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## PULSE PRESSURE VARIATION: WHERE ARE WE TODAY?

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Cannesson M, Aboy M, Hofer CK, Rehman M. Pulse pressure variation: where are we today?

J Clin Monit Comput 2010

**ABSTRACT.** In the present review we will describe and discuss the physiological and technological background necessary in understanding the dynamic parameters of fluid responsiveness and how they relate to recent softwares and algorithms' applications. We will also discuss the potential clinical applications of these parameters in the management of patients under general anesthesia and mechanical ventilation along with the potential improvements in the computational algorithms.

**KEY WORDS.** Fluid responsiveness, fluid optimization, cardiac output, outcome, monitoring, arterial pressure.

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## INTRODUCTION

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Since the 1980 s, a number of studies have evaluated the effects of perioperative hemodynamics as related to the concept of fluid responsiveness [1–14]. The dynamic parameters of fluid responsiveness are related to cardiopulmonary interactions in patients under general anesthesia with mechanical ventilation. This is far superior to static indicators (such as central venous pressure) [1]. The advantage of these dynamic measurements is that they can be derived from a single arterial pressure waveform [systolic pressure variations (SPV), and pulse pressure variations (PPV)]. Measurement of these indicators can predict an increase in cardiac output induced by volume expansion before volume expansion is actually performed. These indices have been described for more than 20 years [15]. Recently new software have been developed to automatically and continuously calculate these indices [8, 10, 16–20]. These new monitoring parameters can more readily predict the need for fluid administration to improve cardiac output and perfusion as compared to more invasive cardiac output monitoring [9]. Recent studies suggest this approach can improve postoperative outcome [21–23]. Moreover, it is now possible to obtain PPV non invasively using respiratory variations in the pulse oximeter plethysmographic waveform amplitude ( $\Delta$ POP) [7, 8, 17, 24–28].

In the present review we will describe and discuss the physiological and technological background necessary in understanding the dynamic parameters of fluid responsiveness and how they relate to recent software and algorithms applications. We will also discuss the potential clinical applications of these parameters in the management of patients under general anesthesia with mechanical

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Received 12 February 2010. Accepted for publication 9 March 2010.

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## FROM KUSSMAUL'S PULSUS PARADOXUS TO RESPIRATORY VARIATIONS IN THE PULSE OXIMETER PLETHYSMOGRAPHIC WAVEFORM AMPLITUDE

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### *Adolf Kussmaul and the Pulsus Paradoxus*

Adolf Kussmaul (Figure 1) was the first to describe the *Pulsus Paradoxus* phenomenon in 1873 in a paper entitled “Ueber Schwielige Mediastino Pericarditis und den Paradoxen Puls”. This phenomenon has been described in spontaneously breathing volunteers presenting with conditions which cause right ventricular dysfunction, impaired right ventricular filling, and raised atrial pressure. *Pulsus Paradoxus* is induced by conditions that exaggerate the physiological mechanisms occurring during spontaneous respiration. During inspiration, there is an increase in negative intrathoracic pressure inducing an increase in venous return to the right heart. When the above-mentioned conditions are present, this induces an exaggerated ventricular interdependence causing a displacement of the septum into the left ventricle and reducing its size and volume. This in turn will increase pulmonary vascular filling, and a decrease in left ventricular filling and stroke volume. These concepts, describing the physiological basis of the cardio-pulmonary interactions, have been applied to patients receiving positive pressure ventilation both in



Fig. 1. Adolf Kussmaul (1822–1902).

critical care and intraoperative settings. These cardiopulmonary interactions, inducing respiratory changes in ventricular stroke volumes and arterial pressure, have been shown to be accurate predictors of fluid responsiveness. Further more continuous analyses of these interactions has the potential clinical implication for optimizing fluid and hemodynamic management in patients under general anesthesia being mechanically ventilated.

### *Preload and preload dependence: revisiting the Frank Starling relationship*

Ventricular preload is defined as the degree of cardiac muscle tension at the initiation of contraction [29]. In clinical practice, it is almost impracticable to measure the degree of tension of cardiac muscle. Consequently, utilizing the Laplace's law (linking tension, pressure and volume) clinicians use pressure or volume parameters to assess preload [30]. The pressure parameters used include left and right ventricular filling pressures, volume parameters consist mainly of left ventricular end-diastolic volume. Left ventricular filling pressure can be assessed indirectly by the pulmonary capillary wedge pressure using a pulmonary artery catheter [31], and right ventricular filling pressure can be obtained from a central venous catheter (central venous pressure). Left ventricular end-diastolic volume can be approximated by the left ventricular end-diastolic area obtained using echocardiography. Indices of preload have been used extensively over the past decades to guide volume expansion [32]. The use of these indices to predict the effects of volume expansion on stroke volume and cardiac output is based upon the Frank-Starling relationship. This relationship describes the intrinsic ability of the heart to adapt to increasing volumes. The Frank-Starling mechanism means that the greater the heart muscle is stretched during filling, the greater is the force of contraction and the volume of blood pumped into the aorta. Or stated another way: “Within physiologic limits, the heart pumps all the blood that returns to it by the way of the veins” [29]. The shape of the Frank-Starling relationship is curvilinear (Figure 2). The initial part of the curve is called the steep portion and the second part is called the plateau. If the heart is operating on the steep portion (low preload), then an increase in preload (induced by volume expansion) will induce a significant increase in stroke volume (here the heart is said to be preload dependent). If the heart is working on the plateau (elevated preload), then an increase in preload (induced by volume expansion) will not induce any significant increase in stroke volume (here the heart is said to be preload independent). According to this observation we instinctively believe that knowing preload will then

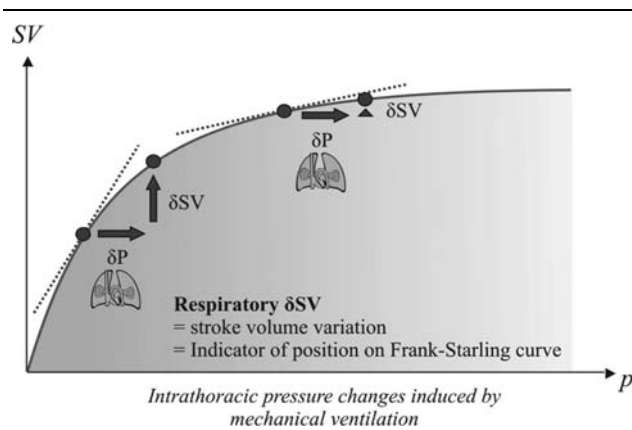


Fig. 2. Stroke volume variation and the Frank-Starling curve. In the zone of the ascending limb of the Frank-Starling curve intrathoracic pressure variations ( $\delta P$ ) induced by mechanical ventilation result in pronounced variations of stroke volume ( $\delta SV$ ) indicating preload reserve (“responders”). In the shallow part of the curve variations of  $\delta P$  and  $\delta SV$  are small (reduced preload reserve, “non-responders”).

help predict fluid responsiveness. However, the Frank-Starling relationship not only depends on preload and stroke volume but also depends on ventricular function and the location on the Frank-Starling curve. Consequently, for a given preload value, it is not possible to predict the effects of an increase in preload on stroke volume. Several studies have demonstrated that, even if measured correctly (at the end expiratory phase), ventricular preload parameters are poor predictor of fluid responsiveness [2, 11, 13, 32–38].

This concept is made more complicated, due to the fact that the relationship between ventricular preload, ventricular volume and ventricular filling pressure is in part related to ventricular compliance. For example, a hypertrophic left ventricle will have a small left ventricular end-diastolic volume with an elevation of left ventricular filling pressure due to a diastolic dysfunction.

In the operating room appropriate volume expansion is based on two assumptions: “will my patient’s cardiac output increase following volume expansion?”, and “is my patient preload dependent or not?” Preload dependence is defined as the ability of the heart to increase stroke volume in response to an increase in preload. As we have seen earlier, preload itself is not predictive of preload dependence. Recently studies have utilized the development of parameters able to accurately predict preload dependence. It appears to be clear that dynamic parameters, based on the analysis of the effects of fluid challenges on stroke volume, are the best predictors of fluid responsiveness [39]. In the operating room setting, cardiopulmonary interactions have been used as a surrogate to assess the effects of a fluid challenge on stroke

volume [1]. In patients under general anesthesia, positive pressure ventilation induces cyclic changes in vena cava blood flow, pulmonary artery flow, and aortic blood flow. During inspiration, vena cava blood flow decreases (venous return decreases) and, according to the Frank-Starling relationship, pulmonary artery flow decreases [1]. Approximately three beats later this decrease in pulmonary artery flow is transmitted to the left ventricle inducing a decrease in aortic stroke volume. Consequently, mechanically ventilated patients under general anesthesia present have cyclic changes in left ventricular stroke volume due to changes in intrathoracic pressure. When the heart is functioning on the steep portion of the Frank-Starling relationship, these respiratory variations are important because little changes in right ventricular preload induced by mechanical ventilation will induce important changes in stroke volume (Frank-Starling), when the heart is working on the plateau of this relationship, respiratory variations are small because changes in right ventricular preload induced by mechanical ventilation have no impact on stroke volume. As arterial pressure parameters are related to stroke volume and arterial compliance, respiratory variations in arterial pressure parameters reflect respiratory variations in left ventricular stroke volume if we consider that arterial compliance is stable during a single respiratory cycle.

In 1978, Rick et al. showed that respiratory variations in the arterial pressure were related to the patient’s fluid status and that SPV was frequently more than 10 mmHg in hypovolemic patients [40]. In 1983, Coyle et al. described the Delta up and Delta down components of SPV in an abstract presented at the American Society of Anesthesiology annual meeting [15]. In 1987, Perel et al. demonstrated that SPV was related to volume status in an animal model [13], and in the 1990 s’ several studies demonstrated that SPV were accurate predictors of fluid responsiveness in adult patients undergoing surgery [14] and in the intensive care unit [11]. In 2000, Michard et al. demonstrated that PPV was superior to SPV for the assessment of fluid responsiveness in mechanically ventilated patients with septic shock [2]. In parallel, non invasive assessment of fluid responsiveness based on the analysis of the respiratory variations in the plethysmographic waveform was studied (Figure 3). The first study suggesting that the respiratory variations in the plethysmographic waveform were related to the patient’s fluid status was published by Partridge et al. in 1987 [41], the same year the paper from Perel et al. focusing on SPV was published [13]. In 1999, Pizov et al. demonstrated the close relationship between SPV and respiratory variations in the peak of the plethysmographic waveform at baseline and after hemorrhage [42]. Finally, in 2007, our team demonstrated that the respiratory variations in the

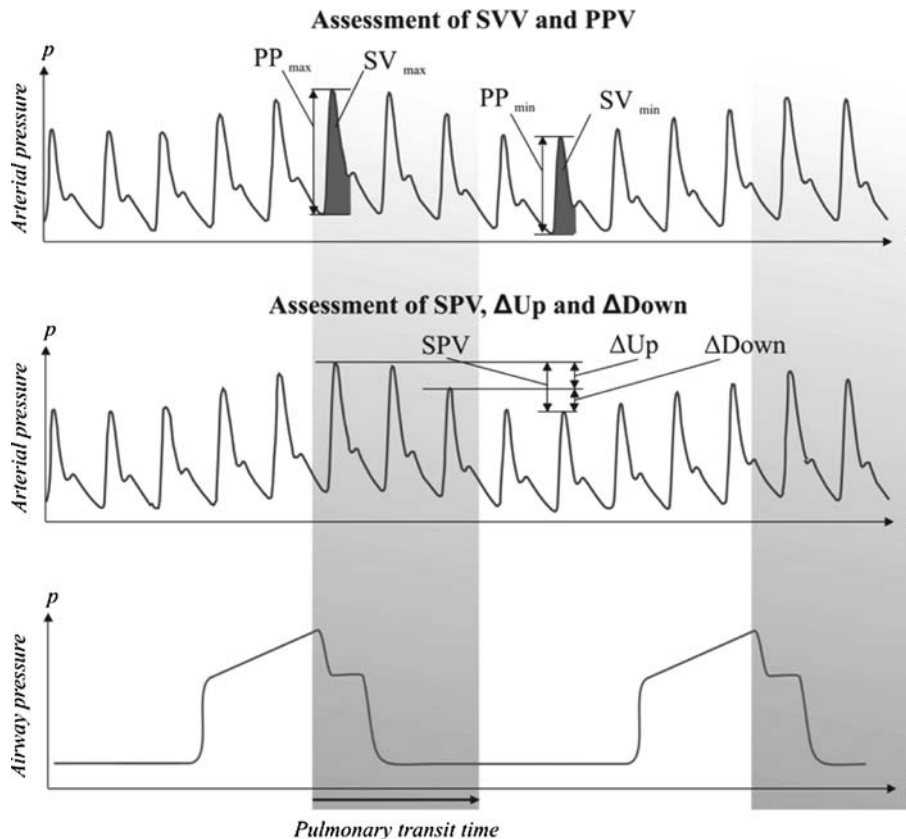


Fig. 3. Assessment of SVV, PPV, SPV and  $\Delta$  components.

amplitude of the plethysmographic waveform are able to predict fluid responsiveness in mechanically ventilated patients [7]. Today, several studies have demonstrated that this parameters is usefull for the purpose of fluid responsiveness prediction in anesthesiology and in intensive care [6, 12, 27, 28, 43].

### MONITORING PULSE PRESSURE VARIATION, STROKE VOLUME VARIATION, AND PLETHYSMOGRAPHIC WAVEFORM VARIATION

Until recently there were no algorithms to automatically calculate and monitor dynamic indicators of fluid responsiveness such as PPV. Initially the only algorithms that enabled for automatic PPV determination were proprietary and part of commercial monitoring systems such as the PICCO system (Pulsion Medical Systems, Germany). The PICCO system played a significant role in the advancement of this field by supporting studies that required automatic determination of PPV. However, these systems have limitations for the research community. One

of the limitations of these commercial systems is that they cannot be used to calculate PPV from arterial blood pressure (ABP) signals already collected and stored in a computer. Other limitations of the available commercial systems include their inability to determine PPV accurately and reliably in situations of abrupt hemodynamic changes or artifacts. Several of these limitations were overcome in 2004 with the publication of the first non-proprietary and publicly available algorithm for automatic determination of PPV from ABP signals [16]. This novel PPV estimation algorithm was described in detail to insure reproducibility in order to enable researchers to implement it in their own software packages and be able to automatically determine PPV from digitally stored ABP. Given its non-proprietary nature, medical device manufacturing companies were also free to implement it as part of their commercially available monitoring systems. The algorithm was adopted by Philips Medical Systems (Suresnes, France), which now enables for real-time display and acquisition of PPV in their Philips Intelivue MP70 monitors. In 2008, the commercial implementation of this algorithm was first independently validated in a clinical setting against the manual gold standard PPV [18]. The results of this study indicated an

agreement between the automatic PPV algorithm and the gold standard of  $0.7 \pm 3.4\%$  (mean bias  $\pm$  SD), and the ability of the automatic PPV algorithm to discriminate between responders and nonresponders of volume expansion with a sensitivity of 82% and a specificity of 85%.

This first publicly available PPV monitoring algorithm was based on automatic beat detection algorithms, kernel smoothing, and rank order filtering, and was designed for mechanically ventilated patients under general anesthesia. In 2009, an enhanced version of this algorithm was published where the initial 2004 automatic algorithm was improved in order to make it robust to periods of abrupt hemodynamic changes and make it applicable to plethysmographic signals [44]. Its performance was compared against the PICCO system in over 40 h of ABP recording from 18 mechanically ventilated crossbred Yorkshire swine who underwent a period of abrupt hemodynamic change after an induced grade V liver injury involving severe blood loss resulting in hemorrhagic shock, followed

by fluid resuscitation. Figure 4 shows a representative example of the PPV results obtained by the enhanced algorithm and PICCO's system. The results of this study indicated that the PICCO system performs well in regions of stable hemodynamic conditions. However, PICCO's algorithm fails to accurately estimate the PPV during the periods between the injury and fluid resuscitation in all the subjects. On the other hand, the enhanced automatic algorithm exhibited superior performance compared to commercial hemodynamic monitoring systems with PPV capabilities. The assessment results showed that the proposed algorithm is capable of accurately estimating the PPV index during periods of significant hemodynamic changes. The study did not include a validation of the algorithm's performance in plethysmographic signals. Its performance as a method for automatic determination of  $\Delta$ POP remains to be studied.

Both of the PPV algorithms mentioned above [16, 18, 44] rely on automatic beat detection algorithms [45] to detect and segment each ABP or plethysmographic beat,

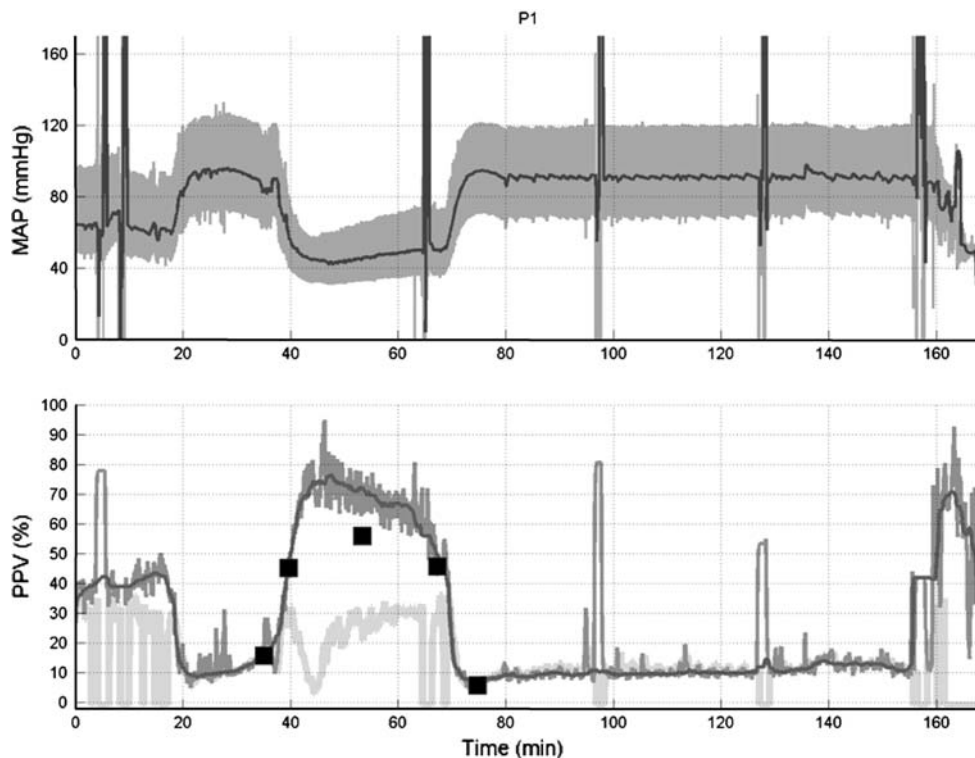


Fig. 4. Representative example of the pulse pressure variation results obtained by the enhanced automatic pulse pressure variation algorithm and the PICCO system. Comparison of the enhanced pulse pressure variation algorithm (bottom plot, dark grey) against a commercial pulse pressure variation monitoring system (bottom, light grey). The top plot shows the arterial blood pressure signal and the bottom plot shows the estimated pulse pressure variation using both algorithms. Five “gold-standard” pulse pressure variation manual annotations calculated by trained experts during periods of abrupt arterial blood pressure changes are shown as black squares on the bottom plot of each subject. Note that both systems are consistent for the most part during periods where the arterial blood pressure signal is relatively stationary. However, the enhanced pulse pressure variation algorithm has better performance than the commercial pulse pressure variation monitoring system during periods of abrupt arterial blood pressure changes.

calculate the pulse pressure in each beat, and estimate the pulse pressure variation envelope due to amplitude modulation of the ABP or plethysmographic signals due to respiration. This is accomplished using linear and nonlinear (rank-order) filters as well as kernel smoothers. Figure 5 shows an example illustrating these steps. An alternative approach is to avoid the use of automatic beat detection algorithms altogether. This is possible by using state-space methods such as Extended Kalman Filters (EKF) and Particle Filters (PF). These techniques require a statistical signal model. An example of such statistical state-space model for cardiovascular signals such as ABP and plethysmographic signals was presented in 2008 and the ability of an EKF to estimate these model parameters and calculate PPV without the need for beat detection algorithms was demonstrated [46]. More recently, another algorithm was described which uses a generalization of this state-state model and a maximum a-posteriori adaptive marginalized particle filter (MAM-PF) to estimate PPV in mechanically ventilated patients [47]. Since the underlying statistical state-space model was designed to model both ABPM and plethysmographic signals, these algorithms can be used to automatically calculate PPV or  $\Delta$ POP. Additionally, it is possible to generalize the statistical state-space model to account for PPV and  $\Delta$ POP during spontaneous breathing. While the initial performance results of these new algorithms based on state-space methods are promising, they still have to be validated in a clinical environment by means of studies similar to the one conducted to assess the performance of the initial publicly available algorithm (Aboy) [16, 18].

In addition to PPV and  $\Delta$ POP algorithms based on beat detection [16, 18, 44], and those based on state-space methods [46, 47], it may be also possible to estimate these type of dynamic indicators or generate equivalent metrics using nonlinear analysis techniques such as Lempel–Ziv Complexity (LZC), Approximate Entropy, and Sample Entropy. The results of a recent study indicate that the LZC of ABP correlates with PPV and may be useful in assessing fluid status and guiding therapy [48]. These methods and metrics may be advantageous since they only require a simple direct computation as opposed to a complex algorithm to estimate PPV.

Given the recent developments in this area, several medical device manufacturing companies have continued developing monitoring systems which include proprietary algorithms to automatically monitor dynamic indicators of fluid responsiveness. For instance, GE Medical System Information Technologies (Milwaukee, WI, US) was awarded US Patent No. 7,056,292 in 2006 for a system and method to calculate the systolic pressure variation, delta up, and delta down continuously. More recently, Edwards Lifesciences (Irvine, CA, US) was awarded US

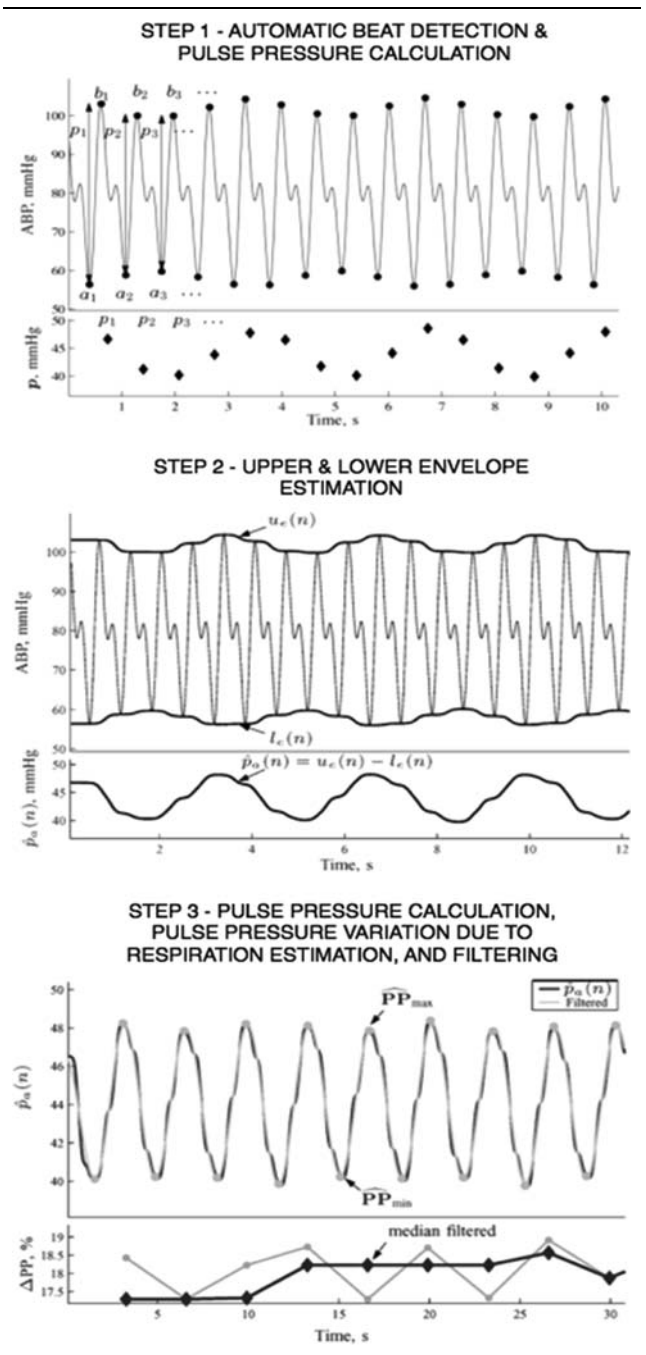


Fig. 5. Example of the steps performed by an automatic pulse pressure variation algorithm based on beat detection and segmentation.

Patent No. 7,422,562 directed to a system for real-time measurement of ventricular stroke volume variation (SVV) based on the standard deviation of the cardiac signal over each cardiac cycle. In addition to these two issued US patents there are over 10 patent applications publications currently under examination by the United States Patent & Trademark Office directed to methods, systems,

and apparatus for real-time monitoring of dynamic parameters of fluid responsiveness.

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## LIMITS OF THE DYNAMIC PARAMETERS OF FLUID RESPONSIVENESS

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Dynamic parameters of fluid responsiveness based on cardiopulmonary interactions have several limitations that need to be clearly stated before they can be adequately used in the clinical setting.

First, these parameters have to be used in mechanically ventilated patients under general anesthesia. Up to now, studies conducted in spontaneously breathing patients failed to demonstrate that PPV, SPV, or  $\Delta$ POP can predict fluid responsiveness in this setting [49–51]. Moreover, tidal volume has an impact on the predictive value of these parameters and a tidal volume of 8 ml/kg of body weight is required to use these indices [52, 53] with a positive end expiratory pressure between 0 and 5 cmH<sub>2</sub>O. Patients have to be in sinus rhythm [1], chest must be closed (open chest as well as open pericardium strongly modify the cardiopulmonary interactions) [54], and intra abdominal pressure has to be within normal ranges [55]. These dynamic indicators need to be further explored in children [56] and in the setting of left ventricular failure [20] and acute respiratory distress syndrome [57, 58].

Apart from these limitations that are common to any dynamic parameters derived from the cardiopulmonary interactions, indices derived from the plethysmographic waveform have specific limitations. The main limitation for the plethysmographic waveform analysis is the vasomotor tone that strongly impacts this waveform [59, 60]. Consequently, patient have to be studied during profound general anesthesia [26, 61, 62] and it seems that  $\Delta$ POP is less stable in the intensive care unit setting than in the anesthesiology setting [63].

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## FLUID OPTIMIZATION: CARDIAC OUTPUT MAXIMIZATION AND PULSE PRESSURE VARIATION MINIMIZATION

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The goal of perioperative fluid optimization is the same than that of the cardiovascular system under normal conditions: an adequate blood flow in vitals and in traumatized tissues, as not to compromise the first and to enable effective wound healing in the latter [64]. In clinical practice, a rational substitution therapy accounts for crystalloids and isooncotic colloids in balanced preparations. It replaces perioperative fluid losses according to the physiological background: crystalloids serve to replace

extracellular losses while colloids should be used when cardiac preload has to be restored in order to optimize cardiac output [64–67]. The current trend is to restrict crystalloids administration and to optimize cardiac output using colloids [65, 67].

### *Impact of cardiac output optimization on postoperative outcome*

Numerous studies have demonstrated that cardiac output maximization using colloids is able to improve postoperative outcome and to decrease the cost of surgery [68–77]. The concept of cardiac output maximization is based on the concept of oxygen delivery optimization [78–80] that is proportional to cardiac output, hemoglobin, and arterial oxygen saturation. These studies have been conducted in various settings (abdominal surgery, orthopedic surgery, cardiac surgery, vascular surgery) and in various countries. Most of them have demonstrated that cardiac output maximization was able to decrease length of stay in the intensive care unit, length of stay in the hospital, incidence of postoperative nausea and vomiting, and several other factors.

As we have shown earlier, cardiac output can be optimized by bringing the patient to the plateau of the Frank-Starling relationship. Most of the studies focusing on cardiac output optimization used a cardiac output monitor to titrate colloids administration in order to reach the plateau of the Frank-Starling curve when cardiac output does not increase anymore after volume expansion. Several positive studies were conducted using esophageal Doppler. However, despite these studies, very few centers use esophageal Doppler and have adopted goal-directed fluid administration protocols in their daily clinical practice. This is probably related to the evolution in how cardiac output is measured in the daily clinical anesthesia practice. The gold-standard for cardiac output measurement still remains the pulmonary artery catheter with intermittent thermodilution [81–84]. In clinical research, most studies evaluating new devices for cardiac output determination compare the tested device to this technique. However, in the clinical setting, the use of pulmonary artery catheter has dramatically decreased because several studies have suggested that the use of pulmonary artery catheter does not improve outcome and, in some cases, even worsened patients' outcome [85–92]. Finally, changes in hemodynamic monitoring over the past 10 years have followed two paths. First, there has been a decrease in invasive monitoring, most notably a reduction in the use of the pulmonary artery catheter because of a presumed lack of efficacy in its use in the management of critically ill patients, with an increased use

of less invasive monitoring. Second, numerous clinical trials have documented improved outcome and decreased costs when early goal-directed protocolized therapies are used in appropriate patient populations, such as patients with septic shock presenting to Emergency Departments and high-risk surgical patients before surgery (pre-optimization) and immediately after surgery (post-optimization) [93].

These observations (importance of cardiac output monitoring and decrease in the use of pulmonary artery catheter to measure cardiac output) are well reflected by the huge industrial interest in developing alternative hemodynamic monitors and in the number of publications and of scientific sessions dedicated to this topic [72, 94–101].

Consequently, the huge interest induced by these dynamic parameters of fluid responsiveness (such as PPV,  $\Delta$ POP, SVV) is probably related to the fact that they have potential to be used for fluid optimization in the operating room [9]. In fact, if cardiac output maximization is achieved by bringing the patient to the plateau of the Framck Starling relationship, it is theoretically possible to achieve this goal by minimizing PPV,  $\Delta$ POP, or SVV. Thus, cardiac output maximization could be replaced by PPV minimization. So far, only three published studies have evaluated the impact of a pulse pressure variations guided fluid management on perioperative outcome [21–23] and five abstracts have been recently presented at the *American Society of Anesthesiology* and at the *European Society of Anesthesiology* annual meetings [102–106]. So far, results are inconclusive and further studies are required to better explore this exciting topic.

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## CONCLUSION

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For years the pulmonary artery catheter has been the gold standard for guiding fluid management in the operating room and in the critical care units. A number of studies have questioned the utilization and the safety of the PA catheter. Non-invasive techniques are being investigated to fill the void caused by the declining use of the PA catheter. The researchers, clinicians and the industry is looking for alternate and preferably non invasive monitors to fill this void. PPV has shown great potential to help optimize hemodynamic parameter using physiological data from non-invasive means. Today PPV can assist with fluid therapy and hemodynamic optimization in patients under general anesthesia receiving mechanical ventilation. With new and improved algorithms the PPV has the potential to help us guide fluid management in sponta-

neous breathing and non ventilated patients both in our operating room and critical care units.

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