

Respiratory Management of Acute Cardiogenic Pulmonary Edema: A Review

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ABSTRACT

Acute cardiogenic pulmonary edema (ACPE) is a common and life-threatening condition among patients with heart failure. The literature contains a large number of reviews discussing the respiratory management aspect of this entity; nonetheless, none of these studies has thoroughly probed into the respiratory management of different cardiac pathologies ending with ACPE, together with the different modes of ventilation and invasive and noninvasive ventilation in the same discussion. The present review seeks to discuss the physiologic bases of lung-heart interactions, the hemodynamic effects of positive pressure ventilation, and the results of studies on the effects of the various modes of ventilation having been used until the writing of this article. Also discussed herein are ACPE in different heart pathologies and their respective ventilator management, as well as the indications, complications, and contraindications of noninvasive positive pressure ventilation and intermittent mandatory ventilation.

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Similar to heart failure, respiratory failure is also accompanied by an inability to deliver sufficient oxygen to the blood and systemic organs and remove carbon dioxide [1-2]. Many diseases can cause congestive heart failure, and if left untreated, they end up with decompensated cardiac failure, acute pulmonary edema, and respiratory failure [3]. On the other hand, heart failure is one of the important causes of weaning failure in patients under mechanical ventilation [4]. The concept of heart-lung interactions, first introduced by Stephen Hales, has been confirmed by such new technologies as ultrasonography and other monitoring devices [5-6]. Before a patient is placed on positive pressure mechanical ventilation (PPV), what should be considered is its impacts on the cardiovascular system depending on the types of cardiac pathology. The major effect of PPV on the left ventricle is a reduction in both preload and afterload. However, its effect on the right

heart is a prominent drop in preload and a rise in the afterload [5,7-8]. Weaning from the ventilator has always been a great challenge for intensive care physicians, especially in patients with underlying cardiac disorders [9]. Changing from PPV to spontaneous breathing during weaning has its own hemodynamic impact on the cardiovascular system [4,10]. There are many reviews that have addressed some of these issues in the past. We herewith reviewed more cardiac pathologies regarding ventilator considerations in order to provide brief evidence for intensive care professionals.

Effects of spontaneous breathing and PPV on cardiovascular hemodynamic

Both spontaneous breathing and PPV increase the lung volume relative to the baseline end-expiratory volume. The former decreases intrathoracic pressure, whereas the latter increases it. This fundamental difference is the

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basis of various hemodynamic changes of these 2 types of respiration [11-13]. The drop in intrapleural pressure during spontaneous inspiration increases the transmural pressure of cardiac atria and ventricles. This negative pressure is the main factor in the return of blood to the right atrium and an increase in the right ventricular end-diastolic volume and the right-side stroke volume [14-15]. Indeed, the pressure gradient between mean systemic filling pressure and the right atrium determines the venous return. The right and left ventricles are interrelated to each other in a common pericardium. Because of this “interdependence”, the increase in venous return increases right ventricular filling, bulging the interventricular septum toward the left ventricle, and consequently decreases left ventricular filling. The pulsus paradoxus can be explained by this mechanism. This effect is transient and eventually, after a few heartbeats, the increased right ventricular output transfers to the left side of the heart and leads to an increase in the cardiac output. In turn, an increase in the cardiac function causes an increase in the venous return by lowering right atrial pressure. Spontaneous inspiration increases the transmural pressure of the left ventricle and the aortic root and, thus, left ventricular afterload, while it causes a reduction in right ventricular afterload.

Although ventilation and perfusion are higher in the dependent regions of the lungs than in the apical regions during spontaneous respiration, these increments are not in the same proportion for perfusion as it increases more relative to ventilation. This causes the V/Q mismatch to be more prominent in the bases. Consequently, some mismatch is a normal phenomenon in a normal lung [16-19]. Inhomogeneity throughout the lung during PPV has also been shown in studies and this varies with change in the value of the pressure-volume of support as well as pulmonary vascular hemodynamics [20-21]. PPV changes the mechanics and geometry of the diaphragm. Unlike spontaneous negative pressure, in which the posterior part of the diaphragm is the predominant part during ventilation, the anterior part of the diaphragm moves more in PPV and this might be the major disadvantage regarding V/Q matching [22]. In addition, better V/Q matching during spontaneous respiration has been shown in animals as well as human studies [23-24]. In both spontaneous and controlled ventilation modes (continuous positive airway pressure [CPAP] and positive end-expiratory pressure [PEEP]), V/Q mismatch is improved by the recruitment of the alveoli and enhanced compliance [25].

During PPV, an increase in intrathoracic pressure has different impacts on the right and left sides of the heart. At a glance, PEEP decreases CO by reducing the venous return to the right atrium. This reduction in right ventricular preload depends on the degree of PEEP, tidal volume, and the compliance of the lung. These factors determine the amount of the extramural pressure of the

right heart during PPV. PEEP also has other opposite effects. For instance, mean systemic filling pressure is increased by the transfer of blood from the pulmonary circulation to the systemic circulation and an increase in intra-abdominal pressure through the compression of the splanchnic veins. The effect of spontaneous and PPV on right ventricular afterload depends on both the lung volume and intrathoracic pressure. Below functional residual capacity, pulmonary vascular resistance is increased due to the tortuosity of the medium and large intrapulmonary blood vessels; while above functional residual capacity, this increase is due to intra-alveolar capillary compression. The moderate level of PEEP recruits more alveoli and, as a result, decreases pulmonary vascular resistance. On the other hand, a high level of PEEP or large tidal volume increases pulmonary vascular resistance by compressing the intra-alveolar capillaries [26-27].

During PPV, the transmural pressure of the aortic root and the left ventricle decreases so the left-heart afterload decreases. Further, a decrease in right ventricular preload leads to reduced left ventricle preload. These beneficial effects are very similar to the desired effects of useful drugs that are usually utilized in the treatment of congestive heart failure and are reversed when patients with heart failure are weaned from the ventilator. Theoretically, an increase in intrathoracic pressure can reduce coronary blood flow, and thereby the contractility of the right ventricle, when aortic pressure is low. However, right ventricular contractility is not usually affected by PPV. The impact of PEEP on right ventricular systolic function in patients with acute respiratory distress syndrome might be due to the evolving respiratory acidosis [28].

As was noted above, a decrease in preload and afterload in the left ventricle leads to decreased wall tension and O₂ demand. Changing PPV to spontaneous ventilation during weaning leads to negative pressure, which has a detrimental effect on myocardial ischemia [29-30]. Left ventricular contractility is usually not affected by PPV under most clinical conditions with a normal left ventricular function. During PPV inspiration, systolic blood pressure increases as ventricular afterload drops and the pulmonary blood return to the left atrium increases “delta up”. Following this rise, systolic blood pressure decreases because, after a few heartbeats, the decrease in right ventricular preload by PPV reaches the left side and left ventricular preload and stroke volume decreases [31-32].

Ventilator consideration in ACPE

ACPE is defined as pulmonary edema due to increased capillary hydrostatic pressure secondary to elevated pulmonary venous pressure. The etiologies of ACPE are various (Table 1). Precipitating and predisposing causes should be addressed; however, the current respiratory

failure should be first treated in acute situations. Medical treatments include medications to reduce preload, afterload, or optimizing myocardial function. The first treatment modality in respiratory management is conventional oxygen therapy with a nasal cannula, face mask, or venturi mask. The next step depends on the clinical presentation and situation of the patient. The high flow nasal cannula (HFNC), CPAP, and other modalities that need ventilators to deliver oxygen are called “noninvasive positive pressure ventilation” (NIPPV or simply NIV). They constitute the main ventilator support and are considered to be effective early therapy in ACPE insofar as they can significantly reduce mortality [2,33-36]. Whereas earlier studies demonstrated no effect on mortality [37-38], subsequent studies showed decreased in-hospital mortality and intubation rates [33-34,39-40].

Table-1- Common Etiologies of Acute Cardiogenic Pulmonary Edema

<u>Cardiac Conditions</u>
Atrial outflow obstruction (ie, mitral stenosis)
Thrombosis of a prosthetic valve
Systolic dysfunction
Cardiomyopathy
Congestive heart failure
Acute myocardial infarction or ischemia
Myocarditis
Chronic valvular disease, aortic stenosis, aortic regurgitation, and mitral regurgitation
New-onset rapid atrial fibrillation and ventricular tachycardia
Atrial myxoma
<u>Non-cardiac Conditions</u>
Severe anemia
Sepsis
Thyrototoxicosis
Volume overload

NIPPV is used as a bridge while other medical treatments begin to exert an effect, and it reduces the rate of intubation in patients with acute cardiac failure [41]. NIPPV does not increase the rate of myocardial infarction, and its effect on increasing the length of hospital stay is unclear [2]. Even in patients with severe ACPE and acidosis, NIPPV has not been associated with adverse outcomes [42]. Nevertheless, the most recent Canadian Medical Association recommendation and the ETS/ATS guidelines strongly suggest the use of NIPPV in ACPE except in patients in shock or patients with acute coronary syndrome candidate for revascularization [43-44].

A study indicated that patients with late or failed NIPPV, as rescue treatment, have a worse outcome [45].

The compliance of both patients and nursing staff has a major role in tolerating the NIPPV device and the success of this modality, although a recent study did not reach this conclusion [2].

CPAP is the simplest type of NIV and is usually the first modality of choice in ACPE. It delivers a selected positive pressure (usually 5–10 CmH₂O) during both inspiration and expiration in patients with spontaneous breathing. CPAP can be provided by a CPAP device or ventilator. The former is usually delivered via a face, oronasal, or nasal mask that has a valve for the adjustment of the level of positive pressure. The leak around the mask and insufficient flow are the major drawbacks of CPAP. The nasal mask has been better tolerated than the oronasal mask, with a similar improvement in acute respiratory failure [46]. It increases functional residual capacity and helps to alleviate atelectasis, improve gas exchange, reduce work of breathing, and reduce the rate of intubation compared with oxygen therapy in ACPE [47-49]. Nonetheless, nasal CPAP should be avoided in acute situations and full-face or oronasal masks should be used, especially with the other modes of NIV [50]. CPAP improves the left ventricular function by reducing left ventricular transmural pressure (afterload) and also left ventricular preload and has improved oxygenation and ventilation in patients with ACPE [51]. Even in severe ACPE and elderly patients, as well as all levels of the left ventricular systolic function, CPAP has been safe and effective [52-55]. For better tolerance, treatment should be commenced with low levels of pressure (5 cm H₂O) before an increase based on tidal volume and PaCO₂.

BiPAP is bi-level CPAP, providing inspiratory positive airway pressure and expiratory positive airway pressure. Other terms for this modality of ventilation are noninvasive pressure support ventilation and NIPPV. BiPAP can be administered through a nasal or face mask. A majority of systematic reviews and meta-analyses have shown that both CPAP and BiPAP equally lead to reduced intubation and mortality rates by comparison with the standard medical therapy in ACPE [34,56-59]. Nonetheless, some other studies have claimed better systolic function and oxygenation in cardiac failure patients with BiPAP added to CPAP, particularly when the patients need a higher level of CPAP [59-60]. It appears that BiPAP is the preferred mode in more critical situations and when a more rapid result is the goal. Upon the initiation of this mode and for more patient's convenience, it begins with low levels (eg, 3 cm of expiratory positive airway pressure and 10 cm of inspiratory positive airway pressure) and then based on the compliance of the patient, PaCO₂, tidal volume, and hemodynamic parameters, it will be modified.

Noninvasive pressure support ventilation

Usually BiPAP is implemented by home NIV ventilators that are used for chronic respiratory problems

or sleep apnea and has a backup rate, whereas noninvasive pressure support ventilation is delivered via hospital ventilators and does not have a backup rate. In BiPAP, spontaneous breaths are flow cycled and ventilator breaths are time cycled, but pressure support ventilation breaths are flow cycled. In a study, patients with hypercapnic ACPE were treated with pressure support ventilation the same as normocapnic patients. The re-intubation rate and hospital stay did not differ even in patients with severe hypercapnia. Only the duration of NIV and the length of ICU stay differed modestly [61]. In a clinical trial on a comparison between noninvasive pressure support ventilation and CPAP in patients with ACPE, the degree of pressure support was adjusted to deliver a tidal volume of 6 to 8 cc/kg by regular ventilators. The results of the trial revealed that pressure support ventilation was associated with a rapid respiratory improvement in severe heart failure and hypercapnic patients, although it did not reduce the rate of intubation and mortality in comparison with CPAP [62]. Other studies have also found similar results and this has been suggested as an alternative modality after CPAP [63-64].

The HFNC is another modality of NIV with good feasibility and tolerability, and it improves the respiratory condition [65]. In this modality, a high flow of fully water-saturated and warm oxygen is delivered to the patient through a nasal cannula. Usually, the flow is 60 l/min (25–80 l/min) and the fraction of inspired oxygen (FiO₂) is between 21% and 100%. Besides providing much more FiO₂, it also produces a steady level of positive pressure [66]. A recent systematic review and meta-analysis concluded that the HFNC is less tolerable than conventional oxygen therapy [67]. In a clinical trial, the respiratory rate at 15, 30, and 60 minutes was lower with HFNC than with conventional oxygen therapy in patients with ACPE [68]. This result, as well as a reduction in preload, has been found in studies including patients with class III congestive heart failure [69]. In a systemic review and meta-analysis, the HFNC was more effective than conventional oxygen therapy in reducing the intubation rate, mechanical ventilation, and level of respiratory support, but not compared with NIV in this study [70]. It has the advantage of preventing the desiccation of upper airway secretions and improving the mucociliary function [71]. In a small randomized cross-over study, nasal high flow decreased the respiratory rate and increased the tidal volume in wakeful patients, while it decreased the tidal volume and caused no change in the respiratory rate during sleep [72]. The nasal high flow had positive effects on clinical and gasometric indices in patients with ACPE [73]. The HFNC may be able to prevent intubation in some patients with ACPE and also is beneficial for patients with severe heart failure [69,74]. It appears that the HFNC is more useful in patients with ACPE who do not respond to conventional oxygen

therapy and who are not good candidates for noninvasive positive pressure ventilation. Recently, the HFNC was compared with NIV in patients with acute congestive heart failure in the emergency department. In this multicenter study, subgroup analysis showed that the HFNC was as effective as NIV in terms of effects on failure to therapy and the intubation rate [75]. It has been recommended that the HFNC be commenced with low levels of flow of about 30 mL/min and a high FiO₂ of 100%. Thereafter, the amount of flow will gradually increase and the fraction of FiO₂ decrease, based on the tolerance of the patient and gasometric parameters.

Adaptive servo-ventilation is another type of NIPPV performed effectively in patients with chronic heart failure in many studies [76-80]. It is a form of pressure preset closed-loop ventilation that has a backup rate, inspiratory positive airway pressure, and expiratory positive airway pressure, adaptive servo-ventilation based on the target ventilation. These pressure support levels are adjusted, so it is better tolerated by patients in comparison with CPAP [81]. Recently, the beneficial effect of this modality has been studied in ACPE. By comparison with standard medical treatment, the addition of adaptive servo-ventilation not only reduces the stress response, dyspnea, and the rate of intubation and hospitalization but also improves the acid-base status [82-84]. It is advisable that adaptive servo-ventilation be initiated as soon as possible when the patient is in respiratory distress. In a study on patients with ACPE, adaptive servo-ventilation was associated with a lower rate of intubation and a shorter length of stay in the ICU than conventional therapy when it was introduced rapidly in the emergency department [85]. Additionally, hypercapnia, even in the absence of underlying lung diseases, is not uncommon in patients with ACPE.

Proportional assist ventilation

As the name indicates, this is a form of mechanical ventilation that works in proportion to the patient's effort or demand. Its work is based on inspiratory flow and hence volume, as well as the resistance and compliance of the patient's respiratory system. It provides more patient synchrony, less weaning failure, and shorter ventilator dependence as compared with pressure support ventilation in patients under invasive mechanical ventilation [86-87]. A study compared CPAP with proportional assist ventilation through face masks in patients with ACPE and reported that the latter was superior to CPAP in terms of the patients' tolerance and efficacy [88].

Neurally adjusted ventilatory assist (NAVA) is a relatively new mode of ventilation that works based on the diaphragmatic electromyography activity achieved via an esophageal electrode placed in the esophagus. In several studies, it has been shown that NAVA helps to have better synchrony in patients with acute respiratory

failure using NIV compared with pressure support ventilation [89-92]. Still, subgroup analysis is required to come to a conclusion within this specific group of the patients. A previous study compared NAVA with pressure support ventilation in patients with acute respiratory failure including 6 patients with ACPE and reported that NAVA was feasible and better in terms of post-intubation NIV use [93].

Effects of NIPPV in different cardiac pathologies

Mitral stenosis:

The main problem in mitral stenosis regarding respiratory issues is the back-pressure through the left atrium to the pulmonary veins and increased systolic pulmonary artery pressure in response to an elevated heart rate and flow. Pulmonary hypertension is a consequence of the moderate and severe forms of mitral stenosis in many patients, indicating a dismal prognosis when it is severe [94]. In mitral stenosis, left atrial passive emptying decreases and active emptying in some cases decreases, although some studies have shown an increase in this function [95]. The cardiac function is dependent on the diastolic time and filling as well as active atrial filling, so any factor that abuts these functional issues is dangerous in patients with mitral stenosis. There are no studies in the literature to show the outcome effects of NIPPV in mitral stenosis patients with pulmonary edema.

Mitral valve regurgitation

In primary mitral regurgitation, pulmonary hypertension is associated with a poor prognosis and is one of the indications for the repair of mitral regurgitation either by surgery or by other interventions. Pulmonary hypertension is seen in patients with secondary mitral regurgitation even in the absence of a decreased left ventricular ejection fraction, which may require mitral valve repair [94]. Aside from the hemodynamic effects of positive pressure, it has been postulated that long-term CPAP reduces the mitral regurgitation fraction of regurgitation in patients with congestive heart failure [96]. In acute mitral regurgitation, regurgitation into a normal-size left atrium causes pulmonary edema. In ACPE due to acute mitral regurgitation, CPAP has been helpful by decreasing the left ventricular end-diastolic volume [97]. Also in patients with functional mitral regurgitation and heart failure, CPAP and BiPAP employed for 30 minutes decrease the fraction of the mitral regurgitation [54,98]. Ten-minute CPAP and adaptive servo-ventilation could alleviate functional mitral regurgitation in patients with systolic heart failure and functional mitral regurgitation [99].

Aortic stenosis

Aortic stenosis can cause ACPE through producing left ventricular failure and elevation of pulmonary venous pressure and, thereby, alveolar-capillary stress failure

[100]. Severe aortic stenosis causes elevated left ventricular end-diastolic pressure and, thus, left ventricular hypertrophy. Over time, left ventricular filling is impaired and diastolic failure ensues. Aortic stenosis can create heart failure with a preserved ejection fraction; therefore, the respiratory management considerations of this entity are similar to those of heart failure with a preserved ejection fraction (will be discussed later). Choric aortic stenosis can lead to central sleep apnea through producing heart failure and pulmonary congestion; it changes the sensitivity of the respiratory center to hypoxia other than hypercapnia. A study evaluating the effect of CPAP and other NIV modalities on reducing central sleep apnea in patients after transcatheter aortic valve implantation showed that the first one was ineffective and BiPAP and adaptive servo-ventilation were more effective in patients with aortic stenosis [101]. Pulmonary hypertension is seen in about 50% of symptomatic aortic stenosis patients. It is accompanied by dismal outcomes and is more related to diastolic dysfunction [94].

Aortic regurgitation

Unlike chronic aortic regurgitation, in acute aortic regurgitation, there is not enough time to accommodate volume regurgitation; as a result, left ventricular end-diastolic pressure exceeds left atrial pressure, resulting in the premature closing of the mitral valve during diastole. Hence, the increased pressure of the left atrium causes an increase in pulmonary pressure and ACPE [102]. Acute aortic regurgitation results from various etiologies including aortic dissection, bicuspid valve, and valve degeneration [103]. It appears that in chronic aortic regurgitation, cardiac enlargement, and volume overload, PPV decreases transmural pressure and improves contractility [104]. There are case reports indicating that ACPE may be one of the severe presentations and complications of aortic dissection. In these cases, usually intubation and IPPV have been the respiratory option until the main surgery or intervention [105-106].

Acute myocardial infarction

In a clinical trial, NIPPV was effective in reducing the intubation rate and improving oxygenation and vital signs in patients with myocardial infarction complicated by ACPE [107]. In an observational study on patients with acute myocardial infarction and acute respiratory failure, the in-hospital mortality rate in patients placed on mechanical ventilation was compared between intermittent mandatory ventilation (IMV) and NIV groups. The first group had a threefold more in-hospital mortality rate than the second one. Additionally, the length of hospital stay was lower in the NIV group [108]. Several studies have shown that NIPPV does not increase the risk of myocardial infarction in patients with acute pulmonary edema [107,109]. However, we should be

cautious in using NIV and generous about using IPPV in patients with acute coronary syndrome because the response to NIV and prognosis are worse than the other etiologies of ACPE [110].

Diastolic dysfunction

In patients with diastolic dysfunction and ACPE, the role of NIV is poorly understood. During the inspiration phase of PPV, unlike spontaneous breathing, right ventricular filling decreases, whereas left ventricular filling increases. These effects are the opposite during the expiratory phase [111]. Because PPV decreases the venous return and the left ventricular end-diastolic volume, it can theoretically aggravate diastolic dysfunction. Because of these and other hemodynamic effects discussed above, these changes should be taken into account during the evaluation of diastolic dysfunction via echocardiography [112]. A study showed that the E' wave increased with an increase in the amount of PEEP, indicating the worsening of the diastolic function. Both insufficient preload and PPV decrease the accuracy of these diastolic echocardiographic indices, especially the E' wave because PPV increases myocardial preload sensitivity. Indeed, a higher E/E' ratio is one of the independent risk factors for weaning failure from the ventilator [113-115]. However, in a study in Italy, it was shown that 10 CmH₂O CPAP was helpful in patients with preserved left ventricular systolic dysfunction (HFpEF) in relieving symptoms and reducing the rate of intubation and hospital mortality as well as in patients with a low ejection fraction [116]. Another study showed that 10 CmH₂O CPAP in 30 minutes reduced plasma brain natriuretic peptide levels in the group with HFpEF but not in the group with a reduced ejection fraction [117]. Based on this information, it appears that if adequate preload and left ventricular end-diastolic volume are provided, PPV is useful in such patients.

Cardiogenic shock: In this situation, intubation should not be deferred in patients who need intubation and IMV [118]. In a multicenter study on 112 patients (shock trial) with cardiogenic shock and based on the clinical condition and common indications and contraindications of IMV and NIV, 12% of the patients underwent NIV and 63% of them needed IMV. The 90-day mortality rate was compared between the 2 groups and yielded no difference. 118 According to a cohort study, in almost half of the patients with cardiogenic shock following myocardial infarction who had acute respiratory failure, both NIV and IMV tended to increase between the year 2000 and the year 2014. Overall, IMV was used in 43.2% and NIV in 4.7% of the study population. Additionally, respiratory failure and IMV were associated with a higher mortality rate. Subgroup analysis is needed to compare IMV to NIV in that study in terms of outcomes [119].

Right-sided heart failure: The hemodynamic effects of PPV on right ventricular preload and afterload and

pulmonary circulation has been mentioned previously. In patients with subpulmonary right ventricular failure and tricuspid regurgitation, PPV decreases CO. Nonetheless, it should be noted that hypoxemia and hypercapnia are also strong pulmonary vasoconstrictors. Accordingly, prudent use of PPV can reduce right ventricular afterload in these situations [120]. Lower tidal volume and P plateau are helpful in these circumstances and improve the right ventricular function. NIV has been safe in terms of hemodynamic changes in patients with acute renal failure following chronic obstructive pulmonary disease and pulmonary hypertension [121-122]. The long-term use of CPAP or NIV in patients with pulmonary hypertension secondary to hypoventilation syndrome has resulted in lower pulmonary artery pressure [123]. It appears that judicious use of PPV along with meticulous hemodynamic monitoring, the use of a low tidal volume, and PEEP could reduce or eliminate these adverse hemodynamic effects of PPV in patients with right ventricular failure [124].

NIV failure in ACPE

The European Respiratory Society/American Thoracic Society (ERS/ATS) guideline has strongly recommended NIV for ACPE. 44 NIV has reduced the rate of nosocomial infections and improved survival in critically ill patients with chronic obstructive pulmonary disease and ACPE [125-126]. Based on the time of failure, NIV failure is usually categorized as early or late. Early failure happens in the first 48 hours after the initiation of NIV, and the late category occurs afterward [127].

Many factors influence the success of NIPPV. The training and competence of health-care staff in NIV implementation is an important factor, especially for nursing staff [128-129]. The success of NIV is dependent on the underlying disease. For the predictors and risk factors of NIV failure in acute respiratory failure, we refer the readers to other sources [127,130-131]. Based on a cohort study in China, the authors developed a HACOR score system for predicting NIV failure in hypoxemic respiratory failures. A HACOR score greater than 5 was associated with failure. The HACOR score comprises heart rate, acidosis, consciousness level, oxygenation, and the respiratory rate [132]. As regards ACPE, which is a kind of hypoxemic respiratory failure, there is no strong study about the predictors for NIV failure. In another cohort study, the failure rate of NIV in ACPE was much lower than that in pneumonia and acute respiratory distress syndrome [133]. According to the results of several small studies, systolic blood pressure less than 140 and severe acidosis (pH \approx 7.03) were among the predictors for the failure of NIPPV in ACPE [134-135]. Killip class IV, a low left ventricular ejection fraction, high brain natriuretic peptide at baseline, and volume overload have been associated with a higher failure rate of NIV [136]. Recently, the relationship

between the fragility scores of patients has been studied. In that study, a clinical fragility score of greater than 5 was associated with NIV among patients suffering from respiratory failure in the ICU [137].

The management of ACPE requires a plan, and even better a protocol for using the NIV modality. Asynchrony is the most important factor in NIV failure. Choosing an interface that is not suitably fit leads to asynchrony because of excessive leakage. Other causes of leakage may be the poor management of secretions and the oversight of the neurological status of patients [127]. Failure to improve the respiratory condition of the patient after an hour of initiation usually indicates NIV failure. In this case, early intubation (<12 h) reduces the mortality rate more than late intubation [132-133]. Early use of NIV is a very important factor in the prevention of intubation [138]. NIV has some adverse effects such as nasal pressure ulcer [139]. There are no differences between outcomes with different modes of ventilation and ventilators (not circuits) [44]. In ACPE, if the duration of ventilation is no longer than a few hours, humidification with heat and moisture exchangers or active humidifiers is not recommended [44]. On rare occasions, patients who are agitated may need sedation in order that they can tolerate interfaces. Based on the results of several studies, we recommend the use of dexmedetomidine in patients with ACPE [140-142]. (See the ERC/ATS for more information on the practical application of NIV) [44]. The complications of NIV based on the interface may include the nasal bridge sore, gastric distention, pulmonary aspiration, barotrauma, and asphyxia [48].

Indications of NIV in acute heart failure

NIV is used in most patients with acute heart failure who have moderate to severe symptoms of respiratory distress ($RR > 25$, $SpO_2 < 90\%$) in spite of using conventional oxygen therapy, but cautiously in pure right-sided heart failure [143]. An important point is that the majority of patients with acute heart failure have dyspnea but fewer than 50% of them present with hypoxia. In acute heart failure patients with more severe symptoms and hypercapnia, NIPPV acts better than CPAP. ACPE is a severe form of acute heart failure, so NIPPV is preferred to CPAP, though both of them can be initiated as initial respiratory management [144].

Invasive mechanical ventilation in ACPE

Besides the adverse effects of PPV, intubation itself has its own complications such as profound hypoxemia, severe hypotension, cardiac arrest, esophageal intubation, mechanical injuries from lips and teeth to bronchi, and association with pneumonia [145-146]. On top of this are the adverse effects of pharmacological agents such as muscle relaxants and anesthetic drugs. Thus, IMV should be avoided as much as possible. The major reasons for

intubation are the protection of the airways in patients with a loss of consciousness and respiratory support. In uncompensated congestive heart failure, mechanical ventilation is a very important life-saving tool, although its abovementioned benefits should be weighed against these hazards [144]. In ACPE, contraindications to NIV are the indications of tracheal intubation and invasive ventilation. These include patient refusal; severe hypotension; vomiting; moderate altered mental status (Glasgow Coma Scale < 8); no improvement in the respiratory condition and blood gases 1–2 hours following the commencement of NIV; and signs of impending respiratory failure such as fatigue, diaphoresis, severe anxiety, and lethargy among others. It is deserving of note once more that positive pressure is useful in acute cardiac failure. Both improvements in hemodynamic parameters and clinical conditions have been shown in previous studies [147]. The amount and duration of intrathoracic pressure may affect hemodynamic parameters more than the modes of IMV, although we could not find any study on ACPE comparing the different modes of IMV [148-153].

A few points should be mentioned with respect to the use of IMV parameters in acute decompensated heart failure. First, recent clinical studies have shown that PEEP is not harmful in contrast to what was believed in the past. Indeed, PEEP improves CO, the left ventricular function, and O₂ delivery in patients with cardiogenic shock. However, in patients with acute myocardial infarction and hypovolemia or euolemia, it should be used with caution and initiated with low levels and increased slowly. High levels of PEEP can be used in uncompensated heart failure guided by hemodynamic monitoring and based on the indices of end-organ perfusion [144]. Secondly, as there is a decrease in lung compliance and an increase in the work of breathing in CHF and ACPE as well as hypoxia due to the inability of the heart to work enough, inspiratory pressure is paramount to offloading the cardiac work. In this regard, the use of assist control mode of ventilation (AC-V or AC-P) is recommended at least in the early phases of IMV [144]. For all the investigations have demonstrated the beneficial role of low tidal volume ventilation in acute respiratory distress syndrome, there is a dearth of information as regards ACPE. Given the protective effect of this strategy in other patients without acute respiratory distress syndrome and a recent randomized controlled trial that found no superiority of low over intermediate tidal volume in patients without acute respiratory distress syndrome in terms of the length of ventilator-free days, it is reasonable to use intermediate tidal volume in patients with ACPE, especially in the presence of metabolic acidosis [154-158]. A preliminary study showed that low tidal volume PPV compared with high tidal volume protects against the left ventricular diastolic function. In that study, however, a very high tidal volume was used in

high tidal volume ventilated rats [159]. In a study on 129 cardiac ICU patients (with acute heart failure or post-CPR) who were initiated on IMV, limited positive inspiratory pressure was more related to lower hospital mortality than low tidal volume. In that study, the authors used a maximum tidal volume of 6 mL/kg and limited positive inspiratory pressure to 30 mm Hg [124].

Conclusion

ACPE is common in patients with acute heart failure. The majority of patients with ACPE initially have respiratory distress without low SpO₂. The first treatment entity is the medical treatment of the underlying disease and the pharmacological treatment of ACPE. Conventional oxygen therapy is the first modality used in the respiratory management of ACPE; however, based on the condition of the patients, NIV modalities may be initially implemented. The ERS/ATS has strongly recommended NIV in ACPE. In patients with moderate-to-severe respiratory distress, it is recommended to begin with noninvasive pressure support ventilation rather than CPAP. There is no consensus regarding the time to start NIV in ACPE. Nonetheless, in acute heart failure patients who have moderate-to-severe respiratory distress in spite of conventional oxygen therapy and with SpO₂ less than 90% and RR greater than 25, it is advisable to begin NIV. NIV has been implemented in the severe cases of ACPE with acidosis and cardiogenic shock–acute renal failure without adverse effects. The predictors of NIV failure should be accorded due attention. Important measures to reduce this failure include the education of patients and medical staff and the use of appropriate interfaces. There are no prominent differences in outcomes between the different modes of ventilation in treating ACPE. The knowledge of applicants about respiratory and cardiovascular physiology, lung-heart interactions, and the effects of PPV on these systems is paramount in the implementation of PPV. Sometimes patients should be sedated to better tolerate the interface. The complications of NIV depend on the kind of interface utilized. When NIV fails, early intubation lowers the mortality rate. When invasive IMV is finally needed, avoiding atelectrauma and volutrauma and limiting asynchronies by adjusting ventilator variables are important. The underlying disease, the type of cardiac pathology, the familiarity of the physician and the personnel, and the setting of the patient's location determine which type of IMV modes is more suitable for use.

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