

# Effects of acute hypoxia on left and right ventricular contractility in chronic obstructive pulmonary disease

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**Abstract:** The purpose of this investigation was to assess the effects of acute hypoxia on left (LV) and right ventricular (RV) contractility in clinically stable chronic obstructive pulmonary disease (COPD) patients. Eleven male patients (mean age  $52.4 \pm 12.6$  years) who were diagnosed to have COPD were included into the study. All of the patients underwent left and right heart catheterization. RV contractility was measured according to the method of Ferlinz and LV contractility according to the method of Kennedy and colleagues using indirect digital subtraction angiography. Mean pulmonary artery pressures (Mean  $P_{PA}$ ) and oxygen saturation of the pulmonary artery ( $S_aO_2$ ) were measured before and at each stage of graded hypoxic exposure 14%, 12%, and 10% of  $O_2$ . Right atrial pressures ( $P_{RA,syst}$ ,  $P_{RA,diast}$ ,  $P_{RA,mean}$ ), RV pressures ( $P_{RV,syst}$ ,  $P_{RV,diast}$ ,  $P_{RV,mean}$ ,  $P_{RV,end-diast}$ ), RV and LV end-diastolic volume index (EDVI), end-systolic volume index (ESVI), stroke volume index (SVI), cardiac index (CI), ejection fraction (EF), and heart rate (HR) were calculated before and after breathing a hypoxic mixture of 10% of  $O_2$  for 30 minutes. Acute hypoxia induced significant elevation of mean  $P_{PA}$ ,  $P_{RA,syst}$ ,  $P_{RA,diast}$ ,  $P_{RA,mean}$ ,  $P_{RV,syst}$ ,  $P_{RV,mean}$ ,  $P_{RV,end-diast}$ , RV EDVI, RV ESVI, LV EDVI, LV ESVI, confidence interval, and HR ( $p < 0.05$ ). Whereas  $S_aO_2$  decreased significantly after acute hypoxia ( $p < 0.05$ ). These findings suggest that the systolic performance of the right and left ventricles were well-maintained during acute hypoxia in patients with COPD.

**Keywords:** acute hypoxia, obstructive pulmonary disease, ventricular contractility.

## Introduction

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema. The airflow obstruction generally progress slowly and accompanied by airway hyper-reactivity to hypoxia (Wietzenblum et al 1984; Marshall and Marshall 1988). Chronic hypoxia causes structural changes of the microvascular vessels and pulmonary vasoconstriction very early in the course of the disease. Pulmonary arterial hypertension and right-sided heart failure develop late in the course of COPD as a result of parenchymal loss and chronic hypoxic vasoconstriction (Fishman 1976; Davies et al 1985; Reid 1986; Magee et al 1988; Wright et al 1992; Hillier et al 1997).

Oxygen therapy prolongs life and ameliorates pulmonary hemodynamic abnormalities in hypoxemic COPD patients (MRC 1981; Lejeune et al 1984; Timms et al 1985; Roberts et al 2001). The cardiopulmonary benefits of oxygen therapy and some of the cardiopulmonary responses to short-term hyperoxia are well described in these patients (MRC 1981; Lejeune et al 1984; Timms et al 1985; Roberts et al 2001; Smit et al 2003). However, although acute hypoxia occurs commonly in humans as a result of cardiorespiratory disease or adverse environmental conditions, the effects of acute hypoxia on pulmonary hemodynamic and myocardial contractility have not been defined yet in COPD patients. Such effects are important in the assessment of pulmonary vasoconstriction and cardiovascular performance in COPD patients with

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fluctuating levels of oxygenation. So, the aim of the present investigation was the assessment of myocardial contractility and pulmonary vascular responses during acute hypoxia in patients with COPD.

## Materials and methods

Eleven male patients (mean age  $52.4 \pm 12.6$  years) who were diagnosed to have COPD according to the criteria of the American Thoracic Society (1995) were included in the study. None had signs of systemic hypertension, valvular heart disease, or coronary artery disease; none had clinical, electrocardiographic, or echocardiographic signs of myocardial involvement. Routine clinical examination, electrocardiography, chest radiograph, and 2D and Doppler echocardiography were performed on all the patients. All of the patients underwent left and right heart catheterization and measurements of the mean pulmonary arterial pressure (mean  $P_{PA}$ ) by standard technique. Mean  $P_{PA}$  was measured and oxygen saturation ( $S_aO_2$ ) of the blood samples taken from the pulmonary artery was calculated at each stage of breathing of the graded hypoxic gas mixtures (14%, 12%, and 10% of  $O_2$ ). The gas mixtures were mixed in a 25-L Douglas bag from separate cylinders fitted with variable flow valves. Patients breathed from this reservoir through a mouthpiece connected by a series of one-way valves, while wearing an occlusive noseclip. Right and left ventriculography were performed in right anterior oblique projection under a  $30^\circ$  angle using "Angioscope D." Right (RV) and left ventricular (LV) contours were estimated twice by independent investigators. Total RV contractility was measured according to the method of Ferlinz (1977) and total LV contractility according to the method of Kennedy and colleagues (1970). Regional contractility was measured by dividing the ventricle into five areas. All the calculations were made using the PDP 11/34 computer system (Digital Equipment Corp, Maynard, MA, USA). The blinded inter- and intra-observer variability of LV and RV contractility measurements were both  $<5\%$ .

Mean  $P_{PA}$  was measured and  $S_aO_2$  of the blood samples taken from the pulmonary artery was calculated at each stage of breathing of the graded hypoxic gas mixtures

(14%, 12%, and 10% of  $O_2$ ). The measurements of total pulmonary artery resistance ( $R_{pulm,tot}$ ), right atrial pressures, RV pressures, RV and LV contractility indexes were done before and after breathing a hypoxic mixture (10% of  $O_2$ ) for 30 minutes.

Statistical significance was assessed by Student's paired t test for the differences in right atrial pressures, RV pressures, RV and LV contractility parameters before and after 10% of  $O_2$  breathing. The analysis of variances for repeated measures was attempted for the changes of mean  $P_{PA}$  and  $S_aO_2$  during graded hypoxic exposure. A probability value of  $p < 0.05$  was considered to be statistically significant.

## Results

During graded acute hypoxia, a statistically significant rise of mean  $P_{PA}$  ( $p < 0.001$ ) and reduction of  $S_aO_2$  in the pulmonary artery ( $p < 0.001$ ) was detected (Table 1).

Hypoxia induced significant elevation of the right atrial pressures ( $P_{RA,syst}$ ,  $P_{RA,diast}$ , and  $P_{RA,mean}$ ) ( $p < 0.05$ ,  $p < 0.01$ , and  $p < 0.01$ , respectively). Right ventricular pressures ( $P_{RV,syst}$ ,  $P_{RV,mean}$ , and  $P_{RV,end-diast}$ ) were increased markedly ( $p < 0.05$ ,  $p < 0.05$ , and  $p < 0.01$ , respectively). Though some increase in RV diastolic pressure ( $P_{RV,diast}$ ) was noted, it was statistically insignificant (Table 2).

RV end-diastolic and end-systolic volume indexes (EDVI and ESVI) were increased significantly after acute hypoxia ( $p < 0.05$ ). Likewise LV EDVI and ESVI were increased significantly after acute hypoxia ( $p < 0.05$ ). Whereas, changes in RV and LV stroke volume indexes (SVI) and ejection fraction (EF) were not statistically significant. Heart rate (HR) was increased after acute hypoxia ( $p < 0.01$ ), causing statistically significant increase of RV and LV cardiac index (CI) ( $p < 0.01$ ).  $P_{RV,syst}/RV$  ESVI ratio was increased significantly after hypoxia ( $p < 0.01$ ). Although a rise in  $R_{pulm,tot}$  was noted it was not statistically significant (Table 3).

## Discussion

The RV and LV functions are preserved in most of the COPD patients with or without pulmonary hypertension (Biernacki

**Table 1** Effects of graded hypoxia on pulmonary arterial pressure and pulmonary arterial oxygen saturation in patients with chronic obstructive pulmonary disease

Variables	1 Baseline	2 14% $O_2$	3 12% $O_2$	4 10% $O_2$	F	Intergroup P
Mean $P_{PA}$ , mmHg	$21.5 \pm 13.2$	$25.8 \pm 12.3$	$27.2 \pm 11.1$	$30.4 \pm 13.7$	4.8	$<0.001$
$S_aO_2$	$75.2 \pm 1.8$	$67.4 \pm 7.1$	$61.7 \pm 6.8$	$56.1 \pm 2.6$	46.7	$<0.001$

**Abbreviations:**  $P_{PA}$ , pulmonary artery pressure;  $S_aO_2$ , pulmonary arterial oxygen saturation.

**Table 2** Effects of acute hypoxia on right atrial and right ventricular pressures in patients with chronic obstructive pulmonary disease

Variables (mmHg)	Baseline	10% O <sub>2</sub>	P
P <sub>RA</sub> ,syst	7.2 ± 2.4	9.3 ± 2.9	<0.05
P <sub>RA</sub> ,diast	2.6 ± 2.1	3.9 ± 2.0	<0.01
P <sub>RA</sub> ,mean	4.8 ± 1.9	6.8 ± 2.3	<0.01
P <sub>RV</sub> ,syst	31.1 ± 13.8	42.4 ± 12.6	<0.05
P <sub>RV</sub> ,diast	3.4 ± 2.1	4.1 ± 2.3	NS
P <sub>RV</sub> ,mean	16.8 ± 10.9	22.6 ± 12.8	<0.05
P <sub>RV</sub> ,end-diast	6.4 ± 2.7	8.4 ± 3.4	<0.01

**Abbreviations:** P<sub>RA</sub>,syst, right atrial systolic pressure; P<sub>RA</sub>,diast, right atrial diastolic pressure; P<sub>RA</sub>,mean, right atrial mean pressure; P<sub>RV</sub>,syst, right ventricular systolic pressure; P<sub>RV</sub>,diast, right ventricular diastolic pressure; P<sub>RV</sub>,mean, right ventricular mean pressure; P<sub>RV</sub>,end-diast, right ventricular end-diastolic pressure; NS, statistically not significant.

et al 1988; Burghuber and Bergman 1988). However, COPD-related pulmonary vascular abnormalities occur too early during the course of the disease (Reid 1986; Magee et al 1988; Wright et al 1992). Hypoxic pulmonary vasoconstriction plays an important role in development of these abnormalities. Hypoxia induces pulmonary vasoconstriction and it frequently results in pulmonary hypertension (Kolar and Ostadol 1991; Hillier et al 1997; Batyraliev et al 1998; Soodanbekova et al 1998). Pulmonary hypertension increases the work of the right ventricle and causes RV enlargement.

There are only a few reports about the effects of acute hypoxia on RV and LV functions. Oliver and collagues (1991) have reported that RV functions are well preserved during acute hypoxia in healthy individuals. Similarly, Cargill and colleagues (1995) have shown that the parameters of LV systolic function and myocardial inotropic state were

not affected by severe hypoxia in healthy men. There is only one study in the literature related to RV and LV functions during acute hypoxia which is performed in patients but not in healthy individuals. In that study, Batyraliev and colleagues (1998) have reported that systolic performance of the right and left ventricles were well-preserved during acute hypoxia in patients with progressive systemic sclerosis and pulmonary hypertension. To our knowledge, there is no report in literature about the effects of acute hypoxia on pulmonary circulation and RV function in COPD patients.

In our study we demonstrated the significant reduction of S<sub>a</sub>O<sub>2</sub> and elevation of pulmonary artery pressure in response to hypoxic exposure. These results confirmed previous reports which have proven the role of hypoxia in the development of COPD patients and have registered the salutary effects of oxygen breathing on pulmonary vascular resistance (MRC 1981; Hillier et al 1997; Smit et al 2003). Hypoxic exposure also leads to several hemodynamic changes of right ventricle. The elevation of pulmonary artery pressure was accompanied by increase of P<sub>RV</sub>,syst and P<sub>RV</sub>,end-diast. However, cardiac index (CI) was preserved against high afterload. That can be explained by compensatory rise of HR and augmentation of EDVI. The changes in the latter were conditioned by modulation of preload as the concomitant elevation of right atrial pressure was noted. So, the ability of right ventricle to maintain cardiac output (CO) against high pulmonary artery pressure can be explained by induction of the Frank Starling mechanism. We also demonstrated an increase in P<sub>RV</sub>,syst/RV ESVI ratio indicating the improvement of RV contractility, whereas no change was obtained in total

**Table 3** Effects of acute hypoxia on right and left ventricular hemodynamic parameters in patients with chronic obstructive pulmonary disease

Right ventricle				Left ventricle			
Variables	Baseline	10% O <sub>2</sub>	p	Variables	Baseline	10% O <sub>2</sub>	P
RV EDVI, ml/m <sup>2</sup>	68.5 ± 2.4	72.4 ± 8.6	<0.05	LV EDVI, ml/m <sup>2</sup>	58.1 ± 1.6	62.0 ± 2.2	<0.05
RV ESVI, ml/m <sup>2</sup>	26.4 ± 2.1	29.0 ± 4.4	<0.05	LV ESVI, ml/m <sup>2</sup>	15.7 ± 1.8	18.2 ± 2.9	<0.05
RV SVI, ml/m <sup>2</sup>	42.1 ± 2.9	43.3 ± 2.3	NS	LV SVI, ml/m <sup>2</sup>	42.6 ± 2.5	43.8 ± 2.7	NS
RV CI, Lmin <sup>-1</sup> m <sup>-2</sup>	3.5 ± 1.2	4.0 ± 0.9	<0.01	LV CI, Lmin <sup>-1</sup> m <sup>-2</sup>	3.6 ± 0.8	4.2 ± 1.0	<0.01
RV EF	0.61 ± 0.03	0.60 ± 0.03	NS	LV EF, %	0.75 ± 0.04	0.72 ± 0.04	NS
RFS 1 %	74.2 ± 1.1	75.3 ± 1.2	NS	RFS 1 %	45.2 ± 0.7	44.9 ± 1.0	NS
RFS 2 %	55.2 ± 1.6	55.0 ± 1.4	NS	RFS 2 %	44.1 ± 0.9	44.8 ± 1.4	NS
RFS 3 %	63.6 ± 0.7	64.8 ± 0.8	NS	RFS 3 %	46.8 ± 0.8	46.4 ± 0.6	NS
RFS 4 %	69.2 ± 0.8	68.9 ± 1.0	NS	RFS 4 %	49.1 ± 1.2	50.0 ± 1.4	NS
RFS 5 %	57.2 ± 5.9	58.0 ± 6.2	NS	RFS 5 %	26.8 ± 1.0	25.9 ± 1.2	NS
P <sub>RV</sub> ,syst/RV ESVI	1.18 ± 0.3	1.46 ± 0.4	<0.01	HR, beats/min	82.3 ± 19.4	94.5 ± 20.8	<0.01
R <sub>pulm,tot</sub> , dyn s cm <sup>-5</sup>	306.2 ± 170.9	397.7 ± 232.7	NS				

**Abbreviations:** CI, cardiac index; EDVI, end-diastolic volume index; EF, ejection fraction; ESVI, end-systolic volume index; HR, heart rate; LV, left ventricle; NS, statistically not significant; RFS, regional fractional shortening; RV, right ventricle; SVI, stroke volume index; P<sub>RV</sub>,syst, right ventricular systolic pressure.

or regional RV EF. Similar findings were revealed in the LV state, with augmentation of CI and absence of LV EF changes. These findings demonstrate that the responses of RV and LV contractility during acute hypoxia in COPD patients are similar to the healthy individuals (Oliver et al 1991; Cargill et al 1995).

Our results are in agreement with previous experimental and clinical investigations on the effects of raised pulmonary artery pressure on RV contractility state. Kolar and Ostadol (1991) found no evidence of RV pump dysfunction in rats with experimental hypoxic pulmonary hypertension. Batyraliev and colleagues (1998) have reported that although pulmonary artery pressure increased, systolic performance of the right ventricle was well-preserved during acute hypoxia in patients with progressive systemic sclerosis who had pulmonary hypertension. Several other clinical studies in patients with COPD have not detected impairment of RV contractility despite increased afterload and the presence of pulmonary hypertension (Biernacki et al 1988; Burghuber and Bergmann 1988; Weitzenblum et al 1994).

Previous work in rats has shown that HR increase after exposure to acute systemic hypoxia is accompanied by a moderate increase in CO (Marshall and Metcalfe 1990; Kuwahira et al 1993). Phillips and colleagues (1988) have reported that increases in CO during hypoxia were the result of positive chronotropic effects rather than any effect on stroke volume. Similarly, Cargill and colleagues (1995) have shown that in healthy men the CO increases during severe hypoxia is due to increases in HR, but not to any effect on stroke volume. The greater CO observed could have been a compensatory mechanism to maintain systemic arterial pressure and thus blood flow as well as oxygen delivery to the brain and myocardium. It seems that this compensatory mechanism is preserved in patients with COPD.

We conclude that, although acute hypoxia causes increase in pulmonary artery pressure, the systolic performance of the right and left ventricles are well-maintained in patients with COPD. CI increases during acute hypoxia is due to increases in HR, but not related to stroke volume.

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