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Assessing fluid responsiveness with the passive leg raising maneuver in patients with increased intra-abdominal pressure: Be aware that not all blood returns!*

In his issue of *Critical Care Medicine*, Mahjoub et al (1) found that the passive leg-raising (PLR) maneuver could not accurately predict fluid responsiveness in patients with intra-abdominal hypertension (IAH). Recently a series of animal studies have looked at stroke volume variation and pulse pressure variation (PPV) during IAH (2). The authors of the present study have to be congratulated for collecting the first prospective data in 41 mechanically ventilated patients with a PPV value >12%. In all these patients, a PLR maneuver was done and after return to baseline, 500 mL of saline was administered. Surprisingly, 10 of 41 patients (24.4%) did not respond to fluid loading and were not further analyzed. The 31 remaining patients were divided into two groups according to their response on PLR; 15 (48%) were nonresponders (and were considered as false-negatives, PLR−). In these patients, the median intra-abdominal pressure (IAP) was significantly higher (20 vs. 11.5 mm Hg in the PLR+ group) and an IAP ≥16 mm Hg was the only good predictor for non responding to PLR.

Previous studies showed that static "barometric" preload indicators like central venous pressure or pulmonary artery occlusion pressure do not allow to discriminate responders from nonresponders. Static "volumetric" parameters like right or global end-diastolic volume index or left ventricular area index obtained by cardiac ultrasound seem to perform better, but still they are far from perfect (3). Functional

*See also p. 1824.

Key Words: abdominal pressure; abdominal compartment; preload; fluid responsiveness; functional hemodynamics; stroke volume variation; pulse pressure variation

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hemodynamic parameters like stroke volume variation or PPV have gained interest as better predictors for fluid responsiveness, but they also have their limitations; the patient must be in regular sinus rhythm and under controlled mechanical ventilation with not too small tidal volumes (4). To overcome these disadvantages, other dynamic tests using heart–lung interactions have been studied like the respiratory systolic variation test (5), the tele-expiratory occlusion test (6), the correction of global end-diastolic volume index for global ejection fraction (7), the mean systemic filling pressure during the inspiratory hold maneuver (8), or even other less invasive techniques like the plethysmographic variability index (9). Also, the classic PLR maneuver as well as the use of the Trendelenburg position experienced a renaissance in this regard; both manipulations led to an endogenous and easily reversible autotransfusion from the lower parts of the body and so result in an endogenous volume loading maneuver. However, the disadvantage is that the extent of endogenous volume loading by the different maneuvers in the individual patient is not known (10, 11). All these techniques try to help the clinician in making the correct diagnosis, guiding early fluid administration but also avoiding futile fluid accumulation (12). During IAH, the classic "barometric" preload indicators are erroneously increased and studies pointed to the superiority of "volumetric" indices (13). Recent animal data also showed that IAH per se increases stroke volume variation and PPV in such a way that our classic thresholds no longer hold true (2).

This study is the first of its kind performed in humans. It shows that approximately 25% of critically ill patients with a PPV >12% are not fluid-responsive, suggesting different thresholds for different conditions. Similar false-positive PPV values have been reported previously and have been related to right ventricular dysfunction (14). It also shows that the PLR test can be false-negative in responders to fluid administration and this is related to increased IAP. Hence, these data suggest that care should be taken when a PLR test is performed, because increased IAP values are not uncommon in intensive care unit patients (25–50%) and can also be related to chronic conditions of IAH like obesity, liver cirrhosis with ascites, peritoneal dialysis, and so on (15, 16). Therefore, an IAP measurement seems needed while interpreting the result of a PLR test.

To play the devil's advocate, one could argue that the questions that the authors tried to answer even raised more issues. Although the study was simple in its concept, it turned out to be quite complex in its execution.

First, the definition of fluid responsiveness that was used both for fluid administration and during PLR (namely an increase of 12% in stroke volume) differs from the more usual 15% threshold that takes into account cumulative errors resulting from the variation in the measurement method.

Second, although the esophageal Doppler technique used in the study allows continuous measurement of aortic blood flow, it remains a user-dependent technique and probe repositioning may be necessary (17).

Third, in the present study, ten of 41 patients with a PPV >12% were excluded because they were nonresponders to fluid administration. This 24.4% is far above what has previously been reported. Maybe these patients had high IAP, intrathoracic pressure, or positive end-expiratory pressure, hence influencing the thresholds for fluid responsiveness. It would have been interesting if the authors had also analyzed in the excluded patients the IAP and positive end-expiratory pressure levels and if they would have tested fluid responsiveness based on a PPV value >15% or 20% in the complete study population.

Fourth, although fluid administration is the best way to assess fluid responsiveness, the biggest disadvantage is the administration of unnecessary volume in case the patient is a nonresponder. The PLR test, however, is difficult to standardize because it does not provide information on the exact amount of endogenous transfusion and there is some debate whether the starting position should be supine or upright (head of bed) or whether the Trendelenburg position should be used. In fact, depending on patient anthropomorphism, the amount of fluid loading with a PLR may vary in an unknown extent. Figures 1 and 2 try to summarize the effects of different PLR tests in patients with normal and increased IAP. During IAH, one can expect an increase in baseline PPV, especially in the 45° head of bed position. Performing a PLR maneuver from head of bed (with the least risk for ventilator-associated pneumonia) will further increase IAP and will only result in a marginal venous return from the legs but not from the mesenteric veins (Fig. 2*A*). Performing a PLR maneuver from supine will have a neutral effect on IAP and result in a better venous return from the legs but not from the mesenteric veins (Fig. 2*B*), whereas the Trendelenburg position will have a beneficial effect on IAP (18) but will negatively influence intracranial pressure (Fig. 2*C*).

Fifth, the preload status in the patients was not very well defined, and

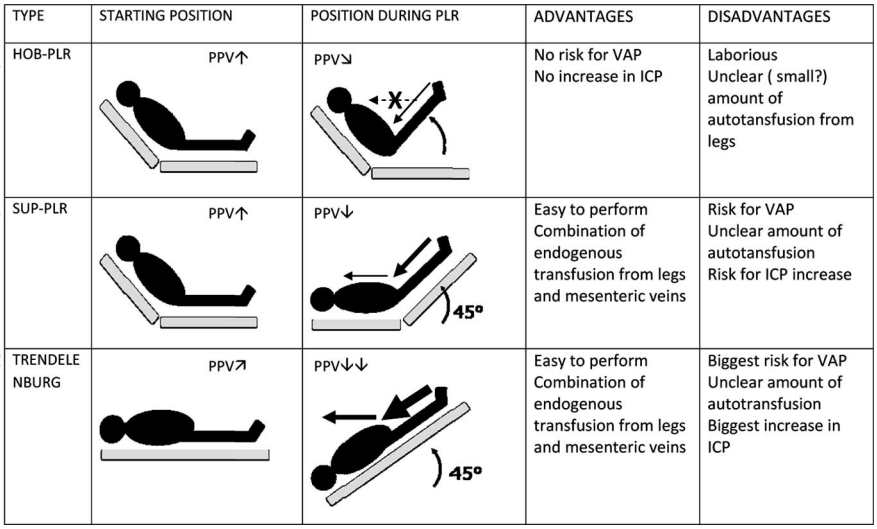

Figure 1. Schematic overview comparing the possible effects and (dis)advantages of different (*PLR*) tests during normal intra-abdominal pressure (*IAP*). The PLR can be performed from head of bed (*HOB*) (*A*) or supine (*SUP*) (*B*) position or putting the patient in the Trendelenburg position (*C*). Endogenous fluid resuscitation comes from venous return from the legs (*oblique arrow*) and the mesenteric veins (*horizontal arrow*). The amount of endogenous fluid resuscitation is indicated by the thickness of the arrow (*dotted line* is smallest, whereas the 3-mm line is the largest amount). A *dotted line* marked with a "X" indicates the absence of endogenous transfusion. *ICP*, intracranial pressure; *PPV*, pulse pressure variation; *VAP*, ventilator-associated pneumonia; ↑ increase; ↑ ↑, big increase; ↗, small increase; ↙, small decrease; ↓, decrease; ↓ ↓, big decrease.

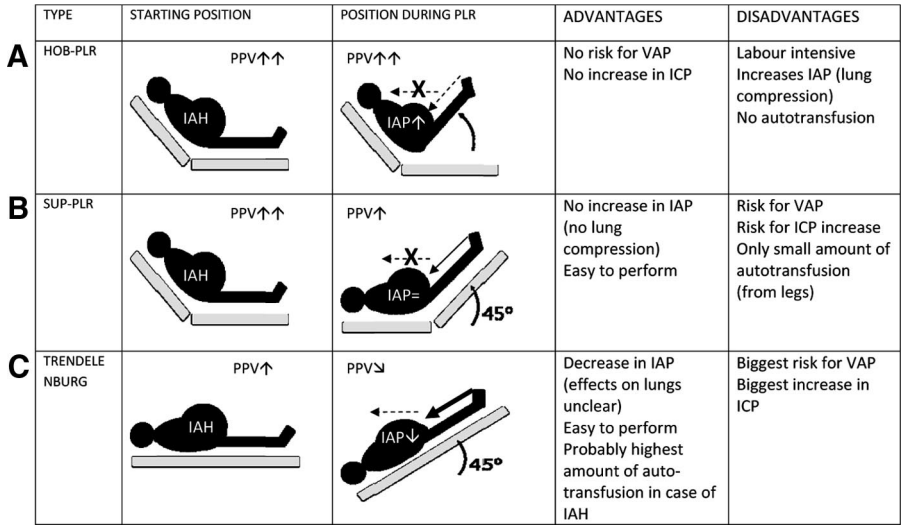

Figure 2. Schematic overview comparing the possible effects and (dis)advantages of different passive leg-raising (*PLR*) tests during increased intra-abdominal pressure (*IAP*). See text for explanation. The PLR can be performed from head of bed (*HOB*) (*A*) or supine (*SUP*) (*B*) position or putting the patient in the Trendelenburg position (*C*). Endogenous fluid resuscitation comes from venous return from the legs (*oblique arrow*) and the mesenteric veins (*horizontal arrow*). The amount endogenous fluid resuscitation is indicated by the thickness of the arrow (*dotted* line is smallest, whereas the 3-mm line is the largest amount). A *dotted line* marked with a "X" indicates the absence of endogenous transfusion. *IAH*, intra-abdominal hypertension; *ICP*, intracranial pressure; *PPV*, pulse pressure variation; *VAP*, ventilator-associated pneumonia; ↑, increase; ↑↑, big increase; ↗, small increase; ↘, small decrease; ↓, decrease; ↓↓, big decrease.

maybe some patients were better filled than others, exhibiting on the flatter part of the Frank Starling curve.

Sixth, although IAP was only measured in the supine position at baseline and the increases in stroke volume by PLR were assessed when IAP was not measured, the authors cannot exclude other effects related to increased IAP during semirecumbent and PLR positions. In fact, a recent multicenter study showed that the head of bed position significantly increased IAP (19, 20).

The data presented in this issue of the Journal raises a lot of questions. However, having said that and having played the devil's advocate, we rest our case; this study is very important and the authors have to be congratulated. Future studies should better identify the preload status of the patients and measure stroke volume with a monitoring technique, which is less observer-dependent and true continuous (for example, pulse contour analysis). Furthermore, the prognostic value of PLR, but also that of tele-expiratory occlusion test, respiratory systolic variation test, or global ejection fraction-corrected global end-diastolic volume index and their change in the presence of long-term elevation of IAH (24–48 hrs) at clinically relevant IAP levels (15–20 mm Hg) should be assessed and brought in relation to body anthropomorphic data (21). Future studies should try to integrate these results with global indices of perfusion (lactate, base deficit, strong ion difference) and the presence of clinical overt shock in critically ill patients.

The results of the present study confirm the importance of IAH and abdominal compartment syndrome and nicely address the difficulty to assess the hemodynamic status, preload, and fluid responsiveness in patients with IAH. Intensivists need to be aware that a patient with septic shock is very different, from a hemodynamic point of view, from a patient with septic shock and IAH.

The World Society of the Abdominal Compartment Syndrome (http://www.wsacs.org) invites interested researchers to join the society, to adhere to the consensus definitions posted at the web site, and to submit some prospective data for the next world congress to be held in Orlando, FL, August 10–13, 2011.

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The Hering-Breuer reflex, feedback control, and mechanical ventilation: The promise of neurally adjusted ventilatory assist*

In 1868, Ewald Hering reported on work done in his laboratory by Joseph Breuer. Breuer found that when inspiration was impeded by occluding the airway at the end of expiration in anesthetized animals, the duration of inspiration was dramatically lengthened, and when the airway was occluded at the end of inspiration, the subsequent expiration was prolonged. Furthermore, when inflation was augmented by insufflating air, inspiration was shortened and the respiratory effort diminished. Hering (1) and Breuer (2) attributed these effects to a central reflex that depended on volume-related information from the lung carried centrally by the vagus. Thus began the study of central control of ventilation. More importantly, the Hering-Breuer reflex was the first description of feedback control in biology (3), and Hering and Breuer recognized the pivotal importance of this concept. It is virtually impossible at the present time to discuss any physiologic system without invoking the idea of feedback.

Subsequently, there has been considerable debate whether the Hering-Breuer reflex exists or is active in awake humans (4, 5). Although complicated protocols can reveal a very small effect of lung volume-dependent feedback on respiratory timing in awake humans (6), there is no compelling evidence that the Hering-Breuer reflex regulates respiratory timing breath by breath in awake humans. But there is another aspect of the Hering-Breuer reflex that has received less attention. Volume-related feedback suppresses the activation of respiratory muscles. If inspiration proceeds smoothly, activation of the phrenic nerve is inhibited by the increasing lung volume, but should the airway be occluded, there is a dramatic increase in respiratory muscle activation, mediated in part by the vagus (7, 8). The Hering-Breuer reflex probably evolved not because of the marginal benefits of infinitesimal changes in respiratory timing in awake subjects but as a defense mechanism to prevent airway obstruction. When the airway is occluded, the absence of lung volume-dependent feedback, as occurs during airway obstruction, effectively enhances respiratory muscle activity, thereby promoting relief of the airway obstruction.

Despite the importance of negative feedback in physiologic control systems, negative feedback has been notable by its absence in the control of mechanical ventilation. Until recently, physicians adjusted the ventilator to minimize the risk of barotrauma, maintain a satisfactory $Paco_2$, and maintain adequate oxygenation by adjusting the fractional inspired oxygen level and the level of positive end-expiratory pressure—the patient, to whom we may imagine ventilation mattered most, was never consulted. That is changing. Proportional assist ventilation augments each respiratory effort in proportion to the inspiratory flow rate, lung volume, and mechanical characteristics of the respiratory system (9). The patient now "chooses" the depth and frequency of ventilation, and we (physicians) can infer what each patient "wants" from the calculated muscle force that the patient generates.

More recently, neurally adjusted ventilatory assist (NAVA) has been developed (10). This method of mechanical ventilation uses the diaphragm electromyogram (EMG) as a source of feedback to control the ventilator. The diaphragm EMG is recorded from a multiarray esophageal electrode that we developed to address an esoteric issue related to the effect of lung volume changes on the diaphragm EMG (11). Alex Grassino and Christer Sinderby (personal communication, 2010), who were cleverer than we, realized that the diaphragm EMG could be used to control the timing and depth of mechanical ventilation because the diaphragm EMG was reliably recorded by the entire multiarray electrode, even though diaphragmatic EMG activity recorded from any single pair of electrodes changed as the diaphragm moved during each breath. In the current issue of *Critical Care Medicine*, Terzi et al (12) compared the physiologic response to NAVA or pressure support ventilation in patients with acute respiratory distress syndrome. The benefit of returning control of ventilation to the patient is apparent in their results: patient-ventilatory synchrony was improved on NAVA without compromising minute ventilation or gas exchange. Furthermore, the action of the Hering-Breuer reflex was readily apparent. As the level of assist (the amplification factor applied to the diaphragmatic EMG signal) was increased and, therefore, the volume

***See also p. 1830.**

Key Words: Hering-Breuer reflex; inspiration; ventilation; feedback

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