

# Safety and potential benefits of low dose diamorphine during exercise in patients with chronic heart failure

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Despite major advances in the past two decades in drugs to improve the prognosis of patients with chronic heart failure (CHF), the quality of life of these patients is still quite poor. Patients with congestive heart failure are limited by exertional dyspnoea, which persists even after resolution of pulmonary oedema. The origin of the dyspnoea is complex. Among the many potential explanations proffered, a major unexplained manifestation is the exaggerated ventilatory response to exercise,<sup>1</sup> characterised by a steeper slope relating minute ventilation (VE) to carbon dioxide production—the VE–V<sub>CO<sub>2</sub></sub> regression slope.

Diamorphine and morphine have been used as standard treatment to alleviate the distressing symptoms of dyspnoea in patients presenting with acute left ventricular failure. The haemodynamic and other effects of diamorphine and morphine are relatively well known in this condition.<sup>2,3</sup> It is unclear whether the respiratory depressant effects of diamorphine are detrimental or beneficial to patients with CHF, especially during exercise. We have therefore conducted an exploratory prospective randomised, double blind, placebo controlled trial to test the hypotheses that low dose diamorphine is safe and improves the ventilatory responses to exercise, thereby enhancing the aerobic exercise capacity of patients with CHF.

## METHODS

Sixteen consecutive patients with stable CHF (15 men, mean (SEM) age 61 (2.2), range 38–75 years, mean left ventricular

ejection fraction 35.3%, range 16–45%) undergoing cardiopulmonary exercise testing were recruited. Immediately before performing a maximal cardiopulmonary exercise test according to the modified Bruce protocol, an intravenous injection through a cannula in the back of the hand of either placebo or 1 or 2 mg of diamorphine was given in a randomised, double blind study on two separate days. Standard exercise parameters and symptom scoring were monitored throughout the test. Values were recorded at rest, three minutes, six minutes, and peak exercise for analysis.<sup>4</sup> At the end of the test, an intravenous injection of naloxone (0.4 mg) was given to reverse the effects of diamorphine. All patients received a written information sheet and gave formal consent for the study. The study was approved by the United Leeds Teaching Hospitals Trust ethics committee and carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. Data are expressed as mean (SEM). Statistical analysis was by paired Student's t test or repeated measures analysis of variance as appropriate. A probability value of  $p < 0.05$  was considered significant.

## RESULTS

All 16 patients completed the study with no adverse effects. Table 1 shows the effect of diamorphine, regardless of dose (data combined for either 1 mg or 2 mg), on standard cardiopulmonary exercise parameters. Baseline resting oxygen consumption (V<sub>O<sub>2</sub></sub>) did not differ between the placebo and diamorphine groups but V<sub>O<sub>2</sub></sub> at peak exercise was significantly greater with diamorphine and at six minutes. Over the entire duration of the exercise test, there was a significant difference in V<sub>O<sub>2</sub></sub> between the placebo and diamorphine groups ( $F = 4.73$ ,  $p = 0.04$ ).

Diamorphine significantly increased tidal volume at rest, at the end of stage I, and at peak exercise. Over the entire duration of the exercise test, there was a significant difference in tidal volume between the placebo and diamorphine groups ( $F = 14.08$ ,  $p = 0.002$ ). The ventilatory response to exercise, characterised by the regression line relating VE to V<sub>CO<sub>2</sub></sub>—the VE–V<sub>CO<sub>2</sub></sub> slope—was significantly reduced from 32.75 (1.96) with placebo to 31.19 (1.71) with diamorphine ( $p = 0.048$ ). There were no significant differences in peak blood pressure, peak heart rate, exercise duration, end tidal partial pressure of carbon dioxide, respiratory rate, or respiratory exchange ratio between the diamorphine and placebo groups.

## DISCUSSION

We found that low dose diamorphine (1–2 mg), given as a single intravenous bolus immediately before exercise testing produced a significant improvement in aerobic exercise capacity through significant reduction in ventilatory response to

Table 1 Cardiopulmonary exercise test results after administration of placebo and diamorphine

	Placebo	Diamorphine	p Value
V <sub>O<sub>2</sub></sub> (ml/kg/min)			
Rest	4.24 (0.3)	4.22 (0.23)	0.97
3 minutes	12.47 (0.68)	13.15 (0.88)	0.31
6 minutes	14.65 (0.88)	15.7 (1)**	0.01
Peak	20.24 (1.49)	21.08 (1.57)*	0.045
Tidal volume (ml)			
Rest	627 (36)	710 (60)*	0.04
3 minutes	1179 (60)	1297 (85)*	0.03
6 minutes	1381 (68)	1481 (94)	0.08
Peak	1853 (122)	1985 (117)*	0.02
VE–V <sub>CO<sub>2</sub></sub> slope	32.75 (1.96)	31.19 (1.71)*	0.048
Exercise duration (s)	673 (5)	685 (58)	0.62
Peak RER	1.08 (0.02)	1.10 (0.02)	0.36
AT (ml/kg/min)	13.34 (0.85)	14.34 (1.11)	0.45
Peak HR (beats/min)	135 (6)	137 (6)	0.75
Peak MAP (mm Hg)	113 (4)	113 (4)	0.96
ETP <sub>CO<sub>2</sub></sub> (mm Hg)	38.1 (1.7)	39 (1.8)	0.11
RR (breaths/min)	31 (2)	29 (1)	0.12

All results expressed as mean (SEM).

\* $p < 0.05$  placebo v diamorphine; \*\* $p < 0.01$  placebo v diamorphine. AT, anaerobic threshold; ETP<sub>CO<sub>2</sub></sub>, end tidal partial pressure of carbon dioxide; HR, heart rate; MAP, mean systemic arterial blood pressure; RER, respiratory exchange ratio; RR, respiratory rate; V<sub>O<sub>2</sub></sub>, oxygen consumption; VE–V<sub>CO<sub>2</sub></sub> slope, slope of the regression line relating minute ventilation to carbon dioxide production during exercise.

Abbreviations: CHF, chronic heart failure; V<sub>CO<sub>2</sub></sub>, carbon dioxide production; VE, minute ventilation; V<sub>O<sub>2</sub></sub>, oxygen consumption

exercise (represented by the  $VE-V_{CO_2}$  regression slope) and an increase in tidal volume. The finding that increase in  $V_{O_2}$  was most apparent at six minutes of exercise with diamorphine (placebo 14.65 (0.88) v diamorphine 15.7 (1.00),  $p = 0.01$ ) suggests that the ability of patients to perform submaximal exercises may be more enhanced with diamorphine than at maximal exercise. Future studies investigating the effects of opiates in patients with CHF should include submaximal exercise test protocols, such as the six minute walk tests.

The only other study that has hitherto explored the effects of an opiate (dihydrocodeine) on exercise capacity in patients with CHF<sup>5</sup> similarly showed a reduction in the  $VE-V_{CO_2}$  slope and an increase in peak  $V_{O_2}$ . However, it did not show significant changes in tidal volume, which in contrast were significantly increased both at rest and during exercise in our study, unaccompanied by significant changes in  $VE$  or respiratory rate. Moreover, unlike the dihydrocodeine effect,<sup>5</sup> the increase in peak  $V_{O_2}$  with diamorphine in the study could not be accounted for by a longer exercise duration. The perceived differences may be secondary to intrinsic differences in the pharmacological properties of the drugs but may also be caused by differences in drug potency or characteristics of the study participants.

This explorative study investigated the acute effects of low dose parenteral diamorphine. We did not explore the effects of chronic opiate treatment, which may be of greater relevance if therapeutic considerations are being contemplated in the future. Having established the safety and beneficial effects of low dose diamorphine, this study may open new avenues of research, exploring the therapeutic possibilities of agents affecting the opioid receptors in the treatment of ambulatory patients with chronic congestive heart failure. Further investigations into the effects of other opiates are warranted with a

view to exploring the mechanisms responsible for the beneficial effects and finding out whether similar agents can reproduce the beneficial effects without the potential unwanted effects of diamorphine.

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