Recent advances in the clinical application of heart-lung interactions

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Clinical applications of heart-lung interactions have centered on the impact of ventilation on regional blood flow and the measures of cardiovascular responsiveness to both positive end-expiratory pressure and fluid resuscitation. These new and exciting applications of established physiology provide new therapeutic options for the caregiver with reduced risk for complications in the patient. This review illustrates several of these studies within the context of known cardiopulmonary physiology. Curr Opin Crit Care 2002, 8:26–31 © 2002 Lippincott Williams & Wilkins, Inc.

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Abbreviations

CPAP	continuous positive airway pressure
HFJV	high-frequency jet ventilation
ITP	intrathoracic pressure
Paw	airway pressure
PEEP	positive end-expiratory pressure
Ppa	pulmonary artery pressure
PAOP	pulmonary artery occlusion pressure
Ppc	pericardial pressure
Pra	right atrial pressure

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The cardiorespiratory unit is a complex and integrated system that balances the ever-changing and often conflicting metabolic demands of the body. Its response to these varying demands is influenced by myocardial reserve, circulating blood volume, blood flow distribution, autonomic tone, and endocrinologic processes as well as by lung volume, intrathoracic pressure (ITP), and the surrounding pressures for the remainder of the circulation. Dramatically different hemodynamic responses to similar ventilatory maneuvers can occur between subjects and are dependent on their preexisting cardiovascular status. Complex cardiopulmonary responses can occur in critically ill patients, limiting the overall effectiveness of advanced resuscitative therapies to treat cardiopulmonary insufficiency.

Several recently published studies have addressed the hemodynamic effects of positive pressure ventilation. In general, these studies tend to support the previous theoretical construct for our understanding of heart-lung interactions, adding incremental clinical applications and guidelines. Thus, these new studies will be presented within the context of our present-day understanding of heart-lung interactions.

Hemodynamic effects of ventilation

Heart-lung interactions can be artificially grouped into interactions involving three basic concepts that often coexist: (1) inspiration increases lung volume above end-expiratory volume, (2) spontaneous inspiration decreases ITP, and (3) positive-pressure ventilation increases ITP.

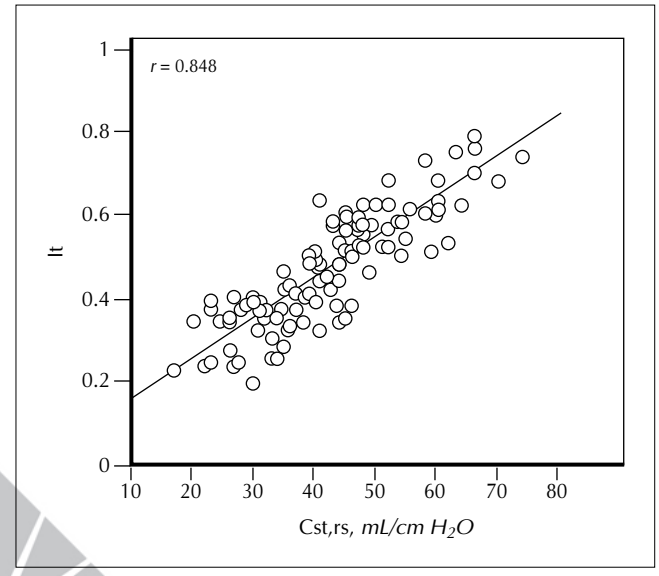
Airway pressure, pleural pressure, intrathoracic pressure, pericardial pressure, and lung volume

Some clinical confusion exists in relating ventilator-induced changes in airway pressure (Paw) and cardiovascular response. A major source of this confusion rests in equating changes in Paw with changes in both ITP and lung volume. Although positive-pressure ventilation increases lung volume only by increasing Paw, the degree to which both ITP and lung volume increase will also be a function of airway resistance and both lung and chest wall compliance. If either lung or chest wall compliance increases, then for the same increase in lung volume during positive-pressure ventilation, Paw will also increase. However, the impact of this increase in Paw on ITP and hemodynamics will be dissimilar. Under conditions in which lung compliance is reduced, such as in acute respiratory distress syndrome, the increase in ITP

will be less for a constant increase in Paw than would occur under conditions wherein chest wall compliance is reduced. Importantly, with decreasing lung compliance, the increase in Paw will be associated with minimal increases in ITP and thus with minimal hemodynamic effects, whereas decreasing chest wall compliance allows Paw to be transmitted to ITP, inducing marked hemodynamic effects. However, changes in lung compliance alone do not alter the increase in ITP if tidal volume is kept constant [1]. Importantly, when tidal volume is reduced to maintain the same end-inspiratory Paw during acute respiratory distress syndrome as during normal control conditions, ITP increases less than when tidal volume is kept constant.

Because right atrial (Pra), pulmonary artery (Ppa), and pulmonary artery occlusion (PAOP) pressures will vary with changes in ITP, knowing only these vascular pressures relative to atmospheric pressure will not define their actual distending pressure unless ITP equals zero. Pinsky *et al.* [2] demonstrated in postoperative cardiac patients without airflow obstruction that the nadir PAOP immediately after airway disconnection accurately reflected actual left ventricular filling pressure than PAOP alone when positive end-expiratory pressure (PEEP) was 10 cm H_2O or greater. However, this "nadir wedge" technique has a few disadvantages that limit its use. First, it requires transient discontinuance of PEEP that may induce lung collapse and hypoxemia. Second, it assumes that alveolar pressure rapidly returns to zero during the brief observation interval (<3 seconds), an invalid assumption in subjects with dynamic hyperinflation or increased airway resistance. To address these problems, Teboul *et al.* [3•] demonstrated that PEEP-induced changes in ITP could be accurately estimated from the observed changes in PAOP during a positive-pressure breath, if one simultaneously knew the delivered tidal volume and the Paw. Because PAOP will vary over a tidal breath, owing primarily to changes in ITP, this ventilation-induced change in PAOP (ΔPAOP) will define the ITP swing during the breath. Because lung compliance is defined as the change in distention pressure over the change in lung volume, one can calculate transmitted pressure from airway to pericardial surface as an index of transmission. If respiratory swings of PAOP (ΔPAOP) are compared with the simultaneous changes of alveolar pressure (ΔPalv = end-inspiratory airway pressure – end-expiratory airway pressure), an index of transmission of pressures from the alveolar compartment to the pulmonary veins would then be obtained (index of transmission = ΔPAOP/ΔPalv). One assumes that stop-flow end-inspiratory and end-expiratory Paw reflect Palv. Not surprisingly, the more compliant the lungs, the greater the It (Fig. 1). These authors demonstrated that in a patient mechanically ventilated with an optimal applied PEEP, left ventricular filling pressure could then be estimated from a calculated transmural PAOP (tmPAOP) by subtracting from the end-expiratory (ee) PAOP the product of total PEEP (PEEPtot) by index of transmission (*ie*, tmPAOP = eePAOP – [PEEPtot × ΔPAOP/ΔPalv]). This report is important because it demonstrates that one can measure tmPAOP even in patients with severe airflow obstruction and dynamic hyperinflation—conditions previously blocked from this measure. Thus, the caregiver at the bedside can measure tmPAOP in a ventilated patient using only PAOP and Paw data without removing the patient from the ventilator or disturbing the patient in other ways. Although it is not clear what value tmPAOP carries in the overall hemodynamic management of the critically ill patient, this value is often sought.

Figure 1. Estimating airway pressure transmission to the pleural space



Relation between the static compliance of the respiratory system (Cst,rs) and the index of transmission of alveolar pressure to pulmonary vascular pressure, estimated from pulmonary artery occlusion pressure (PAOP) tracing on mechanical ventilation (index of transmission) in 49 patients with intrinsic positive end-expiratory pressure (PEEPi) on zero end-expiratory pressure (ZEEP), mechanically ventilated with PEEP. Published with permission [3].

Hemodynamic effects of changes in lung volume

Lung inflation alters autonomic tone and pulmonary vascular resistance and, at high lung volumes, as we have seen above, interacts mechanically with the heart in the cardiac fossa to limit absolute cardiac volumes. Each of these processes is important in determining the hemodynamic response to mechanical ventilation. Although these effects are very important clinically, few recent studies have explored these interactions further. In fact, the use of pressure-limited ventilation strategies has rendered the analysis of lung volume changes on hemodynamics especially difficult to study clinically.

Hemodynamic effects of changes in intrathoracic pressure

The heart within the thorax is a pressure chamber within a pressure chamber. Therefore, changes in ITP will af-

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fect the pressure gradients for both systemic venous return to the right ventricle and systemic outflow from the left ventricle, independent of the heart itself. Increases in ITP, by increasing Pra and decreasing transmural left ventricular systolic pressure, will reduce these pressure gradients and thereby decrease intrathoracic blood volume. According to the same argument, decreases in ITP will augment venous return and impede left ventricular ejection, thereby increasing intrathoracic blood volume.

Systemic venous return

Because Pra is the downstream pressure for venous return, ventilation-induced changes in ITP will induce parallel changes in Pra, causing venous return to change. Accordingly, variations in Pra represent the major factor determining the fluctuation in pressure gradient for systemic venous return during ventilation. With increases in ITP, Pra relative to atmosphere increases, decelerating venous blood flow, decreasing right ventricular filling, and consequently decreasing right ventricular stroke volume [4]. During spontaneous inspiration, the converse occurs.

The positive-pressure ventilation-induced decrease in venous return may be less than expected based solely on changes in Pra. Because inspiration increases lung volume, diaphragmatic descent will simultaneously increase abdominal pressure pressurizing the upstream venous beds so that the upstream pressure for venous return is also increased [5]. Thus, the pressure gradient for venous return may not be reduced by PEEP, especially in patients with hypervolemia. Furthermore, Matuschak *et al.* [6] found that although PEEP decreased blood flow to the liver in proportion to the induced decrease in cardiac output in normovolemic dogs, the liver's ability to clear hepatocytic-specific compounds, such as indocyanine green, was unaltered. Abdominal pressurization by diaphragmatic descent may be the major mechanism by which the decrease in venous return is minimized during positive pressure ventilation [5]. Finally, when cardiac output is restored to pre-PEEP levels by fluid resuscitation while PEEP is maintained, liver clearance mechanisms increase above pre-PEEP levels [6]. A recent clinical study by Aneman *et al.* [7•] examined the effect of PEEP on mesenteric and hepatic blood flow, using ultrasonic flow measures in eight patients undergoing major upper abdominal surgery. They found that PEEP decreased portal flow but increased hepatic flow proportionally, presumably via the hepatic buffer response. These effects occurred independently of vasopressor therapy but proportionally to global blood flow. These data document the effect of diaphragmatic descent on hepatic flow distribution and underscore the potentially complex effects that ventilation may have on the circulation.

Right ventricular filling

Tyberg *et al.* [8] demonstrated that right ventricular filling pressure is insignificantly altered by acute volume loading. Although Pra increases with volume loading, pericardial pressure (Ppc) also increases, such that right ventricular filling pressure remains unchanged. Presumably, conformational changes in the right ventricle more than wall stretch are responsible for RV enlargement [9]. Pinsky *et al.* [10] demonstrated that when right ventricular end-diastolic volume was reduced in postoperative surgical patients by the application of PEEP, both Pra and Ppc increased, but right ventricular filling pressure remained constant. Accordingly, changes in Pra or right ventricular filling pressure do not follow changes in right ventricular end-diastolic volume. Volume loading increases pericardial pressure more than ITP in patients after heart surgery [11], consistent with pericardial restraint. However, increasing PEEP selectively increases ITP until it equals Ppc, then both ITP and Ppc increased equally as PEEP increases further. Thus, PEEP compresses the heart within the cardiac fossa in a fashion analogous to pericardial tamponade. These concepts were used to evaluate Pra as a measure of cardiovascular instability in response to increasing PEEP in a study conducted by Jellinek *et al.* [12•]. They examined the value of end-expiratory Pra in predicting the subsequent change in cardiac output to increasing PEEP from 0 to 30 cm H_2O in 10 cm H_2O increments in *22* ventilator-dependent patients with acute respiratory distress syndrome. They demonstrated that PEEP induced a paradoxical increase in both Pra and PAOP associated with a decrease in cardiac output. They found that a threshold value for Pra existed at 12 mm Hg, below which all patients decreased their cardiac output in response to increasing levels of PEEP. Above this threshold, the cardiac output response was variable (Fig. 2). Furthermore, the increase in Pra during PEEP predicted the fall in cardiac output (Fig. 3). These data are interesting because they give the physician a firm minimal Pra value below which they can be confident that increasing levels of PEEP will impair cardiac function. However, they fail, unfortunately, to help predict the hemodynamic response to PEEP if baseline values of Pra exceed 10 mm Hg.

Left ventricular preload and ventricular interdependence

A change in venous return to the right ventricle results in a change in left ventricular preload both directly, because the two sides of the heart are connected in series, and indirectly through ventricular interdependence in parallel. The series interactions have been used to explain both the decrease in left ventricular output seen during positive-pressure ventilation and its phase relation to the ventilatory cycle [13,14]. A more direct mechanical coupling via ventricular interdependence probably produces most of the ventilation-associated changes in left ventricular output [15]. But for whatever reason, positive-pressure ventilation will phasically alter left ventricular filling pressure.

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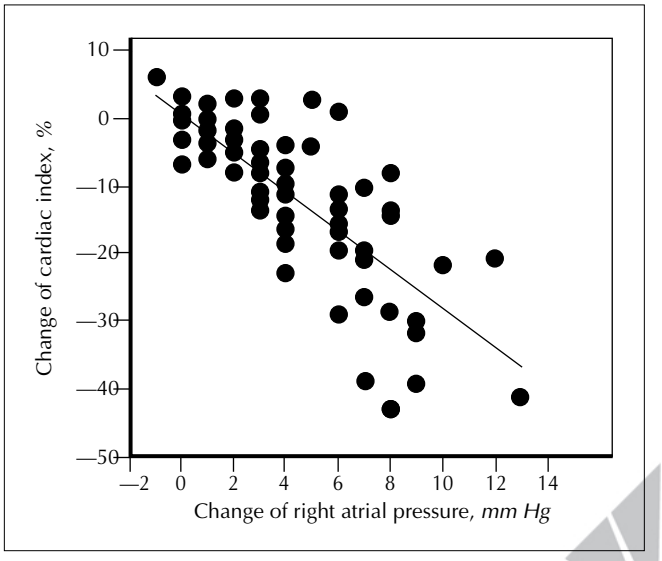
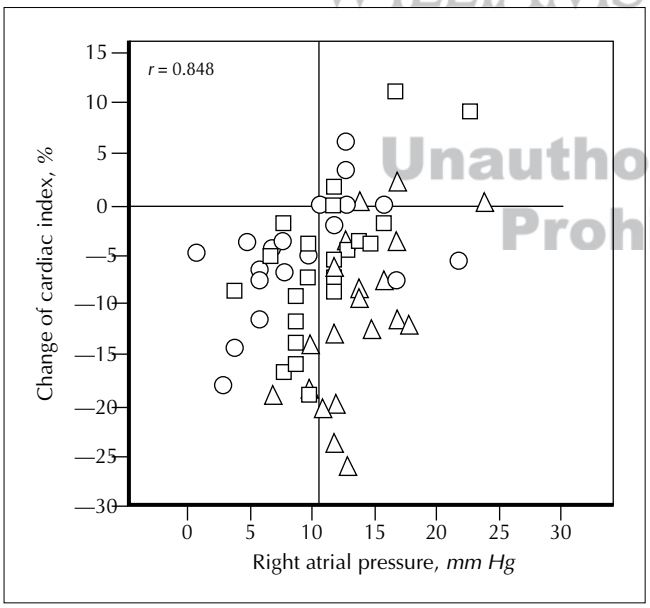
Figure 2. Predicting cardiac index responses for right atrial pressure



Relation between the change of right atrial pressure and the percentage change of cardiac index induced by lung inflation to airway pressures of 10, 20, and 30 cm H_2O; n = 65, $P < 0.0001$, $r^2 = 0.68$. Published with permission [12•].

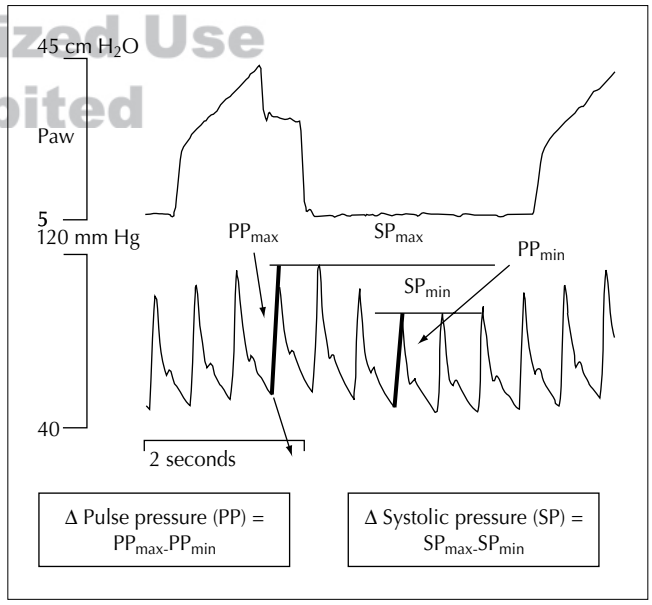
This positive-pressure ventilation-induced sine wave change in left ventricular filling pressure can be used to diagnose preload responsiveness. Because left ventricular filling pressure varies from end-inspiration to end-expiration, if changes in left ventricular filling pressure do not alter stroke volume, then arterial pulse pressure throughout the ventilatory cycle will remain constant. However, if left ventricular stroke volume varies, then arterial pulse pressure will vary as well. Previous researchers have shown a positive correlation between systolic pressure variation and preload responsiveness; however, Denault *et al.* [16•] could not correlate systolic pressure variation with either left ventricular volumes or contractility in cardiac surgery patients studied using transesophageal echocardiography. These data suggest that preload, as measured as left ventricular end-diastolic volume, is not a good predictor of preload responsiveness. Michard *et al.* [17•,18••] took this concept to its logical conclusion. They compared the positive-pressure ventilation-induced systolic pressure and pulse pressure variations and the subsequent change in cardiac output in response to either a 10 cm H_2O increase in PEEP or a rapid fluid bolus infusion. Pulse pressure variation was calculated as the ratio of the difference between maximum and minimum arterial pulse pressures to the mean of those two pulse pressures (Fig. 4). Using a threshold value for either systolic pressure variation or pulse pressure variation of greater than 15% to predict a greater than 15% increase in cardiac output in response to volume loading, Michard *et al.* [18••] demonstrated that the receiver-operator characteristic of this test was close to perfect (Fig. 5). Thus, if the pulse pressure variation was greater than 15%, then cardiac output always increased, and if it was less than 15%, then cardiac output did not increase in response to fluid loading. This is a very important concept because it provides an operating defini-

Figure 3. Basal right atrial pressure levels may predict changes in cardiac index



Relations between the percentage change of cardiac index for the shift in airway pressure from 0 to 10, 10 to 20, and 20 to 30 cm H_2O versus the right atrial pressure at 0, 10, and 20 cm H_2O airway pressure, respectively. For all shifts in airway pressure (circles, 0 to10 cm H_2O; squares, 10 to 20 cm H_2O; triangles, 20 to 30 cm H_2O; $r^2 = 0.22$, 0.48, and 0.36, respectively, $P < 0.05$), marked decrease in cardiac index occurred only in patients with low right atrial pressure. Published with permission [12•].

Figure 4. Trend recording of airway pressure and arterial pressure during two positive pressure breaths



Calculations of systolic arterial pressure variation and pulse pressure variation are shown. Published with permission [17•].

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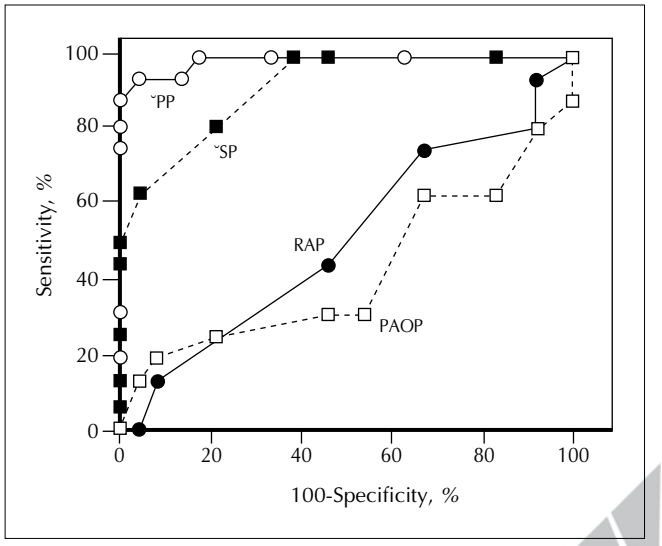
Figure 5. Test characteristics of four common indices of preload responsiveness



Receiver operating characteristic (ROC) curves comparing the ability of the respiratory changes in pulse pressure (ΔPP), the respiratory changes in systolic pressure (ΔSP), the right atrial pressure (RAP), and the pulmonary artery occlusion pressure (PAOP) to discriminate between patients who responded (cardiac index increase = 15%) and who did not respond to volume expansion. The area under the ROC curve for ΔPP was greater than those for ΔSP, RAP, and PAOP ($P < 0.01$). Published with permission [18••].

tion of preload responsiveness that can be readily applied at the bedside.

Left ventricular afterload

Left ventricular or systolic wall tension is proportional to the product of transmural left ventricular pressure and the radius of curvature of the left ventricle. Accordingly, increases in ITP, if associated with no change in arterial pressure, will result in decreased left ventricular wall tension. Likewise, decreases in ITP with a constant arterial pressure will increase left ventricular transmural pressure and thus increase left ventricular afterload, impeding left ventricular ejection [19]. Accordingly, increases in ITP unload the left ventricle, whereas decreases in ITP increase left ventricular afterload [20]. Potentially, increases in ITP should augment left ventricular ejection by decreasing left ventricular afterload [21].

Mechanistically speaking, not only do increases in ITP unload the left ventricle but abolishing negative swings in ITP will also reduce left ventricular afterload. This process is potentially more clinically relevant than increasing ITP for two main reasons. First, many pulmonary disease states are associated with exaggerated decreases in ITP during inspiration [22]. Second, exaggerated decreases in ITP require increased respiratory efforts that increase the work of breathing. Accordingly, abolishing these markedly negative swings in ITP should disproportionally reduce left ventricular afterload more than venous return (left ventricular preload). By the use of similar logic, the institution of PEEP or nasal continuous positive airway pressure (CPAP) in patients with heart failure may further augment left ventricular output by reducing left ventricular afterload, despite the obligatory decrease in left ventricular preload [23]. In support of this concept, Sin *et al.* [24•] studied the effect of CPAP therapy in 66 patients. They demonstrated that hemodynamic improvement occurred only in those with poor left ventricular function, realizing a 66% risk reduction in worsening left ventricle performance and the need for cardiac transplantation at 3 months, and an 81% reduction in mortality at 6 months. No benefit of CPAP therapy was seen in patients without Cheyne-Stokes respiration. These data strongly suggest that the benefit of CPAP therapy resulted from relieving the abnormal breathing pattern associated with negative swings in ITP.

Cardiac cycle–specific increases in intrathoracic pressure

As an extension of the above logic, Pinsky *et al.* [25] demonstrated that increases in ITP synchronized to occur at a specific point within the cardiac cycle and delivered with each heartbeat could selectively alter venous return and isolate left ventricular ejection. Cardiac cycle–specific ventilation is often delivered by use of high-frequency jet ventilation (HFJV). Cardiac cycle–specific increases in ITP timed to occur in systole have been shown to increase steady-state cardiac output in canine models of acute ventricular failure [25] and in patents with congestive cardiomyopathy [26]. Regrettably, Romand *et al.* [27•] were unable to duplicate these findings in a clinically relevant study using HFJV in 20 patients receiving ventilation after cardiac surgery. They examined five 30-minute sequential ventilation periods, interspersing intermittent positive-pressure ventilation (IPPV) with synchronized HFJV. They found no differences in the hemodynamic effects of either ventilatory mode. Furthermore, this lack of an interaction persisted after stratification according to baseline left ventricular contractility, as estimated by ejection fraction. Presumably, this lack of effect was caused by the very low peak airway pressures during HFJV of 7 ± 2 mm Hg. These findings contrast with the beneficial effects of synchronized HFJV on cardiac performance in patients with terminal left ventricular failure when more aggressive HFJV resulting in peak airway pressures of 20 mm Hg was used, resulting in marked hypocapnia. Thus, the use of synchronized HFJV, although initially exciting, is now reserved only for cardiovascular rescue in patients with profound cardiovascular dysfunction.

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- • Of special interest
- •• Of outstanding interest

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