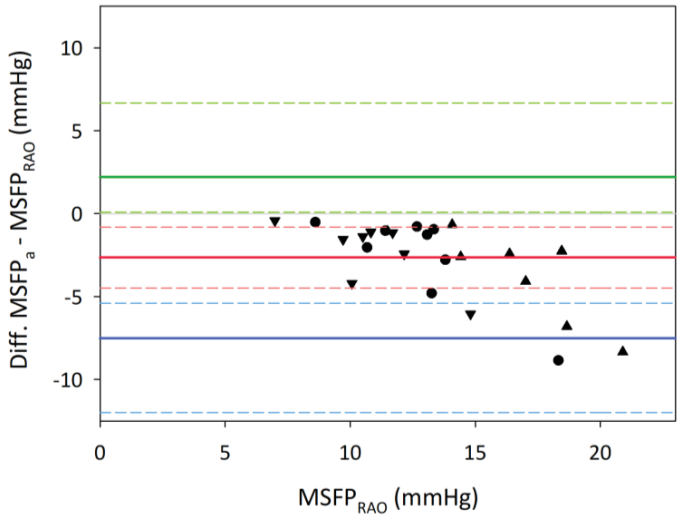
- Mean value of 10 beats during tidal ventilation
- Inspiratory beat – flow decreased from vessel distention
- Expiratory beat – flow increased from vessel recoil
- Nadir Q_{PA} beat from inspiratory hold to four airway-pressure levels
- Venous return reference line
- Linear regression from instantaneous venous return data-pairs
- Linear regression from nadir Q_{PA} from inspiratory hold

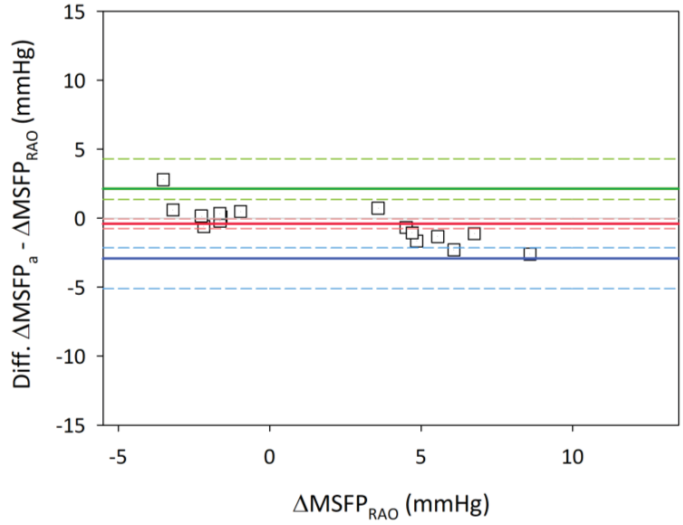


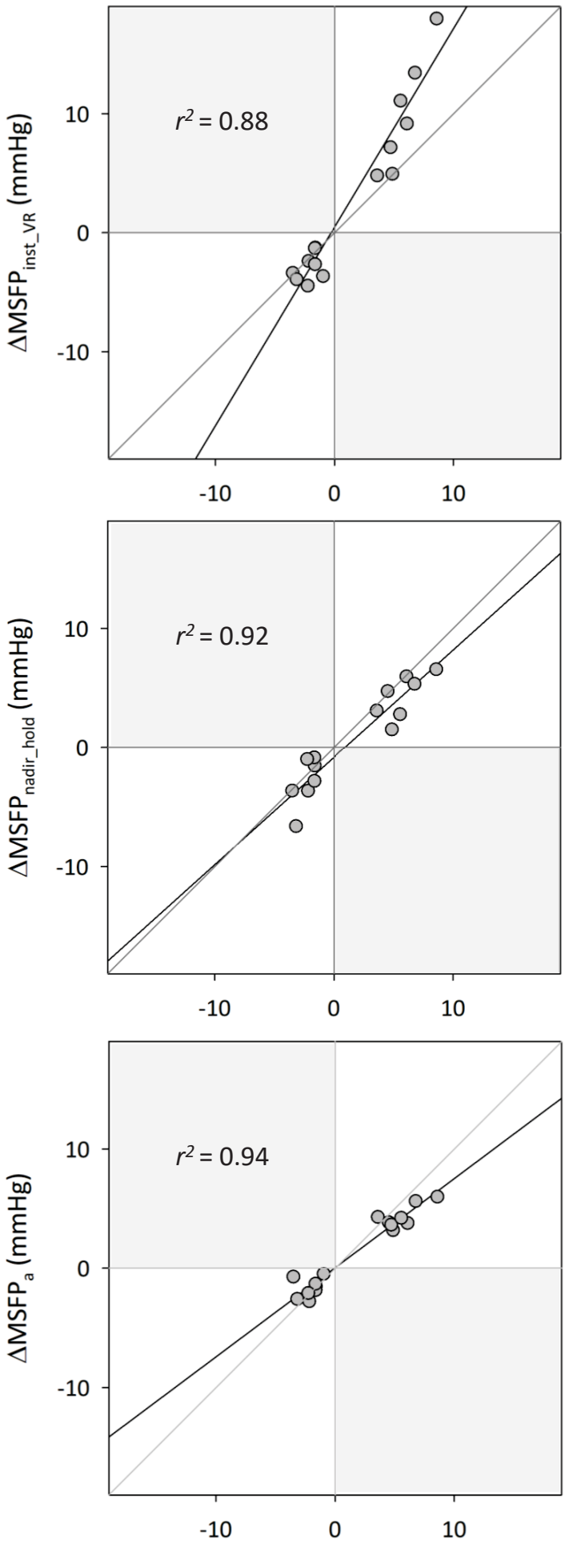












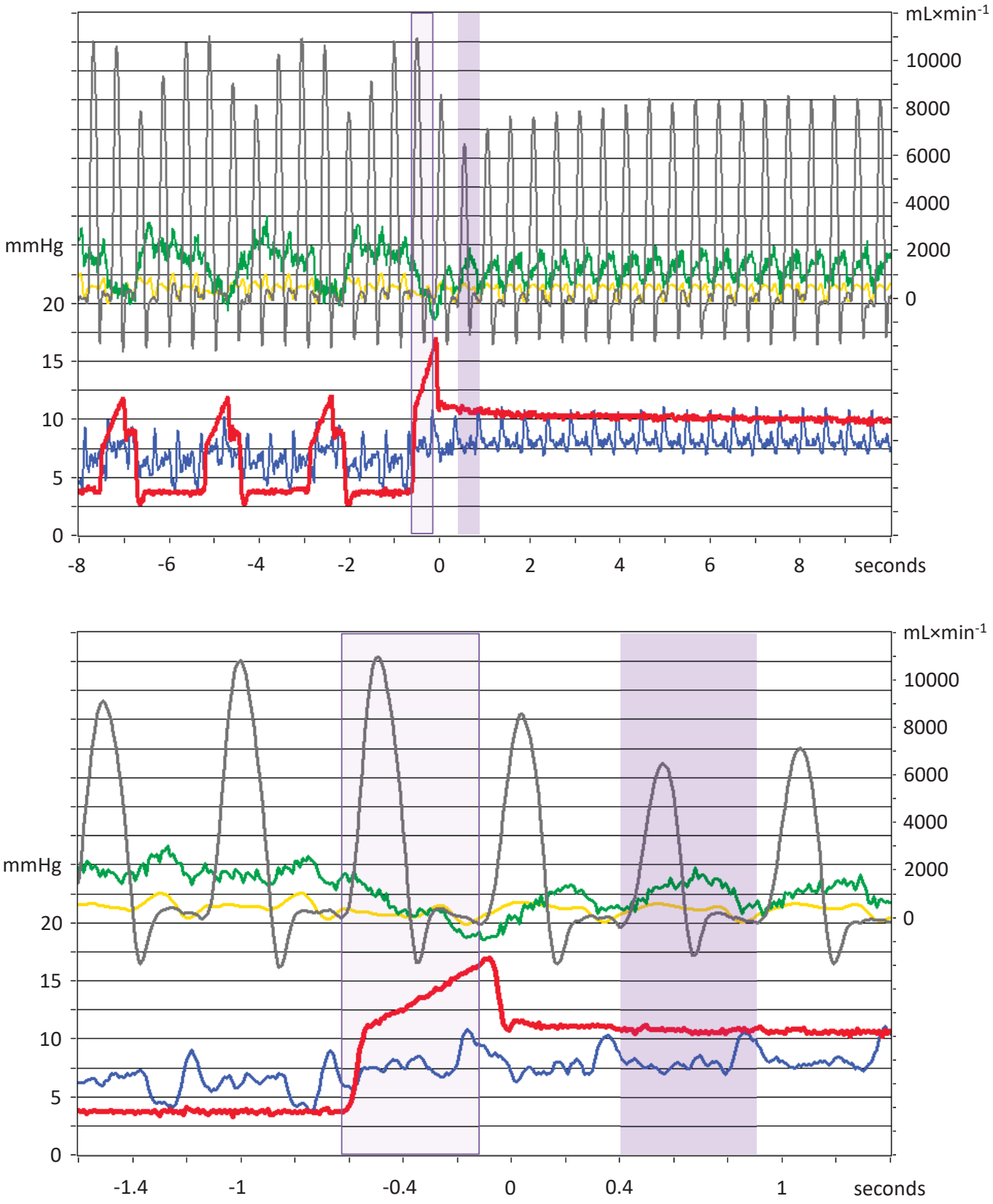


Table I: Hemodynamics over changing volume states

	Euvolemia (n=8)	**Bleeding** (n=8)	**Hypervolemia** (n=8)	*p*
Heart rate: min^{-1}	102 ± 21	129 ± 31	106 ± 20	<0.0005
Q_{PA}: $L \times min^{-1}$	2.80 ± 0.46	2.20 ± 0.42	3.27 ± 0.42	<0.0005
RAP: mmHg	5.9 ± 1.6	5.1 ± 1.7	8.2 ± 1.9	<0.0005
MAP: mmHg	60 ± 10	50 ± 11	63 ± 12	0.003

Data is mean ± SD. Variables were calculated as a mean of 10 cardiac cycles before right atrial balloon occlusion during volume controlled ventilation; tidal volume 300 mL (7.7 ± 0.3 $mL \times kg^{-1}$) at PEEP 5. Q_{PA}: pulmonary artery blood flow; RAP: right atrial pressure; MAP: mean arterial pressure. Repeated measurements ANOVA, within-subjects factor volume state. Part of these data have been previously published (1).

Table II: Mean systemic filling pressure over changing volume states

	n	**Euvolemia:** mmHg	**Bleeding:** mmHg	**Hypervolemia:** mmHg	*p*
$MSFP_{RAO}$	8	13.0 ± 2.8	10.8 ± 2.2[a, b]	16.4 ± 3.0[c]	<0.0005
$MSFP_{inst\_VR}$	7	12.6 ± 1.3	8.7 ± 0.9[a, b]	18.5 ± 5.2	0.003
$MSFP_{nadir\_hold}$	7	11.6 ± 1.6	8.8 ± 1.6[a, b]	13.1 ± 1.4	<0.0005
$MSFP_a$	8	10.2 ± 1.8	8.6 ± 1.6[a, b]	12.9 ± 1.7[c]	<0.0005

Data is mean ± SD. MSFP: mean systemic filling pressure; $MSFP_{RAO}$: measured as the mean of SVC and IVC pressures during 3 s of venous plateau at zero-flow caused by right atrial balloon occlusion; $MSFP_{inst\_VR}$: zero-flow extrapolation of the linear regression from beat-to-beat data-pairs consisting of single beat Q_{PA} matched with RAP from the preceding beat (mean values) over three respiratory cycles of tidal ventilation (instantaneous venous return curve). A total of 24 measurements met the r^2>0.7 criteria [median (range); r^2 0.896 (0.493-0.977)]; $MSFP_{nadir\_hold}$: zero-flow extrapolation of the linear regression from data-pairs consisting of the mean values from nadir single beat Q_{PA} matched with RAP from the preceding beat caused by inspiratory hold to four levels of airway pressure. A total of 23 measurements met the r^2>0.7 criteria [median (range); r^2 0.960 (0.628-0.999)]; $MSFP_a$: dynamic analogue of static MSFP calculated as $MSFP_a=0.96\times RAP+0.04\times MAP+c\times Q_{PA}$, using mean values from 10 beats during tidal ventilation before right atrial balloon occlusion (for the derivation of 'c', please see Appendix I). Repeated measurements ANOVA, within-subject factor volume state and pairwise comparisons with Bonferroni adjustment. Significant difference marked as: [a] Bleeding *vs*. Euvolemia, [b] Bleeding *vs.* Hypervolemia, [c] Hypervolemia *vs.* Euvolemia. As a reference, venous return driving pressure (VRdP) was 6.8 ± 2.4 mmHg in *Euvolemia*. Part of the data on the reference method $MSFP_{RAO}$ has been previously published (1).

Table III: Paired comparisons of methods over – all volume states combined

Method	**n** (pairs)	**MSFP:** mmHg	*p*
$MSFP_{inst\_VR}$	24	12.8 ± 5.0	0.123†
$MSFP_{RAO}$		13.4 ± 3.5	
$MSFP_{nadir\_hold}$	23	11.1 ± 2.3	<0.0005
$MSFP_{RAO}$		13.6 ± 3.5	
$MSFP_{a}$	25	10.5 ± 2.4	<0.0005
$MSFP_{RAO}$		13.3 ± 3.4	

Data is mean ± SD. Paired t-tests (†or Wilcoxon signed ranks test where appropriate). Part of the data on the reference method $MSFP_{RAO}$ has been previously published (1).

Table IV: Effect of method and volume state on estimates of MSFP

	n	**Euvolemia:** mmHg	**Bleeding:** mmHg	**Hypervolemia:** mmHg	Method	Volume state	Inter-action
$MSFP_{inst\_VR}$	7	12.6 ± 1.3	8.7 ± 0.9	18.5 ± 5.2	0.396	0.001	0.020
$MSFP_{RAO}$		13.6 ± 2.3	11.4 ± 1.7	17.1 ± 2.4			
$MSFP_{nadir\_hold}$	7	11.6 ± 1.5	8.8 ± 1.6	13.1 ± 1.4	0.011	<0.0005	0.020
$MSFP_{RAO}$		13.3 ± 2.8	11.0 ± 2.4	16.7 ± 3.1			
$MSFP_a$	8	10.2 ± 1.8	8.6 ± 1.6	12.9 ± 1.7	0.013	<0.0005	0.008
$MSFP_{RAO}$		13.0 ± 2.8	10.8 ± 2.2	16.4 ± 3.0			

Data is mean ± SD. Repeated measurements ANOVA, within-subject factors method and volume state. Part of the data on the reference method $MSFP_{RAO}$ has been previously published (1).

Table V: *Post hoc* analysis: paired method comparisons for the volume conditions

	n	**Euvolemia:** mmHg	*p*		**Bleeding:** mmHg	*p*		**Hypervolemia:** mmHg	*p*
$MSFP_{inst\_VR}$	9	12.0 ± 1.6	0.247	8	8.7 ± 0.9	0.019	7	18.5 ± 5.2	0.424
$MSFP_{RAO}$		12.8 ± 2.7			10.8 ± 2.2			17.1 ± 2.4	
$MSFP_{nadir\_hold}$	8	11.3 ± 1.8	0.012†	7	8.8 ± 1.6	0.026	8	12.8 ± 1.5	0.001
$MSFP_{RAO}$		13.0 ± 2.8			11.0 ± 2.4			16.4 ± 3.0	
$MSFP_{a}$	8	10.2 ± 1.8	0.029	8	8.6 ± 1.6	0.012	8	12.9 ± 17	0.008
$MSFP_{RAO}$		13.0 ± 2.8			10.8 ± 2.2			16.4 ± 3.0	

Data is mean ± SD. Paired t-tests (†or Wilcoxon signed ranks test where appropriate) for comparison between methods. As a consequence of Bonferroni correction for multiple testing (tests performed in three volume states), statistical significance should be accepted only at $p<0.017$. Part of the data on the reference method $MSFP_{RAO}$ has been previously published (1).

Table VI: Bland-Altman analysis

	n (pairs)	**Bias (95% CI):** mmHg	**LoA:** mmHg	**95% CI lower LoA:** mmHg	**95% CI upper LoA:** mmHg	**SD_{diff} ± SE:** mmHg	**ICC ± SE:**
$MSFP_{inst\_VR}$ *vs.* $MSFP_{RAO}$	24	-0.6 (-2.3 to 1.0)	-6.7 to 5.5	-10.4 to -4.9	3.6 to 9.2	3.1 ± 0.5	0.15 ± 0.22
$MSFP_{nadir\_hold}$ *vs.* $MSFP_{RAO}$	23	-2.5 (-3.9 to -1.1)	-6.5 to 1.5	-9.9 to -5.0	0.0 to 4.9	2.1 ± 0.4	0.50 ± 0.19
$MSFP_a$ *vs.* $MSFP_{RAO}$	25	-2.7 (-4.5 to -0.8)	-7.5 to 2.2	-12.0 to -5.4	0.1 to 6.7	2.5 ± 0.6	0.87 ± 0.06

Comparison of methods, with CIs adjusted for repeated measurements over volume states. Bias: grand mean of test method – reference method; LoA: Limits of Agreement; SD_{diff}: standard deviation of differences with its standard error; ICC: intraclass correlation (ratio of between-subjects variance to total variance). Part of the data on the reference method $MSFP_{RAO}$ has been previously published (1).

Table VII: Bland-Altman analysis for changes in MSFP

	n (pairs)	**Bias (95% CI):** mmHg	**LoA:** mmHg	**95% CI lower LoA:** mmHg	**95% CI upper LoA:** mmHg	**SD_{diff} ± SE:** mmHg	**ICC ± SE:**	r^2
$MSFP_{inst\_VR}$ *vs.* $MSFP_{RAO}$	14	1.5 (0.3 to 2.7)	-5.0 to 8.0	-10.8 to -3.0	6.0 to 13.8	3.3 ± 0.7	-0.68 ± 0.82	0.88
$MSFP_{nadir\_hold}$ *vs.* $MSFP_{RAO}$	15	-1.0 (-1.9 to -0.1)	-4.0 to 1.9	-6.5 to -2.9	0.9 to 4.5	1.5 ± 0.3	-0.19 ± 0.47	0.92
$MSFP_a$ *vs.* $MSFP_{RAO}$	16	-0.4 (-0.7 to -0.0)	-2.9 to 2.1	-5.1 to -2.1	1.4 to 4.3	1.3 ± 0.3	-0.80 ± 0.81	0.94

Assessment of method tracking ability, comparing Δ[test method] to Δ[reference method] between Euvolemia and Bleeding and Bleeding and Hypervolemia, with CIs adjusted for repeated measurements. Bias: grand mean of Δ[test method] – Δ[reference method]; LoA: Limits of Agreement; SD_{diff}: standard deviation of differences with its standard error; ICC: intraclass correlation (ratio of between-subjects variance to total variance); r^2: proportion of variance (Pearson correlation coefficient squared). As a reference, venous return driving pressure (VRdP) was 6.8 ± 2.4 mmHg in *Euvolemia*. Part of the data on the reference method $MSFP_{RAO}$ has been previously published (1).