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Pulse pressure variation and stroke volume variation: from flying blind to flying right?

Editor—We read with interest two recent publications in the *British Journal of Anaesthesia* by Gouvea and colleagues[1] who manually assessed pulse pressure variation (PPV) and by Lahner and colleagues[2] about automatically calculated stroke volume variation (SVV). These articles concluded that PPV and SVV are not accurate predictors of fluid responsiveness (FR). As pointed out by the authors themselves, their results are in contradiction with previously published studies. Indeed, more than 25 peer-reviewed articles have demonstrated the value of PPV and SVV as predictors of FR,[3 4] sometimes in similar setting.[5 6] Regrettably no convincing explanation is given as eloquently illustrated by the summary statement of Gouvea and colleagues about PPV: 'The reasons why this dynamic index was unreliable in this setting remain unclear'. Consequently, we feel the need to propose some explanations for these unexpected results.

First, there are some limitations to the use of PPV and SVV. The most common in surgical patients is probably cardiac arrhythmia, but other limitations do exist and have been described in detail elsewhere.[7] Whether these situations have been screened, excluded, or controlled may be questioned.

Secondly, one should consider how fluid-loading-induced changes in stroke volume (SV) have been tracked. Indeed, the classification of patients as responders and non-responders depends on the accuracy and precision of the methods used to measure SV. Gouvea and colleagues[1] have used the 'STAT' mode of the continuous pulmonary artery catheter. Using a single STAT mode value to measure SV is like using a single bolus when measuring SV by classic pulmonary thermodilution. It is well known (and widely accepted in our daily practice) that only the averaging of several measurements is associated with an acceptable precision.[8] Lahner and colleagues[2] have used the Doppler to measure SV. This method is known to be operator-dependent[9] with a precision far above 10%,[10] the exact cut-off value they have used to discriminate between responders and non-responders. We fully agree that Doppler-based optimization protocols have been shown to improve the outcome of high-risk surgical patients, but it would have been fair to disclose that similar findings have also been reported using a strategy based on PPV monitoring and optimization.[11]

Thirdly, one may also question how PPV and SVV have been measured. Gouvea and colleagues[1] have measured PPV using a 'home-made' method actually proposed to quantify systolic pressure variation[12] and maybe less accurate at measuring PPV. Lahner and colleagues[2] have measured SVV with the FloTrac/Vigileo system (Edwards Lifesciences, Irvine, CA, USA). Briefly, this system computes SV from the equation $SV = APsd \times \kappa$, where APsd is the standard deviation of arterial pressure and κ an auto calibration factor derived from biometric variables and 'shape variables' describing in mathematical or statistical terms the shape of the arterial pressure curve. An SV measurement accuracy issue has been discussed and ruled out by Lahner and colleagues[2] using the argument that 'SVV is defined as a per cent change of SV, regardless of the absolute SV values'. We fully agree with this comment and would like to add the following argument: SVV is calculated over a period of 20 s while κ is updated only every minute. Therefore, κ is constant from one beat to the other and hence eliminated from the numerator and denominator when calculating SVV over a 20 s period as follows: $SVV = (SV_{max} - SV_{min})/SV_{mean} = (\kappa \times APsd_{max} - \kappa \times APsd_{min})/\kappa \times APsd_{mean} = (APsd_{max} - APsd_{min})/APsd_{mean}$. In other words, SVV calculation is not at all affected by κ. In this regard, three studies[4–6] have recently confirmed that SVV measured by the FloTrac/Vigileo system is as reliable as PPV to predict FR. Unfortunately, none of them was discussed or referenced.

We believe that there are several situations limiting the use of PPV and SVV in critically ill patients, and these often do not apply to patients undergoing non-cardiac surgery. Anaesthetists have to deal constantly with hypotension related to hypovolaemia, anaesthetic agents, or both. Until recently, they were flying blind, having no idea of the respective role of these two factors in determining systemic hypotension. There is no doubt that, when used appropriately, PPV and SVV are accurate predictors of FR and have the potential to help anaesthetists in the decision-making process regarding intraoperative fluid therapy. However, despite their relative simplicity at first sight, their 'real life' use may be more complicated than expected. This will have to be further explored before these parameters can be implemented in goal-directed fluid optimization protocols.

An overview of studies of FR shows that there are no two protocols alike. Volume expansion strategies, definition of responders, and methods to measure SV differ from one study to another. It might be useful to standardize protocols in order to allow comparisons between studies and parameters. When evaluating new indices, it might also be necessary to compare them with other parameters. For example, Lahner and colleagues may have compared SVV derived from the FloTrac/Vigileo system

with other dynamic parameters such as SVV obtained from oesophageal Doppler, PPV, or both from the arterial line. This would have helped them and also the readers to understand unexpected findings.

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Editor—We would like to thank Dr Cannesson and colleagues for their interest in our work,[2] and appreciate the opportunity to respond to their comments.

First, they suggest that we might have not screened for limitations of SVV when we conducted our study. As most common example they name 'cardiac arrhythmias'. We obtained our SVV measurements according to the manufacturer's user manual (Vigileo/FloTrac © system, Edwards Lifesciences). As mentioned in our publication, we excluded patients with pre-existing cardiac arrhythmias and screened for intraoperative cardiac arrhythmias and other limitations.

Secondly, Dr Cannesson and colleagues argue that the oesophageal Doppler monitor might lack the precision of picking up 10% changes in the SV. This monitor has the capability to detect such changes.[13 14] Besides, most of the oesophageal Doppler-based fluid optimization algorithms have incorporated an increase in SV of 10% or more, as had been shown in clinical studies assessing patient-centred outcome variables such as length of hospital stay or incidence of perioperative complications.[15]

Thirdly, differences in SVV measurements between available devices suggest that those devices are not interchangeable.[16 17]

Fourthly, they claim that we were unfair in not citing the study of Lopes and colleagues.[11] This study investigating PPV monitoring and intraoperative fluid optimization demonstrated significant impact on the length of hospital stay in addition to other outcome parameters. The methods of this trial have been discussed.[18] However, it does not compare with our own study which is not an outcome study, but an assessment of a technical device.

We agree with Dr Cannesson and colleagues that there 'are several situations limiting the use of PPV and SVV in critically ill patients', but not in their belief 'these often do not apply to patients undergoing non-cardiac surgery'. We also agree that the transition of SVV (and PPV) from the scientific bench to the clinical bedside might be 'more complicated than expected', as reported recently.[19] However, it is not the physiology and clinical utility of monitoring heart–lung interaction, and thus FR, that needs to undergo further studies. What needs to be studied is the reliability and usefulness of technical devices that claim to monitor heart–lung interaction. To perform an adequately powered outcome study needs a trustworthy monitor. Sad, but true: not all of them are created equal.

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Editor—We welcome the thoughtful comments on our study[1] by Dr Cannesson and colleagues. They first argue that dynamic indices may have some limitations when used in surgical patients. We fully agree with this statement, and indeed, we believe that our results, among others, may have confirmed this. Many studies evaluating the role of dynamic indices in predicting FR in the intraoperative setting have been conducted in somewhat static conditions, that is, the patient is fluid challenged only once and at a single time point, usually post-induction.[20–23] However, it is reasonable to expect that the Frank–Starling curve of an individual patient may change dynamically during major surgery. Thus, it is likely that the predictive value of dynamic indices might change accordingly. When we designed our study, we decided to fluid challenge our patients at various stages during liver transplantation and, as was shown, the PPV index could not reliably predict FR in this setting.[1] Our results only highlight the fact that PPV may have some limitations and clinicians should be aware of them. We agree when they say that collecting the mean of several cardiac output measurements would improve our data precision. However, we tried to figure out the role of PPV in predicting FR during near 'real-life' situations, particularly in the setting of liver transplantation, where rapid haemodynamic changes usually occur. As a result, we chose the STAT mode because it displays the most online cardiac index value as measured by the pulmonary artery catheter, and clinicians quite often use this screen mode when rapid fluid challenging tracking is to be done. Finally, Cannesson and colleagues have argued that manually assessing PPV may be less accurate. However, to date, there has not been such a gold standard method to quantify dynamic indexes. Indeed, since the first description by Perel and colleagues,[24] the measurement of systolic pressure variation and other dynamic indexes has been made either offline with a computer system or, more recently, with automated algorithms.[25] However, although useful in the experimental setting, computer-based

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measurement is not practical at the bedside. Similarly, automatic measurement of dynamic indexes, though proven useful, has not so far gained widespread clinical acceptance, probably because of cost restraints. On the other hand, the cursor method is less expensive and may be more user-friendly,[12 26] and with some practice, these measurements can be done within 1 min simply using a pocket calculator. Indeed, this method has been validated and used successfully by other investigators.[27 28] Anaesthetists usually have to decide whether or not to fluid challenge their patients many times during major surgery, and the usefulness of dynamic indices in helping with this decision-making process has been proved in different settings. However, it seems that many clinicians have been using the PPV as a dogma, and the key is that PPV may not work well in some situations. Certainly, we have been improving our knowledge about the latter. For example, a recent paper[29] has shown that right ventricular dysfunction may explain some false positive cases of PPV. More studies with dynamic indexes in different settings are clearly needed in order to improve our 'flight', so we can fly right, as quoted by Cannesson and colleagues. With this regard and until more data are available, we believe that the PPV should be used cautiously if at all in the intraoperative setting of liver transplantation.

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Therapeutic dose of acetaminophen may induce fulminant hepatitis in the presence of risk factors: a report of two cases

Editor—The safety profile of acetaminophen (*N*-acetyl-*para*-aminophenol) makes it one of the most widely prescribed analgesics.[1] Acute liver failure due to therapeutic doses of acetaminophen is controversial.[1 2] Some clinicians encourage regular postoperative administration of acetaminophen 4–5 g day^{-1}.[3] However, liver injury with therapeutic doses cannot be excluded.[4] We report two cases of postoperative acute liver failure attributed to therapeutic doses of acetaminophen.

Case 1: A 43-yr-old female (70 kg, 166 cm, BMI 25) was re-operated on for laparoscopic readjustment of her gastric band. Anaesthesia was induced with propofol followed by desflurane, sufentanil, and rocuronium. The surgery was uncomplicated. She received a dose of ketorolac i.v. (30 mg) and acetaminophen 1 g four times a day. On the third day, after a total intake of acetaminophen 11 g, she presented with acute liver failure associated with multiple organ failure (factor V level 5% of normal, prothrombin time: 71 s, INR 12.9, liver cytolysis: ASAT: 5321 U litre^{-1}, ALAT: 3401 U litre^{-1}) (Table 1). Serum concentration of acetaminophen was 31.8 mg litre^{-1} (17 h after the last dose). She was treated with *N*-acetylcysteine (NAC) and supported by a Molecular Adsorbed Recirculation System (MARS). Two days later, an orthotopic liver transplantation (OLT) was successfully performed under desflurane-based anaesthesia. Histopathology of the liver showed generalized steatosis in the viable hepatocytes and major centrolobular necrosis (zone 3) highly suggestive of a toxic origin. The patient was discharged after 6 weeks at home.

Case 2: A 60-yr-old female (90 kg, 160 cm, BMI 35) with a chronic elevation of γ-glutamyl transpeptidase (γGT) (preoperative value: 217 U litre^{-1}) and seizures controlled with valproic acid and carbamazepine presented in acute liver failure 2 days after a re-intervention for a post-lumbar laminectomy dural leak. Anaesthesia, at that time, was induced with propofol followed by sevoflurane, sufentanil, and rocuronium. Analgesia included diclofenac and morphine (48 h). Acetaminophen 1 g four times daily had been given for 10 days before the intensive care unit (ICU) admission. The acute liver failure was associated with a severe coagulopathy and encephalopathy (prothrombin time: 41 s, INR: 2.0, cephalin activated time: 48.5 s, severe thrombocytopenia: 9000 plat μl^{-1}, liver cytolysis: ASAT: 9301 U litre^{-1}, ALAT: 5011 U litre^{-1}, renal insufficiency: serum creatinine 2.7 mg dl^{-1}) (Table 1). Serum concentration of acetaminophen was 10 mg litre^{-1} (48 h after the last dose). She was treated with NAC. Improvement of all parameters permitted discharge from the ICU after 48 h.

In the two cases, CT scan and abdominal ultrasound showed a highly hypodense and hyperechogenic, homogeneous and enlarged liver, clearly suggestive of chronic liver steatosis. In the two patients, serological investigations did not show evidence of viral hepatitis (A, B, or C).

Acetaminophen toxicity proposed in these cases because of well-known risk factors (antiepileptic drugs and liver steatosis), highly suggestive histopathology,

Table 1 Pre- and postoperative laboratory values in two cases of fulminant hepatitis due to acetaminophen. Day 1, day of admission to the ICU. For case 1, MARS started on D2 and OLT performed on D3

	Preop.	D1	D2	D3	D4	D5	D6	D7	D14
Case 1									
ALAT (U litre^{-1})	8	3401	3110	3280	1451	829	513	345	120
ASAT (U litre^{-1})	20	5321	4190	2532	916	261	124	81	61
INR (s)	1.1	12.9	3.14	2.85	2.37	1.09	0.97	0.89	1.11
LDH (U litre^{-1})	494	5481	3770	1090	1018	230	219	194	189
Bilirubin (mg dl^{-1})	0.5	4.5	5.7	7.5	3.9	1.7	1.9	1.4	1.4
γGT (U litre^{-1})	10	24	34	45	22	19	76	150	110
Case 2									
ALAT (U litre^{-1})	27	5011	2535	918	502	—	—	—	51
ASAT (U litre^{-1})	19	9301	5540	1816	493	—	—	—	30
INR (s)	1.0	2.0	1.33	1.23	1.17	—	—	—	1.1
LDH (U litre^{-1})	361	9376	4000	606	351	—	—	—	493
Bilirubin (mg dl^{-1})	0.5	0.9	1.5	2.4	1.9	—	—	—	0.9
γGT (U litre^{-1})	217	712	571	568	551	—	—	—	362