

## Noninvasive Pressure Control Inverse Ratio Ventilation (NIPCIRV) Versus Conventional Oxygen Therapy for Treatment of Acute Cardiogenic Pulmonary Edema

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**Abstract:** Previous studies suggesting the use of non-invasive ventilation modes in patients with Acute Cardiogenic Pulmonary Edema (ACPE). However, there are controversies regarding the benefit of using non-invasive ventilation in patients with ACPE. This study investigated the short-term effects of non Invasive Pressure Control Inverse Ratio Ventilation (NIPCIRV) on respiratory, hemodynamic and oxygenation parameters in patients with acute respiratory failure due to Acute Cardiogenic Pulmonary Edema (ACPE). Moreover, intubation need and the duration of Cardiac Care Unit (CCU) stay in those patients were investigated. In this randomized clinical trial study, 120 patients were assigned conventional oxygen therapy or NIPCIRV by a standard ventilator through a face mask in addition to standardized pharmacological treatment. Physiological parameters were obtained at different time points (0, 15, 30 and 60 min) post NIPCIRV. The main end points were intubation, recorded recovery time (defined as oxygen saturation of 96% or more), respiratory rate <30 breaths/min and duration of CCU stay. Endotracheal intubation was required in 2 (3.3%) of 60 assigned non NIPCIRV and in 12 (20%) of 60 assigned conventional therapy ( $p = 0.001$ ). Recovery time was significantly shorter in the NIPCIRV group ( $48 \pm 8$  h) compared with control group ( $96 \pm 12$  h) ( $p < 0.05$ ). NIPCIRV led to a rapid improvement in oxygenation, respiratory rate, arterial PH, heart rate and blood pressure in the first hour ( $p = 0.0001$ ). There were significant differences in length of stay in coronary care unit, stay from ( $3 \pm 1$  days) in NIPCIRV group vs ( $7 \pm 1$ ) in control group ( $p = 0.0001$ ). Hospital mortality was 17 patients (28.33%) in conventional group and 8 patients (13.33%) in NIPCIRV group ( $p < 0.001$ ). This study confirms that the non-invasive ventilation method of NIPCIRV is superior to conventional oxygen therapy.

**Key words:** Acute cardiogenic pulmonary edema, non-invasive pressure control inverse ratio ventilation, recovery, effects, Iran

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### INTRODUCTION

Acute Cardiopulmonary Edema (ACPE) is a common medical emergency. This condition has a poor prognosis with reported hospital mortality of 10-20% which requires rapid assessment and treatment (Gray *et al.*, 2008; Jessup and Brozena, 2003). Despite standard medical therapy with oxygen, morphine, diuretics and nitrates, ventilatory support may be needed. After the onset of pulmonary edema process due to increases pulmonary congestion, oxygen saturation decreases and resulting in decreased myocardial oxygen supply. This complication leads to ischemia in regions with already borderline blood supply and impairing cardiopulmonary system (Jessup and Brozena, 2003; Agarwal *et al.*, 2005).

Immediate treatment of acute ACPE is required to improve systemic oxygen saturation by giving oxygen with a high flow facemask (Venturi mask), reduction of preload and afterload of both the ventricles by a

combination of morphine, diuretics and nitrates. An important point to consider is that respiratory failure and dyspnea are not directly related to hypoxemia and thus cannot be reversed with oxygen administration alone.

Traditionally, patients who do not have a response to initial therapy often require tracheal intubation and ventilation with the associated potential for complications.

Endotracheal intubation has some well-known risks of complications. These complications are related directly to intubation (injury of vocal cord or trachea), to aspiration of gastric content, irritation or injury due to the endotracheal tubes, edema, nosocomial infection, inflammation and increased mucus production. Furthermore, patients need more sedatives and analgesics.

Non-Invasive Pressure Control Inverse Ratio Ventilation (NIPCIRV) is delivered via a tight-fitting mask

without the need of an endotracheal tube or tracheostomy. Using masks as interfaces is the most important advantage of NIPCIRV.

NIPCIRV preserves normal swallowing, speaking, cough, air warming and humidification and avoids complications associated with endotracheal intubation, such as nosocomial pneumonia and upper airway trauma (Brochard *et al.*, 1989; Meduri *et al.*, 1996).

NIPCIRV can decrease inspiratory work of breathing and improve gas exchange, reducing the need for invasive ventilation in patients with hypercapnic respiratory failure compared with conventional medical therapy (Masip *et al.*, 2000; Nava *et al.*, 2003).

## MATERIALS AND METHODS

This study was approved by the ethics committee of the Kermanshah medical university and all patients or their family gave written informed consent. The study was performed in all patients with ACPE and older than 20 years. Inclusion criteria were diagnosed by cardiologist. Factors such as patient's consciousness, cooperation and their hemodynamic stability were checked.

Patients with the following symptoms were excluded from the study: severely decreased consciousness (Glasgow coma score of 11 or less), severe hemodynamic instability (systolic blood pressure <80 mm Hg) or bradycardia HR<45 min<sup>-1</sup> or tachycardia HR>120 min<sup>-1</sup>, severe ventricular arrhythmia, recent esophageal, facial or cranial trauma or surgery, nausea, vomiting (despite of use antiemetic drugs), lack of cooperation, inability to clear respiratory secretions, tracheotomy or other upper airway disorders, active upper gastrointestinal bleeding, need for emergency intubation and more than one severe organ dysfunction in addition to respiratory failure, respiratory rate >35 min<sup>-1</sup>, PaO<sub>2</sub><50 mm Hg, PaCO<sub>2</sub>>50 mm Hg.

Patients with inclusion criteria were randomly assigned to receive either conventional Oxygen therapy with venturi mask (controlled group) or NIPCIRV through a face mask (NIPCIRV group). Head of the bed was kept elevated at a 45° angle. Heart rate (electrocardiography) and respiratory rate were monitored continuously. Arterial blood gas sampling was obtained through a 18-gauge plastic cannula placed in the radial artery and blood pressure was measured invasively. Pulse oximeter was used to control arterial oxygen using Space Labe monitor.

Respiratory rate, heart rate, blood pressure and arterial blood gases were recorded at different time points (0, 15, 30 and 60 min) and then every 30 min as needed.

Patients were given standardized pharmacological treatment which includes intravenous furosemide 40-320 mg to achieve sufficient urinary output, continuous intravenous nitroglycerin (5-50 μ kg<sup>-1</sup> min<sup>-1</sup>) if systolic blood pressure was above 100 mm Hg, morphine sulphate 5-10 mg and weight-adjusted doses of subcutaneous or intravenous heparin and aspirin if the ECG was suggestive of ischemia. Secondary medical treatment was given as needed basis including continuous infusions of catecholamines (dopamine, dobutamine and adrenaline) if mean blood pressure was below 60 mm Hg and/or urinary output decreased below 0.5 mL kg<sup>-1</sup> h<sup>-1</sup>.

Ventilatory support based on randomization included patients assigned to the conventional Oxygen therapy group receiving oxygen by a venturi mask 10 lit min<sup>-1</sup> (controlled group). In the noninvasive ventilation group, patients were ventilated using the NIPCIRV (NIPCIRV Vision; Respironics Inc., Murrysville, PA). A face mask was used as the first choice but the nasal mask was optionally used if patients did not tolerate the face mask.

Pressure control was started at an inspiratory Positive Airway Pressure (PAP) of 10 cm H<sub>2</sub>O in a 12-16 min<sup>-1</sup> timed mode. Pressure control ventilation can supply up to 20 cm H<sub>2</sub>O. Inspiratory pressures were increased for each patient with in increments of 2 to obtain a respiratory rate <20/min and the resting of respiratory muscles. Slight PEEP (4-7 cm H<sub>2</sub>O) was used to increase PaO<sub>2</sub>, O<sub>2</sub> sat and to prevent atelectasis (Meduri *et al.*,1996; Wysocki, 1999]. All patients were given NIPCIRV for at least 1 h. Clinical stability was defined as an improvement in oxygenation (paO<sub>2</sub>>60 mm Hg or oxygen saturation >90% SaO<sub>2</sub>) with an oxygen flow rate of <3 liters O<sub>2</sub>/min, a respiratory rate of <25 breaths/min with the presence of a normal breathing pattern and a heart rate <110 beats/min (Kramer *et al.*,1995). NIPCIRV was considered successful when patients remained clinically stable after discontinuation of ventilation for >2 h.

Intubation was performed if respiratory rate after 1 h of NIPCIRV was >30 breaths/min, there was persistent hypoxemia, hemodynamic instability (systolic blood pressure <70 mm Hg), agitation or worsened neurological status, inability to tolerate the mask or aspiration of gastric content. All parameters are presented as means±SD. After initiation of treatment, changes in physiological variables and arterial blood gas values were compared with the use of Leven and Student's t-test. The primary analysis compared the rates of 7 day mortality in each group with the need of tracheal intubation in two groups were matched in terms of some qualitative factors

of the chi-square test and Fisher exact test was used. Due to the non-homogeneous distribution of the outlined parameters, a non-parametric test (Mann-Whitney test) was used to assess the effect of NIPCIRV on physiological parameters. For the overall study  $p < 0.05$  was considered statistically significant. Software SPSS 19 was used.

## RESULTS AND DISCUSSION

During the 12 month study period patients with inclusion criteria were randomly assigned to two groups. Control group, received conventional oxygen therapy with venturi mask ( $n = 60$ ) and NIPCIRV group received NIPCIRV ventilation through a face mask ( $n = 60$ ). NIPCIRV was generally well tolerated. Only few side effects were observed. However, none of the subjects had to discontinue NIPCIRV because of these side effects.

No significant differences in terms of age, gender and presence of underlying diseases between the two groups were observed ( $p > 0.05$ ) (Table 1). The 57 patients (47.5%) had an acute MI and 32 patients (26.6%) had ischemic heart disease (Unstable Angina) without a recent MI. Other reasons for ACPE were congestive heart failure in 70 (58.3%), tachyarrhythmia in 3 patients (2.5%) and hypertension in 50 patients (41.7%).

The NIPCIRV led to a rapid improvement in oxygenation, respiratory rate, arterial PH, heart rate and blood pressure in the first hour ( $p = 0.0001$ ). There were no significant  $\text{PaCO}_2$  changes between two groups ( $p = 0.064$ ).

In this study, NIPCIRV rapidly increased  $\text{PaO}_2$ , pH and  $\text{O}_2$  Saturation in patients with respiratory failure due to ACPE while respiratory rate, blood pressure and heart rate significantly decreased (Table 2).

Length of CCU stay was  $3 \pm 1$  days in NIPCIRV group and  $7 \pm 1$  days in controlled group. There was significant differences between the two groups ( $p < 0.001$ ). Recovery time was significantly shorter in the NIPCIRV group ( $48 \pm 8$  h) compared to control group ( $96 \pm 12$  h) ( $p = 0.0001$ ). Endotracheal intubation was required due to persistently high or increasing respiratory rate and/or progressive hypoxemia in 2 of the 60 patients (3.3%) treated in NIPCIRV group and 12 of the 60 patients (20%) treated in controlled group.

Hospital mortality was 28.33% ( $n = 17$ ) patients in control group and 13.33% in NIPCIRV group ( $n = 8$ ). There was significant difference between the mortality rate in two groups ( $p < 0.001$ ) (Table 3).

The mean age of our study was 71 years which is consistent with those described in other studies with an average range of 69-80 years which implies that the elderly are commonly affected (Crane, 2002).

Table 1: Patient characteristics and underlying diseases etiology of ACPE

Variables	Controlled group	NIPCIRV group
Mean age	72±SD	70±SD
Female	22	19
Male	38	41
Heart failure	61.7% (N = 37)	55% (N = 33)
Diabetes mellitus	23.3% (N = 14)	25% (N = 15)
Hypertension	45% (N = 27)	38.3% (N = 23)
Old myocardial infarction	51.6% (N = 31)	48.3% (N = 29)

N = Number of patients; Values are mean±SD

This study confirms previous reports using non-invasive ventilation in the treatment of ACPE (Masip *et al.*, 2000; Pang *et al.*, 1998; Mehta *et al.*, 1997; Rusterholtz *et al.*, 1999; Rasanen *et al.*, 1985). There are some clinical evidence, since respiratory failure in ACPE is not directly related to hypoxemia and cannot be reversed with oxygen therapy alone. Therefore the primary goal of NIPCIRV in ACPE is to support the respiratory muscle activity and decrease respiratory rate that will improve the efficacy of the patient's effort and allows a reduction in the respiratory work (Tokioka *et al.*, 1989; Graaff *et al.*, 1991; Brochard *et al.*, 1989; Supinski *et al.*, 1994), resulting in increased tidal volume and reduced respiratory rate. Based on these mechanisms, NIPCIRV therapy does offer great advantages for patients with cardiogenic pulmonary edema and acute respiratory acidosis.

This study shows that the application of NIPCIRV was successful in improving oxygenation and respiratory distress in patients with ACPE. With respect to outcome measurements, e.g., intubation rate and in-hospital mortality, patients with hypercapnia and respiratory acidosis seem to benefit most. Hypocapnia and low BP however, might be associated with higher intubation and in-hospital mortality rates. Based on our findings and those previously published, we conclude that NIPCIRV should be considered especially in patients with hypercapnic respiratory failure due to ACPE. Also,  $\text{PaCO}_2$  levels should be monitored closely in order to assess the response to treatment.

Non-Invasive Ventilation (NIV) has been shown to be effective in acute respiratory failure of various etiologies' in different health care systems and ward settings. It should be seen as complementary to invasive ventilation and primarily as a means of preventing some patients from deteriorating to the point at which intubation is needed.

General avoidance of intubation and complications associated with invasive mechanical ventilation appear to be the main reasons of improved survival. Our data provide strong evidence for the use of NIPCIRV as a first-line intervention in patients with severe ACPE in the absence of contraindications for using this technique it is best initiated early before assisted ventilation is

Table 2: ABG variables in patients undergoing NIPCI RV versus conventional oxygen therapy at different time points (0, 15, 30 and 60 min)

Variables	T0	T15	T30	T60	p-value
PH (Control group)	7.34±0.03	7.35±0.03	7.35±0.02	7.36±0.03	≤0.001
PH (NIPCI RV group)	7.33±0.02	7.35±0.01	7.35±0.03	7.37±0.04	
O <sub>2</sub> Sat (Control group)	87±3.9	87±4.2	89±3	90±3.2	≤0.0001
O <sub>2</sub> Sat (NIPCI RV group)	85±5	89±4.9	92±4.7	96±3.6	
PaO <sub>2</sub> (Control group)	59±54	60±4	61±3	63±6	≤0.001
PaO <sub>2</sub> (NIPCI RV group)	55±5	66±9	78±12	88±11	
PaCO <sub>2</sub> (Control group)	43.7±6.6	43.2±5.3	43.2±3.7	42.2±3.7	0.064
PaCO <sub>2</sub> (NIPCI RV group)	43.9 ±7.6	43.1±5.2	43.3±3.5	42.4±3.1	

Table 3: CCU stay, recovery time, number of intubation and hospital mortality in two groups

Variable	Controlled group	NIPCI RV group	p-value
CCU stay (day)	7±1	3±1	<0.001
Recovery time (h)	96±12	48±8	<0.0001
Intubation	20% (N = 12)	3.3% (N = 2)	<0.001
Hospital mortality	28.33% (N = 17)	13.33% (N = 8)	<0.001

N = No. of patients; Values are mean±SD

mandatory although, it has been shown to be effective even in very sick patients. Important benefits include the avoidance of endotracheal tube associated infections which carry an important morbidity and mortality and a reduction in hospital stay.

### CONCLUSION

In addition to an appropriate selection of patients and the experience of the attending clinicians and nurses in the use of NIPCI RV, the type of ventilator used may be one of the possible reasons to explain the efficacy of NIV. In this study, we used a ventilator specifically designed for, NIPCI RV able to provide high levels of oxygen, a proper maintenance of the positive pressure levels by leak control.

### REFERENCES

Agarwal, R., A.N. Aggarwal, D. Gupta and S.K. Jindal, 2005. Non-invasive ventilation in acute cardiogenic pulmonary oedema. *Postgraduate Med. J.*, 81: 637-643.

Brochard, L., A. Harf, H. Lorino and F. Lemaire, 1989. Inspiratory pressure support prevents diaphragmatic fatigue during weaning from mechanical ventilation. *Am. Rev. Respir. Dis.*, 139: 513-521.

Crane, S.D., 2002. Epidemiology, treatment and outcome of acidotic, acute, cardiogenic pulmonary oedema presenting to an emergency department. *Eur. J. Emergency Med.*, 9: 320-324.

Graaff, V.D.W.B., K. Gordey, S.E. Dornseif, D.J. Dries and B.S. Kleinman *et al.*, 1991. Pressure support: Changes in ventilatory pattern and components of the work of breathing. *Chest J.*, 100: 1082-1089.

Gray, A., S. Goodacre, D.E. Newby, M. Masson and F. Sampson *et al.*, 2008. Noninvasive ventilation in acute cardiogenic pulmonary edema. *N. Engl. J. Med.*, 359: 142-151.

Jessup, M. and S. Brozena, 2003. Heart failure. *N. Eng. J. Med.*, 348: 2007-2018.

Kramer, N., T.J. Meyer, J. Meharg, R.D. Cece and N.S. Hill, 1995. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am. J. Respir. Crit. Care Med.*, 151: 1799-1806.

Masip, J., A.J. Betbese, J. Paez, F. Vecilla and R. Canizares *et al.*, 2000. Non-invasive pressure support ventilation versus conventional oxygen therapy in acute cardiogenic pulmonary oedema: A randomised trial. *Lancet*, 356: 2126-2132.

Meduri, G.U., R.E. Turner, N.A. Shala, R. Wunderink and E. Tolley, 1996. First-line intervention in patients with acute hypercapnic and hypoxemic respiratory failure. *Chest*, 109: 179-193.

Mehta, S., G.D. Jay, R.H. Woolard, R.A. Hipona and E.M. Connolly *et al.*, 1997. Randomized, prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema. *Crit. Care Med.*, 25: 620-628.

Nava, S., G. Carbone, N. DiBattista, A. Bellone and P. Baiardi *et al.*, 2003. Noninvasive ventilation in cardiogenic pulmonary edema: A multicenter randomized trial. *Am. J. Respir. Crit. Care Med.*, 168: 1432-1437.

Pang, D., S.P. Keenan, D.J. Cook and W.J. Sibbald, 1998. The effect of positive pressure airway support on mortality and the need for intubation in cardiogenic pulmonary edema: A systematic review. *Chest J.*, 114: 1185-1192.

Rasanen, J., J. Heikkila, J. Downs, P. Nikki and I. Vaisanen *et al.*, 1985. Continuous positive airway pressure by face mask in acute cardiogenic pulmonary edema. *Am. J. Cardiol.*, 55: 296-300.

Rusterholtz, T., J. Kempf, C. Berton, S. Gayol and C. Tournoud *et al.*, 1999. Noninvasive Pressure Support Ventilation (NIPSV) with face mask in patients with Acute Cardiogenic Pulmonary Edema (ACPE). *Intensive Care Med.*, 25: 21-28.

Supinski, G.S., 1994. Respiratory muscle rest using nasal BiPAP ventilation in patients with stable severe COPD. *Chest*, 105: 1058-1060.

Tokioka, H., S. Saito and F. Kosaka, 1989. Effect of pressure support ventilation on breathing patterns and respiratory work. *Intensive Care Med.*, 15: 491-494.