Title:

Dynamic filling parameters in patients with atrial fibrillation:

Differentiating Rhythm induced from Ventilation induced variations in Pulse Pressure.

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Running head: Pulse Pressure Variation in Atrial Fibrillation

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**ABSTRACT:**

In patients with sinus rhythm, the magnitude of mechanical ventilation (MV) induced changes in pulse pressure (PP) is known to predict the effect of fluid loading on cardiac output. This approach however is not applicable in patients with atrial fibrillation (AF). We propose a method to isolate this effect of MV from the rhythm induced chaotic changes in PP in patients with AF.

In 10 patients undergoing pulmonary vein ablation for treatment of AF under general anesthesia, ECG and PP waveforms were analysed during apnea (T1) and during MV at tidal volumes of 8ml/kg (T2) and 12ml/kg (T3) respectively. In a first step, 3 mathematical models were compared in their ability to predict individual PP at T1. The best fitting model was then selected as the reference to quantify the effects of MV on PP in these patients.

A local polynomial regression model based on two preceding RR-intervals (LOC2) was found superior over the quadratic models to predict PP. LOC2 was therefore selected to quantify variations in PP induced by MV.

During T2 and T3, magnitude of PP deviations was related with the amplitude of tidal volume (mean bias error (SD) of -5 (6) and -8 (7) mmHg for T2 and T3 respectively; p = 0.003 repeated measures ANOVA). We conclude that LOC2, most accurately predicted rhythm-induced variations in PP. MV induced deviations in PP can be quantified and may therefore provide a method to study cardiopulmonary interactions in the presence of arrhythmia.

**NEW & NOTEWORTHY:** (max 50 words)
We present a theoretical framework that enables a separate analysis of rhythm- and mechanical ventilation-induced changes in pulse pressure in patients with atrial fibrillation. Our findings may provide a basis for the development of a dynamic parameter that enables to predict fluid responsiveness in these patients.

Keywords: Pulse Pressure Variation, cardiopulmonary interaction, Atrial Fibrillation, mechanical ventilation, Fluid Responsiveness.

Glossary:

AF: Atrial fibrillation
APS: Apnoeic Prediction Surface
CVP: Central Venous Pressure
LOC2: A local second order Polynomial Regression Fitting model using RR$_0$ and RR$_1$ as independent variables to predict individual PP’s.
MAE: Mean Absolute Error
MBE: Mean Bias Error
MV: Mechanical Ventilation
PAOP: Pulmonary Artery Occlusion Pressure
PP: Pulse Pressure
PPV: Pulse Pressure Variation: Parameter defined as the percentual changes in Pressure during mechanical ventilation in patients with SR.
Q1: A Quadratic model using RR$_0$ as independent variable to predict individual PP’s
Q2: A Quadratic model using RR$_0$ and RR$_1$ as independent variables to predict individual PP’s.
76  RMSE: Root Mean Square Error
77  RR₀: The length of the RR-interval preceding an individual Pulse
78  RR₁: The length of the second preceding RR-interval of an individual Pulse
79  SR: Sinus Rhythm
80  SV: Stroke Volume
81  SVV: Stroke Volume Variation, parameter defined as the percentual changes in Stroke Volume during mechanical ventilation in patients with SR.
Introduction

Volume replacement is a cornerstone treatment in the hemodynamic management of critically ill patients. The need for volume administration was initially guided on classical static parameters such as central venous pressure and pulmonary artery occlusion pressure. In clinical practice however, these static preload parameters have been shown not to be able to accurately predict fluid responsiveness. (17, 19, 27) Fluid responsiveness relates to the beneficial effect of fluid loading on the cardiac output. During mechanical ventilation (MV) the effects of the cyclic changes in intrathoracic pressures, hence venous return, on the magnitude of beat-to-beat variations in stroke volume, are inversely related to a patient’s intravascular volume. These effects are quantified and expressed as stroke volume variation (SVV) or pulse pressure variation (PPV) (see fig 1) and have been shown to provide a suitable way of detecting hypovolemia and fluid responsiveness (21, 22). Current guidelines therefore recommend the use of these dynamic preload variables, to direct volume therapy in hemodynamically unstable patients. (13) Numerous studies support the validity of this concept (18) however it is only applicable to patients undergoing full mechanical ventilation(35) with sufficiently high tidal volumes(6, 23) and an intact chest wall.(40) Importantly, current recommendations also exclude patients with arrhythmia for dynamic preload assessment, as the available algorithms cannot distinguish pulse variations resulting from irregular heartbeats from those induced by MV (see fig 1). Patients with atrial fibrillation typically have an intrinsic variation in pulse pressure and fluid responsiveness can therefore not readily be quantified by assessing SVV or PPV. The development of an algorithm that allows distinction of effects on variations in pulse pressure or stroke volume by the irregular
heart rhythm and effects induced by MV would greatly enhance the applicability of fluid responsiveness assessment in these patients.

Interestingly, there is a significant amount of relevant studies in cardiology literature, focusing on the analysis of the determinants of PP and SV in patients with AF. A positive curvilinear relation between the RR interval preceding a beat and the subsequent PP has been observed. Moreover, in a number of patients a negative correlation was observed between the pre - preceding RR interval and the corresponding SV.(9)

Rawles incorporated these findings into a mathematical model to predict SV in spontaneously breathing patients.(29) In this study he was able to predict 69% of variations in SV when a quadratic polynomial equation was used. Alternative multivariate regression methods were not tested. Furthermore all the included patients where breathing spontaneously and this model was never tested during MV.

The aim of the current study was to develop a framework to isolate the two interfering mechanisms (rhythm and mechanical ventilation) that result in the observed beat-to-beat variation in PP. This would then enable the development of a dynamic preload parameter that allows to predict fluid responsiveness in a population previously excluded from this monitoring technology.

To address this question we first compared 3 mathematical models in their ability to predict PP in patients with atrial fibrillation when only the effect of an irregular heartbeat is at play. Subsequently the most accurate model was selected as the reference to describe and quantify the superimposed influence of mechanical ventilation on PPV.
Materials and Methods

Study population.

After approval of the institutional trial board and ethics committee of the Ghent University Hospital Ghent, this study was registered with the local code EC/2011/145 and with number B670201110842 for Belgium. Informed consent was obtained from all participants according to the Helsinki Declaration and ICH/GCP.

Ten AF patients who were planned for a pulmonary vein isolation under general anaesthesia were included, if they fulfilled following criteria: (1) Age >18 years, (2) Atrial fibrillation during study period and (3) ASA 1, 2 or 3.

Exclusion criteria were: (1) Participation in a clinical trial within the past 30 days, (2) Chronic Obstructive Pulmonary Disease, (3) Right ventricular failure, (4) Aortic valve insufficiency or stenosis and (5) an average heart rate of >140/minute.

Anaesthesia protocol.

All patients had a standard induction and maintenance of anaesthesia. A combination of bolus sufentanil 0.1-0.2 µg/kg, propofol 2 mg/kg and cisatracurium 0.15 mg/kg were used for induction. After intubation, sevoflurane (End Tidal fraction 1.7-2.0 %) was used for maintenance, supplemented with aliquots of 5 µg sufentanil. Besides the standard monitoring (5 lead ECG, pulse oximetry and noninvasive blood pressure) monitoring, a 3F catheter (Leadercath Arterial, Vygon, France) was placed in the radial artery. The transducer was levelled at the mid-axillary line and zeroed to atmospheric pressure.

Data acquisition.
During the different registration periods, ECG (II and V2) and arterial pressure signals were simultaneously registered. Each registration channel stored the signals with a sample rate of 1000Hz using LabSystem Pro v2.4a (BARD ®Electrophysiology, Lowell, MA, USA).

**Study protocol**

All patients presented with an irregular rhythm, so there was no need to experimentally induce AF.

Three registration periods were included, with each period lasting for 60 seconds. The ventilation mode was the only independent variable that differed between periods. The fixed sequence for every patient was: T1: Apnoe, T2: 12 x 8 ml/kg Tidal Volume (TV), T3: 8 x 12 ml/kg TV. Between every registration period a 5 min period was taken to allow for return to baseline conditions.

Data were analysed off-line. For every individual beat the pulse pressure (PP), and both the preceding RR-interval (RR₀) and the second preceding RR-interval (RR₋₁) (see figure 2), were quantified for subsequent analysis.

**Statistical Analysis**

This study consisted of a two-step analysis:

1. Apnoeic Prediction Surface (APS).

   To assess the variability of PP induced by the chaotic heart rhythm isolated from MV, measurements were taken during T1, a 60sec apnoeic period.

   For every patient three individual prediction models were compared.

   1. Model Q1: A quadratic model using the preceding RR interval (RR₀).

      \[
      PP = a + b*RR₀ + c*(RR₀)^2
      \]

\[ PP = a + b*(RR₋₁) + c*(RR₋₁)^2 + d*(RR₀) + e*(RR₀)^2. \]

3. Model Loc2: A local second order Polynomial Regression Fitting model using RR₀ and RR₋₁ as independent variables. This is a non parametric regression using local second order regression.(4)(see appendix for Model description) A plotted example of such an “apnoeic prediction surface” is shown in figure 2(A).

Both Root Mean Square Error (RMSE) and Mean Absolute Error (MAE) were determined to assess the performance of the individual models. These measures were compared with repeated measures ANOVA. P-values of <0.05 were considered significant. Pair-wise comparisons were made using Holm-Bonferroni correction for p-values.

2. Deviation from APS during ventilation.

To assess the effects of MV as monitoring tool for fluid responsiveness in these patients, we aimed to test two features of MV induced changes in PP. These features were extrapolated from the known mechanisms of cardiopulmonary interactions in patients with SR.

a. MV induces a gradual decrease in PP throughout the cycle, compared to the apnoeic reference PP. (26)

b. The MV induced decreases in PP are proportional to the applied TV (20, 26)

Graded increase of the TV through the 3 registration periods (TV= 0ml/kg (T1), TV=8ml/kg (T2), TV = 12ml/kg) yielded the deviation from the model known to predict a PP solely on the base of the intrinsic irregular rhythm (APS). An example of the effect of implementing the step-wise increase of the Tidal Volume is shown in figure 3.
For each data point, the residual was calculated. If the RR intervals of a data point fell out of the range of the RR intervals on which the APS was built, the residual could not be determined and this data point was discarded from analysis.

Mean bias error (MBE) for each observation period for every individual patient was calculated and compared using ANOVA for repeated measures.

All statistical analyses were made with RStudio Version 0.98.1091 based on R 3.0.2 (39)
Results

Demographic data are given in table 1.

All registration periods were complete except for Patient 8 period T3. Data in that registration segment could not be used due to dampening of the arterial curve.

1. Apnoeic Prediction Surface. (APS)

For every patient the 3 prediction models in apnoeic conditions (T1) were calculated. The RMSE (mmHg) and MAE (mmHg) of every model were determined for all 10 patients. Repeated measures ANOVA showed a significant difference between the models for both RMSE and MAE (p=0.001 for both analyses). The mean (SD) of RMSE was 5 (3), 3(2), 2(1) for Q1, Q2 and LOC2 respectively. The mean (SD) of MAE was 3(2), 2(1), 1(1) for Q1, Q2 and LOC2 respectively. Pairwise comparisons between the 3 models were all significant as can be seen in Figure 4. For every individual patient the LOC2 outperformed the two other quadratic models in predicting the rhythm-induced variability during apnoea. As a consequence, the individual LOC2 model was used as the best APS in the subsequent steps of the study.

2. Deviation from APS during mechanical ventilation.

The residuals and the Mean Bias Error were calculated using the patient specific APS to predict the PP for each time sequence of the study. In all but one case, the deviations from the APS were observed as expected: applying MV induced negative deviations from the APS. This is in line with the known mechanisms investigated in patients with SR(20, 26).

The magnitude of these deviations increases with the magnitude of the applied tidal volume. A repeated measures ANOVA for the MBE was significant (p =
0.003). MBE (mmHg) was 0 (0), -5 (6), -8 (7) for T1, T2 and T3 respectively. The pairwise comparisons using Holm-Bonferroni correction were all significant as can be seen in fig 5.
The main finding of the current study is that it is possible to isolate rhythm-induced changes in PP from MV induced changes in PP in patients with AF. This is of clinical relevance because in patients with SR the MV induced changes in PP are now generally accepted to be superior in predicting fluid responsiveness (= the effect of fluid loading on cardiac output). We present a two-step model that can be used as a framework to analyse the effects of MV independently from heart rhythm disturbances in patients with AF.

Specifically, our data confirm that also in patients with AF, it is possible to predict the PP of an individual heartbeat during an episode of apnoea, when the effect of mechanical ventilation effect is eliminated. Our proposed model of local polynomial quadratic regression based on the two preceding RR intervals outperforms a previous published model(29) and a simple quadratic model based on a single preceding RR-interval. Therefore this model can be used as a reference to determine changes induced by MV.

Subsequently the data demonstrate that the magnitude of the deviations from the APS correlate with the magnitude of the applied tidal volume. These properties enabled use to differentiate PPV in mechanically ventilated patients with AF into two components: the variations induced by the intrinsic chaotic heart rhythm (APS) and variations induced by the cyclic changes in intrathoracic pressures caused by MV (The spread of negative deviations from the APS).

The magnitude of the latter component is known to reflect filling status and predict volume responsiveness in patients with SR.

Full mechanical ventilation offers a unique model to assess perioperative hemodynamics for two reasons: (1) MV imposes intrathoracic pressure changes
affecting different determinants of cardiopulmonary interactions in a reversible way.

The distribution of these pressure changes within the thorax is complex but, in normal subjects, the main effect of this maneuver is a decrease in venous return. (15, 38) This short lived change in loading condition of the right ventricle can be traced as its impact travels through the pulmonary vascular bed and eventually determines cardiac output of the left ventricle.

Taken together, MV enables the practitioner to perform an “inverse fluid challenge” and to make a two point plot of the individual Frank-Starling curve. (2) The second feature of MV that makes it an ideal tool is the fact that it is a perfectly cyclic maneuver. Repeated standardized changes in venous return, coupled to a regular heartbeat, causes predictable oscillations in SV and PP. These oscillations are easily measured, and can be monitored continuously. Different parameters based on these oscillations have been described and studied. The percentual changes in PP and SV, known as Pulse Pressure Variation (PPV) and Stroke Volume Variation (SVV) are available in different commercial available monitors. An automated standardized ventilatory maneuver was proposed the evaluate the impact of MV on systolic blood pressure in a clinical setting (26, 36).

These physiologic and practical advantages affirm the superior clinical performance of the MV induced/dynamic parameters. Marik performed a series of meta-analyses in which he was able to clearly show that the predictive values of these oscillations are improved in comparison with classic “static” parameters like CVP and PAOP to predict the effect of a fluid challenge on cardiac output. (17-19) He found a threshold of 12.5 (+/- 1.6) % and 11.6 (+/-1.9)% variation for PPV and SVV respectively, to have good predictive value. (18) More recently, a grey zone approach was described. Cannesson et al used a more sophisticated method and found that prediction characteristics between
a PPV of 9% and 13% were inconclusive. (3) Incorporating the resolution of the oscillations after a fluid challenge was able to narrow this grey zone. (16)

The clinical superiority of these parameters holds only when the prerequisites are respected: A regular heart rhythm, full mechanical ventilation without spontaneous breathing interfering with the standardised intrathoracic pressure swings and tidal volumes, big enough to have a substantial effect on intrathoracic pressures (14) in a closed thorax (40). Some criticism has been formulated in light of these prerequisites and the complexity of the underlying physiology. (31)

The condition of AF creates an obvious problem in the implementation of these dynamic parameters in clinical practice. This growing population has always been excluded in research protocols. These patients, however, may benefit more than others from meticulous perioperative fluid management.

A first hurdle to address when solving this problem is to find a way to decompose the two sources of variation in PP; the chaotic rhythm and the cyclic MV.

It has long been understood that rhythm induced variations of SV are multifactorial. Different filling times (RR0) of an individual beat are responsible for dispersion of the ejected SV. (1, 9) In some patients, RR-1 was found to have an inverse correlation with SV. (9) This has been explained by changing contractility (2, 11, 30), possibly combined with changes in LV afterload (8, 24).

There have been some attempts to bring this knowledge into practice. Some investigators indexed their beat-to-beat observations according to the RR0/RR-1 ratio. The value when RR0/RR-1 = 1 can sometimes be used as the overall mean. This has been described for E_max (end-systolic pressure-volume ratio) (32, 33), Doppler measured aortic peak flow velocity and TVI (32, 34), dP/dt_max. (25, 34)
To our knowledge there is only one published mathematical model that incorporates the two preceding RR intervals to predict individual SV in patients with AF. Rawles compared different models, even adding up to 4 preceding RR intervals in the analysis to predict SV. Stroke distance, measured with transcutaneous aortovelography was used as the surrogate for SV. After stepwise multiple regressions he selected a quadratic polynomial equation based on $RR_0$ and $RR_{-1}$. With this model he was able to explain 69% of the observed variations. Interestingly, all of these patients were breathing spontaneously. (29)

We found that our model performed better than the Rawles model in predicting the rhythm-induced variation in PP during apnoea. We decided to use the local polynomial regression mainly because of two advantages. Theoretically every curvilinear relation can be reliably described without knowledge of the global relation. Furthermore, in patients with AF it is known that the distribution of RR intervals is not always normal, making a non-parametric method like local polynomial regression a more suitable choice. (10, 37)

This APS forms a good reference to describe and quantify the effects of mechanical ventilation on changes in PP. In line with the knowledge from MV induced changes of PP in patients with SR, the observed deviations behaved as expected: in all but one patient, they produced a depression of PP. Increasing the tidal volume enhanced this effect and widened the spread of deviations. On a 3D plot (see figure 2) these two superimposed effects are easily recognized as the APS (purely rhythm induced) and the vertical spread under the surface (MV added to rhythm).

These findings form the basis for a new framework that can be used to develop a new parameter that is a measure of MV induced PP changes in patients with AF. In analogy
with patients in SR, this principle can be used to determine these variations continuously or to use it in standardised ventilatory maneuver. Further studies to assess the accuracy and clinical usefulness of such parameters are needed. The present findings should be interpreted within the constraints of the methodology used. First, this is a small study that included only 10 patients. Our results were however significant; our model predicted individual PP’s, with sufficient accuracy to clearly disclose MV induced deviations. For this framework to be clinically useful, it should describe these effects with sufficient power. Moreover, we should bear in mind that for each patient a mean of 74 data points per registration period were used to perform the analysis. Secondly, our study does not provide additional insight into mechanisms underlying cardiopulmonary interaction. Our aim was to develop a mathematical and graphical way to isolate the two sources of variation that can form the basis for an intelligent algorithm to quantify cardiopulmonary interactions. The exact interplay of changing venous return, varying contractility, or afterload, can only be assumed from extrapolation of the findings in patients with sinus rhythm. However, the shape and position of the APS may offer additional clues to assess cardiac performance as the relationship between R-R intervals and subsequent PP and SV have been linked to filling status and inotropic state. Thirdly, we used PP as a surrogate for SV. We chose to use PP because it is a parameter easily measured in clinical practice. Furthermore, in adults with SR, PPV was shown to perform at least as good as SVV in predicting fluid responsiveness.(18) The relationship between PP and SV is determined by the compliance of the vascular system. This was one of the suggested reasons why PPV loses its predictive properties in children.(7) The exact role of hypertension or specific antihypertension medication cannot be
determined in this study because of the low number of patients and is subject of further research.

In conclusion, we developed a framework to isolate the two superimposed sources of variation in PP in patients in AF: the chaotic rhythm and the cyclic changes induced by MV. This is based on the use of a modified model that uses the two preceding RR-intervals of a beat to predict the PP during apnoe (APS). The effect of MV can be evaluated based on the sense and the magnitude of deviations from this APS. This principle can be used to develop and investigate a parameter for MV induced changes in PP, potentially a dynamic parameter to predict fluid responsiveness in patients with AF.
Appendix

LOC2 model:

The LOC2 model is a local polynomial regression to predict PP based on RR_0 and RR_{-1}.

Cleveland first described the locally weighted regression or loess-function.(5)

It is a local regression, meaning that general regression is split up in multiple analyses, performed on subsets of the total data. More specifically for each individual data point a regression is performed, using the nearest data points. All the included data in the local regression are weighted, proportional to their proximity to the point being analyzed. For every point-analysis we used a second order polynomial regression.

Eventually all the individual analyses are combined in a global function covering the total data set.

This methodology is computational very intensive but it has the clear advantage that the fitting model is not restricted to one predefined type (e.g. a second order polynomial regression, sinusoidal, exponential function or combinations). This analysis is very flexible, within the dataset.

Specific determinants incorporated in our analysis:

- bandwidth – smoothing parameter – $\alpha$

The proportion of the data that is used for every local fitting is to be defined. This parameter determines the tradeoff between a smooth model and the flexibility to predict individual points. When this parameter is set too small, there is a high
risk of overfitting (see figure 5) because eventually the random error of the data becomes modeled. The bigger the span is set the higher the risk for underfitting. To find the optimal smoothing parameter, we performed a 5-fold cross-validation for every patient. In this procedure, the data are randomly divided into 5 subsets. Four of these subsets are used to calculate a set of models, in which a range of different smoothing parameters are used (= the training subset). In the next step, these different models are used to predict the remaining subset (= the validation subset). These steps are repeated 5 times, until every subset of the data was used as a validation subset. The smoothing parameter with the best overall fit was used in the final analysis.

- Degree of polynomial regression was set at 2
- The traditionally tricubic weight function was used.

\[ W = \left(\frac{1}{\text{Dist}/\text{maxdist}}\right)^3 \]
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Conflicts of interest: None declared
References:


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### Table 1: demographic data of included patients. Summary data are given median(IQR)

<table>
<thead>
<tr>
<th>Sex</th>
<th>M/F</th>
<th>Caucasian (%)</th>
<th>Age (y)</th>
<th>Weight (kg)</th>
<th>Length (cm)</th>
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<td></td>
<td>6/4</td>
<td>100</td>
<td>57.5 (55.5-65.0)</td>
<td>94.5 (71.75-99.25)</td>
<td>180 (170.5-183.0)</td>
</tr>
</tbody>
</table>

**Cardiovascular co-morbidity (n):**

- Hypertension: **6**
- Hypercholesterolemia: **1**
- Ischemic heart disease: **1 (CABG)**
- Corrected valvular disease: **1 (AS)**
- Corrected congenital heart disease: **1 (VSD)**
- Congestive heart failure: **0**

**Diabetes/ metabolic syndrome (n):** **3**

**Stroke/TIA (n):** **2**

**Medication (n):**

- Amiodarone: **2**
- Digoxin: **1**
- Flecaïnide: **2**
- Beta-blockers: **6**
- Calcium channel blockers: **2**
- ACE-Inhibitor/All blockers: **2**
- Diuretics: **3**
Figure Legends

Figure 1: Fig. 1 Schematic representation of the current framework to assess mechanical ventilation induced variation in pulse pressure. Upper panels (A-B) are for patients with sinus rhythm. Lower panels (C-D) are for patients with AF.

Waveforms of 9 consecutive heartbeats during apnoe measured with a radial arterial line are displayed on the left side (A and C). Waveforms of 9 consecutive heartbeats during one respiratory cycle are displayed on the right side (B and D). The distributions of the pulse pressures during apnoe and mechanical ventilation (MV) are shown in the inset in the middle. The formula to quantify the variation in pulse pressure (PPV) is also displayed. It can be seen that this formula is only applicable in SR since there is minimal variation in PP during apnoe. In patients with AF this formula is no longer valid since it fails to correct for the variation in PP before mechanical ventilation is applied. It calculates a percentage of variation that is the resultant of the effect of both rhythm and MV. The aim of our study and the basis for this new frame work is to replace this approach by a model that is capable to minimize the variation between predicted and measured PP during apnoe in patient with AF. This model then, can be used as a reference to measure the variations in PP during Mechanical Ventilation.

Figure 2: Terminology: for every individual beat, the two preceding RR intervals (RR₀ and RR₋₁) were used to construct a prediction model, to predict the Pulse Pressure (PP)

Figure 3: Apnoeic Prediction Surface (APS) and effect of Mechanical Ventilation on deviation from the APS using incremental Tidal Volume: 3D plot examples of the three
registration periods of Patient 2. LOC2 model (red grid) is printed as reference on all the plots.

(A) T1: apnoe during 60 seconds. Individual data points in red.

(B) T2: Individual data points during mechanical ventilation (12 \(^{8}\)ml/kg) are printed as yellow dots.

(C) T3: Individual data points during T3 (8 \(^{12}\) ml/kg) are printed as green dots

\textit{RR intervals (msec), PP(mmHg)}.

\textbf{Figure 4:} \textit{Individual Residual Mean-Square Error (RMSE)} (black dots) and \textit{Mean Absolute Error (MAE)} (open triangles) of the three prediction models (Q1, Q2 and LOC2) during observation period T1 (Apnoe). P-values of the pairwise comparisons using Holm-Bonferroni correction are added.

\textbf{Figure 5:} \textit{Effect of Ventilation on predicted values of PP using APS.} Individual Mean Bias Error (mmHg) of each observation period (T1: Apnoe, T2: 8\(^{12}\)ml/kg, T3: 12\(^{8}\)ml/kg). P-values of the pairwise comparisons using Holm-Bonferroni correction are added.

\textbf{Figure 6:} \textit{Effect of changing the setting of the ‘smoothing’-parameter in the calculation of LOC2.} (A) Overfitting. Detail of LOC2 during T1 of patient 1 when the span parameter was set at 15%.

(B) Optimal fitting. Detail of LOC2 during T1 of patient 1 when the optimal span was set. \textit{RR intervals (msec), PP(mmHg)}
Sinus Rhythm

A. Apnoe

B. Mechanical Ventilation

Atrial Fibrillation

C. Apnoe

D. Mechanical Ventilation

PPV = \frac{PP_{max} - PP_{min}}{(PP_{max} + PP_{min})/2}