Acute improvement of pulmonary artery pressure by non-invasive positive pressure ventilation in the patients with hypercapnic respiratory failure

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ÖZET

Hiperkapnik solunum yetersizliği olan hastalarda noninvaziv pozitif basınçlı ventilasyon tedavisi ile pulmoner arter basıncında akut iyileşmenin gösterilmesi

Kronik obstrüktif akciğer hastalığı (KOAH) olan hastalarda, sağ kalp yetersizliğine ilerleyişi önlemek için, pulmoner arter basıncını (PAB) düşürmek çok önemlidir. Bu çalışmada, hiperkapnik solunum yetersizliği olan hastalarda noninvaziv pozitif basınçlı ventilasyon (NPPV) tedavisi ile PAB'de akut iyileşme saptandığı gösterilmiştir. Yirmi altı KOAH hastası (18 erkek, 8 kadın) fizik muayene, Doppler ekokardiyografi ve arteryel kan gazları analizi ile ilk kabulde ve taburculukta değerlendirilmiştir. PAB, Doppler ekokardiyografi ile ölçülmüştür. Kontrendikasyon yokluğunda ve şu durumlarda NPPV uygulanmıştır: 1- Orta-ciddi dispne ile birlikte solunumsal sıkıntı, 2- Arteryel pH < 7.35 ve $PaCO_2$ > 45 mmHg, 3- Solunum sayısı ≥ 25/dakika. Hastaların ortalama yaşı 62.6 ± 10.8 yıl ve ortalama NPPV kullanımı 12.6 ± 5.5 gün idi. Hastalarda ortalama ve sistolik PAB (43.8 ± 16.9 mmHg ve 66.7 ± 23.3 mmHg), NPPV tedavisi ile anlamlı olarak düştü (sırasıyla 26.6 ± 8.4 mmHg, p< 0.0001 ve 41.8 ± 14.6 mmHg, p< 0.0001). Aynı zamanda arteryel kan gazı parametrelerinin her biri NPPV tedavisi ile anlamlı düzelmeler gösterdi. Akut solunum yetersizliğine bağlı olarak NPPV tedavisi alan KOAH hastalarında ekokardiyografik bir değerlendirme; bu tedavinin solunumsal asidoz, hiperkapni ve hipoksemiyi düzeltici etkilerine ilaveten, bu hastaların takibinde destekleyici bir ölçüm olarak PAB'deki bir iyileşmenin gösterilmesi bakımından kolay ve faydalı bir yöntem olabilir.

Anahtar Kelimeler: *Noninvaziv pozitif basınçlı ventilasyon, kronik obstrüktif akciğer hastalığı, solunum yetersizliği, pulmoner arter basıncı, ekokardiyografi.*

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SUMMARY

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It is very important to decrease pulmonary artery pressure (PAP) in patients with chronic obstructive pulmonary disease (COPD) in order to prevent progression to right heart failure. We showed an acute improvement of PAP by non-invasive positive pressure ventilation (NPPV) treatment in patients with hypercapnic respiratory failure. In 26 patients with COPD (18 males and 8 females), physical examination, Doppler echocardiographic evaluation and arterial blood gases analysis were performed on admission and at discharge. PAP was measured by Doppler echocardiography. NPPV was used when 2 of the following were present without contraindications: 1. Respiratory distress with moderate to severe dyspnea, 2. Arterial pH less than 7.35 with $PaCO_2$ above 45 mmHg, 3. Respiratory rate of 25/minute or greater. Mean age of the patients was 62.6 ± 10.8 year, and mean usage of the NPPV was 12.6 ± 5.5 day. Mean and systolic PAPs of the patients (43.8 ± 16.9 mmHg and 66.7 ± 23.3 mmHg) were significantly decreased with NPPV treatment (26.6 ± 8.4 mmHg, p< 0.0001 and 41.8 ± 14.6 mmHg, p< 0.0001). Also, each parameter of the arterial blood gases was improved significantly with NPPV usage. An echocardiographic assessment in the COPD patients having NPPV treatment due to acute respiratory failure, might be a useful and easy method to show an improvement of PAP as a supportive measure in the management of those patients, in addition to beneficial effects of that treatment on respiratory acidosis, hypercapnia and hypoxemia.

Key Words: *Non-invasive positive pressure ventilation, chronic obstructive pulmonary disease, respiratory failure, pulmonary arterial pressure, echocardiography.*

Pulmonary artery hypertension (PAH) is the primary cardiovascular complication encountered in chronic obstructive pulmonary disease (COPD). The natural history of COPD is characterized by progressive decrements in expiratory airflow, increments in end-expired pulmonary volume, hypoxaemia, hypercapnia, and the progression of PAH (1-3). In particular, PAH in COPD leads to the development of right ventricular hypertrophy, dilatation and failure, the so-called cor pulmonale, which indicates an advanced stage of respiratory disease (1-3). Cor pulmonale is the third most frequent cause of cardiac dysfunction, after coronary and hypertensive heart disease, in patients over the age of 50 (3). The development of PAH and right ventricular dysfunction often has important prognostic implications. Patients with COPD have a three-year mortality of 60% after the onset of right ventricular hypertrophy, and this risk of death varies in proportion to the degree of PAH (3). Furthermore, PAH can be a predictive factor for hospitalization for acute exacerbations in COPD patients (4).

Potential causes proposed to explain the development of PAH in COPD include gas exchange abnormalities, destruction of the pulmonary vascular bed, alterations in respiratory mechanics, changes in intrinsic pulmonary vessel tone, and increased blood viscosity (5). Non-invasive positive pressure ventilation (NPPV) using nasal or face masks has been used as an intervention to manage acute exacerbations of COPD (6). Benefits of NPPV include improved alveolar ventilation and decreased work of breathing, mortality, morbidity, length of hospital stay, and need for invasive mechanical ventilation (7). Hence, NPPV might also be a successful treatment modality to decrease in pulmonary artery pressure (PAP) more rapidly compared with medical therapy. Doppler echocar-

diography is commonly used to estimate PAP, and to diagnose PAH in patients with COPD (8). Because transthoracic echocardiography is an inexpensive, easy, and reproducible method, it is the most commonly used non-invasive diagnostic tool to determine PAP.

Hereby, we aimed to present an acute improvement of PAP by NPPV treatment in the 26 consecutive COPD patients with hypercapnic respiratory failure.

MATERIALS and METHODS

The study included 41 non-randomized consecutive patients (28 males and 13 females) who were admitted to via the emergency room with symptoms of acute exacerbations of COPD. In 26 patients (18 males, 8 females) having type 2 respiratory failure, non-invasive positive pressure ventilation (NPPV) was also used in addition to the optimal medical therapy (patient group). On the other hand, in 15 patients (10 males, 5 females) having type 2 respiratory failure, only optimal medical therapy was applied without NPPV (control group). Nasal O_2 (2 L/min), bronchodilator therapy, systemic corticosteroid and intravenous antibiotic treatment were initiated to the all patients. Exclusion criteria was any known reason for PAH other than COPD, and type 1 respiratory failure (hypoxemia without hypercapnia), and usage of NPPV at home. Physical examination and arterial blood gases (ABG) analysis (ABL 30, Kopenhag) were performed without oxygen or NPPV on admission, and also several times during NPPV usage. ABG was also analysed when the patients were off respiratory support/O_2 at least 20 min at discharge. Doppler echocardiographic evaluation was performed during O_2 supplementation of acute exacerbations of COPD and respiratory failure on admission and at discharge. Also, pulmonary function test (Sensor medics 2400, Netherlands) was performed at rest, while the patients were in a stable state, and all patients had irreversible airflow obstruction. Type 2 respiratory failure was defined as hypoxemia (PaO_2<55 mmHg) and hypercapnia ($PaCO_2$>45 mmHg) with a reduction in pH. COPD was defined by a FEV_1/FVC ratio < 70% according to GOLD criteria (9). Acute exacerbations of COPD was defined as the increased dyspnea or increased cough or sputum in a patient with COPD. Hypertension was defined as BP ≥ 140/90 mmHg or the use of antihypertensive drugs. PAH was defined as mean PAP > 25 mmHg at rest measured by Doppler echocardiography (8).

Echocardiographic Measurements

All measurements were performed with the subjects in the left lateral decubitus position by M mode, two dimensional (2D), and Doppler ultrasound echocardiography by a blinded observer. The ultrasound equipment used was Vivid-7 with a 2.5-MHz probe. Doppler recordings of tricuspid regurgitation velocity and pulmonary flow were attempted from parasternal, apical and subcostal approaches. The "contrast-enhancement" technique (agitated isotonic saline intravenous injections) was used in selected patients to increase the quality of CW Doppler tracings (10). Maximum velocity of tricuspid regurgitation jet (TR) was measured by CW Doppler imaging (8). The simplified Bernoulli equation was used to calculate the systolic transtricuspid gradient which was added to mean right atrial pressure (clinically estimated) to predict systolic PAP, according to a validated technique (11). The pulsed Doppler technique was used to study pulmonary artery systolic flow velocity, as described by Kitabatake et al. (12). Acceleration time (AcT) was defined as the interval between the onset of ejection and peak flow velocity. Right ventricular ejection fraction time (RVET) was defined as the interval between ejection onset to zero flow velocity. We also used the regression equation proposed by Mahan et al. which involves AcT, to predict mean PAP (13). Basic measurements of right atrial and right ventricular dimension in diastole and right ventricular free wall diameter (RVFWD) were measured by M-mode technique.

Non-invasive Positive Pressure Ventilation (NPPV)

NPPV was used in 26 patients, when 2 of the following were present without contraindications (14):

1- Respiratory distress with moderate to severe dyspnea,

2- Arterial pH less than 7.35 with $PaCO_2$ above 45 mmHg,

3- Respiratory rate of 25/min or greater. NPPV was initiated with a O_2 flowrate of 2 L/min delivered via mask, an end-expiratory positive airway pressure (EPAP) of 4 cm H_2O, and a inspiratory positive airway pressure (IPAP) support level of 8 cm H_2O with bilevel positive airway pressure (BIPAP) (Respironics Inc; Murrysville, PA). Then, BIPAP treatment with nasal and oronasal masks has been continued with the increased pressure supports to even 18/5 cm H_2O according to ABG titration of each patient. Optimal IPAP level was decided mainly by $PaCO_2$ and optimal EPAP level was decided mainly by PaO_2 titration. The last day of attack was defined as an improvement in clinical and laboratory parameters of the patients.

Informed written consent was obtained, and the study was approved by the institutional ethics committee.

Statistical Analysis

Measurements are expressed as mean ± SD. A Mann-Whitney-U test was used for the evaluation of basic characteristics and echocardiographic findings of the patients with or without NPPV usage. Also, a Wilcoxon test for related measurements was used to compare primary outcome variables of PAP and ABG before and after NPPV treatment. A p value of < 0.05 was regarded as significant.

RESULTS

Basic characteristics and echocardiographic findings of the subjects having type 2 respiratory failure with (patients) or without (controls) NPPV usage were shown in Table 1. All of these parameters were not significantly different between the patients and controls. While mean usage day was 12.6 ± 5.5 day (6-19 days); the mean usage hour per day was 15.7 ± 4.1 h (12-20 h per day) for NPPV. Tricuspid regurgitation was detected in 36 patients (87.8%), though Doppler recording quality was adequate for velocity measurements in all patients. Pulmonary flow velo-

Table 1. Basic characteristics and echocardiographic findings of the subjects having type 2 respiratory failure with (patients) or without (controls) non-invasive positive pressure ventilation (NPPV) usage.

	Patients (NPPV+) (n= 26)	Controls (NPPV-) (n= 15)	p
Men, n (%)	18 (69.2)	10 (66.7)	NS
Women, n (%)	8 (30.8)	5 (33.3)	NS
Age, years	62.6 ± 10.8	61.4 ± 9.2	NS
SBP, mmHg	117.4 ± 30.8	115.6 ± 31.0	NS
DBP, mmHg	72.2 ± 12.1	70.9 ± 11.5	NS
Smoking, Packet/year	47	46	NS
Hypertension, n (%)	7 (26.9)	4 (26.7)	NS
Diabetes mellitus, n (%)	5 (19.2)	3 (20.0)	NS
NPPV treatment, day	12.6 ± 5.5	0	-
Right atrium, mm	25.9 ± 3.5	24.7 ± 3.6	NS
RVFWD mm (5-8)*	7.9 ± 2.0	7.8 ± 2.1	NS
RVEDD mm (9-26)*	29.4 ± 3.2	28.3 ± 3.1	NS
Mean PAP, mmHg	43.8 ± 16.9	42.7 ± 15.8	NS
Systolic PAP, mmHg	66.7 ± 23.3	64.9 ± 22.6	NS

* Normal values

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, RVFWD: Right ventricular free wall diameter, RVEDD: Right ventricle end-diastolic diameter, PAP: Pulmonary artery pressure, NS: Not significant.

city profiles were obtained from 28 of the 41 COPD patients (68.3%). Also, tracings of these 28 patients sufficed for mean PAP evaluation.

Comparison of ABG and PAP in the first and last day of the patients and controls was shown in Table 2. Each parameter of the ABG was significantly improved at discharge in the patients with or without NPPV usage. Mean and systolic PAPs of the patients (43.8 ± 16.9 mmHg and 66.7 ± 23.3 mmHg) were significantly decreased with NPPV treatment (26.6 ± 8.4 mmHg, $p< 0.0001$ and 41.8 ± 14.6 mmHg, $p< 0.0001$), but neither mean nor systolic PAPs of the controls (42.7 ± 15.8 mmHg and 64.9 ± 22.6 mmHg) were not improved at discharge by optimal medical therapy only (37.8 ± 14.4 mmHg, $p> 0.05$ and 60.8 ± 19.8 mmHg, $p> 0.05$) (Figure 1).

DISCUSSION

The goals of therapy in COPD patients consist of attenuation of PAH, enhancement of right ventricular function, alleviation of clinical symptoms, and improvement in survival. The agents that have been most extensively evaluated for these purposes include oxygen, vasodilators, theophylline, and inotropic medications. Currently, NPPV treatment is increasingly used for the treatment of acute and chronic respiratory failure in patients with COPD (15). NPPV can increase PaO_2 and decrease $PaCO_2$ by correcting the gas exchange in such patients. Studies have suggested that NPPV can improve pH relatively rapidly, at one hour after instituting ventilation (16,17). In our patients, each parameter of the arterial blood gases was improved significantly with NPPV therapy in a short time. NPPV in acute exacerbations of COPD allow time for other conventional therapy to work, thus reversing the progression of respiratory failure, and reducing morbidity and mortality, and also improvements occur in minute ventilation, respiratory rate and transdiaphragmatic activity (18). A study also suggests that intubation rates and complications associated with the use of mechanical ventilation were also reduced with non-invasive ventilation (19).

In the present study, although mean and systolic PAPs were not significantly decreased by only optimal medical therapy (without NPPV), all of

Table 2. Comparison of arterial blood gase analysis and pulmonary artery pressure (PAP) in the first and last day of the subjects with type 2 respiratory failure with (patients) or without (controls) NPPV.

		Patients (NPPV treatment) (n= 26)	
	Before	**After**	**p**
pH	7.3 ± 7.6	7.4 ± 3.5	0.0001
$PaCO_2$, mmHg	63.1 ± 8.8	45.6 ± 7.4	0.0001
PaO_2, mmHg	55.3 ± 21.3	66.7 ± 13.3	0.03
$SatO_2$ %	79.1 ± 13.7	92.0 ± 4.3	0.001
HCO_3, mEq/L	30.8 ± 5.0	28.0 ± 5.2	0.003
Mean PAP, mmHg	43.8 ± 16.9	26.6 ± 8.4	0.0001
Systolic PAP, mmHg	66.7 ± 23.3	41.8 ± 14.6	0.0001
		Controls (without NPPV) (n= 15)	
	First day	**Last day**	**p**
pH	7.31 ± 7.4	7.35 ± 3.3	0.01
$PaCO_2$, mmHg	64.0 ± 8.5	49.7 ± 7.8	0.02
PaO_2, mmHg	54.8 ± 20.7	60.5 ± 15.4	0.03
$SatO_2$ %	79.3 ± 13.2	90.6 ± 4.8	0.02
HCO_3, mEq/L	30.4 ± 5.2	29.0 ± 5.0	0.02
Mean PAP, mmHg	42.7 ± 15.8	37.8 ± 14.4	NS
Systolic PAP, mmHg	64.9 ± 22.6	60.8 ± 19.8	NS

NPPV: Non-invasive positive pressure ventilation, $SatO_2$: Percentage of the arterial oxygen saturation, NS: Not significant.

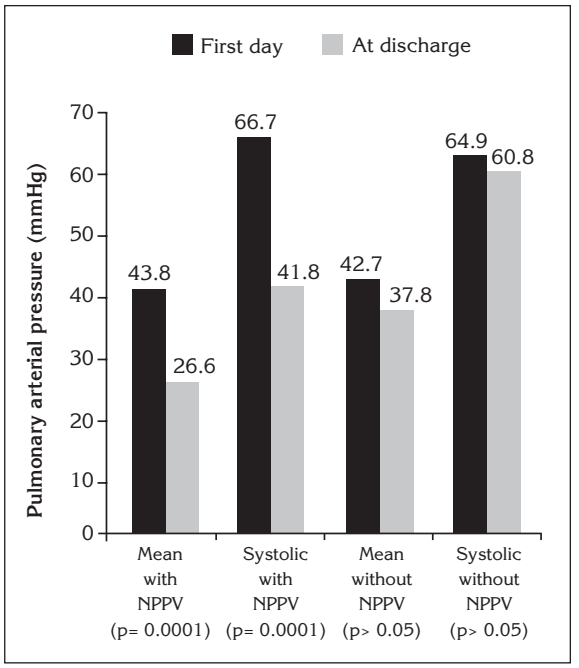

Figure 1. Comparising of the mean and systolic pulmonary arterial pressure in the first and last day (at discharge) of the patients with or without non-invasive positive pressure ventilation (NPPV).

them were improved dramatically with NPPV usage in a mean period of one or two weeks (Figure 1). The acute effect of NPPV on decreasing PAP was seen in patients with respiratory failure, probably due to the effect on cardiac output (20). Two meta-analyses of randomized, controlled trials of NPPV for acute respiratory failure concluded that NPPV reduces mortality, length of hospital stay, and the need for mechanical ventilation (21,22). In one of the analyses, the relative risk of intubation for the NPPV group compared with usual care was 0.42 (95% CI 0.31-0.59) (21).

Doppler echocardiography is a well tolerated, efficient evaluation method that can be used at NPPV initiation in acute COPD patients. It is well known that ultrasound examination of the heart is technically difficult in patients with hyperinflation of the lungs (23). However, expert and motivated echocardiograph technicians can obtain suitable images in up to 80-97% of patients (24,25). The subcostal approach successfully detected adequate Doppler signals in a large proportion of COPD patients (26). Also in a study, Doppler echocardiography is recommended as a useful tool for early detection of haemodynamic alterations due to NPPV application in patients with acute ventilatory failure (27). On the other hand, Fisher MR et al. concluded that Doppler echocardiography might frequently be inaccurate in estimating PAP and cardiac output in patients being evaluated for PAH (28). The authors showed that the magnitude of pressure underestimation was greater than overestimation (-30 +/- 16 vs. + 19 +/- 11 mm Hg; P= 0.03), and mentioned that underestimates by Doppler also led more often to misclassification of the severity of the PAH (28).

In conclusion, NPPV decreases mean and systolic PAPs, and improves pulmonary gas exchange by increasing alveolar ventilation in COPD patients with type 2 respiratory failure. An echocardiographic assessment in the COPD patients having NPPV treatment due to acute respiratory failure, might be a useful and easy method to show an improvement of PAP as a supportive measure in the management of those patients, in addition to well known beneficial effects of that treatment on respiratory acidosis, hypercapnia and hypoxemia. Long-term results of NPPV on PAP are not available, and further research should be obtained.

REFERENCES

1. *American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995; 152: 77-121.*
2. *British Thoracic Society. BTS guidelines for the management of chronic obstructive pulmonary disease. Thorax 1997; 52: 1-28.*
3. *Palevsky HI, Fishman AP. Chronic cor pulmonale. Etiology and management. JAMA 1990; 263: 2347-53.*
4. *Barbera JA, Peinado VI, Santos S. Pulmonary hypertension in chronic obstructive pulmonary disease. Eur Respir J 2003; 21: 892-905.*
5. *Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. N Engl J Med 1995; 333: 214-21.*
6. *Liesching T, Kwok H, Hill NS. Acute applications of noninvasive positive pressure ventilation. Chest 2003; 124: 428-31.*

7. *Mehta S, Hill NS. Noninvasive ventilation. Am J Respir Crit Care Med 2001; 163: 540-77.*
8. *Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation 1984; 70: 657-62.*
9. *Pauwels RA, Buist AS, Calverley PMA, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. Am J Respir Crit Care Med 2001; 163: 1256-76.*
10. *Himelman RB, Stulbarg M, Kircher B, et al. Noninvasive evaluation of pulmonary artery pressure during exercise by saline-enhanced Doppler echocardiography in chronic pulmonary disease. Circulation 1989; 79: 863-71.*
11. *Chan WL, Currie PJ, Seward JB, et al. Comparison of three Doppler ultrasound methods in the prediction of pulmonary artery pressure. J Am Coll Cardiol 1987; 9: 549-54.*
12. *Kitabakate A, Inoue M, Asao M, et al. Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. Circulation 1983; 68: 302-9.*
13. *Mahan G, Dabestani A, Gardin J, et al. Estimation of pulmonary artery pressure by Doppler echocardiography. Circulation 1984; 70 (Suppl 2): 11-363.*
14. *Bach JR, Brougher P, Hess DR, et al. Consensus conference: Noninvasive positive pressure ventilation. Respir Care 1997; 42: 361-5.*
15. *Turkington PM, Elliott MW. Rationale for the use of noninvasive ventilation in chronic ventilatory failure. Thorax 2000; 55: 417-23.*
16. *Bott J, Carroll MP, Conway JH, et al. Randomized controlled trial of nasal ventilation in acute respiratory failure due to chronic obstructive airway disease. Lancet 1993; 341: 1555-7.*
17. *Brochard L, Mancebo J,Wysocki M, et al. Noninvasive ventilation for acute exacerbation of COPD. N Engl J Med 1995; 333: 817-22.*
18. *Wedzicha JA, Mills PR. Management of acute exacerbations of airway diseases. In: Albert R, Spiro S, Jett J, (eds). Comprehensive Respiratory Medicine. Barcelona, Mosby, 1999, 3; pp. 1-38.*
19. *Kramer N, Meyer TJ, Meharg J, et al. Randomized prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 1995; 151: 1799-1806.*
20. *Diaz O, Iglesia R, Ferrer M, et al. Effects of noninvasive ventilation on pulmonary gas exchange and hemodynamics during acute hypercapnic exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997; 156: 1840-5.*
21. *Ram FS, Lightowler JV, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease (Cochrane Review). Cochrane Database Syst Rev 2004; :CD004104.*
22. *Peter JV, Moran JL, Phillips-Hughes J, Warn D. Noninvasive ventilation in acute respiratory failure-a meta-analysis update. Crit Care Med 2002; 30: 555-62.*
23. *Morpurgo M, Saviotti M, Dickele M, et al. Echocardiographic aspects of pulmonary artery hypertension in chronic lung disease. Bull Eur Physiopathol Respit 1984; 20: 251-5.*
24. *Tramarin R, Torbicki A, Marchandise B, et al. Doppler echocardiographic evaluation of pulmonary artery pressure in chronic obstructive pulmonary disease. A European multicenter study. Eur Heart J 1991; 12: 103-11.*
25. *Danchin N, Cornette EA, Henriquez A, et al. Two dimensional echocardiographic assessment of the right ventricle in patients with chronic obstructive lung disease. Chest 1987; 92: 229-33.*
26. *Tramarin R, Saviotti M, Colombo E, et al. Echocardiographic and Doppler evaluation of pulmonary artery pressure in chronic lung disease. In: Morpurgo M, (ed). Pathophysiology and Treatment of Pulmonary Circulation. London: Springer, 1988, pp. 47768.*
27. *Confalonieri M, Gazzaniga P, Gandola L, et al. Haemodynamic response during initiation of non-invasive positive pressure ventilation in COPD patients with acute ventilatory failure. Respiratory Medicine 1998; 92, 331-7.*
28. *Fisher MR, Forfia PR, Chamera E, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 2009; 179: 615-21. Epub 2009 Jan 22.*