REVIEW

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Interactions between respiration and systemic hemodynamics. Part II: practical implications in critical care

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Abstract In Part I of this review, we have covered basic concepts regarding cardiorespiratory interactions. Here, we put this theoretical framework to practical use. We describe mechanisms underlying Kussmaul's sign and pulsus paradoxus. We review the literature on the use of respiratory variations of blood pressure to evaluate volume status. We show the possibilities of attaining the latter aim by investigating with ultrasonography how the geometry of great veins fluctuates with respiration. We provide a Guytonian analysis of the effects of PEEP on cardiac output. We terminate with some remarks on the potential of positive pressure breathing to induce acute cor pulmonale, and on the cardiovascular mechanisms that at times may underly the failure to wean a patient from the ventilator.

Clinical correlates

Kussmaul's sign

Kussmaul's sign is a paradoxical increase in RAP during inspiration. Although first described in constrictive pericarditis, it occurs most frequently in severe right-sided heart failure of any cause [1]. Whether due to pericardial constraint or due to dilation of the ventricular chamber to the limit of distensibility, an abnormally high impedance to right ventricular (RV) diastolic filling is a prerequisite for the appearance of Kussmaul's sign. The traditional explanation is that the rigid RV cannot accommodate the inspiratory increase of venous return [1]. However, if venous return increased solely as a response to the fall in intrathoracic pressure (ITP), RAP measured relative to atmosphere could never become elevated above its end-expiratory value (otherwise, venous return would fall, a contradiction in terms) [2]. Work by Takata and colleagues [3] has shown that an absolute requirement for the occurrence of Kussmaul's sign is an inspiratory increase in abdominal pressure, induced by diaphragmatic descent and presumably raising mean systemic filling pressure (MSFP).

Pulsus paradoxus

In healthy humans breathing spontaneously, the systolic arterial pressure falls slightly (by less than 10 mmHg) in inspiration. It is now well accepted that this phenomenon reflects an inspiratory fall of left ventricular (LV) stroke volume due to diastolic ventricular interdependence (Part I, Section "Respiration and cardiac function") [4].

As originally described by Kussmaul in 1873, pulsus paradoxus referred to the inspiratory disappearance of the radial pulse in patients with tuberculous pericarditis [2, 5].

In its present definition, this term designates an abnormally large fall (>10 mmHg) in systolic arterial blood pressure during spontaneous inspiration. Pulsus paradoxus is a frequent symptom of cardiac tamponade [6] and acute severe asthma [7, 8]. It may be observed as well in other forms of airway obstruction and in hypovolemia. There are occasional reports of pulsus paradoxus in massive pleural effusion [9], pulmonary embolism [10], anaphylactic shock [11], strangulated diaphragmatic hernia [12], and tricuspid atresia [13].

As already suspected by Dornhorst 50 years ago [14], the main mechanism of pulsus paradoxus in cardiac tamponade is a massive amplification of parallel diastolic ventricular interdependence, due to a much tighter mechanical coupling of the cardiac chambers when compressed within a tense, pressurized pericardium [6]. Thus, pulsus paradoxus in experimental tamponade disappeared following extracorporeal bypass of the RV [15]. Accordingly, pulsus paradoxus is minimal or absent in tamponade associated with atrial septal defect, a condition in which RV and LV fillings are no longer competitive [16]. For somewhat less clear reasons, tamponade may also fail to cause pulsus paradoxus in presence of concomitant LV dysfunction [17].

The mechanism of pulsus paradoxus in acute severe asthma differs somewhat from that in tamponade. Jardin and colleagues [7] studied patients admitted to an intensive care unit for acute severe asthma, using 2D echography and invasive hemodynamic monitoring. They found that exaggerated parallel diastolic interdependence, although clearly present in view of the respiratory changes in ventricular end-diastolic volumes and septal geometry, did not suffice to explain the concomitant pulsus paradoxus, because RV stroke volume appeared to fall, rather than increase in inspiration. They concluded that, with severe hyperinflation of the lung, inspiration augmented RV afterload sufficiently to depress RV output, hence LV preload. In other words, pulsus paradoxus in acute severe asthma is an exaggerated form of series (in addition to parallel) ventricular interdependence (Part I, Section "Respiration and cardiac function").

Respiratory fluctuations of vascular pressures for the evaluation of preload-sensitivity at the bedside

When peripheral perfusion is inadequate, a basic question facing the clinician is whether any improvement is to be expected from expansion of the intravascular volume. This is equivalent to asking whether the heart operates on the steep portion (i.e., preload-sensitive cardiac output), or on the plateau of its function curve (preload-insensitive). Little help can be expected in that respect from single determinations of RAP and pulmonary artery occlusion pressure (PAOP), as provided by the Swan-Ganz catheter [18–20]. An essential, although not the only
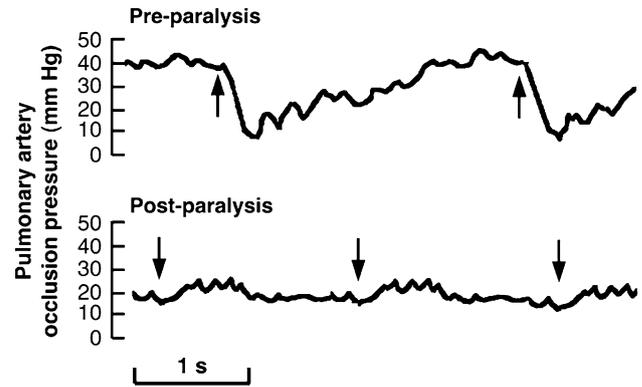
Fig. 1 Impact of active expiration on readings of pulmonary artery occlusion pressure (PAOP) made at end-expiration. In this example obtained in a ventilated patient, the effect is evident from the comparison of recordings made before (upper trace) and after administration of a neuromuscular blocking agent (lower trace). *Arrows* indicate end-expiration. Before paralysis, active inspiration causes a rapid drop in vascular pressure, the transition from end-inspiration to the begin of expiration cannot be recognized, and active expiration is manifested by a progressive increase, reaching a maximum at end-expiration, where the PAOP reads 42 mmHg. After paralysis, passive inflation by the ventilator causes the vascular pressure to increase above the end-expiratory value, which now reads 20 mmHg. In this case, uncritical reading of the upper trace would lead to considerable overestimation of the true PAOP. The wavelets seen on the upper trace might be cardiogenic oscillations (*a* and *v* waves, compatible with a heart rate of approximately 150/min), or artefacts. Modified from [22], with permission

reason is that the PAOP and RAP are intramural rather than true filling (i.e., transmural) pressures [21]. Taking readings at end-expiration is not a foolproof solution, due to frequent active expiration (Fig. 1) [22]. This latter problem may be suspected by abdominal wall palpation to assess for expiratory contraction of abdominal muscles. It may also be detected by observing the respiratory fluctuations of bladder pressure [23]. Also, trends in PAOP and RAP following i.v. fluid administration may be more informative than single measurements [24], an approach which however entails the risk of volume overload. A substitute to fluid challenge devoid of the latter risk might consist in observing the hemodynamic impact of passive leg raising, a maneuver which translocates peripheral blood towards the thorax, and thus may augment cardiac preload [25–27]. Finally, the easily measured respiratory fluctuations of arterial blood pressure and RAP may convey useful information on preload-sensitivity.

In the course of a ventilator-delivered positive pressure breath, the systolic blood pressure transiently increases relative to the stable level obtained in a prolonged expiratory pause (Fig. 2, Δup), and then decreases below that level (Fig. 2, Δdown). The Δup reflects the transient augmentation of LV stroke volume related both to diminished afterload and enhanced pulmonary venous return (blood "squeezed out of the lungs") [28–30]. The Δdown is
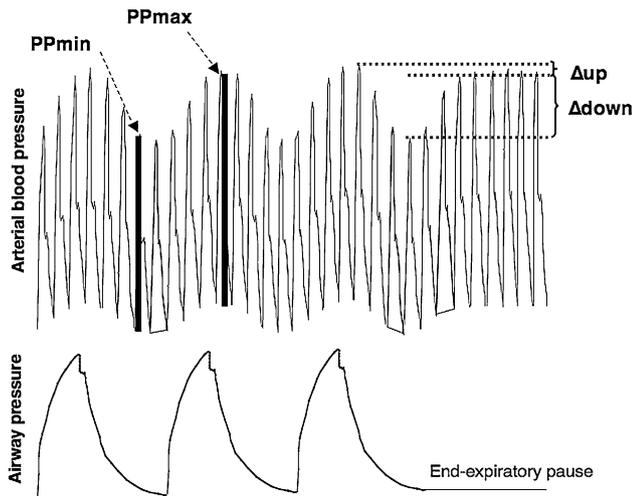
Fig. 2 Respiratory variations of arterial blood pressure in a sedated patient on volume-controlled mechanical ventilation. In such conditions, the respiratory fluctuations of either systolic (Δup and Δdown) or pulse pressure (PP_{max} and PP_{min}) may be used to detect hypovolemia and so determine the need for intravascular volume expansion. The first method requires an end-expiratory pause of sufficient duration for systolic blood pressure to stabilize, to obtain a reference level from which to measure Δup and Δdown as indicated. PP_{max} and PP_{min} can be obtained without interrupting ventilation. A high value of either Δdown or ΔPP (=PP_{max}–PP_{min}) indicates hypovolemia. Detailed explanations in "Respiratory fluctuations of vascular pressures"

caused by the subsequent reduction of LV preload and stroke volume, which takes place in exhalation as the inspiratory depression of RV preload and output propagates to pulmonary venous return with a time lag of a few heartbeats [29]. Thus, preload-insensitivity of the heart should be associated with a blunting or disappearance of the Δdown. The Δup would be less reliable in that respect due to the potential influence of changing LV afterload. This concept has been validated experimentally [31–33]. Two small clinical studies demonstrated a superiority of the Δdown, compared with either PAOP or echographic estimates of LV size, for predicting the response of cardiac output to a fluid challenge in mechanically ventilated postoperative [34] or severely septic patients [19].

A variation of the Δdown approach, which has been similarly validated consists in quantifying the variations of pulse pressure (ΔPP) induced by a positive pressure breath (Fig. 2) [20, 35]. The respiratory fluctuations in the amplitude of the plethysmographic pulse wave (obtained non-invasively from pulse oxymetry) have been used to the same effect [36]. A practical problem with all these methods is the potential confounding influence of cardiac arrythmias, increased abdominal pressure [37], and changes in vascular tone or ventilatory conditions. Indeed, the aforementioned validation studies were carried out in heavily sedated patients ventilated in controlled mode with relatively large tidal volumes (≥ 8 ml/kg) [19, 20, 34]. It is not clear that similar results would be obtained

with smaller tidal volumes [38–40]. A possible answer to this critique has been proposed in the form of applying a succession of three mechanical breaths of progressively increasing plateau pressure and quantifying the effect on systolic blood pressure [41]. We must finally underscore that these methods lose most of their validity with the presence of active inspiratory or expiratory effort, whether in the course of mechanically assisted or spontaneous breathing [25, 26, 42].

With spontaneous breathing, Magder et al. [43] have suggested that the lack of an inspiratory drop in RAP is indicative of an overfilled, non-compliant heart lying on the flat part of its function curve, and therefore predicts the lack of volume responsiveness of cardiac output.

Respiratory fluctuations of great veins geometry

The transmural pressure versus volume relationship of the venae cavae is nonlinear, with a steep slope at low distension and a plateau at full repletion [44]. Thus, one would expect that phasic changes in transmural pressure would more readily translate into respiratory variations in cross-sectional size when imposed on a partially empty vessel (hypovolemia), as opposed to a fully repleted one (normo or hypervolemia). Based on this rationale, the phasic changes in caval diameters, as evaluated from echocardiography, have been proposed as non-invasive indices of intravascular volume status [44–50].

In man, the IVC runs almost entirely intraabdominal, i.e., it enters the right atrium immediately after crossing the diaphragm. Thus, its extramural pressure is abdominal pressure (Pabd), while its intramural pressure lies close to RAP. In the course of a spontaneous inspiration, Pabd increases (diaphragmatic descent) while RAP decreases (transmission of pleural pressure swing), leading to an inspiratory diminution of transmural pressure. The latter, however, only causes the IVC diameter to shrink if the vessel is not fully repleted (i.e., if it operates on the steep part rather than the plateau of its transmural pressure/diameter relationship). Quantified in various ways with transthoracic echocardiography, the inspiratory decrease of IVC diameter has been used to characterize volume status in the course of hemodialysis for end-stage renal disease [45, 46]. In the ICU, we are aware of no similar application in spontaneously breathing subjects. In contrast with spontaneous breathing, positive pressure inflation is expected to dilate an incompletely filled IVC, because the positive swing of pleural pressure is fully transmitted to RAP, but only partially to Pabd, thus causing an inspiratory increase of IVC transmural pressure. Two studies have found that the amplitude of phasic changes in IVC geometry, as measured with transthoracic echocardiography, were highly predictive of cardiac output response to a fluid challenge in sedated septic shock patients ventilated in controlled mode [47, 48]. Although

not documented so far, respiratory fluctuations in IVC diameter are likely to depend not only on volemia, but also on respiratory pattern, prevailing level of mean Pabd, and right ventricular function, as is the case for ΔPP and Δdown.

In contrast to the IVC, the superior vena cava (SVC) runs mainly intrathoracic, so that its extramural pressure is close to pleural pressure. In hypovolemic conditions, positive pressure inflation may transiently create zone 2 conditions (intraluminal pressure <Ppl[1]) in this vessel, leading to its partial inspiratory collapse [49]. Phasic variations of SVC diameter have been found to correlate well with fluid responsiveness of cardiac output in septic patients on controlled mechanical ventilation [50]. This index of hypovolemia has been advocated as superior to that based on IVC diameter [44], notably because it is not influenced by Pabd. In contrast with the IVC, however, the SVC can only be echographically imaged via the transesophageal, but not the transthoracic route.

Effects of PEEP on cardiac output

The effects of PEEP on cardiac output are modulated by a variety of factors, the understanding of which is greatly facilitated by the Guytonian representation of venous return-cardiac function interactions (i.e., Fig. 2d in Part I). In Fig. 3, the venous return curves labeled "ZEEP" (zero end-expiratory pressure) and "PEEP" have been taken from the data presented above [51] (Fig. 3 in Part I). The venous return curve labeled "PEEP + volume" has been drawn under the assumptions that intravascular volume expansion under PEEP would increase MSFP, with little effect on either Rv or Pcrit (Chapter 12 of [52]). Figure 3a depicts events associated with normal cardiac function: the cardiac function curve under ZEEP is steep (Fig. 4 in Part I) and intersects the corresponding venous return curve at point 1 located slightly on the right of and below the critical point [53]. PEEP effects a shift to the right of the cardiac function curve (Fig. 4, lower left, in Part I) and of the critical point by approximately the same amount (equal to the increase in ITP), while depressing the maximal venous return. Under PEEP, the operating point becomes located on the plateau of the new venous return curve (point 2), showing not only that cardiac output must decrease, but also that it becomes insensitive to changes in cardiac function (point 3). In these conditions, volume expansion is mandatory to restore systemic blood flow (point 4), whereas PEEP superimposed on hypovolemia may lead to cardiovascular collapse (point 4a), as is well known to clinicians [54].

Figure 3b shows the possible effects of PEEP in presence of LV failure. Under ZEEP, the cardiac function
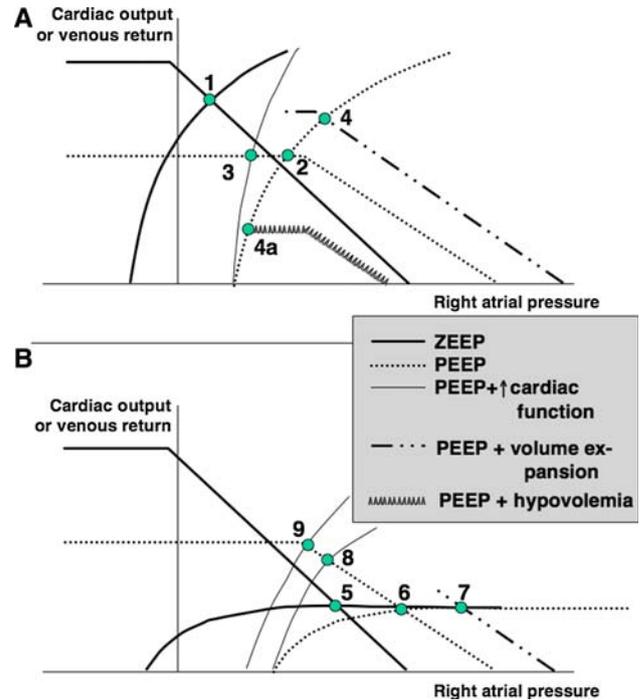
Fig. 3 Various possible effects of PEEP on cardiac output, illustrated with Guyton's graphical analysis: **a** with normal cardiac function, **b** with depressed cardiac function. In both panels **a** and **b**, right atrial pressure is measured relative to atmosphere, i.e., it represents the intracavitary pressure. This is the reason why PEEP shifts the cardiac function curve to the right (see left lower part of Fig. 4 in Part I). PEEP shifts the venous return curve as shown in Fig. 3 of Part I, i.e., the zero flow intercept (which is MSFP) and the critical pressure (Pcrit, at the intersection of the oblique and plateau parts) are increased by approximately equal amounts, while the maximal venous return (height of the plateau part) is depressed. Volume expansion shifts the venous return curve "rightwards" (see Footnote 2 in Part I), whereas hypovolemia has the opposite effect. Pcrit is not affected by changes in volemia. Further explanations in the text ("Effects of PEEP on cardiac output")

curve is so depressed that the operating point is located on its plateau (point 5) and remains so under PEEP if cardiac function is not simultaneously altered, i.e., if the cardiac function curve is merely shifted to the right (point 6). In these conditions, systemic blood flow cannot be increased by volume expansion (point 7). With a failing LV, however, cardiac function becomes sensitive to changes in LV afterload. Reduction of the latter by PEEP or continuous positive airway pressure (CPAP), therefore may cause cardiac output to increase (point 8) [55, 56], or at least to be better preserved [57–59] in normo- or hypervolemic patients with a failing left heart, compared to those with normal LV function.

It is worth noting that PEEP reduces the afterload of the failing LV by increasing LV extramural pressure at all phases of the respiratory cycle, not only at end-expiration. This is especially true when spontaneous inspiratory efforts occur in the context of pulmonary edema: PEEP or

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[1] In analogy with West lung zones, see Part I, Section "Respiration and cardiac function; RV afterload".

CPAP then improve lung mechanics, thereby attenuating the negative inspiratory swings of ITP [59]. Another interesting observation has been made by Huberfeld and colleagues [60], who found in volume loaded sedated pigs that a substantial surface pressure existed on the dilated heart under ZEEP. Application of CPAP in these conditions decreased pericardial pressure, in spite of increasing esophageal pressure (Fig. 4). This paradox was explained by the lower heart size which followed afterload reduction by CPAP. In Fig. 3b, this phenomenon would translate into a shift to the left of the cardiac function curve, with a further increase in cardiac output (point 9). These considerations form in part the basis for the beneficial hemodynamic effects of CPAP or mechanical ventilation with PEEP in LV failure [59, 61–65]. However, a limit would be set to these benefits by the concomitant reduction of maximal venous return. Accordingly, clinical experience has shown that moderate levels of end-expiratory pressure (5–10 cm H_2O) are optimal in these conditions.

Of course, Fig. 3 is an oversimplified representation of two idealized extremes in continuous spectrum of actual situations. However, it is certainly necessary to evaluate in each patient whether he/she stands closer to panel A or B. Such evaluation essentially requires integrated clinical and pathophysiological thinking. Some help may come from observing the phasic fluctuations of arterial pressure or great veins geometry (see previous two sections).

Fig. 4 Differential effects of continuous positive airway pressure (CPAP) on esophageal and pericardial pressure in normovolemic and hypervolemic pigs. Pigs were chronically instrumented with pressure sensors in the pericardial space. On the day of experiment a pressure sensor was inserted into the esophagus. The animals were intubated and connected to a high flow CPAP system. Esophageal (Pes) and pericardial pressure (Pper) were measured synchronously at end-diastole, at various CPAP levels, before (normovolemia) and after volume expansion with i.v. hetastarch (35 ml/kg, hypervolemia). In normovolemia, Pper and Pes track each other. In hypervolemia and without CPAP, Pper exceeds Pes, due to the contact pressure exerted by the lung on the surface of the dilated heart. The progressive institution of CPAP reduces the afterload of the left ventricle (LV), with the following consequences: a smaller LV, a lower global size of the heart, hence release of contact pressure exerted by the lung and finally reduction of Pper. Pes, measured away from the lung surface, increases with CPAP, independent of heart size. From [60], with permission

Fig. 5 Cardiovascular mechanisms of weaning failure. The obligatory cardiovascular effects of withdrawing mechanical assistance (linked by *plain arrows*) are depicted on the left of the *thick vertical dashed line*. The *dashed arrows* point to potential consequences in presence of insufficient cardiovascular reserve. *BP* blood pressure, *CO* cardiac output, *HR* heart rate, *ITP* intrathoracic pressure, *MSFP* mean systemic filling pressure, *LVEDV* left ventricular end-diastolic volume, *LVEDP* left ventricular end-diastolic pressure, *RVEDV* right ventricular end-diastolic volume, *SV* stroke volume, $S\bar{v}O_2$ mixed venous oxygen saturation, *WOB* work of breathing. Upstream effects on the lung and downstream effects on peripheral oxygenation are not necessarily linked: depending on circumstances, one or the other may predominate, or both may occur concomitantly More explanations in "Weaning failure from cardiovascular origin"

Mechanical ventilation and acute cor pulmonale

Acute pulmonary hypertension and associated RV failure (acute cor pulmonale, ACP) are frequent findings in patients on mechanical ventilation for respiratory failure, especially ARDS. An important role in this setting is now attributed to mechanical ventilation itself, which in addition to promoting alveolar-capillary injury, acts by direct mechanical augmentation of RV afterload in the inflation period, leading to RV dilation, abnormal septal motion and low cardiac output [66, 67] (Part I, Section "Ventricular afterload"). Especially when combined with high inflation pressures, ACP in ARDS is associated with a high mortality [68]. One might speculate that the improved mortality seen when patients with ARDS receive smaller tidal volumes [69] may be due in part to improved RV function.

It is essential for clinicians to understand that, in patients with ARDS, a major cause of ventilator-induced hypotension may not be venous return impairment but increased RV afterload. Echography is required to confirm this mechanism, and the correct treatment in this case is primarily a reduction in inflation pressures, especially plateau pressure.

Weaning failure from cardiovascular origin

The switch from assisted to spontaneous breathing stresses the cardiovascular system, akin to an exercise test [70]. As depicted in the left part of Fig. 5. weaning activates the sympathoadrenergic system, with predictable consequences on heart rate and blood pressure. Due to venoconstriction and associated reduction in venous compliance, MSFP increases. At the same time, the mean ITP falls, thus increasing LV afterload (Part I, Section "Ventricular afterload"), to which the failing heart is oversensitive. Furthermore, venous return is boosted, leading to increased right and left ventricular end-diastolic volumes. These chains of events augment the myocardial O_2 demand. A prerequisite to successful weaning is therefore that the heart be able to cope with this situation. With diminished cardiovascular reserve (right hand part of Fig. 5), myocardial ischemia may appear [71], and left ventricular filling pressure may increase disproportionately [72]. The upstream consequences on the lung [72] and downstream consequences on O_2 transport [73] then initiate vicious circles which culminate in florid cardiorespiratory failure and the need to resume mechanical ventilation. Such considerations are of paramount importance when evaluating patients who are difficult to wean [74].

Conclusion

Cardiorespiratory interactions are encountered daily in the clinical practice of critical care. Much of our understanding in this area rests on fundamental knowledge acquired decades ago. These concepts have then been enriched by technological advance, notably the advent and ever greater performance of echocardiography, and are likely to keep evolving as new methods of investigation become available, such as cardiorespiratory-resolved magnetic resonance imaging [75]. We hope to have convinced the reader that understanding cardiorespiratory interactions is not only of academic, but also of practical importance for his or her training as an intensivist. The concepts covered in the present review are essential to the proper use of mechanical ventilatory assistance. Furthermore, they have been put to use in the last decade in order to promote a less invasive approach to hemodynamic monitoring, an area in which progress may be expected in the near future.

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