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What the anaesthesiologist needs to know about heart–lung interactions

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The impact of positive pressure ventilation extends the effect on lungs and gas exchange because the altered intra-thoracic pressure conditions influence determinants of cardiovascular function. These mechanisms are called *heart–lung interactions*, which conceptually can be divided into two components (1) The effect of positive airway pressure on the cardiovascular system, which may be more or less pronounced under various pathologic cardiac conditions, and (2) The effect of cyclic airway pressure swing on the cardiovascular system, which can be useful in the interpretation of the individual patient's current haemodynamic state. It is imperative for the anaesthesiologist to understand the *fundamental* mechanisms of heart–lung interactions, as they are a foundation for the understanding of optimal, personalised cardiovascular treatment of patients undergoing surgery in general anaesthesia. The aim of this review is thus to describe what the anaesthesiologist needs to know about heart–lung interactions.

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Introduction

Positive pressure ventilation during general anaesthesia serves to oxygenate and remove CO_2 from the blood. Yet, the impact of positive pressure ventilation extends these effects because the altered intra-thoracic pressure conditions also influence cardiovascular function. These mechanisms are called *heart–lung interactions*. The term is slightly misleading, as it is generally used for the *unidirectional* effect of the lungs on the cardiovascular system and not the reverse.

Heart–lung interactions can conceptually be divided into two components as highlighted in Fig. 1A:

1. Effect of positive airway pressure on the cardiovascular system

Positive airway pressure affects both the right and left sides of the heart as well as the intra-thoracic and abdominal vessels. These effects may be more or less pronounced under various pathologic cardiac conditions that the anaesthesiologist needs to consider and often prepare before anaesthesia induction.

2. Effect of *cyclic airway pressure swing* on the cardiovascular system

The airway pressure swing in a respiratory cycle also alters determinants of cardiovascular function. The resultant fluctuations in haemodynamic variables can be useful for assessing a patient's current haemodynamic state, although important limitations apply.

Heart–lung interactions are physiologically complex. Still, it is imperative for the anaesthesiologist to understand the *fundamental* mechanisms of heart–lung interactions because they are the foundation for optimal, personalised cardiovascular treatment of patients in general anaesthesia. The aim of this review is thus to describe *what the anaesthesiologist needs to know about heart–lung interactions*: (1) the basic physiological mechanisms underlying the two conceptual components of heart–lung interactions, (2) the haemodynamic effect of the *positive airway pressure component* in patients with specific cardiac comorbidities and (3) the haemodynamic effect of the *cyclic airway pressure swing component* and the relation to preload/fluid responsiveness.

Heart–lung interaction during positive pressure ventilation – basic physiological considerations for the anaesthesiologist

Positive airway pressure

Positive pressure ventilation profoundly influences the basic physiological determinants of both left and right ventricular systolic and diastolic function. Further, as the ventricles function in series, the

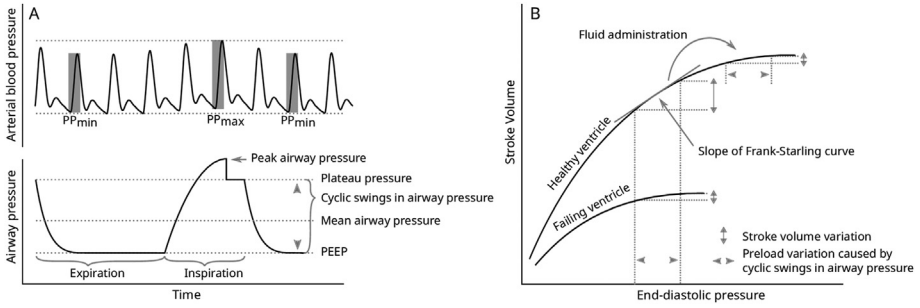

Fig. 1. Panel A: Heart–lung interaction effects can be subdivided as the effect of positive mean airway pressure, which affects the heart in different ways depending on cardiac comorbidities, and the effect of cyclic pressure swings, which creates preload fluctuations and resulting pulse pressure variation or stroke volume variation. Panel B: Frank-Starling curves for a healthy and a failing ventricle. Respiratory preload fluctuations cause stroke volume variation that depicts slope of the Frank-Starling curve, which (within the limitations of stroke volume variation) is synonymous with predicting fluid responsiveness.

effect on one ventricle will alter the function of the other, with a resulting impact on systemic blood pressure and cardiac output [1].

Right ventricle (RV)

Positive airway pressure increases alveolar and thereby pleural pressure, shifting the latter from a state of constant negative pressure to constant positive pressure. Positive pleural pressure increases mediastinal pressure and, to a lesser degree, abdominal pressure, including all structures within. The resulting increase in central venous pressure (CVP) increases the backpressure to venous return, which lowers RV preload and therefore cardiac output. Compensatory mechanisms including squeezing of abdominal capacitance veins due to downward motion of the diaphragm and alpha-receptor-mediated venoconstriction depend on the patient's volume status [2]. Positive pressure ventilation also affects pulmonary artery resistance and hence RV afterload. The relationship between lung stretching and pulmonary artery resistance is U-shaped. Nadir occurs at functional residual capacity and pulmonary artery resistance increases at both lower or higher lung volumes, of which the latter is predominant in positive pressure ventilation [3]. The RV adapts poorly to acutely increased pulmonary artery resistance due to limited contractile reserve, thereby resulting in lower stroke volume (SV) [4]; see Fig. 2.

Left ventricle (LV)

The effects of positive pressure ventilation on LV preload are predominantly mediated by the RV. Decreased RV SV, regardless of cause, transmits into reduced LV preload a few heartbeats later due to pulmonary transit time. Further, if the reduction in RV SV is significant as seen in overt RV failure, its end-diastolic volume increases, which, due to the confinement of both ventricles within the pericardium, will push the interventricular septum leftwards. This reduces LV end-diastolic volume further while elevating LV filling pressure [5].

Additionally, the LV is directly affected by positive pressure ventilation by reducing LV afterload and transiently increasing its preload. The afterload reduction is accomplished by a reduction in LV transmural pressure, as pleural pressure increases. The transmural pressures of extra-thoracic structures including the abdominal aorta are reduced to a lesser extent, and the lowering effect on afterload augments LV SV.

The direct increase in preload, independent of RV performance, is caused by increased alveolar pressure, squeezing the blood pooled in alveolar vessels towards the LV [6,7].

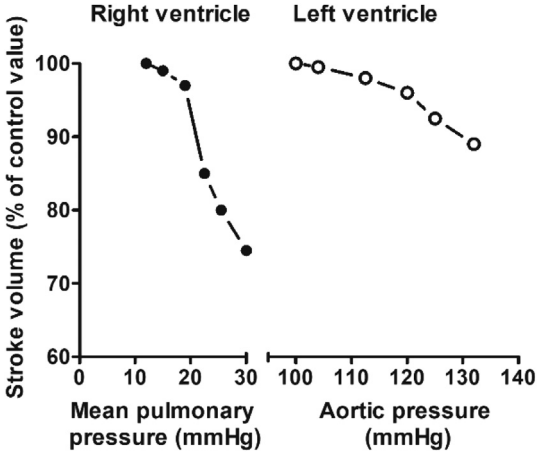

Fig. 2. Effects of increasing afterload on the right and left ventricles. The stroke volume of the left ventricle remains largely unchanged by increasing afterload due to the Anrep effect, which increases left ventricular contractility in response to higher afterload. The stroke volume of the right ventricle decreases markedly in response to afterload increase. Modified from: MacNee W et al. [4]. Reprinted with permission of the American Thoracic Society. Copyright© 2019 American Thoracic Society. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.

Cyclic airway pressure swings

The effect of positive pressure ventilation on LV SV is two-phased [8]. An early increase in SV is caused by the increased preload and reduced afterload to the LV during inspiration, as described above. A following decrease in LV SV is the result of decreased RV SV during inspiration, but because of the pulmonary transit time, the effect is delayed by a few heartbeats; see Fig. 1A. Hence, this effect manifests in the systemic circulation during expiration [8]. Cyclic change in venous return to the RV is regarded as the main mediator of ventilator-induced SV variation (SVV) [9]. SVV therefore represents the heart's response to this change in preload. This is illustrated as the slope at the current Frank-Starling curve operating position; see Fig. 1B. SVV is readily available for visual interpretation in patients equipped with invasive arterial pressure monitoring, as arterial pulse pressure is directly proportional to LV SV [10]. Most current monitors can calculate and display SVV or pulse pressure variation (PPV) automatically, although SVV requires a cardiac output monitor.

Clinical significance of increased mean airway pressure in common cardiac diseases – important considerations for the anaesthesiologist

General anaesthesia requires positive pressure ventilation and infusion of various drugs such as anaesthetics, muscle relaxants and opioids. These interventions can have profound effects on haemodynamics, but the relative contributions of the two are difficult to determine and are subject to choice of anaesthetics, dosage, tidal volume and individual susceptibility. Knowledge of pre-existing cardiac disease assists the anaesthesiologist in choosing anaesthetics with an appropriate haemodynamic profile and in use of vasopressors, inotropes and fluids to proactively counteract the effects of positive pressure ventilation. The following descriptions focus on the effects of positive pressure ventilation and on understanding the physiological principles for initiation of adequate countermeasures. Pharmacodynamic considerations intrinsic to anaesthetics are equally important but outside the scope of this review.

The (relatively) good

LV failure

LV failure is a common issue for the anaesthesiologist. Several aetiologies exist, and it is essential to know the background and type of failure for each individual patient. Therefore, no exact manual can be given, but in the following, we contemplate a patient with a dilated ischaemic LV with an ejection fraction reduced to 10%–30%. Some patients will have overt circulatory failure with dyspnoea and are unable to lie flat; others are compensated in circulation and can seem quite unaffected. A well-treated patient with a dilated LV and decreased EF can have a normal or near-normal SV. However, the myocardium is more sensitive to blood pressure increases, as afterload is already elevated.

- **Maintain systemic blood pressure and heart rate** in the same range as the patient presented before anaesthesia induction. Many patients live on a narrow haemodynamic margin, with blood pressures in the range of 100/50 mmHg, and the range should be maintained throughout anaesthesia. If blood pressure increases too much, the heart will fail, and if the blood pressure decreases, the coronary circulation may be compromised. Even short perioperative periods of hypotension is associated with adverse outcomes such as myocardial injury and acute kidney injury [11]. Many patients cannot vary their SV due to lack of contractile reserve, and therefore, avoidance of bradycardia and aiming for a physiological to slightly elevated heart rate (80–110 min^{-1}) is often preferred to preserve cardiac output and systemic blood pressure.
- **Positive pressure ventilation** is useful because the 'set-point' for generating LV pressure is elevated in comparison with the extra-thoracic compartment, and the heart therefore pumps against a decreased afterload. However, tidal volumes and PEEP should be kept low in case of co-existing RV failure or pulmonary hypertension.

Mitral valve insufficiency

The pathophysiology in mitral valve insufficiency allows blood to enter the left atrium during ventricular systole [12]. In severe mitral valve insufficiency, more than half of the SV enters the left atrium and forward flow is dependent on an elevated preload, LV systolic function and low systemic resistance. Patients with mitral valve insufficiency vary considerably in clinical appearance due to differences in valve pathology and cardiopulmonary comorbidity. In cardiogenic shock, a patient with papillary muscle rupture after an acute myocardial infarction may present with low blood pressure and dyspnoea due to pulmonary congestion. This is in contrast with the elective patient with a degenerated mitral leaflet presenting with almost-normal LV function and no pulmonary congestion, as the left atrium has adapted to receive the regurgitant fraction of the SV.

Still, regardless of aetiology for mitral valve insufficiency, the haemodynamic considerations for these patients remain the same.

- **Maintain preload** to the LV. This may imply fluid therapy, but most patients with mitral valve insufficiency are overhydrated due to some degree of heart failure. In this context of maintaining LV preload, one should remember the importance of RV afterload and maintain normal physiological values of pH, pCO_2, and pO_2 during induction and further into the anaesthesia because derangements can cause pulmonary vasoconstriction. Positive pressure ventilation lowers left ventricular filling and hence decreases the diameter of the mitral valve annulus. This increases coadaptation of the mitral leaflets [13] and, in combination with afterload reduction, forward flow may be increased [14].
- **Decrease afterload.** Most anaesthetics decrease LV afterload by systemic vasodilation. It is generally less dangerous to anaesthetise a patient with a left-sided valve insufficiency than one with a left-sided valve stenosis due to the afterload reducing properties of anaesthetics. Positive pressure ventilation aids with regard to this as previously described, but care should be taken not to exacerbate right-sided problems with high levels of PEEP.
- **Keep heart rate moderately high**, as this will counteract higher end-diastolic volumes of the LV, consequent expansion of the mitral annulus and regurgitant volume. Physiological-to-slightly elevated rates (80–110 min^{-1}) are preferred over bradycardia, the latter unfortunately being an inherent feature of most anaesthetics.
- **Maintain LV pump function.** It can be necessary to use inotropes to increase forward flow. Dobutamine or milrinone are the drugs of choice, as they have vasodilatory and chronotropic properties as well. Dopamine and epinephrine can be used, but they may increase afterload inappropriately.

The bad

Aortic valve stenosis

The systolic intracavitary LV pressure increases dramatically in aortic valve stenosis to overcome the transvalvular pressure drop and maintain systemic perfusion pressure. The LV wall undergoes hypertrophy as a compensatory measure. The decrease in end-diastolic volume will tend to normalise afterload in accordance with the LaPlace principle. Along with fibrosis, myocardial hypertrophy increases stiffness and causes diastolic dysfunction [15,16]. Anaesthesiologists should be wary of patients with moderate-to-severe aortic valve stenosis, as these patients are very susceptible to all components of anaesthesia. Even when the condition is known to the anaesthesiologist, the presence of aortic valve stenosis confers a high risk of perioperative adverse events [17].

Cardinal points of advice include the following:

- **Maintain LV preload.** Patients with diastolic dysfunction require a relatively high filling pressure to obtain a sufficient end-diastolic volume. They are consequently excessively dependent on preload to maintain SV. Failure to maintain SV can reduce systemic blood pressure dramatically. Positive pressure ventilation affects LV preload in the aforementioned ways and, in the patient without pulmonary congestion, focus should be on maintaining preload by keeping tidal volumes low and

ensuring normovolaemia before anaesthesia induction. Further, efforts should be made to keep the patient in sinus rhythm and to treat occurrence of atrial fibrillation aggressively, as atrial contribution to LV filling is particularly important in diastolic dysfunction.

- **Maintain LV afterload (systemic arterial pressure).** Infusion of vasoconstrictors is often necessary to maintain the high diastolic coronary perfusion pressure required in LV hypertrophy. Failure to preserve coronary perfusion pressure may initiate a self-propagating spiral of haemodynamic collapse as LV dysfunction progresses. In addition, vasopressors also constrict abdominal capacitance veins augmenting circulating volume and counteract the reduction in LV afterload commonly caused by anaesthetics. The critical importance of maintaining systemic blood pressure is the reason why spinal block is contraindicated in aortic stenosis.
- **Avoid tachycardia.** It decreases the diastolic period and thereby filling, but it may also compromise coronary perfusion. Intra-mural pressures of the myocardium are very high during systole due to the aortic stenosis, and this effectively precludes systolic coronary flow. Hence, myocardial perfusion is limited to the diastole.

The ugly

RV failure

RV failure may be acute or chronic. Even a healthy RV adapts poorly to acute increases in pulmonary artery resistance and cannot produce a mean pulmonary artery pressure above approximately 40 mmHg [18]; see Fig. 2. In chronic RV failure, right-sided pressures are often higher through hypertrophic adaptation. It is a common misconception that pulmonary pressure is always high in RV failure, as low pulmonary pressure may indeed be a sign of severe failure because the RV is unable to maintain normal SV during normal or increased pulmonary resistance [1]. CVP will, however, be increased. The failing RV is highly susceptible to increased pulmonary artery resistance posed by positive pressure ventilation. If SV cannot be maintained, the RV will dilate. If dilatation is considerable, the diastolic morphology of the interventricular septum changes, which impedes LV filling. Of additional significance, the LV is responsible for up to 40% of the systolic pressure generated in the RV through the shared fibres in the interventricular septum [19]. With impaired LV filling, the contribution of the interventricular septum to RV systole is reduced. As the RV dilates, the tricuspid valve becomes insufficient. This partially counteracts further dilatation. However, the result of a sudden pulmonary artery pressure increase may be a spiralling negative cycle of low SV, RV dilatation, LV diastolic failure and further RV systolic failure. RV ischaemia contributes to this detrimental cycle when the systemic systolic pressure falls below the systolic pulmonary pressure, as the RV is perfused in both systole and diastole, contrary to the LV.

Although these considerations dissuade general anaesthesia for patients with RV failure, the anaesthesiologist has several tools to optimise the chance of a favourable outcome if positive pressure ventilation is necessitated.

- **Maintain systemic blood pressure,** as this not only ensures adequate perfusion pressure of both ventricles but also increases LV end-systolic and hence end-diastolic volumes and pressures. This counteracts the diastolic interventricular pressure difference acting to enlarge the RV and maintains septal contribution to biventricular function. Norepinephrine is the RV's best friend.
- **Optimise ventilation.** Hypercapnia and hypoxia are potent mediators of pulmonary arterial vasoconstriction and should be vigorously avoided. During induction of anaesthesia, the patient should be carefully preoxygenated. Respiratory frequency may be increased but with attention to I:E ratio, securing sufficient expiration time to avoid intrinsic PEEP. A low PEEP should be applied to prevent atelectasis and thereby focal areas of hypercapnia, hypoxia and shunting. Finally, minimising driving pressure and tidal volume reduces pulmonary vascular stretch and thus decrease RV afterload.
- **Actively reduce pulmonary artery resistance.** Inhalation of nitric oxide vapours or prostacyclin analogues relax the pulmonary artery vasculature and reduce pulmonary artery resistance. Nitric oxide may be given through a facemask during induction of anaesthesia, whereas both are available for endotracheal administration. Infusion of dobutamine or milrinone also reduces pulmonary artery resistance and can be given individually or in synergy with nitric oxide [1].

- **As a rule, limit fluids.** Although hypovolaemia and RV failure can coincide, it is unlikely. Supplying fluids to a ventricle that cannot increase SV will cause it to dilate and advance the deleterious cycle described above. If necessary, give a small volume and stop immediately if the CVP increases, indicative of RV overload.

Acute, decompensated left-sided heart disease and positive pressure ventilation

Causes of acute, left-sided cardiac decompensation include ventricular systolic failure, diastolic failure and diseases of the valves. Regardless of aetiology, the clinical manifestation is one of rapidly developing pulmonary congestions, increased respiratory effort and low arterial oxygen saturation, whereas systemic blood pressure may vary. Clinicians may be hesitant to initiate positive pressure ventilation for these patients due to perceived negative effects of RV preload and pulmonary artery resistance. However, physiological conditions change during pulmonary congestion, and positive pressure ventilation, which can be initiated non-invasively through a face mask coupled to a ventilator and therefore easily reversed, may have many beneficial effects on haemodynamics [20].

Positive pressure ventilation lowers LV afterload. This effect decreases LV oxygen consumption and increases systemic oxygen delivery [21]. Applying positive pressure to the airways recruits closed alveoli. When alveolar pressure surpasses the interstitial pressure and the pulmonary venous pressure, West zone IV areas turn into zone III areas and zone III areas turn into zone II areas. By definition, this relieves congestion. In addition, shunting is reduced. These mechanical and hydrostatic mechanisms effectively alleviate the reactive pulmonary vasoconstriction by inducing a higher alveolar oxygen tension, lower carbon dioxide tension and pH elevation. Hence, the net effect of positive pressure ventilation on pulmonary artery resistance is a sum of the vasodilatation caused by alveolar reoxygenation and vasoconstriction mediated by pulmonary vasculature stretch at volumes exceeding functional residual capacity [5]. In addition, clinicians may ignore the potential effects on RV preload. These patients have generally volume excess and will quickly have elevated post-capillary venous pressure in response to any increase in CVP caused by positive pressure ventilation and will therefore maintain the driving pressure to the RV [2]. Finally, patients in severe respiratory compromise use up to 25% of their total energy consumption on respiratory work. This work should preferentially be done by the ventilator, which effectively and significantly reduces the metabolic demand and, in turn, reduces the required cardiopulmonary performance to stay alive; see Fig. 3 for details.

Clinical utility of cyclic airway pressure swings: dynamic variables for prediction of fluid responsiveness

The respiratory fluctuations in LV preload create SVV and PPV due to the Frank-Starling mechanism; see Fig. 1. The magnitude of SVV and PPV therefore identifies the *slope* of the Frank-Starling curve. When predicting whether fluids will increase cardiac output, it is the *slope* of the Frank-Starling curve and not the *specific operating position* that is crucial because the slope will identify fluid responsiveness. The distinction between *operating position* and *slope* of the Frank-Starling curve is pivotal, as it translates directly into the distinction between *preload* and *preload responsiveness*, two very different entities; see Fig. 1B. This is the reason why static markers of *preload*, such as central pressures (i.e. CVP and pulmonary artery occlusion pressure), ultrasound-derived ventricular dimensions and thermodilution-derived variables (e.g. global end-diastolic volume) have failed to predict the haemodynamic *response* to a subsequent fluid challenge [22,23]. On the other hand, the dynamic markers of *preload responsiveness* (SVV, PPV and all their siblings) consistently and across heterogeneous populations predict fluid responsiveness. At a PPV threshold of 12.5%, the area under the classification curve was 0.94 [22].

- **SVV or a PPV of >10–13%** should be used to classify patients as likely fluid responders [24].

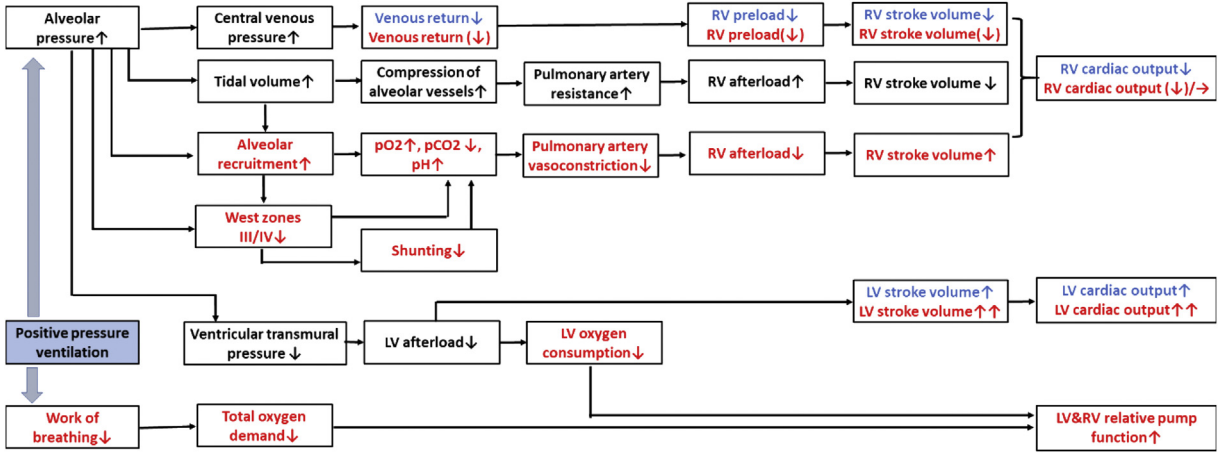

Fig. 3. During acute, decompensated left-sided heart failure, the overall prevailing effects of positive pressure ventilation on basic haemodynamic determinants of **right and left ventricular** function (red font) differ from the effects during normal physiology (blue font). Black font denotes physiological effects of positive pressure ventilation common to both left-sided heart failure and normal physiology. **Compensatory measures subsequently ensure equilibration of right and left ventricular stroke volumes.** RV: right ventricular; LV: left ventricular.

Limitations to dynamic variables

A growing number of clinical limitations have been suggested to the use of SVV and PPV as predictors of fluid responsiveness. It is important for the anaesthesiologist to know and understand these limitations. The LIMITS acronym [25] identifies clinically relevant circumstances where SVV and PPV may not be reliable.

For the *L-I-M*-letters of the acronym, some workarounds may make PPV still reliable:

- **Low heart rate-to-respiratory rate ratio** (HR/RR ratio): When the RR is high in combination with a HR so low that HR/RR < 3.6, the two overall mechanisms causing LV preload variations, namely, the respiratory effects on *each* side of the heart (explained above), start counteracting each other and thereby lower PPV [26]. This is because the two-phased effect on LV preload align more at high RRs in combination with low HRs (the alveolar squeeze towards the LV happens 'too early', i.e. at a time when the alveolar capillaries are not yet 'recharged' with volume) [26]. One could think of this as a *destructive interference* between the two *cyclically varying* effects of on LV preload. A HR/RR of 3.6 is, for example, equivalent to a RR of 15/min and a HR of 54 not seldom seen in general anaesthesia.
  - *Decreasing RR temporarily allows the clinician to circumvent this limitation, resulting in a reliable PPV.*
- **Intra-abdominal hypertension** is encountered in the perioperative setting during pneumoperitoneum for laparoscopic surgery. PPV may be less reliable in intra-abdominal hypertension because of the altered RV preload and LV afterload
  - Clinical studies during laparoscopic surgery suggest that SVV still predicts fluid responsiveness with acceptable accuracy, albeit with optimal thresholds in the range of 12–14% [27–29]. Yet, more and larger studies are needed to substantiate these findings for laparoscopic surgery.
- **Mechanical ventilation with low tidal volume** (Vt): The low Vt limitation was highlighted in 2005 [30]. However, PPV is nearly proportional to the applied Vt with healthy lungs; hence, PPV at a Vt of 6 ml/kg can, for example, estimate what PPV would be at a Vt of 8 ml/kg [31]. Therefore, the Vt limitation of, for example, 8 ml/kg may not be a definitive discriminatory limit, at least not in the perioperative setting where most patients have 'healthy' lungs. In any case,
  - *An initiated Vt of approximately 6 ml/kg as part of lung-protective ventilation can be increased to a Vt of 8 ml/kg temporarily (~1 min) to enable interpreting PPV at 8 ml/kg.*

For the LIMITS acronym letters, *I-T-S*, however, PPV and SVV are not valid:

- **Irregular heart rhythm** refers to frequent ectopic beats or atrial fibrillation. In these cases, the measured PPV originates from the chaotic heart rate rather than cyclic respiratory preload variations, and PPV is therefore typically very high and not interpretable in the context of fluid responsiveness.
- **Open Thorax** hinders the respiratory changes in pleural pressure and in turn the fluctuations in preload. Consequently, PPV is typically low regardless of the patient's fluid responsiveness state.
- **Spontaneous breathing** contrasts controlled mechanical ventilation in numerous ways: It is associated with an opposite phase of respiratory pressures (i.e. the negative airway pressure during inspiration is in contrast to positive pressure ventilation), the length of respiratory cycles can vary substantially and the tidal volume can vary as well. Furthermore, the respiratory component of heart rate variability, which is far more pronounced during spontaneous breathing, contributes to preload variations by varying filling time and, in turn, to the magnitude of dynamic variables [32]. All these mechanisms can cause heterogeneous patterns of preload fluctuations and cause both high and low PPVs, without reflecting fluid responsiveness.

The LIMITS acronym does not include all relevant limitations such as RV dysfunction and one-lung ventilation.

Alternative methods for fluid responsiveness prediction

In situations where PPV and SVV are not reliable, other methods have been suggested. These alternatives are reviewed in more detail [33] and comprise of the following:

- End-expiratory occlusion test [34]
- Recruitment manoeuvre test [35]
- Use of extrasystoles [36]
- Mini-fluid challenge [37]

The first two methods utilise heart–lung interactions, and all methods generally predict fluid responsiveness with acceptable accuracy.

- **The end-expiratory occlusion test** utilises that venous return increases with a 15-s end-expiratory occlusion manoeuvre and thereby elucidates if increased preload will increase SV [34]. It has been investigated in the ICU in one study with excellent results [33] but only in the operating room in two studies [38,39] and with conflicting results, possibly due to methodological issues [40]. Still, this test appears to be the most validated alternative to SVV, as
  - *an SV or cardiac output increases by 5% or more from baseline*; *after performing the end-expiratory occlusion, it has been a consistently sensitive and specific threshold for a positive fluid response* [33].
- **A recruitment manoeuvre** also causes profound heart–lung interactions, and the resulting haemodynamic compromise has been shown to identify fluid responsiveness.
  - *An SV reduction of 16% or more following an increase in PEEP to 25 cmH_2O for 25 s* [35] *or an SV reduction of 30% following an increase in PEEP to 30 cmH_2O for 30 s* [41] *have reliably predicted fluid responsiveness in the perioperative setting*. Still, recruitment manoeuvres are for recruitment and should not be performed solely as a haemodynamic test.
- **The extrasystole method** makes use of the increased preload at the post-ectopic beat (compared with sinus beats, the compensatory pause increases filling time). This method predicts fluid responsiveness with acceptable accuracy in the ICU and in cardiothoracic post-operative care.
  - *A systolic blood pressure increase of 5% or more (compared with sinus beats) was a sensitive and specific threshold for fluid responsiveness* [36,42]. However, the method requires automation and did not work well during cardiothoracic surgery [43].
- T**he mini-fluid challenge** is a fast infusion of 100 ml with subsequent haemodynamic evaluation. Only one study [44] has applied acceptable methodology as recently highlighted [45]. A positive haemodynamic response to a 100 ml mini-fluid challenge should not (based on the current scientific evidence) merit a large fluid challenge of approximately 400–500 ml.
  - *a positive response to a 100 ml fluid challenge could be followed by an equally large (100 ml) fluid challenge to make sure that the fluid treatment is titrated in adequately sized steps of infusions and thereby prevent the associated negative downstream effects of a highly positive post-operative fluid balance* [46].

The place for dynamic variables in the setting of general anaesthesia

When used within their limitations, dynamic variables such as PPV and SVV are the validated variables to answer the question: *Will this patient respond to a fluid challenge with a significantly increased SV and/or cardiac output?* Yet, there are numerous other questions that could be relevant to ask before administering fluids. *Will this patient respond to a fluid challenge with a significantly increased mean arterial blood pressure or enhanced organ function?* This is not a question that SVV or PPV necessarily answers correctly. In fact, the response in blood flow and mean arterial blood pressure can be very divergent. Another question that is not answered by SVV and PPV is whether the patient will encounter side effects and whether the patient can tolerate the side effects. It has never been claimed that SVV or PPV answers anything else other than the first physiological question posed above, which SVV critics tend to forget. Fluid administration to fluid-responsive patients may be merited as prophylactic treatment in general anaesthesia, but it is important to understand, that being *fluid responsive* does not in itself mean *in need of fluids*. On the other hand, lack of fluid responsiveness definitively rules out benefit from fluids. Nonetheless, PPV and particularly SVV are some of very few haemodynamic monitoring variables that have been

implemented into intervention bundles in general anaesthesia, namely, in the framework of *goal-directed therapy*, covered in more detail in this issue [47].

Numerous systematic reviews have summarised goal-directed therapy studies, but it may be problematic to interpret systematic reviews because the underlying randomised trials are clinically too heterogeneous [47]. While it is difficult to completely discard the meta-analytically observed effect on morbidity, better powered, conducted and documented trials are urgently needed. As fluid overload is associated with poor outcome [46], SVV monitoring appears a cornerstone of goal-directed therapy, and it is disappointing that the fluid protocol of the well-powered OPTIMISE-II goal-directed therapy study [48] implements SV maximisation, which was associated with administration of more fluids in the predecessor trial [49]. Nonetheless, it appears well documented that

- **Maintaining an SVV <10–13%** during general anaesthesia in a goal-directed therapy framework does not lead to fluid overload [50].

Summary

The basic physiological mechanisms underlying heart–lung interactions can be subdivided into two components: (1) generally increased mean airway pressure and (2) a cyclic airway pressure swing. A positive airway pressure has specific haemodynamic effects, which depend on the extent of various cardiac comorbidities. The anaesthesiologist has to be cautious when patients have aortic valve stenosis and particularly cautious in the setting of RV failure. On the other hand, in patients with LV dysfunction or mitral valve insufficiency, the increased mean airway pressure may exert a positive haemodynamic effect. Cyclic airway pressure swings constitute a convenient physiological mechanism, which, in most peri-operative patients, can be utilised for fluid responsiveness prediction by interpretation of PPV and/or SVV. Implementing these variables in a goal-directed therapy framework does not lead to fluid overload, but it remains to be determined if such an approach reduces mortality. Still, identifying fluid unresponsiveness with SVV or PPV rules out a direct oxygen delivery benefit from fluids.

Practice points

- The anaesthesiologist has to be aware of positive pressure ventilation-induced heart–lung interactions when patients have aortic valve stenosis and particularly in patients with RV failure.
- In patients with LV dysfunction or mitral valve insufficiency, the increased mean airway pressure may exert a positive haemodynamic effect.
- Stroke volume variation and pulse pressure variation are the best predictors of fluid responsiveness when used within their limitations. Some limitations can be overcome by modification of ventilator settings.
- Lack of fluid responsiveness identified by stroke volume variation or pulse pressure variation definitively rules out a benefit from fluids.
- Goal-directed therapy coupled with stroke volume variation does not lead to fluid overload.

Research points

- The limitations to stroke volume variation and the physiological understanding of these limitations need further research.
- Further research is needed to clarify whether monitoring of stroke volume variation and pulse pressure variation *coupled* with treatment algorithms improves patient outcome.

Conflicts of interest

STV, JG and JNE report no conflicts of interest. PJO has received minor funds from GE Healthcare and Novartis not related to this manuscript.

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