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ABSTRACT

Background Although the haemodynamic effects of oxygen in healthy subjects are well documented, there have been no well-controlled studies of the effects of oxygen in patients with heart failure (HF).

Aims To non-invasively evaluate haemodynamic and neurohumoral effects of oxygen in patients with HF at rest.

Methods and results 13 men with heart failure and left ventricular systolic dysfunction (LVSD) were randomised in a double-blind, placebo-controlled, crossover trial to receive medical air or oxygen (40% and high concentration via Hudson non-rebreathing mask). Haemodynamic measurements were made with applanation tonometry, impedance cardiography and venous occlusion plethysmography. Plasma C-terminal B-type natriuretic peptide and A-type natriuretic peptide were measured. Data were analysed with paired t tests. Cardiac output fell by −0.58 (0.62) l/min on high-flow oxygen compared with −0.02 (0.58) l/min on air, p=0.031. Oxygen caused a reduction in heart rate (−4.02 (4.21) vs 0.41 (5.35) beats/min, respectively, p=0.021) and a trend towards increased systemic vascular resistance (875 (1174) vs 235 (321) dyne/s/m^5, p=0.050). Oxygen led to a paradoxical increase in forearm blood flow (0.513 (0.391) vs 0.024 (0.246) ml/min/100 ml forearm volume on air, p=0.01). Natriuretic peptides were unchanged with oxygen.

Conclusions High-concentration inhaled oxygen has significant haemodynamic effects in patients with LVSD and mild HF. Such effects may be detrimental in patients with decompensated HF.

INTRODUCTION

It has been suggested that oxygen is poorly prescribed and many patients may receive it unnecessarily.[1] A recent literature review of the use of oxygen in acute myocardial infarction questioned the routine use of supplemental oxygen and suggested that in uncomplicated cases it may be associated with increased infarct size and increased mortality.[2 3] Misuse of oxygen may be particularly important in patients with left ventricular systolic dysfunction (LVSD) and heart failure. Administration of oxygen is associated with a decrease in cardiac output, possibly mediated through a reduction in heart rate, and an increase in systemic vascular resistance.[4–6] Although a previous study showed increased exercise efficiency in patients with heart failure breathing increased oxygen concentrations, it was still associated with a drop in cardiac output and heart rate.[7] This cardiodepressant effect of oxygen could clearly be detrimental in decompensated heart failure, given the already precarious haemodynamic state of these patients.

None of the previous studies investigating the haemodynamic effects of oxygen at rest were randomised, controlled or blinded. They also measured haemodynamic variables invasively. Although the 'gold-standard' technique for haemodynamic monitoring, it is now recognised that intravascular instrumentation can itself lead to significant haemodynamic changes, making interpretation of subsequent pharmacological intervention difficult.[8] Furthermore, the previous studies were carried out before treatment with a β blocker became a standard of care in heart failure. Whether β-adrenoceptor antagonists might block the reduction in heart rate and cardiac output purportedly associated with oxygen administration is unknown.

We carried out a randomised, double-blind, controlled, crossover study, comparing the haemodynamic and neurohumoral effects of air and two different concentrations of supplemental oxygen in patients with mild–moderate LVSD at rest. We performed haemodynamic assessments non-invasively.

PATIENTS AND METHODS

Patients

The study was approved by the local hospital ethics committee and all patients gave written informed consent. Patients with heart failure and echocardiographic left ventricular systolic dysfunction were eligible. Exclusion criteria were known chronic lung disease or hypoxaemia, a recent myocardial infarction or cerebrovascular event, diabetes mellitus and uncontrolled hypertension.

Study design

Each patient was studied on two separate occasions in a randomised, double-blind, crossover protocol. All studies were performed by a single operator and carried out in a temperature-controlled environment (21–23°C) with the patient in the supine position. Medical air and oxygen were provided from gas cylinders which had been anonymised and labelled as 1 and 2 by an independent observer, thus maintaining investigator and patient blinding. The order of treatment with either cylinder 1 or 2 as the first treatment was randomly assigned by tossing a coin. Patients were asked to abstain from alcohol, caffeine and nicotine in the 12 h preceding the study and to withhold morning medication on the day of study. A light meal was permitted before the study.

An intravenous cannula was inserted and patients left to rest supine for at least 15 min. A

venous blood sample was then taken for measurement of natriuretic peptides. After a further 15 min, baseline haemodynamic measurements were made using impedance cardiography, applanation tonometry and forearm venous occlusion plethysmography. The patient was asked to breathe a 40% gas mixture obtained at a flow rate of 10 l/min through a Venturi mask. After a further 15 min, haemodynamic measurements were repeated. The patient then breathed high-concentration oxygen using a flow rate of 15 l/min through a Hudson non-rebreathing mask. This has previously been shown to provide inspired oxygen concentrations in the range of 80–85%.[9] After a further 15 min, haemodynamic measurements were repeated and a second blood sample taken and the study completed. Each set of measurements at each time point took approximately 10 min to perform.

The second study visit was conducted within 1 week, with the patient receiving the alternate intervention. Applanation tonometry and venous occlusion plethysmography were recorded on the arm used in the first visit. Trans-thoracic echocardiography had been performed within 6 months of the study date for clinical reasons in all patients. A visual determination of left ventricular systolic function was made, as has been described previously.[10]

Venous occlusion plethysmography protocol

Measurements of forearm blood flow and forearm venous capacitance were taken using venous occlusion plethysmography. Mercury-in-silastic strain gauges (DE Hokanson, Bellevue, Washington) were placed around the forearm at the point of greatest circumference. A suprasystolic wrist cuff excluded the hand from the forearm. Forearm blood flow was measured from the rate of change in forearm circumference, as previously described.[11] Forearm venous capacitance was determined by the equilibration technique, as previously described.[11]

Applanation tonometry protocol

Blood pressure and large and small artery compliance index were measured using applanation tonometry. Patient height, weight and age were entered into a Research Profiling Instrument (software 01.05.63; Hypertension Diagnostics, Eagan, Minnesota, USA). A sphygmomanometer cuff was placed around the upper arm and a pressure sensor over the radial pulse of the opposite arm. The sensor was then adjusted until a suitable, repeatable, pulse waveform was displayed on screen with signal intensity >20%. While the patient was comfortable and at rest, activation recorded a single blood pressure reading, heart rate and arterial pulse waveform over 30 s. This was repeated three times to calculate average values for haemodynamic variables using a modified Windkessel model of the circulation.[12 13]

Impedance cardiography protocol

Impedance cardiography has been shown to be a reliable and reproducible measure of cardiac output in patients in the community with stable heart failure,[14] and to have results comparable to invasive measurement of haemodynamic parameters in patients with decompensated heart failure.[15 16] Cardiac output/index, stroke volume/index, systemic vascular resistance and heart rate were measured using a BioZ haemodynamics monitoring system (software version 2.28.1, Cardiodynamics International, San Diego, California, USA). Impedance cardiography was carried out as previously described.[17] Three recordings were taken and an average of each used for each time point (baseline, 40% and high concentration).

Plasma natriuretic peptide concentrations

C-terminal pro-B type natriuretic peptide (BNP) and C-terminal A-type natriuretic peptide (ANP) were measured as previously described.[18 19]

Power calculation and data analysis

Power calculation was based on venous capacitance (VC) figures from previous studies by our group using venous occlusion plethysmography.[11] With 80% power at 5% significance level with 11 patients, a standardised difference of 0.94 can be detected. The minimum detectable significant difference in VC was 0.4 ml/100 ml forearm volume, with a standard deviation of 0.34. If the SD of the change in VC after intervention is <0.4/0.94 (=0.43) then we could detect the difference with 80% power. As the SD of VC (as opposed to the change in VC) is 0.34, it seems unlikely that the SD of the change will be >0.43. Therefore the study will be adequately powered with 11 patients to detect the 0.4 difference required.

Baseline and subsequently recorded values are presented in the tables and figures as mean±SD. All data were analysed without knowledge of the treatment allocation. Absolute change from baseline at 40% and high concentration air/oxygen were compared by paired two-sided t tests using Minitab version 12.0.

RESULTS

Patients

Thirteen male patients completed the venous occlusion plethysmography, applanation tonometry and impedance cardiography protocols (median (interquartile range) age 66 (64–75) years; table 1). Baseline measurements from applanation tonometry, impedance cardiography and venous occlusion plethysmography are displayed in tables 2–4 respectively.

Cardiac output, stroke volume and heart rate

Supplemental oxygen decreased cardiac output and index (figure 1 and table 2). The absolute change in cardiac output from baseline was −0.023±0.578 l/min on air and −0.577±0.618 l/min on high concentration oxygen (p=0.031). Heart rate also decreased with high concentration oxygen (table 2 and figure 2): absolute change from baseline was 0.41±5.35 beats/min on air and −4.02±4.21 beats/min on

Table 1 Patient demographics

Number of patients		13
Age (median, IQR)		66 (64–75)
NYHA class	I	7
	II	6
Aetiology	Dilated cardiomyopathy	4
	Ischaemic	9
Left ventricular systolic dysfunction	Moderate	3
	Severe	5
	Moderate to severe	5
Medical history	Hypertension	7
	Coronary heart disease	9
	Idiopathic dilated cardiomyopathy	4
	Permanent pacemaker	2
Medical treatment	Angiotensin converting enzyme inhibitor	13
	Angiotensin receptor blocker	2
	β Blocker	10
	Diuretic	9
	Spironolactone	1

Data are presented as total number of patients unless otherwise stated.
NYHA, New York Heart Association.

Table 2 Recorded impedance cardiography values and change from baseline for medical air and oxygen at baseline and following administration of 40% and high concentration medical air and oxygen

	Medical air			Oxygen			Absolute change from baseline to 40%			Absolute change from baseline to high concentration		
	Baseline	40%	High conc.	Baseline	40%	High conc.	Medical air	Oxygen	p Value	Medical air	Oxygen	p Value
Cardiac output (l/min)	5.24 (1.04)	5.03 (0.88)	5.22 (0.99)	5.71 (0.64)	5.36 (0.71)	5.05 (0.59)	−0.208 (0.480)	−0.354 (0.568)	0.452	−0.023 (0.578)	−0.577 (0.618)	**0.031**
Cardiac index (l/min/m^2)	2.66 (0.51)	2.54 (0.46)	2.63 (0.48)	2.91 (0.34)	2.74 (0.43)	2.55 (0.33)	−0.1231 (0.2351)	−0.1692 (0.2463)	0.616	−0.0308 (0.2898)	−0.3077 (0.2957)	**0.030**
Stroke volume (ml/beat)	80.38 (17.42)	80.38 (16.02)	79.97 (17.26)	83.27 (10.85)	82.36 (15.84)	80.00 (16.14)	0.00 (4.73)	−1.08 (7.88)	0.696	−0.46 (5.62)	−2.85 (8.24)	0.462
Stroke volume index (ml/beat/m^2)	40.77 (8.03)	40.46 (7.47)	40.33 (8.39)	42.45 (5.82)	41.95 (8.37)	40.25 (8.17)	−0.32 (2.45)	−0.47 (3.70)	0.911	−0.44 (2.97)	−1.73 (3.79)	0.429
Heart rate (beats/min)	66.21 (10.66)	63.65 (9.87)	66.62 (11.54)	69.42 (10.77)	66.50 (10.80)	64.83 (10.64)	−2.57 (3.57)	−3.06 (4.73)	0.746	0.41 (5.35)	−4.02 (4.21)	**0.021**
SVR (dyne/s/cm^5)	3940 (1017)	4319 (1280)	4175 (1128)	3418 (823)	3892 (1403)	4332 (1748)	379 (470)	396 (887)	0.952	235 (321)	875 (1174)	**0.050**

Data are presented as mean (SD). Significant p values in bold.
SVR, systemic vascular resistance.

Table 3 Recorded applanation tonometry values and change from baseline for medical air and oxygen at baseline and following administration of 40% and high concentration medical air and oxygen

	Medical air			Oxygen			Absolute change from baseline to 40%			Absolute change from baseline to high concentration		
	Baseline	40%	High conc.	Baseline	40%	High conc.	Medical air	Oxygen	p Value	Medical air	Oxygen	p Value
Systolic BP (mm Hg)	119.31 (17.56)	121.77 (22.02)	124.31 (22.81)	119.00 (19.65)	122.23 (23.61)	126.23 (23.66)	2.46 (7.43)	3.23 (8.90)	0.784	5.00 (8.30)	7.23 (8.79)	0.384
Diastolic BP (mm Hg)	67.00 (10.36)	71.85 (12.23)	71.85 (10.74)	68.31 (12.58)	67.62 (11.75)	72.00 (12.92)	4.85 (7.19)	−0.69 (6.18)	0.081	4.85 (6.97)	3.69 (3.71)	0.594
Mean pressure (mm Hg)	87.85 (14.61)	90.46 (17.50)	92.23 (15.74)	84.54 (13.20)	91.62 (17.23)	92.77 (18.37)	2.62 (6.73)	7.08 (6.50)	0.140	4.38 (6.63)	8.23 (8.47)	0.268
Large Artery Compliance Index (ml/mm Hg×10)	15.91 (4.07)	15.01 (4.65)	12.65 (4.49)	16.22 (4.01)	13.99 (3.04)	12.94 (3.37)	−0.90 (8.09)	−2.23 (5.29)	0.655	−3.26 (7.16)	−3.28 (4.89)	0.993
Small Artery Compliance Index (ml/mm Hg×100)	6.37 (4.24)	5.14 (3.04)	5.52 (2.25)	7.85 (3.28)	5.18 (3.28)	4.58 (2.12)	−1.23 (2.67)	−2.68 (4.39)	0.155	−0.85 (3.74)	−3.27 (5.35)	**0.042**

Data are presented as mean (SD). Significant p values in bold.
BP, blood pressure.

Table 4 Recorded venous occlusion plethysmography values and change from baseline for medical air and oxygen at baseline and following administration of 40% and high concentration medical air and oxygen

	Medical air			Oxygen			Absolute change from baseline to 40%			Absolute change from baseline to high concentration		
	Baseline	40%	High conc.	Baseline	40%	High conc.	Medical air	Oxygen	p Value	Medical air	Oxygen	p Value
Forearm blood flow (ml/min/100 ml forearm vol)	1.793 (0.515)	1.659 (0.425)	1.818 (0.509)	1.947 (0.742)	2.227 (0.766)	2.460 (0.720)	-0.1346 (0.2806)	0.2800 (0.2964)	0.02	0.024 (0.246)	0.513 (0.391)	**0.01**
Forearm venous capacitance (ml/ 100 ml forearm vol)	1.275 (0.406)	1.408 (0.487)	1.419 (0.442)	1.296 (0.482)	1.407 (0.609)	1.491 (0.463)	0.1323 (0.3239)	0.1105 (0.2750)	0.824	0.144 (0.381)	0.195 (0.265)	0.609

Data are presented as mean (SD). Significant p values in bold.

oxygen (p=0.021). There was a trend towards a greater reduction in stroke volume with oxygen compared with medical air but the difference was not statistically significant.

Blood pressure, systemic vascular resistance and arterial compliance

Compared with air, there was a greater increase in systemic vascular resistance with supplemental oxygen (figure 3). The absolute change from baseline was 235±321 dyne/s/cm^5 with air compared with 875±1174 dyne/s/cm^5 with oxygen; p=0.050. Large artery compliance did not change with oxygen administration but small artery compliance decreased with increasing oxygen concentration. There was no significant change in blood pressure with oxygen (table 3).

Forearm venous capacitance and forearm blood flow

There was no difference in the change in forearm venous capacitance from baseline between air and oxygen. Forearm blood flow increased with oxygen (table 4 and figure 4). The change from baseline at high concentration was 0.024±0.246 ml/min/100 ml forearm volume on air and 0.513±0.391 ml/min/100 ml forearm volume on oxygen (p=0.01).

Natriuretic peptides

Resting levels of C-terminal BNP were comparable in both treatment groups (119.07±78.79 pg/ml for medical air vs 121.2±81.44 pg/ml for oxygen; p=0.94). Resting levels of C-terminal ANP were also comparable (40.73±15.7 pg/ml for medical air vs 45.33±26.07 for oxygen; p=0.56). Supplemental oxygen was shown to have no effect on plasma levels of C-terminal BNP (absolute change from baseline air versus oxygen, +13.7±29.9 vs +8.7±21.6, respectively; p=0.6) and C-terminal ANP (absolute change from air baseline vs oxygen, +1.5±14.6 vs +0.6±22, respectively; p=0.89).

DISCUSSION

In this first randomised and blinded study of the cardiovascular actions of oxygen in patients with heart failure and LVSD, we found effects that were more varied and complex than previously described. Supplemental oxygen decreased heart rate and cardiac output in our patient population. Although oxygen increased systemic vascular resistance and reduced small artery compliance, it also caused forearm vasodilatation. Administration of oxygen did not change plasma natriuretic peptide concentrations.

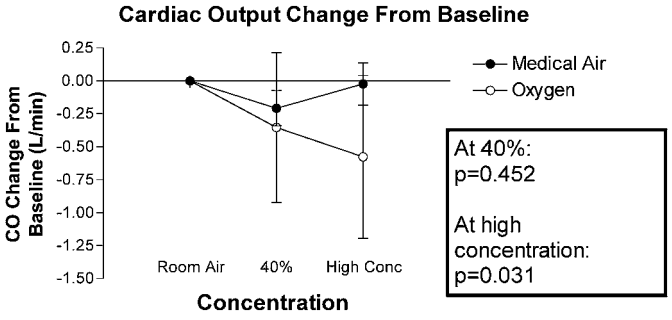

Figure 1 Absolute change in cardiac output from baseline following oxygen or medical air at 40% and high concentration. Data are presented as mean (SD).

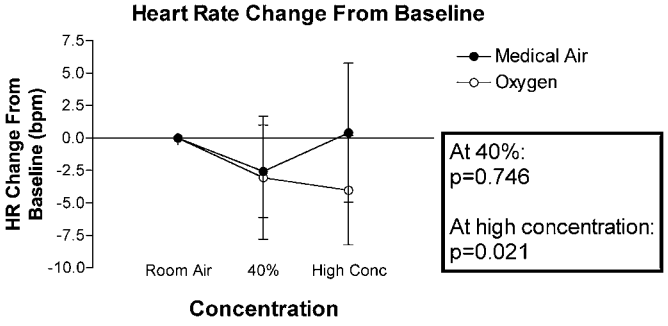

Figure 2 Absolute change in heart rate from baseline following oxygen or medical air at 40% and high concentration. Data are presented as mean (SD).

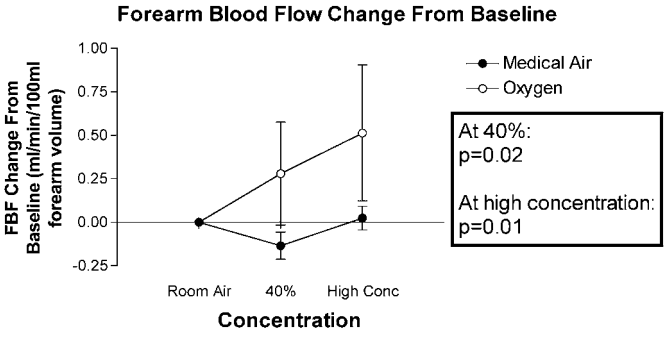

Figure 4 Absolute change in forearm blood flow (FBF) from baseline following oxygen or medical air at 40% and high concentration. Data are presented as mean (SD).

The oxygen-mediated reduction in cardiac output principally reflected a decrease in heart rate, as there was little effect on stroke volume. It should be noted that two patients in our cohort had permanent pacemakers in situ as treatment for bradyarrhythmia. One might expect that these patients would have a less marked heart rate reduction in response to oxygen treatment in view of their conducting tissue disease and the fact that pacemaker activation will treat and therefore mask bradycardia. However, both of these patients displayed a significant reduction in heart rate with high concentration oxygen. A similar effect on heart rate has been reported in healthy subjects but inconsistently in the previous studies of oxygen administration in heart failure.[17 20] Three of the patients in this study were not receiving β-blocker treatment. When these patients were removed from analysis, a significant decrease in heart rate was still seen with oxygen treatment. That the reduction in heart rate occurred even in patients taking a β blocker suggests that the mechanism is not related to suppression of the sympathetic nervous system. That assumption is consistent with the findings of Daly and Bondurant,[21] who abolished the oxygen-mediated reduction in heart rate in healthy subjects with atropine, suggesting that increased parasympathetic activity mediates the bradycardia associated with hyperoxia. That finding is also supported, indirectly, by the lack of effect of oxygen on peroneal muscle sympathetic activity and plasma catecholamines in patients with heart failure.[4 5 22]

The effects of oxygen on vascular function are potentially complex. Whether the increase in systemic vascular resistance is secondary to the fall in cardiac output, a direct effect of oxygen on blood vessels, or both, is uncertain. The effect of oxygen may also vary according to the severity of heart failure. Several direct effects on the vasculature have been hypothesised. It has been suggested that hyperoxia increases reactive oxygen species, thereby reducing the bioavailability of nitric oxide, attenuating endothelial mediated vasodilatation and increasing vascular tone, though findings related to this proposed mechanism have been inconsistent.[23 24] Similarly, though one study supported an increase in α-adrenoceptor-mediated vasoconstriction,[24] other studies have not found evidence of increased sympathetic nervous system activity during oxygen administration.[4 5 22] Hyperoxia has been shown to reduce the production of vasodilator prostanoids in human umbilical arteries.[25 26] It has also been suggested that oxygen may activate the ligand-gated calcium channel in the endothelium, producing an influx of calcium and increase in vascular tone.[27] Alternatively, the observation that prevention of the fall in cardiac output related to oxygen administration also prevents the rise in systemic vascular resistance suggests an indirect rather than direct effect of oxygen on peripheral arterial tone.[4]

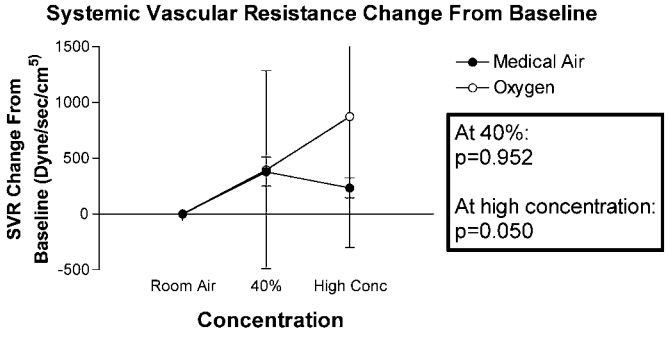

Figure 3 Absolute change in systemic vascular resistance (SVR) from baseline following oxygen or medical air at 40% and high concentration. Data are presented as mean (SD).

Despite these postulated direct and indirect vascular actions of oxygen (and the rise in systemic vascular resistance), we found that oxygen increased resting forearm blood flow in patients with heart failure and LVSD.

It has been reported that oxygen decreases forearm blood flow in healthy subjects,[28–30] possibly as a compensatory mechanism to maintain constant tissue oxygen tension in the presence of hyperoxia. Bird and Telfer, however, suggest a similar mechanism may not exist in patients with compromised limb blood flow—such as those with an ischaemic limb or heart failure, where high tissue oxygen tension may not develop as readily.[28] Prior studies of oxygen administration in patients with heart failure have found conflicting evidence of any effect on forearm blood flow.[24 26] Our data, however, suggests a paradoxical increase in forearm blood flow, agreeing with the hypothesis put forward by Bird and Telfer. Interestingly, the forearm circulation also behaves paradoxically in patients with heart failure during baroreceptor unloading.[31–33] Increased forearm blood flow in our study population may also reflect diversion of blood flow from respiratory muscle to skeletal muscle due to oxygen supplementation, a mechanism which has previously been proposed in exercised patients with heart failure.[7]

A limitation of this study is that we did not measure respiratory rate or minute ventilation that would have indirectly reflected respiratory muscle activity. A further potential explanation is that the sympathetic-mediated systemic vasoconstriction seen in patients with heart failure[34] may have been offset by increased parasympathetic tone, causing vasodilatation and increasing forearm blood flow closer to levels seen in a healthy population.

We found that supplemental oxygen had no effect on circulating natriuretic peptide concentrations. This is perhaps surprising as two previous studies reported an increase in left ventricular filling pressure within minutes of administering oxygen, and C-terminal ANP and BNP are also known to change rapidly.[5 6] However, neither previous study was blinded and both used invasive haemodynamic monitoring. One other explanation is that our patients were clinically stable with New York Heart Association I/II symptoms and receiving appropriate medical treatment at the time of study. Resting filling pressures may have been low and remained low despite a small increase associated with oxygen treatment.

The relatively small number of patients involved limits this study. An increase in patient numbers would have allowed analysis between those patients receiving β-blocker treatment and those not receiving regular β blockers. Small patient numbers may also explain the paradoxical increase in forearm blood flow seen in our study. One other limitation is that we were unable to measure oxygen saturation and thus the degree of hyperoxia induced during the study, as doing so would have unblinded the investigator. We did not carry out invasive vascular instrumentation in our study. Use of an arterial line to measure the partial pressure of oxygen would have enhanced our results.

In conclusion, oxygen treatment has an array of haemodynamic actions in patients with left ventricular systolic dysfunction, some of which are unfavourable. Although further work on longer-term supplemental oxygen in decompensated heart failure is called for, our data suggest that unnecessary oxygen treatment (ie, in the absence of hypoxaemia) might be detrimental in such a patient group.

Competing interests None.

Ethics approval This study was conducted with the approval of the Western Infirmary West Ethics Committee

Provenance and peer review Not commissioned; externally peer reviewed.

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