Heart Failure as a Co-Morbidity in the ICU

M. R. Pinsky

Introduction

We often treat patients with heart failure in the intensive care unit (ICU) setting, and clearly, severe heart failure carries a very high mortality rate. However, non-fatal heart failure commonly accompanies processes that cause patients to become critically ill. In these cases, heart failure becomes a co-morbidity. Although intuitively obvious that one needs forward blood flow to sustain life, it is not clear to what extent decreased cardiac reserve impairs outcome from acute illness other than acute coronary syndrome. It is important, therefore, to consider the impact that heart failure may have on outcome from critical illness.

Heart failure, defined as a reduced ability to sustain forward blood flow, can affect mortality from critical illness in several ways (Table 1). If severe enough, heart failure leads to a low output state associated with organ failure and pulmonary edema. Clearly, if the heart is unable to pump blood, life cannot be sustained. Hypoperfusion causes profound microcirculatory disturbances [1]. However, such events are exceedingly rare, except in the conditions of acute heart failure following myocardial ischemia or cardiac reconstructive surgery. Still, profound cardiovascular collapse is the hallmark of the terminal phase of most critical illness. Where heart failure primarily expresses increased morbidity and mortality is at the start of critical illness and at its resolution. In the early stages of critical illness, being able to sustain an appropriately elevated cardiac output to maintain sufficient tissue oxygen delivery (DO_2) is a major factor determining outcome, whereas increased DO_2 later in the course of critical illness is not associated with improved outcome. Thus, when cardiac reserve limits the initial maximal cardiac response to increasing metabolic demands in patients with severe sepsis and related critical illness, mortality

Table 1. Impact of heart failure on outcome from critical illness

Severe heart failure
▪ Primary organ hypoperfusion
– Gut hypoperfusion
– Pre-renal azotemia
▪ Acute respiratory failure
Mild to moderate heart failure
▪ Failure to attain 'survivor levels' of DO_2
▪ Prolonged mechanical ventilation

increases. Second, following critical illness or insults, impaired cardiac reserve limits maximum exercise tolerance. Cardiovascular impairment is the most common cause of failure to wean from mechanical ventilatory support, prolonging morbidity. Let us review these two distinct processes separately.

Achieving Maximal Oxygen Delivery

All studies of septic shock and high-risk surgical patients have documented that mortality is inversely proportional to the maximal level of DO_2 that can be spontaneously generated by the patient [2]. Although originally considered 'survival levels' of DO_2, these data primarily defend that sustained cardiovascular fitness is associated with improved survival. In support of this concept, the more profound the circulatory shock the greater the degree of anaerobic metabolism and the higher the circulating lactate levels [3]. Thus, the impact of heart failure on outcome from critical illness is complex. It appears to be related more to maximal sustainable levels of cardiac output, than to ventricular pump function *per se*. The case for this argument follows.

Clearly, resuscitation from circulatory and respiratory failure represents the mainstay of emergency and critical care management. Most of the time, resuscitation is done from a position of relative hypovolemia [4]. However, clinical studies have demonstrated that restoration of total blood flow, arterial oxygenation and even arterial pressure to otherwise normal levels by the use of vasoactive agents is not universally good for either organ function or host outcome, if delivered late in the course of critical illness [5]. Exogenous vasopressor therapy impairs normal autoregulation of blood flow among organs and may induce occult tissue ischemia in vital but silent vascular beds, such as the gut mucosa and renal subcortex. Furthermore, microcirculatory oxygen utilization is more a function of local metabolic demands and capillary flow than global blood flow or arterial oxygen content. Regrettably, significant regional ischemia or rescue can occur without perceptible changes in global oxygen uptake (VO_2) [6]. Although fluid and vasopressor therapies may normalize organ perfusion pressure they may not induce normal organ perfusion nor prevent organ dysfunction [7].

Still, it is clear from numerous clinical studies that tissue hypoperfusion is bad and that avoidance of ischemia improves outcome from stress states. Early aggressive resuscitation, referred to as early goal-directed therapy, was shown in one study to improve outcome from severe sepsis if delivered in the Emergency Department of a single medical center [8]. Thus, the rapid restoration of normal hemodynamics by conventional means, including fluid resuscitation and surgical repair, results in a superior outcome than inadequate or delayed resuscitative efforts.

Since critically ill patients often have abnormal blood flow regulation, increasing DO_2 to what would otherwise be considered supranormal levels theoretically may treat the lethal occult tissue hypoxia that is a hallmark of many forms of circulatory shock. Accordingly, interest centered on 'hyper-resuscitation' such that DO_2 is exogenously increased to supranormal levels, levels often seen in subjects who spontaneously survive acute circulatory insults, the so-called 'survivor levels' of DO_2. Most studies that have aimed at augmenting DO_2 or VO_2 to 'survivor levels' have documented that if DO_2 can increase, subjects do better [9]. However, this improvement in survival appears to be independent of whether the subject was part of the group with intentional augmented DO_2.

Only two prospective clinical trials of aggressive resuscitation have data that would allow one to address the issue of the impact of cardiac reserve of resuscitation outcome. The first study was of septic shock patients from a single center. Tuchschmidt et al. [10] studied 51 critically ill patients, 25 of whom were given supranormal DO_2 targets. Just like all other studies that addressed this issue previously, they found that mortality was similar in both groups. However, those patients who spontaneously reached the higher 'survival levels' of DO_2, independent of treatment group, had a markedly improved survival. Though not specifically addressed in this study, these data are consistent with the assumption that baseline cardiac reserve plays a major role in determining outcome from critical illness. The second study was a multicenter study of patients with diverse causes of critical illness. Gattinoni et al. [11] studied 762 critically ill patients from 56 centers. These patients' diagnoses included high-risk surgery, massive blood loss, sepsis, respiratory failure, and trauma. Goals of therapy were separated into three treatment groups: I: CI 2.5–3.5 l/min/m^2; II: CI >4.5 l/min/m^2; and III: SvO2 >70%. Importantly, therapeutic goals were achieved in less than half of group II and group III patients, demonstrating that primary cardiac depression was a central part of the failure to achieve these target resuscitation goals. By *post hoc* analysis those subjects that did not reach these target DO_2 related goals did not have an increased mortality (personal communication). As in the study by Tuchschmidt et al. [10], although these data do not specifically address the issue of cardiac reserve, they are consistent with the assumption that baseline cardiac reserve plays a major role in determining outcome from critical illness.

One can take this concept further in patients with established sepsis. Aggressive therapies aimed at augmenting DO_2 may actually increase mortality because the artificial increase in cardiac output induced by therapy once organ injury has occurred should not improve organ function but will still be associated with the complications of that therapy. In support of that concern, Hayes et al. [5] studied 100 critically ill patients with severe circulatory shock, stratifying them to either aggressive supranormal DO_2 levels or normal DO_2 levels. These investigators found a markedly increased mortality in the treatment group compared to the control (54 v. 34%, $p<0.05$). Thus, the use of aggressive hyper-resuscitation therapies and supranormal levels of DO_2 in patients with established sepsis and organ injury is dangerous and should not be done.

Hence, a low DO_2 in a critically ill patient is probably a marker of critical illness, rather than a parameter of effective resuscitative therapy. Interestingly, the most impressive beneficial outcomes from clinical trials have all included prevention of hypoperfusion rather than resuscitation from shock [8]. This form of preemptive resuscitation, treatment before the insult has even occurred, is referred to as 'pre-optimization'. An impressive number of studies have documented that attaining high levels of DO_2 prior to high-risk surgery [12] or during the initial hour of presentation with severe sepsis [8] improves outcome, even if survivor levels of DO_2 are not achieved [13].

Based on the above evidence, aggressive hemodynamic therapies in patients in septic shock or at risk for development of multiple organ dysfunction and death improves survival if given before or during the onset of tissue injury. Often these benefits are seen without measurable differences in DO_2 or VO_2 during therapy [12, 13]. The cumulative clinical data to date suggest that a major benefit of aggressive resuscitation therapy is realized only if efforts are started very early and primarily when the host can manifest an increased cardiac output response. However,

once circulatory shock and/or organ dysfunction has occurred there appears to be little additional benefit and real risk of harm from aggressive resuscitation therapies that increase DO_2 or VO_2 to levels above what would otherwise be considered normal. Thus, the contribution that ventricular pump function plays once initial resuscitation has finished is unclear, but probably of lesser relevance.

Is Heart Failure a Result of Critical Illness?

Up until this point, we have assumed that the patient presents with critical illness and preexistent heart failure. However, cardiac injury commonly occurs with critical illness due to associated hypotension and decreased coronary perfusion or from direct myocardial injury, as is the case with anterior chest trauma causing myocardial contusions. Still, many critically ill patients, especially those with hypotensive septic shock, often have an increased cardiac output following fluid resuscitation. How then is it possible that they have impaired cardiovascular reserve? This may not be an entirely academic question, because treatments aimed at restoring vasomotor tone increase arterial pressure. Animal studies have long shown that vasopressors induce profound hypoperfusion in septic shock [14]. Similar findings were seen with inhibitors of nitric oxide synthase (NOS) [15]. Several recent clinical trials have documented that patients with severe sepsis have impaired cardiac reserve. However, this impaired reserve is masked by the pathological vasodilation that sustains a decreased left ventricular afterload. Two recent clinical trials of the inducible NOS inhibitor, L-NMMA, in human sepsis underscore this point. Kilbourn et al. [16] showed that NOS inhibition reduced blood flow while restoring blood pressure in cancer patients being treated with interleukin (IL)-2 chemotherapy. Furthermore, the multicenter clinical trial of L-NMMA in the treatment of sepsis was stopped because of increased mortality in the treatment group, which to my thinking was because of the decreased cardiac output and regional blood flow it induced. Thus, cardiac performance is not a major issue in determining outcome from critical illness once stabilized, unless the system is altered artificially to increase its workload. Then, occult heart failure will emerge.

Heart Failure in Severity Scoring Systems

Another way to examine the impact of heart failure on outcome from critical illness is to look at large retrospective data sets used to predict risk. Systems, such as APACHE II, simplified acute physiology system (SAPS) II, and sequential organ failure assessment (SOFA) scores, all attempt to estimate risk of a bad outcome from assessing measures of pre-morbid functional status, physiological state and intensity of interventions. Interestingly, the role played by heart failure, *per se*, figures minimally in these scoring systems. Even if one focuses on the EuroSCORE analysis of post-cardiac surgery mortality risk, the impact of isolated reductions in left ventricular ejection fraction are small [17]. For example, for a 65-year old male without other co-morbidities, having the ejection fraction decrease from $>50\%$ to 30–50% to $<30\%$ increases perioperative mortality risk from 1.3 to 1.9 to 3.8%, respectively, whereas the presence of an acute myocardial infarction in an otherwise healthy (left ventricular ejection fraction $>50\%$) 65 year old male would increase

mortality to 2.2%, or critical perioperative status to 3.2%. Importantly, if one has both depressed ventricular function (left ventricular ejection fraction < 30%) and a critical perioperative state, the risk of death increases to 8.9%. Thus, heart failure and critical illness are coupled in their impact on outcome, not merely additive. However, based on all the data summarized above, the role of heart failure outside of its ability to limit the initial hyperemic response to acute stress is probably minimal.

Preventing Liberation from Mechanical Ventilation

Having said that cardiac reserve is of minimal importance during the recovery phase of critical illness, does heart failure play a role further on in the course of critical illness? The answer is most definitely yes, but in the specific conditions in which sustained increases in DO_2 are needed to support independent function. Here, the most widely studied phenomenon is the role that heart failure plays on the ability to wean from mechanical ventilatory support. Most studies of weaning from mechanical ventilation demonstrate that subjects do not 'wean' *per se*, they merely stop needing ventilatory support. Mechanical ventilation, within the context of respiratory failure, then relates to the work cost of breathing by reversing respiratory muscle fatigue and decreasing the stress on the cardiovascular system, allowing it to deliver blood to other organs. The act of slowly decreasing ventilatory support is done primarily to allow the cardiovascular system to adjust to increased demands and to allow the physician to identify impending cardiovascular collapse prior to it becoming a crisis. The primary presenting sign of cardiogenic shock is acute respiratory failure [18].

The transition from positive-pressure to spontaneous ventilation (weaning) can profoundly alter cardiovascular function via complex, conflicting, and often opposite processes. These processes reflect the interaction between myocardial reserve, ventricular pump function, circulating blood volume, blood flow distribution, autonomic tone, lung volume, intrathoracic pressure, and the surrounding pressures for the remainder of the circulation. Clearly, the final response to ventilatory stress is dependent on the baseline cardiovascular state of the subject.

Lung volume increases in a tidal fashion during both spontaneous and positive-pressure inspiration. However, intrathoracic pressure increases during positive-pressure inspiration due to passive lung expansion to increasing airway pressure, whereas intrathoracic pressure decreases during spontaneous inspiration owing to the contraction of the respiratory muscles. Thus, changes in intrathoracic pressure and the metabolic demand needed to create these changes represent the primary determinants of the hemodynamic differences between positive-pressure and spontaneous ventilation [19].

Spontaneous Ventilation is Exercise

Although ventilation requires normally less than 5% of total DO_2 [20], in lung disease states the work of breathing is increased, such that its metabolic demand for oxygen may reach 25% of total DO_2. If cardiac output reserve is also limited, then blood flow to other organs can be compromised, causing tissue hypoperfusion, ischemic dysfunction, and lactic acidosis [21]. When subjects are weaned from mechanical venti-

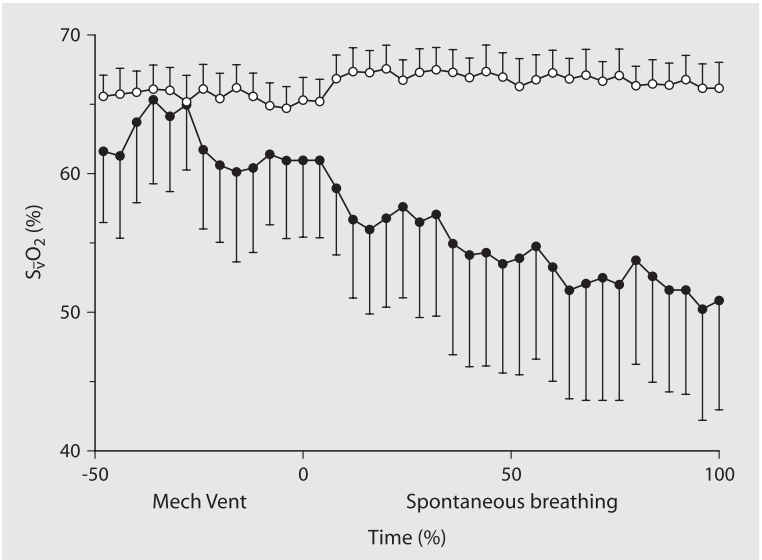

Fig. 1. Dynamic changes in SvO_2 in patients who successfully weaned (open circles) and did not wean (closed circles) from mechanical ventilatory support. From [28] with permission

lation they experience an obligatory increase in the work of breathing, which can be minimized by mask continuous positive airway pressure (CPAP) [22]. The resultant cardiovascular effects of this spontaneous ventilation exercise will include a decreased DO_2 to other organs, increased serum lactate levels, and decreased mixed venous oxygen saturation (SvO_2). The obligatory decrease in SvO_2 may result in a decreased PaO_2 if fixed right-to-left shunts exist, even if cardiac output and gas exchange are maintained at their baseline levels. Finally, if cardiac output is severely limited, respiratory muscle failure develops despite high central neuronal drive, such that many heart failure patients die a respiratory death prior to cardiovascular standstill [23].

Ventilator-dependent patients who fail to wean from mechanical ventilation may display impaired baseline cardiovascular performance [24], but routinely develop signs of heart failure only during weaning. The transition from positive-pressure to spontaneous ventilation can be associated with pulmonary edema [24], myocardial ischemia [25, 26], tachycardia, and gut ischemia [27]. Jubran et al. [28] demonstrated that although all subjects increase their cardiac outputs in response to a weaning trial, consistent with the increased metabolic demand, those who subsequently fail to wean also display a decrease in SvO_2 saturation (Fig. 1). Since weaning from mechanical ventilatory support is a cardiovascular stress, it is not surprising that weaning-associated electrocardiographic (EKG) and thallium cardiac blood flow scan–related signs of ischemia have been reported in both subjects with known coronary artery disease [25] and in otherwise normal patients [26]. Similarly, initiating mechanical ventilation in patients with severe heart failure and/or ischemia can reverse myocardial ischemia [29].

Hemodynamic Effects of Ventilation Depend on Cardiopulmonary Status

In patients who are otherwise normal, their cardiovascular state is characterized by preload-dependency. Thus, in normal subjects or in patients with hypovolemia (e.g., hemorrhagic shock, severe vomiting, diarrhea, loss of vasomotor tone, spinal cord shock) cardiac output and organ perfusion are often increased during the transition to spontaneous ventilation from positive-pressure ventilation. Withdrawal of ventilatory support in patients with limited cardiovascular reserve should be done slowly, because the increased load on the heart can precipitate heart failure and pulmonary edema [24].

Patients with chronic obstructive pulmonary disease (COPD) are at an increased risk of hyperinflation, either due to bronchospasm, loss of lung parenchyma or dynamic hyperinflation (inadequate expiratory time). Hyperinflation will compress the heart, increase pulmonary vascular resistance, and impede right ventricular filling. Intrinsic positive end-expiratory pressure (PEEP, hyperinflation) alters hemodynamic function similar to extrinsic PEEP but carries with it the added burden of increased work of breathing. Importantly, during spontaneous ventilation trials, the degree of hyperinflation determines the decrease in cardiac output [30]. Most of the decrease in cardiac output can be reversed by fluid resuscitation [31, 32]. If cardiac output does not increase with fluid resuscitation, then other processes, such as cor pulmonale, increased pulmonary vascular resistance, or cardiac compression, may also be inducing this cardiovascular depression [30].

The cardiovascular benefits of positive airway pressure can be seen in the extubated spontaneously breathing patient by withdrawing negative swings in intrathoracic pressure. Increasing levels of CPAP improve cardiac function in patients with heart failure, but only once the negative swings in intrathoracic pressure are abolished [33]. Nasal CPAP can also accomplish the same results in patients with obstructive sleep apnea and heart failure [34], although the benefits do not appear to be related to changes in obstructive breathing pattern [35]. Prolonged nighttime nasal CPAP can selectively improve respiratory muscle strength, as well as left ventricular contractile function if the patient has preexisting heart failure [36].

Conclusion

Heart failure is a co-morbidity for critical illness at both the beginning and end of the critically ill process. At the beginning it limits the ability of the host to sustain an adequate DO_2 necessary to prevent the initial ischemia-induced organ injury, while at the end, it limits the host's ability to wean successfully from mechanical ventilatory support. When treating critically ill patients, one must remember that failure to achieve an adequate DO_2 may reflect occult heart failure. Since the treatment for heart failure is often the opposite to the treatment of hypovolemia, which itself is the other major cause of cardiovascular insufficiency, this consideration is of profound practical importance in the management of the critically ill.

Acknowledgement. This work was supported in part by NIH grants HL67181 and HL07820.

References

1. De Backer D, Creteur J, Dubois MJ, Sakr Y, Vincent JL (2004) Microvascular alterations in patients with acute severe heart failure and cardiogenic shock. Am Heart J 147:91–99
2. Bland RD, Shoemaker WC, Abraham E, Cobo JC (1985) Hemodynamic and oxygen transport patterns in surviving and nonsurviving postoperative patients. Crit Care Med 13:85–90
3. Weil MH, Afifi AA (1970) Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). Circulation 41:989–1001
4. Rush BF (1971) Irreversibility in post-transfusion phase of hemorrhagic shock. Adv Exp Med Biol 23:215–221
5. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hindo CJ, Watson D (1994) Evaluation of systemic oxygen delivery in the treatment of the critically ill. N Engl J Med 330:1717–1722
6. Uusaro A, Russell JA, Walley KR, Takala J (2000) Gastric-arterial PCO_2 gradient does not reflect systemic and splanchnic hemodynamics or oxygen transport after cardiac surgery. Shock 14:13–17
7. Banks RO (1988) Vasoconstrictor-induced changes in renal blood flow: role of prostaglandins and histamine. Am J Physiol 254:F470–F476
8. Rivers E, Nguyen B, Havstad S, et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377
9. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS (1988) Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 94:1176–1186
10. Tuchschmidt J, Fried J, Astiz M, Rackow E (1992) Elevation of cardiac output and oxygen delivery improves outcome in septic shock. Chest 102:216–220
11. Gattinoni L, Brazzi L, Pelosi P, et al (1995) A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 333:1025–1032
12. Boyd O, Grounds RM, Bennett DE (1993) A randomized clinical trial of the effect of deliberate perioperative increases in oxygen delivery and mortality in high-risk surgical patients. JAMA 270:2691–2707
13. Lobo SM, Salgado PF, Castillo VG, et al (2000) Maximizing O_2 delivery in high-risk elderly surgery patients improves survivorship without altering O_2 consumption. Crit Care Med 28:3396–3404
14. Breslow MJ, Miller CF, Parker SD, Walman AT, Traystman RJ (1987) Effect of vasopressors on organ blood flow during endotoxin shock in pigs. Am J Physiol 252:H291–H300
15. Klabunde RE, Ritger RC (1991) NG-monomethyl-l-arginine (NMA) restores arterial blood pressure but reduces cardiac output in a canine model of endotoxic shock. Biochem Biophys Res Commun 178:1135–1140
16. Kilbourn RG, Fonseca GA, Griffith OW, et al (1995) NG-methyl-L-arginine, an inhibitor of nitric oxide synthase, reverses interleukin-2-induced hypotension. Crit Care Med 23:1018–1024
17. Nilsson J, Algotsson L, Hoglund L, Luhrs C, Brandt J (2004) EuroSCORE predicts intensive care unit stay and costs of open heart surgery. Ann Thorac Surg 78:1528–1534
18. Aubier M, Viires N, Syllie G, et al (1982) Respiratory muscle contribution to lactic acidosis in low cardiac output. Am Rev Respir Dis 126:648–652
19. Wise RA, Robotham JL, Summer WR (1981) Effects of spontaneous ventilation on the circulation. Lung 159:175–186
20. Roussos C, Macklem PT (1982) The respiratory muscles. N Engl J Med 307:786–797
21. Aubier M, Viires N, Syllie G, et al (1982) Respiratory muscle contribution to lactic acidosis in low cardiac output. Am Rev Respir Dis 126:648–652
22. Baratz DM, Westbrook PR, Shah PK, et al (1992) Effect of nasal continuous positive airway pressure on cardiac output and oxygen delivery in patients with congestive heart failure. Chest 102:1397–1401
23. Viires N, Silley G, Rassidakis A, et al (1980) Effect of mechanical ventilation on respiratory muscle blood flow during shock. Physiologist 23:1–23 (abst)
24. Lemaire F, Teboul JL, Cinotti L, et al (1988) Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. Anesthesiology 69:171–179

25. Hurford WE, Lynch KE, Strauss HW, et al (1991) Myocardial perfusion as assessed by thallium-201 scintigraphy during the discontinuation of mechanical ventilation in ventilator-dependent patients. Anesthesiology 74:1007–1016
26. Srivastava S, Chatila W, Amoateng-Adjepong Y, et al (1999) Myocardial ischemia and weaning failure in patients with coronary artery disease: an update. Crit Care Med 27:2109–2112
27. Mohsenifar Z, Hay A, Hay J, Lewis MI, Koerner SK (1993) Gastric intramural pH as a predictor of success or failure in weaning patients from mechanical ventilation. Ann Intern Med 119:794–798
28. Jubran A, Mathru M, Dries D, et al (1998) Continuous recordings of mixed venous oxygen saturation during weaning from mechanical ventilation and the ramifications thereof. Am J Respir Crit Care Med 158:1763–1769
29. Rasanen J, Vaisanen IT, Heikkila J, et al (1985) Acute myocardial infarction complicated by left ventricular dysfunction and respiratory failure. The effects of continuous positive airway pressure. Chest 87:158–162
30. Schuster S, Erbel R, Weilemann LS, et al (1990) Hemodynamics during PEEP ventilation in patients with severe left ventricular failure studied by transesophageal echocardiography. Chest 97:1181–1189
31. Dhainaut JF, Devaux JY, Monsallier JF, Brunet F, Villemant D, Huyghebaert MF (1986) Mechanisms of decreased left ventricular preload during continuous positive pressure ventilation in ARDS. Chest 90:74–80
32. Huemer G, Kolev N, Kurz A, Zimpfer N (1994) Influence of positive end-expiratory pressure on right and left ventricular performance assessed by Doppler two-dimensional echocardiography. Chest 106:67–73
33. Naughton MT, Rahman MA, Hara K, Floras JS, Bradley TD (1995) Effect of continuous positive airway pressure on intrathoracic and left ventricular transmural pressures in patients with congestive heart failure. Circulation 91:1725–1731
34. Lin M, Yang YF, Chiang HT, Chang MS, Chiang BN, Cheitlin MD (1995) Reappraisal of continuous positive airway pressure therapy in acute cardiogenic pulmonary edema. Short-term results and long-term follow-up. Chest 107:1379–1386
35. Buckle P, Millar T, Kryger M (1992) The effect of short-term nasal CPAP on Cheyne-Stokes respiration in congestive heart failure. Chest 102:31–35
36. Kaneko Y, Floras JS, Usui K, et al (2003) Cardiovascular effects of continuous positive airway pressure in patients with heart failure and obstructive sleep apnea. N Engl J Med 348:1233–1241