Cardiopulmonary physiology: why the heart and lungs are inextricably linked

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TO BETTER UNDERSTAND cardiopulmonary physiology, students should be presented with an understanding of the dynamic interactions that occur between the heart and lungs. The thoracic cavity, when intact and closed, constrains the heart and lungs to a limited space. As such, intrathoracic pressure changes throughout respiratory phases can have varying effects on cardiac function. Exaggerated effort during respiration [for example during exercise or certain pulmonary diseases, such as chronic obstructive pulmonary disease (COPD)] can increase the importance of these interactions. It is well accepted that elevated intrathoracic pressure during mechanical ventilation decreases cardiac output (CO) (9, 10, 14, 15, 17, 20). A thorough review elucidates some important factors influencing these heart-lung interactions, including external constraint to the heart (8, 26, 32, 47), blood volume redistribution (venous return) (7, 21, 29–31, 38), direct ventricular interaction (DVI) (7, 20, 29–31), and left ventricular (LV) afterload (10, 13, 36, 39). It is the intention of this article to highlight important cardiopulmonary interactions and help direct the reader to seminal papers for further review. We have attempted to provide a resource for health science educators and students alike who are teaching and learning the complexities of this physiological interaction.

All animal experiments were approved by the institutional animal care committee whose criteria are consistent with those of the American Physiological Society.

External Constraint

External constraint to the heart influences CO when it limits diastolic filling. As the heart and lungs lie in close proximity, increased intrathoracic pressure with mechanical ventilation or forced expiration (e.g., patients with emphysematous lungs) increases the pressure around the heart and lungs. Under these conditions, the effective LV distending pressure [i.e., transmural pressure (P_{LVTM})], equal to LV end-diastolic pressure (P_{LVED}) minus the surrounding pressure (i.e., pericardial pressure (P_{PERI})) is reduced (6). The surrounding pressure can be influenced by both pericardial constraint and direct ventricular compression by the lungs. Pericardial constraint by itself would only become important in cases where heart blood volume was increased significantly (i.e., volume loading), during pericardial effusion, or in situations with reduced pericardial compliance (i.e., constrictive pericarditis). However, when intrathoracic pressure is increased significantly (as can often occur during mechanical ventilation or forced expiration), a similar increase in P_{PERI} occurs, which tends to be a major contributor to decreasing P_{LVTM}. LV end-diastolic volume (V_{LVED}), LV stroke volume (SV_{LV}) and stroke work (SW_{LV}) (6, 7, 10, 14, 26). An acute tension pneumothorax demonstrates this phenomenon well, as CO decreases rapidly with increasing intrathoracic pressure (42).

Blood Volume Redistribution (Venous Return)

Intrathoracic pressure changes can also affect blood volume redistribution. Under normal conditions, although negative intrathoracic pressure during inspiration increases right ventricular (RV) end-diastolic volume (V_{RVED}), jugular venous pressure [a conduit marker of RV end-diastolic pressure (P_{RVED})] tends to fall. Not surprisingly, the opposite changes occur during normal expiration as jugular venous pressure rises, reflecting an increased P_{RVED} with increased intrathoracic pressure. Under normal conditions, the RV receives slightly more volume during inspiration and less upon expiration due to the respective decreased and increased thoracic pressures.
When intrathoracic pressure is increased with positive pressure ventilation (PPV), there can be a decrease in the venous pressure gradient between the thoracic and abdominal cavities, resulting in a decreased amount of blood returning to the heart (30, 31, 37, 38). Jardin et al. (21) described an increase in measured abdominal inferior vena cava (IVC) size with PPV, suggesting an enhanced extrathoracic venous capacitance due to pressure gradient differences. Compression, and reduced flow through the thoracic vena cava, lends itself to a reduction in RV preload with PPV. However, in the steady state, returning blood volume must equal CO over time; therefore, even during PPV, reestablishment of the pressure gradient between cavities occurs and flow is quickly reestablished (25, 46, 48). Fessler et al. (12) attributed the maintenance of returning blood volume during PPV with positive end-expiratory pressure (PEEP) to baroreceptor feedback increasing peripheral vascular tone. Their data demonstrated an increase in mean systemic pressure with PEEP, which would reestablish the thoracic–abdominal venous pressure gradient and IVC flow ($Q_{IVC}$). This now brings into question the relative contribution of this mechanism to any further reductions in CO.

Another factor to consider is the effect of lung inflation during PPV on LV preload by compression of the pulmonary venous bed (4, 5, 19). Conceptually, the increased VLVED observed during lung inflation may be due to an increased pulmonary venous flow. Brower et al. (5), using an isolated perfused canine lung preparation, clearly demonstrated that lung inflation resulted in a lower lung blood volume with a concomitant increase in pulmonary venous flow when the lungs were in a pulmonary zone 3 condition (pulmonary artery pressure $> $ pulmonary venous pressure $> $ alveolar pressure). Presumably, the increase in alveolar pressure during lung inflation would cause blood to be expressed from the intralveolar vessels into the LV. This process is analogous to increased venous return with pneumatic stockings as blood is forced from capacitance vessels back toward the heart. Previous studies have clearly shown an increased $V_{LVED}$ and $P_{LVTM}$ during lung inflation at various levels of PEEP (30, 31). This also held true when the effects of preceding ventilatory cycles were eliminated (31). As the lungs in the normal physiological model were primarily in a pulmonary zone 3 condition, it raises the question if this increasing preload effect would also occur in pulmonary zone 2 conditions, which is common in sick ventilated patients [sick patients may experience hypovolemia (reduced circulating volume) that may decrease pulmonary venous pressure below alveolar pressure and create a pulmonary zone 2 condition (pulmonary artery pressure $> $ alveolar pressure $> $ pulmonary venous pressure)]. In zone 2 conditions, elevated alveolar pressure may reduce pulmonary vein patency and flow, eliminating any preload increase (17). Similarly, when pulmonary vascular resistance (PVR) increase is due primarily to pulmonary arterial constriction, as seen with hypoxic vasoconstriction, pulmonary blood flow and $V_{LVED}$ can be reduced (1, 35); hypoxic conditions such as these are common in sick patients (e.g., pneumonia and acute lung injury) (35).

Similarly, changes in abdominal pressure may influence venous return and, therefore, LV preload. Takata et al. (48) evaluated zone 2 and 3 abdominal conditions in an open-chest, IVC bypass canine model. Their results suggest that increased LV preload would be unique to abdominal zone 3 conditions (transmural IVC pressure at thoracic inlet $> $ critical closing transmural pressure) in which $Q_{IVC}$ increased. However, $Q_{IVC}$ decreased as abdominal pressure was increased via phrenic nerve stimulation and diaphragm descent to produce an abdominal zone 2 condition (transmural IVC pressure at thoracic inlet $< $ critical closing transmural pressure), demonstrating a vascular waterfall condition. A clinical correlate that may be useful to teach this physiological effect is abdominal compartment syndrome, a condition defined by significantly elevated abdominal pressures due to various etiologies (e.g., ascites and retroperitoneal hematoma). In fact, up to 1.3% of intensive care patients and 36.4% in trauma patients exhibit this decrease in blood return and CO during abdominal compartment syndrome (45). As with the lungs, the abdominal zone conditions are highly influenced by volemic status with zone 3 abdominal condition more likely to be present with normo- and hypervolemia, whereas zone 2 abdominal conditions exist during hypovolemia (46).

**DVI**

DVI can be viewed as the interaction of both ventricles via the septum occurring both on a beat-to-beat basis and during steady-state conditions. Because of the acutely nondistensible pericardium, changes in filling pressure of either ventricle may alter output of the other (16). For example, if RV afterload is increased, $P_{RVED}$ can increase more than $P_{LVED}$ (2, 3). As the diastolic septal position is determined by the transseptal pressure gradient (TSG) ($P_{LVED} - P_{RVED} = TSG$), a greater increase in $P_{RVED}$ than $P_{LVED}$ would decrease the TSG and shift the septum to the left (27, 49). This can be evident under normal physiological conditions, with an initial reduced systemic blood pressure during inspiration; inspiration produces an immediate increase in venous return to the RV, septal shift, and reduced $SV_{LV}$.

Studies using steady-state measurement have not reached a consensus on mechanical ventilation-related DVI. Jardin et al. (20) showed a significant decrease in LV size due to septal shift in 10 patients with acute respiratory distress syndrome. However, the $>20$-cmH$_2$O airway opening pressure used in their study is rarely used clinically. Another study applied increasing PEEP from 0 to 15 cmH$_2$O in dogs; under these conditions, LV volume decreased, whereas RV volume increased (7). However, Fewell et al. (14) refuted PEEP-related DVI and reported simultaneously decreasing $V_{LVED}$ and $V_{RVED}$ under increasing PEEP levels, suggesting a relation to peripheral blood redistribution, as discussed above.

Potential association between RV size, DVI, and increased PVR during PEEP should also be considered (19, 29, 43). PVR is hyperbolic in relation to lung volume, with the nadir near the functional residual capacity; at low volumes, extra-alveolar vessels collapse, resulting in significant PVR (50). However, increases in PVR with lung volumes above functional residual capacity can be attributed to intra-alveolar vessel compression. This may maintain or increase $V_{RVED}$ while the rest of the heart becomes smaller with increased external constraint. Rankin et al. (41) demonstrated DVI as a result of increased RV afterload and PVR from 15-cmH$_2$O airway opening pressure. In another study, $V_{LVED}$ and $SV_{LV}$ were reduced due to DVI as a result of increasing PVR at successively higher levels of PEEP in anesthetized closed chest dogs (30). Figure 1A
demonstrates this process and associated clinical conditions that may be useful while educating students. Hypoxic pulmonary vasoconstriction, such as during high-altitude physiology (35), high PEEP, COPD, hypoxic pulmonary vasoconstriction, acute lung injury, and large tidal volumes, there is increased right ventricular end-diastolic volume, leading to a leftward septal shift, decreased left ventricular end-diastolic volume, and reduced SV_LV. B: as the RV is highly afterload dependent, the reduced PVR (e.g., during acute volume challenge) results in an increased SV_RV, rightward septal shift, and increased LV preload and SV_LV. In noncardiac failure scenarios, the decreased or increased LV diastolic filling may result in decreased or increased LV afterload in a preload-dependent fashion.

Fig. 1. Direct ventricular interaction (DVI) during increased (A) and decreased (B) pulmonary vascular resistance (PVR). As PVR increases (e.g., during PPV with PEEP, COPD, hypoxic pulmonary vasoconstriction, acute lung injury, and large tidal volumes), there is increased right ventricular end-diastolic volume, leading to a leftward septal shift, decreased left ventricular end-diastolic volume, and reduced SV_LV. B: as the RV is highly afterload dependent, the reduced PVR (e.g., during acute volume challenge) results in an increased SV_RV, rightward septal shift, and increased LV preload and SV_LV. In noncardiac failure scenarios, the decreased or increased LV diastolic filling may result in decreased or increased LV afterload in a preload-dependent fashion.

Fig. 2. Magnetic resonance imaging (MRI) of the chest showing the heart during normal and forced inspiration and expiration in a healthy human volunteer. Forced expiration decreased the size of the heart compared with normal inspiration (A), while forced inspiration increased RV size and flattened the septum compared with normal expiration (B).
strate how the functioning (or malfunctioning) of one system or organ can have significant implications to the functioning of another system or organ.

LV Afterload

Afterload represents an impediment to ventricular output, with an increased LV afterload tending to reduce SV\textsubscript{LV} at a given preload. If intrathoracic pressure is increased, one might expect this pressure to compress the thoracic aorta, which would tend to increase LV afterload. Others suggest the opposite: increased intrathoracic pressure will displace blood from the thoracic to the abdominal aorta and decrease afterload (13, 28). This is likely due to a relatively larger intrathoracic pressure compared with abdominal pressure and lower immediate transmural arterial pressures near the LV (28).

It is generally accepted that, with increasing intrathoracic pressure with mechanical ventilation, there is a redistribution of blood from the central circulation to the periphery with concomitant external cardiac compression (18, 24, 30, 31, 33, 37, 38). This tends to decrease LV preload and, by the Frank-Starling mechanism, SW\textsubscript{LV}. In this case, there might be a preload-dependent reduction in afterload with increasing intrathoracic pressure. Jardin et al. (20) studied 10 patients with acute lung injury and demonstrated a decreased CO, leftward septal shift, and decreased end-systolic P\textsubscript{LVTM} (a surrogate marker of LV afterload) with PEEP levels reaching 30 cmH\textsubscript{2}O. Volume loading at 30-cmH\textsubscript{2}O PEEP also produced an increased end-systolic P\textsubscript{LVTM} compared with abdominal pressure and lower immediate transmural arterial pressures near the LV (28).

As PEEP increased from 0 (PEEP 0) to 18 cmH\textsubscript{2}O (PEEP 18), end-diastolic and end-systolic LV afterload, as indicated by either peak systolic P\textsubscript{LVTM} or end-systolic P\textsubscript{LVTM} as determined by the Frank-Starling mechanism), offsets the effects of increased external constraint, which tends to decrease LV preload (Fig. 3). Denault et al. (10) have published data that are in keeping with the preload dependence of afterload. Using directly measured P\textsubscript{PERI} to calculate P\textsubscript{LVTM}, they demonstrated that LV wall stress decreased during lung inflation, and that the decrease was associated with a decreased LV preload. Although the changes in LV preload during inspiration were opposite to ours, the importance here is that wall stress varied with preload in both instances. Peters et al. (36) demonstrated that sustained negative intrathoracic pressure (phrenic nerve stimulation) decreased V\textsubscript{LVED} and SV\textsubscript{LV} by 37 and 31%, respectively. When applied only during systole while preload was kept constant, the increased LV afterload decreased SV\textsubscript{LV} by only 13%. This suggests that, while both increased afterload and decreased preload contributed to the decreased SV\textsubscript{LV}, increased LV afterload was less important than decreased LV preload. Of note, Pinsky et al. (40) demonstrated improved LV function with increased intrathoracic pressure (initiated with chest pneumatic binders) in a canine model of acute ventricular failure induced by large doses of propranolol. Once again, the preferred explanation for the improved LV function was increased intrathoracic pressure augmented LV ejection by reducing the load on the ejecting LV, while preload was presumed to be constant. Not surprisingly, most studies that have attempted to show this preload independent reduction in LV afterload have been in cardiac failure patients/models, where a failing LV with decreased contractility is most certainly preload insensitive and has been shown to be more afterload sensitive (11, 39, 40).

Summary

This teaching review highlights many of the salient aspects of cardiopulmonary physiology, including references of important papers within the area. As the heart and lungs share a

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**Fig. 3.** Single ventilation cycle relationship between representative examples in a normal, anesthetized canine model illustrating the relations between transmural left ventricle pressure (P\textsubscript{LVTM}) and left ventricular area (A\textsubscript{LV}). A and B: one ventilation cycle at each level of PEEP at P\textsubscript{LVED} of 5 and 12 mmHg, respectively. As PEEP increased from 0 (PEEP 0) to 18 cmH\textsubscript{2}O (PEEP 18), end-diastolic and end-systolic A\textsubscript{LV} (volume) decreased, resulting in decreased SV\textsubscript{LV} and SW\textsubscript{LV}, as indicated by the dimension and area of each loop, respectively. LV afterload, as indicated by either peak systolic P\textsubscript{LVTM} or end-systolic P\textsubscript{LVTM} decreased with PEEP. LV afterload was greater at any level of PEEP at P\textsubscript{LVED} of 12 mmHg than 5 mmHg. The decrease in LV afterload at P\textsubscript{LVED} of 12 mmHg was less than at P\textsubscript{LVED} of 5 mmHg from 0- to 18-cmH\textsubscript{2}O PEEP.

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limited amount of space, it is not surprising that the function of one organ is inextricably linked to the other. Interactions including external constraint to the heart, blood volume redistribution (venous return), DVI, and LV afterload are present to one degree or another during normal respiration, but can be significantly amplified during mechanical ventilation, which is often seen clinically. A thorough understanding of these complex principles is important for both health science students and educators alike.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

K.V. and J.R.M. prepared figures; K.V. and J.R.M. drafted manuscript; K.V. and J.R.M. revised manuscript; K.V. and J.R.M. edited and revised manuscript; K.V. and J.R.M. performed experiments; J.R.M. analyzed data; J.R.M. interpreted results of experiments.

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