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CLINICAL COMMENTARY

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Right ventricular function and positive pressure ventilation in clinical practice: from hemodynamic subsets to respirator settings

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Introduction

When used in patients free of previous cardiorespiratory disease, mechanical ventilation with a normal tidal volume does not have any discernible hemodynamic consequences. Conversely, the presence of a pulmonary disease affecting the bronchial tree, lung parenchyma, or both, may induce extreme conditions for mechanical ventilation. In this setting, an adverse hemodynamic effect may seriously complicate respiratory support.

The drop in cardiac output occurring in extreme conditions of mechanical ventilation is usually attributed to a reduced venous return. But the terms "cardiac output"on the one hand and "venous return" on the other refer to the same phenomenon. From a physiological point of view, such an explanation is insufficient, because reduced venous return may, in the same way, be explained by the drop in cardiac output.

We have been interested for about 30 years in the hemodynamic consequences of mechanical ventilation in ARDS patients, and here we try to summarize our experience in this clinical commentary to enable a logical approach to ventilator settings. The major goal of this approach will be to avoid imposing an excessive load on the rignt ventricle. Our experience was first acquired with right heart catheterization, and later by bedside echocardiography. Recent physiological notes published in the present journal have underscored some of the drawbacks of the invasive method [1, 2] and illustrated the advantage of echocardiography [3]. The clinical results of our respiratory strategy in ARDS has been published recently [4].

The hemodynamic consequences of mechanical ventilation are easy to understand by examining the impact upon the right ventricle of applying a positive airway pressure. On the one hand, cyclic (tidal ventilation) or continuous (PEEP application) changes in transpulmonary pressure produced by respiratory support directly affect RV outflow impedance. On the other hand, cyclic (tidal ventilation) or continuous (PEEP application) increase in pleural pressure produced by respiratory support increases RV effective elastance, a factor limiting diastolic filling.

The "venous return" concept

As established by Guyton, the venous return is promoted by a forward pressure, the mean systemic pressure, and impaired by a backward pressure, the right atrial pressure [5]. For several decades it was believed that positive pressure ventilation, by increasing pleural pressure, decreased the pressure gradient for venous return. In 1991, Fessler et al., working in S. Permutt's group, demonstrated in an experimental study in dogs that positive airway

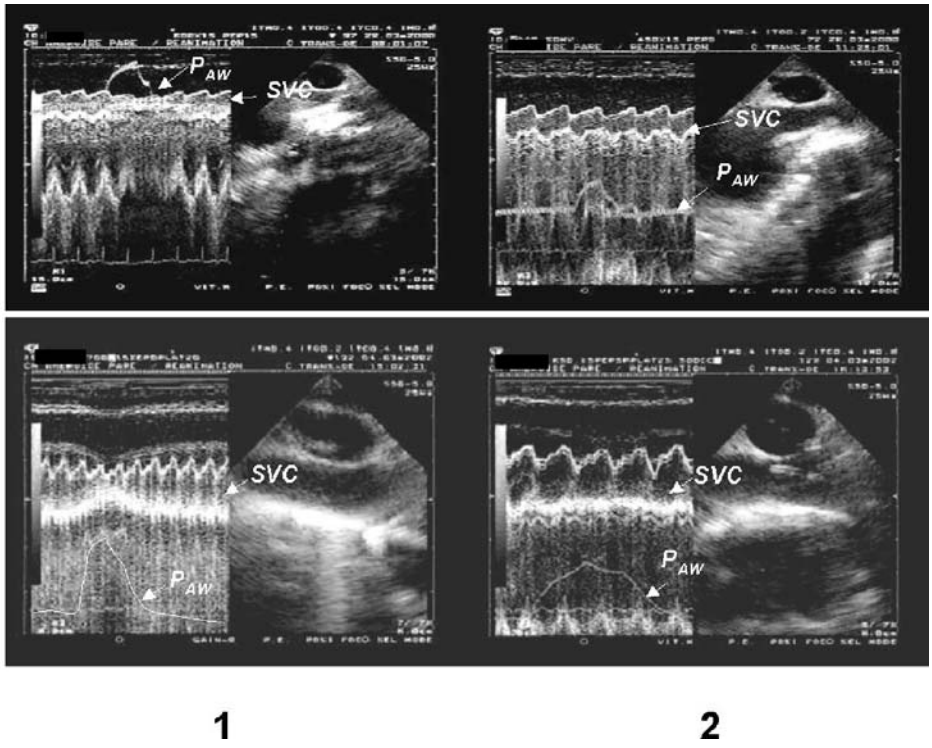

Fig. 1 Transesophageal echocardiographic examination of the superior vena cava (*SVC*) in the *long axis* (with the M-mode study on the *left* and the two-dimensional imaging on the *right* of each record) in two different patients (**A** and **B**). On the left panel (*1*), SVC collapse was observed in these patients during tidal ventilation (airway pressure, P_{AW}, was monitored on the M-mode recording). This collapse was prevented in both patients by blood volume expansion, as illustrated on the right panel (*2*)

pressure did not affect the gradient for venous return, because pleural pressure was transmitted to the same extent to both the mean systemic and right atrial pressures [6]. Van den Berg et al. [7] demonstrated in a recent clinical study that a sustained increase in airway pressure did not decrease venous return because of a concomitant increase in abdominal pressure, an operative mechanism in volume loaded patients, with the inferior vena cava in a zone 3 condition [8]. Also, Fessler et al. observed in another experimental study that venous return was actually reduced by positive pressure ventilation, despite a maintained pressure gradient [9]. They concluded that venous conductance was reduced (or venous resistance was increased) when airway pressure was increased, probably because a collapsible vascular zone was interposed between mean systemic pressure and right atrial pressure [9]. Recently, Jellinek et al. confirmed the validity of this concept in humans, and suggested that liver circulation might constitute this collapsible vascular zone sensitive to pleural pressure transmission throughout the diaphragm [10].

We have also observed another collapsible vascular zone at the level of the thoracic part of the superior vena cava [11]. Placed in a zone 2 condition in a hypovolemic patient, the superior vena cava may partially collapse during tidal ventilation, thus transiently limiting RV filling (Fig. 1, Electronic Supplementary Material Film 1A, B and C). The same phenomenon is not observed at the level of the inferior vena cava, because the thoracic part of this vessel is virtual in humans [11].

Changes in transpulmonary pressure and the impact on right ventricular outflow impedance

Applying the concept of the Starling resistor to the pulmonary circulation, S. Permutt and his co-workers described the relation between the pressures promoting blood flow through the pulmonary circulation [12]. A forward pressure, the pulmonary artery pressure, boosts blood through the pulmonary vascular bed, and a backward pressure, the pulmonary venous pressure, impedes this flow (zone 3 condition). However, alveolar pressure, which directly acts externally on the pulmonary capillary bed, may behave as backward pressure if it rises above venous pressure (zone 2 condition). During tidal volume ventilation, the increase in airway pressure produces an increased zone 2 at the expense of zone 3 (Fig. 2). Thus, during tidal ventilation, alveolar pressure, acting as the backward pressure, impedes pulmonary blood flow. This phenomenon may be important in a mechanically ventilated supine patient. If we assume an average pulmonary venous pressure at the level of the mid-axillary line of 16.5 cmH_2O (12 mmHg), and a 12 cm height between the mid-axillary line and the anterior chest wall, the pulmonary venous pressure in the anterior area of the lungs should be close to 4.5 cmH_2O (i.e., 16.5–12). Thus, in this area, a transpulmonary pressure of 5 cmH_2O would produce a permanent zone 2 condition. Conversely, because of an equal height of 12 cm between the posterior chest wall and the mid-ax-

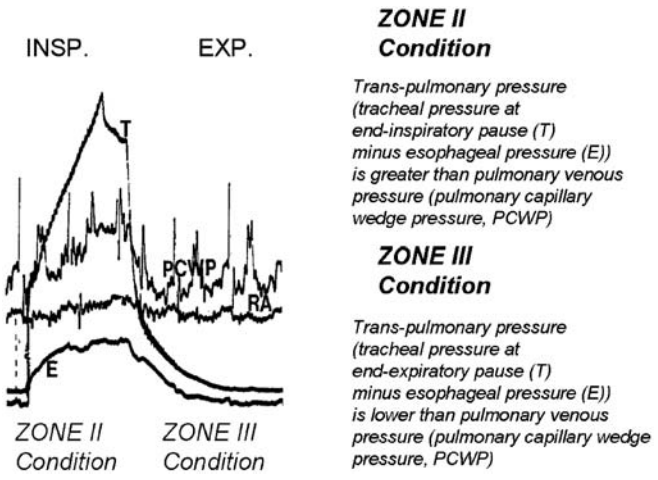

Fig. 2 An example of simultaneous recording of esophageal pressure (*E*), reflecting pleural pressure, right atrial pressure (*RA*), pulmonary capillary wedge pressure (*PCWP*), reflecting pulmonary venous pressure, and tracheal pressure (*T*). During the period of no-flow (end-inspiratory pause and end-expiration), *T* reflects alveolar pressure. Whereas a zone 3 condition is observed at end-expiration (PCWP>T), a zone 2 condition is realized at end-inspiration (T>PCWP). Also note that the increase in *E* during mechanical inspiration is accompanied by a similar increase in PCWP

illary level, dependent areas of the lung are protected against a zone 2 condition.

In fact, it is not alveolar pressure in the strict sense of the term that constitutes backward pressure during tidal ventilation, but alveolar distending pressure (i.e., transpulmonary pressure) as we have recently demonstrated in a clinical study, using chest strapping, a procedure that increases alveolar pressure without a concomitant increase in transpulmonary pressure [13].

By recording simultaneously pulmonary artery and right ventricular pressures in mechanically ventilated patients, we have observed in the past the relation between transpulmonary pressure and right ventricular outflow impedance: when tidal volume is progressively increased, the right ventricle has to develop a more and more elevated pressure to open the pulmonary artery valve (Fig. 3) [14]. We have recently confirmed these results by Doppler analysis of changes in pulmonary artery velocity (Fig. 4, Electronic Supplementary Material Film 2A, B) [13]. Increased transpulmonary pressure during tidal ventilation sharply reduces mean acceleration of blood in the pulmonary artery (Fig. 4), whereas an isolated increase in airway pressure without change in transpulmonary pressure does not affect blood velocity in the pulmonary artery [13].

Indirect evidence of RV afterloading is also provided by the frequency of tricuspid regurgitation during mechanical ventilation [15], which can also be induced by PEEP [16]. An example is given in Fig. 5.

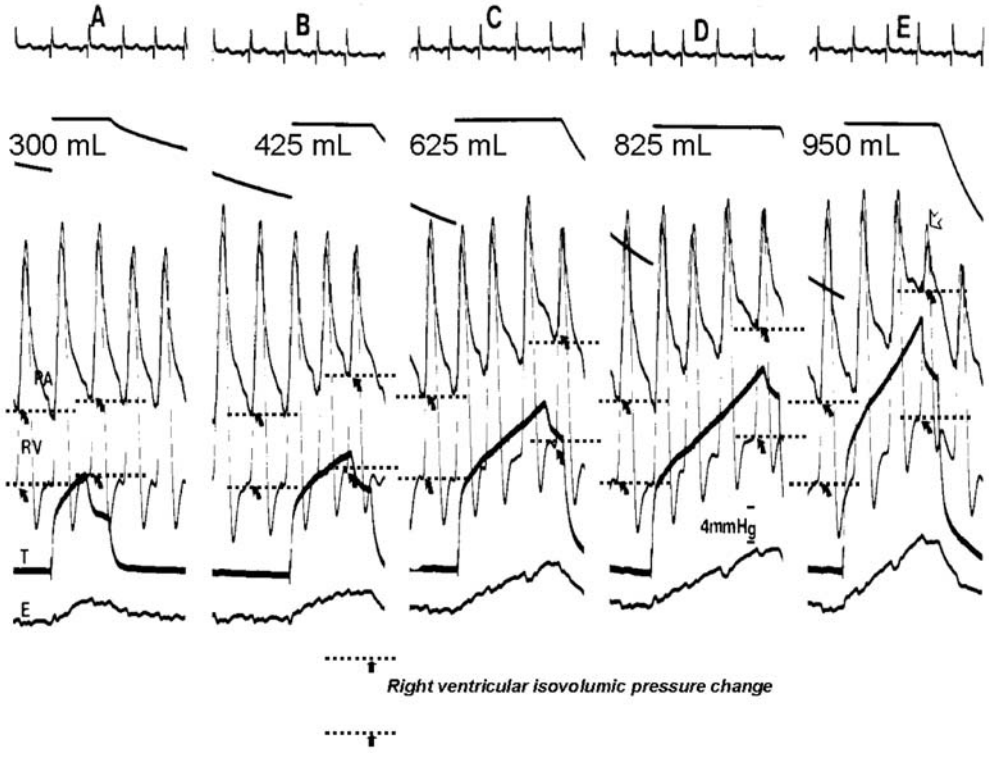

Fig. 3 Simultaneous recordings of expiratory volume (*EV*, ml), pulmonary artery pressure (*PA*, mmHg), right ventricular pressure (*RV*, mmHg), tracheal pressure (*T*, mmHg) and esophageal pressure (*E*, mmHg), during a progressive increase in tidal volume from 300 to 950 ml. This progressive increase in tidal ventilation required a progressive increase in the pressure developed by the RV during its isovolumetric contraction to open the pulmonic valve (i.e., the difference between pulmonary artery diastolic pressure, *small closed arrow*, and right ventricular end-diastolic pressure, *small closed arrow*). Note also that, with the highest tidal volume (*right panel*, *E*), pulmonary artery pulse became negligible (*small open arrow*)

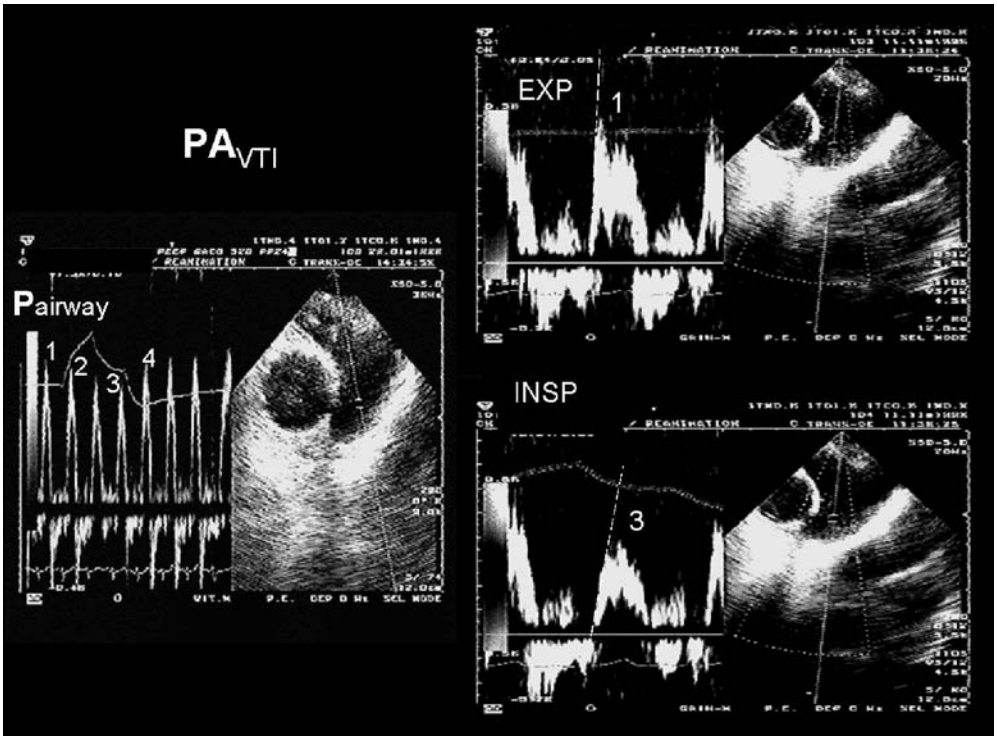

Fig. 4 Cyclic changes in pulmonary artery Doppler flow velocity during tidal ventilation. On the *left panel* these changes are recorded at low speed, illustrating the drop in peak velocity between beat 1 (end-expiratory beat) and beat 2 occurring during the dynamic phase of lung inflation. This drop was accentuated during beat 3, occurring at the end-inspiratory pause, and peak velocity start to return to its baseline value during beat 4, occurring at the onset of expiration. On the *right panel*, recording at high speed demonstrated the associated drop in mean acceleration (i.e., peak velocity divided by acceleration time), which is depicted by the slope of the *broken line* drawn on the initial part of the Doppler profile on beat 1 and beat 3

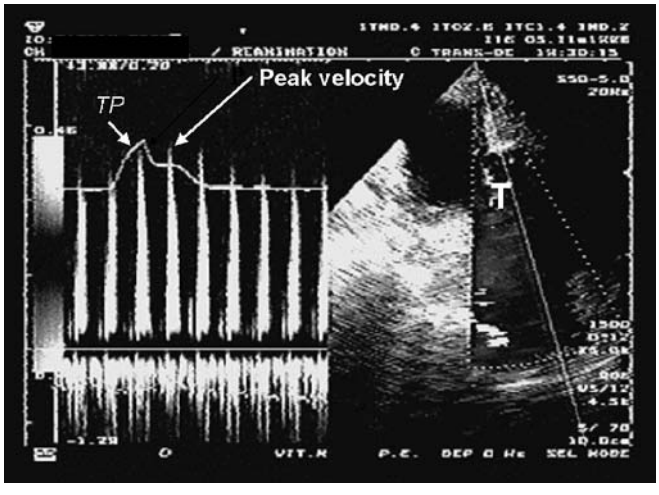

Fig. 5 Examined with a simultaneous recording of tracheal pressure (*TP*), recording of continuous Doppler backward flow velocity at the level of tricuspid valve (*T*) illustrates the increase in peak velocity produced by tidal ventilation

PEEP-related changes in transpulmonary pressure and their hemodynamic impact

In 1975, P. Suter described "best PEEP" as a PEEP resulting in "optimum" oxygen transport in ARDS patients [17]. This PEEP was easy to determine, because it was also associated with the best value of a two-point (quasi-static) compliance of the respiratory system (C_{RS}) [17].

This "best PEEP" was relatively low (8±4 cmH_2O, personal communication from P. Suter). If we assume that changes in C_{RS} in ARDS essentially reflect changes in static compliance of the lung (C_L), we can conclude that the "best PEEP" described by Suter reduced, for a given tidal volume, the required transpulmonary pressure. Thus, a lesser impact of tidal ventilation on right ventricular function should be expected when this PEEP is applied.

This hemodynamic improvement was actually present in Suter's work, where application of the "best PEEP" did not decrease cardiac output despite increased pleural pressure [17]. In accord with Suter's findings, we observed in 1981 that cardiac output was maintained at a low PEEP (<10 cmH_2O), despite pleural pressure increase (–0.6+0.4 mmHg at ZEEP, versus 0.9+1.9 mmHg with PEEP=10 cmH_2O, end-expiratory values) [18]. Conversely, above this PEEP cardiac output fell significantly [18]. Recently, we have corroborated this beneficial hemodynamic effect of a low PEEP by Doppler examination of pulmonary artery flow velocity [19] (Electronic Supplementary Material Film 3A,B).

In Suter's study, C_{RS} was a two-point compliance, calculated as tidal volume divided by plateau pressure minus end-expiratory pressure. The latter was assumed to be external PEEP, because the phenomenon of intrinsic PEEP was unknown at this time. If corrected for intrinsic PEEP [20], which was likely present in ARDS pa-

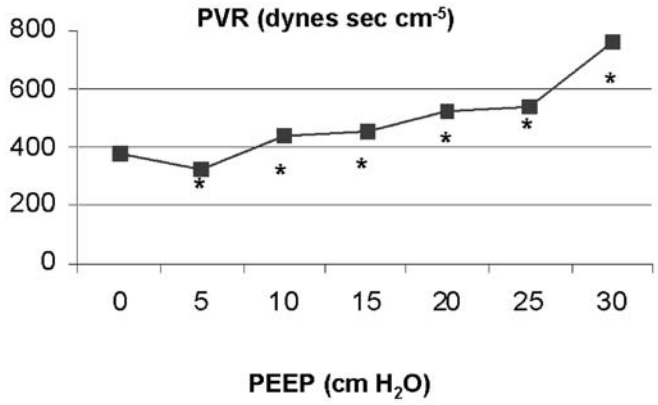

Fig. 6 Average change in pulmonary vascular resistance (*PVR*) during a progressive increase in PEEP in ten ARDS patients studied in 1981 [10]. Error bars are omitted for clarity. PVR was calculated using left ventricular end diastolic pressure measured at end-expiration by the Seldinger method, as reflecting pulmonary venous pressure. Note that PVR was significantly improved at a low PEEP, and was worsened on increasing PEEP above this level (*P<0.05)

tients receiving a high tidal volume (13–15 ml/kg), the C_{RS} in Suter's patients would have probably been unchanged by "best PEEP" application, and the reason for the beneficial hemodynamic effect of this PEEP would probably not be an actual mechanical improvement, permitting reduction in transpulmonary pressure. In the study referred to above [18], we also observed a significant reduction in pulmonary vascular resistance with a low PEEP (between 3 and 8 cmH_2O, Fig. 6). As we have recently emphasized, a "slow compartment" is usually present at a relatively low supportive respiratory rate in ARDS patients, and produces gas trapping [21]. This gas trapping may be responsible for a permanent zone 2 condition in a limited area, and an increased vascular resistance in this specific area. Relieving gas trapping by a low PEEP [21] thus improves blood flow and reduces vascular resistance (Fig. 7).

Effect of an increase in pleural pressure on RV effective diastolic elastance

Pleural pressure is transmitted integrally to the pericardial space [22]. Thus, any increase in pleural pressure induces an increase in pericardial pressure, which limits the distending capacity of the cardiac cavities. During diastole, when pleural pressure is increased, a higher filling pressure is necessary to obtain an adequate end-diastolic volume. We have illustrated in the past the changes in left [18] and right [23] ventricular effective elastance occurring in clinical settings when pleural pressure is progressively increased by raising PEEP, and a schematic representation of theses change is shown in Fig. 8.

As a clinical consequence, a high central venous pressure (>10 mmHg) is required in a mechanically ventilated patient to put the right ventricle on the flat part of its function curve, thus rendering it somewhat insensitive to cyclic change in elastance produced by tidal ventilation

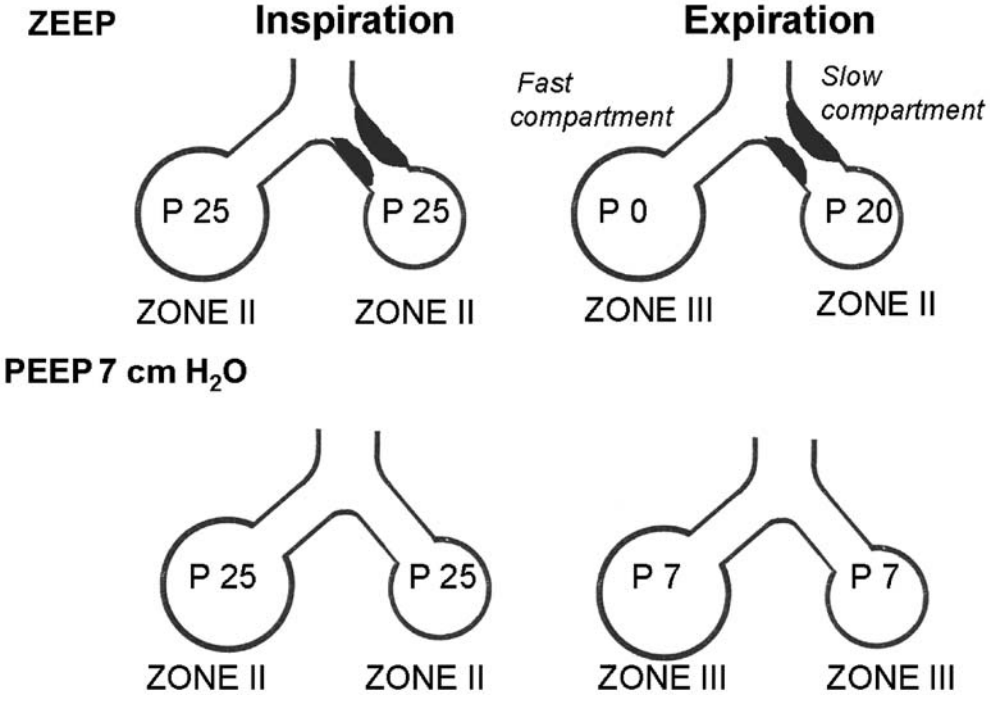

Fig. 7 A schematic representation of the adverse hemodynamic effect of the slow compartment in ARDS. On the *top left panel*, tidal ventilation with ZEEP produces a plateau pressure of 25 cmH_2O, which creates a zone 2 condition. On the *top right panel*, airway pressure in the fast compartment returns to zero at end-expiration with ZEEP, restoring a zone 3 condition, whereas the slow compartment, which cannot empty, is responsible for a permanent zone 2 condition in the corresponding vascular area. On the *bottom panel*, tidal ventilation with PEEP also creates a zone 2 condition (*left*), but the low PEEP of 7 cmH_2O suppresses the slow compartment, so that no zone 2 condition persists at expiration (*right*)

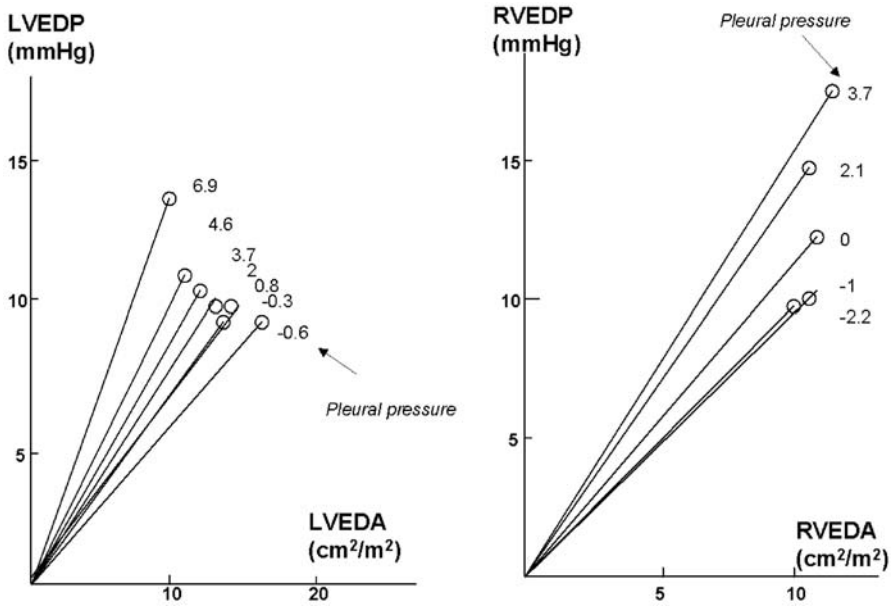

Fig. 8 Simultaneous recording of left ventricular end-diastolic pressure by left ventricular catheterization (*LVEDP*) and right ventricular end-diastolic pressure by right heart catheterization (*RVEDP*) simultaneously with left (*L*) and (*R*) ventricular end-diastolic areas (*EDA*) by two-dimensional echocardiography illustrated the changes in left (*left panel*) and right (*right panel*) ventricular elastance (the slope of the relation) occurring with a progressive increase in pleural pressure produced by a step-by-step application of PEEP. These diagrams were constructed with the data of [18, 23]

[24]. But central venous pressure may be misleading as a monitoring parameter because it is sensitive to venous elastance, which may differ from patient to patient. In our experience, observation of superior vena caval diameter by TEE is fundamental in ensuring that the right ventricle will be on the flat part of its function curve: this is likely the case when cyclic changes in pleural pressure only slightly affect vena caval diameter [11] (Electronic Supplementary Material Films 1A,B,C).

What is the net result of these opposite effects on right ventricular size?

Changes in RV dimensions produced by tidal ventilation or by PEEP application have given apparently conflicting results, some authors emphasizing a reduction in RV dimensions [25], whereas we have demonstrated an increase in RV dimensions [23, 26]. In fact these results are perfectly coherent because, as we have discussed, the two effects of increasing airway pressure have opposite consequences for RV dimensions. Whereas an increase in RV outflow impedance tends to reduce ejection and increase end-diastolic volume (afterload effect, Electronic Supplementary Material Film 4), an increase in RV diastolic elastance tends to reduce end-diastolic volume (preload effect). Thus, the net effect of these opposite actions on RV size is the result of the preponderance of one over the other.

In 1998, Gattinoni et al. [27] introduced a major distinction in the ARDS classification by individualizing, from a mechanical point of view, two different subgroups. Pulmonary ARDS had a markedly reduced C_L, whereas C_W was slightly affected in this subgroup. Extrapulmonary ARDS, on the other hand, had a markedly reduced C_W associated with a relatively preserved C_L. Thus, in pulmonary ARDS, a higher transpulmonary pressure would be required to deliver a given tidal volume. In this setting, one can expect a preeminent afterload effect. Conversely, in extrapulmonary ARDS, a given tidal volume would markedly increase pleural pressure. In this setting, one can expect a preeminent preload effect. Thus, pulmonary ARDS will be subject to RV enlargement with increasing airway pressure, whereas extrapulmonary ARDS will be subject to RV size reduction.

Both effects may also be successively observed in the same patient, with an initial reduction of RV size with a low PEEP, because a concomitant reduction in preload and afterload reduces RV size, and a final enlargement with a higher PEEP, when the increased afterload effect becomes preeminent [23].

Hypercapnia, respiratory rate and RV function

Hypercapnia has been experimentally proved as a deleterious factor for an overloaded RV [28]. With the widespread acceptance of a protective ventilation strategy in clinical practice [29, 30, 31, 32], which requires an airway pressure limitation (plateau pressure <30 cmH_2O), hypercapnia has replaced airway pressure as a direct factor related to acute cor pulmonale in ARDS patients [33, 34]. Clearly, hypercapnia in this setting results from the severity of the disease, but it may only be expressed owing to the new "permissive" respiratory strategy, limiting tidal volume.

Computed tomographic studies in ARDS have illustrated the major reduction in functional alveolar areas observed in this syndrome [35] and have led to the "baby lung" concept. In this concept, ARDS lung is compared to the lung of a baby, admitting only a small tidal volume. Because the respiratory rate of a baby is markedly greater than that of an adult, it has been proposed to limit the level of "permissive" hypecapnia by increasing the respiratory rate [36]. But adult ARDS patients actually exhibited an adult dead space [37], and increasing respiratory rate may produce an adverse intrinsic PEEP [37]. Gas trapping generated by this strategy increased right ventricular outflow impedance [37].

From a hemodynamic point of view, what are the best ventilation strategies in ARDS patients?

First of all, it should be recalled that the differences between cyclic positive airway pressure obtained by tidal ventilation and permanent airway pressure produced by PEEP are profound. Whereas transient increase in inspiratory pressure cannot be adapted because of the fleeting nature of the stress, PEEP induces a steady-state change in cardiovascular conditions, such that altering blood volume by fluid expansion and/or autonomic tone by a vasoactive support usually results in a return to baseline hemodynamic status. However, both interventions may have their own deleterious effects.

In our opinion, a first requirement for a safe mechanical ventilation is to limit transpulmonary pressure. A normal right ventricle may develop a maximal systolic pressure of 30 mmHg. During tidal ventilation, this forward pressure should work against a backward pressure, the transpulmonary pressure. In the past, excessive airway pressure was associated with a high frequency and a marked severity of acute cor pulmonale in ARDS [33]. Airway pressure limitation, which was safely obtained with a medium tidal volume (8 ml/kg of measured body weight) combined with a low PEEP (<10 cmH_2O), has reduced the incidence and clearly improved the prognosis of acute cor pulmonale in ARDS [34]. Additionally, interposing regular periods of ventilation in the prone position, by reversing hydrostatic pressure and its protective effect against a zone 2 situation, might regularly unload the most exposed upper areas of pulmonary vascular bed.

A second requirement for a safe mechanical ventilation is use of a low respiratory rate. The majority of ARDS patients have a localized expiratory flow limitation constituting a "slow compartment" [21], which requires a prolonged expiratory time of 4 s to empty [21]. Additionally, a high respiratory rate produces diffuse expiratory flow limitation and enhances gas trapping [37]. Gas trapping increases both pleural pressure and resistance to flow in the pulmonary vascular bed. However, this requirement is probably not absolute and some increase in respiratory rate may be safe, if it is not associated with intrinsic PEEP [36]. This is the case in a small number of ARDS patients, who exhibit a markedly increased elastic recoil of the lung, associated with a negligible slow compartment. Also instrumental dead space reduction may help to correct excessive hypercapnia [36, 38].

A third requirement for a safe mechanical ventilation is to use at least a low PEEP, thus improving blood flow throughout the pulmonary circulation [19]. As previously stated, the "slow compartment" can not empty with ZEEP when the respiratory rate is greater than 10 breaths/min, because its requires an expiration duration of 4 s [21]. As a result, the airway pressure remains high during the expiratory phase in this area, producing a localized and permanent zone 2. Because a low PEEP is able to reintegrate the "slow compartment" [21], it also permits the return of this area to a zone 3 condition during expiration, and a maximal efficacy of a moderate respiratory rate (15 breaths/min) [2]. This PEEP is actually close to that proposed 25 years ago by P. Suter [17].

Conclusion

The introduction of protective ventilation in 1990 by Hickling has greatly improved ARDS outcome [29]. Unknowingly, this author has also provided better working conditions for the RV, and both are probably in part related [39].

Now, the majority of authors interested in respiratory strategy in ARDS focus on complex mechanical studies to evaluate recruitment. Computed tomography (CT) scanning has been proposed for this purpose [40]. Conversely, few authors are concerned by the impact of the respiratory strategy on pulmonary circulation, and this lack of interest parallels the relative fall from grace of the Swan-Ganz catheter, an inaccurate procedure in mechanically ventilated patients [41]. While lung recruitment appears a justified goal in ARDS treatment, the procedure used for this purpose should remain compatible with the integrity of the pulmonary circulation, also required to obtain recovery [42].

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