Evaluation of the pulse pressure variation index as a predictor of fluid responsiveness during orthotopic liver transplantation

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Background. The pulse pressure variation (PPV) index has been shown to be a reliable predictor of fluid responsiveness (FR) in a variety of clinical settings. However, it has not been formally evaluated in the setting of orthotopic liver transplantation (OLT).

Methods. Fifteen (n=15) patients undergoing OLT were enrolled in this study. All patients were monitored with a modified pulmonary artery catheter which measured the cardiac output on a semi-continuous basis. A fluid challenge (FC) with 350 ml of colloid was attempted during the following stages of surgery: hepatectomy (TH), anhepatic phase (TA), early post-reperfusion (TE)—during the first 30 min, late post-reperfusion (TL)—after hepatic artery anastomosis, and at the beginning of abdominal closure (TC). PPV and stroke volume index (SVI) were recorded at baseline and 5 min after the FC. Each individual FC which raised the SVI more than 10% from baseline was classified as responsive (R); otherwise, it was considered non-responsive (NR).

Results. Forty-one FCs were performed, with 14 (34%) classified as responsive and 27 (66%) as non-responsive. The baseline PPV did not differ significantly between the R and NR groups, showing considerable overlap of its values throughout the procedure [R vs NR; TH: 20% (inter-quartile range 7–32) vs 7% (5–14); TA: 10% (7–14) vs 19% (12–21), and TE+TL: 7% (5–11) vs 9% (7–16)].

Conclusions. Under the conditions of this study, the PPV index was not shown to be a reliable predictor of FR during OLT. Further studies are warranted to elucidate the role of this and other dynamic indexes in this specific setting.

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The major goal of fluid therapy is to optimize tissue perfusion, which is usually achieved by an increase in cardiac output (CO). Whether the latter will occur after a fluid challenge (FC) depends mostly on the position of an individual patient on the cardiac function (Starling) curve. The latter is a plot of preload against stroke volume and has a characteristic concave shape, with the initial part being relatively steep and becoming progressively flat until a plateau is reached. Hence, if a patient lies on the steep side of this curve, stroke volume should increase after preload augmentation. However, the plateau is reached, further increase in preload does not lead to significant increase in stroke volume. Thus, fluid loading in this setting may be hazardous.

Besides preload, the effects of afterload and myocardial contractility also contribute to the shape of Starling curves and are often less well appreciated. Accordingly, ventricles with decreased contractility have a downward shift of their Starling curves, showing less than expected increase in stroke volume after a FC. Likewise, the same pattern follows when afterload is increased. Therefore, these factors should also be considered whenever an individual Starling curve is to be interpreted.

In this light, the concept of fluid responsiveness (FR) has been increasingly used in order to optimize the fluid management of critically ill patients. According to this concept, the patient whose stroke volume increases significantly after a fluid bolus is termed ‘responder’ and the one
who does not ‘non-responder’. Thus, if one could discriminate between the groups, inappropriate fluid loading could be avoided.

Over the past two decades, many studies have been performed searching for the best index to predict FR in a variety of clinical situations. In particular, the so-called dynamic indexes [pulse pressure variation (PPV), stroke volume variation (SVV), systolic pressure variation (SPV), and others] have been shown to be clearly superior to the more commonly measured static preload variables [pulmonary artery occlusion pressure (PAOP) and central venous pressure (CVP)]. However, it should be noted that most of these studies have been performed in either septic or cardiac surgical patients, usually in the postoperative, intensive care unit (ICU) setting. More studies are still warranted to validate the reliability of the dynamic indexes in predicting FR in other settings, especially in the intra-operative period.

The fluid management of cirrhotic patients undergoing orthotopic liver transplantation (OLT) may be challenging and still remains controversial. Some centres have advocated fluid restriction whereas others adopt a more liberal strategy. Whichever the approach, it would be desirable to predict FR in these patients, as they may poorly tolerate fluid overload. The usefulness of the dynamic indexes in the setting of orthotopic liver transplantation has not been formally investigated. The aim of this study was to evaluate whether the dynamic index PPV can reliably predict FR during OLT.

Methods
After Institutional Ethical Committee approval and obtaining informed consent, 15 (n=15) consecutive patients undergoing OLT were enrolled in this study. Patients with arrhythmias, valvular heart disease, pulmonary hypertension, chronic obstructive pulmonary disease, or receiving a continuous infusion of vasopressors were excluded. Induction of anaesthesia was with propofol (1.5 mg kg⁻¹) and succinylcholine (1.5 mg kg⁻¹) to facilitate tracheal intubation. Maintenance was with propofol (50–150 µg kg⁻¹ min⁻¹), remifentanil (0.1–0.5 µg kg⁻¹ min⁻¹), and atracurium (4–12 µg kg⁻¹ min⁻¹) infusions. The bispectral index was continuously monitored (BIS; Aspect XP v4.0) and the aim was to keep BIS levels between 40 and 60 throughout surgery. Neuromuscular transmission was monitored using the train-of-four (TOF) ratio and the maintenance dose of atracurium was titrated in order to keep the TOF ratio <2. Rotational thromboelastometry (ROTEM®; Pentapharm, Germany) was routinely used to monitor coagulation status.

Invasive haemodynamic monitoring was initiated after the induction of anaesthesia. An arterial line was inserted in the left radial artery (20 G catheter), and central venous lines were inserted in the right internal jugular vein and consisted of a double-lumen catheter 8 Fr (Arrows Inc., Pennsylvania, PA, USA) and a pulmonary artery catheter (774HF75 CEDV/SvO₂/CCO, Edwards Lifesciences, Irvine, CA, USA), inserted through an 8.5 Fr percutaneous introducer (Edwards Lifesciences). Cardiac index (CI) and stroke volume index (SVI) were continuously displayed on the Vigilance™ (Baxter-Edwards) monitor. All monitoring transducers were positioned and zeroed at the mid-axillary level. The ventilator settings were standardized with volume-controlled ventilation with a tidal volume of 8–10 ml kg⁻¹ and zero end-expiratory pressure. The ventilatory frequency was adjusted to maintain the end-tidal CO₂ levels within 4–5.3 kPa. A background Ringer’s lactate infusion rate of 4 ml kg⁻¹ h⁻¹ was maintained throughout the surgery in all patients.

Antifibrinolytics were not used in any patient. Criteria for red blood cell transfusion were a haemoglobin concentration of <8 mg dL⁻¹ and an increased oxygen extraction ratio indicated by the mixed venous oxygen saturation (SwO₂). Fresh-frozen plasma, cryoprecipitate, and platelets were transfused only when clinically significant non-surgical bleeding developed, and the results obtained by ROTEM® analysis were then used to guide therapy.

Our surgical team did not use venovenous bypass, and the recipient vena cava was partially clamped in order to perform the venous anastomosis (piggy-back technique).

Intervention protocol
A FC was attempted in each patient at the following stages: hepatectomy (TH), anhepatic phase (TA), early post-reperfusion [(TE)—within 30 min of graft reperfusion], late post-reperfusion [(TL)—after hepatic artery anastomosis], and at the beginning of abdominal closure (TC). The FC was standardized and consisted of 350 ml of colloid [hydroxyethylamid 6% (HAES); Voluven®, Fresenius–Kabi] administered over 10 min through the central venous line. The initiation of the FC was at the discretion of the physician attending the case, based on clinical signs of systemic hypoperfusion, that is, oliguria (urinary output <0.25 ml kg⁻¹ h⁻¹) or any decrease by more than 20% from baseline of the mean arterial pressure (MAP) or CI. Contraindications to the FC were: severe coagulopathy (as judged by clinical evaluation or ROTEM® analysis), history of allergy to Voluven®, or PAOP >18 mm Hg. Data were excluded if any of the following occurred during the interventional protocol: adjustments to anaesthetic drug dosage, any change in patient positioning, and haemodynamic instability because of surgical manoeuvres or major bleeding.

Acquisition of haemodynamic data
Besides PPV, the other haemodynamic data collected were: heart rate (HR), MAP, CVP, PAOP, SVI, and CI. The latter was collected from the STAT mode screen of the Vigilance monitor, which displayed it every 30–60 s.
The SVI was also displayed on the monitor and was calculated dividing the CI by the HR. All data were recorded before each FC (baseline) and 5 min after the FC.

The measurement of the PPV was made using the cursor of the pulmonary wedge pressure measurement menu (from the Datex-Ohmeda AS/5 monitor). The details of this technique are described elsewhere. Briefly, the systemic arterial curve was labelled as pulmonary artery pressure (PAP) and the scale adjusted appropriately. Next, the menu for PAOP measurement was assessed. This menu shows the airway pressure curve above the PAP curve. There is an option to freeze the monitor and manually adjust the ‘PAOP’ value with a line of reference. As we were observing the systemic arterial pressure curve instead of PAP, the line of reference could be moved up and down across the monitor in order to quantify the upper (systolic pressure) and bottommost (diastolic pressure) values of any single curve. Pulse pressure (PP) was defined as the difference between systolic and diastolic pressure within a single curve. PPV was then calculated using the following formula: 

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

where $PP_{\text{max}}$ and $PP_{\text{min}}$ were the maximal and minimal PP within one respiratory cycle.

All data acquisition was performed by the same investigator (G.G.). FCs were divided into two groups, responder and non-responder. Patients were considered to be responsive, if the FC led to an increase in SVI ≥10% from baseline. Conversely, if the SVI decreased or increased <10%, the patient was considered to be a non-responder to the FC.

Statistical analysis
According to the Kolmogorov–Smirnov test, the haemodynamic data were not normally distributed and were expressed as median (inter-quartile range), unless otherwise stated. The Kruskal–Wallis test (followed by the post-hoc Dunn’s multiple comparison test) was used to compare the baseline PPV of both groups throughout the procedure. Since we had some missing values (see below in the discussion), this test was repeated after a full data set had been completed. The latter was accomplished by using a statistical tool that replaced the missing values with the expectation-maximization (EM) method. The Mann–Whitney U-test was used for comparison between the groups in each individual phase. The changes in haemodynamic data in responders and non-responders after the FC were expressed as per cent changes from baseline and were compared by the Mann–Whitney U-test. $P<0.05$ was considered significant. All tests were performed using the GraphPad Prism® v5.0 (GraphPad Software Inc.) and SPSS v8.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results
Patient characteristics are outlined in Table 1. A total of 41 FCs were performed in 15 patients. The FC was successfully completed in all patients (100%) during the hepatectomy stage. Conversely, in the anhepatic and post-reperfusion (both early and late) phases, the protocol was completed in only 12 (80%) and seven (46%) patients, respectively. Only two FCs were performed in the TC stage and were subsequently excluded for analysis. The main reason we failed to complete the interventional protocol in these phases was three-fold: haemodynamic instability during the FC, increased PAOP that precluded a FC in our study, and changes in patient positioning.

The responder group ($n=14$; 34%) was smaller than the non-responder group ($n=27$; 66%). The baseline PPV was not significantly different between the groups throughout all phases studied ($P=0.33$), even when the missing PPV values were replaced by the EM method ($P=0.07$). Indeed, there was considerable overlapping of these values during all OLT phases (Fig. 1).

Also, as is shown in Table 2, no significant differences were found between the baseline PPV values of both groups when each phase was analysed separately [the TE and TL phases were analysed together (TR: post-reperfusion) because of their small sample size].

![Fig 1](https://academic.oup.com/bja/article-abstract/103/2/238/369443)

**Fig 1** There was considerable overlap of the baseline PPV index between the groups during all phases studied. TH, hepatectomy; TA, anhepatic phase; TE, early post-reperfusion; TL, late post-reperfusion.
stroke volume but also on aortic compliance. The latter setting? then did this dynamic index fail to predict FR in this note, only two out of the 14 FCs (14%) that were classi-

The haemodynamic variables followed a predictable pattern after the FC (Table 3), with trends for a greater percentage change from baseline in the responder group. The only exception was for the filling pressures (PAOP and CVP), which showed a greater increase in the NR group during the hepatectomy phase.

Discussion

In this study, we showed that the dynamic index PPV failed to predict FR in cirrhotic patients during OLT. This finding is in contrast to other studies which have found an area under the receiver operating characteristic curve for PPV usually >0.90. In fact, clear threshold values with positive predictive values around 90% have been described for this index, the most cited being 13%. Of note, only two out of the 14 FCs (14%) that were classified as responsive in our study had a PPV >13%. Why then did this dynamic index fail to predict FR in this setting?

It has been shown that the PP depends not only on stroke volume but also on aortic compliance. The latter might be altered in cirrhotic patients since they usually have low systemic vascular resistance (SVR). Whether this could also have influenced the magnitude of PPV induced by mechanical ventilation in our patients remains speculative. If so, this could have been a factor accounting for the low predictive value of PPV found in our study. Previous studies have shown that vascular tone might theoretically have some influence on the accuracy of dynamic indexes. Although we did not collect SVR data in our patients, it was likely to be decreased in our study population as 94% of our patients were classified as either Child-Pugh B or C. Interestingly, a relatively new device that measures the CO through analysis of the PP has recently been tested during OLT and shown to have a low accuracy when compared with thermodilution, particularly in patients with high-grade Child-Pugh score. The authors hypothesized that the low SVR of cirrhotic patients was likely to be responsible for this finding. On the other hand, the usefulness of PPV in predicting FR has been well confirmed in septic patients who often have low SVR.

Another issue of concern is that the slope of the Starling curve for cirrhotic patients might be potentially depressed because of underlying cirrhotic cardiomyopathy. In fact, the latter may be associated with abnormal left ventricle contractile reserve and ventricles with decreased contractility may respond differently to a FC with less increase in SVI than in normal hearts. Moreover, the overall haemodynamic response to a FC depends not only on the left ventricle but also on the right ventilricular function, and we have recently shown that the latter may be influenced by propofol anaesthesia during OLT. Thus, a blunted CO response to a FC could have

The haemodynamic variables followed a predictable pattern after the fluid challenge [given as percentage (%)] from baseline in both groups during each individual phase. Data are expressed as median (inter-quartile range); †P<0.05 between the groups; PPV, pulse pressure variation; PAOP, pulmonary artery occlusion pressure; CVP, central venous pressure; MAP, mean systemic arterial pressure; SVI, stroke volume index; HR, heart rate

### Table 2
Comparison of baseline haemodynamic data between the groups at each individual phase. Data are expressed as median (interquartile range); †P<0.05 between the groups; PPV, pulse pressure variation; PAOP, pulmonary artery occlusion pressure; CVP, central venous pressure; MAP, mean systemic arterial pressure; SVI, stroke volume index; HR, heart rate

<table>
<thead>
<tr>
<th></th>
<th>Responder (n=4)</th>
<th>Non-responder (n=11)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>PPV (%)</td>
<td>20 (7–32)</td>
<td>7 (5–14)</td>
<td>0.18</td>
</tr>
<tr>
<td>PAOP (mm Hg)</td>
<td>13 (11–15)</td>
<td>7 (5–9)</td>
<td>0.03</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>6 (5–9)</td>
<td>5 (3–6)</td>
<td>0.18</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>68 (58–84)</td>
<td>88 (69–94)</td>
<td>0.75</td>
</tr>
<tr>
<td>SVI (ml m(^{-2}))</td>
<td>32 (25–51)</td>
<td>50 (40–57)</td>
<td>0.18</td>
</tr>
<tr>
<td>HR (beats min(^{-1}))</td>
<td>85 (78–88)</td>
<td>86 (77–98)</td>
<td>0.67</td>
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</tbody>
</table>

### Table 3
Changes in the variables after the fluid challenge [given as percentage (Δ%) from baseline] in both groups during each individual phase. Data are expressed as median (inter-quartile range); †P<0.05 between the groups; PPV, pulse pressure variation; PAOP, pulmonary artery occlusion pressure; CVP, central venous pressure; MAP, mean systemic arterial pressure; SVI, stroke volume index; HR, heart rate

<table>
<thead>
<tr>
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<th>Responder (n=4)</th>
<th>Non-responder (n=11)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPV (%)</td>
<td>-50 (-16–77)</td>
<td>7 (-55/25)</td>
<td>0.30</td>
</tr>
<tr>
<td>PAOP (mm Hg)</td>
<td>14 (4–30)</td>
<td>50 (14–100)</td>
<td>0.14</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>16 (8–18)</td>
<td>60 (0–95)</td>
<td>0.45</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>25 (21–34)</td>
<td>9 (3–27)</td>
<td>0.13</td>
</tr>
<tr>
<td>SVI (ml m(^{-2}))</td>
<td>13 (10–22)</td>
<td>0 (2–22)</td>
<td>0.001</td>
</tr>
<tr>
<td>HR (beats min(^{-1}))</td>
<td>-2 (6/0.5)</td>
<td>0 (-5/6)</td>
<td>0.28</td>
</tr>
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Pulse pressure variation and liver transplantation
occurred in many of our patients and this could explain, at least in part, the low prevalence of responses to FCs in our study. We could not identify cirrhotic cardiomyopathy in any of our patients, as we have not followed any strictly diagnostic criteria for this disease. However, recent studies have shown that the diagnosis of cirrhotic cardiomyopathy is usually underestimated and its prevalence may be higher than previously known. Nevertheless, one study, albeit in another setting, validated a dynamic index to predict FR in patients with a decreased left ventricular ejection fraction. However, the PPV was not evaluated in this study.

The baseline PPV in the responsive FCs was higher than the unresponsive FCs only during the hepatectomy (TH) phase, whereas the opposite occurred in the anhepatic (TA) and post-reperfusion phases (TE+TL). It is not clear from our study why this unexpected pattern (PPV higher in the NR group) occurred in these two phases. The anhepatic and post-reperfusion phases are marked by major alterations in preload and afterload conditions. In addition, decreased ventricular contractility may also occur. It is likely that these factors, alone or in combination, may have contributed to this finding. However, this remains to be proven.

The filling pressures slightly increased after the FCs in both the groups. However, it should be noted that the baseline CVP and PAOP were slightly higher in responsive FCs. In addition, both CVP and PAOP showed a greater increase in the non-responsive patients group at TH. Although these findings might be considered as unexpected, actually it should not be, as a number of studies have shown so far that these static preload variables are not good predictors of FRs. This should only reinforce the fact that filling pressures may depend not only on preload but also upon many other factors, such as ventricular compliance and contractility, which could have been different between the groups and during each OLT phase.

The CO monitoring in our study was by the semi-continuous thermodilution method, which may have its accuracy decreased when fluids are administered at a high flow rate through a central venous line. This could have influenced our results, as some FCs might have been erroneously classified as non-responsive. However, haemodynamic data were collected 5 min (rather than immediately) after fluid bolus, theoretically minimizing these effects. In addition, the best time to collect CO data after a FC is controversial, ranging from ‘immediately’ to as long as 30 min. Furthermore, the threshold used to classify a FC as responsive also varies among studies. Increases of >5–20% in either CO or stroke volume have been used by investigators. Whether our results would be different if we had collected CO data longer than 5 min after the FC or had used a different threshold to define the responsive group deserves further investigation.

The type and quantity of fluid used to challenge the cardiovascular system also varies among studies. It could be argued that the 350 ml of colloid used in our study would be insufficient to FC in most of our patients. We chose this regimen because of two main reasons: first, cirrhotic patients might potentially have some degree of capillary leakage, and a colloid would theoretically remain inside the intravascular space more readily; secondly, we chose a relatively small infusion volume for each FC because of concerns of colloid-induced coagulopathy, as it has been shown that the volume threshold to induce coagulopathy may be unexpectedly low in cirrhotic patients undergoing OLT.

Another explanation for our results would be the setting where this study was performed. Accordingly, acute changes in sympathetic tone and preload status might be particularly frequent during major abdominal surgery. Moreover, as aforementioned, cardiac contractility and loading conditions may also change dynamically during OLT. All these events could potentially shift the patient to a new point on the Starling curve, which could theoretically add some caveats to the assessment of FR in the intraoperative setting. This clearly contrasts with the more controlled environment of the ICU setting, wherein the majority of studies of FR have been conducted. Nonetheless, in our study, data were excluded whenever haemodynamic instability occurred during a FC, theoretically minimizing these effects.

We classified each individual FC as responsive or not, rather than classifying each individual patient. This was made because our intention was to FC each patient during various stages of the procedure, as the cardiovascular status may change dynamically during OLT. Therefore, each patient could likely have a different response to the same standardized FC given in different stages of the procedure. This is in contrast to many studies concerning FR in the intraoperative setting, wherein the FC is usually given once, usually at the beginning of the procedure.

Lastly, most investigators use an off-line, computer-based measurement of the PPV index, instead of the bedside manual method used in our study. We chose to use the latter because it can be done quickly, often within 1 min, which may be particularly advantageous in the intraoperative setting. In addition, it is our belief that this technique closely approximates the ‘real-life’ clinical situation. Indeed, some authors have advocated the use of this technique preferentially in the intraoperative setting. This bedside manual method has recently been validated in a study which showed good correlation with the more conventional computer-based method.

In summary, we have shown that under the conditions of this study, the PPV failed to predict FR in cirrhotic patients undergoing OLT. The reasons why this dynamic index was unreliable in this setting remain unclear. As discussed above, several factors could have well played a role, including the characteristic low SVR of cirrhotic patients, underlying cirrhotic cardiomyopathy, the method used for CO monitoring, and intraoperative setting.
Whether other dynamic indexes would yield similar results remain to be seen. Further studies are warranted to elucidate the value of PPV and other dynamic indexes in predicting FR in this specific setting.

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