GHENT UNIVERSITY

FACULTY OF MEDICINE AND HEALTH SCIENCES

Limitations of the use of dynamic filling parameters in mechanically ventilated patients and possible solutions.

Piet Wyffels

Supervisors: Prof. dr. Patrick Wouters
Prof. dr. Stefan De Hert

A dissertation submitted to Ghent University in partial fulfillment of the requirements for the degree of Doctor of Health Sciences

Academic year: 2023-2024

Promotors

Prof. dr. Patrick Wouters

Chair, Department of Basic and Applied Medical Sciences, Faculty of Medicine and Health Sciences, Ghent University, Belgium
Anesthesiology, Perioperative Medicine and Pain Clinic, Ghent University Hospital, Belgium

Prof. dr. Stefan De Hert

Department of Basic and Applied Medical Sciences, Faculty of Medicine and Health Sciences, Ghent University, Belgium
Anesthesiology, Perioperative Medicine and Pain Clinic, Ghent University Hospital, Belgium

Examination Committee:

Chair:

Prof. dr. Saïd Hachimi Idrissi

Department of Basic and Applied Medical Sciences, Faculty of Medicine and Health Sciences, Ghent University, Belgium
Emergency Medicine, Ghent University Hospital, Belgium
Pediatric and Critical Medicine, Vrije Universiteit Brussel, Belgium

Members:

Prof. dr. Wolfgang Buhre

Professor and chair Department of Anesthesiology, Divisions of Vital Functions, Universitair Medisch Centrum Utrecht, the Netherlands.

Prof. dr. Luc De Baerdemaeker

Chair, Anesthesiology, Perioperative Medicine and Pain Clinic, Ghent University Hospital, Belgium
Department of Basic and Applied Medical Sciences, Faculty of Medicine and Health Sciences, Ghent University, Belgium

Prof. dr. Jan De Pooter

Heart Center, University Hospital Ghent, Belgium
Department of Internal Medicine and Pediatrics, Faculty of Medicine and Health Sciences, Ghent University, Belgium

Prof. dr. Anneliese Moerman

Cardiac Anesthesia, Perioperative Medicine and Pain Clinic, Ghent University Hospital, Belgium
Department of Basic and Applied Medical Sciences, Faculty of Medicine and Health Sciences, Ghent University, Belgium

Prof. dr. Steffen Rex

Chair, Department of Anesthesiology and Algology, University Hospitals Leuven, Belgium
Department of Cardiovascular Sciences, Faculty of Medicine, KU Leuven, Belgium

I always wanna do the simplest possible thing that will work. But unfortunately, the simplest possible thing that works, is always a little bit more complicated than the most complicated thing I know how to do.

Andrew Gelman

Learning Bayesian Statistics podcast (Alexandre Andorra) 30/7/2020
#20 Regression and Other Stories, with Andrew Gelman, Jennifer Hill & Aki Vehtar

Dankwoord

‘… Wetenschap doen is vechten tegen de stroom in, vooruit proberen te gaan met constant nieuwe stokken in de wielen. …’ Zoiets moet mijn toenmalige collega gezegd hebben toen ik interesse toonde om een eigen wetenschappelijk project te starten. Ik was net gestart als ‘één van Leuven’ in het ‘UZ van Gent’. En of dat hij gelijk had! Ik had enkel een concreet probleem dat ik wilde oplossen. Een echt plan was er nog niet en mijn zoektocht moest mij nog naar veel doodlopende straatjes en nieuwe inzichten leiden in dat labyrint.

Wat was ik blij toen ***prof. Patrick Wouters*** mij in Rijsel contacteerde met de vraag of ik geen interesse had om te solliciteren in Gent! Natuurlijk had ik interesse…! En toen ik die eerste keer mijn idee op tafel legde wist ik dat de kans op slagen van mijn onderzoek serieus begon te stijgen. Samen met ***prof. Stefan De Hert***, beschikte ik over een perfect team. Twee internationale zwaargewichten (figuurlijk dan) van de anesthesie en de hemodynamica. Soms Yin en Yang. Aan jullie om te oordelen … wie mij pushte om meer diepgang te maken met het onderzoek, en wie er bleef op hameren dat iedere anesthesist het toch (een beetje) moest kunnen begrijpen… Wie mijn ‘manuscripten’ ’s anderendaags al had omgetoverd in een rode zee met correcties (… maar het ziet er al heel goed uit hoor!) en wie die schrijfsels en ideeën enkele weken of maanden liet bezinken om daarna nog enkele (nieuwe) nagels op de kop te slaan. … Wie mij concreet wilde helpen met een monitorsysteem om drukcurves op te slaan, dat bijna mijn bureau liet afbranden alvorens er een bit was opgeslagen, of met wie het heerlijk lachen is op congres en luchthavens daar naartoe (vooral als hij voor een keer niet moet presenteren…). Dikke merci aan jullie alle twee. Ik hoop in de

toekomst deze en nieuwe ideeën ook in goede banen te leiden. Ik heb nog veel van jullie te leren…

Bedankt ook aan de leden van de examen commissie, ***prof. Saïd Hachimi Idrissi, prof. dr. Wolfgang Buhre, Prof. Luc De Baerdemaeker, Prof. Jan De Pooter, Prof. Anneliese Moerman*** en ***Prof. Steffen Rex*** om zich over mijn werk te buigen en de tijd te nemen om het onder de loupe te nemen. Het is verbazingwekkend hoe jullie vragen en opmerkingen mij verplicht hebben om mijn onderzoek vanuit een nieuw perspectief te bekijken.

Een woord van dank voor ***mijn opleiders die*** het zaadje geplant hebben, in het bijzonder de anesthesisten van het toenmalige Heilig Hart ziekenhuis in Roeselare.

Mijn thuis op het UZ is ***de dienst anesthesie***. Bedankt prof. Luc De Baerdemaeker, en tot voor enkele jaren Prof Patrick Wouters, om als diensthoofd de vele moeilijkheden gaande van COVID, starre structuren, dovemans gesprekken, materiaal of chronisch personeelstekort dagelijks het hoofd te bieden. Dit om onze dienst uit deze duistere periode te trekken zodat we als dienst niet alleen een kwaliteitsvolle zorg kunnen garanderen maar ook onze academische taken, opleiding en onderzoek kunnen uitvoeren. Merci aan iedereen van het secretariaat, Tamara, Ann, Sjoert en Geert voor de ondersteuning en vlotte samenwerking in onze projecten. Merci Catherine voor de planning vandaag, merci An voor je ongeëvenaarde volharding als studynurse.

Daarnaast zijn het vooral ***mijn collega-stafleden*** die ervoor zorgen dat het op onze dienst ondanks alles leuk vertoeven is. Bedankt om in te springen als ik eens ‘op mijn bureau zat’ om de teksten en de codes van dit boekje te schrijven. Bedankt om de frustraties van de dag met een kop koffie en een ‘kluchtje’ door te spoelen. Bedankt om het West-Vlaams als tweede officiële taal van de dienst te omarmen…

Het UZ zou het UZ ook niet zijn moesten er niet ieder jaar opnieuw een groep jong geweld neerstrijken. ***Assistenten*** (in opleiding) zijn een zegen om mee samen te werken. Hun 'verfrissende' ideeën, hoe ver ook uit de box of hoe absurd soms, verplichten ons om scherp te blijven en leren me elke dag iets nieuws. Jullie zien ontpoppen in toekomstige collega's is fantastisch.

Zorgen voor patiënten is team work:
Er is de laatste jaren veel veranderd op de PAZA en de komende jaren zal er nog veel veranderen. Aan ***iedereen van de PAZA***; waarschijnlijk zeg ik het te weinig maar jullie leveren fantastisch werk… bij deze… Merci aan ***iedereen van het OK*** en in het bijzonder de verpleegkundigen van ***de buitendiensten***….

Maar gelukkig zijn er ook nog vrienden en familie….

Het grootste gedeelte van mijn vrije momenten in het weekend maak ik mijn hoofd leeg in sporthallen ergens te velde, ergens in Vlaanderen. Dat doe ik samen met de andere supporterende ouders van de ***Rembert familie.*** Vijftien jaar geleden, had ik nooit gedacht dat ik zo gefascineerd en enthousiast zou worden door volleybal. Blijkt dat er toch meer achter zit dan '1-2-3' over… Dikke merci #WeAreRembert.

En als er geen volleybal is, zijn er ***De pedagogen.*** De jaarlijkse weekenden met 'de bende' zijn zalig. Ik ben blij dat ik in deze mengelmoes van alpha mannetjes en vrouwtjes, socio's en standup comedians terecht ben gekomen.

Het wordt ook hoog tijd dat ik weer wat meer tijd in ***De Struistulpjes*** kan steken. Ik mis het repititie kot van ons muziekcollectief waar talent niet van tel is, maar speelplezier des te meer … Ronny, Jan en Lieven: Laat Jeanine, onze denkbeeldige manager, maar terug nieuwe sessies boeken, ik kom eraan.

En dan ***The Dead Chicken Society***, ooit al eens omschreven als een feitelijke vereniging gegroeid uit de vrienden van het college, met een nog nader te bepalen doel waar mensen mekaar uitdagen en uitlachen. Bedankt Lieven, Marieke, Jan, Anne-Katrien, Bert, Monica, Bart, Fée, Ciska en Jan.

Merci aan mijn schoonfamilie. ***Frans en Stine, Bart en Sara*** voor de vele helpende handen: voor de ritjes naar Torhout, de orthodontist of trompetles, de kangoeroe-garage, de reserve auto, de last minute opvang.

Ma en Pa en Jan: Alles is bij jullie begonnen. Mijn interesse in geneeskunde en fascinatie voor wiskundige formules. Mischien heb ik jullie wel het meest van allemaal 'te weinig' bedankt….

Bram,Lotte en Robbe, ik sta eigenlijk met stijgende verbazing en trots te kijken naar jullie. Het is fantastisch thuiskomen bij jullie en het dagelijks vuurwerk waarvoor jullie persoonlijkheden zorgen.

Wat me tenslotte bij jou brengt…***Rebekka***. Iedereen die ons kent weet dat ik maar half de persoon zou zijn zonder jou.

Gent, maart 2024
Piet Wyffels

Table of Contents

List of Abbreviations

ABP:	Arterial Blood Pressure
AF:	Atrial Fibrillation
APS:	Apneic Prediction Surface
BLUP:	Best Linear Unbiased Predictor
CI:	Confidence Interval
CO:	Cardiac Output
CVP:	Central Venous Pressure
∆POP:	Variations in Pulse Oximetry Plethysmography waveforms amplitudes
DO2:	Oxygen Delivery
ECG:	Electrocardiogram
EEOT:	End-Expiratory Occlusion Test
FHT:	Functional Hemodynamic Tests
GAM:	Generalized Additive Model
HR/MVR:	Heart Rate over Mechanical Ventilation Rate Ratio
IAP:	Intra-Abdominal Pressure
ITP:	Intrathoracic Pressure
IQR:	Inter Quartile Range
LOC2:	A local second order Polynomial Regression Fitting model using RR_0 and RR_{-1} as independent variables to predict individual PP's.
MAP:	Mean Arterial Pressure
MAE:	Mean Absolute Error
MBE:	Mean Bias Error
MD:	Mean Difference
MFC:	Mini Fluid Challenge
MV:	Mechanical Ventilation
OR:	Odds Ratio
PAOP:	Pulmonary Artery Occlusion Pressure
PLR:	Passive Leg Raising (test)

Pms:	Mean Systemic Pressure
PP:	Pulse Pressure
P_{Pl}:	Pleural Pressure
PPV:	Pulse Pressure Variation
Pra:	Right Atrial Pressure
PVI:	Pleth Variability Index
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 variable to predict individual PP's.
RC:	Respiratory Cycle
RMSE:	Root Mean Square Error
ROC:	Receiver Operating Characteristic
ROCAUC:	Area under the curve of the Receiver Operating Characteristic
RR:	RR interval: time between two succedent R-waves
RR_0:	The length of the RR-interval preceding an individual Pulse.
RR_{-1}:	The length of the second preceding RR-interval of an individual Pulse.
Rven:	Resistance of the venous circulation
SAP:	Systolic Arterial Pressure
$S_{cv}O_2$:	Central venous oxygen saturation
SPV:	Systolic Pressure Variation
SR:	Sinus Rhythm
SV:	Stroke Volume
S_vO_2:	Mixed venous oxygen saturation
SVI:	Stroke Volume indexed for Body Surface
SVV:	Stroke Volume Variation
TV:	Tidal Volume
TVC:	Tidal Volume Challenge

VPPV:	Ventilation induced Pulse Pressure Variation
VC:	Ventilator Cycle
VR:	Venous Return

Chapter 1

‘ Is everybody in?
Is everybody in?
Is everybody in?
The ceremony is about to begin … ‘

Jim Morrison
An American Prayer, Awake
1978

1

General Introduction

1.1 Wet, Dry or… something else?[1]

Fluid administration has an important place in the everyday practice of each anesthetist caring for patients undergoing surgery. Many issues of fluid therapy, however, remain unresolved even after at least 5 decades of research filled with opposing views, evolving physiologic insights[2,3], furious debates [4], … and even research fraud [5]…

Therefore, it may be useful to start with the basics when studying perioperative fluid therapy. Recently, the goal of IV fluid administration was defined as:
'… To restore and maintain tissue fluid and electrolyte homeostasis and central euvolemia, while avoiding salt and water excess. This will in turn facilitate tissue oxygen delivery without causing harm, …'. [6]

Although somewhat vague, this definition has the merit that it incorporates the origins of the raging debates, and that it emphasizes the importance of perioperative hemodynamic and fluid management of patients. Trying to compensate for fluid deficits and ongoing fluid and blood losses is not

straightforward. Inadequate use of fluid therapy may itself cause morbidity, which may be related to a less-than-optimal macro-hemodynamic result, but also, to endocrine, acid-base, microcirculatory or toxicological effects. These potential adverse effects are the reason for ongoing controversies concerning the optimal composition of the fluids used (crystalloids vs colloids, saline based vs balanced fluids, etc.) and the optimal amount and timing of fluids to be administered. We should bear in mind that none of these aspects can be seen isolated from each other.

Concerning the macrohemodynamic effect of fluid loading, two schools of thought appeared around the beginning of the millennium and dominated the perioperative fluid management debate: ***liberal vs restrictive fluid therapy***.

The first approach goes back to the seminal observation of Shoemaker et al showing that patients surviving shock[7] or major surgery[8] had higher, even supra-normal values of Cardiac Output (CO) and Oxygen Delivery (DO_2) in comparison with non-survivors. In 1988, the same group published a first trial in patients undergoing high risk surgery, showing superiority of striving supra-normal cardiac output and DO2 values, with a dedicated hemodynamic protocol based on fluid and pharmacological support.[9] Later studies, including more patients and using different study designs showed conflicting results, weakening this early enthusiasm.[10]

The restrictive fluid approach stems from the concerns of fluid excess. Researchers pointed out that overzealous administration of fluids may result in cardiac dysfunction, pulmonary complications, kidney injury, abdominal compartment syndrome, gastro-intestinal dysfunction, edema, impaired wound healing and coagulation problems.[11] A recent meta-analysis of the randomized controlled trials conducted in the last 20 years, comparing restricted vs liberal fixed-dose fluid regimens failed to show an overall benefit of either of the two approaches on mortality and on overall morbidity. Liberal fixed dose fluid regimens, however, were associated with less renal complications.[12] Limitations of this meta-analysis, however, are the difficulty of comparing the control groups and the small size of most included studies. In addition, one study consisted of more than half of the pooled patients in this meta-analysis.[13]

In his 2006 editorial, Bellamy tried to reconcile these apparent opposing views. He defined a U-shaped curve describing an increased morbidity in both the liberal and the restrictive fluid therapy tail (See figure 1.1).[1]

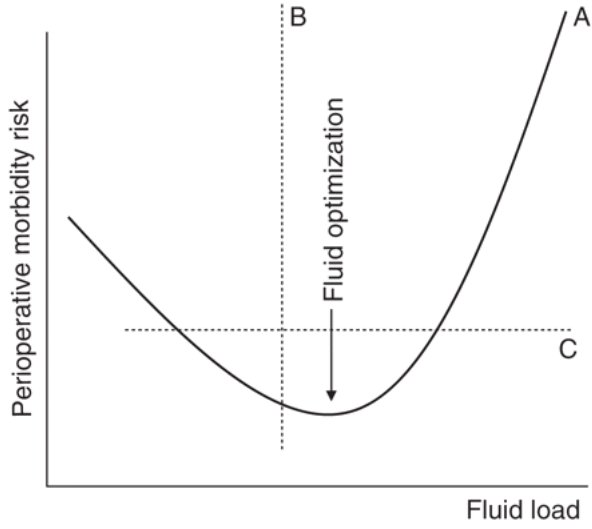


Figure 1.1*: Curve A represents the hypothesized line of the risk. Broken line B represents division between patient groups in a 'wet vs dry' study. Broken line C represents a division between patient and groups in an 'optimized vs non-optimized' study.*[1]

Although hypothetical at the time, this curve was shown to be a realistic representation. In their analysis of a database containing more than 90000 patients, Shin et al found that this curve could be reproduced for 30-day mortality, postoperative respiratory complication, postoperative acute kidney injury, length of stay and total hospital costs.[14]
To find this optimal fluid load Bellamy urged for more reliable *'…physiological measurements tailored to the individual patient…'*.[1]

1.2 Fluid Responsiveness

1.2.1 General definition and physiology

The intended effect of administering fluid to a patient in the perioperative period is to increase CO***. Patients that have an increase in CO after fluid loading are defined as fluid responsive or as fluid responders*** (***general definition***).

In 1895* Otto Frank, described the phenomenon that a cardiac muscle of a frog is able to generate more force when it is stretched before activation.[15] In 1914 Ernest Starling expanded this finding and described the non-linear relationship between venous return/filling of the ventricle and stroke volume.[16] Ever since, the exact molecular mechanisms underlying this intrinsic property of the heart muscle have been further unraveled.[17–20]

Two portions can be discerned on this curve. Increasing preload in an empty heart will rapidly increase stroke volume up until a point where further increasing venous preload will not result in a sustained increase in cardiac output. For clinical purposes it is useful to split the curve in a steep raising part and a plateau part, a fluid responsive and a non-fluid responsive part respectively.
Other determinants of the heart performance, like afterload and contractility, also have an impact on this relation. The interplay between these various determinants explains why the Frank-Starling curve differs between patients and can even change over time in the same patient.

Besides the Frank-Starling approach, another framework explaining the hemodynamic effects of filling was conceived in the 1950's. This alternative view shifted the emphasis from the concept of the heart as a pump generating arterial forward flow, to the concept where the heart is viewed as an accommodator of venous return flow. In his influential writings, Arthur Guyton placed the venous vasculature and venous return at the center place of hemodynamics.

* See Zimmer for a historical overview of the seminal research conducted by Elias Cyon, Joseph Coats and Henry P Bowditch at Carl Ludwig's Physiological Institute at Leipzig in 1866. Otto Frank worked in this institute in 1892-1893 before moving to Munich where he continued his studies. Reference: *Who Discovered the Frank-Starling Mechanism?* Zimmer HG News Physiol Sci 2002; 17: 181-184.
For a full historical overview of the Frank-Starling Law see: *Historical perspective on heart function: The Frank-Starling Law.* Sequeira V, van der Velden J Biophys Rev 2015; 7: 421-447 and: *Ernest Henry Starling, His Predecessors, and the 'Law of Heart'* Katz AM Circulation 2002; 106(23): 2986-2992.

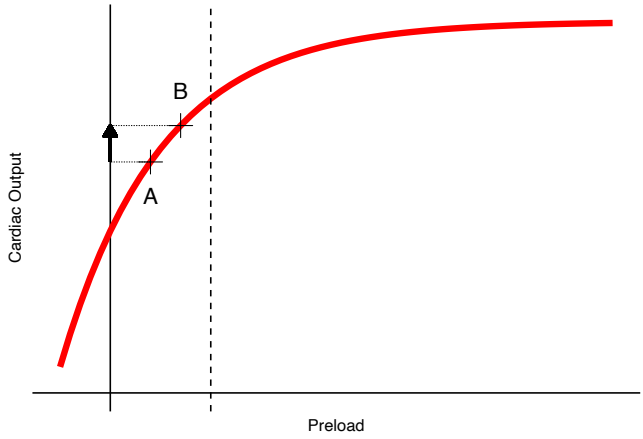


***Figure 1.2**: Cardiac function curve showing the Frank-Starling relation which is a curvilinear relation between preload and Cardiac Output. The dashed line partitions the plot into two portions: on the left, the ascending portion of the curve. On the right the plateau portion of the curve. The shift from A to B represents the effect of administering a fluid bolus in a fluid responder.*[*]

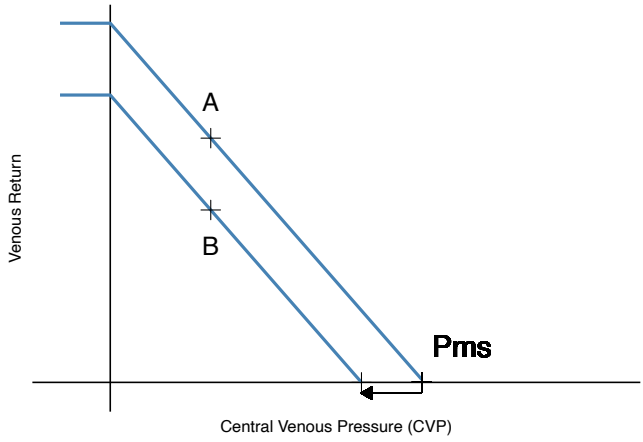


***Figure 1.3**: The venous return curve or vascular function curve showing the relation between CVP and the venous return. The curve consists of two segments: a constant maximal venous return with a CVP < 0 mm Hg and a linear decline. The intercept of the curve with the x-axis, the point where venous return becomes 0, signifies the mean systemic pressure (Pms). The absolute slope of this segment is the reciprocal of the venous resistance (RVen). The shift to the left of the venous return shows the change induced by hypovolemia. If CVP and Rven were kept constant than this degree of hypovolemia would induce a change in venous return, equal to shift of point 'A' to point 'B'.*

[*] An Alternative representation of the Frank-Starling relation is the 'Pump Function Graph' reference: Snapshots of Hemodynamics. 2nd edition Westerhof, Stergiopulos and Noble. Chpt 14 p 87-95. ISBN 978-1-4419-6362-8 Springer 2010

Although still refined[21–24] and debated[25,26], roughly 5 main principles constitute this theory:

1. ***Venous return determines the Cardiac Output***. In the words of Starling: *'… The output of the heart is equal to and determined by the amount of blood flowing into the heart, and may be increased or diminished within very wide limits according to the inflow…'*[16]

2. The driving force of the venous return is the ***Pms****. This is the upstream venous pressure. It can be conceptualized as the pressure, at which all the elastic compartments of the venous system would equilibrate when flow stops.[21–23] †

3. The Pms is regulated through the ***stressed volume***. The pressure in the veins is determined by the volume of blood that resides in these vessels and their elastic properties. The cross-section view of an empty vein can be seen as a flat ellipse. Filling up the vessel will change this cross section view up until it is a circle, with constant circumference. The resulting pressure will be virtually 0. Further filling will result in an increase in circumference of the circle and hence a stretch is forced upon the vessel wall with a concomitant raise in pressure. The volume of blood residing in a vessel up until the pressure starts to raise is called *the unstressed volume*. The extra volume responsible for the development of wall tension, is called the stressed volume.[27] Pms can be regulated through a change in the stress / unstressed volume ratio (e.g.: change in vascular tone). [27,28] ‡

---

* In this thesis the term mean systemic pressure (Pms) will be used. In the literature however, two variants can be found. 'Mean circulatory filling pressure' is the (venous) pressure at zero flow, in line with the above-mentioned definition. 'Mean systemic filling pressure' is the same when excluding the blood and the compliances of the heart and the pulmonary circulation. These two values slightly differ as for the former, there can be an equilibration/shift between the pulmonary and the systemic circulation. This distinction might become important when choosing a method to measure these pressures.[23]

† There are two different interpretations of the Pms. Proponents like Simon Gelman[21] interpret it as a pivot pressure, physically located in the venous system. Others like Sheldon Magder[38] and Soren Sondergaard[37] explain it as an averaged pressure weighted by vessel compliances making it a virtual pressure without a specific location.

‡ For an alternative view on the function of Pms and the place of the stressed volume as driving forces of venous return see Brengelmann[25,26,32] . Starting from the first law of Newton (conservation of energy), he argues that the stressed volume cannot be the driving force of venous return. As the energy stored in the stretch of a vessel wall can only be

4. ***Right atrium pressure (Pra)*** is the back pressure of the venous return. The low-pressure downstream part of the venous return is the right atrium. Increasing the Pra decreases the pressure gradient over the venous vasculature. Consequently, this must affect the resultant flow.[29–31] In clinical practice, CVP is considered interchangeable with Pra.

5. Taken together, venous return can be calculated as: ***VR = (Pms - Pra)/Rven*.*** (Rven = resistance of the venous vasculature.)

The impact of changing these determinants is schematized in the venous return or vascular function curve. (See figure 1.3)

Confronting these two views bears the risk of getting stuck in a chicken and egg problem. Is it the venous return that is the main driver for the CO? *'…The heart can pump only as much as it receives…'.*† Or is it the heart that provides the energy to fill the venous vasculature and maintain the Pms?[25,32,33] *'… The heart can only receive what it pumps. …'* . Or both?[34] Both functions seem to interact with Ra as the negative feedback loop. That is probably the reason why the Guyton diagram[35] (See figure 1.4) is mostly used in the literature, as it elegantly combines both the cardiac function curve and the venous return curve.[23,36–38]

released when it changes its volume. He goes on with a mathematical multicompartment model showing how intravascular volume redistributes among the different compliant compartments in accordance with their flow-dependent distending pressures irrespective of Pms. In the literature a vivid discussion on Brengelmann's proposed views can be found.[24,152–155] .

* There has been some discussion around this formula. First Levy[156] pointed out that, based on the study designs it was based on, that not all the determinants of the formula are independent variables. This argument is also used by Bregelmann.[32] Especially Ra can be seen as a dependent predictor as it both influences flow and is influenced by the flow. See: the Guyton diagram.[35]

† This is a quote from CJ Wiggers from his foreword in: Venous Return. By GA Brecher, NY, Grune & Stratton,1956. *'' … It is axiomatic that the heart can pump only as much blood as it receives. Indeed, the volume of blood returned to the heart is the basic determinant of cardiac output. Since the latter varies enormously under ordinary conditions of daily activity, the mechanisms that facilitate venous return have been the subject of discussion for centuries."*

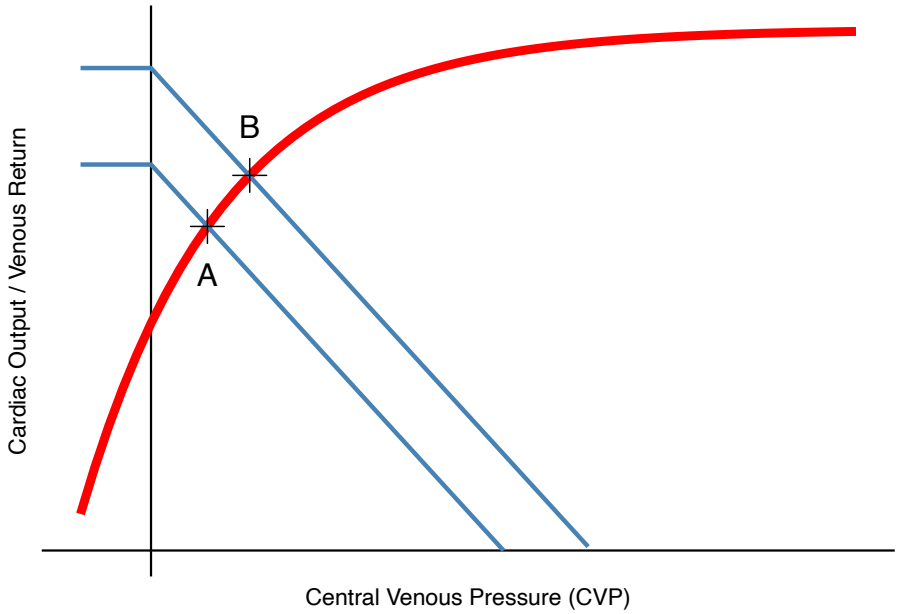


***Figure 1.4**:The Guyton diagram, combining the venous return curve with the cardiac function curve. The effect of fluid loading is shown as the shift to the right of the venous curve and the resulting shift of point A to point B. It shows how the resulting CVP, eventually is the result of its opposing effect on both equilibrated flows.*

1.2.2 A formal definition for research

To apply the concept of the Guyton diagram into applied research, a quantifiable variable needed to be defined.[39] In 1998, Tavernier et al. defined fluid responders, for the first time, as ***patients in whom the cardiac output increased by at least 15% after a fluid challenge of 500mL***. *(specific definition)*

This new definition has some important implications:
- it transforms the outcome of fluid loading from a continuous to a binary outcome. Dichotomizing the outcome made it easier to perform and to interpret studies that predict fluid responsiveness.
- it makes it a more uniform concept that enables to compare studies more easily. Although this formal definition is widely used in the literature, there still is some heterogeneity. A meta-analysis of Marik et al. showed that some studies used different amounts of fluids (e.g., 10 or 20 mL/BMI or a fixed

amount of 250 mL) and a minority using different cut-off values for CO-changes (e.g., 10 or 25%).[40]
Other sources of heterogeneity in the fluid responsiveness literature are on the one hand, the different types of fluids used, each with their own pharmacokinetic profile and, on the other hand, the different methods available to measure the CO changes, each with their specific measurement errors.

1.2.3 What is not in the definition of fluid responsiveness

Although the concept of fluid responsiveness seems straightforward, there still is some misunderstanding among researchers and clinical practitioners. The most important issue is how a fluid responsive patient should be managed. Although it has been pointed out repeatedly in several publications[41–44], being fluid responsive is sometimes wrongly interpreted as diagnosis of hypovolemia or an absolute indication for administering extra fluids.

Being fluid responsive is a normal physiologic condition. Although humans have much better developed homeostatic defense mechanisms to deal with hypovolemia, this preload reserve is one of the few mechanisms against fluid overload.*
On the other hand, when patients are no longer fluid responsive, they become vulnerable to fluid overload and logically, further administration of fluids is doomed to cause harm.
Fluid overload and its resulting increased capillary hydrostatic pressure make tissues prone for extravasation promoting capillary leak syndromes (see figure 1.5).[44]

* Recently, the concept of 'Fluid tolerance' was proposed.[157] In this first 'position paper' fluid tolerance was defined as:' … The degree to which a patient can tolerate administration of fluids without causation of organ dysfunction. …'. Although appealing, this first (vague) version of the concept needs more elaboration before it can be studied as a clinical entity.[158]

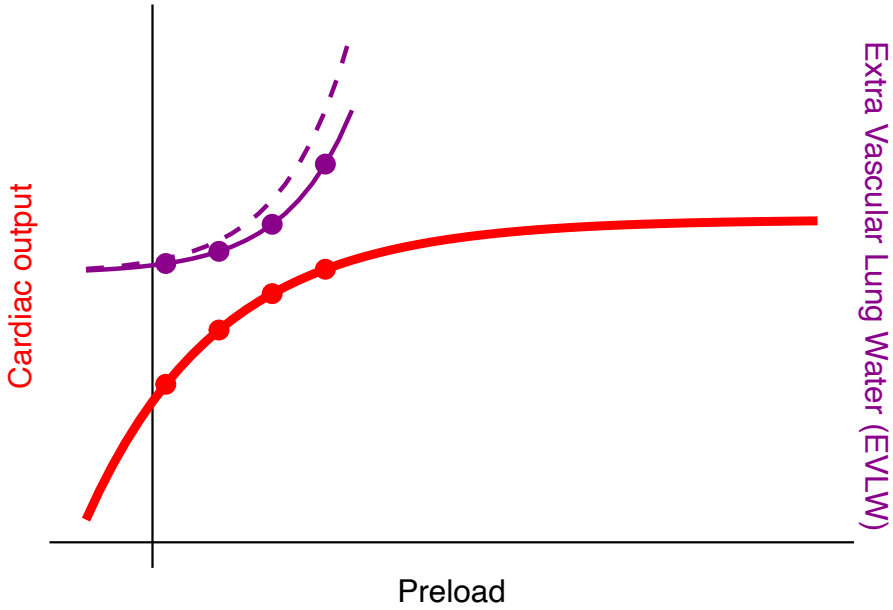


***Figure 1.5**:The cardiac function curve (red) with superimposed Marik-Phillips curve (purple)*. Relation of preload with Cardiac CO and Extra Vascular Lung Water (EVLW). As patients become less fluid responsive with incremental preload, EVLW (and tissue edema) increases significantly. In patients with increased vascular permeability, due to systemic inflammation, sepsis etc., the Marik-Phillips curve shifts to the left.* [44]

Furthermore, perioperative endothelial barrier damage may further exacerbate the detrimental effect of fluid overload.
Several molecular pathways responsible for this effect on endothelial permeability have been unraveled:
- Increased cardiac filling pressures trigger the release of natriuretic peptides. These molecules have shown to cleave the glycocalyx, the most important layer responsible to control the endothelial permeability.[2,45]

* The Marik-Phillips curve describes the relationship between preload and the accumulation of extra vascular lung water (EVLW), indicating the onset of edema formation during fluid loading. This curve, which was introduced in 2014 in an editorial by Marik et Lemson [44], is superimposed on the Frank Starling cardiac function curve. While not formally investigated by these authors, the claim that the elevation in EVLW coincides with the initiation of the plateau phase of the cardiac function curve appears to be rooted in the research of Aman et al. (Crit Care Med 2012; 40: 793-799). However, it's worth noting that the assertion linking this phenomenon to increased cardiac filling pressure and transmitted hydrostatic pressures lacks support from this work.

- Direct tissue injury and ischemia/reperfusion related to surgery result in a local release of DAMP's (damage-associated molecular patterns, e.g., HMGB-1). This family of molecules has a direct effect on the glycocalyx and neutrophil activation. Further activation of the systemic inflammatory response results in the release of multiple cytokines and molecules, most of them causing increased permeability of the endothelium.[3,46,47]

1.3 Predicting Fluid responsiveness

It has long been known that clinicians fail to predict fluid responsiveness. Meta-analyses looking into fluid responsiveness have shown that when left to the discretion of the attending anesthetist or critical care physician, about 50% of fluid challenges were given when the (hypotensive) patient, in fact, was a non-responder.[40,48] This makes that a patient is all too often exposed to a potential harmful fluid management. Being able to predict fluid responsiveness before effectively administering fluids is fully in line with Bellamy's call for *'… physiological measurements tailored to the individual patient…'*.

1.4. Static filling parameters to predict fluid responsiveness

Static filling parameters are variables that are measured at one time point. The most exemplary and historically most used static hemodynamic parameter is the central venous pressure (CVP). CVP is the pressure measured at superior caval vein or the right atrium at end-expiration. The rationale for the use of CVP to assess volume status comes from the premise that it is a good measure for intravascular volume or preload. Old guidelines defined specific target CVP values[49] * , or used changes in CVP to guide fluid management.[50] †

* In the 2012 Surviving Sepsis Guidelines initial hemodynamic goals were defined as: (1) CVP 8-12 mm Hg, (2) MAP >= 65 mmHg, (3) Urine Output >= 0.5 mL .kg-1.h-1 and (4) $S_{cv}O2$ 70% or S_vO2 65%. Since the subsequent 2014 update (Rhodes et al Intensive Care Medicine 2017; 43: 304-377) the use of CVP alone was no longer recommended.

† In this article the '5-2'-rule was recommended to monitor the effect of a fluid challenge:

Fluid challenge		
Observe CVP for 10 min	<8 cm H_2O < 14 cm H_2O ≥ 14 cm H_2O	200 ml x 10 min 100 ml x 10 min 50 ml x 10 min

However, Marik et al showed in 2008, that both a specific CVP value or the change in CVP after a fluid challenge, are poor predictors for fluid responsiveness.[51] In a subsequent update of this meta-analysis, they calculated the ROCAUC of CVP to be 0.56 (0.54-0.58). The overall correlation between baseline CVP and changes Stroke Volume/Cardiac Index was 0.18 (0.1 – 0.25).[48]

Several reasons have been proposed to explain these poor predictive properties[24,36,37]:

- The use of fluid filled catheters to measure CVP warrants to be zeroed and the transducers need to be placed at the correct level. Incorrect placement of the transducer can cause wrong measurement and may be the cause of heterogeneity in some studies. Two studies, in critical care nurses[52] and perioperative health care providers[53], found this critique to apply in clinical practice. These studies both found considerable variability in placement of the transducer.
- The CVP wave form consists of different waves and descends. The pressure measured at the base of the c-wave is the most appropriate value to assess the loading condition of the right ventricle. A pressure value taken at another moment in the cardiac cycle may yield very different values.
- To fully assess the transmural pressure, the CVP relative to the surrounding pressure, the measurement needs to be taken at the end of the expiration. Rogers et al. concluded in their study, however, that CVP-values on a commercial monitor are interchangeable with CVP-values timed at the base of the c-wave at expiration (bias -0.87 mm Hg and precision 1.05 mm Hg).[54]

Although these considerations and pitfalls may partially explain why CVP is such a poor predictor, the main reason is that one single pressure measurement cannot be used to assess the intra and interindividual variability of the Frank Starling/Venous return curve, which is influenced by factors like the compliance of the ventricle, contractility, Pms etc.

The same conclusion can be drawn from other static filling parameters like pulmonary artery wedge pressure, end diastolic Area/Volume.[55]

During infusion 0-9 min	**> 5** cm raise	STOP
Following infusion	**> 2** cm **<5** cm raise **> 2** cm raise $\leq$ **2** cm raise	Wait 10 min Wait STOP Continue infusion

An alternative for the use of the change in CVP following infusion, the '7-3 rule' was also provided, if Pulmonary Artery Wedge Pressure was used instead.

1.5 Dynamic filling parameters to predict fluid responsiveness

If one measurement cannot determine the individual Guyton-diagram, then multiple wisely chosen measurements, might do the job. It has long been known that there is a heart-lung interaction, that respiration has an impact on cardiac function. It turned out, that mechanical ventilation provides a good method, to change loading conditions of the heart. Measuring these cyclic and regular changes provides the framework for a family of dynamic filling parameters.

1.5.1 Physiology of the heart-lung interaction during mechanical ventilation

The heart and the lungs are not only functionally connected, but they also share the same anatomic location within the thorax. Ventilation and respiration alter the intrathoracic pressure (ITP). This makes the heart a ***'pressure chamber in a pressure chamber'***. Altering the ITP affects the gradients between the heart and the extra-thoracic organs but does not change the pressure gradients between the heart and the lung within the thorax.
During full mechanical ventilation ITP increases during insufflation proportional to the Tidal Volume[56]. ITP normalizes during expiration. These swings in ITP have a complex impact on the different determinants of the cardiac function (see figure 1.6).[41,57]

CVP or the Pressure in the right atrium (Pra) is the back pressure of ***the venous return to the right ventricle***. Because Pms is located outside the thorax changing the ITP will change the gradient with Pra. An increase in ITP will result in a decrease in this gradient because it changes the transmural pressure of Pra to the amount of Pra + effective pleural pressure (Ppl)*. Changing the back pressure of the venous return can have an important effect on the resulting right ventricular output.[31,58]
The resultant impact of positive pressure ventilation is shown schematically in figure 1.6 and figure 1.7.

* Provided that the pericardial pressure is negligible.

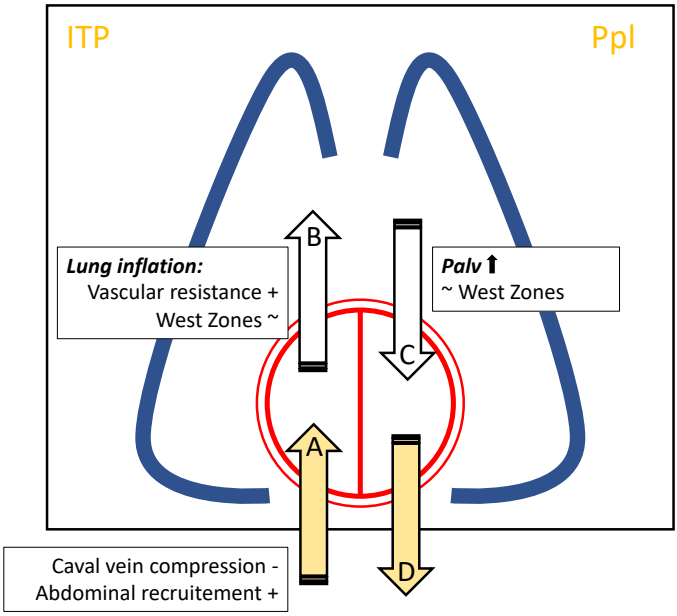


***Figure 1.6**: Schematic representation of the 'pressure chamber in pressure chamber' concept and the impact of positive pressure mechanical ventilation on the different determinants of the cardiac function. Heart and lungs are depicted within the thoracic cage. Arrow A: right ventricular preload, Arrow B: right ventricular afterload, Arrow C: left ventricular preload, Arrow D: left ventricular afterload. ITP: Intrathoracic pressure Ppl: Pleural pressure. Yellow arrows, the arrows crossing the thoracic cage (A-D), are subjected to the effect of changes in transmural pressure due to elevated ITP (or Ppl). Insufflation (increased ITP) will result in decreased venous return to the right ventricle and afterload reduction of the left ventricle. White arrows, RV afterload (B) and LV preload (C) are located withing the thoracic cage. Changes in pleural pressure will not result in changes in pressure gradients between the heart and the lungs. The effect of mechanical ventilation on these determinants are mediated through direct effects on the pulmonary circulation.*

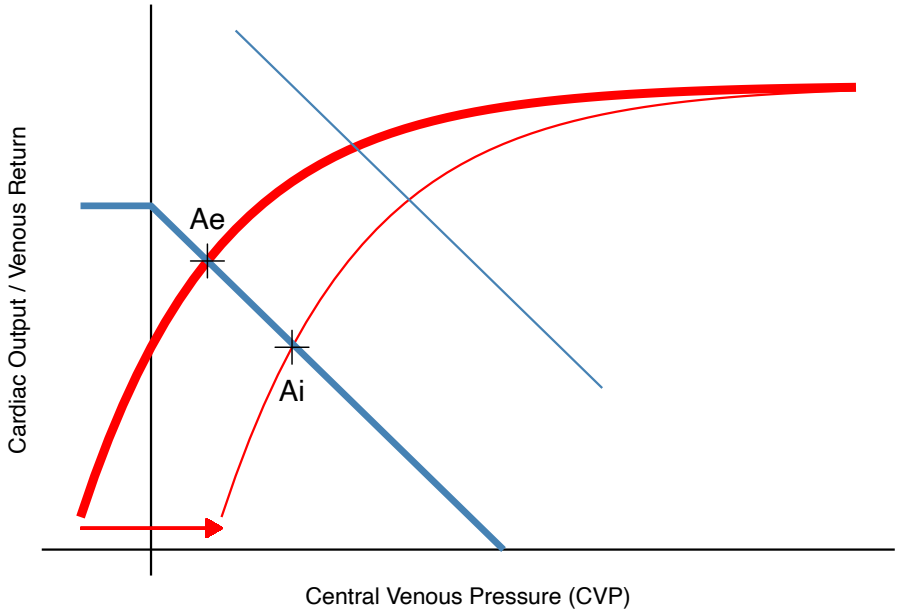


***Figure 1.7**: Schematic representation of the effect of mechanical ventilation on the Guyton diagram. The change of the transmural pressure, during inspiration, is depicted as a shift to the right of the Frank-Starling. The shift from Ae (the working point of the patient during expiration) to Ai (the working point at inspiration) is the effect of Mechanical Ventilation on the venous return and CO.*

Besides the direct effect of ITP changes some other effects have been described:
- Diaphragm excursion can increase venous return by direct compression of liver or increasing the abdominal pressure.[59]
- Direct compression on the caval veins.[60]

As the left ventricle and the lungs are both located in the thorax, changing the ITP, contrary to his right sided counterpart, will not affect the ***venous return to the left ventricle***. The effect of mechanical ventilation on left ventricle venous return will be mediated through direct changes in the pulmonary circulation. The insufflation of the lung results in increased alveolar pressure that can compress alveolar vessels. Depending on the zone

conditions of the lung this may result in a transient preload increase (Zone West 3) or a decrease (Zone West 2).[61]

Likewise, because the lung and the right heart are both located within the thoracic cavity, ***afterload of the right ventricle*** (the force resisting ventricular ejection) is not directly affected by changes in ITP. However, the expansion of the lungs and the stretch on its vasculature, directly alters the pulmonary vascular resistance and elastance as well as pulmonary arterial pressures by changing the distribution of the zones of West in the lung.[62–64]

Increasing the ITP decreases the gradient between LV and the aorta. As a result, positive pressure insufflation decreases ***left ventricular afterload***.[65,66]

To makes things even more complex, additional principles involved during mechanical ventilation need to be clarified:
1. ***Ventricular interdependence***: Both sides of the heart share the septum and reside in the constraints of the pericardial space. This not only makes the influence of pathologies that increase the pericardial pressure (e.g.: pericardial effusions) on the above mentioned more complicated, but it also makes them dependent of each other. Increased or aberrant filling of one ventricle directly impacts the diastolic function of the other ventricle.[67]
2. ***Phase shift***: Blood passing through the heart and the lungs is affected by these different mechanisms at different moments. The effect of inspiratory induced decrease in venous return and RV outflow causes a decrease in LV filling only after its passage through the lungs. As the pulmonary transit time is about 2 seconds, this usually coincides with the expiratory phase of the respiratory cycle. This paradoxical effect (seeing the effect of inspiration, at expiration) was already nicely shown in 1966 by Morgan et al.[68] As such the inspiratory decrease in afterload of the LV and the concomitant decrease in RV output are disconnected and further accentuate the effect of mechanical ventilation on Stroke Volume/Cardiac output.

1.5.2 Dynamic filling parameters

These cyclic effects of mechanical ventilation on CO, can be directly measured or can be determined from an arterial pressure curve. There are, in general, four families of dynamic filling parameters based on the heart-lung interaction, described in the literature:

Systolic Pressure Variation (SPV). SPV was first described by Coyle et al in 1983, as the range of systolic blood pressures during one mechanical ventilation cycle.

$$SPV\ (mmHg) = SAP_{max} - SAP_{min}$$

Perel et al further refined this by splitting SPV into ΔUp and ΔDown. (See figure 1.8) By using an apneic reference systolic pressure, they were able to show that ΔUp correlates with the LV afterload reducing effect and ΔDown correlates with the RV preload reducing effect.*

Pulse Pressure Ventilation (PPV). Because pulse pressure (PP = systolic pressure – diastolic pressure) is proportional to the Stroke Volume, cyclic changes in PP are preferred by some to assess fluid responsiveness. When calculated as a percentual change, and with an arterial compliance assumed to be constant, it should theoretically be equal to the percentual change of stroke volume. The base formula† to calculate PPV is:

$$PPV\ (\%) = 100\ \frac{PP_{max} - PP_{min}}{(PP_{max} + PP_{min})/2}$$

Stroke Volume Variation (SVV). When beat-to-beat stroke volumes are measured, the same formula can be applied to calculate the SVV.

$$SVV\ (\%) = 100\ \frac{SV_{max} - SV_{min}}{(SV_{max} + SV_{min})/2}$$

* Perel et al published the Respiratory Systolic Variation Test based on the Δdown.[159] The test is a standard maneuver for applying incremental airway pressures during ventilation. They used the calculated slope between minimal systolic pressures and airway pressures as a measure to predict fluid responsiveness. Preisman et al found the optimal cut-off value to be > 0.51 mmHg/cm H_20, with a ROCAUC of 0.96, and sensitivity and specificity of 0.93 and 0.89 respectively.[55]

† Recently a new method to determine the cyclic variation in pulse pressure based on Fourier analysis has been published.[160,161] .

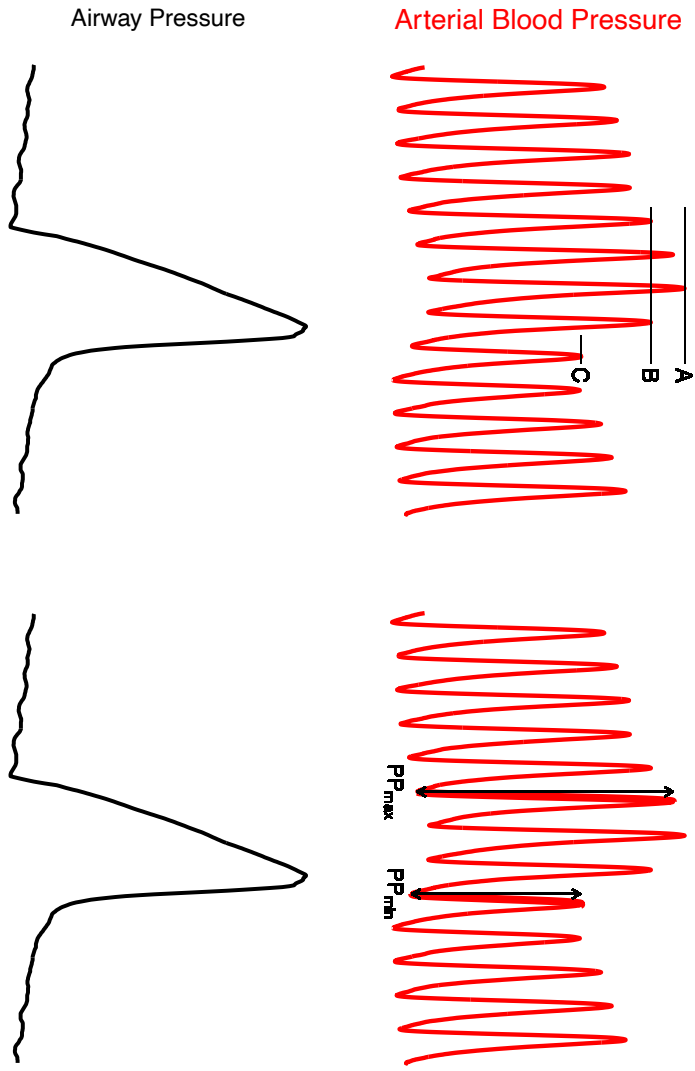


***Figure 1.8**: Determination of **Systolic Pressure Variation (SPV)** and **Pulse Pressure Variation (PPV)** on an invasive arterial blood pressure curve synchronized airway pressure profile. Left side: SPV: A: Maximal systolic pressure during a mechanical ventilation cycle, B: the apneic reference systolic pressure taking before the beginning of insufflation, C: minimum systolic pressure. SPV = A-C, Δup = A-B and Δdown=B-C. Right side: PPV: identification of the maximum and minimum pulse pressure. PPV = 100* (PP_{max}-PP_{min})/(PP_{max}+PP_{min})/2*

There are different methods to determine beat-to-beat stroke volume and SVV, that have been described and that are commercially available like calibrated and non-calibrated arterial pulse contour analysis[69], esophageal doppler,[70] echocardiography[71] and the volume clamp technique.[72]

Other surrogates for SVV can be derived from the ***photo-plethysmography waveform***. Two variants have been described ⊿POP and PVI:
Variations in pulse oximetry plethysmography waveform amplitudes (∆POP), which uses the amplitude of the signal, measured at finger sensor.

$$\text{POP}\ (\%) = \ 100\ \frac{Ampl_{max} - Ampl_{min}}{(Ampl_{max} + Ampl_{min})/_2}$$

Pleth Variability index (PVI). A commercially available variant is based on the beat-to-beat variation in perfusion index (PI)*, also based on this totally non-invasive technology. They used a slightly different formula to calculate this index.

$$PVI\ (\%) = 100\ \frac{PI_{max} - PI_{min}}{PI_{max}}$$

* Perfusion index (PI) is calculated as $100\ \frac{AC}{DC}$. AC stands for 'Alternating Current' and is the pulsatile variation in light absorption measured at the PPG probe. This change in absorption is mainly caused by the pulsatile arteries and their temporal change in blood volume content. DC stands for 'Direct Current'. DC corresponds to the non-pulsatile light absorption from the other tissues, such as bones skin and soft tissues.

1.5.3 First Results

1.5.3.1 Prediction properties

The most studied dynamic parameters are ***PPV and SVV***. Meta-analyses consistently show that these parameters, when used correctly, have excellent prediction properties.[40,73] (See table 1.1) The AUROC of PPV and SVV are above 0.9 and 0.8 respectively. The difference between PPV and SVV was statistically significant in the meta-analysis of Marik et al. The exact reason for this difference is not known. However, different methods to determine beat-to-beat stroke volumes, each with their own principles and their own inherent measurement error, may yield different calculated values of SVV and may be a source of heterogeneity.[74,75] Invasive blood pressure measurement, on the contrary, is probably less prone to measurement error.[75]
For both PPV and SVV it was shown that ***the optimal cutoff was about 12%.*** This corresponds, for PPV with a sensitivity and specificity of 0.89 and 0.88 and diagnostic odds ratio of 59.86. This means that a patient with PPV > 12% is about 60 times more likely to be a fluid responder than a non-responder.*

Later in, 2011, an interesting alternative approach for assessing the predictive properties of PPV was published by Cannesson et al. in a large multicenter study. Instead of using 1 optimal cutoff point, which is customary when using the classic ROC method, they introduced the 'gray zone approach'. In a two-step method they determined two cut-offs. The optimal threshold for excluding fluid responsiveness and the optimal threshold for diagnosing fluid responsiveness. Values between these two thresholds were considered 'inconclusive' and were defined as the 'gray zone'. In their cohort they found the optimal classic threshold to be 12%, in line with the previous studies. ***The gray zone ranged from 9% to 13%***.[76 †]

* Most publications studying the prediction of fluid responders use univariate prediction models. Ikeda et al compared a model containing ventilator settings and right sided hemodynamics with PPV in predicting fluid responsiveness with limited success.[162] Other researchers used multiple logistic regression build on PPV and other parameters measured with the MostCare monitor (arterial elastance, cardiac cycle efficiency and the systolic-dicrotic pressure difference.)[163,164]

† In this original study, about 24% (98/413) of the studied patients had a PPV value before the fluid challenge in this gray zone.

Two meta-analyses assessed the ability of PVI to predict fluid responsiveness.[77,78] The most recent one included 27 studies and found an ROCAUC of 0.82 (0.79-0.85).[78] There was however a wide range of optimal cut-offs. This higher heterogeneity is partly explained by the effect of vasoactive medication like noradrenalin on the signal quality of the photoplethysmogram.[79]

1.5.3.2 Dynamic filling parameters in clinical pathways

Different studies have incorporated these dynamic filling parameters in flow charts and clinical pathways for perioperative hemodynamic management. Deng et al bundled 37 such studies in a recent meta-analysis.[80]
They concluded that pathways solely based on dynamic filling parameters did not significantly change various outcomes compared to the heterogenous control group. Pathways incorporating dynamic parameters (like PPV and SVV) in combination with cardiac output measurements, on the contrary, differed significantly in terms of short-term mortality (OR: 0.45, 95% CI (0.24,0.85)), overall morbidity (OR: 0.41, 95% CI (0.28,0.58))*, length of stay in the ICU (MD= -0.77days, CI (-1.07, -0.46)) and hospital stay (MD -1.18 days, CI (-1.90, -0.46)).
It should be noted however, that there are some considerations to be made with this meta-analysis and that its results still need confirmation in large

* Specific complications were assessed as a secondary outcome:
For trials incorporating both dynamic filling parameters and cardiac output goals[80]:

	OR	95% confidence interval
Cardiac complications:		
Arrhythmia	0.58	0.37 – 0.92
Myocardial infarction	0.35	0.16 – 0.76
Heart/failure/cardiovascular dysfunction	0.31	0.14 – 0.67
Pulmonary Events:		
ALI/ARDS	0.13	0.02 – 0.74
Pneumonia	0.4	0.24 – 0.65
Pulmonary embolism	0.31	0.03 – 3.04
Abdominal Events		
Gastrointestinal bleeding	0.66	0.11 – 4.03
Gastrointestinal obstruction	0.83	0.24 – 2.79
Renal Events		
Acute Kidney Injury	0.49	0.19 – 1.23
Renal failure with dialysis	0.87	0.32 – 2.39

In an older meta-analysis incorporating 14 studies also infectious complications were included and found to be significant (OR: 0.45 95% (0.27 – 0.74)).[165]

scale randomized controlled trials. The most important issues are power of the studies and the heterogeneity of data.[81]
Although this meta-analysis incorporated 37 studies, pooling 2910 patients, no formally power analyses were done. Unknown power can go both ways. As some secondary outcomes and the analysis of studies incorporating only dynamic filling parameters were done on a subset of the total dataset, it is possible that an underlying effect is not detected due to lack of power. On the other hand, effects found to be statistically significant in this meta-analysis might be overestimated or wrongfully identified as a real underlying effect.
A supplementary trial sequence analysis would have provided insight into these issues.[81,82]
Another concern in all meta-analyses looking into perioperative goal-directed therapy is the heterogeneity of both the control groups and the different definitions of outcomes between the different trials.[81,83]

1.5.4 Pre-requisites and applicability

So far, dynamic filling parameters like PPV and SVV, have been presented as near perfect parameters for perioperative fluid management:

- They are reliable in predicting fluid responsiveness, due to the unique interaction between mechanical ventilation and the beating heart to assess the patients' individual cardiac-venous return function.
- Mechanical ventilation turns out be a cyclic maneuver that is perfectly reversible in the sense that no additional fluid is administered. Therefore, the administration of excess fluids to non-responders is minimized.
- These parameters can easily be calculated in an automatic and continuous fashion, without any need for additional actions by the anesthetist.

However, dynamic filling parameters are not a panacea for every patient. Different restrictions for its correct use should be considered.[84,85] As the heart-lung interaction is the underlying principle for these parameters, the restrictions can be largely divided into respiratory restrictions, cardiac restrictions and restrictions based on their interaction. (See figure 1.9).

Respiratory pre-requisites:

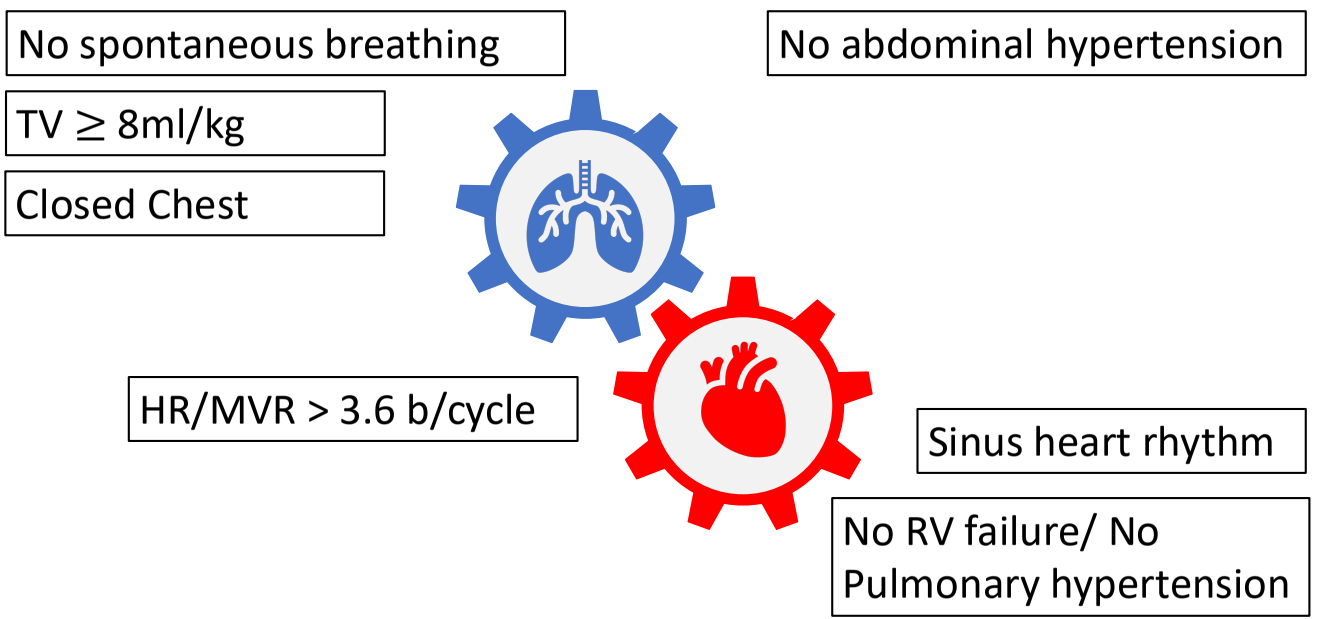
- ***Absence of spontaneous breathing.*** Any phenomenon that interferes with the mechanical ventilation induced regular increases in intrathoracic pressure, undermines the well-functioning of the measured parameter. Because spontaneous physiologic breathing decreases intrathoracic pressure and is slightly irregular, it was always considered an exclusion criterion in the above-mentioned studies. The same goes for intubated patients fighting the ventilator. A few studies confirmed the poor prediction capabilities of PPV in patients with spontaneous breathing. These studies were conducted in intubated patients on pressure support[86,87], in non-intubated patients[88] and in a mixed group of both.[89] *

- ***Tidal Volume ≥ 8mL/kg.†*** The effect of full mechanical ventilation on intrathoracic pressure is proportional to the tidal volume used in patients with normal lung compliances.[57,90] The use of lower tidal volumes in these patients, logically leads to diminished intrathoracic pressure swings and ultimately to lower PPV values.[91] De Backer et al. were the first to show in critically ill patients that a tidal volume of at least 8 mL/kg was a pre-requisite for PPV to have good prediction capabilities for fluid responsiveness.[92] Ever since, several studies, both in ARDS patients and non-ARDS patients, have confirmed the finding that smaller tidal volumes not only lead to smaller cut-off values for PPV, but also diminish the sensitivity and specificity of these adjusted thresholds.[93–97] Different measures to correct for tidal volume were proposed. Vistisen et al proposed, based on their animal study, to index PPV by the tidal volume, because of their consistent proportional relation in different volume states.[98] Liu et al. on the other hand, suggested to adjust PPV by changes in pleural pressure specifically in patients with Acute Respiratory Distress Syndrome.[95]

* Another study by Grassi et al concluded that in intubated patients on pressure support, PPV had excellent prediction capabilities. [166] There are however some serious methodologic issues with this study, not in the least the strictly pressure-based definition used for fluid responsiveness.

† In their study in postoperative cardiac patients Lansdorp et al found that a tidal volume of ≥7mL/kg may be equally reliable.[101] Although later studies confirmed the 8mL/kg instead of the ≥7mL/kg criterium, some authors have used the findings of Lansdorp et al.[117]

Figure 1.9: Overview of the pre-requisites for the correct use of dynamic filling parameters. TV = Tidal Volume, HR = Heart rate, MVR = Mechanical Ventilation Rate, RV = Right Ventricle



- ***Closed chest conditions.*** Opening the thoracic cavity changes the impact and the interplay between the mechanical ventilation and the cardiac function, directly influencing the value and relevance of PPV.[99] Several studies have shown that the loss of a closed thoracic cavity like during thoracic and cardiac procedures, comes with poor reliability of PPV and/or SVV to predict fluid responsiveness.[100]

Cardiac considerations:

- ***Sinus heart rhythm.*** With the loss of a regular heart rhythm, the variation in PP or SV are no longer solely caused by the cyclic changes induced by mechanical ventilation, as the irregular heart rhythm also directly causes variations in PP. The formula used to determine the PPV cannot separate these two effects. This is the reason why almost all studies exclude a patient population with irregular cardiac rhythm. The loss of its good predicting abilities and a decrease in sensitivity and specificity were shown in a mixed ICU population[86] and in postoperative cardiac surgery patients.[101]
- ***No RV failure/ No pulmonary hypertension.*** As already mentioned, mechanical ventilation influences RV afterload. Patients with RV failure and/or pulmonary hypertension are especially sensitive to increases in RV afterload. In these patients, the main effect of mechanical ventilation shifts from the preload to the afterload effect on the RV. This may explain the higher number of patients with high values of PPV which are nevertheless poor fluid responders.[102,103]

Other considerations:

- ***HR/MVR ratio > 3.6:*** De Backer et al. showed that respiratory rate had an impact on dynamic filling parameters. Patients who were ventilated with a high respiratory rate had lower values of PPV and SVV. Besides the direct impact on filling times of the left and the right ventricle, a sampling effect* is probably responsible for this effect.

* If we conceptualize the effect of mechanical ventilation as a cyclic, sinusoidal process that we want to measure, then the heart rate can be seen as the measurement sampling frequency. The ratio of these two frequencies (HR/MVR) has some mathematical consequences:
  - Decreasing the HR/MVR will influence the maximal measured magnitude difference within 1 cycle.

They found the minimal heart rate over mechanical ventilation rate ratio (HR/MVR) should be 3.6 to detect variations in aortic flow or PPV of at least 10%.[104]

- ***No abdominal hypertension.***
  Older animal studies using a pig model, showed that SVV and PPV increase when intra-abdominal pressures (IAP) were increased to 25-30 mmHg. The ability to predict fluid responsiveness was preserved although the optimal threshold was shifted to higher values. Jacques et al. found the optimal threshold for PPV to be 41%,[105] Renner et al. found a shift from 11.5% to 20.5% for optimal PPV values.[106] The heterogeneity in applied IAP (30 vs 25 mmHg) and different tidal volumes used (13 mL/kg vs 10mL/kg) might explain this difference. Duperret et al. showed in an animal model that the effect of IAP on PPV, is biphasic. IAP pressures up to 10-15 mmHg have minimal impact but further increasing IAP had a proportional effect on PPV, SVV and SPV values.[107]
  The studies conducted in patients, were performed during laparoscopy. The IAP applied in these studies were in the lower range: 12-15 mmHg.[108–111] These studies found that PPV and SVV did not significantly change after implementation of these moderate intra-abdominal pressures.
  Of these, the studies using fluid challenges of 500 mL found that PPV (during robot assisted surgery in the Trendelenburg position)[109] and SVV measured with esophageal doppler monitoring[111] were reliable fluid responsiveness predictors with unchanged thresholds. The studies using smaller fluid challenges (250mL[108] and 3mL/kg[110]) showed that PPV correlated with SV changes but was no longer able to reliably predict fluid responsiveness during laparoscopy. A systematic review by Chen et al further underlined this heterogeneity and the need for more robust studies to draw firm conclusions.[112]

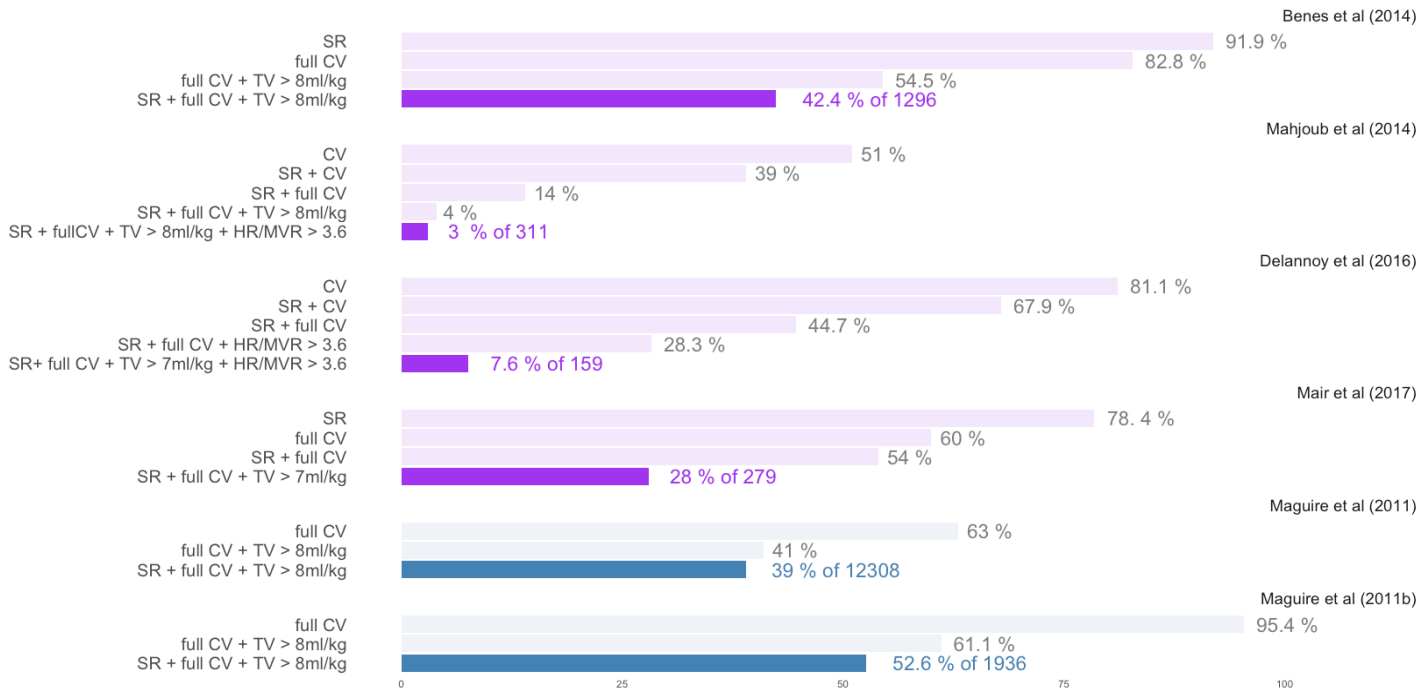
Several observational cross-sectional studies revealed that these pre-requisites undermine the applicability of PPV and SVV in clinical practice (see Figure: 1.10).
Especially in the ICU, both in ARDS and non-ARDS patients, protective mechanical ventilation with low tidal volumes is recommended, with ventilation modes incorporating spontaneous breathing frequently being

- HR/MVR < 2: aliasing effect: the calculated sinusoidal function for MVR will underestimate the frequency of MVR.

used.[113] It was found that in patients admitted to the ICU a considerable percentage of patients admitted did not fulfill the studied pre-requisites. This percentage ranged from 3% to 42.4%.[114–117]

Also, during surgery, a vast proportion of patients is not eligible for the use of dynamic filling parameters. Maguire et al. assessed 12,308 patients during surgery and found only 63% of the patients to fulfill the full mechanical ventilation pre-requisite. The number of patients further decreased to 41% if the tidal volume was considered as well. A sub-analysis of the patients with an arterial line, a population more likely to benefit from a strict hemodynamic management, revealed that after considering the respiratory and arrythmia pre-requisites, only 52.6% of the 1,936 patients were eligible for the use of PPV.[118]

***Figure 1.10*: Schematic overview of the individual and combined pre-requisites for the use of PPV on the applicability in clinical practice.** *Purple = study in ICU patients, Blue = study in OR. SR = Sinus Rhythm, CV = Controlled Ventilation, fullCV = Controlled Ventilation without spontaneous effort, TV = Tidal Volume*



1.5.5 Adjustments and solutions: Functional Hemodynamic Tests.

To overcome some of these restrictions and to increase the applicability of dynamic filling parameters, several solutions were described and tested. These Functional Hemodynamic Tests (FHT) can be divided in 4 well studied categories.* A schematic overview of these FHTs and their advantages and disadvantages, is provided in figure 1.11.

Tidal Volume Challenge (TVC).

TVC was first described by Myatra et al.[119] It consists of a transient increase in TV from 6mL/kg to 8mL/kg. The difference between PPV or SVV measured during these two ventilation-modes, as absolute difference or as relative/percentual change, is used as a new parameter to predict fluid responsiveness.

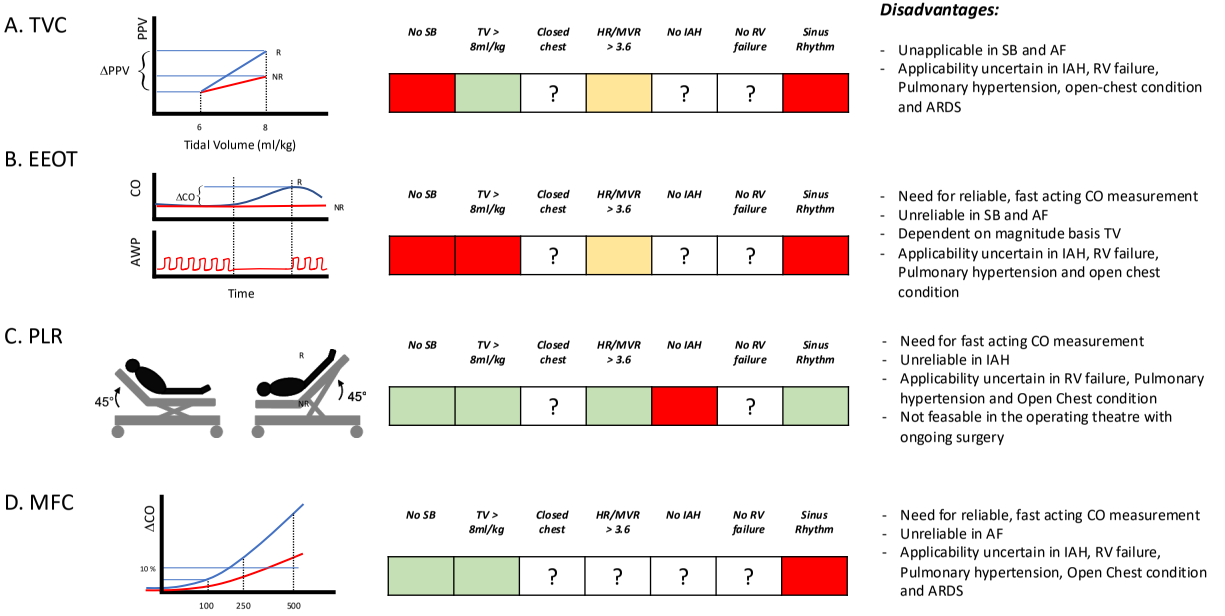
In their original study in ICU-patients, they not only showed that this new parameter has excellent prediction properties, but that it also tended to perform better than the PPV/SVV measured with a Tidal Volume of 8mL/kg.[119] These findings have been reproduced in small studies including patients undergoing surgery and patients admitted to the ICU. (See table 1.2).[120–124]

The advantage of this FHT is the fact that it is simple to perform without the need for advanced hemodynamic monitoring. This makes it possible to intermittently assess fluid responsiveness in patients ventilated with low TVs, even during laparoscopy[122] . Data on the use of TVC in ARDS patients, however, are lacking, because only one study on ICU patients had a small subgroup with ARDS.[124]

Evidently, TVC does not offer a solution for spontaneous breathing and arrhythmia.

* Besides these 4 categories, some other FHT's have been published. Valsalva,[150] lung recruitment maneuvers[148,149] and PEEP[151] test show promising results but have been tested so far in too few studies containing few patients (see table 5). More research on these FHT's is needed.

***Figure 1.11*: Overview of the Functional Hemodynamic Tests (FHT).** TVC = Tidal Volume Challenge, EEOT = End Expiratory Occlusion Test, PLR = passive Leg Raising, MFC = Mini-Fluid Challenge. **Left panel:** schematic representation of the individual FHT, with the hypothetical findings of a fluid responder (R, blue) and a fluid non-responder (NR, red). **Middle panel:** color-coded bar for the solution of classic pre-requisites for the use of PPV or SVV. Red= no solution, green = solution, yellow = weak data, white = unknown. **Right panel:** Disadvantages of the FHT's. SB= Spontaneous Breathing, AF= Atrial Fibrillation, PPV= Pulse Pressure Variation, CO = Cardiac Output, AWP = Airway Pressure. TV = Tidal Volume, HR/MVR = Heart rate over Mechanical Ventilation Rate ratio. IAH = Intra-Abdominal Hypertension, RV failure =



Disadvantages:

- Unapplicable in SB and AF
- Applicability uncertain in IAH, RV failure, Pulmonary hypertension, open-chest condition and ARDS

- Need for reliable, fast acting CO measurement
- Unreliable in SB and AF
- Dependent on magnitude basis TV
- Applicability uncertain in IAH, RV failure, Pulmonary hypertension and open chest condition

- Need for fast acting CO measurement
- Unreliable in IAH
- Applicability uncertain in RV failure, Pulmonary hypertension and Open Chest condition
- Not feasable in the operating theatre with ongoing surgery

- Need for reliable, fast acting CO measurement
- Unreliable in AF
- Applicability uncertain in IAH, RV failure, Pulmonary hypertension, Open Chest condition and ARDS

End-Expiratory Occlusion Test (EEOT).

Monnet et al. described in 2009 the EEOT.[125] It consists of an interruption of ventilation at end expiration for 15 seconds (or longer). The percentual raise of cardiac output associated with this pause is measured with a fast-responding monitor.

A meta-analysis of Messina et al. including 10 studies, concluded EEOT to be a very reliable test. with an optimal cut-off $\Delta SV \geq 5\%$ to predict fluid responsiveness with a sensitivity and specificity of 0.86 and 0.91 respectively.[126]

However, more recent studies, not included in the meta-analysis, were less optimistic. These studies, mostly in surgical patients, found less prediction capabilities as reflected in ROCAUC's below 0.75.[120,121,127,128] (see table 1.3A and table 1.3B) These results seriously question the clinical use of EEOT, especially perioperatively and can be partially explained by baseline TV. As mechanical ventilation with smaller TV's seem to decrease the ROCAUC, sensitivity and specificity.

Further disadvantages of this FHT are the inability to cope with spontaneous breathing, the uncertainty of the effect of prone position and/or ARDS and the need for fast-responding hemodynamic monitoring to measure changes in cardiac output.

Passive Leg Raising (PLR).[*]

Passive leg raising is a Trendelenburg maneuver standardized by Monnet et al. (see figure 1.11) It consists of adjusting the bed position from a semi-recumbent to a legs-up position and back. The change in cardiac output[†] over these three phases is calculated.

[*] There might be some confusion about the PLR. It was originally described as a predictor for the effect of a real fluid challenge on cardiac output. It was shown that a raise in CO of at least 10% reliably predicts fluid responsiveness. Some studies[124,141] however, started using this criterium to define fluid responsiveness. These studies typically determine the predictive ability of some parameter to predict a PLR-induced raise in CO of at least 10%. Switching the PLR from predictor for fluid responsiveness to the definition of fluid responsiveness induces confounding.

[†] Some researchers investigated if PLR induced changes in PP, a variable more easily and reliably measured, was a reliable alternative for CO. However, the meta-analysis of Monnet et al. showed that PP had a pooled sensitivity, specificity and ROCAUC of 0.57 (0.49-0.53),

This makes it possible to perform a reversible fluid challenge without the risk of administering excess fluid.
To perform PLR correctly, attention should be paid to following aspects [129]:

- PLR starts in the semi-recumbent position and not in the supine position. Adding trunk lowering further increases the amount of fluid that is mobilized during this test up to 300mL.
- To track the changes in cardiac output during these different stages, a reliable fast-responding measuring device is needed.
- The maneuver should be performed gently, not to evoke pain, discomfort, awakening etc. as this changes adrenergic levels introducing a confounding factor.

PLR is well studied and seems reliable in patients with spontaneous breathing, low lung compliance or ventilated with low TV and atrial fibrillation.
A meta-analysis including 21 studies found an optimal threshold of a PLR induced $\Delta CO \geq 10\%$ predicting fluid responsiveness with a ROCAUC of 0.95 (0.94-0.96). Sensitivity and specificity were 0.85 (0.81-0.88) and 0.91(0.88-0.93) respectively.[130]
Some disadvantages remain:

- Its reliability in patients with intra-abdominal hypertension is not confirmed.[131]
- Most importantly, PLR is not feasible in the operating theatre with ongoing surgery.

Mini-Fluid challenge (MFC)
Mini-fluid challenge is a test that consists of administering a small amount of fluid, usually 100mL over a short period of time. The increase in cardiac output from this mini fluid bolus was shown to be able to identify fluid responders.[132]
This has been reproduced in surgical and ICU patients. (See table 1.4A and table 1.4B)
In their meta-analysis, Messina et al., estimated the pooled ROCAUC to be 0.91 (0.85-0.97). The optimal threshold was an MFC induced increase in CO of 5% which corresponded with a sensitivity and specificity of 0.82 (0.76-0.88) and 0.83 (0.77-0.89) respectively.[126]

0.83(0.77-0.88) and 0.77 (0.72-0.83) respectively.[130] Recent studies using PLR induced changes in perfusion index (measured with a pulse oximeter)[167] and capillary refill[168] are promising but need confirmation.

The obvious advantage of the test is its applicability in patients with spontaneous breathing[133] and in patients ventilated with small tidal volumes.[127,134] In contrast to PLR this test is feasible during surgery.
The major drawback of this technique is the need for fast-responding cardiac output monitoring. As with the EEOT, small differences in CO need to be reliably determined.
Smorenberg et al. compared two monitors in a step up MFC model. They concluded that each monitor comes with its own measurement error and its own minimal amount that can be used as MFC.[135] Some other authors had to adjust the calculated optimal cutoff, because it was below the sensitivity of their monitor.[127,132]

Mallat el al. proposed an elegant solution.* In their study on ventilated ICU patients, they found that the decrease in PPV induced by the MFC could provide an alternative (ROCAUC = 0.92). An absolute decrease in PPV of at least 2% had a sensitivity and specificity of 0.86 and 0.85 respectively. Another interesting fact is that the mean tidal volume used in study was 6.8ml/kg.[136] Recently they reconfirmed this principle in a new study on ICU patients. In this study the change in PPV after PLR instead of MFC, was used as a predictor, yielding almost identical promising results.[137]

* Besides the clinical advantage there is also a more technical/statistical advantage. As raised by Vistisen and Scheeren,[169] MFC studies have some inherent coupling. Not only are ΔSVI of the mini fluid bolus and 'large' fluid bolus coupled because of their shared baseline, but both the dependent (ΔSVI_{100}) and independent variable (ΔSVI_{250}) in such a study are measured with same device. By using a predictor (ΔPPV_{100}) that differs from the independent variable (ΔSVI_{250}) this coupling and its potential overestimation is overcome.

***Table 1.1*: Results from meta-analyses of the prediction capacity of dynamic filling parameters in ventilated patients.** *SPV: Systolic Pressure Volume, PPV= Pulse Pressure Variation, SVV= Stroke Volume Variation, PVI= Pleth Variability index, DPOP = Variations in Pulse Oximetry Plethysmography waveforms amplitudes. ICU= Intensive care unit, OR = Operating Room, Sens= Sensitivity, Spec= Specificity ROCAUC = area under the curve of the Receiver Operating characteristic. NA= Not available from the publication.*

Parameter	*Reference*	*Patients*		*studies*	*Threshold* *	*ROCAUC*	*Sens*	*Spec*
SPV	***Marik et al*** [40] *2009*	171	ICU + OR	8	NA	0.86 (0.82-0.90)	NA	NA
PPV	***Marik et al*** [40] *2009*	565	ICU + OR	22	≥12.5 % (+/- 1.6 %)	0.94 (0.93-0.95	0.89 (0.82-0.94)	0.88 (0.81-0.92)
	Yang et Du [73] 2014	807	ICU	22	≥12% (IQR: 10-13%)	0.94 (0.91-0.95)	0.88 (0.81 – 0.92)	0.89 (0.84-0.92)
SVV	***Marik et al*** [40] 2009	258	ICU + OR	12	≥11.6% (+/-1.9%)	0.84 (0.78-0.88)	0.82 (0.75-0.98)	0.86 (0.77-0.92)
	Zhang et al [69] 2011	568	ICU + OR	23	≥10% (IQR: 9.5-11.5%)	0.93 (0.91-0.95)*	0.81 (0.77-0.85)	0.80 (0.70-0.88)
ΔPOP	***Sandroni et al*** 2012 [77]	204	ICU + OR	6	≥12% (IQR: 11.6-13.5%)	0.89 (0.82-0.96)	0.85 (0.76 – 0.92)	0.85 (0.72-0.93)
PVI	***Sandroni et al*** 2012 [77]	161	ICU + OR	5	≥10% (IQR: 9.5-11.5%)	0.95 (0.82 -0.96)	0.83 (0.76-0.92)	0.89 (0.70-0.98)
	Liu et al [78] 2019	1035	ICU + OR	25	Range: 7-20%	0.82 (0.79-0.85)	0.77 (0.67-0.85)	0.77 (0.71-0.82)

* Estimate were not formally tested as pooled estimates but as the summary of the individual studies. Reported as median IQR, mean +/-SD or range.

* Sensitivity analysis (after exclusion of 1 trial: Zimmermann et al Eur J Anest 2010; 27: 555-61) the new AUC was 0.84 (0.81-0.87)

***Table 1.2*: Studies on the effects of Tidal Volume challenge:** *TVC = Tidal Volume Challenge, FC volume = volume of Fluid Challenge, CO = Cardiac Output, CI = Cardiac Index, SVI = indexed Stroke Volume, CMV = controlled mechanical ventilation, ACV(V) Volume assisted controlled ventilation, SE = spontaneous efforts, PiCCO PULSION Medical Systems, MostCare Vygon, CardioQ Deltex Medical Ltd, TTE = transthoracic echocardiography. ROCAUC is color-coded: green = ROCAUC >= 0.9, yellow = 0.75 < AUROC < 0.9, red = ROCAUC <0.75*
Sens= Sensitivity, Spec= Specificity.

Reference	*Patients*		*PC's*	*Ventilator mode*	*FHT*	*FC volume*	*Time*	*Reference variable*	*Monitor*	*Threshold*	*ROCAUC*	*Sens*	*Spec*
Myatra et al [119] *2017*	20	ICU	30	ACV(V); noSE	TVC 6/8	7ml/kg	10	ΔCI ≥ 15%	PiCCO	ΔPPV ≥ 3.5 (abs)	0.99 (0.98-1.00)	0.94	1.00
										ΔSVV ≥ 2.5 (abs)	0.97 (0.92-1.0)	0.88	1.00
Messina et al [121] *2019*	40	Neurosurgery	40	CMV	TVC 6/8	250ml	10	ΔSVI ≥ 10%	MostCare	ΔPPV ≥ 13.5% (rel)	0.94 (0.82-0.99)	0.95 (0.74-0.99)	0.76 (0.53-0.92)
										ΔSVV ≥ 12.1% (rel)	0.93 (0.80-0.98)	0.79 (0.54-0.94)	0.95 (0.76-1.00)
Jun et al [122] *2019*	38	Robot-assisted Lap surgery	38	CMV	TVC 6/8	6ml/kg	15	ΔSVI ≥ 15%	CardioQ	ΔPPV > 1 (abs)	0.95 (0.83-0.99)	0.92 (0.73-0.99)	0.86 (0.57-0.98
										ΔSVV > 2 (abs)	0.76 (0.60-0.89)	0.46 (0.26-0.67)	1.00 (0.77-1.00)
Messina et al [120] *2020*	40	Neurosurgery prone	40	CMV	TVC 6/8	250ml	10	SVI ≥ 10%	MostCare	ΔPPV ≥ 12.2% (rel)	0.96 (0.87-1.00)	0.95	0.94
										ΔSVV ≥ 12.1% (rel)	0.96 (0.89-1.00)	0.95	0.95
Elsayed et al [123] *2021*	46	ICU	46	CMV (TV = 6ml/kg)	TVC 6/8	4ml/kg	15	ΔCO ≥ 15%	TTE	ΔPPV ≥ 5% (rel)	0.956 (0.90-1.00)	0.94	0.94
Taccheri et al [124] *2021*	30	ICU	30	CMV (TV = 6ml/kg)	TVC 6/8	PLR		ΔCO ≥ 10%	PiCCO	ΔPPV ≥ 1 (abs)	0.98 (0.96-1.00)	0.93 (0.68-1.00)	1.00 (0.78-1.00)
										ΔSVV≥ 1 (abs)	0.94 (0.92-1.00)	0.93 (0.68-1.00)	0.73 (0.45-0.92)

***Table 1.3A*: Studies on the effect of End expiratory occlusion test on SV in the OR.** *EEOT = End Expiratory Occlusion Test under script = duration of the test in seconds, FC volume = volume of Fluid Challenge, CI = Cardiac Index, SVI = indexed Stroke Volume, CMV = controlled mechanical ventilation, NA = not available, Pulsioflex/ProAQT/PiCCO PULSION Medical Systems, MostCare Vygon, CardioQ Deltex Medical Ltd. ROCAUC is color-coded: green = ROCAUC >= 0.9, yellow = 0.75 < AUROC < 0.9, red = ROCAUC <0.75.* Sens= Sensitivity, Spec= Specificity *References in blue are included in the meta-analysis of Messina et al.*[126]

Reference	*Patients*		*PC's*	*Ventilator mode*	*FHT*	*FC volume*	*Time*	*Reference variable*	*Monitor*	*Treshold*	*ROCAUC*	*Sens*	*Spec*
Guinot et al[138] *2014*	42	Laparascopy	42	CMV (TV = 8ml/kg)	$EEOT_{15}$	500ml	10	SV ≥ 15%	CardioQ	ΔSV >2.3%	0.78 (0.63-0.89)	0.85	0.67
Biais et al[139] *2017*	41	Neurosurgery	41	CMV (TV= 6.8ml/kg)	$EEOT_{30}$	250ml	10	SVI ≥ 10%	ProAQT	ΔSVI >5%	0.91 (0.81-1.00)	1 (0.83-1)	0.81 (0.50-0.95)
Messina et al[121] *2019*	40	Neurosurgery	40	CMV (TV = 6ml/kg)	$EEOT_{30}$	250ml	10	ΔSVI ≥ 10%	MostCare	NA	0.52 (0.33-0.70)	NA	NA
				CMV (TV = 8ml/kg)	$EEOT_{30}$	250ml	10	ΔSVI ≥ 10%	MostCare	ΔSVI≥4.7%	0.95 (0.88-1.00)	0.90 (0.67-0.99)	0.86 (0.64-0.97)
Weil et al[128] *2020*	26	Laparotomy	65	CMV (TV = 8ml/kg)	$EEOT_{15}$	250ml	5	ΔCI ≥ 15%	PulsioFlex	NA	0.58 (0.45-0.70)	NA	NA
	20	Laparotomy	50	CMV (TV = 8ml/kg)	$EEOT_{25}$	250ml	5	ΔCI ≥ 15%	PulsioFlex	NA	0.51 (0.37-0.66)	NA	NA
Messina et al[120] *2020*	40	Neurosurgery Prone	40	CMV (TV = 6ml/kg)	$EEOT_{30}$	250ml	10	SVI ≥ 10%	MostCare	NA	0.64	NA	NA
				CMV (TV = 8ml/kg)	$EEOT_{30}$	250ml	10	SVI ≥ 10%	MostCare	NA	0.65	NA	NA
Messina et al[127] *2021*	103	Elective laparotomy	103	CMV (TV = 7ml/kg)	$EEOT_{20}$	4ml/kg	9	SVI ≥ 10%	MostCare	ΔSV ≥ 4.9%	0.67 (0.57-0.76)	0.87 (0.75-0.95)	0.23 (0.36-0.50)
					$EEOT_{30}$	4ml/kg	9	SVI ≥ 10%	MostCare	ΔSV ≥ 4.7%	0.73 (0.63)	0.92 (0.81-0.97)	0.36 (0.24-0.49)

***Table 1.3B*: Studies on the effect of End-Expiratory Occlusion Test on SV in the ICU:** *EEOT = End Expiratory Occlusion Test under script = duration of the test in seconds, FC volume = volume of Fluid Challenge, CI = Cardiac Index, CO = Cardiac Output, CMV = controlled mechanical ventilation, ACV(V) Volume assisted controlled ventilation, SE = spontaneous efforts, Crs = lung compliance, PiCCO PULSION Medical Systems, MostCare Vygon, TTE = transthoracic echocardiography, ROCAUC is color-coded: green = ROCAUC >= 0.9, yellow = 0.75 < AUROC < 0.9, red = ROCAUC <0.75.* Sens= Sensitivity, Spec= Specificity. *References in blue are included in the meta-analysis of Messina et al.*[126]

Reference	*Patients*		*PC's*	*Ventilator mode*	*FHT*	*FC volume*	*Time*	*Reference variable*	*Monitor*	*Threshold*	*ROCAUC*	*Sens*	*Spec*
Monnet et al [125] *2009*	34	ICU	34	ACV(V); SE	$EEOT_{15}$	500	10	$\Delta CI \geq 15\%$	PiCCO	$\Delta CI \geq 5\%$	0.97 (0.85-0.99)	0.91	1.0
Monnet et al [140] *2012*	27	ICU	27	ACV(V); no SE Crs <30 cmH_20/ml	$EEOT_{15}$	500	20	$\Delta CI \geq 15\%$	PiCCO	$\Delta CI \geq 5\%$	0.97 (0.93-1.00)	0.93	0.91
Monnet et al [140] *2012*	27	ICU	27	ACV(V); no SE Crs >30 cmH_20/ml	EEOT15	500	20	$\Delta CI \geq 15\%$	PiCCO	$\Delta CI \geq 5\%$	0.93 (0.88-0.98)	0.93	0.92
Silva et al [141] *2013*	34	ICU ARDS	34	CMV (TV = 6.7 ml/kg)	$EEOT_{15}$ PEEP = 5	PLR		$\Delta CI \geq 10\%$	PiCCO	$\Delta CI \geq 5\%$	0.90 (0.75-0.98)	0.90 (0.56-1.00)	0.88 (0.68-0.97)
					$EEOT_{15}$ PEEP = 15	PLR		$\Delta CI \geq 10\%$	PiCCO	$\Delta CI \geq 6\%$	0.96 (0.82-0.99)	1.00 (0.75-1.00)	0.9 (0.70-0.99)
Yonis et al[97] *2017*	33	ICU	33	CMV (TV=6ml/kg))	$EEOT_{15}$	500	15	$\Delta CI \geq 15\%$	PiCCO	ΔCI >10%	0.65 (0.46-0.84)	0.33 (0.13-0.60)	1.00 (1.00-1.00)
Jozwiak et al [142] *2017*	30	ICU	30	ACV(V);no SE	$EEOT_{15}$	500	10	$\Delta CI \geq 15\%$	PiCCO	$\Delta CI \geq$ -10.2%	0.98 (0.85-1.0)	0.93	1.00
Myatra et al [119] *2017*	20	ICU	30	ACV(V); no SE, TV=6ml/kg	$EEOT_{15}$	7ml/kg	10	$\Delta CI \geq 15\%$	PiCCO	NA	0.44 (0.23-0.66)	NA	NA
Myatra et al [119] *2017*	20	ICU	30	ACV(V); no SE, TV=8ml/kg	$EEOT_{15}$	7ml/kg	10	$\Delta CI \geq 15\%$	PiCCO	$\Delta CI \geq 4.1\%$	0.95 (0.88-1.0)	0.88	0.93
Georges et al [143] *2018*	50	ICU	50	ACV(V) no SE	$EEOT_{12}$	500	15	$\Delta CO \geq 15\%$	TTE	ΔVTI >=9%	0.96 (0.93-0.99)	0.89 (0.72-0.98)	0.95 (0.77-1.00

***Table 1.4A**: Studies on the effect of mini-fluid-challenges on SV in the OR.*

Reference	*Patients*		*PC's*	*Ventilator mode*	*FHT*	*FC volume*	*Time*	*Reference variable*	*Monitor*	*Threshold*	*ROCAUC*	*Sens*	*Spec*
Guinot et al[133] *2015*	73	Spinal anesthesia	73	SB	FC-100 (60s)	500	10	ΔSV ≥ 15%	NICCOMO	ΔSV ≥7%	0.93 (0.8-0.97	0.89 (0.71-0.98)	0.89 (0.76-0.96)
Biais et al[134] *2017*	44	Surgery Mixed	88	CMV (TV = 6.9ml/kg)	FC-100 (120s)	250	10	ΔSV ≥ 10%	ProAQT	ΔSV ≥6%	0.95 (0.90-0.99)	0.93 (0.77-0.99)	0.85 (0.73-0.93)
Biais et al[134] *2017*	44	Surgery Mixed	88	CMV (TV = 6.9ml/kg)	FC-50 (60s)	250	10	ΔSV ≥ 10%	ProAQT	ΔSV ≥2%	0.83 (0.75-0.92)	0.89 (0.72-98)	0.67 (0.53-0.78
Lee et al[144] *2020*	50	Neurosurgery Prone	50	CMV (TV = 5ml/kg)	FC-100 (60s)	500	15	ΔSV ≥ 15%	FloTrac	ΔSV ≥ 5%	0.90 (0.82-0.99)	0.87 (0.69-0.96)	0.85 (0.62-0.97)
Messina et al[127] *2021*	103	Elective laparotomy	103	CMV (TV = 7ml/kg)	FC-100 (60s)	4ml/kg	9	SVI ≥ 10%	MostCare	ΔSV ≥5.1	0.95 (0.88-0.98)	0.98 (0.90-0.99)	0.85 (0.73-0.92)

***Table 4B**: Studies on the effect of mini-fluid-challenges on SV in the ICU.*

Reference	*Patients*		*PC's*	*Ventilator mode*	*FHT*	*FC volume*	*Time*	*Reference variable*	*Monitor*	*Treshold*	*ROCAUC*	*Sens*	*Spec*
Muller et al[132] *2011*	39	ICU	39	CMV (TV=6.6ml/kg)	FC-100 (60s)	500	15	VTI ≥ 15%	TTE	ΔVTI ≥ 10%*	0.92 (0.78-0.98)	0.95 (0.87-0.99)	0.78 (0.52-0.94)
Wu et al[145] *2014*	50	ICU	50	CMV	FC-50 (10s)	500	15	CO ≥ 15%	TTE	ΔSV ≥ 10%	0.96 (0.87-0.93	0.9	1.0
Xiao-ting et al[146] *2015*	48	ICU	48	CMV	FC-100 (60s)	500	15	CI ≥ 10%	PiCCO	ΔCI ≥ 5.4	0.83 (0.69-0.96)	0.73	0.61
Mallat et al[147] *2015*	49	ICU	49	CMV (TV = 6.8ml/kg)	FC-100 (60s)	500	15	CI ≥ 15%	PiCCO	ΔCI ≥ 5.2	0.78 (0.64-0.88)	0.77	0.74
Mallat et al[147] *2015*	49	ICU	49	CMV (TV = 6.8ml/kg)	FC-100 (60s)	500	15	CI ≥ 15%	PiCCO	ΔPPV ≥ -2	0.92 (0.81-0.98)	0.86	0.85
Smorenberg[135] ***et al*** *2018*	21	ICU	21	CMV (TV = 8ml/kg)	FC-150 (120s)	500	20	CO ≥ 10%	Modelflow	ΔCO ≥ 5%	1.00 (0.84-1.00)	0.92	0.78
Smorenberg[135] ***et al*** *2018*	21	ICU	21	CMV (TV = 8ml/kg)	FC-200 (120s)	500	20	CO ≥ 10%	PulseCO	ΔCO ≥ 6.3%	0.88 (0.66-0.98)	1.00	0.70

FC volume = volume of Fluid Challenge/min fluid challenge, CI = Cardiac Index, CO = Cardiac Output, CMV = controlled mechanical ventilation, PiCCO PULSION Medical Systems, MostCare Vygon, NICCOMO non-invasive continuous cardiac output Imedex France, FloTrac Edwards Lifesciences Irvine CA USA, Modelflow FMS Amsterdam Netherlands, PusleCO LidCOltg Cambridge UK, TTE = transthoracic echocardiography, ROCAUC is color-coded: green = ROCAUC >= 0.9, yellow = 0.75 < AUROC < 0.9, red = ROCAUC <0.75. References in blue are included in the meta-analysis of Messina et al.[126]

*Original cutoff value of ΔVTI was >= 3%. The authors recognized that this was below the sensitivity of the echocardiography and adapted it to ΔVTI was ≥ 10%.

***Table 1.5**: Studies on other Functional Monitoring Test (FMT)*

Reference	*Patients*		*PC's*	*Ventilator mode*	*FHT*	*FC volume*	*Time*	*Reference variable*	*Monitor*	*Treshold*	*ROCAUC*	*Sens*	*Spec*
Biais et al [148] *2017*	28	Surgery	28	CMV (TV = 7ml/kg)	LRM 30/30	250	10	ΔSVI ≥ 10%	ProAQT	ΔSVI >30%	0.96 (0.81-0.99	0.88 (0.62-0.98)	0.92 (0.62-0.99)
De Broca et al [149] *2016*	60	Abdominal Surgery	60	CMV (TV= 6ml/kg)	LRM 25/25	500	10	ΔSV ≥ 15%	CardioQ	ΔSV >16%	0.95 (0.91-0.99)	0.92 (0.78-0.98)	0.96 (0.85-1.0)
Monge Garcia et al *2009* [150]	30	ICU	30	SB	Valsalva 30/10	500	30	ΔSVI ≥ 15%	Flow-Trac	ΔPP > 52%	0.98 (0.84-0.99)	0.91	0.95
Wilkman et al [151] *2014*	20	ICU	20	PCV	PEEP 10 to20 (60-120s)	6ml/kg	30	ΔCO ≥ 15%	TEE	ΔMAP ≥10.2%	0.91 (0.77-1.00)	0.83	0.86

LRM = lung recruitement maneuver FFC volume = volume of Fluid Challenge/min fluid challenge, CI = Cardiac Index, CO = Cardiac Output, SB = spontaneous breathing, PP= Pulse Pressure, MAP = Mean Arterial Pressure, CMV = controlled mechanical ventilation, PCV = pressure controlled ventilation, ProAQT PULSION Medical Systems, FloTrac Edwards Lifesciences Irvine CA USA, CardioQ Deltex Medical Ltd Chichester UK , TTE = transthoracic echocardiography, ROCAUC is color-coded: green = ROCAUC >= 0.9, yellow = 0.75 < AUROC < 0.9, red = ROCAUC <0.75. References in blue are included in the meta-analysis of Messina et al.[126]

Conclusion:

- Fluid management in surgical and ICU patients is challenging. Different philosophies and scientific frameworks have colored the 'vivid' debate on fluid therapy.
- Patients who have an increase in CO after fluid loading are defined as ***fluid responsive***.
- Traditionally ***used (static) filling parameters*** like central venous pressure and pulmonary wedge pressure, fail to reliably predict fluid responsiveness in individual patients.
- ***Dynamic filling parameters*** are based on the impact of full mechanical ventilation on cardiac output, stroke volume or Pulse Pressure.
- ***Pulse Pressure Variation (PPV)*** and ***Stroke Volume Variation (SVV)*** are the best studied dynamic filling parameters. These parameters have shown to be very reliable predictor of fluid responsiveness if correctly applied.
- The most ***important pre-requisites*** for the correct use of dynamic filling parameters are mechanical ventilation without spontaneous effort, Tidal Volume ≥ 8 ml/kg, and absence of arrhythmia's….
- These pre-requisites limit the ***clinical applicability*** in a substantial part of surgical and ICU patients.
- Different ***functional hemodynamic tests (FHT)*** have been investigated. The best studied FHT's are: Tidal Volume Challenge, End Expiratory Occlusion Test, Mini-Fluid Challenge and the Passive Leg Raising test. Each of these FHT's have their individual advantages and disadvantages.

References:

1. Bellamy MC. Wet, dry or something else? *Br J Anaesth*. 2006;97(6):755-757. https://doi.org/10.1093/bja/ael290

2. Woodcock TE, Woodcock TM. Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. *Br J Anaesth*. 2012;108(3):384-394. https://doi.org/10.1093/BJA/AER515

3. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A Rational Approach to Perioperative Fluid Management. *Anesthesiology*. 2008;109:723-763. https://doi.org/10.1097/ALN.0b013e3181863117

4. Meybohm P, Aken H van, Gasperi A de, et al. Re-evaluating currently available data and suggestions for planning randomized controlled studies regarding the use of hydroxyethyl starch in critically ill patients - a multidisciplinary statement. *Crit Care*. 2013;17(4):R166. https://doi.org/10.1186/CC12845

5. Hemmings HC, Shafer SL. Further retractions of articles by Joachim Boldt. *Br J Anaesth*. 2020;125(3):409-411. https://doi.org/10.1016/J.BJA.2020.02.024

6. Miller TE, Myles PS. Perioperative Fluid Therapy for Major Surgery. *Anesthesiology*. 2019;130(5):825-832. https://doi.org/10.1097/ALN.0000000000002603

7. Shoemaker WC, Montgomery ES, Kaplan E, Elwyn DH. Physiologic Patterns in Surviving and Nonsurviving Shock Patients: Use of Sequential Cardiorespiratory Variables in Defining Criteria for Therapeutic Goals and Early Warning of Death. *Archives of Surgery*. 1973;106(5):630-636. https://doi.org/10.1001/ARCHSURG.1973.01350170004003

8. Shoemaker WC. Cardiorespiratory patterns of surviving and nonsurviving postoperative patients. *Surg Gynecol Obstet*. 1972;134(5):810-814. Accessed September 28, 2021. https://pubmed.ncbi.nlm.nih.gov/5031495/

9. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective Trial of Supranormal Values of Survivors as Therapeutic Goals in High-Risk Surgical Patients. *Chest*. 1988;94(6):1176-1186 https://doi.org/10.1378/CHEST.94.6.1176

10. Sandham JD, Hull RD, Brant RF, et al. A Randomized, Controlled Trial of the Use of Pulmonary-Artery Catheters in High-Risk Surgical Patients. *N Engl J Med*. 2009;348(1):5-14. https://doi.org/10.1056/NEJMOA021108

11. Holte K, Sharrock NE, Kehlet H. Pathophysiology and clinical implications of perioperative fluid excess. *Br J Anaesth*. 2002;89(4):622-632. https://doi.org/10.1093/BJA/AEF220

12. Messina A, Robba C, Calabrò L, et al. Perioperative liberal versus restrictive fluid strategies and postoperative outcomes: a systematic review and metanalysis on

randomised-controlled trials in major abdominal elective surgery. *Crit Care*. 2021;25(1). https://doi.org/10.1186/s13054-021-03629-y

13. Myles PS, Bellomo R, Corcoran T, et al. Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery. *N Engl J Med*. 2018;378(24):2263-2274. https://doi.org/10.1056/NEJMOA1801601

14. Shin CH, Long DR, McLean D, et al. Effects of Intraoperative Fluid Management on Postoperative Outcomes: A Hospital Registry Study. *Ann Surg*. 2018;267(6):1084-1092. https://doi.org/10.1097/SLA.0000000000002220

15. Frank O. Zur Dynamik des Herzmuskels. *Z Biol*. 1895;32:370-437.

16. Patterson SW, Starling EH. On the mechanical factors which determine the output of the ventricles. *J Physiol*. 1914;48(5):357. https://doi.org/10.1113/JPHYSIOL.1914.SP001669

17. Vinogradova M. Ca(2+)-regulated structural changes in troponin. *Proc Natl Acad Sci USA*. 2005;102(14):5038-5043 https://doi.org/10.1073/pnas.0408882102

18. Yamada Y, Namba K, Fujii T. Cardiac muscle thin filament structures reveal calcium regulatory mechanism. *Nat Commun*. 2020;11(1):1-9. https://doi.org/10.1038/s41467-019-14008-1

19. Daniels M, Noble MIM, Ter HEDJ, And K, Wohlfartt B. Velocity of Sarcomere shortening in rat cardiac muscle: Relationship to force, sarcomere length, Calcium and time. *J Physiol*. 1984;355:367-381.

20. Sequeira V, Velden J van der. Historical perspective on heart function: the Frank–Starling Law. *Biophys Rev*. 2015;7(4):421. https://doi.org/10.1007/S12551-015-0184-4

21. Gelman S. Venous function and central venous pressure: A physiologic story. *Anesthesiology*. 2008;108(4):735-748. https://doi.org/10.1097/ALN.0b013e3181672607

22. Gelman S, Bigatello L. The physiologic basis for goal-directed hemodynamic and fluid therapy: the pivotal role of the venous circulation. *Canadian Journal of Anesthesia*. 2018;65(3):294-308. https://doi.org/10.1007/s12630-017-1045-3

23. Berger D, Takala J. Determinants of systemic venous return and the impact of positive pressure ventilation. *Ann Transl Med*. 2018;6(18):350-350. https://doi.org/10.21037/ATM.2018.05.27

24. Magder S. Understanding central venous pressure: Not a preload index? *Curr Opin Crit Care*. 2015;21(5):369-375. https://doi.org/10.1097/MCC.0000000000000238

25. Brengelmann GL. Reply to "Letter to the editor: The venous circulation actively alters flow: a brief evolutionary perspective." *Am J Physiol Heart Circ Physiol*. 2021;320(1):H71-H73. https://doi.org/10.1152/AJPHEART.00910.2020

26. Brengelmann GL. Stressed and unstressed volumes of the peripheral vasculature. *Canadian Journal of Anesthesia*. 2018;65(9):1072-1073. https://doi.org/10.1007/S12630-018-1155-6

27. Rothe CF. Reflex control of veins and vascular capacitance. *Physiol Rev*. 1983;63(4):1281-1342. https://doi.org/10.1152/PHYSREV.1983.63.4.1281

28. Tyberg TV. How changes in venous capacitance modulate cardiac output. *Pflugers Arch*. 2002;445(1):10-17. https://doi.org/10.1007/S00424-002-0922-X

29. Moller PW, Winkler B, Hurni S, et al. Right atrial pressure and venous return during cardiopulmonary bypass. *Am J Physiol Heart Circ Physiol*. 2017;313(2):H408-H420. https://doi.org/10.1152/AJPHEART.00081.2017

30. Versprille A, Jansen JR. Mean systemic filling pressure as a characteristic pressure for venous return. *Pflugers Arch*. 1985;405(3):226-233. https://doi.org/10.1007/BF00582565

31. Pinsky MR. Instantaneous venous return curves in an intact canine preparation. *J Appl Physiol Respir Environ Exerc Physiol*. 1984;56(3):765-771. https://doi.org/10.1152/JAPPL.1984.56.3.765

32. Brengelmann GL. Venous return and the physical connection between distribution of segmental pressures and volumes. *Am J Physiol Heart Circ Physiol*. 2019;317:939-953. https://doi.org/10.1152/ajpheart.00381.2019

33. Shahri SMK, Contarino C, Chifari F, Mahmoudi M, Gelman S. Function of arteries and veins in conditions of simulated cardiac arrest. *Bioimpacts*. 2021;11(2):157-164. https://doi.org/10.34172/BI.2021.13

34. Gelman S. What drives venous return? *Eur J Anaesthesiol*. 2022;39(3):196-197. https://doi.org/10.1097/EJA.0000000000001608

35. Guyton AC, Lindsey AW, Abernathy B, Richardson T. Venous return at various right atrial pressures and the normal venous return curve. *Am J Physiol*. 1957;189(3):609-615. https://doi.org/10.1152/AJPLEGACY.1957.189.3.609

36. Magder S. Central venous pressure: A useful but not so simple measurement. *Crit Care Med*. 2006;34(8):2224-2227. https://doi.org/10.1097/01.CCM.0000227646.98423.98

37. Sondergaard S, Parkin G, Aneman A. Central venous pressure: Soon an outcome-Associated matter. *Curr Opin Anaesthesiol*. 2016;29(2):179-185. https://doi.org/10.1097/ACO.0000000000000305

38. Magder S. Volume and its relationship to cardiac output and venous return. *Critical Care 2016 20:1*. 2016;20(1):1-11. https://doi.org/10.1186/S13054-016-1438-7

39. Tavernier B, Makhotine O, Lebuffe G, Dupont J, Scherpereel P. Systolic Pressure Variation as a Guide to Fluid Therapy in Patients with Sepsis-induced Hypotension. *Anesthesiology*. 1998;89(6):1313-1321. https://doi.org/10.1097/00000542-199812000-00007

40. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: A systematic review of the literature. *Crit Care Med*. 2009;37(9):2642-2647. https://doi.org/10.1097/CCM.0B013E3181A590DA

41. Michard F. Changes in arterial pressure during mechanical ventilation. *Anesthesiology*. 2005;103(2):419-428. https://doi.org/10.1097/00000542-200508000-00026

42. Martin GS, Kaufman DA, Marik PE, et al. Perioperative Quality Initiative (POQI) consensus statement on fundamental concepts in perioperative fluid management: fluid responsiveness and venous capacitance. *Perioper Med (Lond)*. 2020;9(1). https://doi.org/10.1186/S13741-020-00142-8

43. van Eijk LT, Servaas S, Slagt C, Malagon I. Predicting fluid responsiveness: Does it answer the right question? *Eur J Anaesthesiol*. 2021;38(5):449-451. https://doi.org/10.1097/EJA.0000000000001455

44. Marik PE, Lemson J. Fluid responsiveness: An evolution of our understanding. *Br J Anaesth*. 2014;112(4):617-620. https://doi.org/10.1093/bja/aet590

45. Jacob M, Saller T, Chappell D, Rehm M, Welsch U, Becker BF. Physiological levels of A-, B- and C-type natriuretic peptide shed the endothelial glycocalyx and enhance vascular permeability. *Basic Res Cardiol*. 2013;108(3). https://doi.org/10.1007/S00395-013-0347-Z

46. Margraf A, Ludwig N, Zarbock A, Rossaint J. Systemic Inflammatory Response Syndrome After Surgery: Mechanisms and Protection. *Anesth Analg*. 2020;131(6):1693-1707. https://doi.org/10.1213/ANE.0000000000005175

47. Parikh SM. Angiopoietins and Tie2 in vascular inflammation. *Curr Opin Hematol*. 2017;24(5):432-438. https://doi.org/10.1097/MOH.0000000000000361

48. Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. *Crit Care Med*. 2013;41(7):1774-1781. https://doi.org/10.1097/CCM.0B013E31828A25FD

49. Dellinger RP, Levy M, Rhodes A, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41(2):580-637. https://doi.org/10.1097/CCM.0B013E31827E83AF

50. Weil MH, Henning RJ. New Concepts in the Diagnosis and Fluid Treatment of Circulatory Shock. Tirtheenth ANnual Becton, Dickinson and Company Oscar Schidetsky Memorial Lecture. *Anesth Analg*. 1979;58(2):124132. Accessed October 27, 2021. https://journals.lww.com/anesthesia-analgesia/Citation/1979/03000/New_Concepts_in_the_Diagnosis_and_Fluid_Treatment.13.aspx

51. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? *Chest*. 2008;134(1):172-178. https://doi.org/10.1378/CHEST.07-2331

52. Sjödin C, Sondergaard S, Johansson L. Variability in alignment of central venous pressure transducer to physiologic reference point in the intensive care unit-A descriptive and correlational study. *Aust Crit Care*. 2019;32(3):213-217. https://doi.org/10.1016/J.AUCC.2018.05.001

53. Figg KK, Nemergut EC. Error in central venous pressure measurement. *Anesth Analg*. 2009;108(4):1209-1211. https://doi.org/10.1213/ANE.0B013E318196482C

54. Roger C, Muller L, Riou B, et al. Comparison of different techniques of central venous pressure measurement in mechanically ventilated critically ill patients. *Br J Anaesth*. 2017;118(2):223-231. https://doi.org/10.1093/BJA/AEW386

55. Preisman S, Kogan S, Berkenstadt H, Perel A. Predicting fluid responsiveness in patients undergoing cardiac surgery: functional haemodynamic parameters including the Respiratory Systolic Variation Test and static preload indicators†. *Br J Anaesth*. 2005;95(6):746-755. https://doi.org/10.1093/BJA/AEI262

56. Lansdorp B, Hofhuizen C, van Lavieren M, et al. Mechanical ventilation-induced intrathoracic pressure distribution and heart-lung interactions*. *Crit Care Med*. 2014;42(9):1983-1990. https://doi.org/10.1097/CCM.0000000000000345

57. Mahmood SS, Pinsky MR. Heart-lung interactions during mechanical ventilation: the basics. *Ann Transl Med*. 2018;6(18):349-349. https://doi.org/10.21037/ATM.2018.04.29

58. Jardin F, Farcot JC, Gueret P, Prost JF, Ozier Y, Bourdarias JP. Cyclic changes in arterial pulse during respiratory support. *Circulation*. 1983;68(2):266-274. https://doi.org/10.1161/01.CIR.68.2.266

59. Takata M, Robotham JL. Effects of inspiratory diaphragmatic descent on inferior vena caval venous return. *J Appl Physiol (1985)*. 1992;72(2):597-607. https://doi.org/10.1152/JAPPL.1992.72.2.597

60. Vieillard-Baron A, Augarde R, Prin S, Page B, Beauchet A, Jardin F. Influence of superior vena caval zone condition on cyclic changes in right ventricular outflow during respiratory support. *Anesthesiology*. 2001;95(5):1083-1088. https://doi.org/10.1097/00000542-200111000-00010

61. Brower R, Wise RA, Hassapoyannes C, Bromberger-Barnea B, Permutt S. Effect of lung inflation on lung blood volume and pulmonary venous flow. *J Appl Physiol*. 1985;58(3):954-963. https://doi.org/10.1152/JAPPL.1985.58.3.954

62. Vieillard-Baron A, Loubieres Y, Schmitt JM, Page B, Dubourg O, Jardin F. Cyclic changes in right ventricular output impedance during mechanical ventilation. *J Appl Physiol*. 1999;87(5):1644-1650. https://doi.org/10.1152/JAPPL.1999.87.5.1644

63. Jardin F, Delorme G, Hardy A, Auvert B, Beauchet A, Bourdarias JP. Reevaluation of hemodynamic consequences of positive pressure ventilation: emphasis on cyclic right ventricular afterloading by mechanical lung inflation. *Anesthesiology*. 1990;72(6):966-970. https://doi.org/10.1097/00000542-199006000-00003

64. Poelaert JI, Visser CA, Everaert JA, de Deyne CS, Decruyenaere J, Colardyn FA. Doppler evaluation of right ventricular outflow impedance during positive-pressure ventilation. *J Cardiothorac Vasc Anesth*. 1994;8(4):392-397. https://doi.org/10.1016/1053-0770(94)90276-3

65. Fessler HE, Brower RG, Wise RA, Permutt S. Mechanism of reduced LV afterload by systolic and diastolic positive pleural pressure. *Journal of applied physiology*. 1988;65(3):1244-1250. https://doi.org/10.1152/JAPPL.1988.65.3.1244

66. Pinsky MR, Matuschak GM, Klain M. Determinants of cardiac augmentation by elevations in intrathoracic pressure. *Journal of applied physiology*. 1985;58(4):1189-1198. https://doi.org/10.1152/JAPPL.1985.58.4.1189

67. Taylor RR, Covell JW, Sonnenblick EH, Ross J. Dependence of ventricular distensibility on filling of the opposite ventricle. *Am J Physiol*. 1967;213(3):711-718. https://doi.org/10.1152/AJPLEGACY.1967.213.3.711

68. Morgan BC, Martin WE, Hornbein TF, Crawford EW, Guntheroth WG. Hemodynamic effects of intermittent positive pressure respiration. *Anesthesiology*. 1966;27(5):584-590. https://doi.org/10.1097/00000542-196609000-00009

69. Zhang Z, Lu B, Sheng X, Jin N. Accuracy of stroke volume variation in predicting fluid responsiveness: a systematic review and meta-analysis. *J Anesth*. 2011;25(6):904-916. https://doi.org/10.1007/S00540-011-1217-1

70. Scheeren TWL, Ramsay MAE. New Developments in Hemodynamic Monitoring. *J Cardiothorac Vasc Anesth*. 2019;33 Suppl 1:S67-S72. https://doi.org/10.1053/J.JVCA.2019.03.043

71. Charron C, Caille V, Jardin F, Vieillard-Baron A. Echocardiographic measurement of fluid responsiveness. *Curr Opin Crit Care*. 2006;12(3):249-254. https://doi.org/10.1097/01.CCX.0000224870.24324.CC

72. Bartels K, Thiele RH. Advances in photoplethysmography: beyond arterial oxygen saturation. *Can J Anaesth*. 2015;62(12):1313-1328. https://doi.org/10.1007/S12630-015-0458-0

73. Yang X, du B. Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis. *Crit Care*. 2014;18(6). https://doi.org/10.1186/S13054-014-0650-6

74. Suzuki T, Suzuki Y, Okuda J, et al. Cardiac output and stroke volume variation measured by the pulse wave transit time method: a comparison with an arterial pressure-based cardiac output system. *Journal of Clinical Monitoring and Computing 2018 33:3*. 2018;33(3):385-392. https://doi.org/10.1007/S10877-018-0171-Y

75. Derichard A, Robin E, Tavernier B, et al. Automated pulse pressure and stroke volume variations from radial artery: evaluation during major abdominal surgery. *BJA: British Journal of Anaesthesia*. 2009;103(5):678-684. https://doi.org/10.1093/BJA/AEP267

76. Cannesson M, le Manach Y, Hofer CK, et al. Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a "gray zone" approach. *Anesthesiology*. 2011;115(2):231-241. https://doi.org/10.1097/ALN.0B013E318225B80A

77. Sandroni C, Cavallaro F, Marano C, Falcone C, de Santis P, Antonelli M. Accuracy of plethysmographic indices as predictors of fluid responsiveness in mechanically ventilated adults: a systematic review and meta-analysis. *Intensive Care Med*. 2012;38(9):1429-1437. https://doi.org/10.1007/S00134-012-2621-1

78. Liu T, Xu C, Wang M, Niu Z, Qi D. Reliability of pleth variability index in predicting preload responsiveness of mechanically ventilated patients under various conditions: a systematic review and meta-analysis. *BMC Anesthesiology 2019 19:1*. 2019;19(1):1-7. https://doi.org/10.1186/S12871-019-0744-4

79. Monnet X, Guérin L, Jozwiak M, et al. Pleth variability index is a weak predictor of fluid responsiveness in patients receiving norepinephrine. *Br J Anaesth*. 2013;110(2):207-213. https://doi.org/10.1093/BJA/AES373

80. Deng QW, Tan WC, Zhao BC, Wen SH, Shen JT, Xu M. Is goal-directed fluid therapy based on dynamic variables alone sufficient to improve clinical outcomes among patients undergoing surgery? A meta-analysis. *Crit Care*. 2018;22(1):298. https://doi.org/10.1186/s13054-018-2251-2

81. Vistisen S, Keus E, Scheeren T. Methodology in systematic reviews of goal-directed therapy: improving but not perfect. *Br J Anaesth*. 2017;119:18-21. https://doi.org/10.1093/bja/aex206

82. Wetterslev J, Jakobsen JC, Gluud C. Trial Sequential Analysis in systematic reviews with meta-analysis. *BMC Med Res Methodol*. 2017;17(1):1-18. https://doi.org/10.1186/S12874-017-0315-7/FIGURES/4

83. Kaufmann T, Clement RP, Scheeren TWL, Saugel B, Keus F, van der Horst ICC. Perioperative goal-directed therapy: A systematic review without meta-analysis. *Acta Anaesthesiol Scand*. 2018;62(10):1340-1355. https://doi.org/10.1111/AAS.13212

84. Sondergaard S. Pavane for a pulse pressure variation defunct. *Crit Care*. 2013;17(6):1-6. https://doi.org/10.1186/CC13109/FIGURES/3

85. Michard F, Chemla D, Teboul JL. Applicability of pulse pressure variation: how many shades of grey? *Crit Care*. 2015;19:144. https://doi.org/10.1186/s13054-015-0869-x

86. Monnet X, Rienzo M, Osman D, et al. Passive leg raising predicts fluid responsiveness in the critically ill. *Crit Care Med*. 2006;34(5):1402-1407. https://doi.org/10.1097/01.CCM.0000215453.11735.06

87. Hamzaoui O, Shi R, Carelli S, et al. Changes in pulse pressure variation to assess preload responsiveness in mechanically ventilated patients with spontaneous breathing activity: an observational study. *Br J Anaesth*. 2021;127(4):532-538. https://doi.org/10.1016/J.BJA.2021.05.034

88. Soubrier S, Saulnier F, Hubert H, et al. Can dynamic indicators help the prediction of fluid responsiveness in spontaneously breathing critically ill patients? *Intensive Care Med*. 2007;33(7):1117-1124. https://doi.org/10.1007/S00134-007-0644-9

89. Heenen S, de Backer D, Vincent JL. How can the response to volume expansion in patients with spontaneous respiratory movements be predicted? *Crit Care*. 2006;10(4). https://doi.org/10.1186/CC4970

90. Kim HK, Pinsky MR. Effect of tidal volume, sampling duration, and cardiac contractility on pulse pressure and stroke volume variation during positive-pressure ventilation. *Crit Care Med*. 2008;36(10):2858-2862. https://doi.org/10.1097/CCM.0b013e3181865aea

91. Liu Y, Lou J sheng, Mi W dong, et al. Pulse pressure variation shows a direct linear correlation with tidal volume in anesthetized healthy patients. Published online 2016. https://doi.org/10.1186/s12871-016-0233-y

92. de Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med*. 2005;31(4):517-523. https://doi.org/10.1007/S00134-005-2586-4

93. Alvarado Sánchez JI, Caicedo Ruiz JD, Diaztagle Fernández JJ, Amaya Zuñiga WF, Ospina-Tascón GA, Cruz Martínez LE. Predictors of fluid responsiveness in critically ill patients mechanically ventilated at low tidal volumes: systematic review and meta-analysis. *Ann Intensive Care*. 2021;11(1). https://doi.org/10.1186/S13613-021-00817-5

94. Myatra SN, Prabu NR, DIvatia JV, Monnet X, Kulkarni AP, Teboul JL. The Changes in Pulse Pressure Variation or Stroke Volume Variation After a "Tidal Volume Challenge" Reliably Predict Fluid Responsiveness During Low Tidal Volume Ventilation. *Crit Care Med*. 2017;45(3):415-421. https://doi.org/10.1097/CCM.0000000000002183

95. Liu Y, Wei LQ, Li GQ, Yu X, Li GF, Li YM. Pulse Pressure Variation Adjusted by Respiratory Changes in Pleural Pressure, Rather Than by Tidal Volume, Reliably Predicts Fluid Responsiveness in Patients with Acute Respiratory Distress Syndrome∗. *Crit Care Med*. 2016;44(2):342-351. https://doi.org/10.1097/CCM.0000000000001371

96. Huang CC, Fu JY, Hu HC, et al. Prediction of fluid responsiveness in acute respiratory distress syndrome patients ventilated with low tidal volume and high positive end-expiratory pressure. *Crit Care Med*. 2008;36(10):2810-2816. https://doi.org/10.1097/CCM.0b013e318186b74e

97. Yonis H, Bitker L, Aublanc M, et al. Change in cardiac output during Trendelenburg maneuver is a reliable predictor of fluid responsiveness in patients with acute respiratory distress syndrome in the prone position under protective ventilation. *Crit Care*. 2017;21(1). https://doi.org/10.1186/S13054-017-1881-0

98. Vistisen ST, Koefoed-Nielsen J, Larsson A. Should dynamic parameters for prediction of fluid responsiveness be indexed to the tidal volume? *Acta Anaesthesiol Scand*. 2010;54(2):191-198. https://doi.org/10.1111/J.1399-6576.2009.02114.X

99. Wyffels PAH, Sergeant P, Wouters PF. The value of pulse pressure and stroke volume variation as predictors of fluid responsiveness during open chest surgery. *Anaesthesia*. 2010;65(7). https://doi.org/10.1111/j.1365-2044.2010.06371.x

100. Piccioni F, Bernasconi F, Tramontano GTA, Langer M. A systematic review of pulse pressure variation and stroke volume variation to predict fluid responsiveness during cardiac and thoracic surgery. *J Clin Monit Comput*. 2017;31(4):677-684. https://doi.org/10.1007/S10877-016-9898-5

101. Lansdorp B, Lemson J, van Putten MJAM, de Keijzer A, van der Hoeven JG, Pickkers P. Dynamic indices do not predict volume responsiveness in routine clinical practice. *Br J Anaesth*. 2012;108(3):395-401. https://doi.org/10.1093/BJA/AER411

102. Mahjoub Y, Pila C, Friggeri A, et al. Assessing fluid responsiveness in critically ill patients: False-positive pulse pressure variation is detected by Doppler

echocardiographic evaluation of the right ventricle. *Crit Care Med*. 2009;37(9):2570-2575. https://doi.org/10.1097/CCM.0B013E3181A380A3

103. Wyler von Ballmoos M, Takala J, Roeck M, et al. Pulse-pressure variation and hemodynamic response in patients with elevated pulmonary artery pressure: a clinical study. *Crit Care*. 2010;14(3). https://doi.org/10.1186/CC9060

104. de Backer D, Taccone FS, Holsten R, Ibrahimi F, Vincent JL. Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. *Anesthesiology*. 2009;110(5):1092-1097. https://doi.org/10.1097/ALN.0B013E31819DB2A1

105. Jacques D, Bendjelid K, Duperret S, Colling J, Piriou V, Viale JP. Pulse pressure variation and stroke volume variation during increased intra-abdominal pressure: an experimental study. *Crit Care*. 2011;15(1). https://doi.org/10.1186/CC9980

106. Renner J, Gruenewald M, Quaden R, et al. Influence of increased intra-abdominal pressure on fluid responsiveness predicted by pulse pressure variation and stroke volume variation in a porcine model. *Crit Care Med*. 2009;37(2):650-658. https://doi.org/10.1097/CCM.0B013E3181959864

107. Duperret S, Lhuillier F, Piriou V, et al. Increased intra-abdominal pressure affects respiratory variations in arterial pressure in normovolaemic and hypovolaemic mechanically ventilated healthy pigs. *Intensive Care Med*. 2007;33:163-171. https://doi.org/10.1007/s00134-006-0412-2

108. Høiseth L, Hoff IE, Myre K, Landsverk SA, Kirkebøen KA. Dynamic variables of fluid responsiveness during pneumoperitoneum and laparoscopic surgery. *Acta Anaesthesiol Scand*. 2012;56(6):777-786. https://doi.org/10.1111/J.1399-6576.2011.02641.X

109. Chin JH, Lee EH, Hwang GS, Hwang JH, Choi WJ. Prediction of Fluid Responsiveness Using Dynamic Preload Indices in Patients Undergoing Robot-Assisted Surgery with Pneumoperitoneum in the Trendelenburg Position. *Anaesth Intensive Care*. 2013;41:515-522. https://doi.org/10.1177/0310057X1304100413

110. Zlicar M, Novak-Jankovic V, Blagus R, Cecconi M. Predictive values of pulse pressure variation and stroke volume variation for fluid responsiveness in patients with pneumoperitoneum. *J Clin Monit Comput*. 2018;32(5):825-832. https://doi.org/10.1007/S10877-017-0081-4

111. Guinot PG, de Broca B, Bernard E, Arab OA, Lorne E, Dupont H. Respiratory stroke volume variation assessed by oesophageal Doppler monitoring predicts fluid responsiveness during laparoscopy. *Br J Anaesth*. 2014;112(4):660-664. https://doi.org/10.1093/BJA/AET430

112. Chen J, Zhao S, Zhu Q. Reliability of stroke volume or pulse pressure variation as dynamic predictors of fluid responsiveness in laparoscopic surgery: a systematic

review. *J Clin Monit Comput*. 2023; 37: 379-387. https://doi.org/10.1007/S10877-022-00939-6

113. Evans L, Rhodes A, Alhazzani W, et al. Executive Summary: Surviving Sepsis Campaign: International Guidelines for the Management of Sepsis and Septic Shock 2021. *Crit Care Med*. 2021;49(11):1974-1982. https://doi.org/10.1097/CCM.0000000000005357

114. Benes J, Zatloukal J, Kletecka J, Simanova A, Haidingerova L, Pradl R. Respiratory induced dynamic variations of stroke volume and its surrogates as predictors of fluid responsiveness: applicability in the early stages of specific critical states. *J Clin Monit Comput*. 2014;28(3):225-231. https://doi.org/10.1007/S10877-013-9524-8

115. Mahjoub Y, Lejeune V, Muller L, et al. Evaluation of pulse pressure variation validity criteria in critically ill patients: a prospective observational multicentre point-prevalence study. *Br J Anaesth*. 2014;112(4):681-685. https://doi.org/10.1093/BJA/AET442

116. Delannoy B, Wallet F, Maucort-Boulch D, et al. Applicability of Pulse Pressure Variation during Unstable Hemodynamic Events in the Intensive Care Unit: A Five-Day Prospective Multicenter Study. *Crit Care Res Pract*. 2016;2016. https://doi.org/10.1155/2016/7162190

117. Mair S, Tschirdewahn J, Götz S, et al. Applicability of stroke volume variation in patients of a general intensive care unit: a longitudinal observational study. *J Clin Monit Comput*. 2017;31(6):1177-1187. https://doi.org/10.1007/S10877-016-9951-4

118. Maguire S, Rinehart J, Vakharia S, Cannesson M. Technical communication: respiratory variation in pulse pressure and plethysmographic waveforms: intraoperative applicability in a North American academic center. *Anesth Analg*. 2011;112(1):94-96. https://doi.org/10.1213/ANE.0B013E318200366B

119. Myatra SN, Prabu NR, DIvatia JV, Monnet X, Kulkarni AP, Teboul JL. The Changes in Pulse Pressure Variation or Stroke Volume Variation after a "tidal Volume Challenge" Reliably Predict Fluid Responsiveness during Low Tidal Volume Ventilation∗. *Crit Care Med*. 2017;45(3):415-421. https://doi.org/10.1097/CCM.0000000000002183

120. Messina A, Montagnini C, Cammarota G, et al. Assessment of Fluid Responsiveness in Prone Neurosurgical Patients Undergoing Protective Ventilation: Role of Dynamic Indices, Tidal Volume Challenge, and End-Expiratory Occlusion Test. *Anesth Analg*. 2020;130(3):752-761. https://doi.org/10.1213/ANE.0000000000004494

121. Messina A, Montagnini C, Cammarota G, et al. Tidal volume challenge to predict fluid responsiveness in the operating room: An observational study. *Eur J Anaesthesiol*. 2019;36(8):583-591. https://doi.org/10.1097/EJA.0000000000000998

122. Jun JH, Chung RK, Baik HJ, et al. The tidal volume challenge improves the reliability of dynamic preload indices during robot-assisted laparoscopic surgery in the

Trendelenburg position with lung-protective ventilation. *BMC Anesthesiol*. 2019;19(1). https://doi.org/10.1186/S12871-019-0807-6

123. Elsayed AI, Selim KAW, Zaghla HE, Mowafy HE, Fakher MA. Comparison of Changes in PPV Using a Tidal Volume Challenge with a Passive Leg Raising Test to Predict Fluid Responsiveness in Patients Ventilated Using Low Tidal Volume. *Indian J Crit Care Med*. 2021;25(6):685-689. https://doi.org/10.5005/JP-JOURNALS-10071-23875

124. Taccheri T, Gavelli F, Teboul JL, Shi R, Monnet X. Do changes in pulse pressure variation and inferior vena cava distensibility during passive leg raising and tidal volume challenge detect preload responsiveness in case of low tidal volume ventilation? *Crit Care*. 2021;25(1). https://doi.org/10.1186/S13054-021-03515-7

125. Monnet X, Osman D, Ridel C, Lamia B, Richard C, Teboul JL. Predicting volume responsiveness by using the end-expiratory occlusion in mechanically ventilated intensive care unit patients. *Crit Care Med*. 2009;37(3):951-956. https://doi.org/10.1097/CCM.0B013E3181968FE1

126. Messina A, Dell'Anna A, Baggiani M, et al. Functional hemodynamic tests: a systematic review and a metanalysis on the reliability of the end-expiratory occlusion test and of the mini-fluid challenge in predicting fluid responsiveness. *Crit Care*. 2019;23(1). https://doi.org/10.1186/S13054-019-2545-Z

127. Messina A, Lionetti G, Foti L, et al. Mini fluid chAllenge aNd End-expiratory occlusion test to assess flUid responsiVEness in the opeRating room (MANEUVER study): A multicentre cohort study. *Eur J Anaesthesiol*. 2021;38(4):422-431. https://doi.org/10.1097/EJA.0000000000001406

128. Weil G, Motamed C, Monnet X, Eghiaian A, le Maho AL. End-Expiratory Occlusion Test to Predict Fluid Responsiveness Is Not Suitable for Laparotomic Surgery. *Anesth Analg*. 2020;130(1):151-158. https://doi.org/10.1213/ANE.0000000000004205

129. Monnet X, Teboul JL. Passive leg raising: five rules, not a drop of fluid! *Crit Care*. 2015;19(1). https://doi.org/10.1186/S13054-014-0708-5

130. Monnet X, Marik P, Teboul JL. Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis. *Intensive Care Med*. 2016;42(12):1935-1947. https://doi.org/10.1007/S00134-015-4134-1

131. Beurton A, Teboul JL, Girotto V, et al. Intra-Abdominal Hypertension Is Responsible for False Negatives to the Passive Leg Raising Test. *Crit Care Med*. 2019;47(8):E639-E647. https://doi.org/10.1097/CCM.0000000000003808

132. Muller L, Toumi M, Bousquet PJ, et al. An increase in aortic blood flow after an infusion of 100 ml colloid over 1 minute can predict fluid responsiveness: the mini-fluid challenge study. *Anesthesiology*. 2011;115(3):541-547. https://doi.org/10.1097/ALN.0B013E318229A500

133. Guinot PG, Bernard E, Defrancq F, et al. Mini-fluid challenge predicts fluid responsiveness during spontaneous breathing under spinal anaesthesia: An observational study. *Eur J Anaesthesiol*. 2015;32(9):645-649. https://doi.org/10.1097/EJA.0000000000000175

134. Biais M, de Courson H, Lanchon R, et al. Mini-fluid Challenge of 100 ml of Crystalloid Predicts Fluid Responsiveness in the Operating Room. *Anesthesiology*. 2017;127(3):450-456. https://doi.org/10.1097/ALN.0000000000001753

135. Smorenberg A, Cherpanath TGV, Geerts BF, et al. A mini-fluid challenge of 150mL predicts fluid responsiveness using Modelflow R pulse contour cardiac output directly after cardiac surgery. *J Clin Anesth*. 2018;46:17-22. https://doi.org/10.1016/J.JCLINANE.2017.12.022

136. Mallat J, Meddour M, Durville E, et al. Decrease in pulse pressure and stroke volume variations after mini-fluid challenge accurately predicts fluid responsiveness. *Br J Anaesth*. 2015;115(3):449-456. https://doi.org/10.1093/bja/aev222

137. Mallat J, Fischer MO, Granier M, et al. Passive leg raising-induced changes in pulse pressure variation to assess fluid responsiveness in mechanically ventilated patients: a multicentre prospective observational study. *Br J Anaesth*. 2022;129(3):308-316. https://doi.org/10.1016/J.BJA.2022.04.031

138. Guinot PG, Godart J, de Broca B, Bernard E, Lorne E, Dupont H. End-expiratory occlusion manoeuvre does not accurately predict fluid responsiveness in the operating theatre. *Br J Anaesth*. 2014;112(6):1050-1054. https://doi.org/10.1093/BJA/AET582

139. Biais M, Larghi M, Henriot J, de Courson H, Sesay M, Nouette-Gaulain K. End-Expiratory Occlusion Test Predicts Fluid Responsiveness in Patients With Protective Ventilation in the Operating Room. *Anesth Analg*. 2017;125(6):1889-1895. https://doi.org/10.1213/ANE.0000000000002322

140. Monnet X, Bleibtreu A, Ferré A, et al. Passive leg-raising and end-expiratory occlusion tests perform better than pulse pressure variation in patients with low respiratory system compliance. *Crit Care Med*. 2012;40(1):152-157. https://doi.org/10.1097/CCM.0B013E31822F08D7

141. Silva S, Jozwiak M, Teboul JL, Persichini R, Richard C, Monnet X. End-expiratory occlusion test predicts preload responsiveness independently of positive end-expiratory pressure during acute respiratory distress syndrome. *Crit Care Med*. 2013;41(7):1692-1701. https://doi.org/10.1097/CCM.0B013E31828A2323

142. Jozwiak M, Depret F, Teboul JL, et al. Predicting Fluid Responsiveness in Critically Ill Patients by Using Combined End-Expiratory and End-Inspiratory Occlusions With Echocardiography. *Crit Care Med*. 2017;45(11):e1131-e1138. https://doi.org/10.1097/CCM.0000000000002704

143. Georges D, de Courson H, Lanchon R, Sesay M, Nouette-Gaulain K, Biais M. End-expiratory occlusion maneuver to predict fluid responsiveness in the intensive care unit: An echocardiographic study. *Crit Care*. 2018;22(1):1-8. https://doi.org/10.1186/S13054-017-1938-0/FIGURES/3

144. Lee CT, Lee TS, Chiu CT, Teng HC, Cheng HL, Wu CY. Mini-fluid challenge test predicts stroke volume and arterial pressure fluid responsiveness during spine surgery in prone position: A STARD-compliant diagnostic accuracy study. *Medicine*. 2020;99(6). https://doi.org/10.1097/MD.0000000000019031

145. Wu Y, Zhou S, Zhou Z, Liu B. A 10-second fluid challenge guided by transthoracic echocardiography can predict fluid responsiveness. *Crit Care*. 2014;18(3). https://doi.org/10.1186/CC13891

146. Xiao-Ting W, Hua Z, Da-Wei L, et al. Changes in end-tidal CO2 could predict fluid responsiveness in the passive leg raising test but not in the mini-fluid challenge test: A prospective and observational study. *J Crit Care*. 2015;30(5):1061-1066. https://doi.org/10.1016/J.JCRC.2015.05.019

147. Mallat J, Meddour M, Durville E, et al. Decrease in pulse pressure and stroke volume variations after mini-fluid challenge accurately predicts fluid responsiveness†. *Br J Anaesth*. 2015;115(3):449-456. https://doi.org/10.1093/BJA/AEV222

148. Biais M, Lanchon R, Sesay M, et al. Changes in Stroke Volume Induced by Lung Recruitment Maneuver Predict Fluid Responsiveness in Mechanically Ventilated Patients in the Operating Room. *Anesthesiology*. 2017;126(2):260-267. https://doi.org/10.1097/ALN.0000000000001459

149. de Broca B, Garnier J, Fischer MO, et al. Stroke volume changes induced by a recruitment maneuver predict fluid responsiveness in patients with protective ventilation in the operating theater. *Medicine*. 2016;95(28). https://doi.org/10.1097/MD.0000000000004259

150. Monge García MI, Gil Cano A, Díaz Monrové JC. Arterial pressure changes during the Valsalva maneuver to predict fluid responsiveness in spontaneously breathing patients. *Intensive Care Med*. 2009;35(1):77-84. https://doi.org/10.1007/S00134-008-1295-1

151. Wilkman E, Kuitunen A, Pettilä V, Varpula M. Fluid responsiveness predicted by elevation of PEEP in patients with septic shock. *Acta Anaesthesiol Scand*. 2014;58(1):27-35. https://doi.org/10.1111/AAS.12229

152. Dalmau R. Stressed volume and fluid responsiveness. *Eur J Anaesthesiol*. 2021;38(1):86-88. https://doi.org/10.1097/EJA.0000000000001281

153. Dalmau R. The “stressed blood volume” revisited. *Canadian Journal of Anesthesia*. 2018;65(9):1070-1071. https://doi.org/10.1007/s12630-018-1154-7

154. Dalmau R. Venous return: a fresh start. *Am J Physiol Heart Circ Physiol*. 2019;317(5):H1102-H1104. https://doi.org/10.1152/AJPHEART.00575.2019

155. Kenny JS. Letter to the editor: The venous circulation actively alters flow: a brief evolutionary perspective. *Am J Physiol Heart Circ Physiol*. 2021;320(1):469-470. https://doi.org/10.1152/AJPHEART.00862.2020

156. Levy MN. The cardiac and vascular factors that determine systemic blood flow. *Circ Res*. 1979;44(6):739-747. https://doi.org/10.1161/01.RES.44.6.739

157. Kattan E, Castro R, Miralles-Aguiar F, Hernández G, Rola P. The emerging concept of fluid tolerance: A position paper. *J Crit Care*. 2022;71. https://doi.org/10.1016/J.JCRC.2022.154070

158. Dalmau R. Letter to the editor: "What is meant by 'fluid tolerance'?". *J Crit Care*. 2022;72:154157. https://doi.org/10.1016/j.jcrc.2022.154157

159. Perel A, Minkovich L, Preisman S, Abiad M, Segal E, Coriat P. Assessing fluid-responsiveness by a standardized ventilatory maneuver: the respiratory systolic variation test. *Anesth Analg*. 2005;100(4):942-945. https://doi.org/10.1213/01.ANE.0000146939.66172.AE

160. Acosta S, Ahmed M, Yin SM, Brady KM, Penny DJ, Rusin CG. A robust Fourier-based method to measure pulse pressure variability. *Biomed Signal Process Control*. 2020;60. https://doi.org/10.1016/J.BSPC.2020.101947

161. Foughty ZC, Tavaslioglu O, Rhee CJ, et al. Novel Method of Calculating Pulse Pressure Variation to Predict Fluid Responsiveness to Transfusion in Very Low Birth Weight Infants. *J Pediatr*. 2021;234:265-268.e1. https://doi.org/10.1016/J.JPEDS.2021.04.012

162. Ikeda K, Smith G, Renehan J, et al. Multiparameter Predictor of Fluid Responsiveness in Cardiac Surgical Patients Receiving Tidal Volumes Less Than 10 mL/kg. *Semin Cardiothorac Vasc Anesth*. 2016;20(3):188-196. https://doi.org/10.1177/1089253216654765

163. Messina A, Romano SM, Ozdemirkan A, et al. Multivariable haemodynamic approach to predict the fluid challenge response: A multicentre cohort study. *Eur J Anaesthesiol*. 2021;38(1):22-31. https://doi.org/10.1097/EJA.0000000000001289

164. Neuschwander A, Barthélémy R, Ditchi D, et al. Accuracy of a multiparametric score based on pulse wave analysis for prediction of fluid responsiveness: ancillary analysis of an observational study. *Can J Anaesth*. 2020;67(9):1162-1169. https://doi.org/10.1007/S12630-020-01736-Y

165. Benes J, Giglio M, Brienza N, Michard F. The effects of goal-directed fluid therapy based on dynamic parameters on post-surgical outcome: a meta-analysis of

randomized controlled trials. *Crit Care*. 2014;18:584. https://doi.org/10.1186/s13054-014-0584-z

166. Grassi P, Grassi P, lo Nigro L, et al. Pulse pressure variation as a predictor of fluid responsiveness in mechanically ventilated patients with spontaneous breathing activity: a pragmatic observational study. *Proc Intensive Care Cardiovasc Anesth*. 2013;5(2):98-109.

167. Beurton A, Teboul JL, Gavelli F, et al. The effects of passive leg raising may be detected by the plethysmographic oxygen saturation signal in critically ill patients. *Crit Care*. 2019;23(1). https://doi.org/10.1186/S13054-019-2306-Z

168. Jacquet-Lagrèze M, Bouhamri N, Portran P, et al. Capillary refill time variation induced by passive leg raising predicts capillary refill time response to volume expansion. *Crit Care*. 2019;23(1). https://doi.org/10.1186/S13054-019-2560-0

169. Vistisen ST, Scheeren TWL. Challenge of the Mini-fluid Challenge: Filling Twice without Creating a Self-fulfilling Prophecy Design. *Anesthesiology*. 2018;128(5):1043-1044. https://doi.org/10.1097/ALN.0000000000002141

Chapter 2

2

Objectives of the Thesis

Dynamic filing parameters like PPV, are well studied and reliable predictors of fluid responsiveness if they are used correctly. The most important prerequisites identified in the literature, are mechanical ventilation without spontaneous effort, tidal volume ≥8mL/kg and absence of arrhythmias. For most of these limitations some solutions have been proposed and investigated. However,….?

This thesis elaborates on the last of these known shortcomings, the need for a regular heart rhythm, without a possible solution so far, and on a new unexplored limitation of the use of PPV in clinical practice.

Objective 1: Atrial Fibrillation and PPV.

Currently there is no solution for the limitations associated with the application of dynamic filling parameters in patients with arrythmias presenting for surgery. A typical and frequently occurring cardiac rhythm

disturbance is atrial fibrillation. Yet, this fragile population would especially benefit from a reliable predictor for fluid responsiveness.
In these patients not only the mechanical ventilation but also the irregular rhythm causes the pulse pressure to continuously vary during surgery. The original way to calculate PPV is unable to filter these two distinct competing effects.
A new dynamic parameter called VPPV (Ventilation induced Pulse Pressure Variation) that is based on a model that can accommodate for both rhythm-induced and ventilation-induced changes in PP, is developed and tested in two steps.

In a first step, we hypothetize that a method can be developed to predict irregular changes in pulse pressure solely due to the chaotic sequence of heartbeats in atrial fibrillation.

Publication 1:
Dynamic filling parameters in patients with atrial fibrillation: Differentiating rhythm induced from ventilation-induced variations in pulse pressure. Wyffels PAH, Van Heuverswyn F, De Hert S, Wouter PF Am J Phsyiol – Heart circ Phys. 2016; 310(9): H1194-H1200.
https://doi.org/10.1152/ajpheart.00712.2015

In a second step, a model is developed that predicts the fluctuations of PP based on this first principle along with other predictors. This proof-of-concept study tests the hypothesis that it is feasible to extract a value from this model defined as VPPV (Ventilation induced Pulse Pressure Variation), that quantifies the isolated impact of mechanical ventilation. We tested the response of this new parameter in a legs-up study protocol mimicking different filling statuses, expecting to find a proportional decrease in VPPV after PLR.

Publication 2:
New algorithm to quantify cardiopulmonary interaction in patients with atrial fibrillation: a proof-of-concept study. Wyffels PAH, De Hert S, Wouters PF. Br J Anesthesia 2021; 126(1): 111-119.
https://doi.org/10.1016/j.bja.2020.09.039

Objective 2: Measurement error of PPV.

Every measurement comes with error. This universal truth also applies for the measurement/calculation of PPV. But the error and the uncertainty that comes with it, is rarely discussed in fluid responsiveness studies.
Based on the data from patients undergoing liver transplantation from the open VitalDB database, a Bayesian model is developed to determine the bias and precision of 4 families of methods to calculate PPV. The impact of these findings on the concept of grey zone uncertainty and on the recently proposed use of PPV in FHT's are simulated and questioned.

Publication 3:
The measurement error of Pulse Pressure Variation. Wyffels PAH, De Hert S, Wouters PF. J Clin Monit Comput 2023 (publ: 8/12/2023) https://doi.org/10.1007/s10877-023-01099-x

Chapter 3

'… Chaos is merely order waiting to be deciphered…'

José Saramago,
O Homen Duplicado, 2002

3

Rhythm induced variations in Pulse Pressure

In this chapter, 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. These findings provide a basis for the development of a dynamic parameter that enables to predict fluid responsiveness in these patients.

***

Wyffels PAH, Van Heuverswyn F, De Hert S, Wouters PF.
Dynamic filling parameters in patients with atrial fibrillation: differentiating rhythm-induced from ventilation-induced variations in pulse pressure.
Published in Am J Physiol Heart Circ Physiol. 2016; 310(9): H1194-200.
https://doi.org/10.1152/ajpheart.00712.2015

3.1 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 analyzed during apnea (T1) and during MV at tidal volumes of 8 mL/kg (T2) and 12 mL/kg (T3), respectively. In a first step, three 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 to be superior to 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.

3.2 Introduction

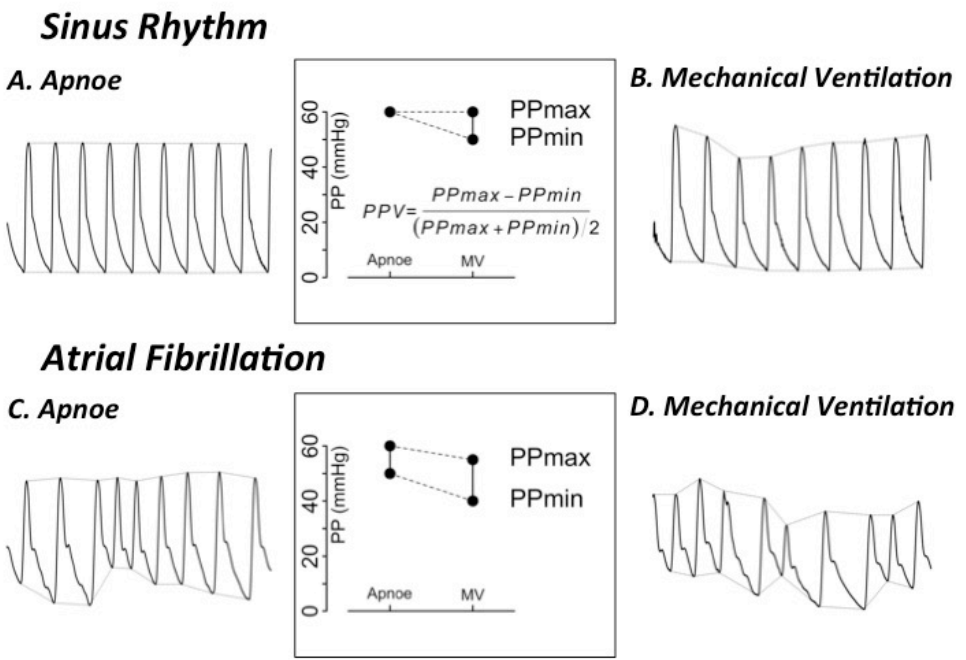
Volume replacement is a corner stone treatment in the hemodynamic management of critically ill patients. The need for volume administration was initially guided on classical static parameters such as central venous pressure and pulmonary artery occlusion pressure. In clinical practice however, these static preload parameters have been shown not to be able to accurately predict fluid responsiveness.[1–3] 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 3.1) and have been shown to provide a suitable way of detecting hypovolemia and fluid responsiveness.[4,5]

Current guidelines therefore recommend the use of these dynamic preload variables, to direct volume therapy in hemodynamically unstable patients.[6] Numerous studies support the validity of this concept[7] however it is only applicable to patients undergoing full mechanical ventilation[8] with sufficiently high tidal volumes[9,10] and an intact chest wall.[11] 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 3.1). 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 number 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 -

Figure 3.1: *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 apnea 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 apnea 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 apnea. 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 framework is to replace this approach by a model that is capable to minimize the variation between predicted and measured PP during apnea in patient with AF. This model then, can be used as a reference to measure the variations in PP during Mechanical Ventilation.



preceding RR interval and the corresponding SV.[12]
Rawles[13] incorporated these findings into a mathematical model to predict SV in spontaneously breathing patients. 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.

3.3 Materials and Methods

3.3.1 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 anesthesia were included, if they fulfilled following criteria: (1) Age >18years, (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.

3.3.2 Anesthesia Protocol

All patients had a standard induction and maintenance of anesthesia. A combination of bolus sufentanil 0.1-0.2 µg/kg, propofol 2 mg/kg and cisatracurium 0.15mg/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 (5lead 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.

3.3.3 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).

3.3.4 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: Apnea, 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 analyzed off-line. For every individual beat the pulse pressure (PP), and both the preceding RR-interval (RR_0) and the second preceding RR-interval (RR_{-1}) (see figure 3.2), were quantified for subsequent analysis.

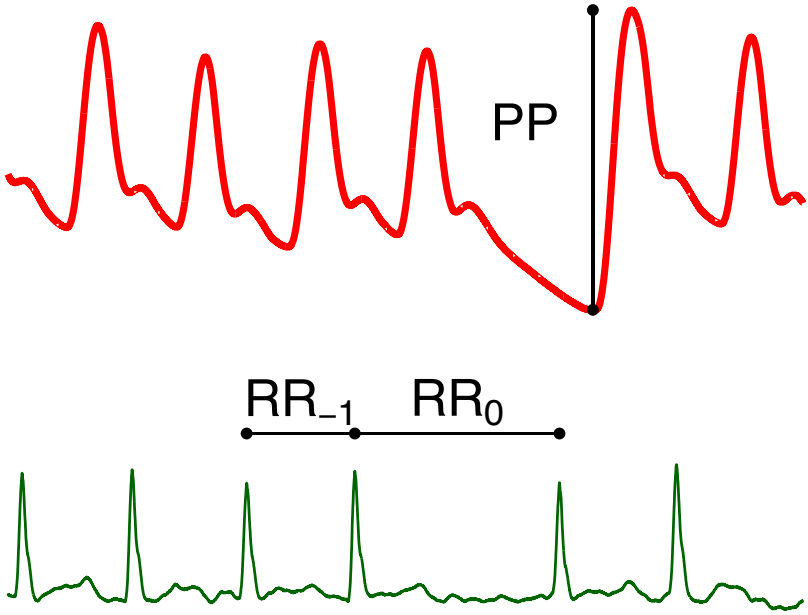


***Figure 3.2*: Terminology**: *for every individual beat, the 2 preceding R-intervals (RR_0 and RR_{-1}) were used to construct a prediction model, to predict the pulse pressure (PP).*

3.3.5 Statistical Analysis

This study consisted of a two-step analysis:

1. Apneic 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 apneic period.
For every patient three individual prediction models were compared.

1. ***Model Q1***: A quadratic model using the preceding RR interval (RR_0).

$$PP = a + b(RR_0) + c(RR_0)^2$$

2. ***Model Q2***: The Rawles model: A polynomial quadratic model based on the two preceding RR intervals (RR_0 and RR_{-1}).

$$PP = a + b(RR_{-1}) + c(RR_{-1})^2 + d(RR_0) + e(RR_0)^2$$

3. ***Model Loc2***: A local second order Polynomial Regression Fitting model using RR_0 and RR_{-1} as independent variables. This is a non-parametric regression using local second order regression.[14] (See Appendix for Model description) A plotted example of such an "apneic prediction surface" is shown in figure 3.3(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.

- MV induces a gradual decrease in PP throughout the cycle, compared to the apneic reference PP.[15]
- The MV induced decreases in PP are proportional to the applied TV.[15,16]

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 stepwise increase of the Tidal Volume is shown in figure 3.3.

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. (RStudio,inc)

3.4 Results

Demographic data are given in table 3.1.
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.

Sex, men/women	6/4
Caucasian, %	100
Age, yr	57.5 (55.5-65.0)
Weight, kg	94.5 (71.8-99.3)
Length, cm	180 (171-183)
Cardiovascular comorbidity, 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/ transient ischemic attack, n	2
Medication, n	
Amiodarone	2
Digoxin	1
Flecainide	2
Beta-blockers	6
Calcium channel blocker	2
ACE inhibitor/ AII blocker	2
Diuretics	3

***Table 3.1*: Demographic data of included patients**. *Summary data are given median (interquartile range). CABG, coronary artery bypass grafting; AS, aortic valve stenosis; VSD, ventricular septal defect.*

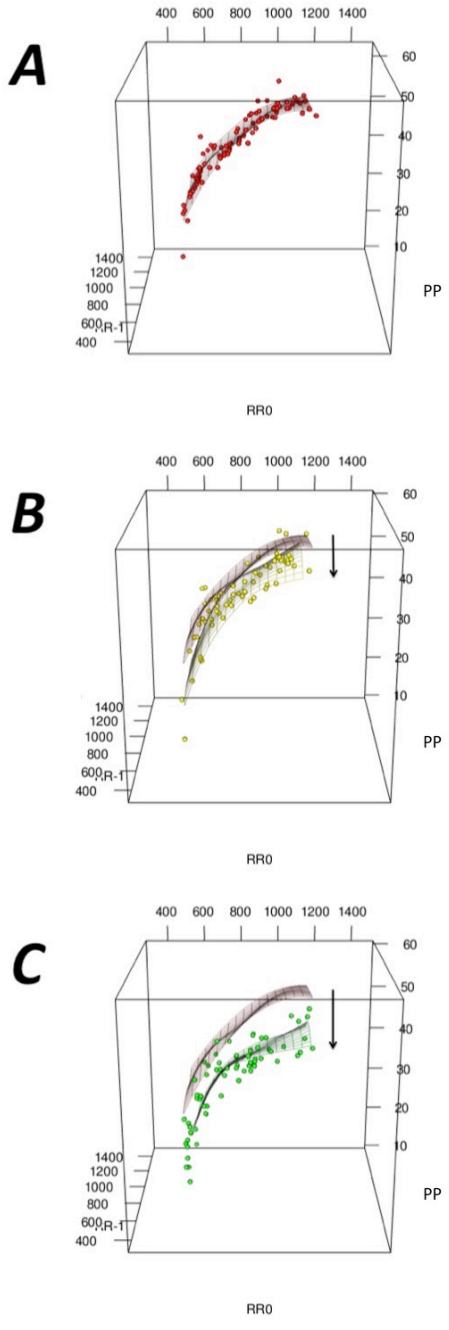

A
400 600 800 1000 1200 1400
60
50
40
30
20
10
PP
1400
1200
1000
800
600
400
RR-1
RR0
B
400 600 800 1000 1200 1400
60
50
40
30
20
10
PP
1400
1200
1000
800
600
400
RR-1
RR0
C
400 600 800 1000 1200 1400
60
50
40
30
20
10
PP
1400
1200
1000
800
600
400
RR-1
RR0

Figure 3.3:

1. Apnoeic Prediction Surface. (APS)

For every patient the 3 prediction models in apneic 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 3.4. For every individual patient the LOC2 outperformed the two other quadratic models in predicting the rhythm-induced variability during apnea. Consequently, 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.[15,16]

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 3.5.

Figure 3.3: *Apneic 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: apnea for *60 seconds. APS with the individual data points in red. (B) T2: APS and individual data points during mechanical ventilation (12 x 8ml/kg) are printed as yellow dots. (C) T3: APS and individual* data points during T3 (8 x 12 ml/kg) are printed as green dots *RR intervals (msec), PP (mmHg).*

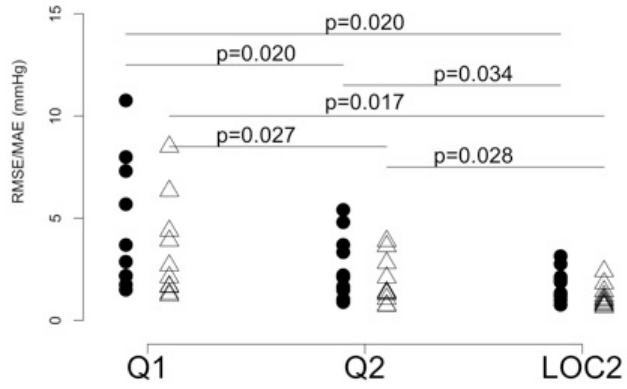


Figure 3.4: *Individual residual mean-square error (RMSE) (black dots) and mean absolute error (MAE) (open triangle) of the 3 prediction models (Q1, Q2, LOC2) during observation period T1 (Apnea). P values of the pairwise comparisons using Holm-Bonferroni correction are added.*

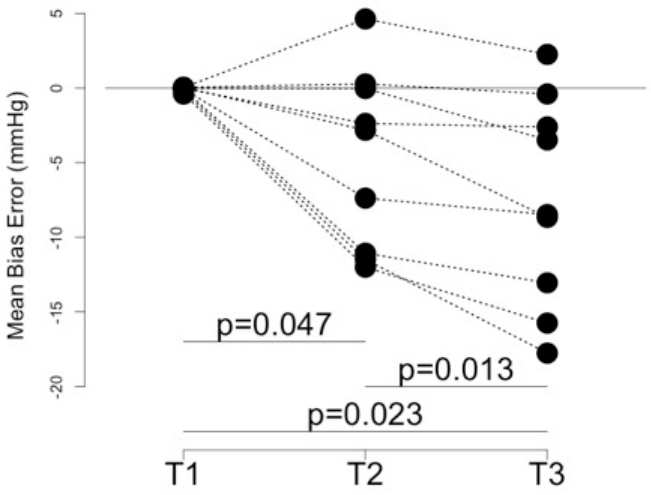


Figure 3.5: *Effect of ventilation on predicted values of PP using APS. Individual mean bias error (mmHg) of each observation period (T1, Apnea; T2, 8 x 12mL/kg; T3, 12 x 8 mL/kg). P values of the pairwise comparisons using Holm-Bonferroni correction are added.*

3.5 Discussion

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 analyze 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 apnea, 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[13] 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 us 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.[17,18] 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.[19]
(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 commercially available monitors. An automated standardized ventilatory maneuver was proposed to evaluate the impact of MV on systolic blood pressure in a clinical setting.[15,20]

These physiologic and practical advantages affirm the superior clinical performance of the MV induced/dynamic parameters. Marik and coworkers[2,7,21] 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. 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.[7] More recently, a grey zone approach was described. Cannesson et al[22] used a more sophisticated method and found that prediction characteristics between a PPV of 9% and 13% were inconclusive. Incorporating the resolution of the oscillations after a fluid challenge was able to narrow this grey zone.[23]

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 standardized intrathoracic pressure swings and tidal volumes, big enough to have a substantial effect on intrathoracic pressures[24] in a closed thorax.[11] Some criticism has been formulated in light of these prerequisites and the complexity of the underlying physiology. [25]

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 (RR_0) of an individual beat are responsible for dispersion of the ejected SV. [12,26] In some patients, RR_{-1} was found to have an inverse correlation with SV.[12] This has been explained by

changing contractility[19,27,28], possibly combined with changes in LV afterload.[29,30]

There have been some attempts to bring this knowledge into practice. Some investigators indexed their beat-to-beat observations according to the RR_0/RR_{-1} ratio. The value when $RR_0/RR_{-1}=1$ can sometimes be used as the overall mean. This has been described for E_{max} (end-systolic pressure-volume ratio)[31,32], Doppler measured aortic peak flow velocity and time-velocity integral[31,33], dP/dt_{max}.[33,34]

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[13] 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 these patients were breathing spontaneously.

We found that our model performed better than the Rawles model in predicting the rhythm-induced variation in PP during apnea. 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.[35,36]

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 3.3) 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 standardized 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.[7] 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.[37] 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 apnea (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.

References

1. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? *Chest*. 2008;134(1):172-178. https://doi.org/10.1378/CHEST.07-2331

2. Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. *Crit Care Med*. 2013;41(7):1774-1781. https://doi.org/10.1097/CCM.0B013E31828A25FD

3. Pinsky MR. Heart lung interactions during mechanical ventilation. *Curr Opin Crit Care*. 2012;18(3):256-260. https://doi.org/10.1097/MCC.0B013E3283532B73

4. Michard F, Teboul JL. Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. *Crit Care*. 2000;4(5):282-289. https://doi.org/10.1186/CC710

5. Michard F. Changes in arterial pressure during mechanical ventilation. *Anesthesiology*. 2005;103(2):419-428. https://doi.org/10.1097/00000542-200508000-00026

6. Kozek-Langenecker SA, Afshari A, Albaladejo P, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol*. 2013;30(6):270-382. https://doi.org/10.1097/EJA.0B013E32835F4D5B

7. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: A systematic review of the literature. *Crit Care Med*. 2009;37(9):2642-2647. https://doi.org/10.1097/CCM.0B013E3181A590DA

8. Teboul JL, Monnet X. Prediction of volume responsiveness in critically ill patients with spontaneous breathing activity. *Curr Opin Crit Care*. 2008;14(3):334-339. https://doi.org/10.1097/MCC.0B013E3282FD6E1E

9. De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med*. 2005;31(4):517-523. https://doi.org/10.1007/S00134-005-2586-4

10. Muller L, Louart G, Bousquet PJ, et al. The influence of the airway driving pressure on pulsed pressure variation as a predictor of fluid responsiveness. *Intensive Care Med*. 2010;36(3):496-503. https://doi.org/10.1007/S00134-009-1686-Y

11. Wyffels PAH, Sergeant P, Wouters PF. The value of pulse pressure and stroke volume variation as predictors of fluid responsiveness during open chest surgery. *Anaesthesia*. 2010;65(7). https://doi.org/10.1111/j.1365-2044.2010.06371.x

12. Greenfield JC, Harley A, Thompson HK, Wallace AG. Pressure-flow studies in man during atrial fibrillation. *J Clin Invest*. 1968;47(10):2411-2421. https://doi.org/10.1172/JCI105924

13. Rawles JM. A mathematical model of left ventricular function in atrial fibrillation. *Int J Biomed Comput*. 1988;23(1-2):57-68. https://doi.org/10.1016/0020-7101(88)90063-3

14. Cleveland WS, Devlin SJ. Locally Weighted Regression: An Approach to Regression Analysis by Local Fitting. *J Am Stat Assoc*. 1988;83(403):596. https://doi.org/10.2307/2289282

15. Perel A, Minkovich L, Preisman S, Abiad M, Segal E, Coriat P. Assessing fluid-responsiveness by a standardized ventilatory maneuver: the respiratory systolic variation test. *Anesth Analg*. 2005;100(4):942-945. https://doi.org/10.1213/01.ANE.0000146939.66172.AE

16. Mesquida J, Kim HK, Pinsky MR. Effect of tidal volume, intrathoracic pressure, and cardiac contractility on variations in pulse pressure, stroke volume, and intrathoracic blood volume. *Intensive Care Med*. 2011;37(10):1672-1679. https://doi.org/10.1007/S00134-011-2304-3

17. Lansdorp B, Hofhuizen C, Van Lavieren M, et al. Mechanical ventilation-induced intrathoracic pressure distribution and heart-lung interactions*. *Crit Care Med*. 2014;42(9):1983-1990. https://doi.org/10.1097/CCM.0000000000000345

18. Van Den Berg PCM, Jansen JRC, Pinsky MR. Effect of positive pressure on venous return in volume-loaded cardiac surgical patients. *J Appl Physiol (1985)*. 2002;92(3):1223-1231. https://doi.org/10.1152/JAPPLPHYSIOL.00487.2001

19. Brookes CIO, White PA, Staples M, et al. Myocardial contractility is not constant during spontaneous atrial fibrillation in patients. *Circulation*. 1998;98(17):1762-1768. https://doi.org/10.1161/01.CIR.98.17.1762

20. Trepte CJC, Eichhorn V, Haas SA, et al. Comparison of an automated respiratory systolic variation test with dynamic preload indicators to predict fluid responsiveness after major surgery. *Br J Anaesth*. 2013;111(5):736-742. https://doi.org/10.1093/BJA/AET204

21. Marik PE, Lemson J. Fluid responsiveness: An evolution of our understanding. *Br J Anaesth*. 2014;112(4):617-620. https://doi.org/10.1093/bja/aet590

22. Cannesson M, Le Manach Y, Hofer CK, et al. Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a “gray zone” approach. *Anesthesiology*. 2011;115(2):231-241. https://doi.org/10.1097/ALN.0B013E318225B80A

23. Le Manach Y, Hofer CK, Lehot JJ, et al. Can changes in arterial pressure be used to detect changes in cardiac output during volume expansion in the perioperative period? *Anesthesiology*. 2012;117(6):1165-1174. https://doi.org/10.1097/ALN.0B013E318275561D

24. Lakhal K, Ehrmann S, Benzekri-Lefèvre D, et al. Respiratory pulse pressure variation fails to predict fluid responsiveness in acute respiratory distress syndrome. *Crit Care*. 2011;15(2). https://doi.org/10.1186/CC10083

25. Sondergaard S. Pavane for a pulse pressure variation defunct. *Crit Care*. 2013;17(6):1-6. https://doi.org/10.1186/CC13109/FIGURES/3

26. Braunwald E, Frye RL, Aygen MM, Gilbert JW. Studies on Starling'law of the heart. III. Observations in patients with mitral stenosis and atrial fibrillation on the relationships between left ventricular end-diastolic segment length, filling pressure, and the characteristics of ventricular contraction. *J Clin Invest*. 1960;39(12):1874-1884. https://doi.org/10.1172/JCI104211

27. Schneider F, Martin DT, Schick EC, Gaasch WH. Interval-dependent changes in left ventricular contractile state in lone atrial fibrillation and in atrial fibrillation associated with coronary artery disease. *American Journal of Cardiology*. 1997;80(5):586-590. https://doi.org/10.1016/S0002-9149(97)00426-8

28. Hardman SMC, Noble MIM, Seed WA. Postextrasystolic potentiation and its contribution to the beat-to-beat variation of the pulse during atrial fibrillation. *Circulation*. 1992;86(4):1223-1232. https://doi.org/10.1161/01.CIR.86.4.1223

29. Muntinga HJ, Gosselink ATM, Blanksma PK, De Kam PJ, Van Der Wall EE, Crijns HJGM. Left ventricular beat to beat performance in atrial fibrillation: Dependence on contractility, preload, and afterload. *Heart*. 1999;82(5):575-580. https://doi.org/10.1136/hrt.82.5.575

30. Gosselink ATM, Blanksma PK, Crijns HJGM, et al. Left ventricular beat-to-beat performance in atrial fibrillation: contribution of Frank-Starling mechanism after short rather than long RR intervals. *J Am Coll Cardiol*. 1995;26(6):1516-1521. https://doi.org/10.1016/0735-1097(95)00340-1

31. Sumida T, Tanabe K, Yagi T, et al. Single-beat Determination of Doppler-derived Aortic Flow Measurement in Patients with Atrial Fibrillation. *Journal of the American Society of Echocardiography*. 2003;16(7):712-715. https://doi.org/10.1016/S0894-7317(03)00275-X

32. Suzuki S, Araki J, Morita T, et al. Ventricular contractility in atrial fibrillation is predictable by mechanical restitution and potentiation. *Am J Physiol*. 1998;275(5). https://doi.org/10.1152/AJPHEART.1998.275.5.H1513

33. Tabata T, Grimm RA, Greenberg NL, et al. Assessment of LV systolic function in atrial fibrillation using an index of preceding cardiac cycles. *Am J Physiol Heart Circ Physiol*. 2001;281(2). https://doi.org/10.1152/AJPHEART.2001.281.2.H573

34. Nakamura Y, Konishi T, Nonogi H, Sakurai T, Sasayama S, Kawai C. Myocardial relaxation in atrial fibrillation. *J Am Coll Cardiol*. 1986;7(1):68-73. https://doi.org/10.1016/S0735-1097(86)80261-3

35. Van Den Berg MP, Van Noord T, Brouwer J, et al. Clustering of RR intervals predicts effective electrical cardioversion for atrial fibrillation. *J Cardiovasc Electrophysiol*. 2004;15(9):1027-1033. https://doi.org/10.1046/J.1540-8167.2004.03686.X

36. Guo XH, Gallagher MM, Bland JM, Camm AJ. A distinctly bimodal distribution pattern in the RR interval histogram predicts early recurrence of atrial fibrillation after electrical cardioversion. *Int J Cardiol*. 2010;145(2):244-245. https://doi.org/10.1016/J.IJCARD.2009.08.012

37. Gan H, Cannesson M, Chandler JR, Ansermino JM. Predicting fluid responsiveness in children: a systematic review. *Anesth Analg*. 2013;117(6):1380-1392. https://doi.org/10.1213/ANE.0B013E3182A9557E

38. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. *J Am Stat Assoc*. 1979;74(368):829-836. https://doi.org/10.1080/01621459.1979.10481038

Chapter 4

“The proof of the pudding is in the eating.”

Miguel de Cervantes, Don Quixote (1615)
Nicolas Boileau-Despréaux, Le luttin (1682)

4

VPPV: Ventilation induced Variations in Pulse Pressure

In this chapter, we extend the findings on modelling the rhythm induced beat-to-beat changes in pulse pressure in atrial fibrillation introduced in the previous chapter. A new, more complex model that simultaneous predicts both rhythm-induced and ventilation induced changes in pulse pressure, is presented. This model is the basis for a new measure, Ventilation induced Pulse Pressure Variation (VPPV) that quantifies the impact of mechanical ventilation on PP. The robustness of this new measure, VPPV, was tested in leg ups study-design.

***

Wyffels PAH, De Hert S, Wouters PF.
A new algorithm to quantify cardiopulmonary interaction in patients with atrial fibrillation: A proof-of-concept study.
Published in Br J Anaesth. 2021; 126(1): 111-119.
https://doi.org/10.1016/j.bja.2020.09.039

4.1 Abstract

Background: Traditional formulas to calculate Pulse Pressure Variation (PPV) cannot be used in patients with atrial fibrillation (AF). We have developed a new algorithm that accounts for arrhythmia-induced pulse pressure changes, allowing us to isolate and quantify Ventilation-induced Pulse Pressure Variation (VPPV). The robustness of the algorithm was tested in patients subjected to altered loading conditions. We investigated whether changes in VPPV imposed by passive leg raising (PLR) were proportional to the pre-PLR values.

Methods: Consenting patients with active AF scheduled for an ablation of the pulmonary vein under general anaesthesia and mechanical ventilation were included. Loading conditions were altered by PLR. ECG and invasive pressure data were acquired during 60 second periods before and after PLR. A generalized additive model was constructed for each patient on each observation period. The impact of AF was modelled on the 2 preceding RR intervals of each beat (RR_0, RR_{-1}). The impact of ventilation and long-term PP trends were modelled as separate splines. VPPV was defined as the percentage of the maximal change in PP during the ventilation cycle.

Results: 9 patients were studied. The predictive abilities of the models had a median r^2 of 0.92 [89.2-94.2 IQR]. Pre-PLR VPPV ranged from 0.1% to 27.9%. After PLR, VPPV decreased to 0%-11.3% ($p<0.014$). The relation between the Pre-PLR values and the magnitude of the changes imposed by the PLR was statistically significant ($p<0.001$).

Conclusions:
This algorithm enables quantification of ventilation induced PPV in patients with AF with the ability to detect changing loading conditions.

4.2 Introduction

Dynamic filling parameters like Stroke Volume Variation (SVV) and Pulse Pressure Variation (PPV), have obtained a central place in haemodynamic management and volume therapy because of their reliability in predicting fluid responsiveness.[1] [2] National and international guidelines [3] [4] advise on perioperative use of these parameters for goal-directed treatment and they form the backbone of closed loop haemodynamic systems that are being developed.[5] Still, there are some prerequisites to correctly use SVV and PPV.[6] These include closed chest conditions [7] [8], full mechanical ventilation at sufficiently high tidal volumes [9], the absence of spontaneous breathing [10] and the presence of a sinus rhythm (SR).[11] [12] Some alternatives have been proposed to overcome the constraints for ventilator settings. [13] [14] Major arrhythmias such as AF, however, remain an unresolved issue in this context. The prevalence of AF in patients presenting for surgery ranges from 0.8% to 3.7% [15], a number that is only expected to raise in the future with an ageing population.[16] The inability to isolate the haemodynamic effects of an intrinsic irregular heart rhythm from those induced by mechanical ventilation precludes the clinical use of dynamic preload assessment with traditional monitoring techniques.

We have previously developed a model to predict the effect of an irregular heart rhythm on the beat-to-beat variation in pulse pressure (PP) in patients with AF, based on the duration of the 2 preceding RR-intervals of each individual heartbeat.[11] This model, however, did not allow for quantification of other potential influencing factors on PP changes. Beat-to-beat changes of PP are indeed influenced by various additional factors.[17] In the current study we present the principles of an adapted algorithm based on deconvolution of the blood pressure signal into separate functions. This allows separation of such distinct factors and the isolation, as well as the potential quantification of Ventilation induced Pulse Pressure Variation (VPPV).

To prove this, we tested the response of this new parameter to alterated loading conditions induced by a passive leg raising (PLR) manoeuvre. Extrapolating from the knowledge of PPV in patients with a regular heartbeat[18] [19], we investigated the relationship between changes in VPPV imposed by PLR and the pre-PLR value. We hypothesized a proportional decrease of VPPV.

4.3 Methods

Compliance with ethical standards

After approval of the institutional trial board and ethics committee of the 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. The study took place between 12/2011 and 3/2014. This report concerns the second part of the study. The first part of the study consists of the same cohort of patients and is previously published.[11] Due to practical reasons (the presence of the researcher, availability of study monitors etc) a convenience sample was taken of consecutive patients who were planned for a pulmonary vein isolation under general anaesthesia. Patients were included, if they fulfilled following criteria: (1) Age >18 years, (2) Atrial fibrillation during the 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 beats/min.

Study procedure

All patients had a standard induction and maintenance of anaesthesia. A combination of bolus sufentanil 0.1-0.2 mcg/kg, propofol 2 mg/kg and cisatracurium 0.15 mg/kg was used for induction. After intubation, sevoflurane (end-tidal concentration 1.7-2.0 %) was used for maintenance of anaesthesia and supplemented with aliquots of 5 mcg sufentanil to control analgesia. Besides the standard monitoring (5-lead ECG, pulse oximetry and non-invasive blood pressure), 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.
During the different registration periods, ECG (lead II and V2) and arterial pressure signals were stored at a sample rate of 1000 Hz using LabSystem Pro v2.4a (BARD ® Electrophysiology, Lowell, MA, USA). Two registration periods of 60 seconds were used for further analysis: After stabilisation, a baseline measurement was taken with the anaesthetized patient in semi-recumbent position and the same measurements were repeated immediately after

careful adjustment of the bed position to perform the PLR manoeuvre as previously described. [20]
Ventilator settings were the same for both periods: respiratory frequency of 12 per minute with a I:E ratio of 1:2 and a tidal volume of 8mL/kg with PEEP set at 5cm H_2O.

Data Analysis

Data were analysed off-line using a personal Matlab®-script based on the methods described by Li et al.[21] For each observation period, PPV was calculated in the traditional way as previously published.[22] These calculated values are referred to as 'PPV'. From the raw data of a 60 sec observation period (Figure 4.1A), 4 variables were determined in addition to pulse pressure (PP) for every individual beat. The first two variables, the preceding RR-interval (RR_0) and the second preceding RR-interval (RR_{-1}) were determined as previously described.[11] (figure 4.1B) The third variable is the relative timing of the R wave of the ECG of the particular heart beat within the 5 second respiratory cycle. (Figure 4.1B, line 3) The fourth variable that accounts for trending, is the absolute time of the particular heartbeat within the 60 s observation period. (Figure 4.1B, line4)

Modelling

Starting from the raw PP data of each observation period of 60 s (figure 4.2 upper panel), the individual impact of each of the variables was identified. A generalized additive model (GAM) was determined to predict PP based on 'RR_0' and 'RR_{-1}' (the effect of an irregular heartbeat), 'Ventilation' (the effect of ventilation) and trending of the PP over time (the effect of low-frequency changes in PP).[17] GAM is an expansion of the traditional multiple linear regression model, allowing a non-linear function for each of the variables as follows.[23]

$$Gam\ formula$$

$$\boldsymbol{PP = \beta_0 + f(RR_0) + f(RR_{-1}) + f(Ventilation) + f(Trend) + \varepsilon}$$

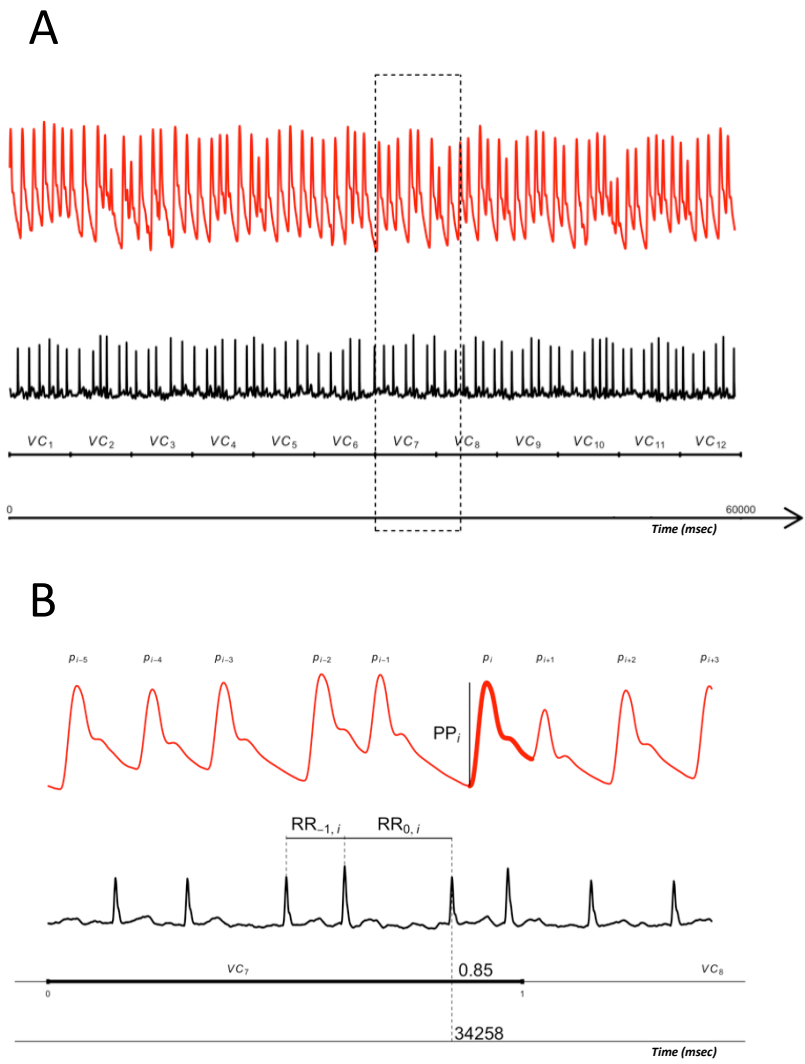


***Figure 4.1**: Terminology and schematic representation of the analysis of the raw data.* *A: Raw data of a 60s observation period. The arterial pressure (line 1, red) and the ECG signal (line2) of the consecutive beats are shown. Line 3 shows the timing of the ventilator cycles (VC).*

B: detail from A. For each pulse (p_i) the pulse pressure (PP) and 4 variables were extracted. The 2 preceding RR intervals ($RR_{0,i}$ and $RR_{-1,i}$) as previously described[14], the relative timing within each VC (line 3) and its timestamp (line 4). This procedure is repeated for every pulse within the 60s input window.

The functions used in the model were penalized natural cubic splines for RR_0, RR_{-1} and Trend, and cyclic splines for Ventilation, allowing for flexible non-linear modelling (for further explanation see Appendix).
VPPV was calculated, in analogy of the classical model for PPV, as the range of impact of ventilation on PP, normalized for the mean of PP. The intercept of the GAM, β_0, is mathematically equal to the mean of the PPs of the data points included in the model.

$$\boldsymbol{VPPV}\ (\%) = \mathbf{100}\frac{(\boldsymbol{f(Ventilation)_{max}} - \boldsymbol{f(Ventilation)_{min}})}{\boldsymbol{\beta_0}}$$

The impact of variations in the length of the observation window was estimated in a *post-hoc* analysis as follows. The algorithm to quantify VPPV was applied successively in progressively shorter windows, starting at the reference episode of 60 s with successive reductions of 1 s until the model indicated failure to solve the function. The resulting VPPVs were calculated for every step in the procedure and absolute differences with the corresponding reference value ($VPPV_{60}$) were determined.

Statistical Analysis

After testing for normality with the Shapiro Wilk test, data are reported as median [IQR] or mean (SD) as appropriate. Comparisons between the 2 measurement periods were performed using a paired t-test or a paired Wilcoxon test for PPV and VPPV values. Correlation was assessed using the Spearman rank correlation coefficient. P values < 0.05 were considered statistically significant. Goodness of fit of each individual GAM model was assessed based on the r^2. All statistical analyses were done using R (version 3.5.0)[24] base packages and 'mgcv' package (1.8-24) for gam.[25]

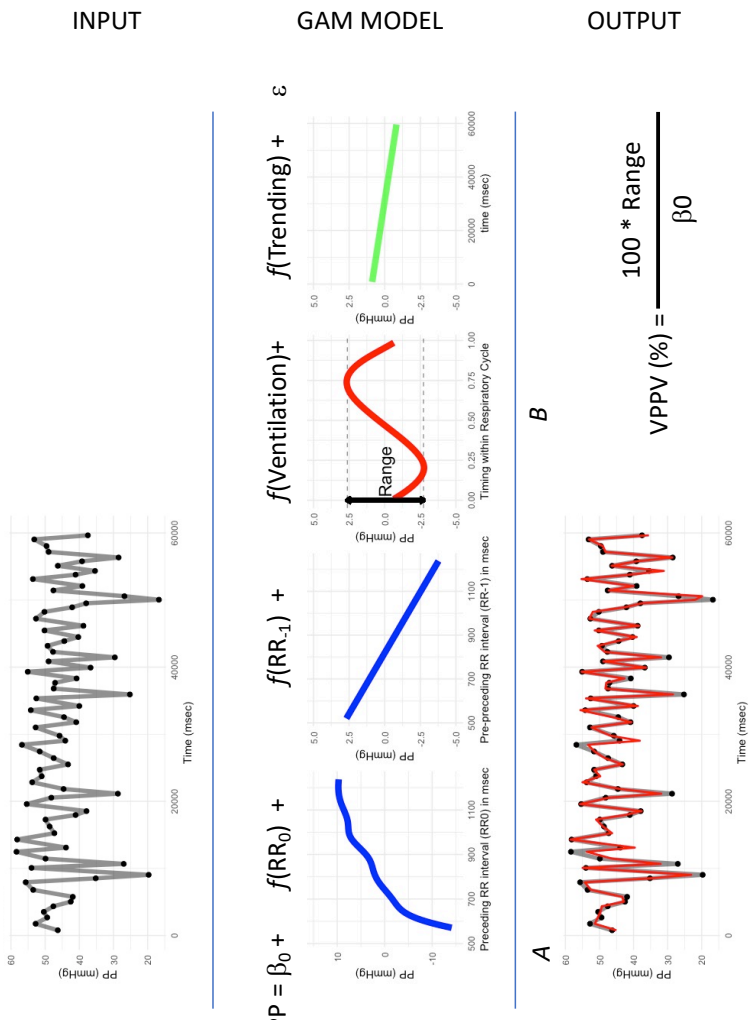

INPUT
GAM MODEL
OUTPUT
PP = β0 +
f(RR0) +
f(RR-1) +
f(Ventilation)+
f(Trending) +
ε
PP (mmHg)
Time (msec)
Preceding RR interval (RR0) in msec
Pre-preceding RR interval (RR-1) in msec
Timing within Respiratory Cycle
time (msec)
Range
A
B
VPPV (%) = 100 * Range / β0

Figure 4.2

4.4 Results

10 patients were included in the study. Due to a technical problem with the invasive arterial blood pressure measurement, 1 patient was excluded. Patient characteristics are displayed in table 4.1.
For all 18 observation periods (baseline and PLR in 9 patients), the goodness of fit of the model was determined. The median amount of deviation of PP explained by the model, was 91.3% (IQR: 89.2-94.2).
RR_0 and RR_{-1}, the two predictors used to describe the effect of atrial fibrillation were statistically significant in all 18 observation periods. Trending, the predictor for overall PP changes during the observation period was significant in 7 of the 18 observation periods. The Ventilation function was statistically significant in 7 of the 9 observation periods before PLR, suggesting the presence of significant cardiopulmonary interaction. After PLR, this distinct cyclic ventilation pattern, was present in only 2 out of 9 patients. The shape of the ventilation spline ranged from a horizontal line (no effect) to a clear sinus like curve. The relative timing of the predicted peak was not constant. The time, however, between the functions' maximum and minimum values was 51% (+/- 3%) of the duration of the ventilatory cycle.
The magnitude of VPPV decreased significantly after PLR, while PP increased significantly with this manoeuvre. (Table 4.2) There was a linear relationship between baseline VPPV's and the change in VPPV after PLR ($p < 0.0001$). The Spearman's rank correlation coefficient was -0.92 ($p = <0.001$), indicating a strong negative correlation. (Figure 4.3) In comparison to VPPV values calculated with this new method in AF patients, the corresponding PPV values

***Figure 4.2*: Schematic presentation of the analysis procedure.**
INPUT (upper panel): example of a full 60s window. All consecutive, time stamped beats are plotted against the individual PP (mmHg). All individual beats are coded according to the procedure described in figure 1.
MODELLING (middle panel): A General Additive Model is calculated. PP is predicted as the sum of intercept (β_0) and the 4 functions: RR_0, RR_{-1}, the timing within the ventilation cycle and the timestamp of each beat.
OUTPUT (lower panel): A. Example of the reconstructed signal. The fitted values for PP, based on the unique values of predictors of every beat are projected in red over the raw signal for comparison. B. Formula for quantification of the effect of ventilation (red function, middle panel) as a percentage of the range of the function over the intercept of the model.

Sex, men/women	6/3
Caucasian, %	100
Age, yr	59 (55-78)
Weight, kg	95 (65-112)
Length, cm	183 (160-185)
Cardiovascular comorbidity, n	
Hypertension	6
Hypercholesterolemia	1
Ischemic heart disease	1
Corrected valvular disease	1
Corrected congenital heart disease	1
Congestive heart failure	0
Diabetes/ metabolic syndrome, n	3
Stroke/ transient ischemic attack, n	2
Medication, n	
Amiodarone	2
Digoxin	1
Flecainide	2
Beta-blockers	6
Calcium channel blocker	2
ACE inhibitor/ AII blocker	2
Diuretics	3
CHA2DS2-VASc score	1.5 (1-5)
ASA physical status	2(2-3)

***Table 4.1**: **Patient characteristics of included patients**. Data are expressed as median (range). ACE, angiotensin-converting enzyme; CHA2DS2-VASc, congestive heart failure, hypertension, age, diabetes mellitus, and stroke-vascular disease, age, and sex category.*

obtained with the traditional algorithm were much higher although PPV before and after the PLR differed significantly (Table 4.2). However, the Spearman's rank correlation coefficient between pre-PLR value and its absolute change was -0.38 (p=0.21) indicating a weaker correlation for PPV than for VPPV. (Figure 4.3). The median RR interval and its variation changed profoundly after PLR in one particular participant. Excluding the data of this results. (See Appendix)

The *post-hoc* analysis on the impact of the length of observation window showed that the minimum period needed for the model to have enough data points to determine its coefficients was 23 s [20 s-26 s] (median, IQR). If a standard window of 46 seconds was used, all 18 models would have been able to calculate a VPPV value. This corresponds to a minimal number of data points of 28 [27-30] (median, IQR), which was independent of the individual HR. The overall absolute differences between the VPPV calculated with a shorter observation window and the $VPPV_{60s}$ were 0.0% [-1.0%, 3%] (median, IQR). (See Appendix)

	Pre PLR	***Post PLR***	***P-value***
VPPV (%)	9.9 [0.1-27.9]	1.4 [0 - 11.3]	0.014
PPV (%)	134 [14.5 – 197.9]	36.8 [7.6-192.7]	0.019
HR:			
beats (min-1)	80 [73 - 91]	73 [64 - 75]	0.09
Median RR (ms)	777 [660 – 827]	828 [804 – 940]	0.222
Range RR (ms)	718 [506 – 990]	787 [628 – 1088]	0.667
PP (mmHg)	33 [32, 40]	48 [42, 52]	0.027

***Table 4.2**: **Comparison between pre and post passive leg raising (PLR).** VPPV: Ventilation induced Pulse Pressure Variation, PPV: Pulse Pressure Variation, HR is described using 3 criteria: number of heart beats per minute, the median of the RR-intervals and the range of the RR-intervals for each observation period. PP: Pulse Pressure in mmHg is calculated as the median of the PP of each observation period. Data are presented as median [IQR]*

4.5 Discussion

The main finding of our study is that the impact of mechanical ventilation on PP can be quantified in patients with AF. Traditional algorithms used to assess PPV fail to discriminate between the effects of arrhythmia and cardiopulmonary interaction in patients with irregular heart rate and cannot be used to predict volume responsiveness in this subgroup. Our new approach is based on the separation of the blood pressure signals into the different components affecting the beat-to-beat variation in PP. It behaves like the classic dynamic filling parameters such as PPV in that an increase in venous return decreases the impact of mechanical ventilation on the PP, especially when the baseline value is high. Applying the classic formula in AF patients overestimates the ventilation induced changes in PP [26], because it cannot distinguish between the intrinsic beat-to-beat variation in PP based on the irregularity of the heart rhythm on the one hand and the cyclic change imposed by the ventilator on the other hand (See Table 4.2, Figure 4.3).

In a first step to separate these 2 effects, we previously described a method to predict individual PP's in apnoeic patients in AF (See Figure 4.1).[11] This method was based on the findings of Rawles [27] who first developed a 2-factor mathematical model to describe the influence of a preceding R-R interval (RR_0) and pre-preceding R-R interval (RR_{-1}) on the pulse pressure (and stroke volume) of each individual beat respectively. Different physiologic explanations have been proposed to explain this interaction between R-R intervals and PP. A direct non-linear relationship between RR_0 and PP (See Figure 4.2) has been attributed to effect of ventricular filling time during diastole [28]. The indirect relationship between RR_{-1} and PP (See Figure 4.2) is explained by the effects of diastolic time on calcium reuptake, translating into calcium availability during subsequent myocardial contraction [29] , and/or a potential alteration of LV afterload.[30] Regardless of the mechanism, in the current study we combined this approach with two other possible sources of changes in PP's, which are ventilation and trending over time. Our model is able to retrospectively decompose the successive beat to beat changes in PP, into these 3 sources: intrinsic irregular heart rhythm, mechanical ventilation, and slow PP changes over time. Interestingly, our data show that among the 4 variables of the model, RR_0 is the predictor with the greatest predictive power. This explains why, in contrast to patients with regular heart rhythm, the ventilation induced cyclic changes in PP cannot easily be recognised visually on screen, even when the ventilatory effect is substantial.

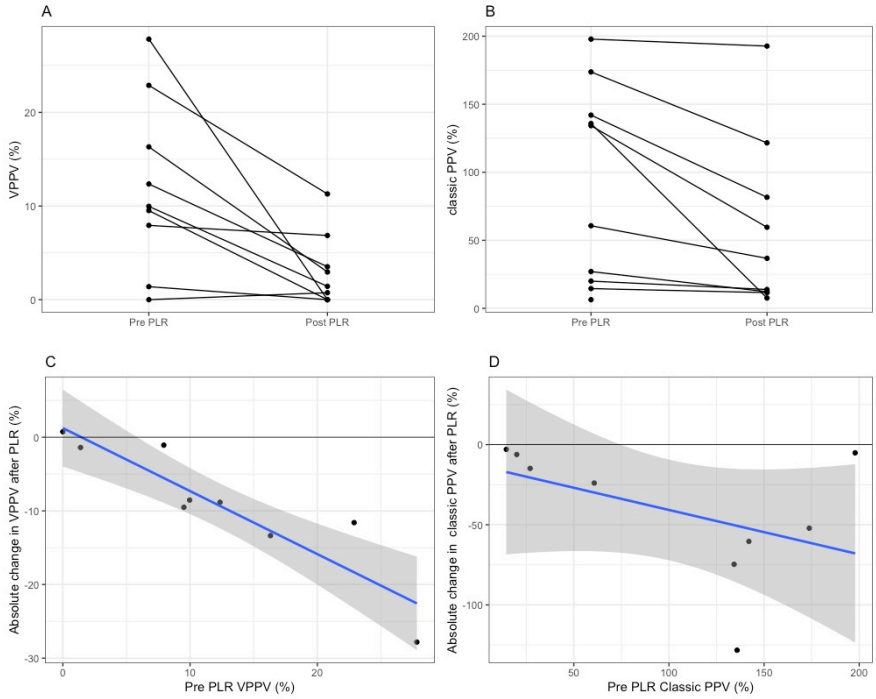


***Figure 4.3*: Pre- and post-PLR plots of (a) VPPV and (b) PPV**. *Individual values before PLR are plotted against their absolute change after the LR manoeuvre for (c) VPPV and (d) PPV. Spearman's rank correlation coefficients are 0.92 and 0.38 for VPPV and PPV, respectively, indicating a strong negative correlation between baseline VPPV and changes in VPPV with leg raising. PLR, passive leg raising; PPV, pulse pressure variation (%); VPPV, ventilation-induced pulse pressure variation (%). Shadow of the regression line signifies it is 95% confidence interval.*

We used a generalized additive model (GAM). This modelling technique has two advantages. First, it is very flexible. The relationship of each predictor with the dependent variable can be described by splines, a smoothing exact shape or coefficients (See Appendix).

Second, these relationships are calculated simultaneously and are additive. This means that the model consists of a simple sum of these individual functions. The function of each predictor is determined independent of each other. Because of these two properties we used this approach to quantify the isolated impact of ventilation. To do this, we slightly changed the traditional formula to calculate PPV: The range of changes in PP imposed by the ventilator was divided by the mean value of PP (β_0 of the model, Figure 4.2).

In patients with AF there is lack of good evidence to reliably predict fluid responsiveness. However, some alternatives have been proposed previously in the literature. PLR has the theoretical advantage that it is a ventilator independent technique with minor impact of the heart rhythm. A recent meta-analysis, that pooled the data of 23 clinical trials failed to conclude on the ability of PLR to predict fluid responsiveness in AF, because the majority of the included patients had sinus rhythm.[31] Kim et al studied the capability of 2 techniques to predict fluid responsiveness in a group of 43 patients with AF.[32] The first technique, PEEP induced changes in CVP failed to discriminate between responders and non-responders after a fluid bolus of 300 ml of colloids. PLR, on the contrary had some predictive abilities. A raise of 7.3% in SVI after PLR had a sensitivity of 71% and specificity of 79% to predict a cardiac output raise of 10%. Their reported discriminatory power (ROC of 0.771) is lower than that reported for patients in sinus rhythm however.[31] One explanation for this result could be that the cardiac output measurements, especially the smaller ones after PLR are less reliably measured due to AF.[33] [34] On top of this, PLR is very unpractical to perform with on-going surgery, which undermines its widespread use in the operating theatre. Bortolotti et al reported on the use of respiratory changes of the inferior caval vein diameter in a group of spontaneously breathing patients with AF (53%) or frequent extrasystoles (47%) [35] presenting with septic shock in the ICU. Surprisingly their results were more optimistic than the results of a recent meta-analysis comparing the ability of inferior caval vein collapsibility to predict fluid responsiveness with different ventilator settings (High TV, low PEEP vs Low TV high PEEP).[36] So, these findings need to be reconfirmed.

Beside AF, extrasystoles may also be a reason for irregular heartbeat. Cannesson et al. showed in a dog model, that it is possible to correct classic SVV for extrasystoles. After excluding extra systoles along with the following beat and after extrapolation based on the remaining beats, their corrected SVV performed markedly better in predicting fluid responsiveness than the uncorrected SVV (ROC 0.892 vs 0.596).[12] In contrast to Cannesson et al., Vistissen et al did not leave out the extrasystolic beats but used them. Their concept is based on the idea to use the prolonged extra systolic filling time, as a preload changing technique. Although this principle has been confirmed [37], recent clinical data were disappointing.[38] Interestingly, their concept is partially related to our model as their method can be seen as an attempt to provide a two-point plot of our RR_0-PP relation of the beat that follows an

extra-systolic beat. It does not, however, take the effect of RR_{-1} into account, which Rawles et al. demonstrated to be significant.[27]

The novelty of our approach is that we developed a method to filter the whole signal into its different driving processes. This enables us to quantify the isolated effect of mechanical ventilation on PP. The current study was intended to demonstrate proof of concept. It does not provide direct proof that the proposed variable is a good predictor for fluid responsiveness. We developed an algorithm that is able to quantify the impact of mechanical ventilation on PP and we showed that this measured value changes in the same way PPV changes in patients with SR, when the venous return is increased. In our protocol we used PLR to provoke such changes. Although PLR is used in clinical practice, it is a surrogate for a real fluid challenge and when performed suboptimal, it might lose its reliability.[20] We performed the classical PLR manoeuvre. However, we decided not to measure cardiac output as it has previously been shown that the measurement error for both absolute values and changes in cardiac output increases in patients with AF.[33 39] This lack of accuracy is only partially corrected when longer measuring periods are used.[39] The limited power to estimate real changes in cardiac output during AF complicates its use as a gold standard to detect short-lived effects of PLR in this study. Without this reference, only indirect indicators, such as the increase in MAP and PP, could serve to assess the global haemodynamic effect of PLR. We also did not perform a control measurement after the return to the semi-recumbent post PLR because of procedural time constraints. A return of VPPV to its baseline value, would have been useful to affirm the reliability and applicability of the manoeuvre. Another limitation of our study is the low number of included patients. The primary goal of our study was to investigate the correlation between pre-PLR values for VPPV and its changes imposed by PLR. Low and mediocre correlation coefficients would undermine the usefulness of this parameter in clinical practice as it would indicate a low signal-to-noise ratio. A post-hoc analysis reveals that setting $\alpha = 0.05$ and $\beta = 0.2$, a correlation coefficient of 0.8 or higher can be detected in a sample of 9 patients. The determination of the exact correlation coefficient, however, would have been more reliable if more patients had been included. Since calculation of VPPV is based on a regression model, some degree of measurement uncertainty must be considered. The exact interplay between distinct functions within the algorithm and their subsequent effect on sensitivity of this new variable remains to be determined. Some of the settings of the model, like epoch and exact timing of the ventilator, were arbitrarily chosen. We based our model

on a 60s window, because this epoch seemed a reasonable period in clinical practice. Theoretically, a shorter epoch would be able to pick up more short-term changes. This advantage, however, may come with the cost of a more inaccurate determination of the parameter, limiting its use in clinical practice. Calculations based on a wider window on the other hand may provide a more stable but damped model. Our post hoc analysis suggests that a shorter epoch is able to calculate a VPPV value. Interestingly, the minimal number of beats for the algorithm to calculate its coefficients was constant for all periods, independent of the individual HR. The accuracy of these values is still unclear. Future research, based on longitudinal data, is needed to determine the optimal epoch or the optimal number of beats.
The exact timing of the ventilation could not be measured in our protocol. As a result, shifts of the real to the arbitrarily set respiratory cycle in the current study have occurred in our analysis. This explains why the timing of the functions' maximum is not consistent. There was, however, a minimal variance in time between maximum and minimum predicted values of about half the respiratory cycle. This might be explained by the combined direct afterload reduction effect and the delayed effect of decreased venous return of insufflation that results in a dispersion of the effect on PP from a 1:2 (I:E) ratio to a 1:1 ratio. Although we think that this lack of synchronisation does not impact the measurement of the range of these cyclic changes, incorporating the exact time-stamped data from the ventilator mechanics into the model may provide a more accurate physiologic insight into these studied interactions.
All these issues need to be resolved before this model and its derived parameter, VPPV, can ultimately be tested for its ability to predict fluid responsiveness i.e., as sole parameter or incorporated in a tidal volume challenge.

In conclusion, our findings show the ability of a new algorithm to quantify ventilation induced variations in PP in patients with AF in the presence of different loading conditions, thereby providing a potential tool for future studies to assess fluid responsiveness in patients with AF.

References

1. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med* 2009; **37:** 2642–7. https://doi.org/10.1097/CCM.0b013e3181a590da

2. Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. *Crit Care Med* 2013; **41:** 1774–81. https://doi.org/10.1097/CCM.0b013e31828a25fd

3. Marx G, Schindler AW, Mosch C, et al. Intravascular volume therapy in adults: Guidelines from the Association of the Scientific Medical Societies in Germany. *Eur J Anaesthesiol* 2016; **33:** 488–521. https://doi.org/10.1097/EJA.0000000000000447

4. Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: First update 2016. *Eur J Anaesthesiol* 2017; **34:** 332–95. https://doi.org/10.1097/EJA.0000000000000630

5. Rinehart J, Liu N, Alexander B, Cannesson M. Review article: closed-loop systems in anesthesia: is there a potential for closed-loop fluid management and hemodynamic optimization? *Anesth Analg* 2012; **114:** 130–43. https://doi.org/10.1213/ANE.0b013e318230e9e0

6. Sondergaard S. Pavane for a pulse pressure variation defunct. *Crit Care* 2013; **17:** 327. https://doi.org/10.1186/cc13109

7. Wyffels Piet, Sergeant P, Wouters PF. The value of pulse pressure and stroke volume variation as predictors of fluid responsiveness during open chest surgery. *Anaesthesia* 2010; **65:** 704–9. https://doi.org/10.1111/j.1365-2044.2010.06371.x

8. Piccioni F, Bernasconi F, Tramontano GTA, Langer M. A systematic review of pulse pressure variation and stroke volume variation to predict fluid responsiveness during cardiac and thoracic surgery. *J Clin Monit Comput* 2017; **31:** 677–84. https://doi.org/10.1007/s10877-016-9898-5

9. Michard F, Teboul J-L, Richard C. Influence of tidal volume on stroke volume variation. Does it really matter? *Intensive Care Med* 2003; **29:** 1613–3. https://doi.org/10.1007/s00134-003-1886-9

10. Heenen S, De Backer D, Vincent J-L. How can the response to volume expansion in patients with spontaneous respiratory movements be predicted? *Crit Care* 2006; **10:** R102. https://doi.org/10.1189/cc4970

11. Wyffels PAH, Van Heuverswyn F, De Hert S, Wouters PF. Dynamic filling parameters in patients with atrial fibrillation: Differentiating Rhythm induced from Ventilation induced variations in Pulse Pressure. *Am J Physiol Heart Circ Physiol* 2016; **310:** H1194-200. https://doi.org/10.1152/ajpheart.00712.2015

12. Cannesson M, Tran NP, Cho M, Hatib F, Michard F. Predicting fluid responsiveness with stroke volume variation despite multiple extrasystoles. *Crit Care Med* 2012; **40:** 193–8. https://doi.org/10.1097/CCM.0b013e31822ea119

13. Myatra SN, Prabu NR, Divatia JV, Monnet X, Kulkarni AP, Teboul J-L. The Changes in Pulse Pressure Variation or Stroke Volume Variation After a 'Tidal Volume Challenge' Reliably Predict Fluid Responsiveness During Low Tidal Volume Ventilation. *Crit Care Med* 2017; **45:** 415–21. https://doi.org/10.1097/CCM.0000000000002183

14. Vistisen ST, Juhl-Olsen P. Where are we heading with fluid responsiveness research? *Curr Opin Crit Care* 2017; **23:** 318–25. https://doi.org/10.1097/MCC.0000000000000412

15. Maguire S, Rinehart J, Vakharia S, Cannesson M. Technical communication: respiratory variation in pulse pressure and plethysmographic waveforms: intraoperative applicability in a North American academic center. *Anesth Analg* 2011; **112:** 94–6. https://doi.org/10.1213/ANE.0b013e318200366b

16. Lane DA, Skjøth F, Lip GYH, Larsen TB, Kotecha D. Temporal Trends in Incidence, Prevalence, and Mortality of Atrial Fibrillation in Primary Care. *J Am Heart Assoc* 2017; **6:** 3250. https://doi.org/10.1161/JAHA.116.005155

17. Julien C. The enigma of Mayer waves: Facts and models. *Cardiovasc Res* 2006; **70:** 12–21. https://doi.org/10.1016/j.cardiores.2005.11.008

18. Lafanechere A, Pene F, Goulenok C, et al. Changes in aortic blood flow induced by passive leg raising predict fluid responsiveness in critically ill patients. *Crit Care* 2006; **10:** R132. https://doi.org/10.1186/cc5044

19. Mallat J, Meddour M, Durville E, et al. Decrease in pulse pressure and stroke volume variations after mini-fluid challenge accurately predicts fluid responsiveness. *Br J Anaesth* 2015; **115:** 449–56. https://doi.org/10.1093/bja/aev22

20. Monnet X, Teboul J-L. Passive leg raising: five rules, not a drop of fluid! *Crit Care* 2015; **19:** 18–3. https://doi.org/10.1186/s13054-014-0708-5

21. Li BN, Dong MC, Vai MI. On an automatic delineator for arterial blood pressure waveforms. *Biomed Signal Process Control* 2010; **5:** 76–81.

22. Michard F. Changes in arterial pressure during mechanical ventilation. *Anesthesiology* 2005; **103:** 419–28. https://doi.org/10.1097/00000542-200508000-00026

23. Hastie T, Tibshirani R, Friedman J. *The Elements of Statistical Learning.* New York, NY: Springer Science & Business Media; 2013

24. R Core Team. *R: A language and environment for statistical computing. R Foundation for Statistical Computing,* Vienna, Austria; 2013. URL: http://www.R-project.org/.

25. Wood SN. *Generalized Additive Models.* New York, NY: CRC Press; 2017

26. Michard F, Chemla D, Teboul J-L. Applicability of pulse pressure variation: how many shades of grey? *Crit Care* 2015; **19:** 144. https://doi.org/10.1186/s13054-015-0869-x

27. Rawles JM. A mathematical model of left ventricular function in atrial fibrillation. *Int J Biomed Comput* 1988; **23:** 57–68. https://doi.org/10.1016/0020-7101(88)90063-3

28. Greenfield JC, Harley A, Thompson HK, Wallace AG. Pressure-flow studies in man during atrial fibrillation. *J Clin Invest* 1968; **47:** 2411–21. https://doi.org/10.1172/JCI105924

29. Brookes CI, White PA, Staples M, et al. Myocardial contractility is not constant during spontaneous atrial fibrillation in patients. *Circulation* 1998; **98:** 1762–8. https://doi.org/10.1161/01.cir.98.17.1762

30. Muntinga HJ, Gosselink AT, Blanksma PK, de Kam PJ, Van Der Wall EE, Crijns HJ. Left ventricular beat to beat performance in atrial fibrillation: dependence on contractility, preload, and afterload. *Heart* 1999; **82:** 575–80. https://doi.org/

31. Cherpanath TGV, Hirsch A, Geerts BF, et al. Predicting Fluid Responsiveness by Passive Leg Raising: A Systematic Review and Meta-Analysis of 23 Clinical Trials. *Crit Care Med* 2016; **44:** 981–91. https://doi.org/10.1136/hrt.82.5.575

32. Kim N, Shim J-K, Choi HG, Kim MK, Kim JY, Kwak Y-L. Comparison of positive end-expiratory pressure-induced increase in central venous pressure and passive leg raising to predict fluid responsiveness in patients with atrial fibrillation. Thompson JP, editor. *Br J Anaesth* 2016; **116:** 350–6. https://doi.org/10.1093/bja/aev359

33. Ostergaard M, Nilsson LB, Nilsson JC, Rasmussen JP, Berthelsen PG. Precision of bolus thermodilution cardiac output measurements in patients with atrial

fibrillation. *Acta Anaesthesiol Scand* 2005; **49:** 366–72. https://doi.org/10.1111/j.1399-6576.2005.00613.x

34. Lakhal K, Ehrmann S, Boulain T. Predictive performance of passive leg raising in patients with atrial fibrillation. *Br J Anaesth* 2016; **117:** 399–9. https://doi.org/10.1093/bja/aew233

35. Bortolotti P, Colling D, Colas V, et al. Respiratory changes of the inferior vena cava diameter predict fluid responsiveness in spontaneously breathing patients with cardiac arrhythmias. *Ann Intensive Care* 2018; **8:** 79. https://doi.org/10.1186/s13613-018-0427-1

36. Si X, Xu H, Liu Z, et al. Does Respiratory Variation in Inferior Vena Cava Diameter Predict Fluid Responsiveness in Mechanically Ventilated Patients? A Systematic Review and Meta-analysis. *Anesth Analg* 2018; **127:** 1157–64. https://doi.org/10.1213/ANE.0000000000003459

37. Vistisen ST. Using extra systoles to predict fluid responsiveness in cardiothoracic critical care patients. *J Clin Monit Comput* 2016; **113:** 740–7. https://doi.org/10.1007/s10877-016-9907-8

38. Vistisen ST, Berg JM, Boekel MF, et al. Using extra systoles and the micro-fluid challenge to predict fluid responsiveness during cardiac surgery. *J Clin Monit Comput* 2018; **103:** 1–10. https://doi.org/10.1007/s10877-018-0218-0

39. Dubrey SW, Falk RH. Optimal number of beats for the Doppler measurement of cardiac output in atrial fibrillation. *J Am Soc Echocardiogr* 1997; **10:** 67–71. https://doi.org/10.1016/s0894-7317(97)80034-x

Chapter 5

'… Measurement:
A quantitatively expressed
reduction of uncertainty based
on one or more observations. …'

Douglas W Hubbard

5

Measurement Error of Pulse Pressure Variation

In this chapter, we investigate an unexplored limitation in current research concerning dynamic filling parameters like Pulse Pressure Variation. As different methods to calculate PPV have been used in clinical studies and each one of these methods come with an intrinsic measurement error, this often-overlooked source of uncertainty may impact the interpretation of literature and the use of PPV in clinical practice. Based on a Bayesian model build with data from the VitalDb, we estimate the measurement error of 3 classes of approaches to calculate PPV and simulate the impact of these measurement errors on the uncertainty of measured PPV values.

***

Wyffels PAH, De Hert S, Wouters PF.
Measurement error of pulse pressure variation.
Journal of Clinical Monitoring and Computing. (8/12/2023)
https://doi.org/10.1007/s10877-023-01099-x

5.1 Abstract

Background: Dynamic preload parameters are used to guide perioperative fluid management. However, reported cut-off values vary and the presence of a gray zone complicates clinical decision making. Measurement error, intrinsic to the calculation of pulse pressure variation (PPV) has not been studied but could contribute to this level of uncertainty. The purpose of this study was to quantify and compare measurement errors associated with PPV calculations.

Methods: Hemodynamic data of patients undergoing liver transplantation were extracted from the open-source VitalDatabase. During these surgeries, 3 algorithms were applied to calculate PPV based on 1 minute observation periods. For each method, different durations of sampling periods were assessed.
Best Linear Unbiased Prediction was determined as the reference PPV-value for each observation period. A Bayesian model was used to determine bias and precision of each method and to simulate the uncertainty of measured PPV-values.

Results: All methods were associated with measurement error. The range of differential and proportional bias were [-0.04%,1.64%] and [0.92%,1.17%] respectively. Heteroscedasticity influenced by sampling period was detected in all methods. This resulted in a predicted range of reference PPV-values for a measured PPV of 12% of [10.2%,13.9%] and [10.3%,15.1%] for two selected methods. The predicted range in reference PPV-value changes for a measured absolute change of 1% was [-1.3%,3.3%] and [-1.9%,4%] for these two methods.

Conclusion: We showed that all methods that calculate PPV come with varying degrees of uncertainty. Accounting for bias and precision may have important implications for the interpretation of measured PPV-values or PPV-changes.

5.2 Introduction

***'… It is one of those contradictions of life that although measurement always carries uncertainty, the uncertainty in measurement is rarely discussed. …** '.*

Leonard Mlodinow [1]

The impact of measurement error is often neglected in medical research. This specifically applies to the research concerning dynamic filling parameters.
Several decades ago, the physiologic mechanisms that are at play when a patient is mechanically ventilated were unraveled.[2] Parameters like Pulse Pressure Ventilation (PPV) and Stroke Volume Variation have been defined to quantify these mechanisms and have shown to reliably predict the effect of fluid loading on cardiac output (fluid responsiveness).[3,4] The reliability was further refined with the identification of a grey zone for optimal thresholds[5] and the pre-requisites for the correct use of these parameters in clinical practice were specified. (e.g., tidal volume restrictions, the need for a regular heart rhythm, closed chest conditions, no spontaneous breathing …).[6-9] Most recent studies, in this area of hemodynamic research, concentrated on overcoming these restrictions. Tidal Volume challenge has been proposed as a work-around when lower tidal volumes are used.[10,11] An algorithm to correct for irregular heartbeat has been described[12] and several variants on the Passive Leg-Raising test (PLR), as a universally applicable method in intensive care settings have been investigated.[13,14]

However, although calculating PPV is intuitive and easy, over the years, some slight methodologic variations can be found in the literature. One of these subtle differences is the number of respiratory cycles used in the calculations. The vast majority is based on 3 consecutive respiratory cycles[15], but numbers up to 8 have been reported.[16] Furthermore, the procedure for the identification of minimum and maximum Pulse Pressures (PP) can differ between research groups. It is mostly determined for each respiratory cycle individually and then averaged, but some variant methodologies have been described.[6,16]
Clinicians, and more recently also some research groups[10,11], use commercially available monitors that automatically and continuously calculate dynamic filling parameters like PPV. Only few research has been

done to compare these automated values with the manually calculated values used in research setting. Although these studies found a high correlation between methods, interchangeability between these methods could not be withheld.[17,18]
This heterogeneity in methods may well be an important source of variability in reported cutoff values, grey zones, and prediction properties …
The purpose of our study is to systematically explore the measurement error for different variants to calculate PPV and the uncertainty that comes with it.

5.3 Methods

Data acquisition and extraction

For this analysis the open on-line VitalDB database was used. This database harbors high-fidelity bio-signals of 6388 surgeries and was originally registered under the number NCT02914444. The development and the structure of the data set, the technical specifications and demographics of the studied population have been recently described.[19] The vitaldb-Python package[20] was used to filter out only the adult liver transplantation cases. For each case, 4 timestamped waveforms were identified: Electrocardiogram (ECGII, 500Hz), invasive radial artery blood pressure (Art, 500Hz), ventilatory pressure profiles (AWP, 62.5 Hz) and end-tidal CO2 (ETCO2, 62.5Hz). Respiratory Rate (RR), measured with plethysmography was extracted as a timestamped list.

For each included case, 6 data strips, consisting of the 4 synchronized waveforms, with an observation window of 60sec were selected. All data strips met the following criteria:

- No artifacts in the arterial wave forms
- Full mechanical ventilation as evidenced by the AWP and ETCO2
- Hemodynamic stability in the observation window
- At least 10 minutes in-between the adjacent observation windows

These data strips were identified using a personalized R-code and manually validated after visual inspection.
An adapted Matlab® script based on Li et al, was used to identify diastolic, systolic and pulse pressure for each beat[21], along with the respiratory rate of each strip.

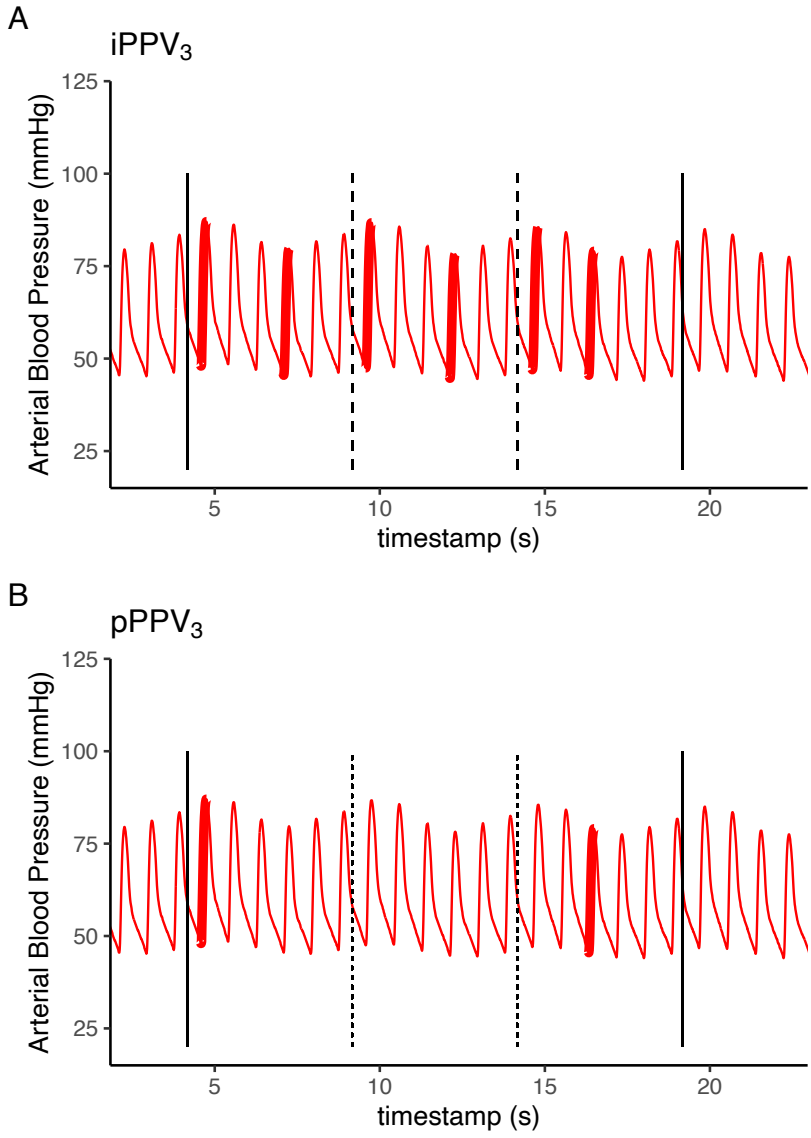


Figure 5.1: ***'iPPV'-family and 'pPPV'-family of the respiratory cycle-based methods to calculate PPV.*** Example to explain the difference between the two methods based on the same 3 Respiratory Cycles (RC). Upper Panel A: minimum and maximal Pulse Pressure (PP) are depicted in bold for each individual cycle. PPV, using the base formula, is calculated for each individual RC. The value of $iPPV_3$ is the mean of these 3 values. Lower Panel B: minimum and maximum PP of all the beats pooled together from the 3 RC's are identified and used in the base formula to calculate $pPPV_3$. Vertical lines identify the beginning or ending of a respiratory cycle.

Different methods to calculate PPV

All methods to calculate PPV are based on the same base formula:

$$PPV\ (\%) = 100\frac{(PP_{max} - PP_{min})}{(PP_{max} + PP_{min})/2}$$

The different approaches to apply this formula were grouped into three classes.

A. ***<u>'Individual RC PPV'-class: iPPV</u>***
The base formula is applied to each RC individually. The average of these individual adjacent PPV's is taken. (See: figure 5.1) e.g., $iPPV_3$ averages the PPV of 3 successive RC's. In our study, $iPPV_1$ up to $iPPV_5$ was determined from each data strip. (See figure 5.2)

B. ***<u>'Pooled RC PPV'-class: pPPV</u>***
The base formula is applied to all the PP's of all successive RC's pooled together. This way, the formula is applied only once. (See: figure 5.1) e.g., $pPPV_3$, pools all measured PP's of 3 adjacent RC's together. As such, the maximal PP and the minimal PP do not necessarily come from the same RC.[16] In our study, $pPPV_1$ up to $pPPV_5$ is determined for each data strip (See figure 5.2).

C. ***<u>Time window-based class: tPPV.</u>***
Because most of the algorithms of the commercially available monitors are not publicly available, we choose to assess only one frequently cited method. A detailed description of this algorithm was publicized by Aboy et al.[16,22] In contrast to the 2 preceding classes, tPPV is not based on a predefined number RC's but on a fixed time window to include the PP's for calculation. For our analysis, we used the following predefined windows: 12sec, 15sec, 20sec, 30sec and 60sec. e.g., $tPPV_{20}$ is the value using this algorithm on a 20 sec data strip. (See figure 5.2).

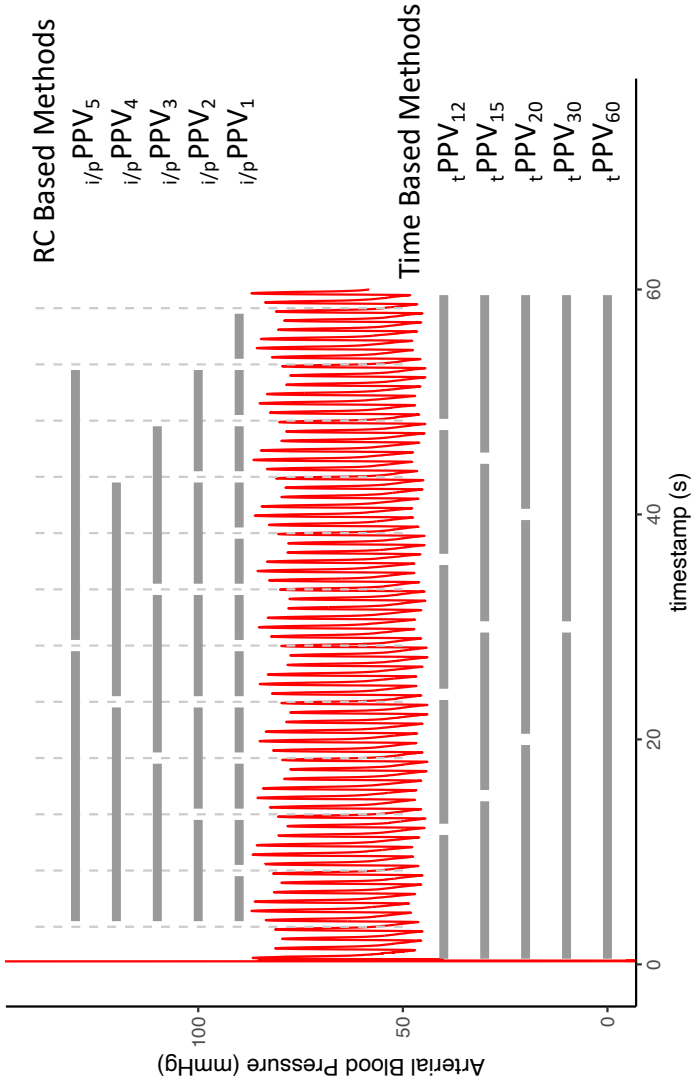


Figure 5.2: Selected windows of the independent PPV measures for each group.

The invasive arterial pressure wave of a 60s observation windows, is depicted. Vertical lines identify the beginning and end of a Respiratory Cycle. The grey horizontal boxes depict the windows used to calculate the independent replicates. Above the arterial waveform the boxes for the RC-based method (iPPV and pPPV) are depicted. The number of included RC- s is ordered from 1 to 5. Underneath the arterial waveform the boxes for the fixed time-window based method (tPPV) are shown. The length of the time window is ordered from 12sec to 60sec.

Statistics

P(measuredPPV| BLUP)

To study the measurement error in this study, with different numbers of replicates per method, a Bayesian model based on the two-step approach by Taffé was used.[23]

- Model development:

A. Bias and Precision

The measurements of each method (M) can be modelled as:

$$M(x_j)_i = \beta_0 + \beta_1 x_j + \varepsilon(M(x_j))_i$$

Or

$$M(x_j)_i \sim N(\beta_0 + \beta_1 x_j, \sigma^2_{M(x_j)})$$

Where $M(x_j)_i$ is the i[th] replicate of the measurement of the real (unknown) value x_j by model M. Each independent measurement of x_j can be seen as a random sample from a normal distribution with both a mean and a variance that changes in function of x_j. This formula is used to determine the measurement error that consists of bias and precision:
The mean of this normal distribution is equal to $(\beta_0 + \beta_1 x_j)$. This function is further decomposed into a *differential bias* (β_0, the fixed bias irrespective of the value x_j) and a *proportional bias* ($\beta_1 - 1$, the bias in function of x_j). The spread of the replicate measurements of $M(x_j)_i, \sigma^2_{M(x_j)}$, is a measure for *the precision* of the method. Heteroskedasticity, non-constant variance or in this case precision, is coded into the formula as a linear relation:

$$\varepsilon(M(x_j))_i \sim N(0, e^{\alpha_0 + \alpha_1 x_j})$$

Now for each method, the distribution of the measurement of a real value x_j can be written as:

$$M_1(x_j) \sim N\left(\beta_{0M_1} + \beta_{1M_1} x_j, e^{\alpha_{0M_1} + \alpha_{1M_1} x_j}\right)$$
$$M_2(x_j) \sim N(\beta_{0M_2} + \beta_{1M_2} x_j, e^{\alpha_{0M_2} + \alpha_{1M_2} x_j})$$
$$M_3(x_j) \sim N(\beta_{0M_3} + \beta_{1M_3} x_j, e^{\alpha_{0M_3} + \alpha_{1M_3} x_j})$$
$$\dots$$

B. A Reference Method

To simplify calculations and to overcome the identification problem, a surrogate reference method is chosen. This means, more specifically, that bias for this method is set to 0 and bias-parameters of the other methods are determined in relation to the reference method.
Choosing M1 as reference method this makes:

$$M_1(x_j) \sim N\left(0 + 1.x_j, e^{\alpha_{0M_1} + \alpha_{1M_1} x_j}\right)$$
$$M_2(x_j) \sim N(\beta_{0M_2} + \beta_{1M_2} x_j, e^{\alpha_{0M_2} + \alpha_{1M_2} x_j})$$
$$M_3(x_j) \sim N(\beta_{0M_3} + \beta_{1M_3} x_j, e^{\alpha_{0M_3} + \alpha_{1M_3} x_j})$$
$$\dots$$

C. Best Linear Unbiased Predictor (BLUP)

After choosing a reference method, we applied the same method as Taffé to estimate the underlying true values. In this study, $iPPV_1$ was chosen as reference, because of its highest number of replicates. Based on a regression model for $M_y(x_j)$, by marginal maximum likelihood allowing heteroscedasticity they predict x_j by the mean of its posterior distribution. This predicted value is called the BLUP (Best Linear Unbiased Predictor).[23]

$$M_1\left(BLUP_j\right) \sim N\left(0 + 1.BLUP_j, e^{\alpha_{0M_1} + \alpha_{1M_1} BLUP_j}\right)$$

$$M_2\left(BLUP_j\right) \sim N\left(\beta_{0M_2} + \beta_{1M_2} BLUP_j, e^{\alpha_{0M_2} + \alpha_{1M_2} BLUP_j}\right)$$

$$M_3\left(BLUP_j\right) \sim N\left(\beta_{0M_3} + \beta_{1M_3} BLUP_j, e^{\alpha_{0M_3} + \alpha_{1M_3} BLUP_j}\right)$$

…

D. Combining all methods

A Bayesian interaction model to determine the linear components of bias and error for each measurement method was build. A weakly informative prior for all components was used. With a sample size of more than 15000 measurements for 530 independent values we expected the likelihood would dominate the posterior. A detailed description of the model and the used priors can be found in Appendix C.

- Visualization

Results are visualized in 3 plots: A Bias plot is generated where the linear function for bias ($\beta_{0M_y} + (\beta_{1M_y} - 1)\ BLUP_j$) and its uncertainty is depicted, grouped per method-class. A Precision plot is generated where the transformed linear function for error ($\alpha_{0M_y} + \alpha_{1M_y} BLUP_j$) and its uncertainty is depicted, grouped per method-class. Finally, the prediction of each model with its uncertainty over the full range of $BLUP_j$ is generated. (P(Measured PPV | BLUP) : the expected distribution of measured PPV values conditional on a specific BLUP value.)

P(BLUP| measured PPV) and P(ΔBLUP| Δmeasured PPV) for the iPPV$_3$ and tPPV$_{15}$ method.

To simulate the impact of the measurement error on clinical decision making and to assess the density of a BLUP conditional on a measured value, the original model was adapted:
A set of data points were added to the original data set containing a range of measured iPPV$_3$ values and tPPV$_{15}$ values from 9 to 15, with a missing BLUP-value. The formula of the model was adjusted, allowing imputation for missing predictor data. These imputed densities for the missing data were

used to simulate the densities of changes in x_j given a change in measured values $M_i(x_j)$ (See: Github/supplementary data) $iPPV_3$ and $tPPV_{15}$ were chosen to compare because, (1) $iPPV_3$ is the most used method in the literature and (2) these 2 methods have the best comparable observation windows.

Software

Statistical analysis and visualization were performed with R (R, version 4.2.0, Core Team, Vienna, Austria, 2016) using the tidyverse-package (1.3.1) and MethodCompare-package (0.1.2).[24] Bayesian modeling was done with STAN through brms (2.17.0), bayesplot-package (1.9.0) and tidybayes-package (3.0.2).
The exact code, the source-data and guidance for repeating our analysis, is publicly available on GitHub: https://github.com/pwyffels/Measurement-Error-PPV

5.4 Results

In total 98 adult patients undergoing liver-transplantation are included in VitalDB. Import of complete data sets failed for 10 cases. Demographic description of the remaining 88 cases that were included for analysis can be found in table 5.1. Per case, 6 data strips were selected. For one case only 4 data strips were included due to artifacts and periods of atrial fibrillation, resulting in a total of 526 data strips of 1 minute.

A. P (measured PPV | BLUP)

For each method the coefficients of the model were calculated and can be found in table 5.2. Bias and Precision plots for visualization of the 2 components of measurement error can be found in figure 5.3.
The ‘Individual RC PPV’-class showed minimal bias. Precision decreased for higher values of BLUP. This heteroscedasticity decreased with increasing numbers of included respiratory cycles. For the ‘Pooled RC PPV’-class both

***Table 5.1**: Demographics of included patients as reported in the VitalDB.*
Data are given median[range] for continuous data and number(percentage) for categorical data.

***Age** (year)*	53.5 [18-82]
Sex M	27/88 (31%)
***Weight** (kg)*	59.1 [36.5-81.4]
***Height** (cm)*	166 [139 – 181]
***BMI** (kg/m2)*	21.4 [13.9 – 29.2]
ASA	
I	3 (4%)
II	29 (35%)
III	46 (55%)
IV	5 (6%)
nan	5 (6%)
***HR** (beats/min)*	86 [46-141]
***MAP** (mm Hg)*	67.7 [32-109]
***MVR** (RC/min)*	14 [8 – 23]
***HR/MVR** (beats/RC)*	5.9 [2.6 – 12.1]

differential (β_0) and proportional ($1-\beta_1$) bias were detected which increased when higher numbers of respiratory cycles were included. ($pPPV_1$: β_0 = -0,04 (-0.1, 0.02), $1-\beta_1$ = 0.00 (0.00, 0.01), $pPVV_5$: β_0 = 1.64 (1.43, 1.86), $1-\beta_1$ = 0.17 (0.14, 0.19)). Precision decreased for higher values of BLUP and decreased, as opposed to the 'Individual RC PPV'-class, even further with increasing numbers of included RC. ($pPPV_1$: α_0 = -0.11 (-0.14, -0.08), α_1 = 0.05 (0.05, 0.05), $pPVV_5$: α_0 = 0.21 (0.13, 0.30), α_1 = 0.06 (0.05, 0.06)).
The 'Time window based PPV'-class methods to calculate PPV showed increasing proportional bias that, in contrast to the 'Pooled RC PPV'-class, diminishes with inclusion of longer time windows. ($tPPV_{12}$: $1-\beta_1$ = -0.08 (-0.09, -0.06), tPVV60: $1-\beta_1$ = -0.01 (-0.01, 0.00)). Precision showed a similar trend as the 'Individual RC PPV'-class methods. ($tPPV_{12}$: α_0 = -0.43 (-0.49, 0.38), α_1 = 0.07 (0.07, 0.08), $tPVV_{60}$: α_0 = -1.66 (-1.78, -1.55), α_1 = 0.06 (0.05, 0.07)).

***Measurement** methods*	β_0	β_1	α_0	α_1
'Individual RC PPV'-Class				
$iPPV_1$	-0.04 (-0.10, 0.02)	**1.00 (1.00, 1.01)**	-0.11 (-0.14,-0.08)	0.05 (0.04, 0.05)
$iPPV_2$	-0.06 (-0.12,-0.00)	**1.01 (1.00, 1.01)**	-0.47 (-0.52,-0.42)	0.06 (0.05, 0.06)
$iPPV_3$	-0.07 (-0.13, 0.00)	**1.01 (1.00, 1.02)**	-0.68 (-0.74,-0.62)	0.05 (0.05, 0.06)
$iPPV_4$	-0.07 (-0.13,-0.01)	**1.01 (1.00, 1.02)**	-0.87 (-0.94,-0.80)	0.06 (0.05, 0.06)
$iPPV_5$	-0.06 (-0.12, 0.00)	**1.01 (1.00, 1.02)**	-1.05 (-1.13,-0.98)	0.06 (0.05, 0.07)
'Pooled RC PPV'-Class				
$pPPV_1$	-0.04 (-0.10, 0.02)	1.00 (1.00, 1.01)	-0.11 (-0.14,-0.08)	0.05 (0.05, 0.05)
$pPPV_2$	0.60 (0.50, 0.69)	1.07 (1.06, 1.08)	-0.06 (-0.11,-0.01)	0.05 (0.05, 0.06)
$pPPV_3$	1.02 (0.89, 1.15)	1.11 (1.10, 1.13)	0.06 (0.00, 0.12)	0.05 (0.05, 0.06)
$pPPV_4$	1.38 (1.21, 1.55)	1.14 (1.12, 1.16)	0.17 (0.10, 0.25)	0.05 (0.05, 0.06)
$pPPV_5$	1.64 (1.43, 1.86)	1.17 (1.14, 1.19)	0.21 (0.13, 0.30)	0.06 (0.05, 0.06)
'Time window-based PPV'-Class				
$tPPV_{12}$				
$tPPV_{15}$	-0.14 (-0.22,-0.05)	0.92 0.91, 0.94)	-0.43 (-0.49,-0.38)	0.07 (0.07, 0.08)
$tPPV_{20}$	-0.16 (-0.23,-0.09)	0.97 (0.96, 0.98)	-0.61 (-0.67,-0.55)	0.06 (0.06, 0.07)
$tPPV_{30}$	-0.10 (-0.16,-0.03)	0.98 (0.97, 0.98)	-0.78 (-0.85,-0.71)	0.06 (0.05, 0.06)
$tPPV_{60}$	-0.06 (-0.12, 0.01)	0.99 (0.98, 1.00)	-1.00 (-1.09,-0.91)	0.06 (0.05, 0.07)
	-0.06 (-0.12,-0.01)	0.99 (0.99, 1.00)	-1.66 (-1.78,-1.55)	0.06 (0.05, 0.07)

***Table 5.2**: Estimates of the coefficients of all measurement models.*
Estimates are reported as expected value and its 95% probability mass.

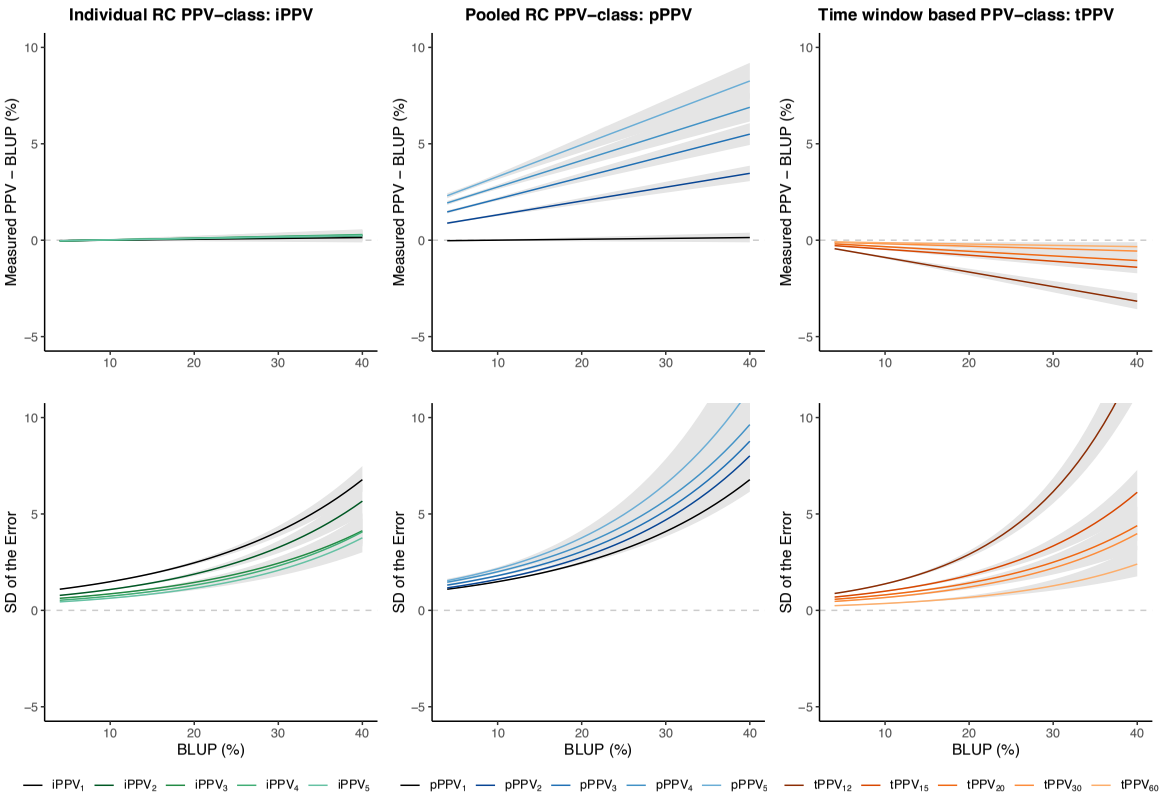


***Figure 5.3:** Bias plots and Precision plots of all the method grouped per PPV-class.*

B. P (BLUP| measured PPV)

Based on the model with imputed missing values, densities for the predicted BLUP given a specific measured value using the $iPPV_3$ method could be determined. These densities were calculated for measured values ranging from 9% to 14% and can be found in table 5.3.

C. P (ΔBLUP| Δmeasured PPV)

Based on the model with imputed missing values, and after contrasting the densities of the predicted BLUP-distributions, expected real underlying changes could be sampled. These densities were determined for an absolute change from 0.5 % (9.5 % vs 9 %) to 3.5 % (12.5 % vs 9 %) in aliquots of 0.5 %. (See table 5.4)
The chance for detecting a real increase was determined and ranged from 0.664 to 0.997 and from 0.641 to 0.987 (for a measured absolute increase of 0.5 to 3.5% in $iPPV_3$ and $tPPV_{15}$ respectively). (See Table 4)

Observed value of PPV (%)	**P(BLUP|measured PPV)**	
	$iPPV_3$	$tPPV_{15}$
9	7.5 - 10.7	7.6 – 11.6
10	8.4 - 11.8	8.6 – 12.8
11	9.4 - 12.8	9.4 – 13.8
12	10.2 - 13.9	10.3 – 15.1
13	11.1 - 14.9	11.3 – 16.2
14	12.0 - 16.0	12.1 – 17.3
15	12.8 - 17.1	12.9 – 18.4

Table 5.3: ***P(BLUP|measured PPV)***.
Distribution of the predicted value of BLUP given a measured value of PPV for two methods: $iPPV_3$ and $tPPV_{15}$. Distribution is expressed as high-density interval (HDI). HDI determined as the 95% probability mass.

Measured change in $iPPV_3$	***$P(\Delta BLUP \mid \Delta iPPV_3)$***	***$P(\Delta BLUP > 0 \mid \Delta iPPV_3)$***
0.5	-1.78 – 2.82	0.664
1.0	-1.34 – 3.31	0.797
1.5	-0.886 – 3.82	0.891
2.0	-0.396 – 4.35	0.948
2.5	0.123 – 4.98	0.978
3.0	0.461 – 5.38	0.991
3.5	0.954 – 5.89	0.997
Measured change in $tPPV_{15}$	***$P(\Delta BLUP \mid \Delta tPPV_{15})$***	***$P(\Delta BLUP > 0 \mid \Delta tPPV_{15})$***
0.5	-2.29 – 3.38	0.641
1.0	-1.9 – 3.95	0.758
1.5	-1.41 – 4.48	0.852
2.0	-0.93 – 5.11	0.923
2.5	-0.49 – 5.59	0.953
3.0	-0.10 – 6.15	0.975
3.5	0.44 – 6.73	0.987

***Table 5.4:* $P(\Delta BLUP \mid \Delta measuredPPV)$.**
Distribution of the predicted BLUP changes given a measured change in PPV values for two methods: $iPPV_3$ and $tPPV_{15}$. Distributions are expressed as expected value and high-density interval (HDI). HDI is determined as the 95% probability mass. $P(\Delta BLUP > 0 \mid \Delta iPPV_3)$: the chance that the measured change in $iPPV_3$ is a real increase in BLUP.

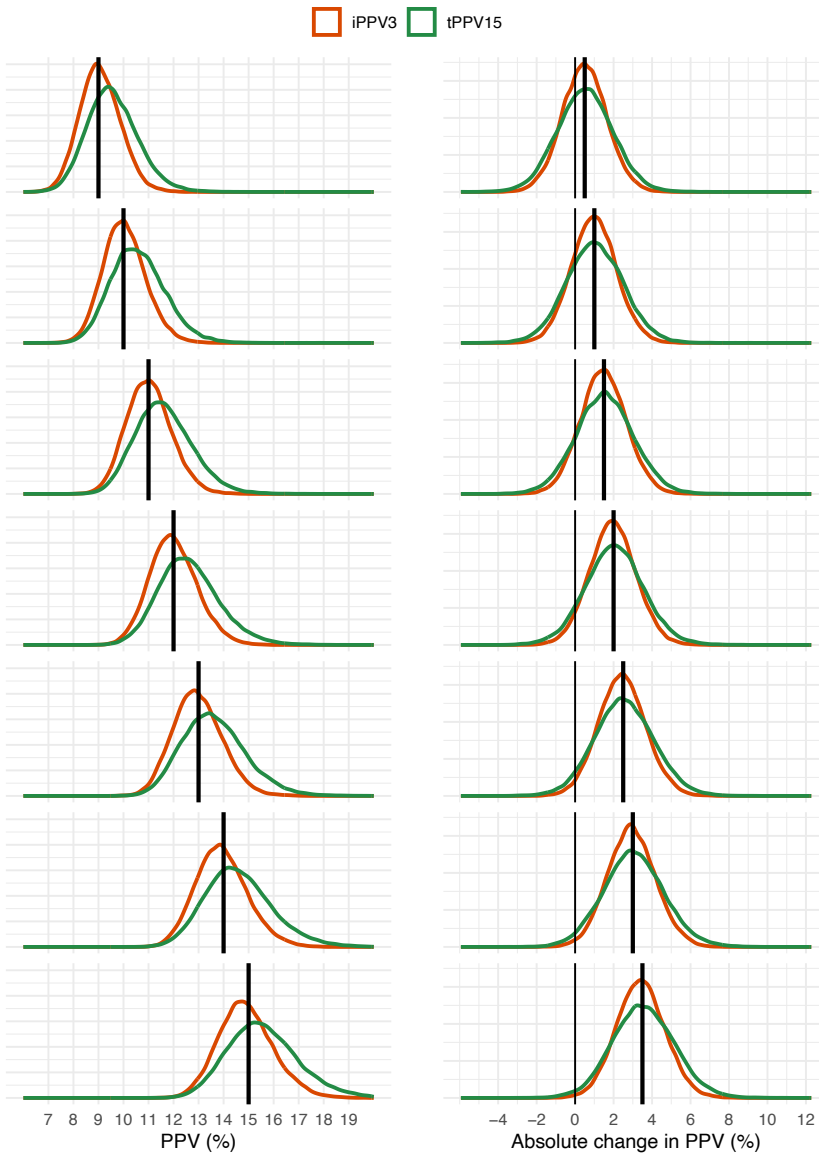


***Figure 5.4*: Distribution of imputed models**

Left hand side: Distribution of P(BLUP| measured PPV) for 7 different measured values of PPV. Vertical line as reference of the measured value ordered from 9% to 15%. Right hand side: Distribution of P(ΔBLUP| measured ΔPPV) for 7 difference. Bold vertical lines: measured ΔPPV ordered from 0.5% to 3.5%. thin vertical line: reference through the origin. Green lines: $iPPV_3$, Red lines: $tPPV_{15}$

5.5 Discussion

In this study we estimated the measurement error for 3 conceptually different approaches to calculate PPV. Although all investigated methods basically use the same formula to calculate PPV, we identified 3 variants in the literature in how different methods handle and define the observation window on which this formula is applied. A first class of methods were based on a fixed number of respiratory cycles (RC). PPV is calculated for each individual RC before averaging in the 'Individual RC PPV'- class (iPPV).[15] In the 'Pooled RC PPV'-class (pPPV), on the other hand, all included PPs are pooled before applying the formula once[16] (see figure 5.1). We further investigated another method found in the literature that bases its observation window on a fixed time-period, regardless of the number of RCs contained in the chosen time frame. ('Time window based PPV'-class (tPPV)[22]).

All studied methods had some degree of measurement error. The whole spectrum of measurement errors was found over the studied methods (see figure 5.3). In short, pPPV-methods systematically produced higher values compared to the corresponding values obtained with the iPPV-methods. The discrepancy was larger for higher values of PPV. Alongside this bias, the precision of the pPPV-methods was lower in comparison to the iPPV-methods. This difference was even more pronounced for the methods that include more RCs. Opposing effects were found for the 'Time window based PPV'-class. In these methods, a decreasing bias and an increasing precision with longer observation windows were identified.
Our findings are in line with previous reports. Kim et al, using the pPPV-methods, observed that the measured values of PPV increased with longer sampling duration. This effect seemed maximal with 5 included RC's.[16,17] Derichard et al, using a commercially available monitor based on an algorithm closely resembling tPPV, found that these automated values of PPV closely correlated with the corresponding $iPPV_3$ values, but tended to overestimate them.[17] The same monitor was used by Cannesson et al who reaffirmed the correlation between $iPPV_3$ and the automated values. Their Bland-Altman analysis, however, revealed an agreement of 0.7% (+/-4.4%) (mean bias +/- SD).[18]
Most studies comparing different measurement methods use Bland-Altman analysis. For this study, we did not consider this appropriate. Firstly, multiple methods using a varying number of replicate measurements, are compared

with each other. Along with the expected proportionality in bias and precision, this warrants the use of adapted Bland-Altman methods that limit the interpretations of study results.[25] But most importantly, our research question isn't answered by Bland Altman analysis.[26] We did not investigate interchangeability between methods, instead we aimed to assess bias and precision for each individual method. For this reason, we used a Bayesian framework based on the work of Taffé.[23] The advantage of this lies in the fact that knowing the uncertainties of (each) measurement, enables to decompose the propagation of these measurement errors into the analysis, rendering a more appropriate interpretation of the results and application in clinical practice. A reliable quantification of these uncertainties for each measurement method would make it even possible to (partially) correct for them.[27]

4.1 Importance of the results

Neglecting the uncertainties of a measurement may have a profound impact on data analysis and subsequent study results.

Firstly, it is known that adding error to a predictor not only induces uncertainty to its prediction but can also cause bias (a phenomenon known as regression dilution or regression attenuation).[26,28] This particularly applies to studies using baseline PPV as a predictor for fluid responsiveness. The neglected measurement uncertainty in PPV measurements (predictor) and in Cardiac Output changes (outcome) probably accounts for some part of the grey-zone, a concept first described by Cannesson et al.[5] Interestingly, the simulations in our study showed that the 95% credibility interval of the observed $iPPV_3$ for a real PPV of 12% ranged from 10.2% to 13.9%, which is in close resemblance with optimal threshold and the original grey zone found for PPV (12% (9%-14%)).[5]

Secondly, when optimal thresholds from different studies are compared, the specific bias and precision of the used methods, should be accounted for.

Finally, for studies investigating small changes in PPV (e.g. tidal volume test [10,11,29]) as a predictor for fluid responsiveness, the impact of precision is of even greater importance. Our simulations show that small difference up to 1.5% absolute change, may not be reliably detected. Because such an observed absolute raise in PPV may in fact have a 15% chance of being an actual decrease in PPV (see table 5.4). In their study, de Courson et al, also cautioned that small changes in PPV may be difficult to detect reliably.[30] In contrast to our study, their methodology to estimate the least significant change, did not account for heteroscedasticity. The problem of detectability has already emerged in some earlier studies looking into predictors for fluid

responsiveness.[31,32] These authors had to adjust the calculated optimal cut-off of their predictor, because it fell below the sensitivity of the monitor they used.

Besides the statistical implication of accounting for measurement error, this obviously is important for clinicians. Unaware of the bias of the displayed values on their specific monitors, they might have been using different thresholds to administer fluid than the protocols they thought they were following.

4.2 Limitations

There are some limitations of our study. We used a full Bayesian model based on the work of Taffé.[23] This model has several advantages; its flexibility in a repeated measures study design, the ability to compare bias and precision between different methods, the possibility to model both bias and precision in function of estimated underlying real values and the intuitive visualization with distinct plots. The main limitation, however, is the fact that these estimated underlying real values are based on an arbitrary reference method. The consequence is that all reported biases should be interpreted as the bias relative to the reference method.

In our analysis we choose $iPPV_1$ as the reference method in line with the original Taffé method.[23] Because both the differential and proportional bias of $iPPV_3$, the most frequently used method in clinical studies, are minimal, this choice seemed acceptable to us. Another limitation is the fact that the impact of HR/MVR, a known factor impacting prediction capabilities of PPV[33], on bias and precision was not assessed. Lastly, the time-based models (tPPV) are only one example of algorithms used in clinical monitors. The exact algorithms used in nowadays monitors to automatically calculate PPV are not publicly available and therefore could not be studied. Therefore, our study can only underline the importance of these neglected features when using a device in clinical practice or in a research setting.

In conclusion, we showed that all methods that calculate PPV come with varying degrees of measure error. Although neglected, accounting for bias and precision of each method may have important implications and may help explain important concepts, like the grey zone of prediction and the minimal detectable change of PPV, to guide perioperative fluid management.

References

1. Leonard Mlodinow (2008) The drunkard's Walk: How Randomness Rules Our Lives. Pantheon Books

2. Mahmood SS, Pinsky MR (2018) Heart-lung interactions during mechanical ventilation: the basics. Ann Transl Med 6:349–349. https://doi.org/10.21037/atm.2018.04.29

3. Marik PE, Cavallazzi R, Vasu T, Hirani A (2009) Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: A systematic review of the literature. Crit Care Med 37:2642–2647. https://doi.org/10.1097/CCM.0b013e3181a590da

4. Michard F (2005) Changes in arterial pressure during mechanical ventilation. Anesthesiology 103:419–428. https://doi.org/10.1097/00000542-200508000-00026

5. Cannesson M, le Manach Y, Hofer CK, Goarin JP, Lehot JJ, Vallet B, Tavernier B (2011) Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a "gray zone" approach. Anesthesiology 115:231–241. https://doi.org/10.1097/ALN.0b013e318225b80a

6. Lansdorp B, Lemson J, van Putten MJAM, de Keijzer A, van der Hoeven JG, Pickkers P (2012) Dynamic indices do not predict volume responsiveness in routine clinical practice. Br J Anaesth 108:395–401. https://doi.org/10.1093/bja/aer411

7. de Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL (2005) Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. Intensive Care Med 31:517–523. https://doi.org/10.1007/s00134-005-2586-4

8. Michard F, Chemla D, Teboul J-L (2015) Applicability of pulse pressure variation: how many shades of grey? Crit Care 19:144. https://doi.org/10.1186/s13054-015-0869-x

9. Wyffels PAH, Sergeant P, Wouters PF (2010) The value of pulse pressure and stroke volume variation as predictors of fluid responsiveness during open chest surgery. Anaesthesia. 65:704-9. https://doi.org/10.1111/j.1365-2044.2010.06371.x

10. Myatra SN, Prabu NR, DIvatia JV, Monnet X, Kulkarni AP, Teboul JL (2017) The Changes in Pulse Pressure Variation or Stroke Volume Variation after a "tidal Volume Challenge" Reliably Predict Fluid Responsiveness during Low Tidal Volume Ventilation. Crit Care Med 45:415–421. https://doi.org/10.1097/CCM.0000000000002183

11. Messina A, Montagnini C, Cammarota G, Giuliani F, Muratore L, Baggiani M, Bennett V, della Corte F, Navalesi P, Cecconi M (2020) Assessment of Fluid Responsiveness in Prone Neurosurgical Patients Undergoing Protective Ventilation: Role of Dynamic Indices, Tidal Volume Challenge, and End-Expiratory Occlusion Test. Anesth Analg 130:752–761. https://doi.org/10.1213/ANE.0000000000004494

12. Wyffels PAH, de Hert S, Wouters PF (2021) New algorithm to quantify cardiopulmonary interaction in patients with atrial fibrillation: a proof-of-concept study. Br J Anaesth 126:111–119. https://doi.org/10.1016/j.bja.2020.09.039

13. Monnet X, Marik P, Teboul JL (2016) Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis. Intensive Care Med 42:1935–1947. https://doi.org/10.1007/s00134-015-4134-1

14. Mallat J, Fischer M-O, Granier M, et al (2022) Passive leg raising-induced changes in pulse pressure variation to assess fluid responsiveness in mechanically ventilated patients: a multicentre prospective observational study. Br J Anaesth 129:308–316. https://doi.org/10.1016/j.bja.2022.04.031

15. Michard F, Boussat S, Chemla D, Anguel N, Mercat A, Lecarpentier Y, Richard C, Pinsky MR, Teboul JL (2000) Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 162:134–138. https://doi.org/10.1164/ajrccm.162.1.9903035

16. Kim HK, Pinsky MR (2008) Effect of tidal volume, sampling duration, and cardiac contractility on pulse pressure and stroke volume variation during positive-pressure ventilation. Crit Care Med 36:2858–2862. https://doi.org/10.1097/CCM.0b013e3181865aea

17. Derichard A, Robin E, Tavernier B, Costecalde M, Fleyfel M, Onimus J, Lebuffe G, Chambon JP, Vallet B (2009) Automated pulse pressure and stroke volume variations from radial artery: Evaluation during major abdominal surgery. Br J Anaesth 103:678–684. https://doi.org/10.1093/bja/aep267

18. Cannesson M, Slieker J, Desebbe O, Bauer C, Chiari P, Hénaine R, Lehot J-J (2008) The Ability of a Novel Algorithm for Automatic Estimation of the Respiratory Variations in Arterial Pulse Pressure to Monitor Fluid Responsiveness in the Operating Room. Anesth Analg 106:1195–1200. https://doi.org/10.1213/01.ane.0000297291.01615.5c

19. Lee H-C, Park Y, Yoon S bin, Yang SM, Park D, Jung C-W (2022) VitalDB, a high-fidelity multi-parameter vital signs database in surgical patients. Sci Data. 9:279. https://doi.org/10.1038/S41597-022-01411-5

20. GitHub - vitaldb/pyvital: Open source python implementation of medical algorithms. https://github.com/vitaldb/pyvital. Accessed 18 Jul 2022

21. Li BN, Dong MC, Vai MI (2010) On an automatic delineator for arterial blood pressure waveforms. Biomed Signal Process Control 5: 76-81. https://doi.org/10.1016/j.bspc.2009.06.002

22. Aboy M, McNames J, Thong T, Phillips CR, Ellenby MS, Goldstein B (2004) A novel algorithm to estimate the pulse pressure variation index deltaPP. IEEE Trans Biomed Eng 51:2198–2203. https://doi.org/10.1109/TBME.2004.834295

23. Taffé P (2018) Effective plots to assess bias and precision in method comparison studies. Stat Methods Med Res 27:1650–1660. https://doi.org/10.1177/0962280216666667

24. Taffé P, Peng M, Stagg V, Williamson T (2019) MethodCompare: An R package to assess bias and precision in method comparison studies. Stat Methods Med Res 28:2557–2565. https://doi.org/10.1177/0962280218759693

25. Montenij LJ, Buhre WF, Jansen JR, Kruitwagen CL, de Waal EE (2016) Methodology of method comparison studies evaluating the validity of cardiac output monitors: a stepwise approach and checklist. Br J Anaesth 116:750–758. https://doi.org/10.1093/bja/aew094

26. Mansournia MA, Waters R, Nazemipour M, Bland M, Altman DG (2021) Bland-Altman methods for comparing methods of measurement and response to criticisms. Glob Epidemiol 3:100045. https://doi.org/10.1016/j.gloepi.2020.100045

27. van Smeden M, Penning de Vries BBL, Nab L, Groenwold RHH (2021) Approaches to addressing missing values, measurement error, and confounding in epidemiologic studies. J Clin Epidemiol 131:89–100. https://doi.org/10.1016/j.jclinepi.2020.11.006

28. van Smeden M, Lash TL, Groenwold RHH (2020) Reflection on modern methods: five myths about measurement error in epidemiological research. Int J Epidemiol 49:338. https://doi.org/10.1093/ije/dyz251

29. Messina A, Montagnini C, Cammarota G, de Rosa S, Giuliani F, Muratore L, Corte F della, Navalesi P, Cecconi M (2019) Tidal volume challenge to predict fluid responsiveness in the operating room: An observational study. Eur J Anaesthesiol 36:583–591. https://doi.org/10.1097/EJA.0000000000000998

30. de Courson H, Ferrer L, Cane G, Verchère E, Sesay M, Nouette-Gaulain K, Biais M (2019) Evaluation of least significant changes of pulse contour analysis-derived parameters. Ann Intensive Care ç:116. https://doi.org/10.1186/S13613-019-0590-Z

31. Messina A, Lionetti G, Foti L, et al (2021) Mini fluid chAllenge aNd End-expiratory occlusion test to assess flUid responsiVEness in the opeRating room (MANEUVER

study): A multicentre cohort study. Eur J Anaesthesiol 38:422–431. https://doi.org/10.1097/EJA.0000000000001406

32. Muller L, Toumi M, Bousquet PJ, et al (2011) An increase in aortic blood flow after an infusion of 100 ml colloid over 1 minute can predict fluid responsiveness: the mini-fluid challenge study. Anesthesiology 115:541–547. https://doi.org/10.1097/ALN.0b013e318229a500

33. de Backer D, Taccone FS, Holsten R, Ibrahimi F, Vincent JL (2009) Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. Anesthesiology 110:1092–1097. https://doi.org/10.1097/ALN0b013e31819db2a1

Chapter 6

'…The future ain't what it used to be … '

Lawrence Peter 'Yogi' Berra
1925-2015

Catcher NY Yankees
'Wisest fool of the past 50 year' dixit NY times

6

Discussion and Future Perspectives

***

In this thesis, we explored the applicability of Pulse Pressure Variation, a dynamic filling parameter, to predict fluid responsiveness in clinical practice. More specifically, we addressed the 2 concrete challenges put forward in chapter 2:

- Is it possible to develop a new dynamic filling parameter that can be used in patients with atrial fibrillation?
- What is the intrinsic measurement error associated with the clinical assessment of PPV?

6.1 Discussion

6.1.1 Objective 1: PPV and Atrial Fibrillation.

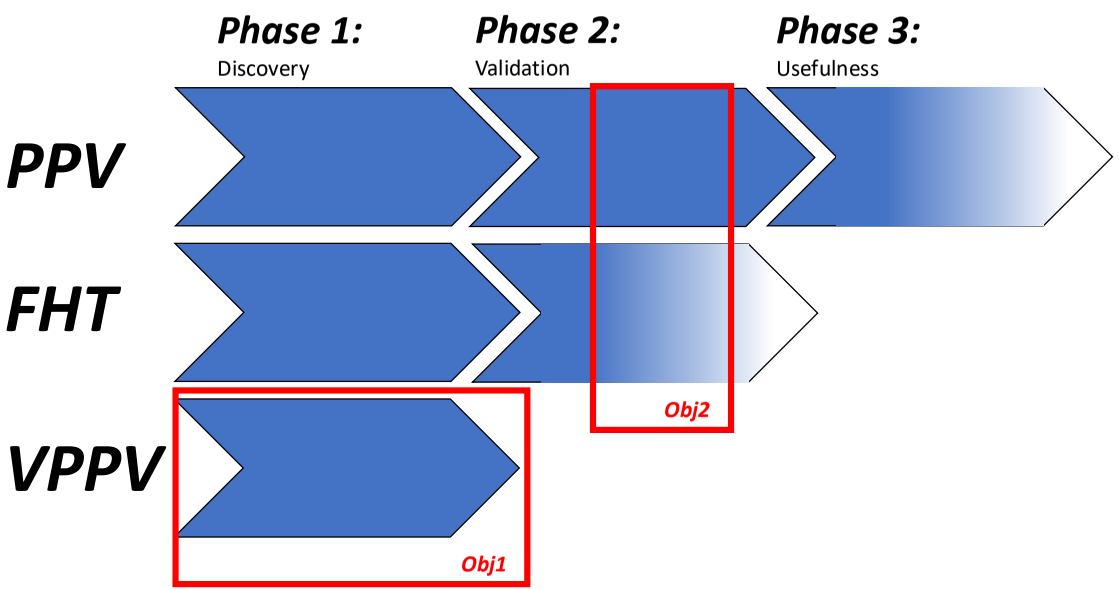
Dynamic filling parameters are diagnostic tests that predict the change in CO in response to a fluid challenge, from the magnitude of hemodynamic effects induced by positive pressure ventilation. PPV is one of the best studied filling parameters in this context. The development of all new diagnostic tests (like PPV and biomarkers...) consists of different ***chronological phases*** [1] :

- Phase 1: Discovery – proof of principle
- Phase 2: Validation: evaluation of predictive (or diagnostic) properties
- Phase 3: Usefulness: Assessment of incremental value
    - when added to existing clinical prediction (or diagnostic) tools.
    - when added to clinical pathways.*

As depicted in figure 6.1, research on ***PPV*** has passed all 3 phases: After decades of physiologic research into cardiopulmonary interactions[2], PPV and other variants of dynamic filling pressure were proposed (Phase 1).[3] Soon after the introduction of the fluid responsiveness concept, dozens of validation studies were published and bundled in a first meta-analysis in 2009 (Phase 2).[4] Thereafter, dynamic filling parameters were implemented in the hemodynamic management protocols of interventional trials (Phase 3).[5] Although PPV showed to be a reliable predictor for fluid responsiveness, it was immediately clear that this reliability can only be expected when certain pre-requisites (like closed chest-conditions, lack of spontaneous breathing efforts, TV >= ml/kg, regular heart rhythm…) are met. Such limitations undermine the applicability in clinical practice [6–10] and probably partially explains some of the mixed phase-3-results.[5,11]

* This classification of chronological phases is based on the process described by Soussi et al [1] for studies on biomarkers used in perioperative medicine and critical care. However, we adjusted their classification slightly by adjusting the name of each phase and expanding phase 3 by adding the clinical pathway. These adjustments were based on a previous publication of Ray et al.[26]

***Figure 6.1*: The 3 Phases of Diagnostic Research**: *Schematic representation of the different phases for Pulse Pressure Variation (PPV), Functional Hemodynamic Tests (FHTs) and Ventilation induced Pulse Pressure Variation (VPPV) with superimposed the place of the presented studies on the two main objectives of the thesis.*



The ***Functional Hemodynamic Tests (FHT***) (like Passive Leg Raising Test (PLR) and Tidal Volume Challenge (TVC)) were developed to overcome some of these pre-requisites (e.g., the ventilator setting restrictions, spontaneous breathing). Studies on these tests are currently in Phase 2 of the development scale. A varying number of small studies were conducted to assess the prediction properties of these FHT's. Larger studies are scarce and interventional studies implementing these tests in a clinical pathway are lacking.

While FHT address primarily the ventilation component, until now little attention has been directed towards the heart rhythm issue. Exactly this point was addressed in the first part of our research. We focused on overcoming the need for a regular electrical and mechanical cardiac activity, i.e., a steady heart rate and rhythm.
Up to now, variations in PP were measured assuming only 1 determinant of variation, namely mechanical ventilation. The interaction between the regular swings in intrathoracic pressure associated with mechanical ventilation and a regular heart rhythm provided a unique setting to assess fluid responsiveness. However, the traditional technique used to quantify this variation becomes meaningless when an additional source of variation comes into play: the irregular beat-to-beat changes caused by the chaotic timing of individual heartbeats in atrial fibrillation. Our challenge was to filter out these effects and to quantify the isolated effect of mechanical ventilation.
As the development of ***VPPV***, our new dynamic filling parameter, was challenging, the 2 studies presented in chapter 3 and chapter 4 can be classified as Phase-1-research. The process can be broken down into 5 steps:

Step 1: Predicting individual PP's due to an irregular heartbeat.
In Chapter 3 we showed that a mathematical model can accurately predict individual PPs in patients during an apneic period. This model is based on the length of the cardiac cycle (measured as the RR-interval) of the 2 preceding heartbeats.

Step 2: Does ventilation increase variations in PP in 'a dose response' way?
In Chapter 3 we also showed that when patients with AF were subsequently ventilated, deviations from the apneic model were related to the magnitude of the tidal volumes (TV) used. These two properties of this model make it a good basis for further development. However, two (practical) problems still need to be accounted for:

- The need for an apneic reference makes it impractical. One of the advantages of classic PPV, is that a monitor can easily determine it automatically and continuously without the need for a manual change in ventilator settings.*
- In step 2, the deviations from the step 1 model were used to assess the magnitude of the effect of mechanical ventilation. Unfortunately, this approach does not quantify the magnitude of the effect of MV relative to some kind of reference PP (like the classic PPV measurement does). As such, it does not have the intuitiveness of a percentual change and makes this method unsuitable to develop a parameter.

In chapter 4 these problems were addressed.

Step 3: *Predicting individual PP's due to an irregular heartbeat and mechanical ventilation.* In chapter 4 a new model is used that incorporates the principles of the mathematical model of step 1 alongside other predictors. To do this a General Additive Model (GAM) was used. (See Figure 4.2, chapter 4). This multivariable prediction model can combine different predictors without (or with minimal) specification of the exact underlying relation (splines). The shapes of these splines are locally calculated from the data and can vary from simple to complex mathematical relations (e.g. linear, sinusoidal, exponential…). We showed that a gam model based on the RR intervals of the two-preceding heartbeats, a predictor for the timing of the respiratory cycle and a predictor for slow changes in PP can reliable predict PPs of the individual heartbeats, without the need for an apneic period.

Step 4: *Define a measure that quantifies the ventilation induced variation in PP: VPPV.*
From this new model in step 3 the mean PP (the intercept of the model) and the maximum and minimum PP from the ventilation function can be determined. These 3 values can be used to calculate VPPV:

* All FHT's (PLR, mini-FC, TVC, EEOT) have the disadvantage of losing the automaticity of a monitor that provides a continuous parameter. All FHT's demand some action from a bedside care-provider. Not only does this make the test laborious to perform, undermining its user-friendliness, it also has the risk that at each active step measurement errors may theoretically undermine its accuracy.

$$VPPV = \frac{vPP_{max} - vPP_{min}}{PP_{mean}} = \frac{vPP_{max} - vPP_{min}}{\beta_0}$$

The advantage of this approach is the close resemblance to the classic formula for PPV.

Step 5: *Does VPPV behave like a dynamic filling parameter in response to a fluid bolus?* In the last step of the development/discovery phase of VPPV we showed that VPPV, in contrast to classic PPV, decreases in response to leg raising in patients with active AF. This decrease in VPPV, after an endogenous fluid bolus, was especially apparent when baseline VPPV was high. This is similar to the physiologic response quantified by PPV in patients with normal sinus rhythm.

After these 5 steps, we conclude the phase-1-research in development of a new parameter based on cardiopulmonary interaction, to predict fluid responsiveness in patients with an irregular heart-rhythm. For the first time such a parameter is identified and ready to be tested in next phase research.

6.1.2 Objective 2: Measurement error of PPV

So far, most of the phase-2 research on PPV as diagnostic/predictive tool, has focused on the diagnostic aspect of validation studies. Optimal cutoffs for maximal diagnostic performance, measured as maximal sensitivities, specificities and likelihoods to predict fluid responsiveness have been determined and compared. Another aspect of validation studies, however, has been neglected systematically.* The analytic performance, consisting of the measurement error and reproducibility of PPV has been ignored in most of these studies. Although older studies showed that PPV values, obtained with commercially available devices, were not always interchangeable with manual calculation, later research ignored this source of uncertainty. In

* In 1997 Shaah et Hoover[27] proposed two kinds of sensitivity and specificity, in their 'medical writings' on the correct reporting and interpretation of biomarker studies. The analytical and the diagnostic sensitivity and specificity. The analytical aspect concerns measurement error and reproducibility. They define analytical sensitivity of a biomarker essay as the smallest amount of a substance that can be accurately measured in a biological sample. Analytical specificity as the ability to measure a particular organism or substance, rather than another, in a sample. As opposed to the diagnostic sensitivity (the percentage of persons who have a condition of interest with a positive result) and diagnostic specificity (the percentage of persons who do not have the condition with a negative test.)

addition, even more variants on the method to quantify PPV were introduced over time assuming that all of these would provide the same result. Inevitably, each method comes with its specific measurement error and its associated impact on the diagnostic performance.
Ideally, the analytical performance of a test should have been assessed prior to the study of its diagnostic performance.

In the absence of data on analytical performance, we conducted a study to systematically determine the measurement error of different methods, found in the literature, used to assess PVV. Based on a sample of more than 500 recordings from patients undergoing liver transplantations provided by the open-source VitalDB- database, we showed that all studied methods come with some degree of error, expressed as bias and imprecision. Based on these results we were able to simulate the impact of such uncertainties on the diagnostic value of PPV, i.e., the accuracy to determine the threshold values of PPV and of changes in PVV (cfr Tidal Volume Challenge test).

For this purpose, we introduced two new methodological approaches in our research: one being a new statistical technique and the second characterized by the modern trend to data sharing and open research communication.

A. A new analytical/statistical approach: Bayes.

In Anesthesia and Critical Care literature, most studies comparing measurement methods or techniques, have adopted a technique described by Bland and Altman to overcome the limitations of regression analysis.[12] In assessing the limits of agreements, or the range of values within which most differences between two measurements (of the same variable) are likely to fall[*] , the Bland-Altman analysis aims at estimating the interchangeability of

[*] More specifically, the Bland Altman analysis is a graphical method that depicts the difference between the measurement of two methods in function of the mean of the two measurements. The region of these (expected differences) is described in function of the bias (the systematic difference between the two measurements, depicted as the center line) and the limits of agreement (the range/ width of the rectangular region around the bias including 95% of all observed differences.) Depending on a prespecified bias and limits of agreement criterium, the two assessed methods can be found interchangeable or not. Different modifications have been publicized ever since, to be able to apply in different study designs.[28,29]

two imperfect methods.* For the validation of hemodynamic monitors, especially monitors using various physical principles to determine cardiac output, the Bland-Altman analysis is widely accepted as the new reference method.[13]

In our work, interchangeability between different methods to calculate PPV was not of primordial interest. Instead, we intended to estimate the measurement error of each method individually† and then model the impact of the uncertainty for each measurement in the clinical decision process, when assessing fluid responsiveness. Bayesian statistics are especially well suited for this purpose. In contrast to the popular frequentist statistics, the Bayesian approach uses a framework and mathematical method that inherently accounts for uncertainties in all levels of the analysis.‡ As such this approach is especially appealing as it is able to model the impact of these uncertainties in a decision model. (= propagation of measurement error/uncertainty).

B. Tapping into the potential of Open-Source data analysis.

Since the conception of the study, we felt it would be a big step forward to conduct research in the spirit of open-source sharing of data and scientific

* Interchangeability is assessed based on prespecified bias and limits of agreement criteria. It remains a difficult task to define these criteria. Devices that measure temperature, blood pressure, cardiac output, or serum troponin, all need specific criteria. Specific criteria that need to define how much interchangeability is to be clinical reliable. For comparing cardiac output monitors there are accepted bias and limit of agreement criteria since the publication of Critchley and Critchley.[13] It should be pointed out however, that these criteria were based on the most basic Bland Altman analysis assuming no repeated measures, constant bias and variance.

† It is important to notice that the limit of agreement is a measure for the precision of the two methods combined. Individual bias or precision is not calculated with the Bland Altman method.

‡ The difference between the frequentist and the Bayesian framework is essential. As a 'micro' introduction, one can say that frequentist theory is essentially based on hypothesis testing: $P(D|H_0)$ = the probability for the observed data of the study (or more extreme values) provided that the null hypothesis is true. (This is also the definition for the p-value of an applied test-statistic.)

In contrast, Bayesian estimate P(H|D): the probability of the hypotheses given the observed data. It does so by applying the Bayes theorem: $P(H|D) \alpha P(D|H) P(H)$. alternatively: the posterior probability of the different hypotheses (P(H|D)) is proportional to probability of the observed data for each considered hypotheses (P(D|H) = likelihood) corrected for the prior knowledge of the probability of the hypotheses (P(H)). For a more detailed discussion for the use of Bayesian statistics in anesthesia research we recommend two recent reviews by Itrona et al [30] and Ferreira et al [31] .

results. Our experience with open-source software facilitated our acceptance into the open access community and gave access to a valuable online database (VitalDB).[14] Using the online available python-scripts[15] we were able to data-mine into VitalDB. Our dataset and the R codes, used in the analysis, are made publicly available to the scientific community on the GitHub platform. This enables other research teams to verify our results with open access to all methodological details and data sets. It also allows peer-review to continue beyond the official peer review and publication of a study in traditional scientific media. Finally, we belief that this modern scientific attitude is a strong basis for open collaboration in a scientific network of kindred spirits. Open access to our code overcomes a lot of barriers for colleagues interested in testing and optimizing our Bayesian model. Although questioned by some[16], we feel this way of working offers a lot of possibilities and should be promoted more in order to maximize the efficiency of research.

6.2 Future Perspectives

Before embarking in the logical phase 2 research part for VPPV and before setting up a classic fluid challenge study to assess the prediction capabilities of VPPV for fluid responsiveness, some insights gained in the previous chapters, may shape the approach to such a study and future research.

6.2.1 Measurement error is ubiquitous and should be accounted for…

The archetypical fluid challenge study-design can be found in figure 6.2. Essentially at the beginning of the study two measurements are taken: The predictor and the baseline cardiac output. After a certain amount of fluid is given to the patient, the cardiac output is measured again, and the effect of the fluid challenge (the difference in cardiac output) is calculated.

***Figure 6.2*: The minimal Prototypical fluid challenge study design.** *At baseline and after stabilization, cardiac output and the predictor(s) of interest are measured. After performing a fluid challenge and after stabilization cardiac output is measured again. Difference in cardiac output is predicted in function of the predictor. Most studies use a method to determine the best cut-off value of the predictor to predict a predefined minimal percentual raise in cardiac output (E.g., 10 or 15%). CO = Cardiac Output, t= time*

The data analysis consists of a procedure to assess the ability of the predictor to predict the effect. A schematic representation of this procedure can be found in figure 6.3. This resembles the approach of the research so far: PPV or changes PPV induced by some kind of maneuver (e.g., tidal volume test) at baseline were used to discriminate those patients that had their cardiac output raised by a certain percentage after fluid loading.

However, when we take a closer look to the study-design, there has been a discrepancy between how results were interpreted (See figure 6.3 Scenario 1) and what was exactly studied (See figure 6.3 Scenario 1). In reality, the ability of the ***measured value of the predictor*** to predict the ***measured effect*** was studied. This means that the measurement error of each device has an impact on this analysis. Using measurement methods that are imprecise risk obscuring the predictive power of the real predictor-effect relation. In chapter 5 we showed that this concern for PPV as predictor, or as part of a FHT, is valid. The measurement error for VPPV cannot be determined yet using our Bayesian model, as for the moment, we do not have an alternative method to compare.
Concerning the measurement of the effect: there is vast literature on the measurement error of cardiac output monitors. In clinical practice, and in

Figure 6.3 *: **Diagrams of the different approaches to predicting fluid responsiveness**. The relation between the predictor (red circle) and the estimand/outcome (blue circle) is depicted in 3 scenario`s using DAG-like schemes_Scenario A: (real) Pulse Pressure Variation (PPV) is used to predict the (real) increase in Cardiac Output (DCO). Scenario B: the measured value of PPV (PPV*) (= real PPV + measurement error) is used to predict the measured change in CO (real change in CO + measurement error). Scenario C: the measured value of PPV is used to predict the real change in CO. DAG = Directed Acyclic Graph*

incorporated technology, algorithms and in invasiveness. The measurement error of these devices can be substantial and is sometimes even problematic.[17,18] When planning for a phase 2 study in patients with AF the measurement error of these devices becomes even more important.[19]

What is the way forward then?
In clinical practice the relevant question boils down to: 'what is the ability of the ***measured (V)PPV*** to predict the ***real impact of fluid loading on cardiac output***?' (See figure 6.3 scenario C). To analyze this problem, some additional issues need to be clarified:

- Obvious first principle is the need to use research devices that are as accurate as possible. In this specific setting of AF, this applies especially to the measurement of cardiac output.
- However, minimizing the measurement error is not enough. More advanced statistical methods, like regression calibration, multiple imputations or Bayesian hierarchical models, are able to correct for measurement error and to provide a corrected, more reliable, estimate of the real effect.[20–22]
- When planning for the use of these more advanced statistical techniques, more fundamental questions deserve reconsideration. Why did we start defining the effect of fluid loading on cardiac output as a binary outcome? Is the classification into responders (e.g., a raise in CO of $\geq$ 15%) and non-responders really more intuitive? Or would an interval of the most likely expected changes in CO for an individual measured (V)PPV value provide more information to make clinical decisions? * Why are (almost) all fluid responsiveness studies conceptualized as a univariate prediction model? It is quite unlikely that one predictor can perfectly assess fluid responsiveness in all patients. Not only is it more likely that dynamic filling parameters have different predicting capabilities in different patient populations, but it is also very probable that other predictors and the interaction between them, resembling the different mechanistic pathways in

* Dichotomization of continuous variables should be avoided. Altman already advised against this practice since the 90's of the past century. It should be discouraged because '*…it wastes information*" [32,33]: Why would a patient with a PPV of 9% and patient with 15% differ as much as a patient with a PPV of 9% and a patient with a PPV of 25%. Splitting up the predictor in two categories clearly ignores that the expected effect raises with increasing values of measured PPV. Likewise, are we sure that a patient with a raise of 14% in cardiac output really differs from a patient with a measured change in cardiac output of 16% after fluid loading?

hemodynamics, can increase the accuracy of predicting fluid responsiveness.

In conclusion, validation of VPPV to predict fluid responsiveness comes with specific methodologic issues. Identification of these analytic hurdles have unraveled the weaknesses of currently used methods. New, more modern methods should not only make it possible to validate VPPV, but they might also create a better paradigm to translate their and older results into the clinical setting.

6.2.2 VPPV vs PPV

VPPV was developed as an alternative for PPV when patients have an irregular heart rhythm. If proven accurate in this specific situation, there are at least 2 potential applications that will further expand their use in clinical practice.

The ***combination of FHT's with VPPV*** would make it possible to overcome multiple restrictions for the correct use of dynamic filling parameters.
Tidal Volume challenge, one of the FHTs proposed to use when low TVs are applied perioperatively, is based on changes in PPV.[23] Theoretically, for patients with an irregular heart beat the same method can be used replacing PPV with VPPV. Other FHT's like PLR and MFC do not use PPV. These tests use changes in cardiac output induced by a change in body position or after a mini fluid bolus to predict the response when a large(r) fluid bolus is given (see figure 1.11). Mallat et al however, described a variant of both PLR [24] and MFC [25] by replacing the change in CO by PPV. Although their results are promising and suggest that this modification of the test might be more accurate*, their results need to be confirmed.

* In their first study, Mallat et al[25] showed in their ROC, that the AUC of ΔPPV_{100} (the absolute change in PPV after a mini fluid bolus of 100ml) was significantly higher than the AUC of ΔCCI_{100} (the change in cardiac output after the mini fluid challenge), 0.92 (95% CI: 0.81-0.98) vs 0.78 (95% CI: 0.80-0.97). In their second study [24] on ΔPPV_{PLR} ((absolute and relative) change in PPV after the PLR maneuver) the comparison with classic PLR test (ΔCCI_{PLR}) was not reported. This higher accuracy can probably be partially explained by the difference in measurement error between PPV and (small) changes in cardiac output. It has been shown that different monitors come with different minimum changes in CO that can be confidently picked up. For some monitors the change in CO imposed by a bolus of 100ml cannot be reliably measured. [34]

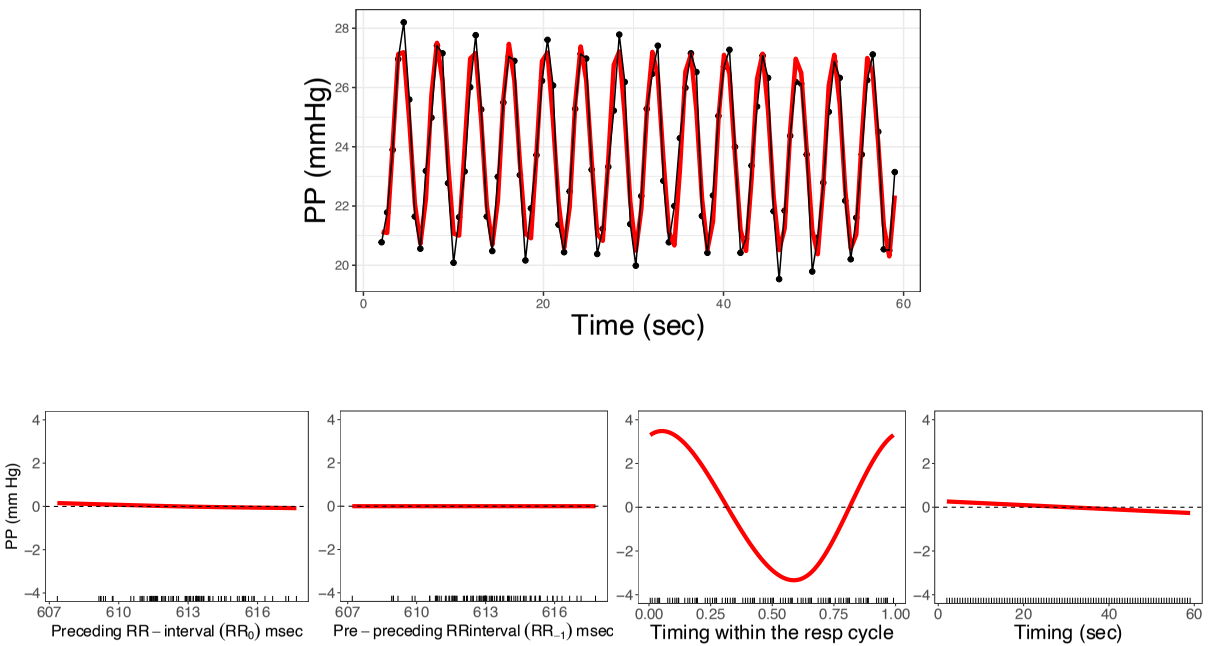
With VPPV we have for the first time a valid alternative to (potentially) predict fluid responsiveness in patients with AF. If proven accurate, PPV and VPPV will be at our disposal, as a single predictor or incorporated in an FHT, depending on the heart rhythm of the patient: sinus rhythm or atrial fibrillation. However, an important question in this context is whether sinus rhythm and AF are indeed to be considered as two distinct heart rhythms.[*] To explain this seemingly contradictory statement, two imaginary patients with AF are presented. It is easily understood that the degree of irregularity can differ between these two patients. A simple method to quantify the irregularity of AF is to determine the range of RR-intervals observed during a certain observation period.[†] The more furiously the heart rate fluctuates, the wider the distribution of the observed RR-intervals. The narrower the range of RR-intervals, the lower the degree of irregularity. Taken to its lower limit, this ultimately results in a very narrow range approaching 0… In this sense a regular rhythm can be seen as a special case of irregular rhythm.[‡] This is easily visualized in our GAM model (See: figure 6.4)

[*] It is evident that there is a difference between a sinus rhythm and atrial fibrillation. There are clear electrophysiological criteria (absence of P-wave on the ECG) and functional characteristics (the absence of the atrial kick) that discern these two rhythms from each other. It is not clear however if these differences have an important role within the context of fluid responsiveness. Especially as it has long been known that for example with aging, atrial dysfunction is present in both SR and AF patients. [35,36]

[†] A more sophisticated method to quantify irregularity can be found in Keidar et al. [37] In their method to detect AF one of the predictors they use is 'variability' defined as standard deviation of the Modified entropy scale (MESC) over the mean of beat intervals (BI). In its most simple form (MESC grade=0) this becomes: $\frac{\sigma_{MESC^0}}{\overline{BI}} = \frac{\sigma_{BI}}{\overline{BI}}$

[‡] Seeing a sinus rhythm as a low degree irregular rhythm is not that abstract. Heart rate variability (HRV) in sinus rhythm is even a physiologic phenomenon. It is the result of the balance between the sympathetic and the parasympathethic nervous system. Different medications used during anesthesia have an impact on this equilibrium. HRV is sometimes investigated as a prognostic factor, and it is used to measure nociception; [38]

Figure 6.4: Determining VPPV in a patient with SR: an example. *Upper panel: Black plot: raw data of the consecutive PP during a 60 s observation period. Red plot: predicted values of the GAM -model for each individual beat. Lower panel: Visualization of the 4 functions used in the gam model ($PP = \beta_0 + f(RR_0) + f(RR_{-1}) + f(Ventilation) + f(Time) + \epsilon$) used to predict individual PP` s. From left to right: $\boldsymbol{f(RR_0)}$ impact of the preceding RR interval of each beat, $\boldsymbol{f(RR_{-1})}$ impact of the ` pre-preceding` RR interval of each beat, $\boldsymbol{f(Ventilation)}$ impact of the mechanical ventilation and $\boldsymbol{f(Time)}$ the impact of changes over time. The maximum and minimum value of the $f(Ventilation)$, vPP_{max} and vPP_{min} respectively, and the β-intercept (β_0) of the model is used for the calculation of VPPV.*



This makes our model especially attractive as it not only has the potential to calculate the ventilation induced changes for the whole range of irregular rhythms (including a sinus rhythm), these, calculated VPPV values in case of a regular heart rhythm should closely relate to the PPV values.* If proven accurate, we did not find an alternative for PPV in a special circumstance, instead we potentially developed ***VPPV, a new standard method to quantify the impact of MV on variation of PPs***. PPV might well be a special case within the spectrum of VPPV and not the other way around!†

* Our model can be written as: $PP = \beta_0 + f(RR_0) + f(RR_{-1}) + f(Ventilation) + f(Time) + \epsilon$

In figure 6.4 it can be seen that in this patient with SR:

1. The range of RR0 and RR-1 is minimal (compare with fig 4.2 in AF)
2. The impact of the RR0, RR-1 and Time function in the prediction model is limited. For all predictors within the observed range, the added value to predict PP is minimal.
3. Our formula can be rewritten as:

$$PP = \beta_0 + 0 + 0 + f(Ventilation) + 0 + \varepsilon$$
$$PP = \beta_0 + f(Ventilation) + \varepsilon$$

4. This makes the calculation of VPPV similar to PPV:

$$VPPV = \frac{vPP_{max} - vPP_{min}}{\beta_0} \; vs \; PPV = \frac{PP_{max} - PP_{min}}{(PP_{max} - PP_{min})/2}$$

† 2 remarks are in place here. First, as explained above, a sinus rhythm is not necessarily completely regular. The ability to account for this irregularity has the potential for VPPV to be more accurate in SR than PPV itself. It is, however, not known if this low-grade irregularity that has been neglected when calculating PPV, is important.
Secondly, so far, we have only considered atrial fibrillation when irregularity was discussed. Other forms of irregular heart rhythms like extra systoles and AV blocks have not been included in our research. It remains to be proven that these arrythmias, sometimes categorized as regular irregularities [37], can be handled by our model.

References:

1. Soussi S, Collins GS, Jüni P, Mebazaa A, Gayat E, Le Manach Y. Evaluation of Biomarkers in Critical Care and Perioperative Medicine: A Clinician's Overview of Traditional Statistical Methods and Machine Learning Algorithms. *Anesthesiology*. 2021;134(1):15-25. https://doi.org/10.1097/ALN.0000000000003600

2. Mahmood SS, Pinsky MR. Heart-lung interactions during mechanical ventilation: the basics. *Ann Transl Med*. 2018;6(18):349-349. https://doi.org/10.21037/ATM.2018.04.29

3. Michard F. Changes in arterial pressure during mechanical ventilation. *Anesthesiology*. 2005;103(2):419-428. https://doi.org/10.1097/00000542-200508000-00026

4. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: A systematic review of the literature. *Crit Care Med*. 2009;37(9):2642-2647. https://doi.org/10.1097/CCM.0B013E3181A590DA

5. Deng QW, Tan WC, Zhao BC, Wen SH, Shen JT, Xu M. Is goal-directed fluid therapy based on dynamic variables alone sufficient to improve clinical outcomes among patients undergoing surgery? A meta-analysis. *Crit Care*. 2018;22(1):298. https://doi.org/10.1186/s13054-018-2251-2

6. Maguire S, Rinehart J, Vakharia S, Cannesson M. Technical communication: respiratory variation in pulse pressure and plethysmographic waveforms: intraoperative applicability in a North American academic center. *Anesth Analg*. 2011;112(1):94-96. https://doi.org/10.1213/ANE.0B013E318200366B

7. Mair S, Tschirdewahn J, Götz S, et al. Applicability of stroke volume variation in patients of a general intensive care unit: a longitudinal observational study. *J Clin Monit Comput*. 2017;31(6):1177-1187. https://doi.org/10.1007/S10877-016-9951-4

8. Delannoy B, Wallet F, Maucort-Boulch D, et al. Applicability of Pulse Pressure Variation during Unstable Hemodynamic Events in the Intensive Care Unit: A Five-Day Prospective Multicenter Study. *Crit Care Res Pract*. 2016;2016. https://doi.org/10.1155/2016/7162190

9. Mahjoub Y, Lejeune V, Muller L, et al. Evaluation of pulse pressure variation validity criteria in critically ill patients: a prospective observational multicentre point-prevalence study. *Br J Anaesth*. 2014;112(4):681-685. https://doi.org/10.1093/BJA/AET442

10. Benes J, Zatloukal J, Kletecka J, Simanova A, Haidingerova L, Pradl R. Respiratory induced dynamic variations of stroke volume and its surrogates as predictors of

fluid responsiveness: applicability in the early stages of specific critical states. *J Clin Monit Comput*. 2014;28(3):225-231. https://doi.org/10.1007/S10877-013-9524-8

11. Benes J, Giglio M, Brienza N, Michard F. The effects of goal-directed fluid therapy based on dynamic parameters on post-surgical outcome: a meta-analysis of randomized controlled trials. *Crit Care*. 2014;18:584. https://doi.org/10.1186/s13054-014-0584-z

12. Martin Bland J, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1(8476):307-310. https://doi.org/10.1016/S0140-6736(86)90837-8

13. Critchley LAH, Critchley JAJH. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput*. 1999;15(2):85-91. https://doi.org/10.1023/A:1009982611386

14. Lee HC, Park Y, Yoon S Bin, Yang SM, Park D, Jung CW. VitalDB, a high-fidelity multi-parameter vital signs database in surgical patients. *Sci Data*. 2022;9(1). https://doi.org/10.1038/S41597-022-01411-5

15. GitHub - vitaldb/pyvital: Open source python implementation of medical algorithms. Accessed July 18, 2022. https://github.com/vitaldb/pyvital

16. Melvin RL, Barker SJ, Kiani J, Berkowitz DE. Pro-Con Debate: Should Code Sharing Be Mandatory for Publication? *Anesth Analg*. 2022;135(2):241-245. https://doi.org/10.1213/ANE.0000000000005848

17. Joosten A, Desebbe O, Suehiro K, et al. Accuracy and precision of non-invasive cardiac output monitoring devices in perioperative medicine: a systematic review and meta-analysis†. *Br J Anaesth*. 2017;118(3):298-310. https://doi.org/10.1093/BJA/AEW461

18. Saugel B, Hoppe P, Nicklas JY, et al. Continuous noninvasive pulse wave analysis using finger cuff technologies for arterial blood pressure and cardiac output monitoring in perioperative and intensive care medicine: a systematic review and meta-analysis. *Br J Anaesth*. 2020;125(1):25-37. https://doi.org/10.1016/J.BJA.2020.03.013

19. Østergaard M, Nilsson LB, Nilsson JC, Rasmussen JP, Berthelsen PG. Precision of bolus thermodilution cardiac output measurements in patients with atrial fibrillation. *Acta Anaesthesiol Scand*. 2005;49(3):366-372. https://doi.org/10.1111/J.1399-6576.2005.00613.X

20. van Smeden M, Penning de Vries BBL, Nab L, Groenwold RHH. Approaches to addressing missing values, measurement error, and confounding in epidemiologic studies. *J Clin Epidemiol*. 2021;131:89-100. https://doi.org/10.1016/J.JCLINEPI.2020.11.006

21. Bartlett JW, Keogh RH. Bayesian correction for covariate measurement error: A frequentist evaluation and comparison with regression calibration. *Stat Methods Med Res*. 2018;27(6):1695-1708. https://doi.org/10.1177/0962280216667764

22. Keogh RH, White IR. A toolkit for measurement error correction, with a focus on nutritional epidemiology. *Stat Med*. 2014;33(12):2137. https://doi.org/10.1002/SIM.6095

23. Myatra SN, Prabu NR, DIvatia JV, Monnet X, Kulkarni AP, Teboul JL. The Changes in Pulse Pressure Variation or Stroke Volume Variation after a "tidal Volume Challenge" Reliably Predict Fluid Responsiveness during Low Tidal Volume Ventilation∗. *Crit Care Med*. 2017;45(3):415-421. https://doi.org/10.1097/CCM.0000000000002183

24. Mallat J, Fischer MO, Granier M, et al. Passive leg raising-induced changes in pulse pressure variation to assess fluid responsiveness in mechanically ventilated patients: a multicentre prospective observational study. *Br J Anaesth*. 2022;129(3):308-316. https://doi.org/10.1016/J.BJA.2022.04.031

25. Mallat J, Meddour M, Durville E, et al. Decrease in pulse pressure and stroke volume variations after mini-fluid challenge accurately predicts fluid responsiveness. *Br J Anaesth*. 2015;115(3):449-456. https://doi.org/10.1093/bja/aev222

26. Ray P, Manach Y Le, Riou B, Houle TT. Statistical Evaluation of a Biomarker. *Anesthesiology*. 2010;112(4):1023-1040. https://doi.org/10.1097/ALN.0B013E3181D47604

27. Saah AJ, Hoover DR. "Sensitivity" and "specificity" reconsidered: the meaning of these terms in analytical and diagnostic settings. *Ann Intern Med*. 1997;126(1):91-94. https://doi.org/10.7326/0003-4819-126-1-199701010-00026

28. Myles PS, Cui J. Using the Bland-Altman method to measure agreement with repeated measures. *Br J Anaesth*. 2007;99(3):309-311. https://doi.org/10.1093/BJA/AEM214

29. Montenij LJ, Buhre WF, Jansen JR, Kruitwagen CL, De Waal EE. Methodology of method comparison studies evaluating the validity of cardiac output monitors: a stepwise approach and checklist. *Br J Anaesth*. 2016;116(6):750-758. https://doi.org/10.1093/BJA/AEW094

30. Introna M, van den Berg JP, Eleveld DJ, Struys MMRF. Bayesian statistics in anesthesia practice: a tutorial for anesthesiologists. *J Anesth*. 2022;36(2):294-302. https://doi.org/10.1007/S00540-022-03044-9

31. Ferreira D, Barthoulot M, Pottecher J, Torp KD, Diemunsch P, Meyer N. Theory and practical use of Bayesian methods in interpreting clinical trial data: a narrative

review. *Br J Anaesth*. 2020;125(2):201-207. https://doi.org/10.1016/J.BJA.2020.04.092

32. Altman DG, Lausen B, Sauerbrei W, Schumacher M. Dangers of using "optimal" cutpoints in the evaluation of prognostic factors. *J Natl Cancer Inst*. 1994;86(11):829-835. https://doi.org/10.1093/JNCI/86.11.829

33. Altman DG, Royston P. The cost of dichotomising continuous variables. *BMJ*. 2006;332(7549):1080. https://doi.org/10.1136/BMJ.332.7549.1080

34. Smorenberg A, Cherpanath TGV, Geerts BF, et al. A mini-fluid challenge of 150mL predicts fluid responsiveness using Modelflow R pulse contour cardiac output directly after cardiac surgery. *J Clin Anesth*. 2018;46:17-22. https://doi.org/10.1016/J.JCLINANE.2017.12.022

35. Roşca M, Lancellotti P, Popescu BA, Piérard LA. Left atrial function: pathophysiology, echocardiographic assessment, and clinical applications. *Heart*. 2011;97(23):1982-1989. https://doi.org/10.1136/HEARTJNL-2011-300069

36. Gupta DK, Shah AM, Giugliano RP, et al. Left atrial structure and function in atrial fibrillation: ENGAGE AF-TIMI 48. *Eur Heart J*. 2014;35(22):1457-1465. https://doi.org/10.1093/EURHEARTJ/EHT500

37. Keidar N, Elul Y, Schuster A, Yaniv Y. Visualizing and Quantifying Irregular Heart Rate Irregularities to Identify Atrial Fibrillation Events. *Front Physiol*. 2021;12. https://doi.org/10.3389/FPHYS.2021.637680

38. Anderson TA. Heart rate variability: implications for perioperative anesthesia care. *Curr Opin Anaesthesiol*. 2017;30(6):691-697. https://doi.org/10.1097/ACO.0000000000000530

Chapter 7

“oet dad ier nog lange goat deurn,
goat dad ier rap gedoan zin.”

“Als het hier nog lang zal duren,
Zal het snel gedaan zijn.”

West-Vlaamse wijsheid

7

Summary – Samenvatting

***

English

During surgery, a patient may lose fluid for various reasons. In addition to blood loss, there is also fluid that evaporates from open wounds, and patients usually do not drink or eat in the last few hours before an operation. Therefore, it is challenging for an anesthesiologist to correct this deficit.
Too small volumes of circulating fluids cause the blood flow that the heart pumps around to become insufficient, leading to a lack of oxygen supply to various organs. However, if too much fluid is administered, fluid can accumulate in the tissues, causing edema, which can also have adverse effects on a patient.

To assess whether administering fluids will increase the CO, an anesthesiologist can use the so-called dynamic filling parameters. During surgery, under general anesthesia, a patient is mechanically ventilated. The positive pressure insufflation used for this purpose affects heart function. The magnitude of the impact of positive pressure ventilation has a predictive value on the chance that extra fluids will increase the cardiac output: the greater the effect, the greater the chance. The most well-studied dynamic filling parameter is PPV, which is the percentage change in blood pressure during different ventilation cycles. These parameters, such as PPV, are the most reliable as long as certain conditions are met. An important pre-requisite is the need for the patient to have a regular heartbeat. In patients with an irregular heart rhythm, such as Atrial Fibrillation (AF), there are two causes of blood pressure variation: regular ventilation and the chaotic heartbeat, which cause blood pressure to vary from beat to beat. Therefore, the traditional way of calculating PPV is no longer applicable.

In the first part of our research, we looked for a way to isolate the impact of the different causes of blood pressure changes in patients with AF. For this, we first tested a method that can predict the influence of an irregular rhythm on blood pressure. It turns out that based on the length of the two previous beats (RR0 and RR-1), the blood pressure of an individual heartbeat can be retrospectively predicted.
In a second study, we incorporated this method into a model that can simultaneously predict the impact of different causes of beat-to-beat blood pressure changes, both ventilation and heart rhythm, in patients with AF. Based on this model, a new parameter, Ventilation-induced Pulse Pressure Variation (VPPV), can be calculated. This new parameter is the calculated

isolated percentage change in blood pressure caused by ventilation only. In the last step of our research, we examined the changes in VPPV caused by altering the circulating blood volume. After these initial studies, we can conclude that we have found a way to measure the different causes of blood pressure changes. The reliability of VPPV in predicting increased flow after administering extra fluids can now be tested in patients, both with irregular and regular heart rates.

In the second part of our research, we focused on the measurement error of PPV calculations in patients with a regular rhythm. It turns out that over the years, different methods have been used in the literature. On the one hand there are several ways to manually calculate PPV and on the other hand, there are different commercially available measuring devices that each use their own algorithm. Despite the fact that older studies showed such devices do not always generate the same values compared to the original manual method, very little research has been done on the measurement error and the impact of such an error on the predictive value of PPV. In a third publication, we systematically determined the measurement error of different methods for calculating PPV in patients with a regular heart rhythm. For this, we used the online open VitalDB database. Based on the data of the patients in this database who underwent liver transplantation, we were able to compare the PPV values calculated with different methods. Using a Bayesian statistical model, we calculated the measurement error, split up into bias and precision for each method, and we could simulate the impact of such measurement errors on the reliability of the measurement values to predict cardiac output changes. We can now conclude that the identified measurement errors do indeed have an impact on the interpretation of the results of some studies and on the use of these values in clinical practice.

Nederlands

Tijdens een operatie kan een patiënt omwille van verschillende redenen vocht verliezen. Naast bloedverlies is er ook vocht dat verdampt vanuit open wonden en is het zo dat een patiënt de laatste uren voor zijn ingreep in principe niets meer eet of drinkt. Het is dan ook geen sinecure voor een anesthesist om dit tekort te corrigeren.
Een te klein volume circulerend vocht zorgt ervoor dat het debiet bloed dat het hart rondpompt in het lichaam te klein wordt. Hierdoor kan er een zuurstoftekort ontstaan in verschillende organen. Maar als er daarentegen te veel vocht toegediend wordt, kan vocht zich opstapelen in de weefsels en ontstaat er oedeem, wat ook nadelige gevolgen kan hebben voor de patiënt. Om in te schatten of het toedienen van vocht het hartdebiet zal verhogen, kan een anesthesist gebruik maken van de zogenoemde dynamische vullingsparameters. Tijdens een ingreep onder algemene anesthesie wordt een patiënt mechanisch beademd. De drukveranderingen in de longen die hierdoor optreden, hebben een invloed op de hartfunctie. De grootte van de impact van de positieve druk beademing heeft een voorspellende waarde of extra vocht het hartdebiet zal verhogen: hoe groter het effect van de positieve druk, hoe groter die kans. De best bestudeerde dynamische vullingsparameter is 'Pulse Pressure Variation' (PPV), wat de procentuele verandering van de bloeddruk is tijdens verschillende beademingscycli. Deze parameters, zoals PPV, zijn de meest betrouwbare parameters zolang er rekening gehouden wordt met enkele voorwaarden. Een belangrijke voorwaarde is dat de patiënt een regelmatige hartslag heeft. Bij patiënten met een onregelmatige hartslag (zoals bij voorkamer fibrillatie, VKF) zijn er twee oorzaken waardoor de bloeddruk kan variëren: (1) De regelmatige beademing en (2) het chaotische hartritme dat ervoor zorgt dat de bloeddruk slag-om-slag varieert. Hierdoor is de traditionele manier om PPV te berekenen niet langer toepasbaar.

In het eerste gedeelte van ons onderzoek zijn we op zoek gegaan naar een manier om bij patiënten met VKF, de impact van de verschillende oorzaken van bloeddruk veranderingen te isoleren van elkaar. Hiervoor hebben we in een eerste studie, een manier getest die in staat is om de invloed van een onregelmatig ritme op de bloeddruk te voorspellen. Blijkt dat op basis van de duur tussen de twee voorgaande slagen (RR_0 en RR_{-1}) de bloeddruk van een individuele hartslag voorspeld kan worden.

In een tweede studie hebben we deze manier geïncorporeerd in een model dat de impact van verschillende oorzaken van slag-om-slag bloeddruk veranderingen, zowel door de ventilatie als door het hartritme, simultaan kan voorspellen bij patiënten met VKF. Op basis van dit model kan dan een nieuwe parameter, 'Ventilation induced Pulse Pressure Variation' (VPPV), berekend worden. Deze nieuwe parameter is de berekende procentuele verandering van de bloeddruk die enkel door de beademing veroorzaakt wordt. In een laatste stap in ons onderzoek, onderzochten we de veranderingen van VPPV veroorzaakt door extra circulerend bloedvolume. Na deze eerste onderzoeken kunnen we besluiten dat we een manier gevonden hebben die de verschillende oorzaken van bloeddruk veranderingen kunnen meten. De betrouwbaarheid van VPPV om debietverhoging te voorspellen voor het toedienen van extra vocht, kan nu getest worden, zowel bij patiënten met een onregelmatig ritme als met een regelmatig ritme.

In het tweede gedeelte van ons onderzoek, hebben we ons geconcentreerd op de meetfout van de PPV-berekening bij patiënten met een regelmatig ritme. Blijkt namelijk dat er, door de jaren heen, verschillende manieren gebruikt werden in de literatuur. Er zijn enerzijds verschillende manieren om PPV manueel te berekenen en anderzijds zijn er verschillende commercieel verkrijgbare monitors die elk een eigen algoritme gebruiken. Ondanks het feit dat er oudere studies voorhanden zijn die aangetoond hebben dat dergelijke apparaten niet altijd dezelfde waardes genereren in vergelijking met de, oorspronkelijke, manuele manier, is er zeer weinig onderzoek gebeurd naar de meetfout en de impact van zo'n meetfout op de voorspellende waarde van PPV. Wij hebben in een derde publicatie, de meetfout van de verschillende manieren om PPV te berekenen bij patiënten met een regelmatig ritme op een systematische manier in kaart gebracht. Hiervoor maakten we gebruik van de online open VitalDB database. Op basis van de gegevens van de patiënten uit deze database die een levertransplantatie ondergingen konden we de PPV-waardes, berekend met verschillende methodes, vergelijken. Met behulp van een Bayesiaans statistisch model berekende we de meetfout, opgesplitst in bias en precisie voor de verschillende methodes. Daarnaast konden we ook de impact van dergelijke meetfouten op de betrouwbaarheid van gemeten PPV-waarden, om hartdebiet verhoging te voorspelling simuleren. We kunnen concluderen dat de geïdentificeerde meetfouten voor sommige methodes wel degelijk impact hebben op de interpretatie van de resultaten van sommige studies en op het gebruik van deze waardes in de klinische praktijk.

Appendices

APPENDIX:

[əp'pendiks, *mv* -es, -dices -iz, -disi:z]
A small, fingerlike pouch that sticks out from the cecum (the first part of the large intestine near the end of the small intestine).

A

Supplementary information on the article: Dynamic filling parameters in Patients with atrial fibrillation: differentiating rhythm-induced from ventilation induced variations in pulse pressure.

***

Wyffels PAH, Van Heuverswyn F, De Hert S, Wouters PF.
Published in Am J Physiol Heart Circ Physiol. 2016; 310(9): H1194-200.
https://doi.org/10.1152/ajpheart.00712.2015

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.[38]
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 – α
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 3.6) 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.

$$W = \left[1 - \left({}^{Dist}/_{maxDist}\right)^3\right]^3$$

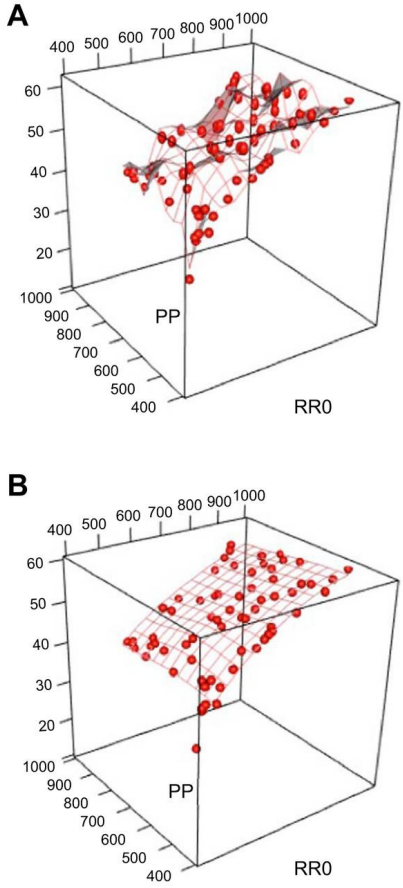


Figure A.1*: Effect of changing the setting of the "smoothing" parameter in the calculation of LOC2. A: overfitting. Detail of LOC2 during T1 of patient 1 when the span parameter was set at 15%. B: optimal fitting. Detail of LOC2 during T1 of patient 1 when the optimal span was set. RR intervals (ms), PP (mmHg).*

B

Supplementary information on the article: A new algorithm to quantify cardiopulmonary interaction in patients with atrial fibrillation: A proof- of-concept study.

***

Wyffels PAH, De Hert S, Wouters PF.
Published in Br J Anaesth. 2021; 126(1): 111-119.
https://doi.org/10.1016/j.bja.2020.09.039

Principles of Splines

The individual functions used in our General Additive Model are natural cubic splines. This is a specific type of spline. Splines are an elegant method to perform a regression when not knowing the exact underlying relation between independent and dependent variables. Hypothetically, this relation can have all forms from linear to higher order polynomials, from exponential to sinusoidal etc. This method has some specific characteristics. Spline regression is a ***penalized***, ***local***, ***smoothing technique*** based on a ***cubic polynomial regression***.

1. Cubic polynomial

The basis for this method is the cubic polynomial:

$$f(x) = \beta_0 + \beta_1 x + \beta_2 x^2 + \beta_3 x^3$$

2. Local

The cubic polynomial formula is not applied to the whole data set, but only to a subset. Figure B.1 shows the individual data points of a 60s observation period. For simplicity, only the relation between RR_0 and PP is considered. In this example, the whole data set is divided into 9 subsets. The exact place of the 10 boundaries ('knots') is based on the percentiles of the RR_0 values. Each subset has an equal amount of datapoints. For each subset a cubic polynomial is (locally) applied. So, the formula for a model with k knots can be written as:

$$y_i = \begin{cases} \beta_{0,1} + \beta_{1,1} x_i + \beta_{2,1} x_i^2 + \beta_{3,1} x_i^3, & \text{if } k_1 < x_i < k_2 \\ \beta_{0,2} + \beta_{1,2} x_i + \beta_{2,2} x_i^2 + \beta_{3,2} x_i^3, & \text{if } k_2 < x_i < k_3 \\ & \dots \\ \beta_{0,k-1} + \beta_{1,k-1} x_i + \beta_{2,k-1} x_i^2 + \beta_{3,k-1} x_i^3, & \text{if } k_{k-1} < x_i < k_k \end{cases}$$

or as:

$$f_j(x_i) = \beta_{0,j} + \beta_{1,j} x_i + \beta_{2,j} x_i^2 + \beta_{3,j} x_i^3 \quad \text{if } k_j < x_i < k_{j+1}$$

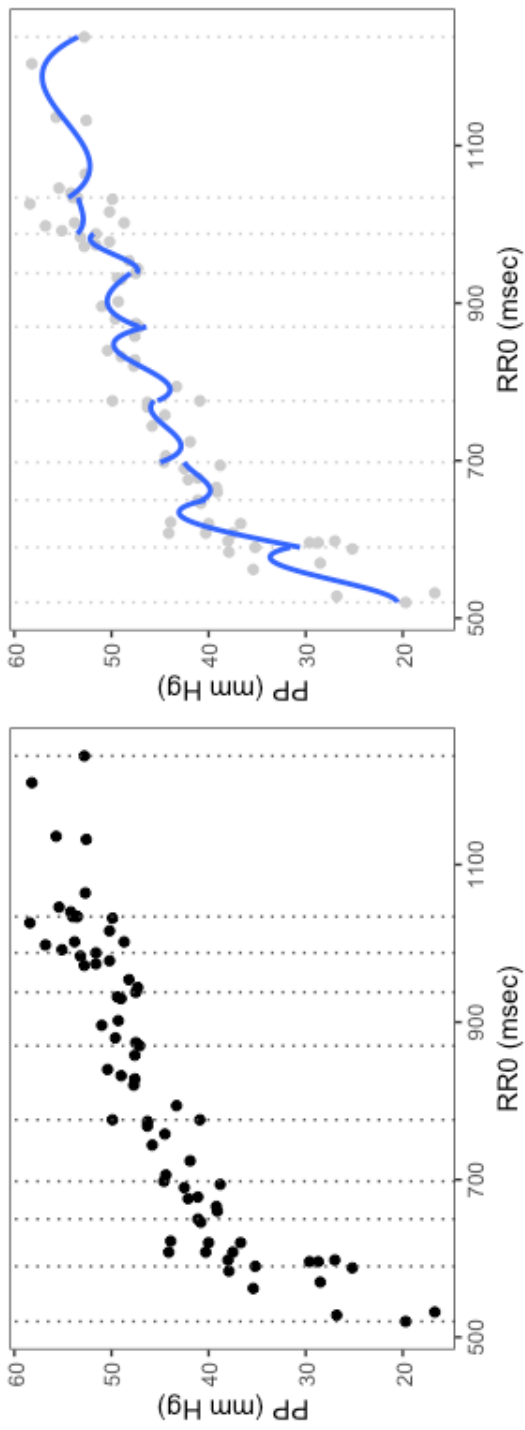


***Figure B.1**: Left Panel: Raw data divided in 9 regions using 10 knots. Right Panel: Individual cubic polynomial fits to the 9 regions without constraints*

3. Smoothing technique

If no constraints are placed on these 9 different cubic polynomial fits, the resulting graphical display of the model would look like figure B.1 Right Panel.

There are at least 2 problems with this regression. First, these 9 individual regressions are not continuous. An example of this is the transition at the 4th and 8th knot. There seems to be a 'jump' in the regression function at RR_0 = 698 msec and RR_0 =1034 msec. Secondly, in some knots the data seems to be continuous, but the regression line has an overly sharp edge. This phenomenon can be seen at the 6th knot (RR_0 = 870 msec). To overcome these problems and optimize the smoothing properties of the model, the following constraints are defined to the individual cubic polynomial fits. At each knot the functions need to be continuous up to the second derivative.

$$\begin{cases} f_i(k_j) = f_{i+1}(k_j) \\ f'_i(k_j) = f'_{i+1}(k_j) \\ f''_i(k_j) = f''_{i+1}(k_j) \end{cases}$$

Some examples of such a fit can be seen in figure B.2.

If this set of restrictions for continuity, is also applied to the 'exterior' knots (k_1 and k_{10}), the spline becomes a cyclic spline.

$$\begin{cases} f_1(k_1) = f_9(k_{10}) \\ f'_1(k_1) = f'_9(k_{10}) \\ f''_1(k_1) = f''_9(k_{10}) \end{cases}$$

This technique was used for modelling the cyclic effect of ventilation on PP.

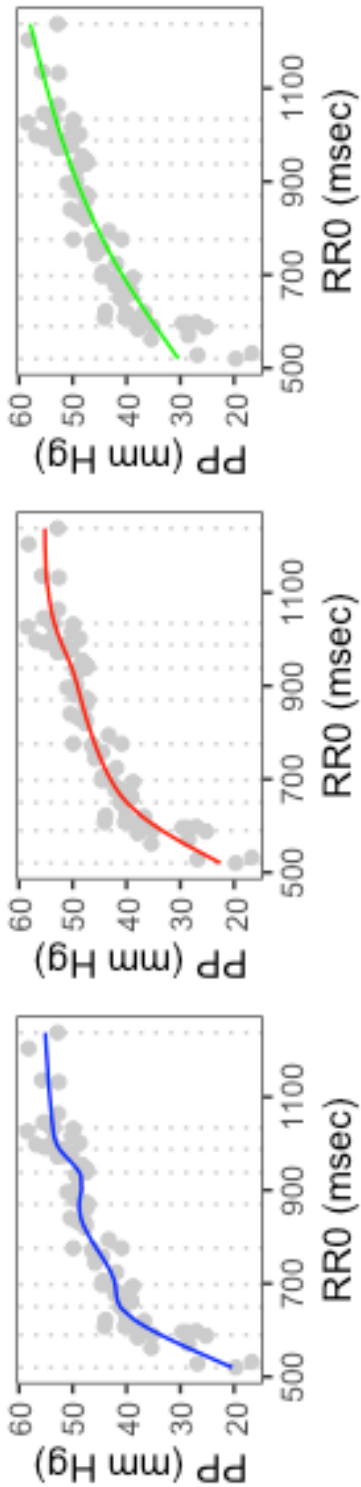


***Figure.B.2**: 3 examples of splines for the raw data with increasing penalty factor. Left: overfitted curve, middle: optimal fitting, right: underfitted.*

4. Penalization

As can been seen in figure B.2, there are still multiple solutions to the formula. The minimalization of the following formula is used to choose the optimal fit, to find the optimum between overfitted (green) and underfitted (blue) models.

$$\sum_{i=1}^{n}(y_i - f(x_i))^2 + \lambda \int f''(t)dt$$

This formula consists of 2 parts. On the left is the classical RSS (Residual Sum of Squares). Minimizing this part of the formula leads to a model that has the least overall prediction error but has the highest tendency for overfitting. The right part of the formula measures for the impact of the higher-order coefficients (second derivative) and counterbalances this tendency. λ is a penalty factor. Chosing a low λ yields a model that is allowed to be 'wiggly'. Higher λ's shifts the model to less flexible versions, ultimately leading to a linear function. There are different ways of determining the optimal λ. In our analysis we used the REML (Restricted Maximum Likelihood) approach.

useful further readings:

- James G, Witten D, Hastie T and Tibshirani R. An introduction to Statistical Learning. Chapter 7. Moving beyond Linearity. P 265-302. 2017 New York, NY: Springer Science & Business Media 2017. ISBN 978-1-4614-7137-0
- Wood N, General Additive Models. Chapter 5 smoothers p195-246. 2017 Boca Raton, FL: CRC press (Taylor & Francis Group) ISBN 978-1-4987-2833-1

Sensitivity analysis

The median RR interval and its variation changed profoundly after PLR in Patient 9. We do not know the exact reason why this patient developed an AF with slow ventricular response. We excluded the data of this potential outlier and repeated the analysis. The results of this re-analysis are given below, alongside with the findings of the full data-set.

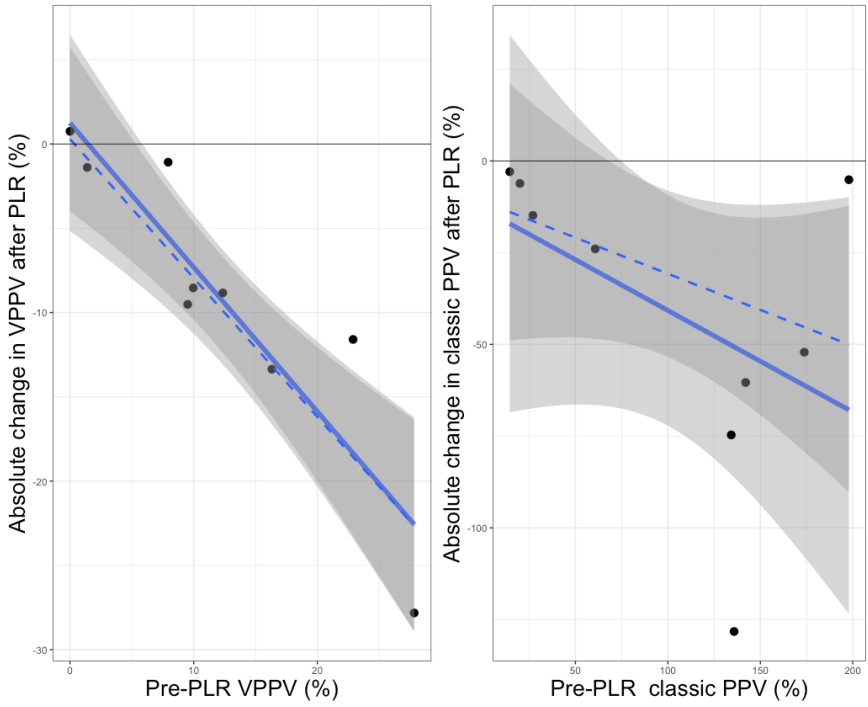
- The impact of re-analysis (excluding pt 9) on the difference between pre and post PLR values:

	Pre PLR	Post PLR	p-value
Full data set			
VPPV	9.9 [0.1 – 29.9]	1.4 [0, 11.3]	0.014
PPV	134 [14.5 – 197.9]	36.8 [7.6 – 192.7]	0.019
Data set without pt 9			
VPPV	11.2 [7.5 -18.0]	1.1 [0 – 3.1]	0.014
PPV	97.5 [25.3-150]	48.2 [13.4 -91.6]	0.020

- The impact of excluding patient 9, on the linear relationship between Pre-PLR VPPV or classic PPV and its change after PLR, are given in this table.

	Formula	R^2	p-value	rho
Full data set				
VPPV	Y = 1.25 – 0.86x	0.8447	0.0007	-0.917
PPV	Y = -13.7 – 0.28x	0.2083	0.2083	-0.383
Data set without pt 9				
VPPV	Y = 0.29 – 0.82x	0.8449	0.001	-0.905
PPV	Y = -11.09 -0.197x	0.2666	0.1902	-0.405

- Figure 4.3 was reproduced, and the result of the re-analysis leaving patient 9 out of the data set is depicted as a dashed blue line



Length of the observation window.

The algorithm to quantify VPPV was applied successively in progressively shorter windows, starting at the reference episode of 60 seconds with successive reductions of 1 second until the model indicated failure to solve the function.

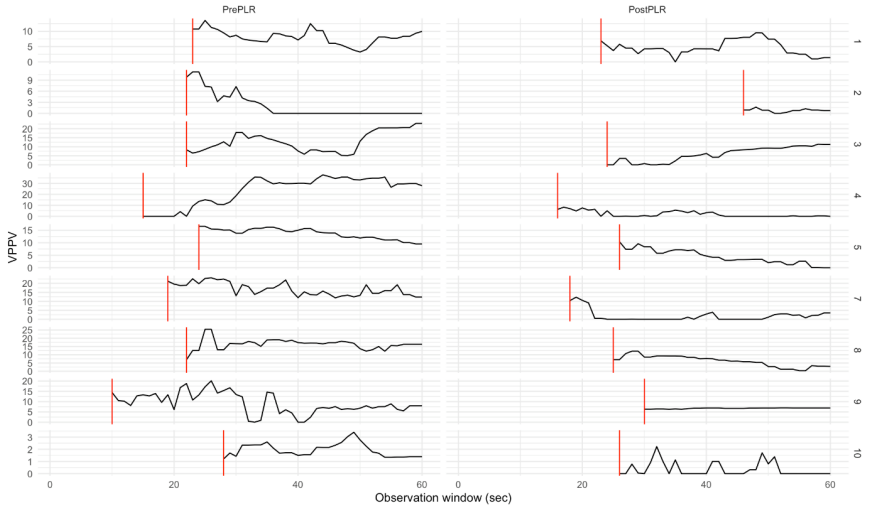


Figure B.3 *Individual plots of the calculated VPPV in function of the length of the observation window. (VPPV = calculated value of Ventilation induced Pulse Pressure Ventilation (%), Observation window = the length of data strip used to develop the model, Red vertical line= the individual minimal length of the observation window for the algorithm to determine its coefficients)*

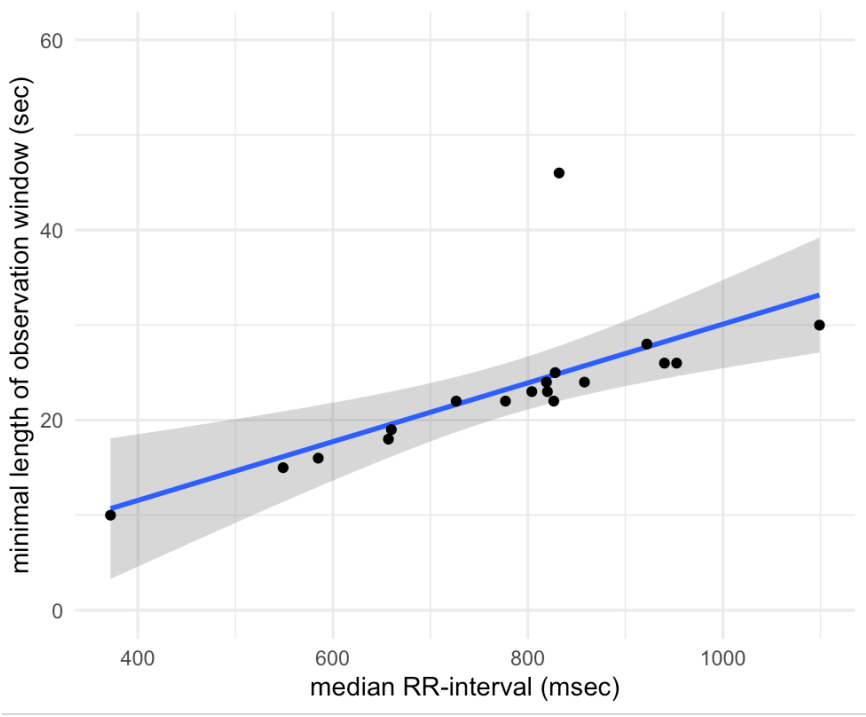


***Figure B.4**: Plot of the **relation between the minimal length of observation period and the median RR-interval** of each observation period. To depict the impact of heart rate on the performance of the model, the minimal length of the observation window (for each patient/period) was plotted against the median RR-interval of that observation period. There is a linear relationship (r^2=0.49, p = 0.001) showing that the minimal observation period for the algorithm to calculate a value for VPPV is longer with a slower heart rate. (Median RR-interval of an observation period in msec. Minimal length of observation of the observation window in seconds. The linear relation and its confidence interval are depicted as a blue line and a grey shade, respectively)*

C

Supplementary information on the article: Measurement error of Pulse Pressure Variation.

***

Wyffels PAH, De Hert S, Wouters PF.

Submitted to Journal of Clinical Monitoring and Computing.

Further extra information can be found on Github:
https://github.com/pwyffels/Measurement-Error-PPV

General Model

Procedure and setting of the model.

For each class of measurement methods ('iPPV', 'pPPV', 'tandPPV'), a regression model was built with BLUP as a predictor for the replicates. The model used the factor method as an interaction factor both in the linear model and to correct for heteroskedasticity:

$$\begin{cases} M_1(BLUP_j) \sim N(0 + 1.BLUP_j, e^{\alpha_{0M_1} + \alpha_{1M_1} BLUP_j}) \\ M_2(BLUP_j) \sim N(\beta_{0M_2} + \beta_{1M_2} BLUP_j, e^{\alpha_{0M_2} + \alpha_{1M_2} BLUP_j}) \\ M_3(BLUP_j) \sim N(\beta_{0M_3} + \beta_{1M_3} BLUP_j, e^{\alpha_{0M_3} + \alpha_{1M_3} BL\square\square P_j}) \\ \dots \end{cases}$$

In the code, BLUP is coded as PPVref and the measurement of a BLUP is coded as PPV, making the follow compact model brms -code:

$$\begin{bmatrix} PPV = PPVref * method \\ sigma = PPVref * method \end{bmatrix}$$

Each Bayesian model was done using a Markov Chain Monte Carlo simulation (Hamiltonian Monte Carlo with no-U-turn sampler (NUTS)) with four chains. All models considered a warm-up of 2,000 iterations, with sampling from a further 8,000 iterations for each chain. All chains were required to be free of divergent transitions. To monitor convergence, trace plots, and the Gelman–Rubin convergence diagnostic (Rhat < 1.01) were used for all parameters. Max_treedepth setting was adjusted to augment sampling efficiency.

Non-informative priors, using the default priors-selection of the brms package were used for modeling. See table C.1.

PRIOR	CLASS	COEFICIENT	DPAR
FLAT	b		
FLAT	b	methodxPPV_2/15	
FLAT	b	methodxPPV_3/20	
FLAT	b	methodxPPV_4/30	
FLAT	b	methodxPPV_5/60	
FLAT	b	PPVref	
FLAT	b	PPVref:methodxPPV_2/15	
FLAT	b	PPVref:methodxPPV_3/20	
FLAT	b	PPVref:methodxPPV_4/30	
FLAT	b	PPVref:methodxPPV_5/60	
STUDENT_T (3, 7.9, 4.9)	Intercept		
FLAT	b		sigma
FLAT	b	methodxPPV_2/15	sigma
FLAT	b	methodxPPV_3/20	sigma
FLAT	b	methodxPPV_4/30	sigma
FLAT	b	methodxPPV_5/60	sigma
FLAT	b	PPVref	sigma
FLAT	b	PPVref:methodxPPV_2/15	sigma
FLAT	b	PPVref:methodxPPV_3/20	sigma
FLAT	b	PPVref:methodxPPV_4/30	sigma
FLAT	b	PPVref:methodxPPV_5/60	sigma
STUDENT_T (3, 0, 2.5)	Intercept		sigma

Table C.1: ***Priors used for modelling.*** A generic notation for the individual models of the different classes is used.

Generic Stan code:

```
// generated with brms 2.17.0
functions {
}
data {
  int<lower=1> N;  // total number of observations
  vector[N] Y;  // response variable
  int<lower=1> K;  // number of population-level effects
  matrix[N, K] X;  // population-level design matrix
  int<lower=1> K_sigma;  // number of population-level effects
  matrix[N, K_sigma] X_sigma;  // population-level design matrix
  int prior_only;  // should the likelihood be ignored?
}
transformed data {
  int Kc = K - 1;
  matrix[N, Kc] Xc;  // centered version of X without an intercept
  vector[Kc] means_X;  // column means of X before centering
  int Kc_sigma = K_sigma - 1;
  matrix[N, Kc_sigma] Xc_sigma;  // centered version of X_sigma without an intercept
  vector[Kc_sigma] means_X_sigma;  // column means of X_sigma before centering
  for (i in 2:K) {
    means_X[i - 1] = mean(X[, i]);
    Xc[, i - 1] = X[, i] - means_X[i - 1];
  }
  for (i in 2:K_sigma) {
    means_X_sigma[i - 1] = mean(X_sigma[, i]);
    Xc_sigma[, i - 1] = X_sigma[, i] - means_X_sigma[i - 1];
  }
}
parameters {
  vector[Kc] b;  // population-level effects
  real Intercept;  // temporary intercept for centered predictors
  vector[Kc_sigma] b_sigma;  // population-level effects
  real Intercept_sigma;  // temporary intercept for centered predictors
}
transformed parameters {
  real lprior = 0;  // prior contributions to the log posterior
  lprior += student_t_lpdf(Intercept | 3, 7.9, 4.9);
  lprior += student_t_lpdf(Intercept_sigma | 3, 0, 2.5);
}
model {
  // likelihood including constants
  if (!prior_only) {
    // initialize linear predictor term
    vector[N] mu = Intercept + Xc * b;
    // initialize linear predictor term
    vector[N] sigma = Intercept_sigma + Xc_sigma * b_sigma;
```

```
   for (n in 1:N) {
     // apply the inverse link function
     sigma[n] = exp(sigma[n]);
   }
   target += normal_lpdf(Y | mu, sigma);
  }
  // priors including constants
  target += lprior;
}
generated quantities {
  // actual population-level intercept
  real b_Intercept = Intercept - dot_product(means_X, b);
  // actual population-level intercept
  real b_sigma_Intercept = Intercept_sigma - dot_product(means_X_sigma, b_sigma);
}
```

'Individual RC PPV'-class: iPPV-model

Results

Table C.2.1 provides the densities of all parameters (as mean, estimated error, and the 95% credible intervals) of the model, along with the Gelman–Rubin convergence diagnostic (Rhat) and the assessment of effective sampling (Bulk_ESS, Tail_ESS) (ESS = effective sampling size)
Figure C.2.1 provides the density plots and trace plots of each chain for all parameters.

***Table C.2.1*: Results of the Bayesian model for the iPPV-class of measurement methods.**

Family: gaussian. Links: mu = identity; sigma = log
Brms Formula:
*PPV ~ PPVref * method*
*sigma ~ PPVref * method*
Data: master_dataset_i (Number of observations: 15569)
Draws: 4 chains, each with iter = 10000; warmup = 2000; thin = 1; total post-warmup draws = 32000
Population-Level Effects:

	Estimate	*Est.Error*	*l-95% CI*	*u-95% CI*	*Rhat*	*Bulk_ESS*	*Tail_ESS*
b_Intercept	-0.042	0.03	-0.101	0.017	1.00	11407	17182
b_sigma_Intercept	-0.109	0.017	-0.142	-0.076	1.00	12741	18480
b_PPVref	1.004	0.004	0.997	1.012	1.00	13358	18840
b_methodiPPV_2	-0.02	0.043	-0.106	0.064	1.00	14769	19145
b_methodiPPV_3	-0.023	0.043	-0.108	0.062	1.00	12901	18281
b_methodiPPV_4	-0.029	0.043	-0.114	0.056	1.00	12086	17378
b_methodiPPV_5	-0.014	0.043	-0.098	0.07	1.00	14269	20353
b_PPVref:methodiPPV_2	0.003	0.006	-0.008	0.014	1.00	14198	20206
b_PPVref:methodiPPV_3	0.004	0.006	-0.007	0.015	1.00	15224	19880
b_PPVref:methodiPPV_4	0.005	0.006	-0.006	0.016	1.00	13992	19469
b_PPVref:methodiPPV_5	0.003	0.006	-0.008	0.014	1.00	20498	24911
b_sigma_PPVref	0.051	0.002	0.047	0.054	1.00	24904	25279
b_sigma_methodiPPV_2	-0.363	0.03	-0.423	-0.305	1.00	17080	19998
b_sigma_methodiPPV_3	-0.568	0.035	-0.637	-0.498	1.00	22006	21818
b_sigma_methodiPPV_4	-0.763	0.04	-0.84	-0.684	1.00	23214	21588
b_sigma_methodiPPV_5	-0.945	0.043	-1.03	-0.86	1.00	20198	25072
b_sigma_PPVref:methodiPPV_2	0.005	0.003	-0.001	0.01	1.00	24367	23989
b_sigma_PPVref:methodiPPV_3	0.002	0.003	-0.005	0.008	1.00	15983	20360
b_sigma_PPVref:methodiPPV_4	0.006	0.004	-0.001	0.014	1.00	22237	22716
b_sigma_PPVref:methodiPPV_5	0.009	0.004	0.001	0.017	1.00	22996	21294

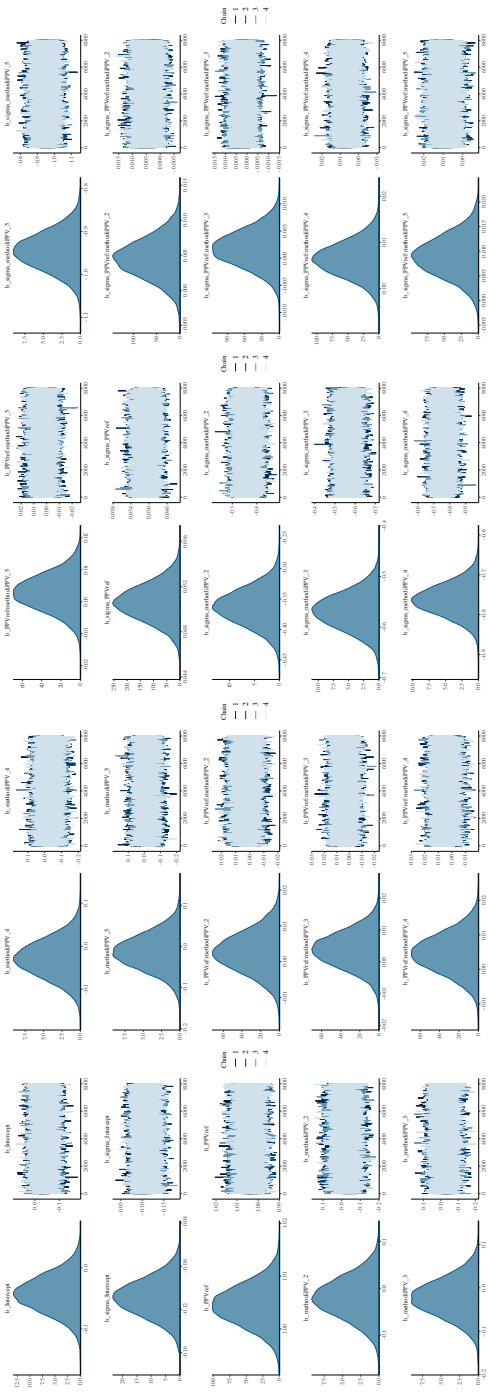


Figure C.2.1: Trace-plots and density-plots of each parameter of the iPPV-model

Visualization

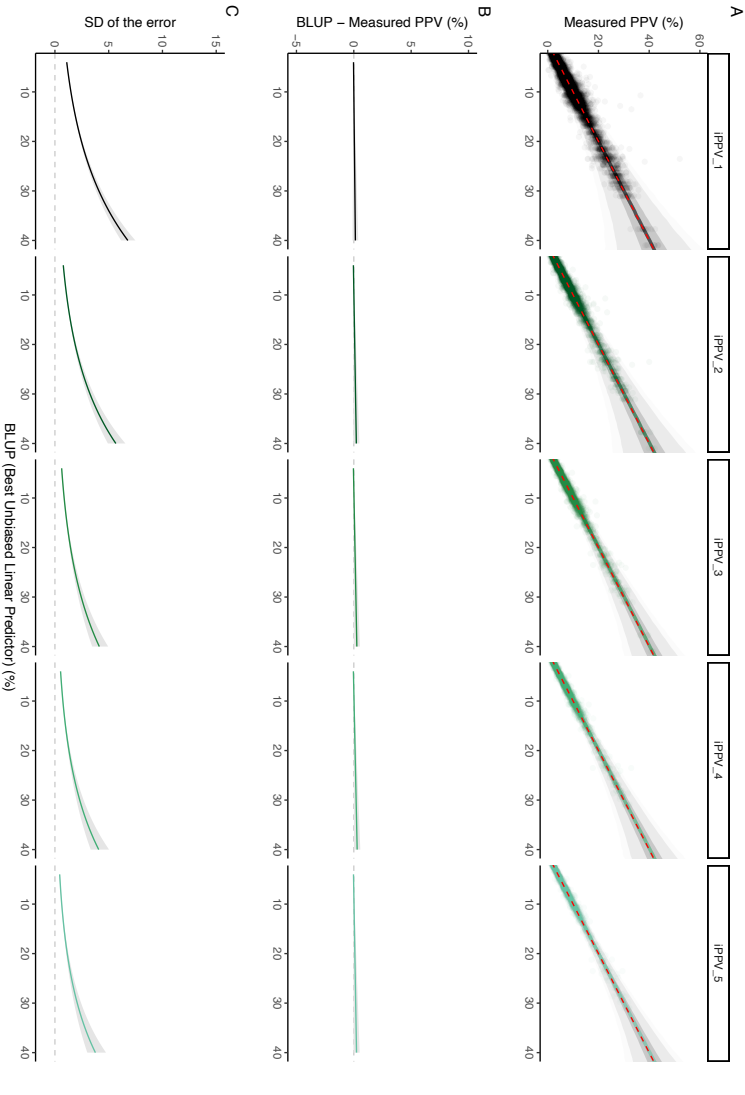


***Figure C.2.2:** Visualization of the model split up in a (A) prediction plot, (B) bias plot and (C) precision plot for each method of the iPPV-class.*

‘Pooled RC PPV’-class: pPPV-model

Results

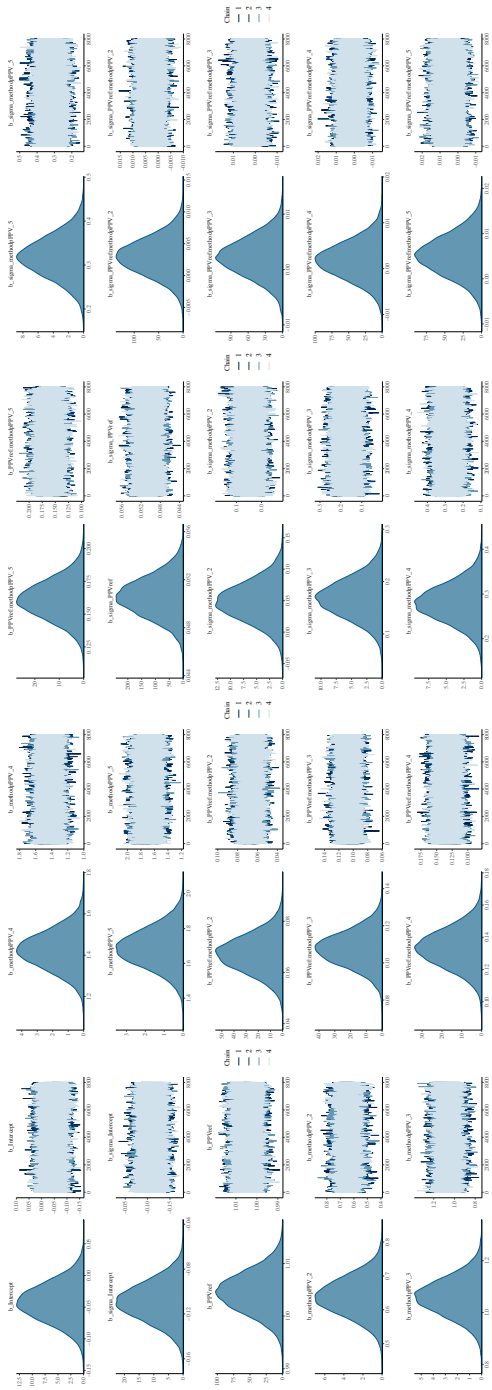
Table C.3.1 provides the densities of all parameters (as mean, estimated error, and the 95% credible intervals) of the model, along with the Gelman–Rubin convergence diagnostic (Rhat) and the assessment of effective sampling (Bulk_ESS, Tail_ESS) (ESS = effective sampling size)

Table C.3.1 Results from the Bayesian model for the pPPV-class of measurement methods.

Familiy: gaussian. Links: mu=identity; sigma=log
Brms Formula:
*PPV ~PPVref*method*
*Sigma ~PPVref*method*
Data: master_dataset_p (Number of observatons:15569)
Draws: 4 chains, each with iter = 10000; warmup = 2000 ; thin = 1;
total post-warmup draws=32000
Population-Level Effects:

	Estimate	*Est.Error*	*l-95% CI*	*u-95% CI*	*Rhat*	*Bulk_ESS*	*Tail_ESS*
b_Intercept	−0.043	0.030	−0.101	0.016	1.000	19804	24439
sigma_Intercept	−0.109	0.017	−0.143	−0.075	1.000	24687	26029
PPVref	1.005	0.004	0.997	1.012	1.000	21122	23050
methodpPPV_2	0.639	0.056	0.529	0.747	1.000	15978	16848
methodpPPV_3	1.060	0.073	0.918	1.202	1.000	14845	17126
methodpPPV_4	1.424	0.092	1.245	1.605	1.000	27192	24531
methodpPPV_5	1.688	0.111	1.469	1.906	1.000	20595	20732
PPVref:methodpPPV_2	0.067	0.007	0.053	0.081	1.000	17444	20249
PPVref:methodpPPV_3	0.108	0.009	0.089	0.126	1.001	15932	19119
PPVref:methodpPPV_4	0.133	0.012	0.110	0.157	1.000	25672	24294
PPVref:methodpPPV_5	0.161	0.015	0.132	0.190	1.000	22139	22642
sigma_PPVref	0.051	0.002	0.047	0.054	1.000	24754	25171
sigma_methodpPPV_2	0.048	0.031	−0.012	0.110	1.000	27815	24989
sigma_methodpPPV_3	0.168	0.037	0.096	0.241	1.000	21407	20406
sigma_methodpPPV_4	0.280	0.042	0.197	0.363	1.000	22494	21460
sigma_methodpPPV_5	0.319	0.047	0.227	0.411	1.000	29432	24450
sigma_PPVref:methodpPPV_2	0.003	0.003	−0.003	0.009	1.000	27709	24764
sigma_PPVref:methodpPPV_3	0.002	0.003	−0.005	0.009	1.000	20844	20277
sigma_PPVref:methodpPPV_4	0.002	0.004	−0.006	0.010	1.000	22240	21265
sigma_PPVref:methodpPPV_5	0.005	0.004	−0.004	0.014	1.000	29194	24995

Figure C.3.1: Density-plots and Trace-plots (of all chains) for each parameter of the pPPV-model



Visualization

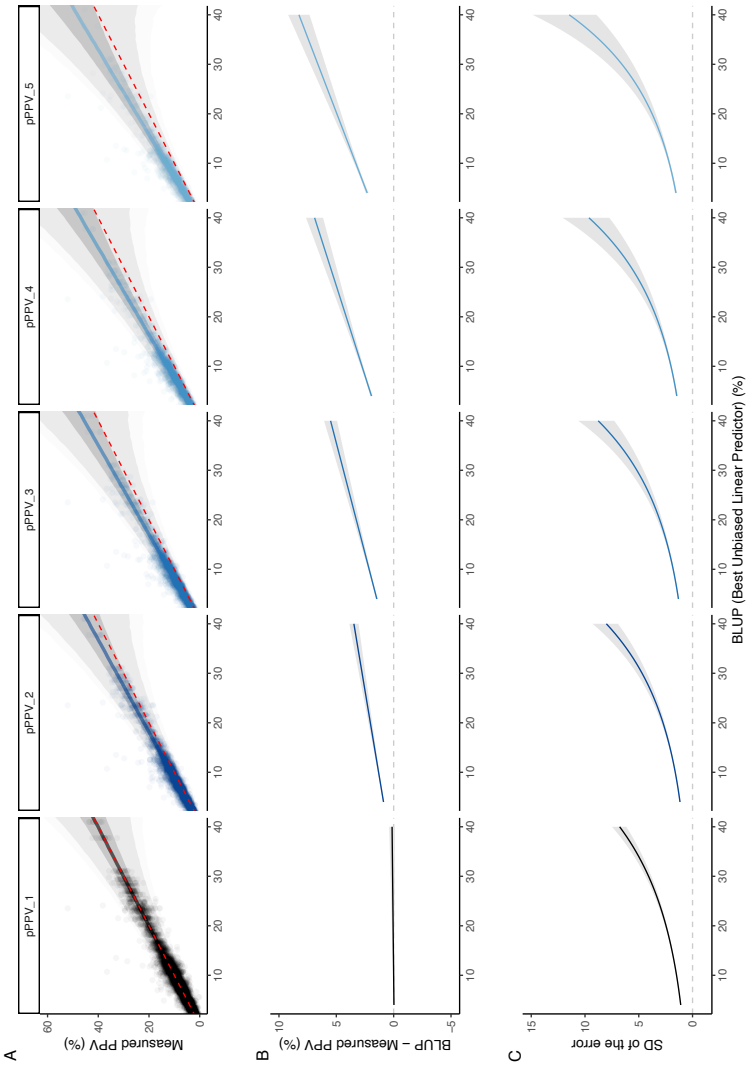


***Figure C.3.2:** Visualization of the model split up in a (A) prediction plot, (B) bias plot and (C) precision plot for each method of the pPPV-class*

'Time window-based' class: tPPV-model

Results

Table C.4.1 provides the densities of all parameters (as mean, estimated error, and the 95% credible intervals) of the model, along with the Gelman–Rubin convergence diagnostic (Rhat) and the assessment of effective sampling (Bulk_ESS, Tail_ESS) (ESS = effective sampling size)

***Table C.4.1*: Results of the Bayesian model for the tPPV-class of measurement methods.**

Family: gaussian. Links: mu = identity; sigma = log
Brms Formula:
*PPV ~ PPVref * method*
*sigma ~ PPVref * method*
Data: master_dataset_t (Number of observations:7950)
Draws: 4 chains, each with iter = 10000; warmup = 2000; thin = 1;
total post-warmup draws = 32000

Population-Level Effects:

	Estimate	*Est.Error*	*l-95% CI*	*u-95% CI*	*Rhat*	*Bulk_ESS*	*Tail_ESS*
Intercept	−0.138	0.043	−0.223	−0.053	1.00	10913	15972
sigma_Intercept	−0.432	0.028	−0.487	−0.376	1.00	17343	21450
PPVref	0.924	0.006	0.912	0.936	1.00	10623	15427
methodtPPV_15	−0.018	0.057	−0.130	0.091	1.00	13184	19671
methodtPPV_20	0.042	0.055	−0.066	0.152	1.00	13830	19605
methodtPPV_30	0.082	0.055	−0.026	0.191	1.00	13784	18445
methodtPPV_60	0.073	0.051	−0.026	0.172	1.00	11495	15090
PPVref:methodtPPV_15	0.045	0.008	0.030	0.060	1.00	12931	18860
PPVref:methodtPPV_20	0.052	0.008	0.037	0.067	1.00	12875	18671
PPVref:methodtPPV_30	0.063	0.008	0.048	0.078	1.00	12796	18176
PPVref:methodtPPV_60	0.069	0.007	0.055	0.083	1.00	11091	16185
sigma_PPVref	0.075	0.003	0.070	0.080	1.00	16796	20990
sigma_methodtPPV_15	−0.181	0.042	−0.264	−0.097	1.00	20211	22530
sigma_methodtPPV_20	−0.350	0.046	−0.440	−0.259	1.00	17897	20604
sigma_methodtPPV_30	−0.573	0.054	−0.677	−0.468	1.00	22621	21915
sigma_methodtPPV_60	−1.232	0.066	−1.361	−1.102	1.00	21781	23387
sigma_PPVref:methodtPPV_15	−0.014	0.004	−0.022	−0.007	1.00	19752	21949
sigma_PPVref:methodtPPV_20	−0.018	0.004	−0.027	−0.010	1.00	16667	18513
sigma_PPVref:methodtPPV_30	−0.015	0.005	−0.025	−0.006	1.00	22854	23669
sigma_PPVref:methodtPPV_60	−0.011	0.006	−0.023	0.000	1.00	21126	22531

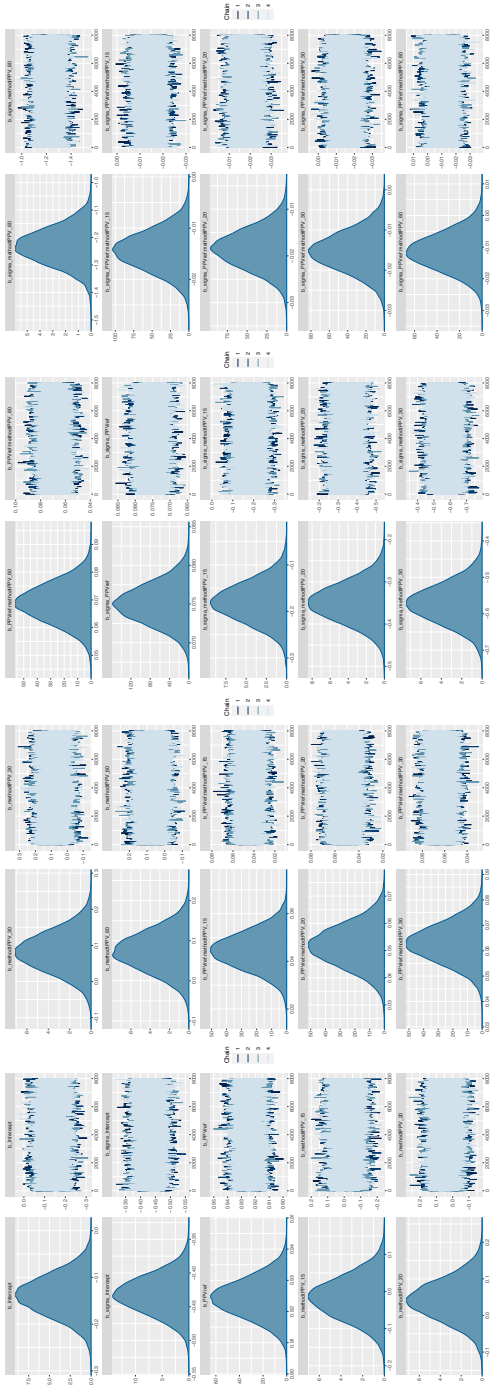


Figure C.4.1: Density-plots and Trace-plots (of all chains) for each parameter of the tPPV-model:

Visualization

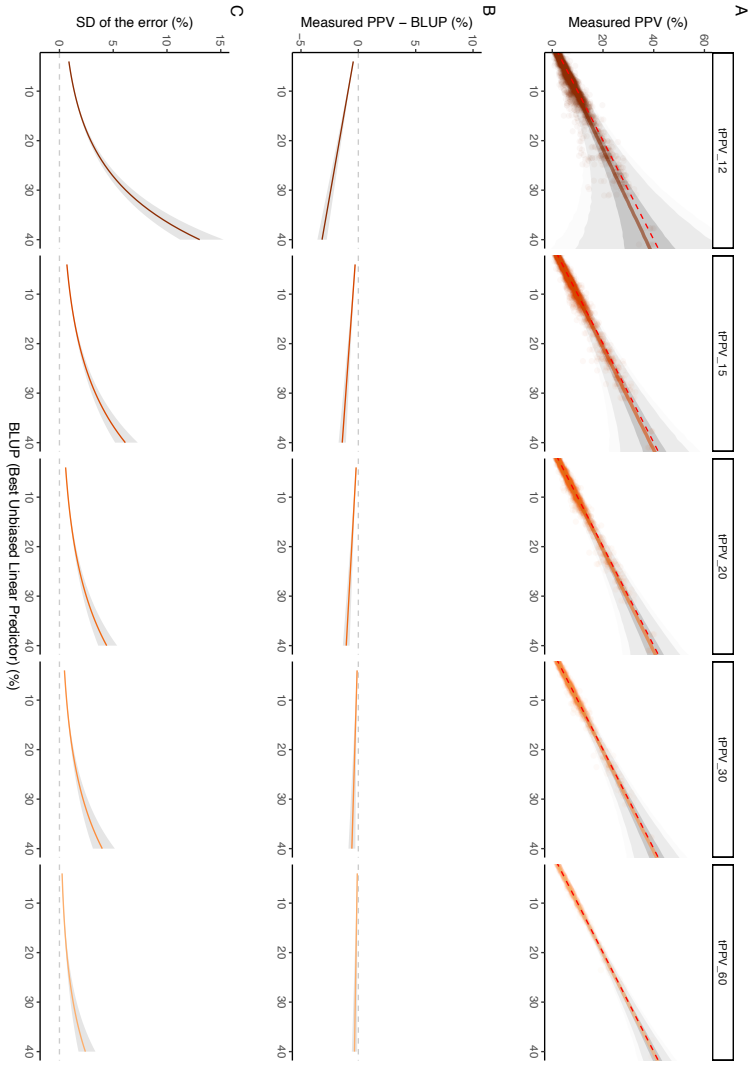


Figure C.4.2: *Visualization of the model split up in a (A) prediction plot, (B) bias plot and (C) precision plot for each method of the tPPV-class*

Imputed Model for iPPV3

Results

Table C.6.1 provides the densities of all parameters (as mean, estimated error, and the 95% credible intervals) of the model, along with the Gelman–Rubin convergence diagnostic (Rhat) and the assessment of effective sampling (Bulk_ESS, Tail_ESS) (ESS = effective sampling size)
Figure C.6.1 provides the density plots and trace plots of each chain for all parameters.

***Table C.6.1.* Results of the Bayesian model for the imputed iPPV_3 model.**

Family: MV(gaussian, gaussian).
Links:
mu = identity; sigma = log
mu = identity; sigma = identity
Formula:
PPV ~ mi(PPVref)
Sigma ~ mi(PPVref)
PPVref | mi() ~ 1
Data: master_dataset_iPPV3_mi (Number of observations: 2210)
Draws: 4 chains, each with iter = 10000; warmup = 2000; thin = 1;
total post-warmup draws = 32000

Population-Level Effects:

	Estimate	*Est.Error*	*l-95%*	*u-95%*	*Rhat*	*Bulk_ ESS*	*Tail_ ESS*
PPV_Intercept	-0.06	0.03	-0.13	-0.00	1.00	44417	24436
sigma_PPV_Intercept	-0.68	0.03	-0.74	-0.62	1.00	48978	23488
PPVref_Intercept	9.32	0.13	9.05	9.58	1.00	71420	23442
PPV_miPPVref	1.01	0.00	1.00	1.02	1.00	43290	24558
Sigma_PPV_miPPVref	0.05	0.00	0.05	0.06	1.00	48541	25746

Family Specific Parameters:

	Estimate	*Est.Error*	*l-95%I*	*u-95%I*	*Rhat*	*Bulk_ ESS*	*Tail_ ESS*
sigma_PPVref	6.32	0.09	6.14	6.51	1.00	70073	21955

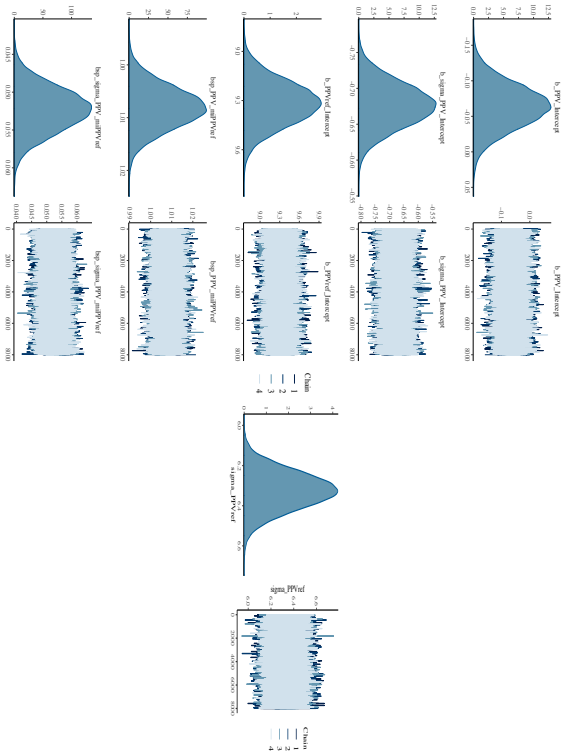


Figure C.6.1:Density plot and trace plot (of all chains) for each parameters of the iPPV-imputed-model

Visualization

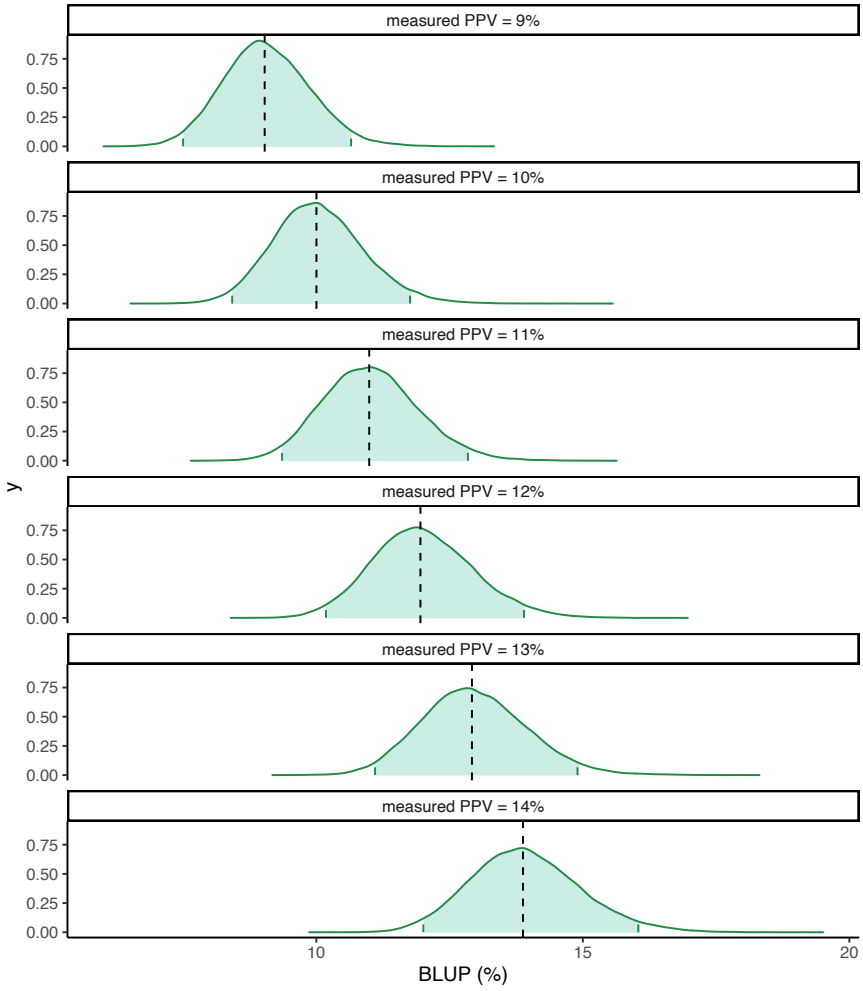


Figure C.6.2a: ***Visualization of the posterior of P(BLUP\|measured iPPV$_3$) (imputed missing data).***

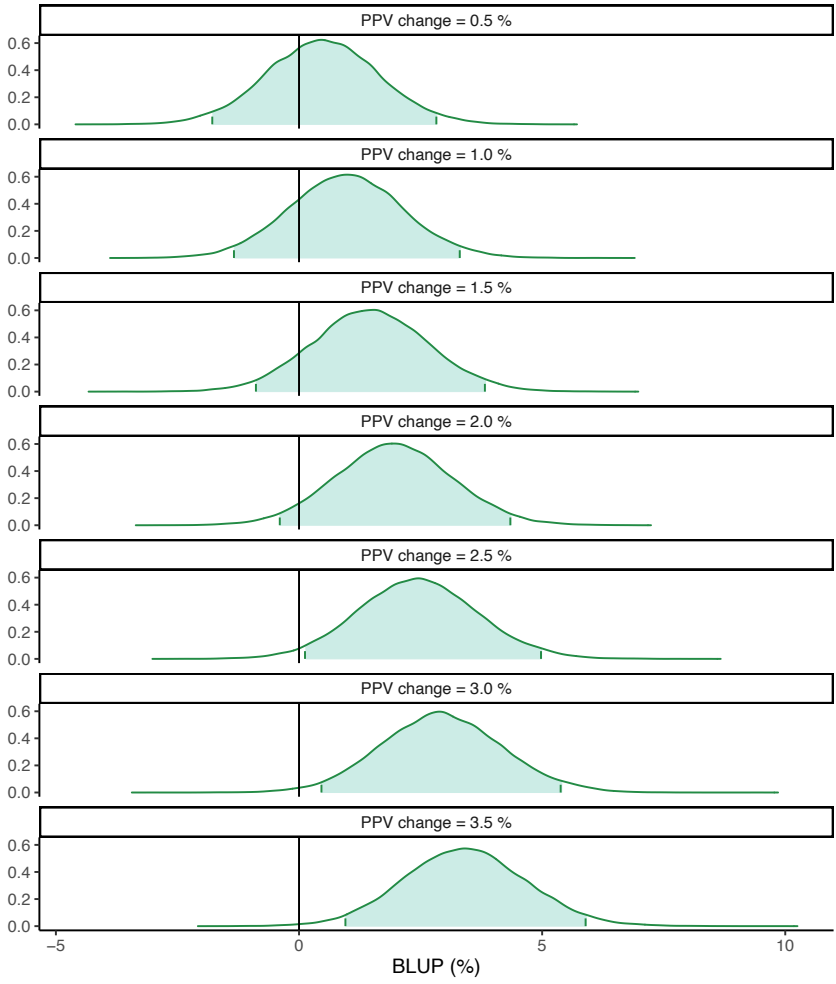


Figure C.6.2b: *Visualization for the posterior of measured differences. P(ΔBLUP| Δmeasured iPPV$_3$).*

Imputed Model for tPPV3

Results

Table C.7.1 provides the densities of all parameters (as mean, estimated error, and the 95% credible intervals) of the model, along with the Gelman–Rubin convergence diagnostic (Rhat) and the assessment of effective sampling (Bulk_ESS, Tail_ESS) (ESS = effective sampling size)
Figure C.7.1 provides the density plots and trace plots of each chain for all parameters.

Table C.7.1. Results of the Bayesian model for the imputed iPPV_3 model.

Family: MV(gaussian, gaussian).
Links:
mu = identity; sigma = log
mu = identity; sigma = identity
Formula:
PPV ~ mi(PPVref)
Sigma ~ mi(PPVref)
PPVref | mi() ~ 1
Data: master_dataset_aPPV15_mi (Number of observations: 2134)
Draws: 4 chains, each with iter = 10000; warmup = 2000; thin = 1;
total post-warmup draws = 32000

Population-Level Effects:

	Estimate	*Est.Error*	*l-95%*	*u-95%*	*Rhat*	*Bulk_ ESS*	*Tail_ESS*
PPV_Intercept	-0.15	0.04	-0.23	-0.08	1.00	39044	25895
sigma_PPV_Intercept	-0.61	0.03	-0.67	-0.55	1.00	42348	25248
PPVref_Intercept	9.69	0.14	9.41	9.96	1.00	65003	24320
PPV_miPPVref	0.97	0.00	0.96	0.98	1.00	39213	27174
Sigma_PPV_miPPVref	0.06	0.00	0.06	0.07	1.00	40719	26578

Family Specific Parameters:

	Estimate	*Est.Error*	*l-95%*	*u-95%*	*Rhat*	*Bulk_ ESS*	*Tail_ ESS*
sigma_PPVref	6.60	0.10	6.40	6.80	1.00	74412	21343

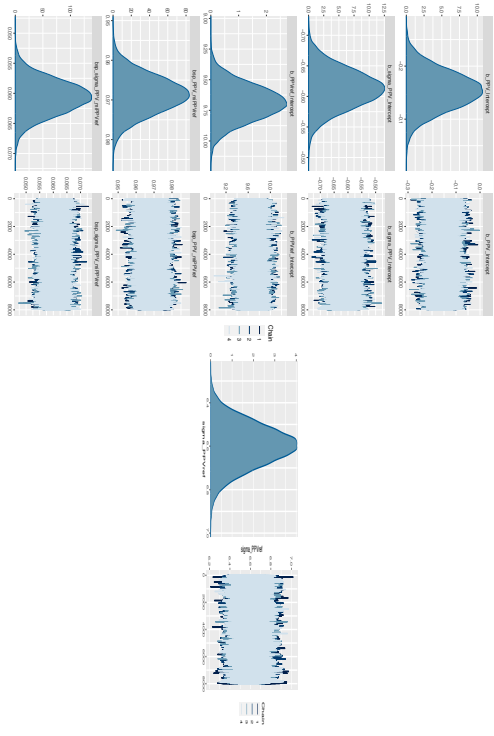


Figure C.7.1: Density plot and trace plot (of all chains) for each parameters of the tPPV-imputed-model

Visualization

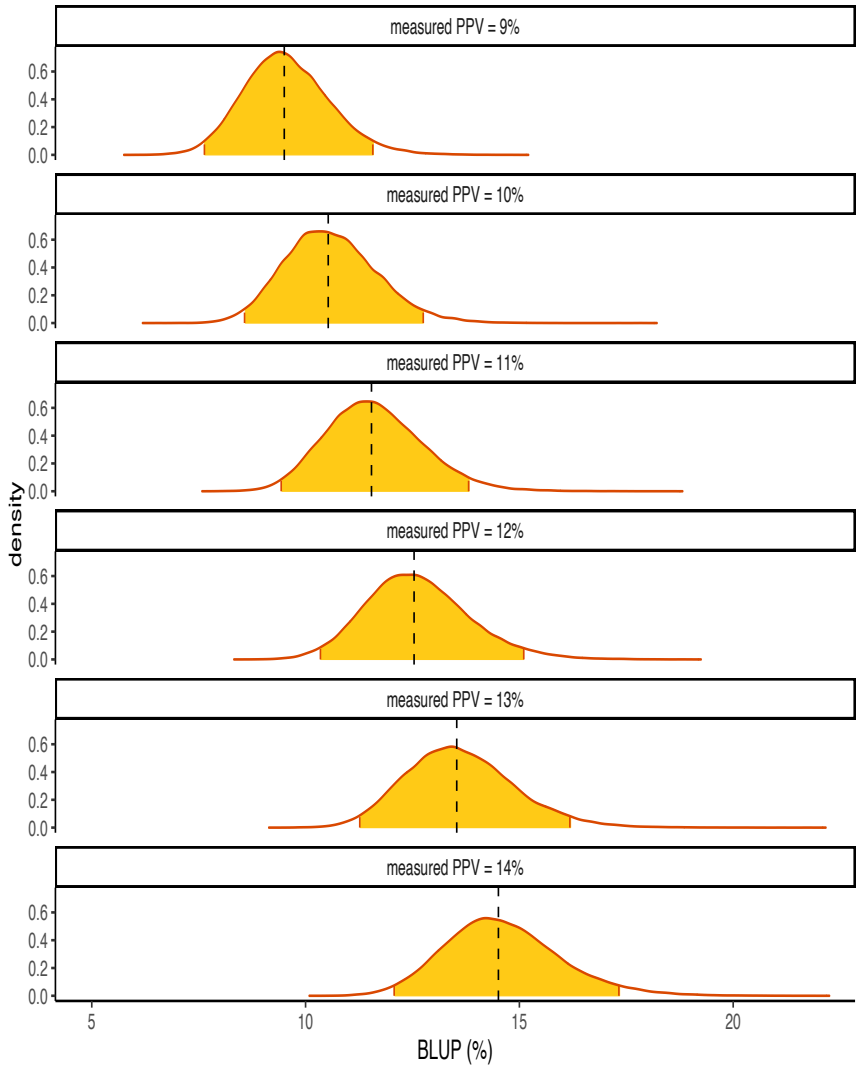


***Figure C.7.2a**: Visualization of the posterior of P(BLUP| measured $tPPV_{15}$). (imputed missing data)*

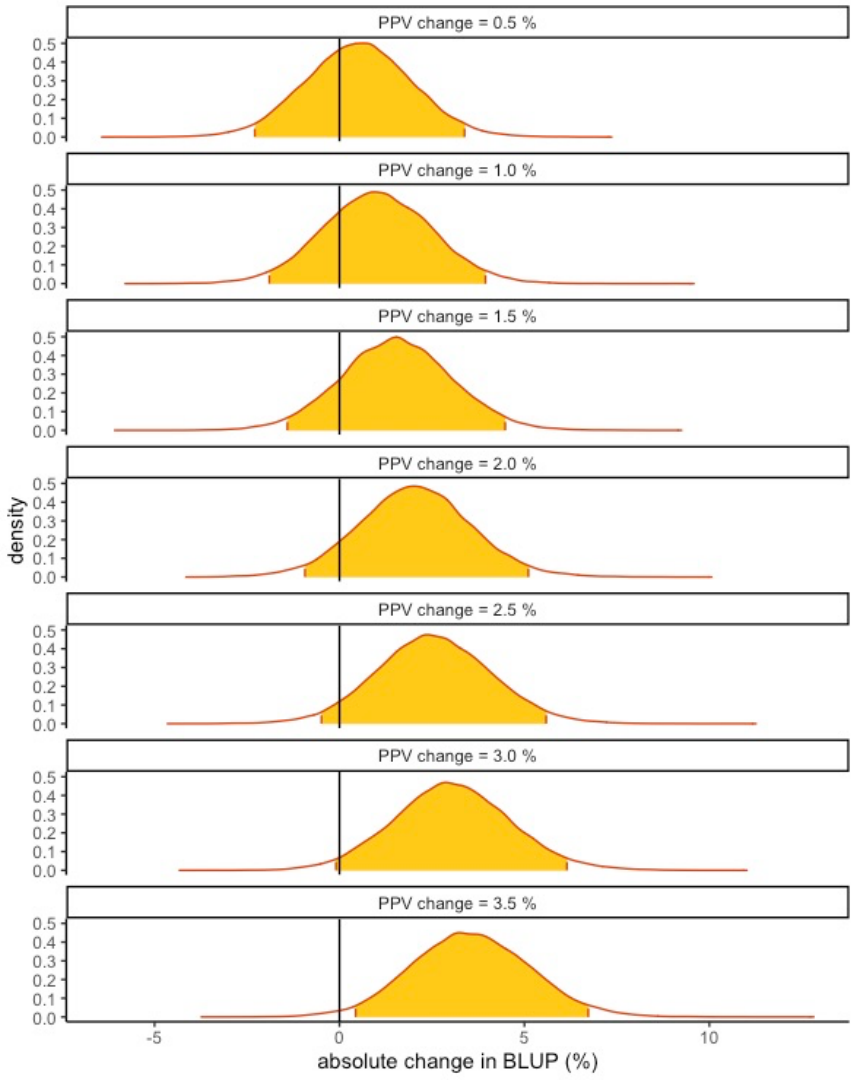


Figure C.7.3b: ***Visualization of the posterior of measured differences. $P(\Delta BLUB \mid \Delta measured\ tPPV_{15})$***

Curriculum Vitae

PW

About the author

Name:

Piet Albert Henri, WYFFELS
°17/08/1977, Roeselare, Belgium.
L: 56 cm, W: 5100 gr
ORCID: 0000-0002-6035-4340

Education:

General Medicine

Catholic University of Louvain, Louvain, Belgium. 2002

Tropical Medicine

Prins Leopold Instituut voor tropische geneeskunde, Antwerp, Belgium, 2003

Anesthesiology and Reanimation,

Catholic University Louvain, Louvain, Belgium, 2008

-University Hospitals Gasthuisberg, Louvain, Belgium, Prof. dr. E Vermeersch

-Heilig Hart Ziekenhuis Roeselare, Belgium, Dr. D De Kegel

Experience:

CHRU Lille, Département d'Aneshtésie, Prof. dr. B Vallet, France, 2008-2009

- Adult urology, CHRU Lille, Hôpital Huriez.
- Thoracic anesthesia, CHRU Lille, Hôpital Calmette.

University Hospital Ghent, Department of Anesthesiology,

- Prof. dr. P Wouters, 2009-2022
- Prof. dr. L De Baerdemaeker, 2022-…

Field of clinical expertise:

- Posterative Care Unit
- General Anesthesia
- Anesthesia for Liver transplantation
- Anesthesia for outside the Operating Room

Personal Publications:

- ***Evaluation of risk prediction model for perioperative respiratory adverse events in pediatric anesthesia.*** D'Haene A, Bauters A, Heyse B, Wyffels P. Acta Anaesth Belg. 2023; 74(2): 51-59. https://doi.org/10.56126/74.2.08

- ***A novel methodology for low-range heparin detection: A single-centre prospective diagnostic study.*** Vandenheuvel M, Vandewiele K, Van Gompel C, De Kesel PM, Wyffels P, De Somer F, Devreese KMJ, Wouters PF. Eur J Anaesthesiol. 2023; 40(1): 57-60. https://doi.org/10.1097/EJA.0000000000001747

- ***Effect of norepinephrine infusion on hepatic blood flow and its interaction with somatostatin: an observational cohort study.*** Van Limmen J, Ituttiagagoitia Bassos X, Verougstraete M, Wyffels P, Berrevoet F, Abreu De Carvalho L, De Hert S, De Baerdemaeker L. BMC Anesthesiol. 2022; 22:202. https://doi.org/10.1186/s12871-022-01741-2 https://rdcu.be/cQR8r

- ***Comparison of coagulation monitoring using ROTEM and Sonoclot devices in cardiac surgery A single-center prospective observational study.*** Vandenheuvel MA,Van Gompel C, Vandewiele K, De Kesel PM, Wyffels P, De Somer F, Devreese KM, Wouters PF. Minerva Anestesiol. 2022; 88(9):680-689. https://doi.org/10.23736/S0375-9393.22.16119-5

- ***A new algorithm to quantify cardio-pulmonary interaction in patients with atrial fibrillation: A proof of concept study.*** Wyffels PAH, De Hert S, Wouters PF. Br J Anaesth 2021; 126(1): 111-119. https://doi.org/10.1016/j.bja.2020.09.039

- ***Effects of Propofol and sevoflurane on hepatic blood flow: a randomized controlled trial.*** Van Limmen J, Wyffels P, Berrevoet F, Van Lander A, Coeman L, Wouters P, De Hert S, De Baerdemaeker L. BMC Anesthesiol. 2020; 20(1): 241.https://doi.org/10.1186/s12871-020-01150-3

- ***Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: First update 2016.guidelines from the European Society of Anesthesiology.*** Sibylle A. Kozek-Langenecker, Aamer B. Ahmed, Arash Afshari, Pierre Albaladejo, Cesar Aldecoa, Guidrius Barauskas, Edoardo De Robertis, David Faraoni, Daniela C. Filipescu, Dietmar Fries, Thorsten Haas, Matthias Jacob, Marcus D. Lancé, Juan V.L. Pitarch, Susan Mallett, Jens Meier, Zsolt L. Molnar, Niels Rahe-Meyer, Charles M. Samama, Jakob Stensballe, Philippe J.F. Van der Linden, Anne J. Wikkelsø, Patrick Wouters, Piet Wyffels and Kai Zacharowski . Eur J Anestesiol 2017; 34: 332-395. https://doi.org/10.1097/EJA.0000000000000630

- ***Dynamic filling parameters in patients with atrial fibrillation: Differentiating Rhythm induced from Ventilation induced variations in Pulse Pressure.*** Wyffels

PAH, Van Heuverswyn F, De Hert S, Wouters PF. AJP- Heart and Circ 2016; 310: H1194-H1200. https://doi.org/10.1152/ajpheart.00712.2015

- ***Guidelines on the management of severe perioperative bleeding.*** Kozek-Langenecker et al. EJA 2013; 30(6): 270-382. https://doi.org/10.1097/EJA.0b013e32835f4d5b

- ***The "Grey Zone Approach": Assessing the Accuracy of Pulse Pressure Variation without Considering the Prevalence?-*** *letter to the editor.* Wyffels P and Wouters PF. Anesthesiology 2012; 116(3):740-741. https://doi.org/10.1097/ALN.0b013e318247235d

- ***Anaphylactic shock and hyperfibrinolysis measured with thrombo- elastography.*** Parashchanka A, Wyffels PAH, Van Limmen JGM and Wouters PF. Acta Anaesthesiologica Belgica 2011; 62: 207-211.

- ***The value of pulse pressure and stroke volume variation as predictors of fluid responsiveness during open chest surgery.*** Wyffels P, Sergeant P and Wouters PF. Anaesthesia 2010; 65: 704-709. https://doi.org/10.1111/j.1365-2044.2010.06371.x

- ***Ventilation induced Plethysmographic Variations predict Fluid Responsiveness in Ventilated Postoperative Cardiac Surgery Patients.*** Wyffels P, Durnez PJ, Helderweirt J, Stockman WA and De Kegel D. Anesth Analg 2007; 105(2): 448-452. https://doi.org/10.1213/01.ane.0000267520.16003.17

NetWork Publications:

- International Surgical Outcome Study Group

- ***Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high income countries.*** International Surgical Outcome Study group. Br J Anaesth 2016; 117(5): 601-609. https://doi.org/10.1093/bja/aew316

- ***Critical care admission following elective surgery was not associated with survival benefit: prospective analysis of data from 27 countries.*** Kahan BC, Kouleti D, Arvaniti K, Beavis V, Campbell D, Chan M, Moreno R, Pearse RM; international Surgical Outcomes Study (ISOS) group. Intensive Care Med. 2017; 372(Suppl 2):139-9. https://doi.org/10.1007/s00134-016-4633-8

- ***The surgical safety checklist and patient outcomes after surgery: a prospective observational cohort study, systematic review and meta-analysis.*** Abbott TEF, Ahmad T, Phull MK, Fowler AJ, Hewson R, Biccard BM, Chew MS, Gillies M, Pearse

RM; International Surgical Outcomes Study (ISOS) group. Br J Anaesth 2018; 120(1): 146-155. https://doi.org/10.1016/j.bja.2017.08.002

- ***Prospective observational cohort study on grading the severity of postoperative complications in global surgery research.*** International Surgical Outcomes Study (ISOS) group. Br J Surg. 2019; 106(2): e73-e80. https://doi.org/10.1002/bjs.11025

- Clinical Trial Network of the European Society of Anaesthesiology.

1. European Transfusion Practice and Outcome Study (ETPOS):

- ***Intraoperative transfusion practices and perioperative outcome in the European elderly: A secondary analysis of the observational ETPOS study.*** Grüber L, Keszei A, Coburn M, Rossaint R, Ziemann S, Kowark A; ETPOS Study Group. PLoS One 2022; 17(1) https://doi.org/10.1371/journal.pone.0262110

- ***Intraoperative transfusion practices in Europe***. J Meier, Filiprescu D, Kozek-Langenecker S et al. Br J Anaesth 2016;116(2):255-6. https://doi.org/10.1093/bja/aev456

2. PROtective Ventilation Network (PROVE NET):

2.1 Local Assessment of Ventilatory Management During General Anesthesia for Surgery (LAS VEGAS)

- ***Epidemiology, practice of ventilation and outcome for patients at increased risk of postoperative pulmonary complications: LAS VEGAS – an oberservational study in 29 countries***. LAS VEGAS investigators. Eur J Anaesthesiol 2017; 34(8): 492-507. https://doi.org/10.1097/EJA.0000000000000646

- ***Association between night-time surgery and occurrence of intraopertive adverse events and postoperative pulmonary complications.*** Cortegiani A, Gregoretti C, Neto AS et al Br J Anaesth 2019; 122(3):361-369. https://doi.org/10.1016/j.bja.2018.10.063

- ***Intraoperative ventilator settings and their association with postoperative pulmonary complications in neurosurgical patients: post-hoc analysis of LAS VEGAS study.*** Robba C, Hemmes SNT, Neta AS et al. BMC Anesthesiol. 2020 20(1): 73. https://doi.org/10.1186/s12871-020-00988-x

- ***The Association of Intraoperative driving pressure with postoperative pulmonary complications in open versus closed abdominal surgery patients – a posthoc propensity score-weighted cohort analysis of the LAS VEGAS Study.*** Mazzinari G, Serpa Neto A, Hemmes SNT, Hedenstierna G, Jaber S, Hiesmayr M, Hollmann MW, Mills GH, Vidal Melo MF, Pearse RM, Putensen C, Schmid W, Severgnini P, Wrigge H, Cambronero OD, Ball L, de Abreu MG, Pelosi P, Schultz MJ; LAS VEGAS study –

investigators; PROVE network and the Clinical Trial Network of the European Society of Anaesthesiology. BMC Anesthesiol. 2021; 21(1):84. https://doi.org/10.1186/s12871-021-01268-y

- ***Sex difference and intra- operative tidal volume: insights from the LAS VEGAS study.*** Nijbroek SG, Hol L, Swart P, Hemmes SNT, Serpa Neto A, Binnekade JM, Hedenstierna G, Jaber S, Hiesmayr M, Hollman MW, Mills GH, Vidal Melo MF, Putensen C, Schmid W, Severgnini P, Wrigge H, Gama de Abreu M, Pelosi P, Schultz MJ; LAS VEGAS study investigators, the PROVE Network and the Clinical Trial network of the European Society of Anaethesiology. Eur J Anaesthesiol. 2021; 38(10): 1034-1041. https://doi.org/10.1097/EJA.0000000000001476

2.2 Protective Ventilation with Higher eversus Lower PEEP during General Anesthesia for Surgery in OBESE Patients (PROBESE)

- ***Effect of Intraoperative High Positive End-Expiratory Pressure (PEEP) With Recruitment Maneuvers vs Low PEEP on Postoperative Pulmonary Complications in Obese Patients: A Randomized Clinical Trial.*** PROBESE Collaborative Group of the PROVEnet for Clinical Trial Network of the ESA, Bluth T, Serpa Neto A, Schultz MJ, Pelosi P Gama de Abreu M. JAMA 2019; 321(23): 2292-2305. https://doi.org/10.1001/jama.2019.7505

3 Anaesthesia PRactice In Children Observational Trial (APRICOT)

- ***Incidence of severe critical events in paediatric anaesthesia (APRICOT): a prospective multicentre observational study in 261 hospitals in Europe.*** Habre W, Disma N, Virag K et al. Lancet Respir Med 2017;5(5): 412-425. https://doi.org/10.1016/S2213-2600(17)30116-9

4 Neonate-Children sTudy of Anaesthesia pRactice IN Europe. (NECTARINE)

- ***Neonates undergoing pyloric stenosis repair are at increased risk of difficult airway management: secondary analysis of the Neonate and Children audiT of Anaesthesia pRactice IN Europe***. Disma N, Engelhardt T, Hansen TG, de Graaff JC, Virag K, Habre W; NECTARINE Group of the European Society of Anaesthesiology and Internsive Care. Br J Anaesth 2022; 129(5): 734-739. https://doi.org/10.1016/j.bja.2022.07.041

- ***Morbidity and mortality after anaesthesia in early life: results of the European prospective multicentre observational study, neonate and children audit of anaesthesia practice in Europe (NECTARINE).*** Disma N, Veyckemans F, Virag K, Hansen TG, Becke K, Harlet P, Vutskits L, Walker SM, de Graaff JC, Zielinska M, Simic D, Engelhardt T, Habre W; NECTARINE Group of the European Society of

Anaesthesiology Clinical Trial Network. Br J Anaesth. 2021; 126(6): 1157-1172. https://doi.org/10.1016/j.bja.2021.02.016

- ***Difficult tracheal intubation in neonates and infants. NEonate and Children audit of Anaesthesia pRactice IN Europe (NECTARINE): a prospective European multicenter observational study.*** Disma N, Virag K, Riva T, Kaufmann J, Engelhardt T, Habre W; NECTARINE group of the European Society of Anaesthesiology Clinical Trial network. Br J Anaesth. 2021; 126(6): 1173-1181. https://doi.org/10.1016/j.bja.2021.02.021

'… Closing time,
every new beginning
comes from some other
beginning's end. …'

Semisonic
Closing Times, 1998