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Weaning-induced cardiac dysfunction: where are we today?

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Abstract *Introduction:* The concept of weaning-induced cardiac dysfunction emerged 26 years ago with the publication of a clinical study conducted by François Lemaire and collaborators. *Objectives:* One objective of this article is to remember the results and the historical context under which our pivotal study was conducted. Another objective is to review some of the subsequent studies that aimed to analyze the underlying mechanisms, to noninvasively detect the cardiac origin of weaning failure, and to propose specific therapies enabling weaning success. *Conclusion:* Weaning-induced cardiac dysfunction has become an established cause of weaning failure. Underlying mechanisms may differ from one patient to another. Important progress has already been made in its diagnosis thanks to relevant clinical research studies. Ongoing and future technological advances in ultrasonography and in biomarker research should certainly help in diagnosing weaning induced-pulmonary edema and in identifying the main mechanisms responsible for its development. Progress on appropriate therapeutic options on an individual basis is still expected.

Keywords Weaning · Cardiac function · Pulmonary edema · B-type natriuretic peptide · Hemoconcentration · Diuretics

Introduction

Weaning failure is estimated to occur in about 30–40 % of critically ill patients who receive mechanical ventilation [1]. Causes of weaning failure are numerous and include respiratory muscle weakness, excessive workload due to infection, secretions, unresolved sepsis, or accumulation of sedative drugs [1]. Today, fluid overload and left heart failure are also recognized as important causes of weaning failure [1], which was not the case several years ago. This review narrates how the thought of weaning-induced cardiac dysfunction originated and led to an important clinical study [2]. It also describes how the evidence has evolved thereafter, resulting in a paradigm shift and a better understanding of the pathophysiology of weaning-induced cardiac dysfunction, current diagnostic techniques, management and future perspectives.

How it all began

Thirty years ago, I was a resident in the intensive care unit (ICU) at Henri Mondor Hospital in Creteil (France). Professor Maurice Rapin, one of the founders of intensive care in Europe, was the head of the ICU and Prof. François Lemaire was his deputy. One day, when I was accompanying François Lemaire on bedside rounds, a nurse asked us to see a patient who was complaining of

chest pain during a spontaneous breathing trial (SBT). This was a 65-year-old patient, with no known coronary artery disease (CAD), being mechanically ventilated for an acute exacerbation of chronic obstructive pulmonary disease (COPD). The electrocardiogram performed during the SBT showed marked abnormalities, suggestive of acute myocardial infarction, better known today as ST elevation myocardial infarction. This suggested that some deleterious heart–lung interactions leading to myocardial ischemia had probably occurred during weaning. Intrigued by this unusual event, Prof. François Lemaire decided to conduct a clinical study to further investigate heart–lung interactions during weaning [2]. During this period, very few methods were available to assess the hemodynamic status of ICU patients. For this study, we used the pulmonary artery catheter (PAC) to measure cardiac output, pulmonary artery pressure, and cardiac filling pressures. Radionuclide angiocardiography (^{99}Tc) was used to measure cardiac chamber volumes and the ejection fractions of the right and the left ventricles. After ethics committee approval from the Société de Réanimation de Langue Française, we included 15 difficult-to-wean patients with severe COPD [2]. Many patients also had a history of left ventricular (LV) disease or systemic hypertension. In all patients, acute exacerbation of lung disease resolved after several days. Pulmonary artery catheter (PAC) and cardiac ^{99}Tc scintigraphy measurements were performed just before and during an SBT. Esophageal pressure was also measured to correct the changes in intrathoracic pressure, which could interfere with the interpretation of changes in cardiac filling pressures. In a subset of patients with COPD, we percutaneously inserted a pigtail catheter into the left ventricle through a femoral artery, to ensure that the pulmonary artery occlusion pressure (PAOP) in these patients reflected the LV end-diastolic pressure (LVEDP). I was invited to participate in this study because I had acquired some experience in performing LV catheterization without videoscopy in another study in ICU patients [3]. Thereafter, I contributed not only in collecting the hemodynamic data along with Fekri Abroug, but also in analyzing the data, writing the manuscript, and replying to the comments of reviewers of *Anesthesiology*, along with Francois Lemaire and Warren Zapol. Working with these two giants in the field of intensive care was an unforgettable experience.

What did this study show?

The most striking finding was that the unsuccessful SBTs (lasting around 10 min) were associated with a huge increase in transmural PAOP (from 8 to 25 mmHg on an average) [2]. This suggested that the intolerance to spontaneous breathing was related to the development of acute cardiogenic pulmonary edema. Figure 1 shows a spectacular increase in PAOP (up to 50 mmHg) in one of these patients during an SBT that had to be terminated after only 9 min owing to development of severe respiratory distress. Mechanical ventilation was reinstituted in all patients who failed SBT. In addition, the patients

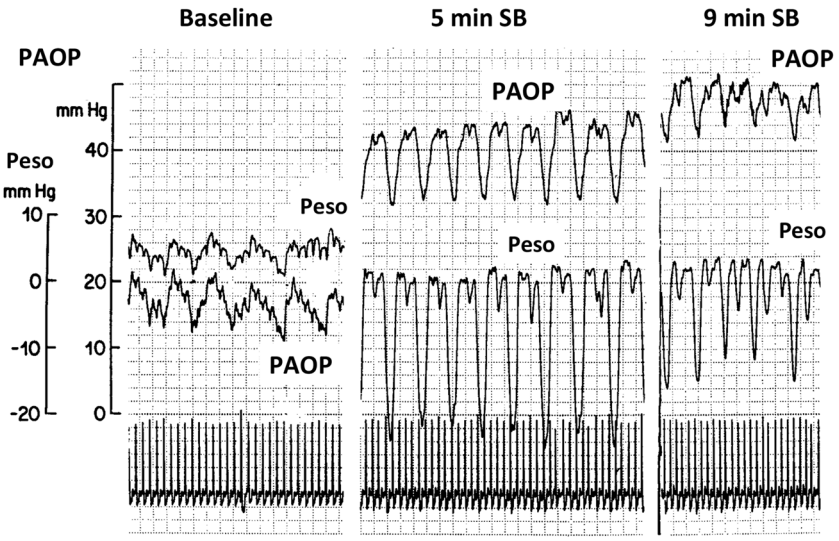

Fig. 1 Illustrative pressure recordings in a patient who failed to wean from mechanical ventilation owing to the rapid onset of weaning-induced cardiac dysfunction. After 5 min of spontaneous ventilation (SV), the pulmonary artery occlusion pressure (PAOP) increased markedly while the esophageal pressure (Peso) exhibited marked negative swings at inspiration. After 9 min of SV, the PAOP value was about 50 mmHg (development of severe pulmonary edema) while the negative swings in PAOP were less marked. It can be postulated that some diaphragmatic fatigue occurred at that time contributing to hypercapnia and weaning failure (adapted with permission from Lemaire et al. [2])

received intravenous furosemide, which resulted in 5 L of fluid loss within a few days. After diuretic therapy, hemodynamic evaluation was repeated. The transmural PAOP was lower at the end of the SBT than it was before treatment (9 vs. 25 mmHg). Importantly, most of the patients were able to breathe spontaneously and were eventually extubated successfully.

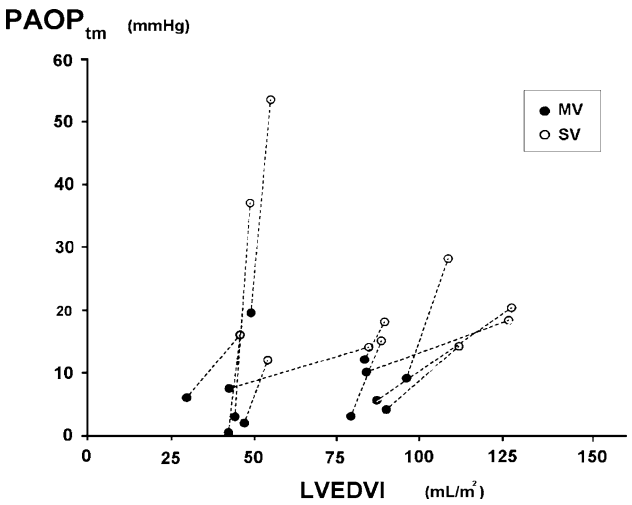

Fig. 2 Changes in transmural pulmonary artery occlusion pressure ($PAOP_{tm}$) and left ventricular end-diastolic volume (LVEDVI) during the transfer from mechanical ventilation (MV) to spontaneous ventilation (SV) in 12 patients in the study by Lemaire et al. [2]. Note that some patients exhibited a large increase in both $PAOP_{tm}$ and LVEDVI while others exhibited a large increase in $PAOP_{tm}$ with a small increase in LVEDVi. This suggests that different mechanisms are responsible for the occurrence of pulmonary edema during weaning (adapted with permission from Lemaire et al. [2])

Interestingly, during the pretreatment failing SBTs, simultaneous measurements of the PAOP and the volume of the cardiac chambers suggested that there is not just a single pattern in the increase in PAOP during weaning and that different mechanisms can result in acute development of cardiogenic pulmonary edema. Schematically, some patients exhibited simultaneous increases in PAOP and LV end-diastolic volume (LVEDV), whereas others exhibited a marked increase in PAOP without any marked increase in LVEDV (Fig. 2). Simultaneous increases in PAOP and in LVEDV can be related to an increase in LV preload and/or an increase in LV afterload and/or a decrease in LV contractility. An increase in PAOP without a significant increase in LVEDV is suggestive of a decrease in LV compliance.

Although this paper [2] could not conclusively define the predominant mechanism of the weaning-induced LV dysfunction, it promoted discussion about the potential mechanisms involved. Marked decrease in intrathoracic pressure, activation of the adrenergic tone, hypoxemia, hypercapnia, and increased work of breathing are five important consequences of unsuccessful weaning which interact with the circulatory system and may eventually lead to an acute increase in LVEDP and cardiogenic pulmonary edema [4] (Fig. 3).

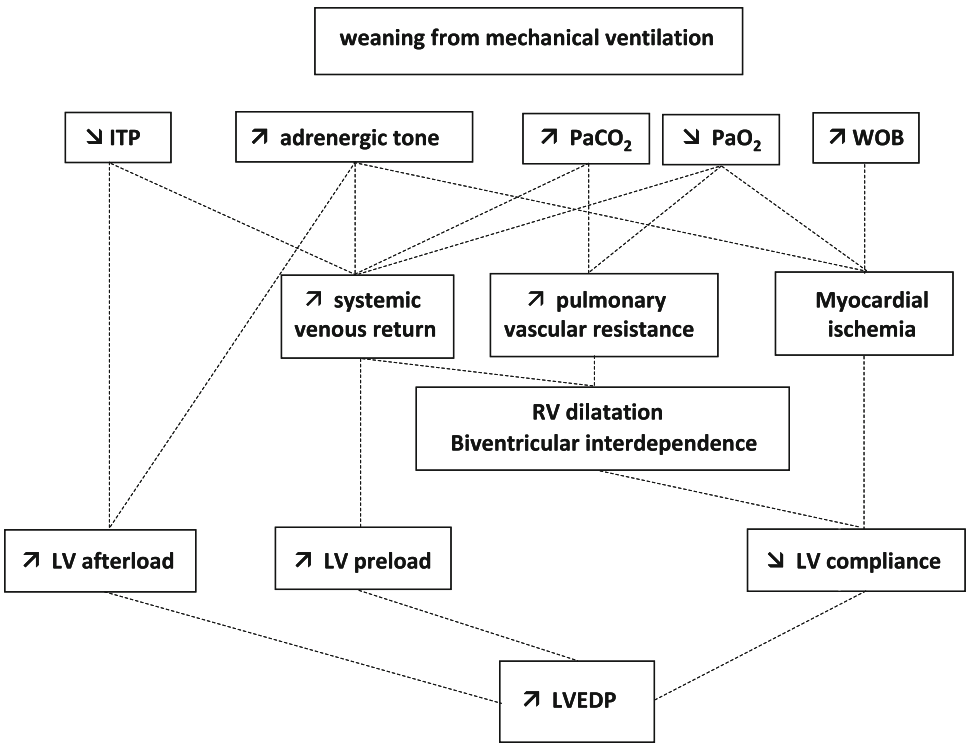

Fig. 3 Main mechanisms potentially involved in the development of weaning-induced pulmonary edema. *ITP* intrathoracic pressure, *LV* left ventricular, *LVEDP* left ventricular end-diastolic pressure, PaO_2 oxygen arterial pressure, $PaCO_2$ carbon dioxide arterial pressure, *RV* right ventricular, *WOB* work of breathing

Decrease in intrathoracic pressure during spontaneous breathing was documented in our study [2] by a profound decrease in esophageal pressure, during inspiration. Decrease in intrathoracic pressure tends to increase the systemic venous return pressure gradient, the right ventricular (RV) preload, the central blood volume, and the LV preload [5]. It also decreases the LV ejection pressure gradient thus increasing the LV afterload [6].

Increase in adrenergic tone was documented in our study [2] by an increase in serum catecholamine levels during SBTs. Emotional stress occurring during the transfer from mechanical ventilation to spontaneous breathing probably contributes to this. This phenomenon could result in the redistribution of venous blood from the unstressed volume toward the stressed volume and hence an increase in systemic venous pressure gradient and RV preload [7], all mechanisms that contribute to increase the central blood volume and the LV preload. Additionally, increased adrenergic tone also increases systolic arterial pressure and heart rate, which was documented in our patients [2]. Increased systolic arterial pressure increases the LV afterload. Myocardial oxygen demand also increases, as suggested by the increase in the double product (heart rate × systolic arterial pressure), which is a recognized marker of myocardial oxygen demand [8].

Although increase in the work of breathing during weaning was not documented in our study, it probably did occur, as the failing SBTs were associated with respiratory distress, marked swings in intrathoracic pressure, and an increase in global oxygen consumption [2]. The increased breathing efforts should result in increased cardiac work and myocardial oxygen demand.

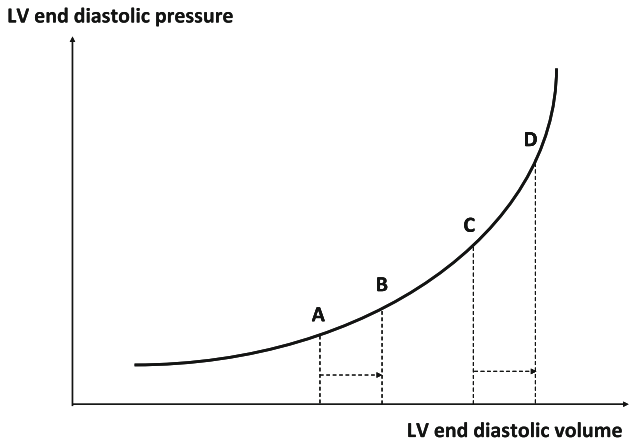

Fig. 4 Effect of weaning-induced increase in left ventricular (LV) preload on the level of LV preload during mechanical ventilation. An increase in LV end-diastolic volume during weaning can result (1) in a small increase in LV end-diastolic pressure (from *A* to *B*) when the LV end-diastolic volume is normal or low during mechanical ventilation, or (2) in a large increase in LV end-diastolic pressure (from *C* to *D*) when the left ventricle is already dilated during mechanical ventilation

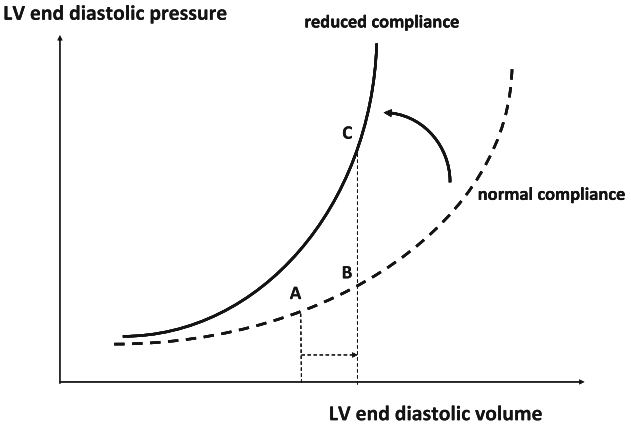

Fig. 5 Leftward shift of the left ventricular (LV) diastolic function curve and weaning. In some patients in whom myocardial ischemia or biventricular interdependence phenomenon occurs during weaning, a huge increase in LV end-diastolic pressure can occur in relation to a weaning-induced leftward shift of the LV diastolic function curve (reduced LV compliance). The potential increase in LV preload during weaning could result in a small increase in LV end-diastolic pressure (from *A* to *B*) in case of normal LV compliance; however, it could result in a huge increase in LV end-diastolic pressure (from *A* to *C*) in case of concomitant occurrence of weaning-induced reduction in LV compliance

Elevation of the LV filling pressure can occur during weaning, owing to an increase in LV preload (Fig. 4) and/or decrease in LV compliance (Fig. 5) and/or increase in LV afterload. These phenomena are amplified in patients with prior CAD, congestive heart failure, or COPD because of the following reasons:

In patients with pre-existing CAD, myocardial ischemia can occur because of the marked increase in myocardial oxygen demand, as shown in our study by the marked increase in the double product. It is noteworthy that three out of the 15 patients in our study [2] had scintigraphic evidence of abnormal LV wall motion abnormalities during mechanical ventilation, which worsened during spontaneous breathing. This strongly suggests that ischemia occurred in some areas of the myocardium in these patients. Myocardial ischemia is a potential factor contributing to the reduction in LV compliance and the resultant elevation in the LV filling pressure. It is interesting to note that except the first case described earlier none of the patients enrolled in this study, nor the thousands of patients I have managed in the last 25 years, exhibited such dramatic effects during weaning. We were fortunate to have observed such an extreme case that prompted us to conduct our pilot study.

In patients with congestive heart failure, LVEDV is larger than normal. As a result of the curvilinear shape of the LV diastolic function curve, a further increase in LVEDV secondary to the increased venous return and/or increased LV afterload should result in a markedly greater increase in LV filling pressure in such patients, as compared to those having a normal LVEDV (Fig. 4).

In patients with COPD, as a result of airway obstruction, large negative distending pressures are required to generate adequate tidal volume. This results in markedly negative intrathoracic pressure during weaning with resultant effects on systemic venous return and LV afterload. Systemic venous return may also increase owing to development of hypoxemia and/or hypercapnia. Airway obstruction is also responsible for a large increase in work of breathing with its inherent risks of myocardial ischemia in patients with associated CAD. In addition, in COPD patients, an increase in RV afterload can occur during weaning, because of the potential worsening of hypoxemia, hypercapnia, and intrinsic positive end-expiratory pressure. Along with the simultaneous increase in systemic venous return, this may result in a marked RV dilatation, which impedes the diastolic filling of the left ventricle through a biventricular interdependence mechanism, another factor contributing to increase in the LV filling pressure. It is well known that patients suffering from both COPD and LV disease have a greater potential to experience acute LV dysfunction and cardiogenic pulmonary edema during weaning.

The major merit of the Lemaire et al. paper [2] was that it was the first to point out cardiogenic pulmonary edema as a major cause of weaning failure in difficult-to-wean patients. Another merit was that the probable underlying mechanisms responsible for this phenomenon were discussed, as cardiac chamber volumes and pressures were simultaneously measured in this study. As mentioned earlier, this study was approved by an ethics committee and the investigators strictly respected all the ethical rules that existed at that time. These have evolved over time, and we wonder whether such a study would be approved today. Nevertheless, it would be a shame if this study had not been undertaken, as it was important not only to understand the concepts but also to provide useful practical solutions to important problems encountered in many mechanically ventilated patients.

Despite its merits, our study [2] must be viewed in the context of the 1980s. Firstly, drug therapy and acute and chronic management of diseases such as COPD, CAD, and congestive heart failure were markedly different from our current practices. Secondly, the potentially deleterious heart–lung interaction of the combination of COPD and LV disease was less recognized than it is today, except by some renowned experts in the field [9, 10]. As a result of these complex interactions, it cannot be ruled out that some of the patients in our study had been intubated for an episode of cardiogenic pulmonary edema and not for a classical acute exacerbation of COPD [2]. Thirdly, use of endotracheal intubation and mechanical ventilation was the rule in the 1980s. Today, noninvasive ventilation (NIV) is preferentially used for cardiogenic pulmonary edema or for acute exacerbation of COPD [11]. Hence it is likely that most of the patients enrolled in the study by Lemaire et al. [2] would have benefited from NIV had they been admitted in 2014. If already intubated, they would have benefited from NIV after extubation. Through mechanisms that are opposite to the mechanisms described above, NIV can improve cardiac function during exacerbation of COPD especially in patients with associated LV disease. NIV increases intrathoracic pressure, and decreases hypoxemia, hypercapnia, and work of breathing. Fourthly, during the 1980s, invasive mechanical ventilation was usually applied using heavy sedation and often neuromuscular blockade. Current strategies, using lighter levels of sedation, are associated with reduction in the duration of mechanical ventilation [12]. Whether this approach has also reduced the incidence of weaning-induced pulmonary edema remains unknown.

Finally, our study [2] could not answer several questions because of the small number of patients included and because the techniques of cardiovascular assessment used at that time were not suitable to analyze the underlying mechanisms in detail. Nevertheless, this paper led to multiple clinical studies that attempted to analyze the underlying mechanisms, devise newer techniques to noninvasively detect the cardiac origin of weaning failure and to identify specific therapies to enable weaning success.

What has been published in this field since the publication of our pilot study?

Several other studies thereafter confirmed that difficult-to-wean patients may exhibit a marked increase in PAOP during weaning, and have suggested that this increase was one of the major causes of weaning failure [13–21]. However, in the absence of left heart disease, the rise in pulmonary artery occlusion pressure (PAOP) is limited [22, 23]. The incidence of a large increase in LV filling pressure during weaning is difficult to quantify with certainty. In the study by Jubran et al. [14], all the eight patients who failed the first SBT (T piece), exhibited PAOP values greater than 18 mmHg at the end of the SBT, whereas all the 11 patients who passed the SBT had a PAOP less than 18 mmHg at the end of the SBT. Incidence rates of SBT-associated PAOP elevation of 74 % [18] and 52 % [15] were reported in studies including more than 40 patients who already failed at least one SBT.

Studies aimed at analyzing the underlying mechanisms of weaning-induced cardiac dysfunction

Richard et al. [24] studied 12 COPD patients without any known CAD or LV disease. Myocardial thallium-201 single photon emission computed tomography performed

during the SBT did not show any defect in the left ventricle suggestive of myocardial ischemia [24]. In all patients, LV ejection fraction measured using ^{99}Tc angioscintigraphy decreased during the SBT (T piece) [24]. This decrease, which was homogenous with no patent regional wall motion abnormalities of the left ventricle, was logically attributed to an increase in LV afterload rather than a decrease in LV contractility [24]. Since systolic arterial pressure did not increase during the SBT, the increased LV afterload was attributed to a marked decrease in intrathoracic pressure related to airway obstruction. Recent developments in Doppler echocardiography imaging have enabled us to better assess cardiac function during weaning. This allows us to assess LV systolic function through the calculation of LV ejection fraction and diastolic function through the analysis of the transmitral inflow (pulsed-wave Doppler) and the mitral annular velocity (tissue Doppler imaging). The LV filling pressure can be estimated by the ratio of early (E) to late (A) peak diastolic velocities (E/A) of the transmitral inflow [25] or even better by the ratio of E to peak of early diastolic mitral annular velocity (E′ or Ea) [26]. Using such indices, several studies have confirmed that the LV filling pressure may increase in patients who fail to wean compared to patients who succeed [27–29]. Some studies showed that these indices, as well as PAOP, increased in only half the patients who failed to wean [16]. Interestingly, Ait-Oufella et al. [30] reported LV diastolic function abnormalities using echocardiography even during successful weaning, irrespective of the presence of LV or RV dysfunction at baseline. In contrast, in a series of 113 patients who were successfully weaned, Caille et al. [27] found LV diastolic function abnormalities during SBTs mostly in patients with LV systolic dysfunction at baseline. These authors attributed these abnormalities to either reduction of LV compliance or onset of silent myocardial ischemia [27]. Moschietto et al. found that E' (or Ea) increased during an SBT in the group that was successfully weaned, whereas no change occurred in the group that failed [28]. They suggested that inability to enhance the LV relaxation rate during the SBT is an important factor contributing to weaning failure. It is noteworthy that most of the echocardiographic studies have emphasized the occurrence of LV diastolic dysfunction, rather than LV systolic dysfunction during weaning [16, 20, 27, 28, 31].

Studies aimed at testing specific methods to detect weaning failure of cardiac origin

Simple parameters like changes in respiratory rate or arterial oxygen tension cannot help differentiate between a respiratory or cardiac origin of weaning failure [15, 16, 19]. Several studies used an estimation of LV filling pressure and its change during an SBT. Others tried to assess the development of acute pulmonary edema.

- Theoretically, the best way to estimate the LV filling pressure is to measure the PAOP using a PAC [32]. It must be emphasized however, that determining the exact value of PAOP is difficult in patients with respiratory distress, especially in those experiencing intrinsic positive end-expiratory pressure. In addition to diagnosing weaning-induced hydrostatic pulmonary edema by showing an elevation of PAOP greater than 18 mmHg during the SBT, the use of PAC can provide information on the behavior of the right ventricle through the changes in right atrial and pulmonary artery pressures. It can also provide information on the global oxygen consumption/oxygen delivery relationship and its change during the SBT. In this regard, Jubran et al. [14] found that mixed venous oxygen saturation (SvO_2) decreased in patients who failed to wean while it did not change in patients who succeeded. Whether monitoring central venous oxygen saturation ($ScvO_2$) alone allows one to diagnose weaning-induced LV dysfunction is still unknown although a decrease in $ScvO_2$ during SBT was associated with extubation failure [33].
- Noninvasive estimation of LV filling pressure has been proposed as an alternative method to the PAC. Using echocardiography, Lamia et al. [16] tested the hypothesis that elevated E/A, and/or E/Ea at the end of the SBT can identify patients who fail to wean because of acute onset of pulmonary edema. SBT-induced pulmonary edema was defined as intolerance to spontaneous breathing and a PAOP greater than 18 mmHg at the end of the SBT [16]. Neither E/A alone nor E/Ea alone could diagnose weaning-induced pulmonary edema with acceptable accuracy [16]. However, the combination of both indices provided a better estimation of SBT-induced pulmonary edema [16]. In addition to help in diagnosing weaning-induced pulmonary edema, echocardiography allows us to explore the mechanisms potentially responsible for the acute LV dysfunction during weaning. However, echocardiography is an operator-dependent technique requiring a long training period and can only be applied in patients with favorable echogenicity.
- Other investigators measured B-type natriuretic peptide (BNP) or amino terminal pro BNP (NT-proBNP) before and during an SBT [19, 21, 29–31, 34, 35]. These peptides are synthesized by the cardiomyocytes in response to an increased myocardial stretch. Thus, high circulating BNP and NT-proBNP levels are observed in case of increased LV filling pressure, whether owing to systolic or diastolic LV dysfunction. Several studies have addressed whether BNP and/or NT-proBNP and/or their changes could be used to identify patients who fail to wean for cardiac reasons [19, 21, 29–31, 34, 35]. In theory, following changes in

BNP might be more suitable than following changes in NT-proBNP during an SBT, because BNP has a shorter half-time than NT-proBNP (around 20 min vs. 60–90 min) [36]. Mekontso-Dessap et al. [34] showed that the plasma BNP concentration obtained before the first SBT was higher in patients with subsequent weaning failure. A cutoff value of 275 pg/ml was associated with the best prediction of weaning failure with an overall diagnostic accuracy of 86 % [34]. However, the cardiac origin of weaning failure was not determined in this study. Hence a high pre-SBT BNP concentration in patients who subsequently failed the SBT did not prove that pulmonary edema occurred during the SBT. In this regard, there was no difference between the pre-SBT plasma BNP concentration and the plasma BNP concentration at the end of the SBT in the two groups of patients [34]. High baseline plasma BNP concentration before the SBT may reflect a more severe global condition in patients who do not tolerate the SBT. It must be emphasized that plasma BNP concentration can also be elevated in cases of advanced age, sepsis, and renal dysfunction, even in the absence of LV dysfunction. Other investigators found that SBT-induced changes in either plasma BNP concentration [35] or plasma NT-proBNP concentration [29] and not the baseline values predicted weaning failure. Grasso et al. [31] showed that an elevated plasma NT-proBNP concentration during SBT but not at baseline predicted weaning-induced cardiac dysfunction with acceptable accuracy in COPD patients. Zapata et al. [19] evaluated the value of both BNP and NT-proBNP and their changes during an SBT to predict weaning failure of cardiac origin. They defined weaning failure of cardiac origin as either an increase in PAOP greater than 18 mmHg during an SBT or SBT-induced changes in Doppler transmitral inflow (E/A; and Doppler tissue echocardiography, DTE) suggestive of increase in LV filling pressure [19]. They found that (1) the two natriuretic peptides could predict weaning failure of cardiac origin, (2) increases in natriuretic peptides during SBT could diagnose weaning failure from cardiac origin with acceptable accuracy, and (3) BNP performed better than NT-proBNP in prediction and diagnosis of weaning failure from cardiac origin [19]. In a study that we recently performed in patients who failed the first SBT, we defined weaning-induced pulmonary edema with the association of signs of clinical intolerance and a PAOP of 18 mmHg or higher at the end of an SBT [21]. Baseline values of plasma BNP could not distinguish the cases with and without weaning-induced pulmonary edema. However, an increase in plasma BNP concentration higher than 12 % during the SBT detected weaning-induced pulmonary edema with a sensitivity of 76 % and a specificity of 78 % [21]. In disagreement with the results reported in some of the aforementioned studies [19, 21, 29, 31, 35], Ait-Oufella et al. [30] found that plasma BNP increased significantly and by a large amount even during successful SBTs in patients with pre-existing LV dysfunction.

Thus, the literature about the utility of natriuretic peptides has provided divergent results, perhaps because the methodology used to diagnose weaning-induced pulmonary edema differed among studies. In my opinion, suspicion of acute cardiac dysfunction during weaning using BNP and/or NT-proBNP and/or their changes during an SBT should prompt further cardiac evaluation (e.g., echocardiography) aimed at confirming the cardiac origin of weaning failure.

- A different way to diagnose weaning-induced pulmonary edema is to (directly or indirectly) detect the acute development of pulmonary edema instead of estimating the LV filling pressure during an SBT.

  – A direct method is to measure extravascular lung water (EVLW) during an SBT. EVLW can be obtained with a transpulmonary thermodilution device. In a recent study in difficult-to-wean patients, Dres et al. [21] showed that an increase in EVLW of 14 % or higher diagnosed weaning-induced pulmonary edema with a sensitivity of 67 % and a specificity of 100 %. However, this method is still invasive because it needs both a femoral artery catheter and a central venous catheter in place at the time of weaning.
  – An indirect method based on the following hypothesis was proposed by Anguel et al. [15]. Weaning-induced pulmonary edema is assumed to be a hydrostatic pulmonary edema and thus accompanied by transfer of a hypo-oncotic fluid from the lumen of the pulmonary capillaries toward the interstitium. When the amount of transferred fluid is large enough, it may result in hemoconcentration. Thus, acute development of hydrostatic pulmonary edema could be detected by acute increase in plasma protein or hemoglobin concentrations. In their study, Anguel et al. [15] hypothesized that an acute increase in hemoconcentration indices during weaning could help to diagnose weaning-induced pulmonary edema defined as intolerance to spontaneous breathing and elevation of PAOP above 18 mmHg at the end of an SBT. A PAC was inserted in 46 patients who failed two consecutive SBTs although there was no obvious cause of weaning failure [15]. Twenty-four of these patients experienced weaning-induced pulmonary edema with an increase in the median value of PAOP from 13 to 26 mmHg during the third SBT [15]. An increase in the plasma protein concentration greater than 6 % and in hemoglobin concentration greater than 6.5 % during the weaning trial enabled detection of weaning-induced pulmonary edema with a sensitivity of 87 % and a specificity of 95 % and of

93 % and of 77 %, respectively [15]. Recent data confirmed that changes in hemoconcentration indices during an SBT are valuable to diagnose weaning-induced pulmonary edema [21]. The main advantage of this method is that it is easy to assess because the baseline values of hemoconcentration indices are usually obtained in the daily blood sampling. However, this method can only indicate the occurrence of pulmonary edema, but does not provide any information about the potential underlying mechanisms. Use of echocardiography is thus mandatory to determine the underlying mechanisms responsible for the onset of weaning-induced cardiac dysfunction.

Studies addressing prevention and management of cardiac dysfunction occurring during weaning

Different categories of drugs such as diuretics, nitrates, and other vasodilators can be used for this purpose.

- The rationale to administer diuretics in this situation is to reduce a presumed global volume overload. In patients with large LVEDV, even a small decrease in LVEDV secondary to diuretic therapy will result in a marked decrease in LVEDP. In contrast, in patients with nondilated left ventricle, even a large decrease in LVEDV cannot result in a significant decrease in LVEDP because the LV diastolic function curve is curvilinear. However, in patients with enlarged right ventricle and small LVEDV, diuretic therapy could decrease the LVEDP through a reduction of RV end-diastolic volume and thus of the degree of biventricular interdependence. In the study by Lemaire et al. [2], we administered furosemide to all the patients who failed to wean. One week later, the average loss of weight was around 5 kg. Pulmonary artery catheterization was performed again in eight patients who were eventually extubated [2]. In all of them PAOP (9 ± 3 mmHg) did not increase further during the last SBT. It is plausible that in some COPD patients with enlarged right ventricle, the diuretic therapy resulted in attenuation of the biventricular interdependence phenomenon. In some others, the diuretic therapy was probably responsible for a reduction of a previously elevated LVEDV. In a recent randomized controlled multicenter study, two weaning strategies were compared. In 152 patients, a BNP-driven strategy was used and in 152 other patients, a physician-driven strategy was used [37]. In the BNP-guided group, on days with a BNP level of 200 pg/ml or higher, fluid intake restriction and furosemide administration were undertaken and continued for at least 24 h after extubation. In the control group, the clinicians were blinded to the BNP assay results, and all treatments, including diuretics, were performed according to usual care, with no explicit protocol. The BNP-guided fluid management strategy was associated with increased diuretic use, a more negative fluid balance, and a shorter duration of mechanical ventilation, especially in patients with LV dysfunction [37]. The important messages from this study are that (1) guiding fluid management according to BNP is beneficial during the weaning period, especially in patients with pre-existing LV dysfunction, and (2) administration of diuretics is probably important in this context. However, it should be emphasized that this study did not specifically address the issue of diagnosis and treatment of weaning-induced pulmonary edema. Fluid restriction and diuretics were undertaken in patients with high BNP levels during mechanical ventilation and not in patients who exhibited signs of weaning-induced pulmonary edema, which was not investigated [37]. Therefore, in my opinion, the important message of this study is that BNP levels could be useful for detecting the patients that are not ready to wean because of fluid overload. This is in agreement with the idea that a positive fluid balance is associated with prolonged mechanical ventilation [38].
- Administration of nitrates is another therapeutic option in case of weaning-induced pulmonary edema. Three pharmacological properties of nitrates are particularly useful in this context: systemic venous dilatation leading to a reduction of central blood volume, arterial vasodilatation leading to a reduction in LV afterload, and coronary vasodilatation leading to improved oxygen delivery to the myocardium. These pharmacological properties make nitrates an important therapeutic option when weaning-induced pulmonary edema is associated with a large increase in systolic arterial pressure and/or when myocardial ischemia is suspected to be a predominant cause of weaning failure. Routsi et al. [17] elegantly pointed out the utility of administration of nitrates in case of weaning failure associated with large increase in PAOP and systolic arterial pressure during a failed SBT in 12 difficult-to-wean COPD patients. When nitrates were intravenously administered at the beginning of the following SBT, neither PAOP nor systolic arterial pressure increased during the SBT and most of the patients were successfully extubated [17].
- Enoximone, a phosphodiesterase inhibitor, was also shown to be a good therapeutic option in cardiac surgery patients who failed to wean because of the onset of pulmonary edema [13]. It is still unclear whether the beneficial effect of this inodilator was related to its inotropic effect or its systemic vasodilatory effect.

- Levosimendan, which belongs to the calcium-sensitizer drug class, is also an inodilator. It has been compared with dobutamine in ten COPD patients who experienced weaning difficulties in relation to acute onset of pulmonary edema [20]. Both drugs significantly reduced the level of PAOP increase during the SBT but levosimendan had a greater effect than dobutamine [20]. A lower increase in the double product during the SBT was also observed with levosimendan, suggesting a beneficial effect on the increase in myocardial oxygen demand during weaning with levosimendan as compared to dobutamine. It is noteworthy that before administration of the drugs, the LV ejection fraction was normal and did not change during SBT. Thus, it is unlikely that the beneficial effect of levosimendan in this study was related to any improvement in the systolic function of the left ventricle. It is rather plausible that levosimendan more than dobutamine improved the LV diastolic function through reduction in myocardial oxygen demand and decreased the RV afterload through pulmonary vasodilatation. Use of levosimendan leading to success during weaning failure in patients with dilated myocardiopathy has also been reported [39].
- In my opinion, giving dobutamine to the patients who experience weaning-induced pulmonary edema is not judicious for several reasons. As described above and elsewhere [4, 5], weaning failure involves changes in LV preload, LV afterload, and LV diastolic function more than the changes in LV contractility. In addition, this context is associated with a marked increase in the catecholamines level [2], which is assumed to be responsible for a great part of the occurrence of pulmonary edema. Additional catecholamine load could further deteriorate rather than improve the clinical condition during weaning. Finally, the study by Ouanes-Besbes [20] suggested that dobutamine is far from being the magic drug in this specific situation. Although it was performed in a small number of patients, this study is important because it opposes the naïve idea that dobutamine should be given in all patients who are suspected to fail to wean owing to LV dysfunction. This practice was quite strong in the 1990s when the concept of weaning failure from cardiac origin became more and more popular. Fortunately, further evidence has changed this practice. It is possible that routine performance of echocardiography showing more frequently diastolic than systolic LV abnormalities in this setting has contributed to this change in practice. It cannot be excluded that a pharmacologically opposite treatment (i.e., beta-blockers) would be beneficial in some patients during weaning. Further studies to help identify patients who could benefit from beta-blocker therapy are required.

Future perspectives

Concepts have evolved greatly over the last 25 years and ICU physicians today are well aware that weaning failure may be due to an acute onset of cardiogenic pulmonary edema. We even fear that some difficult-to-wean patients receive diuretics empirically without any attempt to diagnose weaning-induced pulmonary edema with certainty. Unjustified administration of diuretics may have deleterious consequences such as dehydration with the risk of microatelectasis related to bronchiolar obstruction by dry bronchial secretions. On the other hand, a patient with normal volume status at the time of weaning may experience weaning-induced pulmonary edema due to mechanisms such as acute increase in LV afterload or acute LV diastolic dysfunction (Fig. 3), which sometimes require being targeted with treatments other than diuretics. Thus, efforts should be made not only to accurately diagnose cardiogenic pulmonary edema but also identify the mechanisms responsible for its development during weaning. The future should belong to minimally invasive methods accurate enough to detect pulmonary edema and identify its mechanisms. Ongoing and future technological progress in ultrasonography will certainly help in this regard. Recent development of biomarker research has led to the emergence of promising novel cardiac biomarkers, which are expected to help us better manage patients with congestive heart failure [36]. Plasma C-terminal-pro-endothelin-1 (CT-pro-ET-1), mid-regional pro-adrenomedullin (MR-proADM), and mid-regional pro-atrial natriuretic peptide (MR-proANP) were shown to change during the first 24 h after initial therapy of acute decompensated heart failure [40]. Whether their changes can be adequately interpreted during a short-term test such as an SBT needs to be determined. However, it must be emphasized that CT-pro-ET-1 and MR-proADM lack specificity as they are also elevated during pulmonary hypertension and acute exacerbation of COPD [41]. Other new biomarkers such as high sensitive troponin and copeptin [36] could be tested in future to detect weaning-induced myocardial ischemia.

Conclusion

Weaning-induced cardiac dysfunction has become an established cause of weaning failure. Underlying mechanisms may differ from one patient to another. Important progress has been made in the diagnosis, thanks to relevant clinical research studies. Progress on appropriate therapeutic options on an individual basis is still expected.

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References

1. Perren A, Brochard L (2013) Managing the apparent and hidden difficulties in weaning from mechanical ventilation. Intensive Care Med 39:1885–1895
2. Lemaire F, Teboul JL, Cinotti L, Giotto G, Abrouk F, Steg G, Macquin-Mavier I, Zapol WM (1988) Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. Anesthesiology 69:171–179
3. Teboul JL, Zapol WM, Brun-Buisson C, Abrouk F, Rauss A, Lemaire F (1989) A comparison of pulmonary artery occlusion pressure and left ventricular end-diastolic pressure during mechanical ventilation with PEEP in patients with severe ARDS. Anesthesiology 70:261–266
4. Teboul JL, Monnet X, Richard C (2010) Weaning failure from cardiac origin: recent advances. Crit Care 14:211
5. Pinsky MR (2000) Breathing as exercise: the cardiovascular response to weaning from mechanical ventilation. Intensive Care Med 26:1164–1166
6. Buda AJ, Pinsky MR, Ingels NB Jr, Daughters GT 2nd, Stinson EB, Alderman EL (1979) Effect of intrathoracic pressure on left ventricular performance. N Engl J Med 301:453–459
7. Persichini R, Silva S, Teboul JL, Jozwiak M, Chemla D, Richard C, Monnet X (2012) Effects of norepinephrine on mean systemic pressure and venous return in human septic shock. Crit Care Med 40:3146–3153
8. Gobel FL, Norstrom LA, Nelson RR, Jorgensen CR, Wang Y (1978) The rate pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. Circulation 57:549–556
9. Pinsky MR, Summer WR, Wise RA, Permutt S, Bromberger-Barnea B (1983) Augmentation of cardiac function by elevation of intrathoracic pressure. J Appl Physiol Respir Environ Exerc Physiol 54:950–955
10. Robotham JL, Scharf SM (1983) Effects of positive and negative pressure ventilation on cardiac performance. Clin Chest Med 4:161–187
11. Keenan SP, Sinuff T, Burns KE, Muscedere J, Kutsogiannis J, Mehta S, Cook DJ, Ayas N, Adhikari NK, Hand L, Scales DC, Pagnotta R, Lazosky L, Rocker G, Dial S, Laupland K, Sanders K, Dodek P, Canadian Critical Care Trials Group/Canadian Critical Care Society Noninvasive Ventilation Guidelines Group (2011) Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. CMAJ 183:E195–E214
12. Kress JP, Pohlman AS, O'Connor MF, Hall JB (2000) Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 342:1471–1477
13. Paulus S, Lehot JJ, Bastien O, Piriou V, George M, Estanove S (1994) Enoximone and acute left ventricular failure during weaning from mechanical ventilation after cardiac surgery. Crit Care Med 22:74–80
14. Jubran A, Mathru M, Dries D, Tobin MJ (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
15. Anguel N, Monnet X, Osman D, Castelain V, Richard C, Teboul JL (2008) Increase in plasma protein concentration for diagnosing weaning-induced pulmonary oedema. Intensive Care Med 34:1231–1238
16. Lamia B, Maizel J, Ochagavia A, Chemla D, Osman D, Richard C, Teboul JL (2009) Echocardiographic diagnosis of pulmonary artery occlusion pressure elevation during weaning from mechanical ventilation. Crit Care Med 37:1696–1701
17. Routsi C, Stanopoulos I, Zakynthinos E, Politis P, Papas V, Zervakis D, Zakynthinos S (2010) Nitroglycerin can facilitate weaning of difficult-to-wean chronic obstructive pulmonary disease patients: a prospective interventional non-randomized study. Crit Care 14:R204
18. Cabello B, Thille AW, Roche-Campo F, Brochard L, Gómez FJ, Mancebo J (2010) Physiological comparison of three spontaneous breathing trials in difficult-to-wean patients. Intensive Care Med 36:1171–1179
19. Zapata L, Vera P, Roglan A, Gich I, Ordonez-Llanos J, Betbesé AJ (2011) B-type natriuretic peptides for prediction and diagnosis of weaning failure from cardiac origin. Intensive Care Med 37:477–485
20. Ouanes-Besbes L, Ouanes I, Dachraoui F, Dimassi S, Mebazaa A, Abroug F (2011) Weaning difficult-to-wean chronic obstructive pulmonary disease patients: a pilot study comparing initial hemodynamic effects of levosimendan and dobutamine. J Crit Care 26:15–21
21. Dres M, Teboul JL, Anguel N, Guerin L, Richard C, Monnet X (2014) Extravascular lung water, B-type natriuretic peptide and blood volume contraction enable diagnosis of weaning-induced pulmonary edema. Crit Care Med (in press)
22. Teboul JL, Abrouk F, Lemaire (1988) Right ventricular function in COPD patients during weaning from mechanical ventilation. Intensive Care Med 14:483–485
23. De Backer D, Haddad PE, Preiser JC, Vincent JL (2000) Hemodynamic responses to successful weaning from mechanical ventilation after cardiovascular surgery. Intensive Care Med 26:1201–1206
24. Richard C, Teboul JL, Archambaud F, Hebert JL, Michaut P, Auzepy P (1994) Left ventricular function during weaning of patients with chronic obstructive pulmonary disease. Intensive Care Med 20:181–186
25. Vanoverschelde JL, Robert AR, Gerbaux A, Michel X, Hanet C, Wijns W (1995) Noninvasive estimation of pulmonary arterial wedge pressure with Doppler transmitral flow velocity pattern in patients with known heart disease. Am J Cardiol 75:383–389
26. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA (1997) Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 30:1527–1533
27. Caille V, Amiel JB, Charron C, Belliard G, Vieillard-Baron A, Vignon P (2010) Echocardiography: a help in the weaning process. Crit Care 14:R120

28. Moschietto S, Doyen D, Grech L, Dellamonica J, Hyvernat H, Bernardin G (2012) Transthoracic echocardiography with Doppler tissue imaging predicts weaning failure from mechanical ventilation: evolution of the left ventricle relaxation rate during a spontaneous breathing trial is the key factor in weaning outcome. Crit Care 16:R81
29. Gerbaud E, Erickson M, Grenouillet-Delacre M, Beauvieux MC, Coste P, Durrieu-Jaïs C, Hilbert G, Castaing Y, Vargas F (2012) Echocardiographic evaluation and N-terminal pro-brain natriuretic peptide measurement of patients hospitalized for heart failure during weaning from mechanical ventilation. Minerva Anestesiol 78:415–425
30. Ait-Oufella H, Tharaux PL, Baudel JL, Vandermeersch S, Meyer P, Tonnellier M, Dussaule JC, Guidet B, Offenstadt G, Maury E (2007) Variation in natriuretic peptides and mitral flow indexes during successful ventilatory weaning: a preliminary study. Intensive Care Med 33:1183–1186
31. Grasso S, Leone A, De Michele M, Anaclerio R, Cafarelli A, Ancona G, Stripoli T, Bruno F, Pugliese P, Dambrosio M, Dalfino L, Di Serio F, Fiore T (2007) Use of N-terminal pro-brain natriuretic peptide to detect acute cardiac dysfunction during weaning failure in difficult-to-wean patients with chronic obstructive pulmonary disease. Crit Care Med 35:96–105
32. Richard C, Teboul JL (2005) Weaning failure from cardiovascular origin. Intensive Care Med 31:1605–1607
33. Teixeira C, da Silva NB, Savi A, Vieira SR, Nasi LA, Friedman G, Oliveira RP, Cremonese RV, Tonietto TF, Bressel MA, Maccari JG, Wickert R, Borges LG (2010) Central venous saturation is a predictor of reintubation in difficult-to-wean patients. Crit Care Med 38:491–496
34. Mekontso-Dessap A, de Prost N, Girou E, Braconnier F, Lemaire F, Brun-Buisson C, Brochard L (2006) B-type natriuretic peptide and weaning from mechanical ventilation. Intensive Care Med 32:1529–1536
35. Chien JY, Lin MS, Huang YC, Chien YF, Yu CJ, Yang PC (2008) Changes in B-type natriuretic peptide improve weaning outcome predicted by spontaneous breathing trial. Crit Care Med 36:1421–1426
36. Iqbal N, Wentworth B, Choudhary R, Landa Ade L, Kipper B, Fard A, Maisel AS (2012) Cardiac biomarkers: new tools for heart failure management. Cardiovasc Diagn Ther 2:147–164
37. Mekontso Dessap A, Roche-Campo F, Kouatchet A, Tomicic V, Beduneau G, Sonneville R, Cabello B, Jaber S, Azoulay E, Castanares-Zapatero D, Devaquet J, Lellouche F, Katsahian S, Brochard L (2012) Natriuretic peptide-driven fluid management during ventilator weaning: a randomized controlled trial. Am J Respir Crit Care Med 186:1256–1263
38. Upadya A, Tilluckdharry L, Muralidharan V, Amoateng-Adjepong Y, Manthous CA (2005) Fluid balance and weaning outcomes. Intensive Care Med 31:1643–1647
39. Meaudre E, Jego C, Goutorbe P, Bordes J, Asencio Y, Montcriol A, Kenane N, Palmier B (2009) Weaning failure from mechanical ventilation due to dilated cardiomyopathy: successful use of levosimendan. Acta Anaesthesiol Scand 53:416–417
40. Boyer B, Hart KW, Sperling MI, Lindsell CJ, Collins SP (2012) Biomarker changes during acute heart failure treatment. Congest Heart Fail 18:91–97
41. Stolz D, Christ-Crain M, Morgenthaler NG, Miedinger D, Leuppi J, Müller C, Bingisser R, Struck J, Müller B, Tamm M (2008) Plasma pro-adrenomedullin but not plasma pro-endothelin predicts survival in exacerbations of COPD. Chest 134:263–272