Functional hemodynamic monitoring and dynamic indices of fluid responsiveness

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ABSTRACT

Knowing whether or not a fluid infusion can improve cardiac output (fluid responsiveness) is crucial when treating hemodynamically unstable patients. Generally, cardiac filling pressures (central venous pressure, pulmonary artery occlusion [“wedge”] pressure) and volumes (end-diastolic left and right ventricular volume) are used, although they are not reliable predictors of fluid responsiveness. For this reason, new indices, the so-called dynamic indices of fluid responsiveness, have been recently introduced in clinical use. If stroke volume, or stroke volume-derived parameters (pulse pressure and aortic flow) show wide variation during mechanical ventilation, a good response to fluid therapy can be predicted. As these indices are based upon the effects of controlled mechanical ventilation on stroke volume, they can be used in deeply sedated or apneic patients whose cardiac rhythm is regular. To overcome these limitations, new dynamic indices have been introduced. Among them, variation of cardiac output induced by passive leg raising (PLR) has raised particular interest since it can identify fluid responders even among spontaneously breathing and non-sinus rhythm patients. Although promising, the dynamic indices of fluid responsiveness have been studied only retrospectively in a relatively small number of patients and evidence that clinical use of these indices can improve outcome is still limited. Further investigations are needed to confirm their clinical validity.

Key words: Hypovolemia - Shock - Hemodynamics - Stroke volume.
curve to increase cardiac output in response to preload expansion.

To overcome the limitations of these “static” indices, “dynamic” circulatory indices have been recently introduced and validated. These indices are based on the response of circulatory system to a controlled preload variation, a sort of reversible fluid challenge in which preload variation is not induced by an external fluid infusion but by specific maneuvers redistributing blood volume (e.g., mechanical ventilation or leg raising).

The present review uses the most current evidence to focus on the major dynamic indices of fluid responsiveness to evaluate advantages and limitations.

### Materials and methods

We performed a MEDLINE search from 1990 with the keywords “fluid responsiveness”, “fluid challenge”, “preload”, “preload responsiveness”, “preload assessment”, “heart-lung interactions” and “functional hemodynamic monitoring”. We also considered papers cited in the references of the initially identified articles and the “Consensus Conference on Hemodynamic Monitoring” held in Paris on April 27-28th 2006, organized by the following societies: European Society of Intensive Care Medicine (ESICM), American Thoracic Society (ATS), European Respiratory Society (ERS), Society of Critical Care Medicine (SCCM) and Société de Réanimation de Langue Française (SRLF). Forty-eight papers were considered, including human and animal experimental studies and review articles, all of which were published in the English language.

### Classification of dynamic indices

Dynamic indices evaluate the response of the cardio-circulatory system to a controlled and reversible preload variation, and can be divided into three groups according to the methodology used to obtain such preload variation (Table II).

The first group consists of those indices based on cyclic variations in stroke volume or stroke volume-related hemodynamic parameters (such as pulse pressure or aortic flow), determined by mechanical ventilation-induced cyclic variation in intrathoracic pressure.

The second group consists of those indices based on cyclic variations of non-stroke volume-related hemodynamic parameters (such as the vena cava diameter or ventricular pre-ejection period) determined by mechanical ventilation.

The third group consists of those indices based on preload-redistribution maneuvers, different from standard mechanical ventilation, e.g. passive leg raising.

Table II describes the main dynamic indices with their related references.

### Physiological rationale of dynamic indices

Some concepts about heart-lung interactions during mechanical ventilation are useful in understanding why dynamic indices can predict fluid responsiveness.

**Effects of mechanical ventilation on left and right ventricular stroke volume**

During mechanical inspiration, the right ventricular stroke volume (RVSV) decreases and the
### TABLE II. — Classification of dynamic indices of fluid responsiveness.

<table>
<thead>
<tr>
<th>Index</th>
<th>Description</th>
<th>Calculation</th>
<th>Measurement/instruments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delta down</strong></td>
<td>Difference between apnoeic and tele-expiratory systolic arterial pressure (SAP) (minimal value during mechanical ventilatory cycle)</td>
<td>$SAP_{apnea} - SAP_{exp}$</td>
<td>Invasive arterial pressure monitoring and dedicated monitor</td>
<td>10 (Figure 2)</td>
</tr>
<tr>
<td><strong>Delta up</strong></td>
<td>Difference between tele-inspiratory (maximal value during mechanical ventilatory cycle) and apnoeic systolic arterial pressure (SAP)</td>
<td>$SAP_{insp} - SAP_{apnea}$</td>
<td>Invasive arterial pressure monitoring and dedicated monitor</td>
<td>10 (Figure 2)</td>
</tr>
<tr>
<td><strong>Systolic pressure variation (SPV)</strong></td>
<td>Systolic arterial pressure (SAP) variation during mechanical ventilatory cycle; it is the sum of $\Delta$up + $\Delta$down</td>
<td></td>
<td>Invasive arterial pressure monitoring and dedicated monitor</td>
<td>10 (Figure 2)</td>
</tr>
<tr>
<td><strong>Pulse pressure variation (PPV)</strong></td>
<td>Arterial pulse pressure (PP) variation during mechanical ventilatory cycle</td>
<td>$PP_{max} - PP_{min}$ $\frac{1}{2}(PP_{max} + PP_{min}) \times 100$</td>
<td>Invasive arterial pressure monitoring and dedicated monitor</td>
<td>11 (Figure 3)</td>
</tr>
<tr>
<td><strong>Stroke volume variation (SVV)</strong></td>
<td>Stroke volume variation during mechanical ventilatory cycle</td>
<td>$SV_{max} - SV_{min}$ $\frac{1}{2}(SV_{max} + SV_{min}) \times 100$</td>
<td>PiCCO®, LiDCO®</td>
<td>11</td>
</tr>
<tr>
<td><strong>Peak aortic flow velocity variation (Vpeak)</strong></td>
<td>Peak aortic blood flow velocity (Vpeak) variation during mechanical ventilatory cycle</td>
<td>$V_{peak_{max}} - V_{peak_{min}}$ $\frac{1}{2}(V_{peak_{max}} + V_{peak_{min}}) \times 100$</td>
<td>Transesophageal ecocardiography</td>
<td>12 (Figure 5)</td>
</tr>
<tr>
<td><strong>Peak aortic flow velocity variation (Vpeak) or Aortic blood flow variation (ABF)</strong></td>
<td>Peak aortic blood flow velocity (Vpeak) variation or aortic blood flow variation (ABF) during mechanical ventilatory cycle</td>
<td></td>
<td>Esophageal Doppler</td>
<td>13</td>
</tr>
</tbody>
</table>

**GROUP B: Indices based on mechanical ventilation-induced variations of non-stroke volume-derived parameters.**

<table>
<thead>
<tr>
<th>Index</th>
<th>Description</th>
<th>Calculation</th>
<th>Measurement/instruments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left ventricle pre-ejection period variation (ΔPEP)</strong></td>
<td>Ventilation-induced variation of left ventricle pre-ejection period, or isovolumetric contraction time (interval from ECG R wave to the foot of invasive arterial pressure wave)</td>
<td>$PE_{exp} - PE_{insp}$ $\frac{1}{2}(PE_{exp} + PE_{insp}) \times 100$</td>
<td>Dedicated monitor, ECG and invasive arterial pressure</td>
<td>14, 15</td>
</tr>
<tr>
<td><strong>Plethysmography ΔPEP</strong></td>
<td>ΔPEP calculated as interval from ECG R wave to the foot of plethysmographic wave</td>
<td>$PE_{exp} - PE_{insp}$ $\frac{1}{2}(PE_{exp} + PE_{insp}) \times 100$</td>
<td>Dedicated monitor, ECG and plethysmograph</td>
<td>14</td>
</tr>
<tr>
<td><strong>Superior vena cava collapsibility index (SVC-CI)</strong></td>
<td>Ventilation-induced variation of superior vena cava diameter (it collapses on inspiration)</td>
<td>$\frac{Diam_{max} - Diam_{min}}{Diam_{min}} \times 100$</td>
<td>Transesophageal ecocardiography</td>
<td>16, 17 (Figure 1)</td>
</tr>
<tr>
<td><strong>Inferior vena cava distensibility index (dIVC)</strong></td>
<td>Ventilation-induced variation of inferior vena cava diameter (it dilates on inspiration)</td>
<td>$\frac{Diam_{max} - Diam_{min}}{Diam_{min}} \times 100$</td>
<td>Transthoracic ecocardiography or abdominal echography</td>
<td>18 (Figure 4)</td>
</tr>
</tbody>
</table>
GROUP C: Indices based on preload-redistributing maneuvers different from standard mechanical ventilation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Formula</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspiratory right atrial pressure variations (ARAP)</td>
<td>Spontaneous inspiration-induced right atrial pressure variations</td>
<td>RAP - RAP\textsubscript{insp}</td>
<td>CVP and PAOP curves</td>
</tr>
<tr>
<td>Aortic blood flow variation induced by passive leg raising (PLR-ΔABF)</td>
<td>Difference between aortic blood flow during passive leg raising and baseline aortic blood flow</td>
<td>ABF\textsubscript{PLR} - ABF</td>
<td>Esophageal Doppler</td>
</tr>
<tr>
<td>Respiratory Systolic Variation Test (RSVT)</td>
<td>Lungs are inflated with increasing airway pressures; systolic arterial pressure is measured after every inflation, so inflation-induced systolic pressure variation can be determined</td>
<td></td>
<td>Invasive arterial pressure, airway pressure, dedicated recording system for off-line analysis</td>
</tr>
</tbody>
</table>

left ventricular stroke volume (LVSV) increases, while the opposite phenomenon is observed during expiration. These cyclic variations in SV are physiologically observed in all patients, but are much wider in hypovolemic states, as their amplitude is predictive of fluid responsiveness.

The inspiratory decrease of RVSV can be explained as follows:

a) a reduction of right ventricular preload (right ventricular end-diastolic volume – RVEDV);

b) an increase of right ventricular (RV) afterload.

Guyton’s model\textsuperscript{26} states that the venous return is determined by the gradient between the mean systemic pressure (Pms) and right atrial pressure (RAP) (Pms-RAP). According to this model, the RV preload should decrease during inspiration because an increased intrathoracic pressure is transmitted to the right atrium, increasing RAP and decreasing venous return gradient (Pms-RAP).

An alternative explanation of inspiratory RV preload reduction is the collapse of the superior vena cava (SVC). In mechanically ventilated septic patients, Vieillard Baron\textit{et al.}\textsuperscript{16, 17} observed that the SVC showed a high inspiratory collapsibility in a group of subjects (Figure 1). In these patients, an important inspiratory reduction of RVSV was observed by Doppler, presumably due to the interruption of venous inflow from the SVC. A colloid bolus (7 mL/kg) increased the SVC intravascular pressure, reduced SVC collapsibility index, abolished the respiratory oscillations of RVSV and resulted in a significant increase in cardiac output in this subgroup of patients. Takata\textit{et al.}\textsuperscript{27} hypothesize that a similar phenomenon occurs in the intrathoracic portion of the inferior vena cava (IVC).

Beyond reducing RV preload, the pulmonary inflation increases RV afterload, since small peri-alveolar vessels are compressed and their resistance to blood flow increases when the lungs are inflated. Vieillard-Baron\textit{et al.}\textsuperscript{28} using echocardiography, demonstrated that every mechanical inspiration produces the following effects on RV: a constant end-diastolic area (RVEDA), an increase in the end-systolic area, and a reduction in RVSV and RV fractional area contraction (RVFAC).

These findings suggest that the reduction of RVSV is determined more by an increase in afterload than by a decrease in preload, since the RVEDA remained constant. However, the relative contribution of the two determinants to RVSV variations is still under debate and can be variable in different subjects.

During coronary artery bypass graft surgery, in open-chest patients, cyclic oscillation in RVSV is observed.\textsuperscript{29} In open-chest conditions, the intrathoracic pressure never becomes positive, so it cannot impede venous return. Therefore, respiratory variations in RVSV in these conditions can be explained only by alveolar vessel compression and increases in afterload without any modification of preload.

Mechanical ventilation exerts the opposite effects.
on the left ventricle (LV). Using Doppler echocardiography, Vieillard-Baron et al.25 observed that during inspiration, the LV stroke volume (LVSV) increases, which is responsible for delta up (i.e., the inspiratory increase of systolic arterial pressure) (Figure 2). Inspiratory increase of LVSV can be explained as follows:

a) An increase in LV preload: an increase in left atrial volume and in pulmonary venous flow exists in all patients with a significant delta up. In patients not exhibiting a delta up, left atrial dimensions and pulmonary venous flow were constant. The increase in transpulmonary pressure during mechanical inflation could exert a “squeezing” effect on the pulmonary capillary bed.25

b) A decrease in LV afterload: intrathoracic pressure (ITP) is the pressure surrounding the LV. Therefore, when ITP increases, LV transmural pressure is reduced. LV afterload depends on LV wall stress, which is the product of transmural pressure and LV radius, so any increase in ITP decreases LV afterload. In this respect, mechanical inspiration can be compared to a LV assisting device. This mechanism is particularly important when LV contractility is reduced, while in normal conditions this afterload reduction has less influence. In a recent paper from Vieillard-Baron,25 patients with no cardiac abnormalities were enrolled and no significant inspiratory reduction in LV afterload was recorded by echocardiography in this population. Pinsky et al.31 demonstrated that positive pressure enhances LV performance only when a state of heart failure is pharmacologically induced in an animal experimental study, while in normal-

Table III.—Threshold and predictive value of dynamic indices.

<table>
<thead>
<tr>
<th>Index</th>
<th>Best threshold</th>
<th>AUC</th>
<th>Sensitivity /specificity</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δdown</td>
<td>5 mmHg</td>
<td>0.97</td>
<td>*</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>5 mmHg</td>
<td>0.92</td>
<td>86%/86%</td>
<td>23</td>
</tr>
<tr>
<td>SPV</td>
<td>10 mmHg</td>
<td>0.91</td>
<td>—</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>0.91</td>
<td>—</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>8.5 mmHg</td>
<td>0.92</td>
<td>82%/86%</td>
<td>23</td>
</tr>
<tr>
<td>PPV</td>
<td>13%</td>
<td>0.98</td>
<td>94%/96%</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>12%</td>
<td>0.94</td>
<td>90%/87%</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>9.4%</td>
<td>0.95</td>
<td>86%/89%</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>17%</td>
<td>0.96</td>
<td>85%/100%</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>12%</td>
<td>0.91 **</td>
<td>88%/93%</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>0.40 *</td>
<td>—</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>12%</td>
<td>0.78</td>
<td>70%/92%</td>
<td>22</td>
</tr>
<tr>
<td>SVV</td>
<td>9.5%</td>
<td>0.88</td>
<td>79%/85%</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>11.5%</td>
<td>0.87</td>
<td>81%/82%</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>—</td>
<td>0.52 *</td>
<td>—</td>
<td>45</td>
</tr>
<tr>
<td>ΔVpeak</td>
<td>12%</td>
<td>—</td>
<td>100%/89%</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>13%</td>
<td>0.82</td>
<td>80%/72%</td>
<td>13</td>
</tr>
<tr>
<td>ΔABF</td>
<td>18%</td>
<td>0.93</td>
<td>90%/94%</td>
<td>13</td>
</tr>
<tr>
<td>ΔPEP</td>
<td>4%</td>
<td>0.97</td>
<td>92%/89%</td>
<td>15</td>
</tr>
<tr>
<td>ΔPEP plet</td>
<td>4%</td>
<td>0.94</td>
<td>100%/67%</td>
<td>15</td>
</tr>
<tr>
<td>SVC collapsibility</td>
<td>36%</td>
<td>0.99</td>
<td>90%/100%</td>
<td>17</td>
</tr>
<tr>
<td>DIVC</td>
<td>18%</td>
<td>0.91</td>
<td>90%/90%</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>12%</td>
<td>—</td>
<td>93%/92%</td>
<td>54</td>
</tr>
<tr>
<td>ΔRAP</td>
<td>1 mmHg</td>
<td>—</td>
<td>93%/84%</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>1 mmHg</td>
<td>0.53</td>
<td>—</td>
<td>46</td>
</tr>
<tr>
<td>PLR - ΔABF</td>
<td>10%</td>
<td>0.91 **</td>
<td>—</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>0.96 ***</td>
<td>97%/94%</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>8%</td>
<td>0.95</td>
<td>90%/83%</td>
<td>22</td>
</tr>
<tr>
<td>RSVT slope</td>
<td>-0.24 mmHg/cmH2O</td>
<td>0.90</td>
<td>87%/83%</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>-0.51 mmHg/cmH2O</td>
<td>0.96</td>
<td>93%/89%</td>
<td>24</td>
</tr>
</tbody>
</table>

*Positive predictive value 95% / negative predictive value 93%; *includes patients with spontaneous breathing or with spontaneous inspiratory efforts; ** in a subgroup of patients in sinus rhythm without inspiratory efforts; *** in all enrolled patients. SPV: systolic pressure variation; PPV: pulse pressure variation; SVV: stroke volume variation; ΔVpeak: variation of peak aortic blood flow velocity; ΔABF: variation of aortic blood flow; ΔPEP: variation of pre-ejection period; ΔPEP plet: plethysmographic ΔPEP; SVC: superior vena cava; DIVC: variation of inferior vena cava diameter; ΔRAP: variation of right atrial pressure; PLR-ΔABF: passive leg raising-induced variation of aortic blood flow; RSVT: respiratory systolic variation test.
ly contracting hearts positive pressure decreases myocardial performance.

c) A direct compression of the heart exerted by the lungs: a magnetic resonance imaging study on healthy volunteers under positive end-expiratory pressure (PEEP) has shown that expanded lungs can exert a direct compression on the heart, which in turn, could theoretically enhance LV ejection.

d) Ventricular interdependence: if the RV is dilated, a shift of the interventricular septum can impede LV filling and induce LV diastolic dysfunction. In these conditions, if venous return is reduced and RVEDV decreases during mechanical inspiration, LV diastolic filling is improved and LVSV increases.30, 33 During mechanical expiration, the opposite hemodynamic events occur. RVSV increases because venous return increases and RV afterload decreases. LVSV decreases, which is responsible for delta down or the expiratory reduction in systolic arterial pressure (Figure 2).

LVSV expiratory reduction is the consequence of the inspiratory reduction in RVSV, after pulmonary transit time has elapsed. According to a Vieillard-Baron’s model,25 the pulmonary capillary bed can be seen as a “filling reserve” from which LV takes its preload and which is cyclically recharged by RV. When RVSV decreases, after a few beats (pulmonary transit time), the LVSV also decreases because the filling reserve is empty. In this respect, mechanical ventilation can be seen as an “additional circulatory pump”, which helps to mobilize blood from the pulmonary capillary bed into the left atrium on every insufflation.

Influence of volemic state on heart-lung interaction

Amplitude of respiratory variations in RV and LV stroke volume is strictly related to the ability of the cardio-circulatory system to increase cardiac output in response to fluid infusion (fluid responsiveness). If delta down, systolic pressure variation, pulse pressure variation and stroke volume variation are elevated, they indicate a state of fluid responsiveness.10, 11 This can be explained as follows.
a) In hypovolemic patients, SVC (and probably also IVC) collapses on every mechanical inflation determining huge oscillations in RVSV and consequently in LVSV and arterial pressure. This condition can be abolished by a fluid infusion, thus significantly increasing cardiac output.

b) In the steep part of Frank-Starling’s curve, the ventricle increases its stroke volume if end-diastolic volume increases (preload-dependence), while the stroke volume does not increase in response to volume variations (preload independence) in the flat portion of curve. The steepness of the curve is determined by ventricular contractility. If mechanical ventilation-induced preload variation causes wide oscillations in SV and arterial pressure, this suggests that both ventricles are working on the steep part of the Frank-Starling’s curve and are preload-dependent and will presumably increase stroke volume in response to volume expansion.

Predictive value and limitations of dynamic indices

Predictive value of group A indices

Table III summarizes the results of experimental studies in which the predictive value of dynamic indices is evaluated.

Synthetically, among group A indices (see classification in Table II), delta down (Figure 2) and PPV (Figure 3) have demonstrated the best predictive value, as their Areas Under the ROC Curve (AUC) are 0.97 and 0.98, respectively. SPV has been proven slightly less reliable than delta down and PPV. This difference can be partially explained by Denault et al., who observed that SPV could not reflect just the LVSV variations because it can also be influenced by direct transmission of pleural pressure to the thoracic aorta. SVV directly measures cardiac output variation instead of estimating them through the variations of arterial pressure. Nevertheless, this index has been proven less accurate than others or completely inadequate. The reason is still unknown, however, but this may be because calculation of SVV requires a beat-to-beat SV measure using a pulse contour analysis algorithm (a morphologic analysis from the invasive arterial pressure curve), which has still not been validated in all clinical conditions.

Delta up does not predict fluid responsiveness. In fact, delta up is increased in normo- or hypovolemic patients with heart failure who cannot take advantage of fluid infusion. Pizov et al. observed that in animals with heart failure a large systolic pressure variation (i.e., the sum delta up...
In normal sinus rhythm. If cardiac rhythm is irregular, arterial pressure, stroke volume and aortic flow vary from beat to beat and it is impossible to measure their respiratory variations. Moreover, the indices have been studied in patients totally adapted to the ventilator, unable to make any spontaneous inspiratory effort. If the patient is spontaneously breathing or makes inspiratory efforts, in fact, the phases of negative intrathoracic pressure interrupt the cyclic ventilatory oscillation in intrathoracic pressure, and the pressure gradients are altered and ventilation-derived indices become unreliable in prediction of fluid responsiveness.

Monnet et al. observed that PPV loses its high predictive value in patients making spontaneous inspiratory efforts (AUC 0.56). Perner et al. found that SVV has no predictive value (AUC 0.52) in septic shock patients in pressure support ventilation. Heenen et al. evaluated PPV in patients making inspiratory efforts or spontaneously breathing and found it less predictive than the static indices PAOP and RAP (AUC 0.40).

Another important limitation of group A indices is that the majority of studies used a tidal volume of 8 mL/kg, somewhat higher than that which was recommended by the ARDS network. Moreover, differences in tidal volume can affect predictive value and the threshold of indices. Charron et al., using different tidal volumes, observed a correlation between PPV and tidal volume, both before and after blood volume expansion. Thus, PPV can vary with tidal volume independently from blood volume status and fluid responsiveness. De Backer et al. evaluated the predictive value of PPV in 60 patients divided in 3 subgroups (tidal volume <7 mL/kg, 7-8 mL/kg, >8 mL/kg) and observed that PPV is a good predictor (AUC 0.89) with tidal volume >8 mL/kg, and the best threshold is 12%, although a tidal volume <8 mL/kg leads to a significantly lower (AUC 0.65) predictive value and a different optimal threshold is identified (8%).

In a study from Lafanechère et al., using a mean tidal volume of 7 mL/kg, the predictive value of PPV was limited (AUC 0.78, best threshold 12%).

Finally, some clinical conditions can affect reliability of group A indices should be noted. Vieillard-Baron and Jardin raised the issue that an elevated delta down can be observed in case of...
**right ventricular failure** because a failing RV significantly decreases its stroke output in response to inspiratory increase in RV afterload. In this condition, in spite of an elevated *delta down*, stroke volume cannot be increased by fluid infusion. Berkenstadt *et al.*,47 in an animal hemorrhagic shock model, observed that when the blood loss is massive and rapid (about 50% of total blood volume), some parameters (*e.g.* PPV, SVV) can result in falsely elevated and overestimate fluid responsiveness. Nouira48 and Charron43 observed that noradrenaline infusion can increase SPV and PPV independently from volemic state and fluid responsiveness.

**Group B indices**

Indices listed in the Group B of Table II are based on mechanical ventilation-induced variations of non-stroke volume-derived parameters. Among these parameters, ΔPEP demonstrated a very good predictive value (AUC 0.97) in a study from Feissel *et al.*14 ΔPEP is a potentially interesting index because it is easy to measure, since only
ECG and arterial pressure recording are needed. Plethysmographic APEP is even less invasive because the plethysmographic wave is used in spite of invasive arterial pressure wave, and the reliability of PEPplet is quite good (AUC 0.94), although its specificity is suboptimal (67%).

Indices derived from oscillations in great diameter vessels are good predictors. For SVC collapsibility index, an AUC of 0.993 has been reported. This striking discriminating ability (the best of all parameters described) can be explained in the selected population by the SVC collapsibility index, which showed a bimodal distribution with an all-or-nothing phenomenon (in one group of subjects SVC showed high collapsibility during lung inflation, in another group the vessel did not collapse at all), so a sharp separation of responders from non-responders was possible. In the same paper, the combined use of SVC collapsibility index and PPV obtained sensitivity and specificity of 100%. In another paper, a fair correlation between SVC collapsibility index and delta down was demonstrated.

IVC distensibility index (dIVC) has the advantage of being less invasive, as transthoracic echocardiography or abdominal ultrasound is used instead of transesophageal echocardiography (Figure 4). While SVC collapses during mechanical inspiration, IVC is distended by an increase of its transmural pressure. In papers from Barbier and Feissel dIVC showed a good predictive value (AUC 0.91, sensitivity and specificity 290%).

Similar to group A, group B indices have been validated in sinus rhythm and controlled ventilation without spontaneous breathing. SVC collapsibility index and dIVC could theoretically be useful in patients with arrhythmias or spontaneous inspiratory efforts, since they rely on the vessel diameter and not on the cyclic SV variations. However, these aspects have not yet been studied.

**Group C indices**

Indices listed in group C of Table III are based on preload-redistributing maneuvers different from standard mechanical ventilation, and have been introduced in attempt to overcome some limitations of group A and group B indices.

Monnet et al. used passive leg raising as a preload-redistribution maneuver. PLR increases Pms and venous return, subsequently generating a sort of blood "autotransfusion", a completely reversible fluid challenge, independent from mechanical ventilation and virtually suitable for all kind of patients. The authors evaluated the effects of PLR on cardiac output, estimated by aortic flow, and observed that the PLR-induced increase in aortic blood flow (ΔABF) directly correlated with volume-induced increase in cardiac output. The main point of interest is that patients with arrhythmias or spontaneous inspiratory efforts were included, and PLR-ΔABF showed a good predictive value also in this population, where other dynamic indices had previously been proven to be unreliable.

In fact, when only the subgroup of patients in controlled ventilation and sinus rhythm were considered, PLR-ΔABF (threshold 10%) and
PPV (threshold 12%) showed similar predictive value (AUC 0.91±0.06 versus 0.91±0.05). Conversely, PLR-ΔABF had significantly better performance than PPV in a subgroup of patients with spontaneous inspiratory efforts (AUC 1.00±0.00 versus 0.56±0.14). In a subgroup of patients with arrhythmias, it was impossible to calculate PPV, where PLR-ΔABF was still predictive (AUC 1.00).

These results are of great interest, but obviously need to be confirmed in a larger clinical sample.

Lafenechère et al.22 studied PLR-ΔABF and observed a similar predictive value (AUC 0.95) and a slightly lower threshold (8%). A previous paper by Boulain et al.49 demonstrated that PLR-induced variation of both SV (measured by pulmonary artery catheter) and radial artery pulse pressure directly correlated with volume-induced increase in SV. The studies from Lafenechère and Boulain were conducted on patients in sinus rhythm without spontaneous inspiratory efforts.

Perel and Preisman et al.23, 24 introduced the Respiratory Systolic Variation Test (RSVT) in order to identify a dynamic index which could be independent from tidal volume. Here, they administered three consecutive mechanical inspirations in presomometric mode, increasing the airway pressure breath by breath and recorded invasive arterial pressure. Analyzing the off-line arterial pressure tracing, they identified the lowest systolic pressure after each breath and plotted these arterial pressure values versus the corresponding airway pressure values, obtaining a straight line. The slope of the line (called RSVT slope) is the desired dynamic index and it quantifies the negative effect exerted from Paw to arterial pressure. Perel et al.24 reported an AUC 0.90 for RSVT slope; Preisman et al. made a comparison between several dynamic indices and found that RSVT slope had a similar predictive value than PPV (AUC 0.96 versus 0.95) and a better predictive value than SPV, delta down and SVV.

The RSVT slope represents a physiologically valid approximation of the slope of Frank-Starling’s curve. RSVT is independent from tidal volume and can be calculated even in patients ventilated with “protective” small tidal volume, only changing ventilator settings for a brief time.

Limitations of RSVT are that the sinus rhythm and absence of spontaneous efforts are necessary and measurement is not very easy and not suitable in a clinical routine.

Magder et al.19 focused on spontaneously breathing patients. This group studied the oscillation in RAP (ΔRAP) (measured as CVP by central venous catheter) during spontaneous inspiration and demonstrated that if CVP decreases at least by 1 mmHg during inspiration, then cardiac output can be increased by volume expansion. ΔRAP has low specificity since 16% of subjects classified as responders really did not respond to volume expansion. Moreover, in a recent paper by Heenen et al.34 12 of 21 patients were spontaneously breathing and the ΔRAP demonstrated no predictive value on fluid responsiveness (AUC 0.53).

General consideration

A common limitation of all indices is that they can predict fluid responsiveness but they do not indicate the need for fluids. The concept of “fluid responsiveness” is that a fluid infusion can improve cardiac output, although the fluid-responsive patient does not necessarily need fluid. For example, every patient in good cardiovasculare status undergoing general anesthesia is virtually fluid responsive but has stable haemodynamic conditions, resulting in no need for fluid infusion. Thus, when a dynamic index indicates the state of fluid responsiveness, the decision to give fluid depends on the clinical status and on the effective need to improve hemodynamic conditions.

Limitations of the study

All the studies included in this review were focused only on the evaluation of the predictive value of dynamic indices on fluid responsiveness. No randomized clinical trial focusing on the patient outcome has been published to date, so evidence that clinical use of dynamic indices can improve outcome is still limited.

It has been observed 50 that predictive value has always been evaluated retrospectively, i.e., after fluid administration. It would be advisable to instead conduct a prospective assessment where the patient should be first predicted to be either fluid responder or non-responder and then this prediction should be verified using fluid infusion and measuring cardiac output.
Finally, each index has been evaluated on a relatively small number of subjects. In fact, among papers considered in the current review, the number of enrolled subjects ranged from 14 to 71, with a median of 22. Therefore, further studies on larger samples are needed.

Conclusions

Hemodynamic stabilization, preload optimization and correct management of fluid therapy is of utmost importance in critical care. Reliable predictors of the cardiac output response to a blood volume expansion are needed. Static pressometric and volumetric indices have been proven to be poorly predictive. Dynamic indices, based on the response of the circulatory system to standardized preload-modifying maneuvers, have been proven to be both predictive and reliable.

Dynamic indices based on respiratory variations of stroke volume or stroke volume-derived parameters, particularly pulse pressure variation and delta down, are the most widely studied and validated. Stroke volume variation has been extensively studied with controversial results, but it remains one of the most easily measured indices, because it is automatically calculated in real time using monitor PiCCO®.

Delta pre-ejection period (ΔPEP) and indices based on the variation of vena cava diameter are potentially interesting, but they need further study and validation on larger samples.

All these indices have been proven effective in patients with sinus rhythm and controlled ventilation. However, in other conditions their predictive value is considerably reduced.

To overcome these limitations, “alternative” dynamic indices have been introduced, which are based on preload-modifying maneuvers different from mechanical ventilation.

Among them, Respiratory Systolic Variation Test can be suitable for intubated and ventilated patients and is independent from ventilation modality but it requires sinus rhythm and controlled ventilation.

Passive leg raising-induced variation of aortic blood flow (PLR-ΔABF) seems particularly promising because it is predictive even in those patients making spontaneous inspiratory efforts or in non-sinus rhythm. However, it has been studied only in few patients, and confirming studies including a larger number of patients are warranted.

References


Acknowledgements. — We wish to thank Dr. Jennifer Wykes for her revision of the English language.

Received on February 9, 2007 - Accepted for publication on August 28, 2007.

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