Cardiopulmonary Interactions

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Objectives: The objectives of this review are to discuss the mechanisms by which respiration impacts cardiovascular function and vice versa, with an emphasis on the impact of these interactions in pediatric cardiac critical care.

Data source: A search of MEDLINE was conducted using PubMed.

Conclusions: In the presence of underlying cardiac and respiratory disease, the interplay between these two systems is significant and plays a pivotal role in the pathophysiology of acute and chronic phases of a wide spectrum of diseases. An understanding of these relationships is essential to optimizing the care of critically ill patients. (Pediatr Crit Care Med 2016; 17:S182–S193)

Key Words: cardiopulmonary interactions; pediatrics; transmural pressure; ventricular interaction

An understanding of the interactions between the respiratory and circulatory systems is essential for the optimal care of the critically ill patient. In this review, we will discuss the physiologic underpinnings of this interplay. Under normal conditions, the interaction between these organs systems is inconsequential; however, they may become exaggerated and of great importance in certain disease states. This review focuses on the volume-pressure and pressure-flow relationships of the cardiovascular and pulmonary systems; the effects that changes in intrathoracic pressure (ITP) and lung volumes have on right and left ventricular (LV) loading conditions; the effects of respiration on cardiovascular function in patients with cardiac disease; the effects of heart failure on respiratory function; and the effects of respiratory disease on cardiac function. An understanding of these complex cardiopulmonary interactions is essential to the management of critically ill children.

VOLUME-PRESSURE AND PRESSURE-FLOW RELATIONSHIPS

The physiologic underpinnings of cardiopulmonary interactions are largely based on the general laws of hydrodynamics applied to a distensible or compressible structure. The extent to which a structure undergoes deformation in response to a force depends on its compliance and the magnitude and direction of the pressure exerted across its wall or its transmural pressure ($P_{tm}$), the difference between the inside and surrounding pressures. A positive $P_{tm}$ distends the structure, and may result from an increase in the internal pressure or from a fall in the surrounding pressure. A negative $P_{tm}$ causes the structure to decrease in size, and may result from a decrease in the internal pressure or from an increase in the surrounding pressure. Compliance describes the pressure-volume relationship for a distensible structure, such that for a given $P_{tm}$, a more compliant structure undergoes greater deformation than a less compliant structure.

The physical properties that govern the flow of fluids (liquid or air) through conducting passages, such as vessels and airways, whether rigid or collapsible, are based on the general laws of hydrodynamics. The behavior of flow ($Q$) through a collapsible structure depends on the inflow pressure ($P_i$), outflow pressure ($P_o$), the surrounding pressure ($P_a$), the $P_{tm}$ and the compliance of the structure (Fig. 1). When the $P_{tm}$ throughout the structure is positive, the tube is widely patent and $Q$ is proportional to the pressure gradient $P_i - P_o$ (also known as “zone III conditions”). With a constant $P_i$ and $P_o$, as the $P_i$ increases, the $P_{tm}$ decreases. As a result, the volume of the structure decreases, the pressure within increases, and as a result, volume is translocated from this compartment to the next. Resistance to flow has increased, and flow is now proportional to the pressure gradient $P_i - P_o$ (zone II conditions). With a greater increase in the $P_i$, the $P_{tm}$ decreases further, and as...
the $P_{tm}$ becomes negative, the structure collapses and $P_t$ greater than $P_i$ and flow ceases (zone I conditions). The physiologic significance of these principles is that many structures within the pulmonary and cardiovascular systems behave analogously as intrathoracic, intra-abdominal, and intravascular pressures and volumes vary.

**THE EFFECTS OF RESPIRATION ON CARDIOVASCULAR FUNCTION**

The Effects of Respiration on Right Ventricular (RV) Preload

Respiration has a significant impact on systemic venous return, thus, a review of the determinants of systemic venous return is germane to any discussion of cardiopulmonary interactions. The force responsible for driving systemic venous return from the periphery to the central venous structures is the pressure gradient that exists between the systemic venous reservoirs and the right atrium (1). The resistance to venous return remains remarkably constant under a number of conditions, including large adrenergic stimulation (2–5). The resistance to venous return changes appreciably with extremes in viscosity, arterial venous fistulae, and with collapse of the vena cava due to the generation of a negative $P_{tm}$ at the thoracic inlet (to be discussed below) (1, 6).

The pressure within the systemic venous reservoirs is equal to the mean systemic pressure ($P_{ms}$). The $P_{ms}$ is derived by arresting the circulation, allowing blood to redistribute and for pressures throughout the entire circulation to equilibrate prior to activation of compensatory circulatory reflexes. Guyton et al (1) found the $P_{ms}$ to be 7 mm Hg in dogs and the normal mean right atrial pressure is 2 mm Hg, producing a driving pressure for systemic venous return under normal conditions of approximately 5 mm Hg.

The $P_{ms}$ is a function of intravascular volume and vascular capacitance, the vast majority of which reside within and with the systemic venous reservoirs (7). These venous reservoirs, the most important of which are located within the splanchnic, splenic and hepatic circulations, are 18 times more compliant than the systemic arterial resistance vessels and thus contain the majority of intravascular volume (upwards of 70% of total). The $P_{ms}$ increases as intravascular volume expands, which occurs over hours with stimulation of neurohormonal pathways, or acutely with the administration of volume. Intravascular volume expansion produces a linear increase in the $P_{ms}$ (8). An immediate compensatory increase in the $P_{ms}$ occurs with vasoconstriction of the venous capacitance vessels. An increase in venomotor tone reduces the capacity of the venous reservoirs, increasing the pressure within (8, 9). Studies have demonstrated that venoconstriction increases the $P_{ms}$ then plateaus, with the most pronounced increase in venomotor tone occurring with the Cushing reflex (8). Endogenous catecholamines, angiotensin, and vasopressin are the primary mediators of this acute compensatory circulatory mechanism for maintaining systemic venous return. Pharmacologic agents such as furosemide, nitric oxide donors, and combined inodilators such as milrinone and dobutamine vasodilate venous reservoirs, increasing their capacitance, and decreasing the $P_{ms}$ and systemic venous return. Pathophysiologic states, such as sepsis, may induce venoconstriction paresis increasing venous capacitance while decreasing intravascular volume as a result of increases in microvascular permeability. The net effect is a marked reduction in the $P_{ms}$ and systemic venous return. Based on the conceptual framework provided for systemic venous return, the systemic arterial pressure is unrelated to venous return and that the flow into the systemic arterial circuit is only relevant insofar as it is responsible for maintaining the volume of the venous reservoirs (Fig. 2) (10–13).

![Figure 1. The physical principles that govern the flow (Q) of fluids through a collapsible tube. $P_i$ = inflow pressure, $P_0$ = outflow pressure, $P_s$ = surrounding pressure, $P_{tm}$ = transmural pressure.](image-url)
During spontaneous respiration, venous return increases as right atrial pressure decreases and then plateaus. The negative ITP is transmitted to the right atrium and to the vena cava as they enter the thorax. When the vascular \( P_{\text{in}} \) becomes negative at the thoracic inlet, as may occur with marked inspiratory effort, the vena cava collapse as they enter the chest limiting venous return (zone I conditions are created). Further decreases in right atrial pressure have no effect on systemic venous return because flow is now a function of the difference between \( P_{\text{in}} \) and atmospheric pressure (for the superior vena cava) or abdominal pressure (for the inferior vena cava) (21). When the outflow or downstream pressure is elevated, as in heart failure, the propensity for the \( P_{\text{in}} \) of the vena cava at the thoracic inlet to become negative decreases.

With positive pressure ventilation (PPV), the opposite occurs. During PPV, the ITP throughout the respiratory cycle is above atmospheric pressure, which decreases the \( P_{\text{in}} \) for the right atrium thereby increasing right atrial pressure. For a given \( P_{\text{in}} \), an increase of only 1 mm Hg in right atrial pressure decreases systemic venous return by 14%. As the right atrial pressure approaches \( P_{\text{in}} \), systemic venous return ceases unless circulatory reflexes compensate by increasing \( P_{\text{in}} \) (13). As described above, this is accomplished acutely with adrenergic stimulation and over time with retention of intravascular volume (22, 23).

It is important to recognize that the increase in right atrial pressure that occurs during PPV results from an increase in ITP and decrease in the right atrial \( P_{\text{in}} \) and not from an increase in systemic venous return and right atrial filling. It may seem counterintuitive that an increase in right atrial pressure may be associated with a decrease in systemic venous return, right atrial filling, and ultimately RV stroke volume because right atrial pressure is used as an indicator of RV preload. However, the increase in right atrial pressure is due to a decrease in its effective compliance as a result of an increase in the surrounding pressure. Pinsky et al (24) demonstrated that it is the effect of interventions such as changes in ITP or intravascular volume on the right atrial \( P_{\text{in}} \) and not the right atrial pressure per se that correlates with RV preload and stroke volume.

In addition to the adequacy of compensatory circulatory reflexes, the extent to which systemic venous return is affected by PPV depends on where the RV resides on its pressure-stroke volume curve and on the degree to which alveolar pressure is transmitted to the cardiac fossa. A congested ventricle will tolerate a decrease in systemic venous return (i.e., stroke volume will be unchanged) so long as it remains operating on the flat portion of its pressure stroke volume curve, and the magnitude of airway pressure and the degree to which lung compliance is impaired determine the extent to which airway pressure is transmitted to the cardiac fossa. In addition to inducing changes in RV loading conditions, respiration alters the effective compliance of the RV by altering the ventricular diastolic \( P_{\text{in}} \) (25–27). A noncompliant ventricle or one surrounded by positive pressure requires a higher than normal intracavitary pressure to achieve an adequate end-diastolic volume (Fig. 3).

**Figure 2.** Tub analogy. Water in a tub represents blood within the systemic venous reservoirs. The inflow tap represents the arterial flow. The water leaves the tub (systemic venous return [VR]) at a rate that depends on the diameter of the hole (resistance to VR) and the height of the water above the hole. Venoconstriction is represented by a downward displacement of the hole, or an increase in the height of the water above the hole, and venodilation by an upward displacement of the hole, or a decrease in the height of the water above the hole.

The downstream pressure for systemic venous return is the right atrial pressure, which is affected by a number of factors, specifically cardiac function and the cardiac cycle (so-called “cardiac suction factors”) (14–16), and respiration. During spontaneous respiration, ITP decreases and the \( P_{\text{in}} \) for the right atrium increases, and as a result, the right atrium distends and the pressure within falls, driving systemic venous return. Contributing to the pressure gradient for systemic venous return is diaphragmatic descent, which increases intra-abdominal pressure, causing the \( P_{\text{in}} \) and the capacity of the intra-abdominal venous reservoirs to decrease and the pressure within to rise (17–20). This creates a longitudinal pressure gradient for systemic venous return from the largest of venous reservoirs. In other words, during inspiration, systemic venous return from the abdominal compartment results from a phasic decrease in right atrial pressure and increase in the \( P_{\text{in}} \) within the abdominal venous reservoirs. This is in contrast to venous return from the head and neck vessels, which are exposed to atmospheric pressure.
Hypoxic pulmonary vasoconstriction ensues, and the resistance, at low end-expiratory lung volumes, alveoli collapse and the cross-sectional area of the extra-alveolar vessel. In addition, the pulmonary interstitium diminishes, leading to a decrease in pulmonary vascular resistance. Alveolar pressure is the surrounding pressure for these vessels. Extra-alveolar vessels are located in the interstitium and are exposed to intrapleural pressure. Because alveolar and extra-alveolar vessels are in series, the resistance provided by each are additive. Functional residual capacity (FRC) is the lung volume from which normal tidal volume breathing occurs. PVR is lowest near the FRC and increases at both high and low lung volumes.

At low lung volumes, the radial traction provided by the pulmonary interstitium diminishes, leading to a decrease in the cross-sectional area of the extra-alveolar vessel. In addition, at low end-expiratory lung volumes, alveoli collapse and hypoxic pulmonary vasoconstriction ensues, and the resistance of extra-alveolar vessels increases further. However, the $P_{in}$ of alveolar vessels increases at low lung volumes because the alveolar $P_{in}$ falls. Nonetheless, the net effect is for PVR to increase with lung volumes well below FRC.

As lung volumes rise well above FRC, PVR increases. Large tidal volumes or tidal volumes superimposed on an elevated FRC significantly increase PVR. With large lung volumes, distended alveoli compress interalveolar vessels, decreasing the $P_{in}$ for the interalveolar vessel (creating zone I and II conditions) and increasing PVR. With PPV, the interstitial pressure is positive, decreasing the $P_{in}$ for the extra-alveolar vessels as well, contributing to PPV-induced increases in PVR. In other words, during PPV, alveolar and intrapleural pressures are positive during inspiration and expiration, and resistance is elevated in both alveolar and extra-alveolar vessels throughout the respiratory cycle. This is in contrast to an increase in lung volume due to negative pressure ventilation where interstitial pressure is negative. This is an important consideration when using PPV, particularly in patients with a normal pulmonary venous pressure and in patients with underlying pulmonary vascular disease and right heart dysfunction (to be discussed below).

The extent to which lung volume affects PVR also depends on pulmonary vascular hydrostatic pressures. In the lung, pulmonary arterial pressure is the inflow pressure ($P_i$), pulmonary venous pressure is the outflow downstream pressure ($P_o$), and alveolar pressure is the surrounding pressure ($P_a$). In addition, there is a vertical hydrostatic pressure gradient from the most dependent to the most superior portions of the lung. Because the weight of air is negligible, there is no measurable vertical gradient for alveolar pressure. In the gravity-dependent portions of the lung, $P_i$ and $P_o$ are greater than $P_a$ and the $P_{in}$ for the alveolar vessel is positive throughout (zone III conditions) (Fig. 1). With progression to the nongravity-dependent regions of the lung, PVR begins to increase as $P_i$ becomes greater than $P_a$ but remains less than $P_o$ (zone II conditions) (Fig. 1). In the event that $P_i$ becomes greater than $P_o$ and the $P_{in}$ for the alveolar vessel becomes negative, the vessel collapses and flow ceases (zone I conditions) (Fig. 1). In the absence of cardiopulmonary disease, zone I conditions do not exist. However, the proportion of lung units under zone I and II conditions increases in a variety of clinical settings. The use of PPV in patients with a normal $P_i$ (pulmonary venous pressure) increases the proportion of lung units under zone I and II conditions. Conversely, left heart failure with its attendant pulmonary venous hypertension will increase the proportion of lung units under zone III conditions, rendering the pulmonary vasculature less vulnerable to large lung volume induced increases in PVR.

The interaction between lung volumes and PVR is compounded by the impact of this interplay on gas exchange. Large lung volumes create high ventilation-to-perfusion ratios (V-to-Q ratios), which leads to wasted ventilation and is characterized by an elevated arterial to end-tidal $CO_2$ gradient. Increasing ventilatory support may seem intuitive as the arterial $PCO_2$ is elevated; however, this exacerbates the inefficiency in gas exchange by further increasing the V-to-Q ratio by increasing lung volumes while decreasing RV output, which is due to the effects of increases in ITP on RV loading conditions. Large V-to-Q ratios do not directly cause pulmonary venous admixture. However, a worsening of oxygenation may occur due to the creation of zone I conditions. This occurs if blood flow is shunted from over distended lung units to normally or
The Effect of Respiration on LV Preload

Respiration affects LV preload by altering RV loading conditions and the RV diastolic \( P_{\text{tm}} \), as reviewed above. Another important determinant of the impact of respiration on LV preload is RV systolic function. As a thin-walled structure that functions as a bellow during shortening, the unprepared RV has much less contractile reserve than the LV, and is therefore much more sensitive to increases in afterload (28). Further, with PPV-induced increases in RV afterload, the effect of increases in ITP on the pressure gradient for systemic venous return may limit the extent of RV preload reserve, contributing to a fall in RV output.

Right heart dysfunction compromises LV filling by three mechanisms. In addition to a decrease in RV stroke volume and output, right heart dysfunction compromises LV output as a result of ventricular interdependence (28). RV dysfunction leads to RV diastolic hypertension, which decreases the normal transseptal pressure gradient. Under normal conditions, LV diastolic pressure is greater than right causing the interventricular septum to bow into the RV (Fig. 4). With RV diastolic hypertension, the interventricular septum occupies a more neutral position between the two ventricles (Fig. 4). If RV diastolic pressures were to rise above left, the septum would actually bow into the LV. In either case, the LV becomes restrained not only by RV pressure and the deviated septum but also its free wall becomes constrained by the pericardium. These factors decrease the effective compliance of the LV. Even though the LV filling pressure is elevated, intrapericardial pressure has risen to a greater extent, and the net effect is a reduced LV diastolic \( P_{\text{tm}} \) and LV filling. This phenomenon is known as “diastolic ventricular interdependence.” This also occurs in the normal circulation albeit to a lesser extent. During spontaneous respiration, increases in systemic venous return and RV filling and pressure alter the position of the interventricular septum. This mechanism is the diastolic component of pulsus paradoxus, the decrease in systolic arterial blood pressure that occurs during spontaneous inspiration (29).

Finally, as LV filling decreases, the pressure generating capabilities of the LV are diminished. The significance of this as it relates to the circulation with impaired RV systolic function and increased RV afterload is that the LV is responsible for generating upwards of 40% of RV systolic pressure (30). This decrease in LV assistance to RV ejection leads to further increases in RV volume and pressure, which further impairs LV filling and pressure generating capabilities. This phenomenon is known as “systolic ventricular interdependence,” and plays an essential role in the pathophysiology of low cardiac output due to pulmonary arterial hypertension.

The effects of PPV on the right heart depend on the extent to which increases in ITP are transmitted to thoracic structures and on the extent to which changes in ITP affect LV afterload (31, 32). As will be discussed below, PPV increases cardiac output in patients with LV systolic heart failure and pulmonary venous hypertension, but may decrease cardiac output in patients with normal ventricular loading conditions.

The Effects of Respiration on LV Afterload

Respiration has a profound impact on LV output. Changes in ITP modulate not only the pressure gradient for systemic venous return but also the pressure gradient responsible for propelling blood from the thoracic cavity. While the right atrium and vena cava are much more compliant than the systemic arterial vessels, it is the compliance and \( P_{\text{tm}} \) for the thoracic arterial vessels that determine the extent to which changes in ITP contribute to the pressure gradient for driving blood from the chest, and therefore to the extent that changes in ITP affect LV afterload (33).

During spontaneous respiration, the fall in ITP increases the \( P_{\text{tm}} \) and therefore volume for the thoracic arterial system. As a result, the pressure within the thoracic arterial system decreases relative to the extrathoracic arterial system and LV afterload increases (34). The effect of a decrease in ITP on LV afterload is physiologic the same as a rise in the systemic arterial blood pressure. According to Laplace law, LV afterload increases as the systolic \( P_{\text{tm}} \) increases which occurs with a decrease in ITP or rise in systemic arterial systolic pressure (Fig. 5).

If the fall in ITP occurs during ventricular diastole, antegrade flow runoff decreases, resulting in an increase in thoracic arterial blood volume and an increase in the inertial forces opposing ejection during the following systole. A fall in ITP during ventricular systole decreases the egress of blood from the thorax as well as LV ejection and stroke volume (35, 36). The distension of the thoracic arterial vessels and decrease in LV output are responsible for the decrease in blood pressure during systole that occurs with spontaneous respiration, and is the mechanism responsible for the systolic component of pulsus paradoxus (34). As LV systolic function wanes or as ITP becomes more negative, the adverse impact of respiration on LV afterload increases. Further, during exaggerated negative pressure breathing, the sympathetic nervous system is...
Ultimately, the various therapies that may be deployed must consider interdependence plays in the pathophysiologic process.

The primary problem is ventricular filling or emptying; and whether RV or LV dysfunction is present and to what extent the primary problem is ventricular filling or emptying; and whether RV and LV afterload is affected and to what extent ventricular interdependence plays in the pathophysiologic process. Ultimately, the various therapies that may be deployed must optimize systemic oxygen delivery.

**THE IMPACT OF RESPIRATION ON CARDIOVASCULAR FUNCTION IN PATIENTS WITH CONGENITAL AND ACQUIRED CARDIAC DISEASE**

**LV Systolic Dysfunction**

In patients with LV systolic dysfunction, stroke volume and cardiac output are low despite elevated ventricular volumes and pressures. Thus, the predominant effect of PPV is on reducing LV afterload. If systemic venous return is reduced, so long as the ventricles remain on the flat portion of their pressure stroke volume curve the reduction in preload does not compromise stroke volume. Studies have demonstrated in patients with systolic heart failure that cardiac output increases significantly so long as an adequate albeit elevated LV filling pressure is present at baseline (39, 40).

In addition to improving cardiac output, PPV improves the myocardial and global oxygen supply demand relationship by reducing myocardial and respiratory muscle oxygen consumption. In accordance with Laplace law, by decreasing the ventricular diastolic and systolic \( P_{tm} \) PPV reduces myocardial oxygen demand. In patients with cardiogenic pulmonary edema and exaggerated negative pressure breathing, the PPV-induced reduction in the ventricular systolic \( P_{tm} \) is profound. In addition, by unloading the respiratory muscles, PPV reduces respiratory muscle oxygen demand and in doing so allows for a redistribution of a limited cardiac output to other vital organs (to be discussed further below). The unloading of the respiratory pump and cardiovascular system during PPV also leads to a partial withdrawing of sympathetic nervous system activity, contributing to a reduction in ventricular afterload (41).

The importance of these principles has been demonstrated in several studies and in different lines of investigation. Räsänen et al (42) found that progressing from PPV to spontaneous respiration adversely affected the myocardial oxygen supply demand relationship in patients with acute myocardial infarction complicated by respiratory failure, resulting in myocardial ischemia and significant elevations in the LV filling pressure. Scharf et al (43) demonstrated acute LV regional akinesis in patients with preexisting LV dysfunction during performance of the Mueller maneuver (inspiration against a closed glottis). Ju bran et al (44) demonstrated in adult patients with underlying cardiopulmonary disease receiving PPV, that patients who failed a spontaneous breathing trial were unable to increase their cardiac output in order to meet the metabolic demand of the respiratory muscles, which was reflected in the progressive increase in their oxygen extraction ratios, and developed a 2.5-fold increase in LV filling pressures. In contrast, those patients who tolerated the spontaneous breathing trial demonstrated a significant compensatory increase in cardiac output and maintained a normal oxygen extraction ratio and LV filling pressure.

Continuous positive airway pressure (CPAP) or PPV may be delivered noninvasively so long as the patient is cooperative. In adult patients with decompensated LV systolic heart failure and pulmonary edema, meta-analyses have shown a significant reduction in the need for intubation and early mortality with noninvasive positive airway pressure (45, 46). The long-term benefits of noninvasive positive airway pressure have also been demonstrated in adult patients with chronic heart failure.

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**Figure 5.** Illustration of the left ventricle, thoracic cavity, and aorta. Similar changes in the left ventricular systolic transmural pressure \( P_{tm} \) can be generated by manipulating aortic or intrathoracic pressure (ITP). When negative ITPs are exaggerated, as occurs with respiratory disease, the \( P_{tm} \) increases significantly. PPV = positive pressure ventilation.

stimulated, which leads to an increase in endogenous catecholamine release, systemic vascular resistance, and arterial blood pressure, contributing to further increases in LV afterload, and a vicious cycle ensues.

With PPV, the decrease in \( P_{tm} \) for the thoracic arterial system increases the pressure within creating a waterfall-like effect, driving blood into the extrathoracic compartments. If the increase in ITP is confined to diastole, the LV ejects into a relatively depleted thoracic aorta with reduced inertial forces opposing ejection, while a selective increase in ITP during ventricular systole augments LV ejection without compromising the gradient for systemic venous return. An increase in ITP therefore unloads the LV while increasing aortic diastolic and systolic pressures (reverse pulsus paradoxus) (37, 38). Even though aortic pressures increase, the LV \( P_{tm} \) has decreased, as ITP has risen to a greater extent than LV and thoracic arterial pressures.

Understanding the physiologic principles that govern the interplay between cardiovascular and respiratory systems is essential to optimizing the care of critically ill patients. Consideration must be given to intravascular volume status and the function of the venous capacitance vessels; whether RV or LV dysfunction is present and to what extent the primary problem is ventricular filling or emptying; and whether RV and LV afterload is affected and to what extent ventricular interdependence plays in the pathophysiologic process. Ultimately, the various therapies that may be deployed must optimize systemic oxygen delivery.
Haruki et al (47) found that the prolonged use of noninvasive PPV delivered for at least 4 hours per day for 6 months led to ventricular remodeling and significantly improved LV ventricular diastolic and systolic function.

**Ventricular Diastolic Dysfunction**

Restrictive cardiomyopathy and to a lesser extent hypertrophic cardiomyopathies are characterized by varying degrees of ventricular diastolic dysfunction while LV systolic function is maintained. Ventricular end diastolic volumes are normal if not reduced thus one would expect that the predominant effect of PPV would be on the right heart, and that the determinants of the $P_{mm}$ would be of particular relevance in these patients (48). Further, in hypertrophic cardiomyopathies, if the substrate for an obstruction to LV outflow is present, by decreasing LV preload and afterload, PPV may create or exacerbate an intracavitary obstruction by reducing LV operating volumes (49).

The impact of respiration on ventricular loading conditions in the setting of ventricular diastolic disease is exemplified in the postoperative management of patients following repair of tetralogy of Fallot. In these patients, biventricular systolic function is normal; however, RV diastolic dysfunction is common, and in a subset of these patients restrictive RV physiology is present, which is characterized by a severe reduction in myocardial compliance and elevation in RV diastolic pressure (50, 51). Shekerdemian et al (52) demonstrated a significant increase in stroke volume and cardiac output when patients were converted from PPV to negative pressure ventilation using a cuirass. In contrast to patients with LV systolic dysfunction, where spontaneous ventilation decreases cardiac output while increasing respiratory muscle oxygen consumption, in patients with diastolic dysfunction, the improvement in cardiac output with progression to spontaneous respiration may be offset by the attendant increase in respiratory muscle oxygen demand. Bronicki et al (53) demonstrated in patients following repair of tetralogy of Fallot that while cardiac output increased with spontaneous respiration, mesenteric oxygenation decreased significantly, suggesting that cardiac output remained limited and was redistributed to meet the increase demands of the respiratory pump. Although negative pressure ventilation is impractical, the discussion highlights the impact of changes in ITP on cardiac output in the setting of diastolic dysfunction. Consideration should be given toward minimizing airway pressure, maintaining adequate intravascular volume and proceeding to spontaneous respiration as soon as it is feasible.

**The Fontan Circulation**

Following the Fontan procedure, as in the normal circulation, the $P_{mm}$ is the upstream pressure for driving systemic venous return, while the pressure within the confluence of the vena cavae and pulmonary artery is the downstream pressure (54). However, because the Fontan circulation lacks a subpulmonary pumping chamber, the $P_{mm}$ is the upstream pressure for driving systemic venous return not only to the central confluence of the vena cavae and pulmonary artery but also the pressure responsible for driving blood across the pulmonary circulation to the common atrium (54, 55). Changes in ITP affect the confluence of the vena cavae and pulmonary circulation and the common atrium equally, while decreases in the common atrial pressure during the cardiac cycle contribute to the pressure gradient for driving pulmonary venous return (56, 57). Finally, because the Fontan circulation relies on the $P_{mm}$ as the upstream pressure for driving systemic venous return and pulmonary blood flow, it is particularly sensitive to increases in PVR (58) and decreases in systemic ventricular function.

Following the Fontan procedure, systolic function is generally normal while there is invariably some degree of ventricular diastolic dysfunction, with incoordinate wall motion further compromising ventricular filling (59–64). For these reasons, the effects of changes in ITP on systemic venous return and on the $P_{mm}$ for the common atrium predominate over its effects on afterload of the systemic ventricle. Shekerdemian et al (65) demonstrated a marked increase in pulmonary blood flow and cardiac output when patients were transitioned form PPV to negative pressure ventilation using a cuirass immediately following and remote from the Fontan procedure.

While a fall in ITP promotes systemic venous return, it is interesting to speculate as to what maintains systemic venous return in the presence of PPV (conventional or high frequency oscillatory ventilation), where ITP remains greater than atmospheric throughout the respiratory cycle. Studies in patients with the acute respiratory distress syndrome (ARDS) have demonstrated the vital role that circulatory reflexes play in generating a compensatory increase in the $P_{mm}$ in response to a significant increase in ITP due to PPV (23, 66).

Studies have demonstrated that immediately following the Fontan procedure neurohormonal pathways are activated, leading to a compensatory increase in the $P_{mm}$ (55, 67, 68). Several studies have also demonstrated adaptive changes taking place over time in the peripheral circulation that serve to maintain a chronically elevated $P_{mm}$ (55, 67, 68). Krishnan et al (68) studied patients remote from the Fontan procedure and found significantly reduced venous capacitance as well as significantly elevated microvascular filtration thresholds and $P_{mm}$.

A further example of the vulnerability of the Fontan circulation to factors that compromise systemic venous return is the hemodynamic consequence of hemidiaphragmatic paralysis. As discussed, inspiration and diaphragmatic descent increase intra-abdominal pressure and ultimately contribute to the longitudinal pressure gradient for systemic venous return. Phrenic nerve injury following the Fontan procedure and resulting hemidiaphragmatic paresis would be expected to compromise venous return from the largest of venous reservoirs. Indeed, several studies have demonstrated reduced hepatic venous flow during inspiration, and portal venous flow loses its normal expiratory augmentation in patients with hemidiaphragmatic paralysis (69–72). In these patients, hemi-diaphragmatic plication only partially restores sub-diaphragmatic venous return, as this does not compensate for the loss of diaphragmatic descent during inspiration.
THE EFFECTS OF RESPIRATORY DISEASE ON CARDIOVASCULAR FUNCTION

Sleep Disordered Breathing

Obstructive sleep disordered breathing (OSDB) is a relatively common respiratory disorder occurring in approximately 3% of all children, and is associated with other conditions commonly found in the critical care setting, such as Down syndrome, neuromuscular disease, and heart failure. OSDB like other diseases of the respiratory system primarily affects cardiovascular function by altering ITP. OSDB is characterized by repetitive episodes of inspiratory flow limitation or cessation of inspiratory flow and occurs when sleep-related withdrawal of respiratory drive to the upper airway dilator muscles is superimposed on an upper airway with underlying structural and or functional abnormalities, leading to the generation of exaggerated negative ITP. Upper airway obstruction also causes hypoxia and acidosis, increasing PVR. The increase in the work of breathing also activates the sympathetic nervous system and renin-angiotensin-aldosterone systems, contributing to increases in biventricular afterload (73). Exaggerated negative pressure breathing also leads to an increase in system venous return and diastolic ventricular interaction, contributing to a decrease in LV output.

The impact of exaggerated negative pressure breathing and an increase in biventricular afterload on cardiovascular function is greatest in subjects with underlying LV systolic dysfunction. Contributing to the spectrum of sleep-disordered breathing seen in patients with heart failure is the relatively common finding of central sleep apnea, which is manifested as Cheyne-Stokes respiration, a form of periodic breathing with a crescendo-decrescendo pattern of breathing (74). Stimulation of pulmonary vagal irritant receptors by pulmonary edema augments the respiratory drive causing hyperventilation and a decrease in the 

\[ \text{Paco}_2 \]

which falls below the apnea threshold, leading to a loss of central drive. Ventilation returns as \( \text{CO}_2 \) production increases the \( \text{Paco}_2 \) to levels above the apnea threshold, stimulating hyperventilation, which in turn causes the \( \text{Paco}_2 \) to fall below the apnea threshold. Bradley et al (40) demonstrated that central events alone did not cause stroke volume to decrease while isolated obstructive events caused a significant decrease in stroke volume in adult patients with heart failure (75).

The net effect of obstructive and central sleep apnea in patients with a limited cardiac output is a disturbance in the oxygen supply demand relationship for all viscera, including the brain and myocardium, leading to repeated episodes of ischemia reperfusion injury (74). The adverse impact of these effects on the myocardium are exemplified in the findings by Kuniyoshi et al (76) who evaluated the relationship between the day and night variation of presentation for acute myocardial infarction. The odds of having OSDB in those patients whose acute myocardial infarction occurred during sleeping hours was six-fold higher than in those having an acute myocardial infarction during the remainder of the day, and of all the patients having an acute myocardial infarction between midnight and 6 AM, 91% had OSDB.

The cumulative effects of sleep disordered breathing on cardiovascular function can precipitate or contribute to the development of ventricular remodeling and RV and LV diastolic and systolic disease (74, 77–80). Noninvasive CPAP has been shown to reverse ventricular remodeling and improve biventricular diastolic and systolic function while chronically lowering systemic blood pressure (77, 81).

ARDS and Cardiovascular Function

The use of PPV in patients with the ARDS may induce significant cardiopulmonary interactions that adversely impact gas exchange, cardiac output, and ultimately systemic oxygen delivery. As discussed, increases in ITP may compromise systemic venous return as well as the effective compliance of the RV. The extent to which increases in ITP affect RV filling depends on lung compliance and the extent to which ITP is transmitted to intrathoracic structures, as well as intravascular volume and the adequacy of circulatory reflexes to maintain the \( P_{pa} \) (31, 32).

Another important effect of PPV on the right heart in patients with ARDS results from the effects of the alveolar \( P_{alveolus} \) and resulting lung volume on RV afterload. Jardin et al (82, 83) evaluated patients receiving PPV for ARDS and found a significant decrease in RV shortening and increase in RV systolic dimensions consistent with an increase in RV impedance, which was temporally related to the inspiratory phase of PPV. RV end diastolic dimensions remained unchanged consistent with a limitation of systemic venous return, since an increase in RV afterload should lead to an increase in RV end diastolic volume. Additional factors that dictate the extent to which PPV-induced increases in RV afterload reduces RV output are intravascular volume status, RV systolic function and the extent to which ventricular interdependence compromises the effective compliance of the LV (84).

An additional related interaction between the cardiovascular and pulmonary systems that is seen in patients receiving PPV for ARDS is the not uncommon occurrence of a patent foramen ovale, which allows for right to left atrial shunting (85). The presence of right to left shunting in patients with a patent foramen ovale has been shown to be associated with significantly greater pulmonary arterial pressures and RV dimensions than seen in patients with a patent foramen ovale and no cardiac shunting (85). It is important to consider not only the impact of CPAP and PPV on oxygenation in patients with hypoxic respiratory failure but also to consider the impact of these therapies on cardiac output and ultimately systemic oxygen delivery.

THE IMPACT OF CARDIOVASCULAR DISEASE ON RESPIRATORY FUNCTION

Heart Failure and Respiratory Function

In a low cardiac output state perfusion of the respiratory muscles contributes to a competition amongst viscera for a limited cardiac output. The importance of this phenomenon is that it impacts the acute management of patients in...
shock, and highlights the shortcomings of the commonly held belief that cerebral perfusion is protected at the expense of all other organs, becoming compromised only with a significant decrease in the cerebral perfusion pressure (CPP) (i.e., the CPP falling below the lower inflection point of the cerebral pressure autoregulation curve).

In subjects without underlying cardiac disease undergoing strenuous exercise, perfusion of the brain as well as muscles of locomotion becomes relatively limited, as manifested by changes in near infrared spectroscopy-derived oxygenation indices (86, 87). In patients at rest with compensated heart failure cerebral oxygenation may be significantly depressed (88–90). In patients with compensated heart failure undergoing exercise, oxygenation of the cerebrum decreases further as muscles of respiration and locomotion become loaded (91–93). Furthermore, with therapies that improve cardiac output such as cardiac transplantation, cardiac resynchronization, and afterload reduction, cerebral blood flow increases significantly (90, 94, 95). Not only may cerebral blood flow be limited and contribute to impaired cognition in patients with chronic heart failure (96, 97), but in patients with decompensated heart failure, cerebral oxygenation may become more depressed and approach if not exceed the anaerobic threshold for the brain in the absence of hypotension. Studies in animals have demonstrated that as the cerebral oxygen extraction exceeds 60%, there is a progression from neurologic impairment to ischemia with elevations in brain lactate levels (98–103). The discussion of competition for a limited cardiac output in spontaneously breathing subjects is germane to a review of cardiopulmonary interaction, because it highlights an important and unique interplay between the two systems that plays a key role in the acute management of heart failure and shock.

Under normal conditions, the diaphragm consumes less than 3% of global oxygen consumption and receives less than 5% of cardiac output. However, with an increase in respiratory load, diaphragmatic oxygen consumption may increase to values over 50% of total oxygen consumption (104). The increase in respiratory muscle oxygen consumption correlates with an increase in minute ventilation, and increases further with impairment of respiratory mechanics. Because the baseline arteriovenous oxygen content difference for the diaphragm is high, diaphragmatic blood flow must increase to meet the increase in oxygen demand, which if cardiac output is limited occurs at the expense of other vital organs (104, 105). Studies using animal models of cardiogenic and septic shock have evaluated the distribution of cardiac output during spontaneous and mechanical ventilation (106, 107). Viïres et al (106) as well as Hussain et al (107) demonstrated that respiratory muscle blood flow increases significantly in animal models of shock. Both studies demonstrated that in animals receiving mechanical ventilation, respiratory muscle blood flow is significantly less and perfusion to other vital organs, including the brain, is significantly greater than that seen in the spontaneously breathing animals. These studies demonstrate that diaphragmatic blood flow is protected to an equal or even greater extent than is cerebral blood flow when cardiac output is limited, and that by unloading the respiratory pump, mechanical ventilation allows for a redistribution of a limited cardiac output to other vital organs. Separate from PPV-induced increased in ITP and decreases in ventricular afterload, mechanical ventilation represents an additional tool in the armamentarium to treat low cardiac output states.

**Congenital Heart Disease With Left-to-Right Shunting and Respiratory Function**

Congenital heart defects with a large amount of left-to-right shunting leads to pulmonary venous hypertension. In addition, with a large nonrestrictive communication at the ventricular level or at the level of the great vessels, pulmonary arterial systolic pressure equilibrates with systemic arterial pressure. Interstitial edema develops as extravascular lung water formation exceeds pulmonary lymphatic clearance, decreasing lung compliance. Small airway resistance increases as fluid accumulates within the bronchovascular sheath, leading to external compression of bronchioles (108). In addition, lower airway disease leads to incomplete alveolar emptying, hyperinflation, and flattened diaphragms, resulting in a decrease in diaphragmatic preload and ventilatory capacity at a time when the diaphragmatic load is elevated. In addition, impaired respiratory mechanics lead to exaggerated negative pressure breathing, which increases ventricular afterload while increasing caloric expenditure.

**Pulmonary Hypertension and Lung Mechanics**

In patients with pulmonary arterial hypertension experiencing a pulmonary hypertensive crisis, a characteristic observation during these episodes is that the patient becomes acutely difficult to ventilate. Ventilatory difficulties during an acute pulmonary hypertensive crisis are at least in part due to a compensatory pneumoconstriction, which serves to optimize the relationship between ventilation and perfusion (109, 110).

**CONCLUSION**

Under normal conditions, the interplay between the respiratory and cardiovascular systems is inconsequential. However, in the presence of underlying cardiopulmonary disease, the importance of the interaction between these two organ systems cannot be overstated. A thorough understanding and the clinical application of cardiopulmonary interactions are essential to the practice of cardiac critical care and for optimizing patient care.

**REFERENCES**


