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Stroke volume variation and pulse pressure variation measured at pulmonary arterial level versus pulse pressure variation measured at systemic arterial level: an exploratory study

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Abstract: *Problem:* Optimized fluid management reduces morbidity and mortality in major operations, including cardiac surgery (1, 2). Validated dynamic parameters were developed to predict fluid responsiveness but have limitations (3-5). This study explores the potential added value of stroke volume variation and pulse pressure variation measured at pulmonary arterial level in predicting fluid responsiveness (6).
Methods: In twenty adult patients undergoing coronary artery bridging and/or aortic valve replacement, the systemic and pulmonary arterial (SA and PA) pressure curves were stored using Datagrabber software. A custom-made MATLAB code automatically analyzed the pulse pressures, from which the SA and PA pulse pressure variations (PPV_SA and PPV_PA) were calculated. Simultaneously, stroke volumes in the pulmonary artery were measured and PA stroke volume variation (SVV_PA) was calculated. These three parameters were determined in both closed and open chest situations and further analyzed using RStudio software.
Results: No correlation could be established between SVV_PA and fluid responsiveness as defined by PPV_SA above 12% (3). In the case of PPV_PA, a mild correlation was seen with the above-mentioned fluid responsiveness, with an R^2 of 25%. Bland Altman analysis of PPV_PA and PPV_SA showed proportional bias with broad limits of agreement. ROC curve analysis attempted to determine a new cutoff value for PPV_PA, which was 33% (sensitivity 100%, specificity 86%).
Conclusions: SVV_PA could not be correlated with fluid responsiveness as previously defined. PPV_PA appears to be mildly correlated with fluid responsiveness and has a relatively faster increase in variation than PPV_SA. Therefore, a new fluid responsiveness cutoff for PPV_PA is proposed. Further research is needed to confirm these findings and to explore further the sensitivity and specificity regarding fluid responsiveness.

Keywords: Fluid therapy; stroke volume; pulmonary artery; hemodynamic monitoring; cardiac output.

Introduction

Major changes in intravascular volume status are often seen during major/cardiac surgery. These changes can be so great as to trigger a systemic inflammatory response resulting in microcirculatory failure, tissue hypoxia, and organ dysfunction. Early goal-directed therapy (EGDT) aims a rapid identification and treatment of these pathological changes and can reduce the number of postoperative complications and admission days in cardiac surgery (7). One of the cornerstones of this hemodynamic management is effective fluid supplementation. Through fluid administration, one aims to optimize tissue perfusion and oxygenation by maintaining or improving stroke volume (SV) and cardiac output (CO). However, not every fluid administration increases CO, resulting in a concept called fluid responsiveness (1, 2).

Fluid responsiveness can be explained by the Frank-Starling curve, which shows the relationship between preload and stroke volume. The steep segment of the curve shows the preload reserve, in exchange for a small increase in preload a large increase in stroke volume is seen (responder). Instead, when operating on the flat segment of the curve, a large increase in preload results in a small increase in stroke volume (no responder).

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This study was approved by the independent medical ethics committee of Ghent University Hospital and registered under the number EC/2017/0902. Informed consent was obtained from all patients by means of a written informed consent, in accordance with good clinical practice standard and the Declaration of Helsinki.

Predicting fluid responsiveness

Given the potentially beneficial and harmful effect of fluid administration, correctly predicting fluid responsiveness is critical (8).

Static parameters

Historically, static parameters were used for this purpose. Static parameters are parameters that attempt to determine preload by means of a measured unchanging value.

Parameters that attempt to estimate left ventricular filling pressures are examples of static parameters. Classically, filling pressures such as central venous pressure (CVD) and pulmonary artery wedge pressure (PCWP) are used for this purpose. However, factors such as an increase in intra-thoracic pressures and stiffening of the ventricle, can lead to an over- or underestimation of the actual preload. Other examples of static parameters, bypassing these problems, are techniques to estimate end-diastolic volume, such as thermodilution and ultrasound-determined end-diastolic area calculation. However, cardiovascular response to filling depends not only on the initial preload or increase in preload, but also on the patient's ventricular function and the morphology of the Frank-Starling curve. Static parameters of preload, however accurate, are limited in this way. If it is unknown what the patient's ventricular function curve is and at which region of the curve the patient is operating, no predictions about fluid responsiveness can be made (5, 9).

Therefore, static parameters do not appear to provide good prediction of fluid responsiveness, even when examining the trend and/or the effect of a fluid bolus (8).

Dynamic parameters

Dynamic parameters provide an estimate of cardiac function during transient changes in preload. By quantifying the fluctuations in cardiac function due to changes in preload, they allow estimation of the region of the Frank-Starling curve at which the ventricles are located (9).

Most dynamic parameters are based on the heart-lung interactions in positive pressure ventilated patients and their effects on the left ventricle.

These heart-lung interactions can be summarized into 4 major elements.

Delta down:

1: Decrease in venous return due to compression on the vena cava and an increase in right atrial pressure.

2: Increased alveolar pressure, transmitted to the pulmonary capillaries, causing increased right ventricular afterload.

The result is a decrease in right ventricular stroke volume that takes place in the inspiratory phase. Because of the time it takes for the blood to flow through the lungs (pulmonary transit time), this causes a delayed reduction in left ventricular stroke volume in the expiratory phase.

Delta up:

3: Increased left ventricular preload due to squeezing of the pulmonary vascular bed during inspiration.

4: Left ventricle afterload reduction due to increased extracardiac pressure (10).

As a result, left ventricle stroke volume increases in the inspiratory phase.

These ventilations induced variations in stroke volume are more pronounced when the ventricles operate on the steep part of the Frank-Starling curve, making them likely to be fluid responsive (4, 5, 9, 11).

Stroke volume variation and pulse pressure variation measured at the systemic arterial level

Two of the first and most validated dynamic parameters are stroke volume variation and pulse pressure variation measured at the systemic arterial level.

Despite the high degree of evidence in predicting fluid responsiveness, there are important restrictions in their use:

– Mechanical ventilation with inadequately large tidal volumes (< 8ml per kg of ideal body weight). (*1)

– Presence of spontaneous respiratory activity. (*2)

– Decreased lung compliance (e.g. ARDS). (*3)

– Intra-abdominal hypertension. (*4)

– Open chest surgery. (*5)

(*1-5) Dynamic parameters require an unequivocal, significant intra-thoracic pressure change to obtain the necessary sensitivity (3, 4, 9, 11-14).

– Arrhythmias and/or extrasystoles, due to the difference in diastolic filling time, cause varying

stroke volumes which therefore are no longer unambiguously attributable to the difference in preload (15).

– At a heart rate respiratory rate less than or equal to 3.6, a point is reached where the number of heartbeats per respiratory cycle is insufficient to cause stroke volume variations (16).

– In right ventricle failure, the cyclic increase in right ventricular afterload, together with the inability of the right ventricle to empty against an increased afterload, can cause stroke volume variability (9).

Dynamic parameters at pulmonary arterial level

The validated predictors of fluid responsiveness are measured at systemic arterial level but have limitations. Can the analysis of heart-lung interactions in the pulmonary arterial system add value?

Based on experimental studies on pigs, Kubitz et al. propose right ventricular stroke volume variation as a dynamic parameter for fluid responsiveness in the presence of right heart failure (6).

Right ventricular stroke volume can be measured via transesophageal ultrasound; a tool with increasing use in cardiac surgery and high-risk noncardiac surgery (17).

Using doppler analysis, the maximum blood velocity at the level of the pulmonary artery can be plotted as a function of time. The area under the curve is called velocity time integral (VTI) and represents stroke distance. Given that the cross-sectional area of the pulmonary artery does not change significantly during systole, its product with stroke distance (VTI) represents stroke volume (17, 18).

Purpose of the study

The purpose of this study is to conduct exploratory work on the added value of stroke volume variation and pulse pressure variation measured at pulmonary arterial level in predicting fluid responsiveness.

Materials and Methods

In this study, a sub analysis was made of the data available from a previous study investigating right ventricular monitoring. This original study was approved by the independent medical ethics committee of Ghent University Hospital and registered under the number EC/2017/0902. Informed consent was obtained from all patients by means of a written informed consent, in accordance with good clinical practice standard and the Declaration of Helsinki.

Study Design

In this prospective, observational, non-blinded, non-randomized study, patients undergoing cardiac surgery were screened for inclusion for 9 months (October 2017 through January 2018).

Inclusion criteria:

– Elective coronary artery bypass grafting and/or aortic valve replacement

– Signed informed consent

Exclusion criteria:

– Atrial fibrillation

– Latex allergy (contraindication Swan Ganz catheter placement)

– Pregnancy

– Minors

– Surgery in urgent setting

– Right ventricular failure

– Refusal of participation by the patient

Anesthesia

Anesthesia followed a standardized protocol, induction with fentanyl (3microgram/kg), propofol (titrated, target 1mg/kg) and rocuronium (1mg/kg). Anesthesia maintenance with sevoflurane, continuous muscle relaxation with cisatracurium (0.12mg/kg/hr).

Peroperative monitoring was provided via:

– 5-lead ECG, saturation measurement, non-invasive blood pressure measurement at upper arm level

– Temperature measurement, rectal and esophageal

– EEG monitoring (bispectral index monitoring) with NeuroSENSE NS-901

– NIRS monitoring (Near-Infrared Spectroscopy with NIRO- 200NX)

– 4 lumen central venous catheter (7F, 16cm from Arrow) with continuous CVP measurement

– Transesophageal ultrasound with Philips Epiq 7 with 3D TEE probe X7-2T

– System arterial invasive pressure measurement (4F, 25 cm, Vygon catheter) at the level of the arteria radialis or brachialis.

– Pulmonary arterial invasive pressure measurement (7.5F, 110 cm, Edwars Lifescience catheter)

No standardized ventilation protocol was used in the original study, a post hoc analysis of the ventilation settings was made earlier by another study group.

Mean tidal volumes were 8.7 and 9.3 ml/kg ideal body weight, according to the retained definition of ideal body weight (Broca and Lemmens formula, respectively). The respiratory rate averaged 14 times per minute and the positive end-expiratory pressure averaged 5 cm H2O.

Within the study population, one patient underwent a solitary aortic valve replacement, one patient underwent a combined aortic valve replacement/CABG, the remaining patients all underwent CABG. All patients had normal to slightly decreased cardiac function preoperatively, echographically assessed.

Data Collection

Specific observational periods were implemented after induction, in which the best possible high-esophageal long axis view of the pulmonary artery was sought.

For approximately one-minute, pulsed-wave doppler images were taken of the pulmonary artery (Figure 1A).

Simultaneously, the systemic arterial and pulmonary arterial (SA and PA) pressure as well as the accompanying ECG were digitally stored, using the software program Datagrabber,

Before and after these observational periods, flush codes were implemented in the SA pressure curve (Figure 1B). These flush codes were registered in the study logbook, along with the corresponding ultrasound images.

Data Analysis

Each observational period (approximately 1 min) consisted of several sequences of ultrasound images (approximately 6 heartbeats). At each heartbeat, the contour of the maximum velocity curve was manually identified and VTI was calculated using pulse contour analysis (Figure 1A). Each observational period was assigned an identity and registered in the study logbook, also specifying whether the observation occurred during closed or opened chest.

Using RStudio, interactive figures of the SA and PA pressure curves were made. The flush codes were identified and linked to the corresponding observational period.

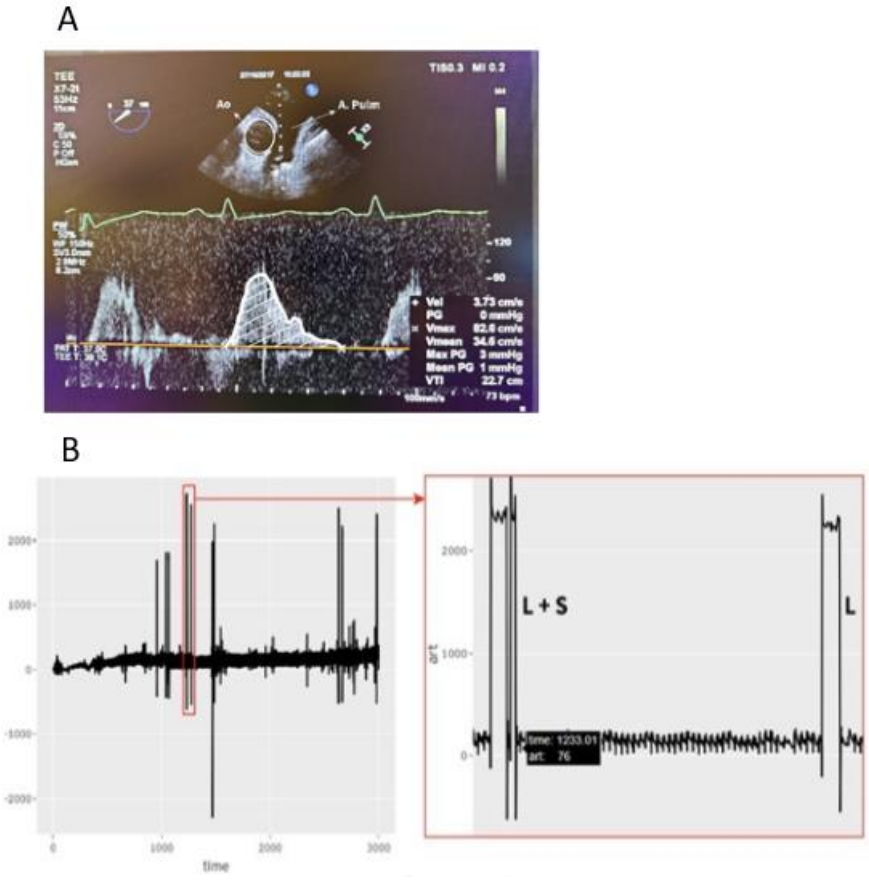

Figure 1. — Illustrations from study logbook.
A: Example of pulsed-wave doppler images of the A. pulmonalis (A. Pulm). The maximum velocity curve was traced to calculate the area under the curve (VTI). The aorta (Ao) is also shown. B: Example of interactive figure with identification of observational periods using flush codes. In this example, one long (L) + short flush (S) indicates the beginning and one long flush (L) the end of an observational period.

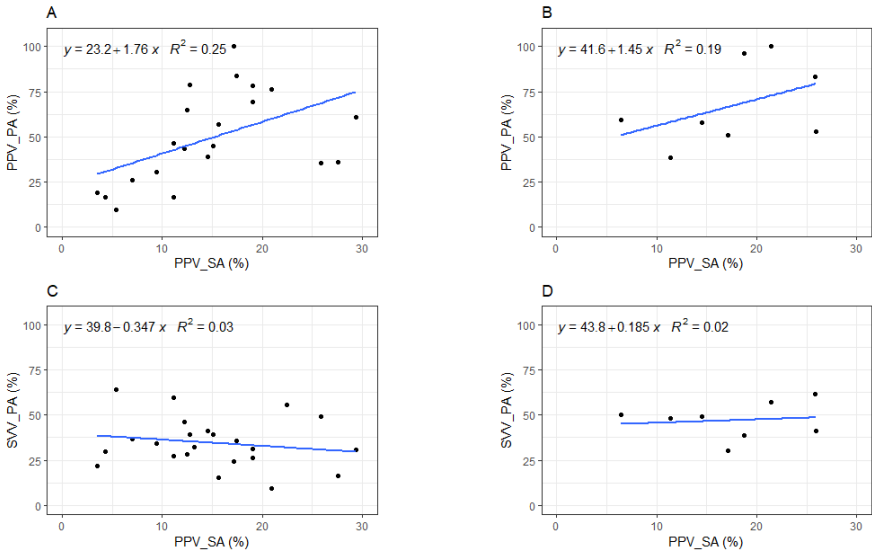

Figure 2. — Correlation plots
A: Correlation plot between PPV_SA and PPV_PA in closed chest. B: Correlation plot between PPV_SA and PPV_PA in open chest. C: Correlation plot between PPV_SA and SVV_PA in closed chest. D: Correlation plot between PPV_SA and SVV_PA in open chest.

An internally written MATLAB code analyzed the SA pressure curve and automatically detected the systolic and diastolic blood pressure for each heartbeat.

These data were added to the original database in RStudio, whereafter the entire process was repeated for the PA pressure curve.

All subsequent data manipulation and analysis was done using RStudio unless otherwise noted.

To ensure the completion of at least one respiratory cycle, observational periods with three or fewer measurements were removed from the database.

The stroke volume was determined by the following equation, with r being the radius of the pulmonary artery:

$$SV = VTI.\pi r^2$$

Equation 1 : Stroke volume

It was assumed that, within the time frame of surgery, the radius of the pulmonary artery did not undergo significant changes during a heartbeat. Therefore, stroke volume was calculated using the mean PA radius (19).

Next, stroke volume variation (SVV) was determined using the following equation:

$$SVV = \frac{SV\ max - SV\ min}{SV\ mean}$$

Equation 2 : Stroke volume variation

Where SV (max), SV (min) and SV (mean) represent the maximum, minimum and average stroke volumes, respectively, within a given observation.

Pulse pressure variation (PPV) for both SA and PA arterial systems were calculated using the following equation:

$$PPV = \frac{P\ max - PP\ min}{PP\ mean}$$

Equation 3: Pulse pressure variation

Where PP (max), PP (min), and PP (mean) represent the maximum, minimum, and average pulse pressures, respectively, within a given observation.

Thus, in a total of twenty patients, three parameters, PA stroke volume variation (SVV_PA), PA pulse pressure variation (PPV_PA) and SA pulse pressure variation (PPV_SA), were calculated in both closed and open chest.

Results

Correlation plots

Correlation graphs were created by plotting SVV_PA and PPV_PA against PPV_SA, both in situations with closed chest, where the PPV_SA constitutes the gold standard and by extension in situations with open chest (Figure 2).

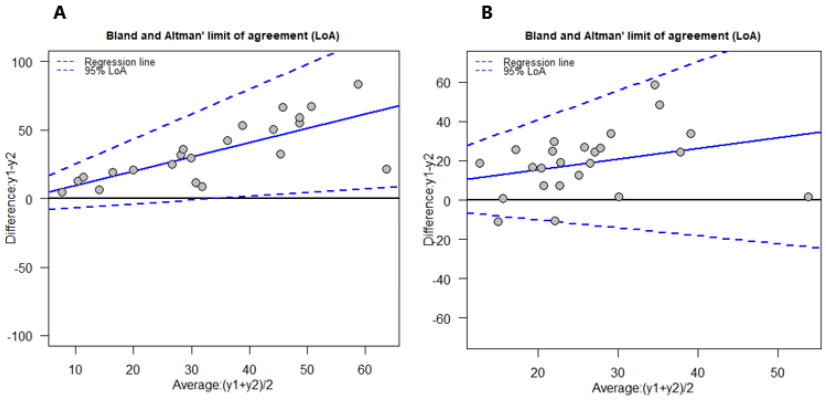

Figure 3. — Bland- Altman plots
A: Bland- Altman plot of PPV_SA and PPV_PA. B: Bland- Altman plot of PPV_SA and SVV_PA.

Analysis of the correlation plots show no correlation between SVV_PA and PPV_SA, whereas some correlation can be suspected when comparing PPV_PA and PPV_SA. The coefficient of determination is 25% and 19% in closed and open chest, respectively.

Bland-Altman plots

A second analysis was made using Bland-Altman plots to analyze the level of agreement between the different methods of measurement (Figure 3).

When comparing PPV_SA and PPV_PA, a phenomenon called proportional bias can be seen. Meaning, as variability increases there is an increasing difference in value between the two methods of measurement. This phenomenon is also observed when comparing SVV_PA and PPV_SA. However, in this situation the intersection with the y-axis does not approach zero, suggesting a combination of proportional bias and constant bias.

Boxplots

Boxplot analysis show the variability of each measurement method for each patient, both in closed and open chest (Figure 4).

Variation levels seem to be higher when measured at PA level (both SVV and PPV) than at SA level. Thus, the classical cutoff values to predict fluid responsiveness at SA level presumably cannot be used when measuring variability at PA level.

ROC curve

By means of receiver operating characteristic (ROC) curve analysis, new limits of fluid responsiveness for the latter measurement methods were investigated (Figure 5).

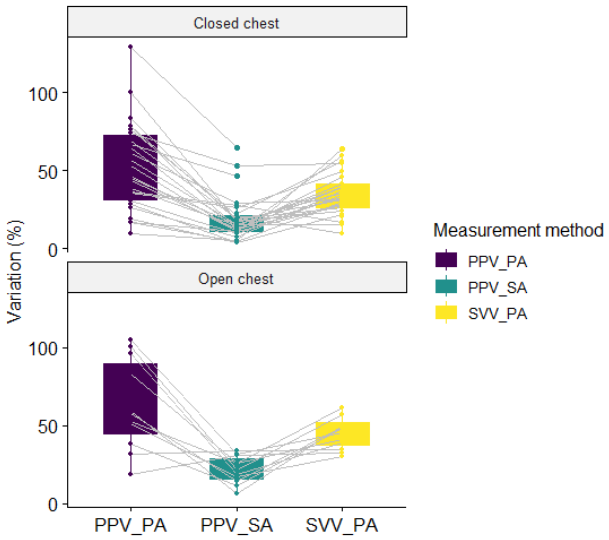

Figure 4. —Variability plotted by measurement method
Boxplot plotting variability by measurement method, showing trendlines for each patient, both for situations with closed and open chest.

ROC curves represent possible cutoff values with a trade-off between sensitivity and specificity. One way to determine the maximum potential effectiveness of the diagnostic marker is the Youden index (J). The Youden index represents the optimal limit when equal value is given to sensitivity and specificity (20).

Presence of disease was determined by presence of fluid responsiveness predicted by the golden standard, PPV_SA > 12%.

These analyses were only performed in situations where the gold standard is validated, being closed chest.

The cutoff value, according to the Youden Index (J), for predicting fluid responsiveness is 33

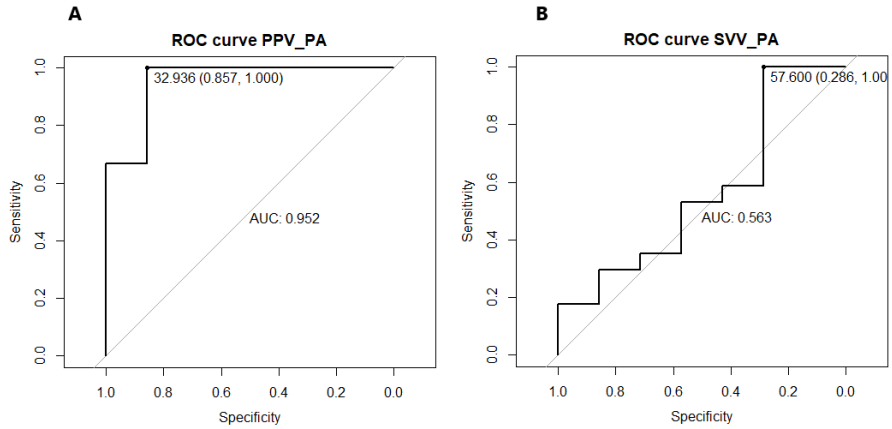

Figure 5. — ROC curves

A: ROC curve of PPV_PA compared with the gold standard PPV_SA (>12%) The new cutoff value, determined according to the Youden Index (J) is shown, along with the specificity and sensitivity, as well as the area under the curve (AUC). B: A: ROC curve of SVV_PA compared with the gold standard PPV_SA (>12%) The new cutoff value, determined according to the Youden Index (J) is shown, along with the specificity and sensitivity, as well as the area under the curve (AUC).

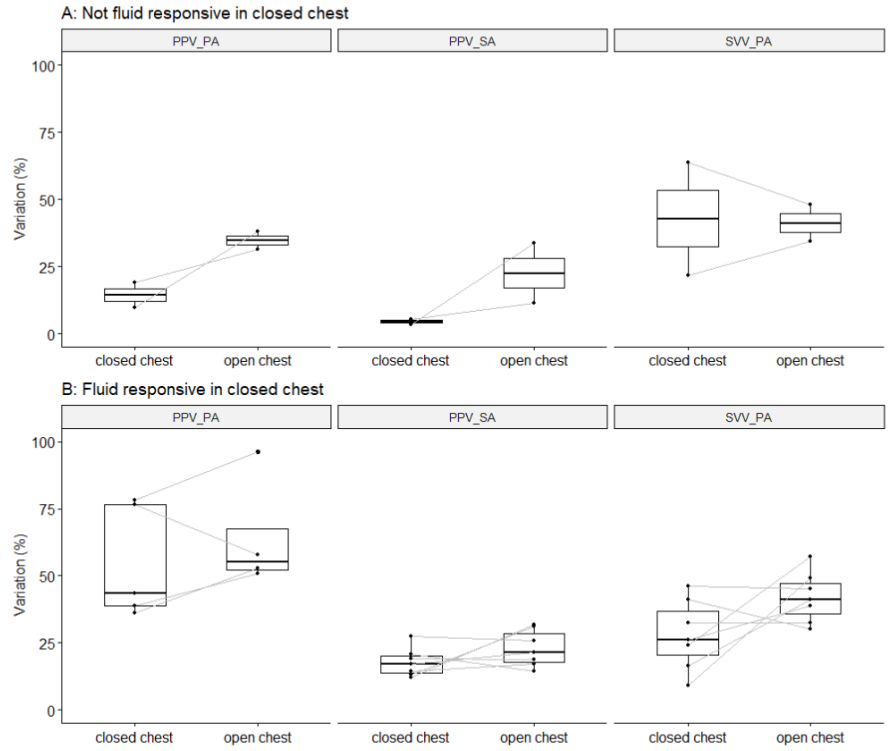

Figure 6. — Effect of opening thorax on the 3 parameters (PPV_PA, PPV_SA, SVV_PA)

A: Patients who are not fluid-responsive when the thorax is closed according to PPV_SA (≤12%). B: Patients who are fluid-responsive when the thorax is closed according to PPV_SA (>12%).

percent for PPV_PA (sens 100%, spec 86%) and 58 percent for SVV_PA (sens 100%, spec 29%). In the case of PPV_PA this corresponds to a positive predictive value (PPV) of 93.33% and negative predictive value (NPV) of 100%. In case of SVV_PA, the PPV is 0% and the NPV is 23.81%.

Effect of opening the chest

Finally, the effect of opening the thorax on the 3 different parameters (PPV_PA, PPV_SA, and SVV_PA) was evaluated (Figure 6). A distinction was made between patients who were considered

fluid responsive, according to the PPV_SA >12%. The graph shows an increasing trend in variability after opening the thorax for all parameters. In the case of both PPV_PA and PPV_SA, a preservation in "architecture" can be seen after opening the thorax. In other words, patients with low variability before opening the thorax retain low variability relatively to the patient population after opening the thorax.

Discussion

Situation in closed chest

PPV_PA

Although mild correlation can be seen between PPV_PA and PPV_SA, Bland-Altman plot analysis shows proportional bias between these parameters. This does not mean that PPV_PA cannot be a parameter of fluid responsiveness. It does confirm however that this parameter is not just a (more invasive) measurement method to calculate the exact same variable that can be obtained using PPV_SA.

Bland-Altman plots show a proportional bias, namely an increase in difference between the two measurement methods with increasing mean variation. These data suggest that the cutoff point between a responder and non-responder in PPV_PA is higher than the 12 percent generally used in PPV_SA.

A possible explanation can be the fact that the PA system has a low pressure, high compliance vascular bed. Pulse pressure is directly proportional to stroke volume and inversely proportional to arterial compliance. A small change in stroke volume will, in case of high arterial compliance, produce a larger difference in pulse pressure.

Consequently, PPV_PA may have higher sensitivity and/or specificity in predicting fluid responsiveness.

In this study, a way to propose a new cutoff point of PPV_PA on fluid responsiveness was developed. Further research in a larger patient population is needed to validate these findings.

SVV_PA

No correlation could be observed between SVV_PA and PPV_SA. This is an unusual finding since correlation could be shown with the surrogate parameter, PPV_PA.

However, SVV_PA is not a static value, variability is present. One possible explanation is that SVV_PA could be a manifestation of another clinical parameter. Kubitz et al. proposed SVV_PA as a predictor of fluid responsiveness in right ventricular failure. They induced right ventricular failure (50% increase in mean PA pressure) in 15 ventilated pigs and examined the effect of volume depletion and retransfusion on dynamic parameters. Their findings showed a change in variability of SA dynamic parameters that could not be correlated with fluid responsiveness, whereas SVV_PA could be (6).

No right ventricular failure was documented in this study, so this hypothesis was not further explored.

Another possible explanation may be an analytical error. Previous studies reported difficulties in using the velocity-time integral (VTI), measured in the left ventricular outflow tract, to determine stroke volume and cardiac output. Fixating the echo probe in the correct position over the entire time course of the measurement period can cause practical problems. This may result in an underestimation of flow rates over some or all heartbeats.

Furthermore, the use of the VTI is not reliable in the presence of subvalvular stenosis and/or the presence of pulmonary valve insufficiency (19). Given that a Swan-Ganz catheter was routinely placed in this study, iatrogenic pulmonary valve insufficiency was induced to some extent in each patient. It is not known to the investigators whether this iatrogenic induced insufficiency is clinically significant.

Finally, it is well known that tricuspid valve insufficiency affects forward stroke volume. Extensive literature review by the authors could not clarify whether this also affects stroke volume variation.

Further research is necessary to determine the added value of SVV_PA in predicting fluid responsiveness, the effect of right ventricular failure, and other clinically relevant phenomena.

Situation in open chest

In this study, increased variability is seen in all three studied parameters (PPV_PA, PPV_SA and SVV_PA), after opening the thorax. This contrasts sharply with what is known so far in literature, where a decrease in variability is expected after opening the thorax and reducing intra thoracic pressures.

This phenomenon could be explained by the fact that these two observational periods did not occur at the same time. Changes in intravascular volume between these two periods cannot be excluded,

but significant blood loss before cardiopulmonary bypass is unlikely and was not documented in this study. Moreover, the architecture seems to be preserved within the patient population. That is, patients with low variability before also appear to have low variability after opening the thorax, which adds to the credibility of the results.

Classically, the most important factor in heart-lung interactions contributing to prediction in fluid responsiveness is thought to be the effect of intra-thoracic pressure on right ventricular preload. If so, a decrease in variability is expected in the prediction parameters after opening of the thorax. In this patient population, in need of a CABG and/or aortic valve replacement, elements in the heart-lung interactions other than right ventricle preload may gain relative importance. Possibly, the loss of afterload reduction upon opening the thorax takes precedence in this cardiac-loaded patient population. The left ventricle may have difficulty emptying in the event of a sudden afterload increase, especially in the case of a pre-existing aortic valve stenosis.

Finally, it should be considered that these findings are based on a low number of registrations.

Further research is needed to confirm these findings, but the lack of a golden standard makes it difficult to make conclusive statements about fluid responsiveness in open chest. Therefore, preference is given to studies using a fluid bolus and assessing its effect on cardiac output.

Conclusion

This study investigated the added value of pulmonary arterial pulse pressure variation and stroke volume variation (PPV_PA and SVV_PA) in predicting fluid responsiveness in twenty patients. No correlation could be demonstrated between SVV_PA and fluid responsiveness, as determined by systemic arterial pulse pressure variation (PPV_SA) >12%. Further research is necessary to demonstrate whether the observed variability in SVV_PA is dependent on one or more explanatory parameters other than fluid responsiveness. Previous animal studies suggested the value of SVV_PA in predicting fluid responsiveness in right ventricular failure. However, this could not be verified in this study since no right ventricular failure was reported (6).

In closed thorax, mild correlation could be demonstrated between PPV_PA and fluid responsiveness, as determined according to PPV_SA >12%. Compared to PPV_SA, a relatively faster increase in variation was observed in this highly compliant vascular bed. Further investigation should reveal whether this may result in higher specificity and/or sensitivity of PPV_PA in predicting fluid responsiveness. It also means that cutoff values for PPV_PA and PPV_SA are not interchangeable. In this study, a proposal was made to determine a new cutoff value for PPV_PA. Further large-scale research is needed to sharpen this cutoff value with clinically relevant sensitivity and specificity.

Finally, in this study, an increase in variability was seen in all studied parameters (PPV_PA, PPV_SA and SVV_PA) after opening the thorax. To the authors' knowledge, this was not previously reported. Literature review suggests a decrease in variability after opening the thorax, due to an increase in preload of the right ventricle. Further investigation of these parameters and their relationship with fluid responsiveness in open chest is necessary. Given the lack of golden standard in this situation, preference is given to studies using fluid boluses and their effect on cardiac output.

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