ARTICLE

Cardiopulmonary interactions

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Any treatise on cardiopulmonary interactions has at its foundation a thorough understanding of both pulmonary and cardiac physiology. Although recent articles have addressed advances in the field[1] or applications to a particular subspecialty,[2-5] the reader is advised to have basic physiological articles available for a complete background.[6,7] As such, the authors hope to highlight the clinical settings in which a thorough knowledge of cardiopulmonary interactions is essential to the caregiver at the bedside. This review aims to provide the reader with a solid infrastructure in the principles of oxygen supply and demand, the effects of cardiopulmonary interaction on both the right and left ventricles, and application of these principles to both conventional and non-conventional forms of ventilation.

Balancing oxygen supply and demand

At its foundation, human survival is dependent on the organism's ability to maintain an appropriate balance of oxygen supply and demand. More importantly, it is sustained by the adequate delivery of oxygen to tissue, or DO_2. As the oxygen needs of the tissue increase, whether due to a pathophysiological event or routine exercise, delivery must be increased to meet demand. Tissue delivery of oxygen (DO_2) is determined by both cardiac output (CO) and the oxygen content of arterial blood (CaO_2). Mathematically, this can be expressed in the form of equation 1:

$$DO_2 = CO \times CaO_2 \quad \text{(Equation 1), where}$$

$$CaO_2 = (p_aO_2 \times 0.003) + (1.34 \times [Hgb] \times s_aO_2), \text{ and}$$

$$CO = \text{heart rate} \times \text{stroke volume}.$$

Thus, increasing cardiac output or increasing the oxygen content of arterial blood can augment oxygen delivery. Specifically, cardiac output can be improved by optimising inotropy and chronotropy, which in itself is worthy of an entire review article topic. Oxygen content can be increased by raising Hgb, p_aO_2 or s_aO_2. Mathematically, the contribution of p_aO_2 to total CaO_2 is relatively minor, except in cases of significantly increased p_aO_2, such as hyperbaric oxygen therapy. Additionally, optimising the balance of oxygen delivery can be enhanced by decreasing a patient's oxygen consumption. The following review will therefore examine the various interactions of the cardiac and pulmonary systems that impact on the delivery of oxygen.

The heart

Because the heart lies within the thorax, it can be conceptualised as a pressure chamber within a pressure chamber. As a result, changes in the intrathoracic pressure affect all components of the heart equally. However, movement of blood into and out of the thorax is governed by the relationship between the intrathoracic and extrathoracic pressures. Although the effects of cardiopulmonary interactions may be minimal when cardiac and pulmonary functions are normal, they become increasingly important in clinical situations frequently encountered in the modern intensive care unit. Interventions such as positive-pressure ventilation (PPV), medically necessary for acute respiratory failure, may inadvertently have adverse haemodynamic effects. When evaluating the overall effect of interventions on cardiopulmonary interactions, it is important to consider each ventricle separately as phasic changes in intrathoracic pressure have differing effects on the right and left ventricles. Ultimately, it is important to know the predominant effect of cardiopulmonary interactions in the setting in which multiple physiological consequences are in direct opposition to one another.

Right ventricle

Changes in intrathoracic pressure may have a substantial effect on right ventricular (RV) haemodynamics. Because systemic venous return is proportional to the pressure gradient driving blood from the vena cavae to the right atrium, intrathoracic pressure is a significant determinant of both right atrial filling and RV preload (Fig. 1). Because of the highly compliant nature of the right atrium, changes in intrathoracic pressure are readily reflected as changes in the right atrial pressure (P_{ra}), and it is this

pressure that limits systemic venous return. During spontaneous ventilation, the decrease in intrathoracic pressure is transmitted to the right atrium with a resultant increase in systemic venous return. If P_{ra} falls below zero, flow from the systemic venous system is maximised and no further increase in venous return occurs (Fig. 2).

PPV, conversely, results in an increase in intrathoracic pressure during inspiration that is transmitted directly to the right atrium. The subsequent increase in P_{ra} results in decreased venous return during the inspiratory phase. As a result, RV end-diastolic volume (RVEDV) is decreased, as is RV stroke volume. Therefore, manoeuvres that increase intrathoracic pressure result in decreased output from the right ventricle. In contrast to spontaneous ventilation, venous return during PPV is maximal during expiration. As such, increases in the duration of exhalation may help to optimise venous return to the right atrium.

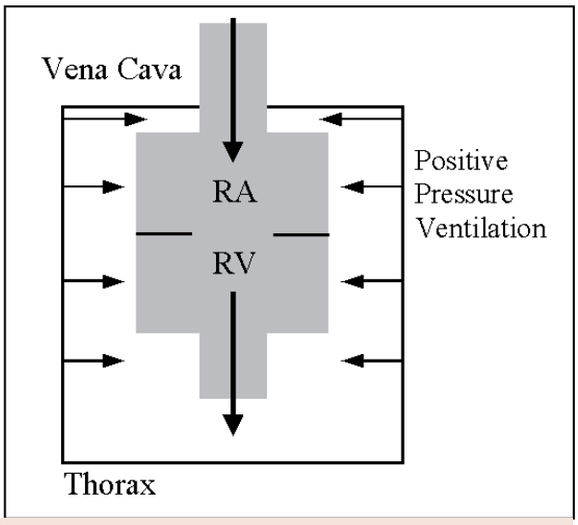

Fig. 1. Schematic diagram of effects of intrathoracic pressure on right ventricle (RV) and right atrium (RA).

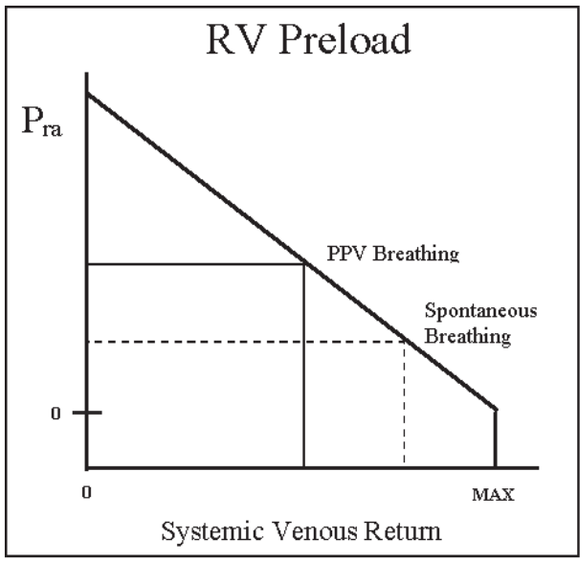

Fig. 2. Graph of right atrial pressure (P_{ra}) versus systemic venous return. Dashed line represents spontaneously breathing and solid line represents positive pressure ventilation (PPV). Note: during PPV the intrathoracic increase in P_{ra} results in a decrease in systemic venous return.

Left ventricle

Changes in intrathoracic pressure may also directly affect the left ventricle. Firstly, changes in intrathoracic pressure can alter left ventricular (LV) preload. For example, negative intrathoracic pressures result in an increase in preload delivered to the left ventricle by virtue of increased pulmonary blood flow. Secondly, changes in intrathoracic pressure can alter LV afterload. Physiologically, the afterload on the left ventricle is the wall stress (T), which must be overcome for the left ventricle to eject blood into the aorta. LV afterload is best described by LaPlace's law, which relates the wall tension (T) of a chamber to the radius (R), wall thickness (H) and transmural pressure (Ptm) (Equation 2).

$$T = P_{tm} \times R^2/2H \qquad \text{(Equation 2)}$$

Transmural pressure is, therefore, a primary (and alterable) determinant of LV afterload. It is conceptually equal to the difference of the forces acting on the internal and external wall of the left ventricle. Whereas LV end-diastolic pressure (LVEDP) acts on the interior of the left ventricular cavity, intrathoracic pressure (often estimated using oesophageal pressure) acts externally on the left ventricle. The transmural pressure across the wall of the left ventricle is equal to the intracavitary pressure minus the absolute value of the pleural pressure. It is a useful concept in the clinical setting, as it is proportional to systolic wall stress as well as myocardial O_2 demand.

During spontaneous ventilation a decrease in pleural pressure results in an increase in LV transmural pressure and therefore increased afterload on the left ventricle, for a given aortic pressure (Fig. 3). Conversely, when intrathoracic pressure is increased in the setting of PPV, transmural pressure and LV afterload are reduced. That is, for a given stroke volume, the transmural pressure generated is decreased in the patient who is mechanically ventilated compared with the spontaneously breathing patient. These changes can produce clinically significant changes in LV performance. Multiple studies have shown an improvement in LV performance in the presence of end-stage heart failure and myocardial ischaemia following initiation of PPV.[8,9]

The principal effects of PPV on the left ventricle are therefore a reduction in LV preload due to diminished pulmonary blood flow and a simultaneous decrease in LV afterload. Provided the decrease in pulmonary blood flow is not deleterious, PPV can improve the performance of the failing left ventricle. In patients with severe congestive heart failure, administration of continuous positive airway pressure (CPAP) via facemask can acutely increase cardiac output.[10,11]

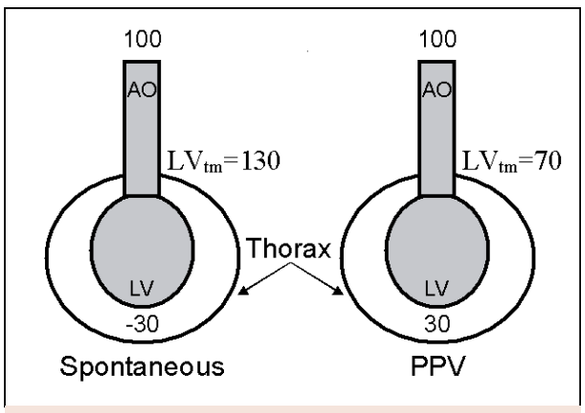

Fig. 3. Diagram of effects of intrathoracic pressure on left ventricle (LV) afterload. Ao = aorta; LVtm = left ventricular transmural pressure; PPV = positive-pressure ventilation. Note: a negative intrathoracic pressure requires the LV to overcome a larger LVtm to eject to the same Ao pressure.

Accordingly, the transition from positive pressure to spontaneous ventilation results in an increase in RV ejection, LV preload and LV afterload.[12,13] This transition is well tolerated in patients without heart disease. However, acute circulatory changes may precipitate myocardial ischaemia or clinical deterioration in patients with marginally compensated heart failure.

The lung

Pulmonary vascular resistance

Changes in lung volume affect pulmonary vascular resistance (PVR) and affect the distribution of pulmonary blood flow (Q_p). In general, pulmonary blood flow is determined by the output of the right ventricle, which is the product of heart rate and RV stroke volume. Output of the right ventricle is dependent upon RV preload, contractility and afterload and inversely proportional to PVR. Using Ohm's law, it is known that PVR = (mean PAP – mean LAP)/Q_p. PVR is determined by the interactions of the large capacitance vessels of the pulmonary arterial tree and the smaller vessels surrounding the alveoli. During spontaneous ventilation, large capacitance vessels are exposed to the negative pleural pressure, which creates radial traction and increases their diameter, thereby lowering their resistance to blood flow. As such, the pulmonary vessels act as a reservoir for the pooling of blood. Extra-alveolar vessels located in the alveolar septae act in much the same way. The smaller pulmonary arterioles, capillaries and venules located in close proximity to the alveolus, however, are exposed to alveolar pressures and compression of these peri-alveolar vessels in the setting of high lung volumes results in an increase in PVR. Because the resistance of alveolar and extra-alveolar vessels differs, the distribution of PVR is complex. Extra-alveolar vessels are exposed to the interstitial pressure, which varies with each respiratory cycle, whereas alveolar vessels behave as if exposed to alveolar pressure. Net PVR therefore is a result of the additive effect of these two forces (Fig. 4). At lung volumes below functional residual capacity (FRC), vessel kinking, atelectasis, and hypoxic pulmonary vasoconstriction result in an increase in PVR. Ultimately, the total PVR across the entire system is the linear sum of these components, which is minimised at FRC.

Distribution of pulmonary blood flow

The two major determinants of the distribution of pulmonary blood flow are gravity and hypoxic pulmonary vasoconstriction. Because the pulmonary vascular bed is a low-pressure system, small gravitational differences between the apical and basal segments of the lung can result in significant differences in regional perfusion pressures. The perfusion to an individual alveolus is dependent upon the relationship between the pulmonary arteriolar pressure, pulmonary alveolar pressure and pulmonary venous pressure. These pressure relationships are dynamic, with significant variation during the course of a respiratory cycle. The West Zones[14] describe the distribution of blood flow within the pulmonary circulation in relation to relative pressures of the pulmonary arteriole, pulmonary venous systems, alveolus and pulmonary interstitium (Fig. 5).

In the spontaneously breathing patient, there is a variable distribution of blood flow within the lung. In West Zone I areas of the lung, alveolar pressure exceeds both pulmonary arteriolar and pulmonary venous pressure, which results in extrinsic compression of these small vessels. Although Zone I conditions do not occur in normal lungs to any great degree, they are often encountered in the intensive care patient.

In Zone II, arterial pressure exceeds alveolar pressure and pulmonary blood flow to these regions is

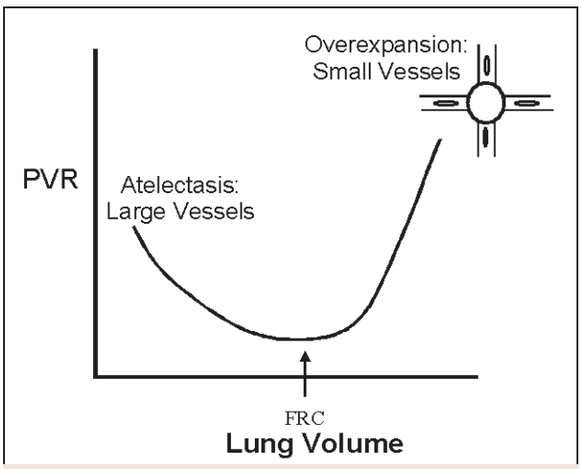

Fig. 4. Idealised graph of pulmonary vascular resistance (PVR) versus lung volume. At low lung volumes atelectasis affects the larger vessels and increases PVR. At large lung volumes overexpansion leads to small-vessel compression and increases PVR. PVR is minimal at FRC.

determined by the arterial-alveolar pressure difference. In Zone III conditions, pulmonary arterial blood flow is not inhibited since both arterial and venous pressures exceed alveolar pressure. In Zone IV, pulmonary interstitial pressure is greater than pulmonary venous and alveolar pressure. The driving force for pulmonary blood flow in these regions is therefore the pressure gradient between the pulmonary arteriolar pressure and the pulmonary interstitial pressure.

In patients with significant lung disease and in those undergoing PPV, alveolar hyperinflation results in compression of pulmonary vessels and an increase in PVR. Cheifetz *et al.* examined the effect of increasing tidal volumes and resulting alveolar overdistension on PVR in a swine model. Using pulmonary artery catheters and an ultrasonic flow probe they were able to quantify the effect of increasing tidal volume and positive end-expiratory pressure (PEEP) on PVR. As would be predicted, their results indicated that PVR increased and cardiac output decreased with increasing tidal volume and that this phenomenon was exacerbated with increasing PEEP.[15]

In patients with RV dysfunction and lung disease, PEEP may be used to increase lung volume towards FRC as a means of decreasing PVR. Additionally, the use of more moderate tidal volumes (6 - 8 ml/kg) minimises the likelihood of alveolar overinflation and subsequently increased PVR.

Carbon dioxide

Carbon dioxide exerts its effect on the cardiopulmonary system primarily via its effect on pH. Uncompensated hypercapnia results in a respiratory acidosis and a subsequent increase in PVR and decrease in systemic vascular resistance. It therefore increases RV afterload and decreases LV afterload. Because of its effects of pH, hypercapnia may also result in a concomitant depression of myocardial contractility. This principle is often used in the management of infants with hypoplastic left heart syndrome (HLHS), whose pulmonary and systemic output is determined by the balance of their relative pulmonary and systemic vascular resistances. Addition of 3 - 5% CO_2 to the inhaled gas mixture is often used to increase PVR, thereby decreasing pulmonary blood flow and improving systemic cardiac output. In an animal model of HLHS, inhaled 5% CO_2 resulted in a 21% reduction in the ratio of pulmonary to systemic (Q_p/Q_s) blood flow.[16] Because elevated p_aCO_2 results in enhanced respiratory drive in these patients, they may require additional sedation in order to blunt stimulation of their respiratory drive.

Hypocapnia, in contrast, results in a decrease in PVR and an increase in systemic vascular resistance. Hypocapnia also decreases ionised calcium levels and results in decreased coronary blood flow and myocardial contractility. Hypocapnia is often used to treat life-threatening pulmonary hypertensive crises in the immediate postoperative period because of its ability to substantially decrease PVR. In a series of 14 patients with postoperative pulmonary hypertensive crises from a variety of left-to-right shunt lesions, hyperventilation resulted in a 32% decrease in mean PA pressures as well as a 30% increase in cardiac index.[17] Similarly, in patients with PPHN, hyperventilation resulted in a 14% increase in the ratio of pulmonary to systemic blood flow and an increase in p_aO_2. Of note, however, is the fact that there can be serious detrimental effects to hyperventilation, primarily related to the decrease in cerebral blood flow seen with acute respiratory alkalosis. Given the availability of agents that act as pulmonary vasodilators, hyperventilation is seldom necessary except in acute periods during which other therapies are being initiated.

In summary, we have briefly described the predominant effects of changes in intrathoracic pressure on both the right and left ventricle, as well as PVR. Now we will examine the predominant effects of changes in intrathoracic pressure secondary to various modes of PPV.

Cardiopulmonary interactions and conventional ventilation

Cardiovascular performance can be improved by the initiation of PPV in patients with increased work of breathing, pulmonary oedema, upper airway obstruction, and impaired LV pump function. Spontaneous breathing may generate large negative intrathoracic pressure swings that increase venous return as well as LV afterload. The result can be the development of pulmonary oedema. Heart failure and pulmonary oedema can create a scenario that results in worsening oedema and hypoxia.

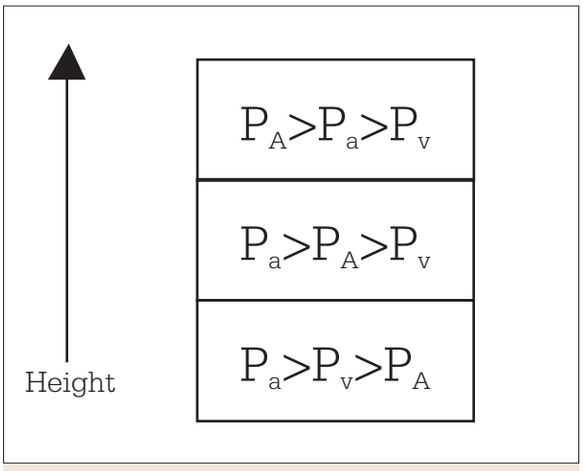

Fig. 5. West zones of the lung indicating effect of gravity on pulmonary vasculature. P_a = alveolar pressure; P_A = arteriolar pressure; P_v = venous pressure. Zone I: Alveolar pressure exceeds arteriolar pressure exceeds venous pressure, Zone II: Arteriolar pressure exceeds alveolar pressure exceeds venous pressure, Zone III: Arteriolar pressure exceeds venous pressure exceeds alveolar pressure.

PPV and the subsequent decrease in venous return is the most commonly observed cardiopulmonary interaction in the intensive care unit. It is a major contributor to cardiovascular decompensation following endotracheal intubation or initiation of bag mask ventilation. The decrease in venous return results in decreased RV end-diastolic volume (RVEDV) and therefore a decrease in RV stroke volume. This effect may be magnified in patients with pulmonary hyperinflation secondary to expiratory airflow limitation. The transition to PPV therefore results in decreased output from the right ventricle. Management in this setting is aimed at reducing right atrial pressure by decreasing intrathoracic pressure, which may be accomplished by decreasing tidal volume, decreasing inspiratory time, or minimising PEEP.

In a patient who is positive-pressure ventilated, increased intrathoracic pressure results in a decrease in LV afterload and an increase in LV stroke volume. However, after a few cardiac cycles, LV preload is diminished owing to a decrease in pulmonary blood flow. This results in a phase lag in which the decreased venous return takes time to manifest in a decrease in LV preload.

If PPV results in a decrease in aortic diastolic pressure and an increase in right atrial pressure, coronary blood flow may be compromised. Intrathoracic pressure may also result in changes in coronary blood flow because of its effects on myocardial O_2 consumption. Because a decrease in intrathoracic pressure results in an increase in LV afterload and an increase in myocardial O_2 demand, coronary blood flow is increased as a result of autoregulation of the coronary vascular bed. It is important also to recognise that excessive pressure surrounding the heart (i.e. excessive PEEP) may result in mechanical compression of coronary vessels.

Alveolar dead space is increased during mechanical ventilation when the lungs are overdistended or pulmonary arterial blood flow is decreased. This augmentation of alveolar dead space is reflected in an increase in the end tidal-arterial CO_2 difference. In the setting of low cardiac output, this gradient becomes dependent almost entirely on pulmonary blood flow and may be accompanied by hypotension. Mechanical ventilation even with standard TV and minimal PEEP may result in overdistension of healthy lungs units relative to perfusion pressure. This results in an increase in West Zones I and II and thus the ratio of dead space to tidal volume (V_D/V_T) increases.

Right-to-left shunting resulting in desaturation may be either intracardiac or extracardiac. When PEEP is applied in the setting of non-homogeneous lung disease, the pressure is preferentially distributed to the more compliant aerated alveolar units. This redirects pulmonary blood flow to less aerated units and may result in an increase in alveolar dead space. This increase in intrapulmonary shunting results in an increase in shunt fraction, venous admixture, and worsening gas exchange. High intrathoracic pressures may also result in an increase in right atrial pressure (P_{ra}) sufficient to result in right-to-left shunting across a patent foramen ovale.

Cardiopulmonary interactions and non-conventional ventilation

High-frequency oscillatory ventilation

High-frequency oscillatory ventilation (HFOV) remains a mainstay of intensive care therapy for severe respiratory disease in infants and children.[18,19] As the patient's pulmonary status worsens and the application of conventional mechanical ventilation results in shear forces toxic to the lung tissue, HFOV becomes a therapeutic alternative. Practically, application of HFOV involves forced oscillations at frequencies of 6 - 9 hertz (360 - 540 bpm) above a set mean airway pressure (P_{aw}). Usually, the set P_{aw} can range from 25 to 35 cm H_20, although higher mean airway pressures may be required. As a result, the most significant cardiopulmonary effect of initiating HFOV is the dramatic rise in P_{aw} and its direct effect on right-sided filling pressures. Patients who do not tolerate the transition to HFOV usually have a poorly compliant RV and concomitant hypovolaemia. To date, the literature is mixed with regard to the net effect of HFOV on cardiac output, as some studies controlled for preload and others did not. The results suggest that strict maintenance of intravascular volume and the anticipation of the decrease in systemic venous return secondary to initiation of HFOV resulted in an increased likelihood of tolerating this mode of ventilation.[20-23]

High-frequency jet ventilation

Although used less commonly, high-frequency jet ventilation (HFJV) is a form of non-conventional ventilation that has utility due to its beneficial effects on cardiopulmonary interactions. In this modality, a small jet of air during inspiration is applied at 240 to 660 bpm delivered over a smaller conventional mechanical ventilator breath (1 - 3 ml/kg). As a result, the increase in conventional settings and potentially harmful cardiopulmonary interactions can be avoided and ventilation maintained. In infants and children after cardiac surgery, HFJV was shown to achieve better ventilation and oxygenation without detrimental effects on haemodynamic parameters associated with conventional ventilation.[24] In addition, in post-operative Fontan patients with single-ventricle physiology, for the same ventilation and oxygenation, HFJV decreased P_{aw} by 50% and decreased PVR by 59% compared with conventional ventilation.[25] The end result was improved systemic venous return.

Negative-pressure ventilation

Negative-pressure ventilation (NPV) has several theoretical advantages when compared with PPV, but its application in the intensive care unit is often not practical. Firstly, the use of the classic 'iron lung' has little utility in the intensive care setting owing to its limitation of routine patient care. However, the feasibility of NPV has been demonstrated by use of a breastplate or chest cuirass. The breast plate is strapped to the patient's chest wall and the application of suction provides external expansion of the chest wall and resulting inspiration.[26] This mode of ventilation avoids the potential complications of tracheal intubation and PPV, has minimal sedation requirements and may improve the tolerance of enteral nutrition. From the standpoint of cardiopulmonary interactions, the negative mean intrathoracic pressure should decrease RV afterload as well as improve systemic venous return. In postoperative paediatric cardiac patients with passive pulmonary blood flow, Shekerdemian *et al.* showed improved RV function using NPV when compared to PPV.[27-29] As may be predicted by its effect on the LV transmural pressure, NPV results in an increase in LV afterload relative to PPV. Patients with poor LV function may therefore not tolerate NPV. In this setting the clinician must weigh the feasibility of initiating NPV and its haemodynamic consequences.

Inhaled nitric oxide

Inhaled nitric oxide (iNO) has found clinical utility as a means of decreasing PVR. As an inhaled vasodilator, NO is rapidly inactivated by haemoglobin in the pulmonary circulation and therefore has no effects on systemic vascular resistance. In the intensive care setting, the application of this gas is usually concomitant with mechanical ventilation. As such, it has relevance to direct effects on cardiopulmonary interactions. To date, it has been shown to be effective for persistent pulmonary hypertension of the neonate[30] and is beneficial for postoperative pulmonary hypertension in the cardiac population. Patients with elevated PA pressures after cardiac surgery (> 50% systemic) showed a 26% decrease in PA pressure and a 37% decrease in PVR after initiation of iNO at 2 ppm. These patients also had a 10% reduction in SVR associated with iNO.[31] iNO's clinical utility lies in its ability to improve ventilation/perfusion matching. Local delivery of iNO to ventilated alveoli results in local pulmonary vasodilation. As a result, some of the untoward effects of PPV on pulmonary blood flow can be abrogated. It appears that iNO is of substantial benefit in patients with severe pulmonary hypertension, but in patients with acute respiratory distress sydrome (ARDS) the results are less compelling. Studies of paediatric patients with ARDS showed improvement in oxygenation indices acutely although no significant increase in patient survival was observed.[32] This effect was enhanced when iNO was delivered concomitantly with HFOV.[33] Recently, a randomised trial with low-dose iNO in non-septic adults with ALI found an acute increase in p_aO_2 but no difference in morbidity or mortality.[34]

Conclusion

In conclusion, a thorough understanding of cardiopulmonary interactions is necessary for management of patients in the intensive care unit. The combination of cardiac disease and respiratory illness creates a unique scenario in which pathophysiology and the physiology of our therapeutic interventions must be well recognised. In addition, these interactions can vary depending on whether the patient is an infant, child, or an adult. While many of our examples come from infants and children with heart disease, the concepts we have described are equally applicable to the adult population. The important message is that cardiopulmonary interactions are multifactorial in that a benefit on one component of the system may be injurious to another. PPV, while beneficial to the failing left ventricle, may be deleterious to the concomitantly failing right ventricle. It is therefore up to the caregiver at the bedside to determine their importance and contribution to management.

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