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Hemodynamic Effects of Supplemental Oxygen Administration in Congestive Heart Failure

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Objectives. **This study sought to determine the hemodynamic effects of oxygen therapy in heart failure.**

Background. **High dose oxygen has detrimental hemodynamic effects in normal subjects, yet oxygen is a common therapy for heart failure. Whether oxygen alters hemodynamic variables in heart failure is unknown.**

Methods. **We studied 10 patients with New York Heart Association functional class III and IV congestive heart failure who inhaled room air and 100% oxygen for 20 min. Variables measured included cardiac output, stroke volume, pulmonary capillary wedge pressure, systemic and pulmonary vascular resistance, mean arterial pressure and heart rate. Graded oxygen concentrations were also studied (room air, 24%, 40% and 100% oxygen, respectively; n = 7). In five separate patients, muscle sympathetic nerve activity and ventilation were measured during 100% oxygen.**

Results. **The 100% oxygen reduced cardiac output (from 3.7 ± 0.3 to 3.1 ± 0.4 liters/min [mean ± SE], $p < 0.01$) and stroke volume (from 46 ± 4 to 38 ± 5 ml/beat per min, $p < 0.01$) and increased pulmonary capillary wedge pressure (from 25 ± 2 to 29 ± 3 mm Hg, $p < 0.05$) and systemic vascular resistance (from 1,628 ± 154 to 2,203 ± 199 dynes·s/cm^5, $p < 0.01$). Graded oxygen led to a progressive decline in cardiac output (one-way analysis of variance, $p < 0.0001$) and stroke volume ($p < 0.017$) and an increase in systemic vascular resistance ($p < 0.005$). The 100% oxygen did not alter sympathetic activity or ventilation.**

Conclusions. **In heart failure, oxygen has a detrimental effect on cardiac output, stroke volume, pulmonary capillary wedge pressure and systemic vascular resistance. These changes are independent of sympathetic activity and ventilation.**

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Patients with severe congestive heart failure are often dyspneic and hypoxic. In patients with oxygen saturation <90%, it is recommended that supplemental oxygen be given (1). However, it has been our impression that supplemental oxygen is often used empirically without an appropriate assessment of blood oxygen saturation. Despite the frequent use of supplemental oxygen, there has been little investigation of its effects on hemodynamic variables in heart failure. This would seem an important area of investigation because 1) previous studies in normal subjects have suggested that 100% oxygen administration may lower cardiac output and raise peripheral vascular resistance (2–4), and 2) cardiac output may be precariously low and vascular resistance excessively high in patients with heart failure with rest symptoms (5). Accordingly, in the present report we examined the effects of various levels of supplemental oxygen on rest hemodynamic variables in subjects with severe congestive heart failure. The results of our studies suggest that short-term supplemental oxygen can have a detrimental hemodynamic effect.

Methods

Subjects. We performed three separate experiments in 22 subjects with congestive heart failure. The characteristics of these subjects are shown in Table 1. All subjects were admitted to the hospital for severe heart failure, and the majority were being evaluated for orthotopic heart transplantation.

In experiment 1 (10 subjects [Subjects 1 to 10 in Table 1]), we compared hemodynamic variables during room air breathing to those observed after 100% supplemental oxygen was delivered by a nonrebreathing face mask for 20 min. On the basis of the results of experiment 1, we performed experiment 2 in which we compared hemodynamic variables during room air breathing to those seen during three different levels of supplemental oxygen: 24%, 40% and 100% oxygen (seven subjects [Subjects 11 to 17 in Table 1]). For 24% and 40%, oxygen was given by a face mask using the Venturi technique; 100% oxygen was again delivered by a nonrebreathing mask.

Because the results of the first two experiments demonstrated that oxygen therapy lowered cardiac output and raised

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Table 1. Clinical Characteristics of 22 Study Subjects

Subject No.	Age (yr)*/ Gend·	Etiology of CHF	NYHA Functional Class	Ejection Fraction Estimates (%)†
1	51/F	Idiopathic CM	III	15
2	57/F	Idiopathic CM	IV	15
3	30/M	Ischemic CM	III	20
4	52/M	Valvular CM	IV	10
5	55/M	Ischemic CM	III	15
6	56/M	Idiopathic CM	III–IV	10
7	54/M	Ischemic CM	III	35
8	51/M	Idiopathic CM	III	10
9	40/M	Hypertrophic CM	III	10
10	51/M	Ischemic CM	IV	10
11	51/F	Idiopathic CM	IV	10
12	56/M	Idiopathic CM	IV	10
13	64/F	Idiopathic CM	III	20
14	55/M	Valvular CM	IV	15
15	57/M	Ischemic CM	III	15
16	66/M	Idiopathic CM	III	20
17	62/M	Ischemic CM	IV	15
18	36/M	Idiopathic CM	III	10
19	75/M	Ischemic CM	IV	15
20	45/M	Ischemic CM	III	25
21	49/M	Ischemic CM	IV	15
22	59/M	Ischemic CM	IV	15

*Mean ± SE age 53.3 ± 2.1 years. †From two-dimensional echocardiography. All subjects were receiving the following cardiac medications: digoxin, loop diuretic drugs, vasodilators (i.e., angiotensin-converting enzyme inhibitor or hydralazine/nitrates). Four patients were receiving dopamine and dobutamine at the time of study. CHF = congestive heart failure; CM = cardiomyopathy; F = female; M = male; NYHA = New York Heart Association.

systemic vascular resistance, we performed experiment 3 in which we examined the effects of 100% oxygen on sympathetic nerve activity and ventilation (five subjects [Subjects 18 to 22 in Table 1]).

The majority of subjects in experiments 1 and 2 were studied in the cardiac catheterization laboratory as part of a standard heart transplantation evaluation. The subjects in experiment 3 were studied in the intensive care unit or in the medical intermediate care unit. Written informed consent was obtained from each subject before any procedures were done.

Experiment 1: effect of 100% oxygen administration on hemodynamic variables. The subjects were studied in the supine position. Baseline variables were recorded with the subjects breathing room air and after 20 min of breathing 100% oxygen by a nonrebreather mask. No subject received sedatives during the experiments.

Heart rate was measured continuously by electrocardiography and blood pressure was recorded using an automated device that employed the oscillometric method (Dinamap). A Swan-Ganz catheter was inserted for the measurement of pressures, the determination of cardiac output (thermodilution method) and for the measurement of pulmonary artery oxygen saturations. Pressure measurements were read on a paper recording. Thermal dilution cardiac outputs represented the mean of three to five determinations. In experiments 1 and 2, 15 of 17 experiments were performed by two operators (B.S.C., J.B.). An ear or finger oximeter was used to estimate arterial oxygen saturation. Systemic vascular resistance and pulmonary vascular resistance were calculated using standard formulas. Mixed venous oxygen content was calculated as 1.34 × Hemoglobin × Pulmonary artery oxygen saturation. Pulmonary artery oxygen saturation was determined using a co-oximeter.

Experiment 2: effects of 24%, 40% and 100% oxygen administration on hemodynamic variables. The design of experiment 2 was similar to that of experiment 1. Because of the number of interventions, the exposure to each level of supplemental oxygen was 5 min before performing the measurements. In experiment 1, we gave 100% oxygen as the first (and only) intervention. Accordingly, in this experiment, 24% oxygen was the first intervention, and 100% oxygen was the last in the majority of subjects (five of seven). In two of seven subjects the sequence was reversed.

Experiment 3: effect of 100% oxygen administration on sympathetic nerve activity. Peroneal nerve recordings of muscle sympathetic nerve activity were our index of sympathoexcitation. This technique provides a "direct" measure of sympathetic outflow directed to blood vessels in skeletal muscle (6). Multiunit sympathetic nerve recordings were obtained by placing a tungsten microelectrode (200-μm shaft and 1 to 5-μm tip) in a muscle fascicle within the peroneal nerve and a reference electrode in the adjacent subcutaneous tissue. The signal was amplified by a preamplifier (1,000×) and an amplifier (50 to 90×). The raw signal was filtered (700 and 2,000 Hz) and integrated to obtain a mean voltage neurogram (6–8). This was manually analyzed by counting the number of bursts

Table 2. Hemodynamic Variables at Baseline and After 100% Oxygen Administration (experiment 1)

	Baseline	Oxygen
Cardiac output (liters/min)	3.7 ± 0.3	3.1 ± 0.4*
Stroke volume (ml/beat)	46 ± 4	38 ± 5*
Pulmonary capillary wedge pressure (mm Hg)	25 ± 2	29 ± 3†
Mean pulmonary artery pressure (mm Hg)	38 ± 3	42 ± 3†
Pulmonary vascular resistance (dynes·s/cm^5)	308 ± 51	352 ± 57
Systemic vascular resistance (dynes·s/cm^5)	1,628 ± 154	2,203 ± 199*
Heart rate (beats/min)	82 ± 3	83 ± 3
Mean arterial pressure (mm Hg)	79 ± 2	81 ± 2
Mixed venous oxygen content (ml/dl)	8.8 ± 0.6	10.4 ± 0.6*

*$p < 0.01$. †$p < 0.05$. Data presented are mean value ± SE.

per minute. Muscle sympathetic nerve activity was obtained at baseline and during breathing 100% oxygen for 5 min.

Because of the potential influence of ventilation on sympathetic nerve activity (9), and because oxygen therapy might alter ventilation and sympathetic drive (10,11), we also measured ventilatory variables (i.e., minute ventilation and end-tidal carbon dioxide) using a respiratory gas monitor (Ohmeda 5250).

Analysis and statistical design. In experiments 1 and 3, the effects of 100% oxygen were analyzed using a paired *t* test. In experiment 2 the various levels of oxygen were analyzed using a one-way analysis of variance for repeated measures. When significant F values were found, pairwise comparisons were made using the Neuman-Keuls method (12). A p value <0.05 was considered statistically significant. Results are presented as mean value ± SE.

Results

Experiment 1. Oxygen administration resulted in an increase in oxygen saturation (baseline 92.6 ± 1.2%, oxygen therapy 99.8 ± 0.2%, $p < 0.0001$). The mean value of oxygen saturation for 20 control subjects in our laboratory is 97.3 ± 0.3%. The hemodynamic responses to oxygen administration are displayed in Table 2, and individual data are presented in Figure 1. The 100% oxygen administration decreased cardiac output from 3.7 ± 0.3 to 3.1 ± 0.4 liters/min ($p < 0.01$) (Fig. 1a) and stroke volume from 46 ± 4 to 38 ± 5 ml/beat ($p < 0.01$). Pulmonary capillary wedge pressure increased from 25 ± 2 to 29 ± 3 mm Hg ($p < 0.05$) (Fig. 1b), and mean pulmonary artery pressure increased from 38.4 ± 3.2 to 41.6 ± 3.4 mm Hg ($p < 0.05$). Systemic vascular resistance increased during oxygen administration, from 1,628 ± 154 to 2,203 ± 199 dynes·s/cm^5 ($p < 0.01$) (Fig. 1c). Oxygen administration did not result in significant changes in mean arterial pressure, heart rate or pulmonary vascular resistance. Mixed venous oxygen content increased from 8.8 ± 0.6 to 10.4 ± 0.6 ml/dl ($p < 0.002$).

Experiment 2. Oxygen administration led to a progressive rise in oxygen saturation (Table 3). Importantly, supplemental

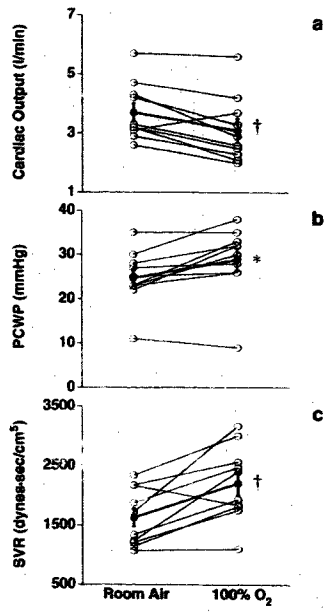


Figure 1. Hemodynamic changes with oxygen breathing in individual patients (**open circles**). PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance. **Solid circles** = mean value ± SE. *$p < 0.05$. †$p < 0.01$.

oxygen also led to a dose-dependent reduction in cardiac output such that the value at 24% was lower than that at baseline, that at 40% was lower than the 24% value, and that at 100% was lower than the 40% value (Table 3, Fig. 2). Stroke volume also declined with increasing levels of oxygen ($F = 4.6$, $p < 0.017$) (Table 3). Although pulmonary capillary wedge pressure was higher during 100% than during baseline in six of seven subjects, there was no "main effect" of oxygen on pulmonary capillary wedge pressure (Table 3). If the seven subjects from experiment 2 were added to those in experiment 1, the pulmonary capillary wedge pressure at 100% oxygen would be greater than that at baseline (baseline 26 ± 2 vs. 100% oxygen 30 ± 2 mm Hg, $p < 0.001$). Supplemental oxygen had no effect on mean pulmonary artery pressure (Table 3). Supplemental oxygen administration led to a rise in systemic vascular resistance ($F = 6.1$, $p < 0.005$). Post hoc analysis demonstrated that the 100% oxygen value was different from the room air value. Although systemic vascular resistance during the 40% oxygen intervention was not statistically different from the baseline value, it was greater at the higher oxygen level in six of the seven subjects studied. The different levels of supplemental oxygen did not change the other hemodynamic parameters except for calculated mixed venous oxygen content, which rose as a function of oxygen delivery ($F = 5.9$, $p < 0.007$).

Experiment 3. Administration of 100% oxygen did not result in a significant change in muscle sympathetic nerve activity (62.6 ± 3.8 vs. 63.9 ± 4.7 bursts/min, p = NS). Minute

Table 3. Hemodynamic Data (mean ± SE) During Graded Oxygen Administration (experiment 2)

		Oxygen			Main Statistical Effects (one-way analysis of variance)
	RA	24%	40%	100%	
CO (liters/min)* (n = 7)	3.8 ± 0.5	3.5 ± 0.5	3.2 ± 0.4	2.9 ± 0.5	F = 17.0 p < 0.0001
SV (ml/beat) (n = 6)	43 ± 10	42 ± 10	38 ± 9	35 ± 9†	F = 4.6 p < 0.017
PCWP (mm Hg) (n = 7)	28 ± 5	30 ± 5	32 ± 5	32 ± 5	F = 2.7 P = NS (<0.08)
$\overline{PA}$ (mm Hg) (n = 7)	42 ± 7	40 ± 6	41 ± 6	41 ± 6	F = 0.65 p = NS
PVR (dynes·s/cm^5) (n = 7)	294 ± 45	279 ± 58	238 ± 42	321 ± 75	F = 0.8 p = NS
SVR (dynes·s/cm^5) (n = 7)	1,753 ± 199	2,010 ± 229	2,057 ± 234	2,346 ± 300‡	F = 6.1 p < 0.005
HR (beats/min) (n = 6)	102 ± 12	100 ± 14	98 ± 14	99 ± 14	F = 0.3 p = NS
MAP (mm Hg) (n = 7)	91 ± 5	97 ± 5	92 ± 3	92 ± 2	F = 0.8 p = NS
MV O_2 CT (ml/dl) (n = 6)	9.7 ± 1.3	9.5 ± 1.2	10.4 ± 1.3	11.0 ± 1.3†	F = 5.9 p = 0.007
SaO_2 (%)* (n = 7)	93.6 ± 1.5	96.1 ± 1.2	98.1 ± 0.09	100.0 ± 0.0	F = 15.5 p < 0.0001

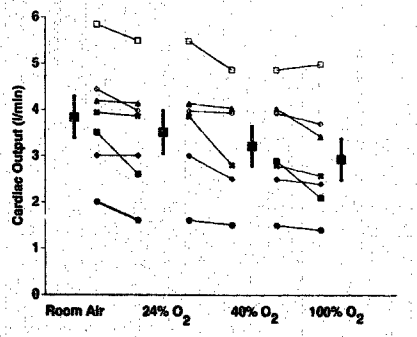
*All values different from one another ($p < 0.01$ for all comparisons) using Newman-Keuls post hoc analysis. †Different from room air (RA) and 24% oxygen. ‡Different from room air ($p \leq 0.01$). CO = cardiac output; SV = stroke volume; PCWP = pulmonary capillary wedge pressure; $\overline{PA}$ = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; HR = heart rate; MAP = mean arterial blood pressure; MV O_2 CT = mixed venous oxygen content; SaO_2 = arterial oxygen saturation.

ventilation (6.8 ± 0.2 vs. 7.0 ± 0.2 liters/min, p = NS) and end-tidal carbon dioxide (5.4 ± 0.1% vs. 5.7 ± 0.1%, p = NS) were unchanged by supplemental oxygen.

Discussion

Study findings. In the present report we have demonstrated that supplemental oxygen had a potentially deleterious effect on hemodynamic variables in class III and IV congestive heart failure. Experiment 1 demonstrated that the administration of 100% oxygen to these patients resulted in reduced cardiac output and stroke volume, increased pulmonary capillary wedge pressure and increased systemic vascular resistance. The 100% oxygen did not change blood pressure or heart rate. In experiment 2, the results suggested that graded concentrations of supplemental oxygen caused a progressive decline in cardiac output. In experiment 3, we observed no change in muscle sympathetic nerve activity or in ventilatory variables with oxygen administration. We believe that our findings are of potential clinical significance because oxygen is commonly used during the hospital period in symptomatic patients with heart failure, and subjects with class III and IV heart failure often have precariously low cardiac outputs and elevated left ventricular filling pressure values at rest.

Figure 2. Hemodynamic responses to three levels of supplemental oxygen in experiment 2 for individual subjects. **Vertical bars with large squares** = mean value ± SE. Statistics are presented in Table 3. **Open squares and diamonds** = the two subjects in whom the sequence of supplemental oxygen delivery was reversed.



Previous work. Previous studies have investigated the hemodynamic responses to high concentrations of oxygen administered to normal subjects (3,13), patients with acute myocardial infarction (4) and those with primary pulmonary diseases. These studies have demonstrated a characteristic pattern of hemodynamic effects, including decreases in cardiac output and heart rate and increased systemic vascular resistance and blood pressure. Of note, oxygen administration may decrease coronary blood flow, cardiac contractility and systemic oxygen consumption (13–15).

Our results in patients with congestive heart failure resemble those seen in normal human subjects in earlier studies (2,3). There are some important differences, however. The significant increase in pulmonary capillary wedge pressure after 100% oxygen in this group was not seen in earlier studies (15). Additionally, heart rate did not change in our heart

failure patients as compared to reductions seen in previously studied normal subjects (2–4). Because heart rate did not fall as oxygen was administered, the fall in cardiac output that we observed must have resulted entirely from a decrease in stroke volume.

Potential mechanisms. The underlying mechanisms responsible for our results are unclear. Activation of various neurohumoral mechanisms may have been responsible for some of the described hemodynamic responses. However, we observed no change in muscle sympathetic nerve activity, and this suggests a nonneural, direct effect of oxygen.

Pilot data from one subject with end-stage heart failure who required a left ventricular assist device provide evidence that the presumed nonneural effect observed in our report may have been related to the effects of oxygen on the peripheral circulation and not to a primary cardiac effect. In this one subject, we held the assist device cardiac output constant. Using echocardiography, we determined that native cardiac output was negligible (the aortic value did not open). At rest this subject was receiving 2 liters/min oxygen via nasal cannula. We then gave this subject 100% oxygen to breathe for 5 min. This caused mean blood pressure to rise from 80 to 90 mm Hg. After 100% oxygen was removed and nasal cannula was replaced, blood pressure fell to 84 mm Hg. Because output was held constant, the rise in blood pressure must have resulted from an increase in peripheral vascular resistance. Further experiments in these interesting subjects will be required to characterize this presumed nonneural, noncardiac effect of oxygen.

It should be emphasized that prior data do indeed suggest that oxygen has effects on the peripheral circulation, acting either directly or through vasoactive autacoids such as endothelium-derived relaxing factor (16–18) or prostaglandins (19). Endothelium-derived relaxing factor, believed to be nitric oxide or a related compound, may mediate the peripheral vasodilation seen in hypoxia because hypoxia leads to the release of endothelium-derived relaxing factor (17,18). Hyperoxia, in contrast, attenuates the endothelium-dependent relaxation of vascular smooth muscle. Superoxide anions and hyperoxia have been shown to inactivate endothelium-derived relaxing factor, one of the most important vasodilators involved in circulatory control (16,20). Interestingly, the hemodynamic effects of inhibitors of nitric oxide resemble those seen with 100% oxygen in our study (21).

Alternative explanations and conclusions. Because mean arterial pressure was unchanged and stroke volume fell, derived stroke work also fell. This could be considered a beneficial effect of hyperoxia on myocardial dynamics. However, it must be emphasized that this fall in stroke work was associated with an increase in left ventricular filling pressures. The potential negative impact of this increase in pulmonary capillary wedge pressure on myocardial oxygen consumption and coronary blood flow and the sensation of dyspnea can only be surmised. Additional ventilatory and hemodynamic experiments will be necessary to clarify this important issue.

Conclusions. The present study demonstrates that in patients with severe congestive heart failure, a significant and possibly detrimental effect on hemodynamic variables may be seen after short-term administration of oxygen, and this effect is independent of the sympathetic nervous system. On the basis of our findings, we would suggest that in the absence of substantial arterial desaturation, supplemental oxygen should be used cautiously during the hospital period in subjects with severe heart failure.

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