

Dichloroacetate Enhances Performance and Reduces Blood Lactate during Maximal Cycle Exercise in Chronic Obstructive Pulmonary Disease

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Rationale: Impaired skeletal muscle function contributes to exercise limitation in patients with chronic obstructive pulmonary disease (COPD). This is characterized by reduced mitochondrial adenosine triphosphate generation, and greater reliance on nonmitochondrial energy production. Dichloroacetate (DCA) infusion activates muscle pyruvate dehydrogenase complex (PDC) at rest, reducing inertia in mitochondrial energy delivery at the onset of exercise and diminishing anaerobic energy production.

Objectives: This study aimed to determine whether DCA infusion enhanced mitochondrial energy delivery during symptom-limited maximal exercise, thereby reducing exercise-induced lactate and ammonia accumulation and, consequently, improving exercise performance in patients with COPD.

Methods: A randomized, double-blind crossover design was used. Eighteen subjects with COPD performed maximal cycle exercise after an intravenous infusion of DCA (50 mg/kg body mass) or saline (control). Exercise work output was determined, and blood lactate and ammonia concentrations were measured at rest, 1 and 2 minutes of exercise, peak exercise, and 2 minutes postexercise.

Measurements and Main Results: DCA infusion reduced peak blood lactate concentration by 20% (mean [SE]; difference, 0.48 [0.11] mmol/L, $P < 0.001$) and peak blood ammonia concentration by 15% (mean [SE]; difference, 14.2 [2.9] $\mu\text{mol/L}$, $P < 0.001$) compared with control. After DCA, peak exercise workload improved significantly by a mean (SE) of 8 (1) W ($P < 0.001$) and peak oxygen consumption by 1.2 (0.5) ml/kg/minute ($P = 0.03$) compared with control.

Conclusions: We have shown that a pharmacologic intervention known to activate muscle PDC can reduce blood lactate and ammonia accumulation during exercise and improve maximal exercise performance in subjects with COPD. Skeletal muscle PDC activation may be a target for pharmacologic intervention in the management of exercise intolerance in COPD.

Keywords: exercise limitation; chronic obstructive pulmonary disease; energy metabolism; dichloroacetate; skeletal muscle dysfunction

Improving physical performance is an important therapeutic goal in chronic obstructive pulmonary disease (COPD). Recent evidence has demonstrated that muscle mitochondrial (oxidative) capacity is reduced in COPD and that this contributes to

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Impaired skeletal muscle function contributes to exercise limitation and disability in patients with chronic obstructive pulmonary disease (COPD). Pharmacologic interventions that enhance skeletal muscle energy metabolism have not been reported in subjects with COPD.

What This Study Adds to the Field

Pharmacologic intervention known to activate muscle PDC can reduce blood lactate and ammonia accumulation during exercise and improve maximal exercise performance in subjects with COPD. Skeletal muscle PDC activation may be a target for pharmacologic intervention in the management of exercise intolerance in COPD.

exercise intolerance in this population (1). Importantly, impairment in skeletal muscle function may be a remediable feature of an otherwise largely irreversible disease. Currently, there are no pharmacologic therapies that specifically target skeletal muscle oxidative energy metabolism, but such interventions have therapeutic potential for improving disability in COPD and other chronic diseases in which exercise limitation due to skeletal muscle dysfunction is a key feature.

Several studies indicate that mitochondrial oxidative energy production is reduced in the skeletal muscles of patients with COPD (2–5). Recently, we have demonstrated significant muscle adenine nucleotide loss during exercise in subjects with COPD. This suggests that ATP resynthesis is unable to meet the energy demands of exercise even at the low absolute exercise intensities patients with COPD can achieve (6).

Mitochondrial ATP production does not increase instantaneously at the onset of exercise, resulting in the reliance on nonoxidative sources of energy production to meet this shortfall in ATP supply in the early stages of exercise. Recent evidence suggests that this inertia in mitochondrial ATP production resides at the level of the pyruvate dehydrogenase complex (PDC), a mitochondrial multienzyme complex that catalyzes the conversion of pyruvate to mitochondrial acetyl coenzyme A (CoA) (7). This period of metabolic inertia may be particularly relevant in conditions such as COPD in which the capacity for mitochondrial energy delivery is already reduced.

Dichloroacetate (DCA) activates PDC by inhibiting the kinase responsible for inactivating the enzyme complex (8). DCA has been shown in animal studies (9, 10) and studies involving healthy humans (11, 12) to reduce reliance on nonoxidative production of ATP in muscle, particularly in the first 30 to 120

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seconds of exercise, thereby reducing muscle lactic acidosis. DCA has also been shown to reduce exercise-induced muscle lactate accumulation under ischemic conditions in healthy volunteers (13) and in contracting heart muscle (14).

The aim of this study was to determine the effects of an infusion of DCA at rest on maximal exercise performance and on blood lactate and ammonia accumulation during exercise in patients with COPD. We hypothesized that DCA, by activating PDC, would reduce the inertia in mitochondrial ATP production at the onset of exercise. The net effect of this would be better matching of the ATP demands of contraction by mitochondrial ATP generation, thereby reducing reliance on nonoxidative sources of ATP and consequently blood lactate accumulation. We also hypothesized that this increase in mitochondrial ATP production would result in the reduction of muscle adenine nucleotide loss, resulting in reduced accumulation of blood ammonia (a product of adenosine-5'-monophosphate deamination). Finally, we hypothesized that overcoming metabolic inertia by activation of PDC would result in increased maximal exercise performance.

METHODS

Eighteen stable patients (aged 50–85 yr) who met clinical and spirometric GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria for COPD (15, 16) were recruited from outpatient clinics at Glenfield Hospital (Leicester, UK). Full approval was obtained from the Leicestershire Research Ethics Committee, and all participants provided informed, written consent. Exclusion criteria and further methodologic details are provided in the online supplement.

Outcome Measures

The primary outcome for this study was peak exercise blood lactate concentration. Secondary outcomes were peak exercise workload and oxygen consumption, and exercise-induced changes in blood lactate and ammonia concentrations.

Participants attended an initial visit to collect baseline data and familiarize themselves with the exercise test. On a subsequent visit at least 1 week later, subjects performed a maximal (symptom-limited) incremental exercise test on an electrically braked cycle ergometer. After a 1- to 2-minute warm-up period, workload increased by 10 W/minute using a ramp protocol until subjects stopped due to symptom limitation. Ventilation and gas exchange measurements were made throughout the test using a breath-by-breath computerized system (Zan-680 ErgoTest; Zan Messgeraete GmbH, Oberthulba, Germany). After a 2-week washout period, subjects repeated the exercise challenge. Before exercise, participants received either 50 mg/kg body mass of DCA (25 mg/ml, sodium salt) or an equivalent volume of normal saline as an intravenous infusion into a forearm vein over 45 minutes. After the infusion, subjects rested for 30 minutes before undergoing exercise to ensure PDC activation was achieved. The order in which subjects received DCA and placebo was randomized and all investigators and research participants were blinded. Unblinding of the study did not occur until the last patient had completed his/her final assessment.

Blood Analysis for Ammonia and Lactate

Half an hour before exercise, a 12-g retrograde cannula was inserted into a superficial lower forearm vein and placed inside a hand warmer, and warmed to 50–55°C. Arterialized venous blood samples were taken at rest, at 1 and 2 minutes after the onset of exercise, at peak exercise, and at 2 minutes after cessation of exercise. Whole blood lactate concentrations were measured immediately after exercise using a benchtop analyzer (YSI 1500 Sport I-Lactate analyzer; YSI, Inc., Yellow Springs, OH) and plasma ammonia analyzed by a validated enzyme assay technique (Sigma-Aldrich Co. Ltd, Dorset, UK). The coefficient of variation determined from standards was 2% for lactate and 5% for ammonia.

Statistical Analysis

The study was powered at 80% to detect a 0.8-mmol reduction in peak exercise blood lactate at a 5% level of significance, giving a sample size of 18 (STPLAN, Double Precision Study Planning Calculations software

package; University of Texas, Houston, TX). A standard deviation of 0.82 mmol was taken from our previous studies on subjects with COPD (17). Data were originally analyzed with SPSS version 14 (SPSS, Inc., Chicago, IL) using paired *t* tests to look for any differences between drug and placebo conditions (significance assumed at *P* value < 0.05). Shapiro-Wilks tests were performed on each difference score to assess the normality of the drug minus placebo differences, and in each case the test failed to reject normality (*P* > 0.05). Data were subsequently analyzed using SAS Proc Mixed (version 9.1; SAS Institute, Cary, NC), and for each dependent variable the treatment effect was adjusted for a period effect and also for a treatment by period interaction.

RESULTS

Patient Characteristics

Baseline characteristics are shown in Table 1. Subjects were either ex-smokers (*n* = 11) or current smokers (*n* = 7). All patients reported breathlessness on exertion (MRC [Medical Research Council] breathlessness score 4 [*n* = 10], 3 [*n* = 5], or 2 [*n* = 3]). No adverse events occurred during DCA infusions and no side effects were reported. For all data, the treatment effect was significant and there was no evidence of either a significant period effect or a significant period by treatment interaction.

Blood Lactate and Ammonia

DCA infusion resulted in a small but statistically significant reduction in blood lactate concentration at rest compared with control (mean [SE] difference, 0.18 [0.04] mmol/L; *P* < 0.001) (Table 2). Plasma ammonia concentration at rest was not affected (mean [SE] difference, 2.1 [2.4] μmol/L; *P* = 0.4). At all time points during exercise, absolute blood lactate concentration was significantly reduced by DCA infusion compared with control (Figure 1A). Peak blood lactate concentration was reduced by 20% (mean [SE] difference, 0.48 [0.11] mmol/L; *P* < 0.001). The exercise-induced rise in blood lactate above the resting concentration was also significantly reduced by DCA (mean [SE] difference, 0.30 [0.12] mmol/L; *P* = 0.02). The largest reduction in blood lactate concentration with DCA was seen during the first 2 minutes of exercise (39% at 1 min and 41% at 2 min). DCA infusion also significantly reduced exercise-induced plasma ammonia accumulation compared with control (Figure 1B), and this effect was greatest at peak exercise (15% reduction; mean [SE] difference, 14.2 [2.9] μmol/L; *P* < 0.001).

Exercise Parameters

Data from the incremental exercise test performed after DCA and normal saline infusion are shown in Table 3. DCA improved indices of exercise performance, but peak heart rate and perceived breathlessness and exertion were similar. Peak work-

TABLE 1. BASELINE CHARACTERISTICS FOR SUBJECTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (*n* = 18)

	COPD
Age, yr	68 (7)
Male sex, <i>n</i>	16
FEV ₁ , % predicted	45 (15)
FEV ₁ , L	1.16 (0.47)
BMI, kg/m ²	29 (6)
FFMI, kg/m ²	19 (3)
Isometric leg strength, N·m	138 (44)
Oxygen saturation at rest, %	95 (2)

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; FFMI = fat-free mass index.

Values are expressed as mean (SD). Details of the measurement methods for measuring FFMI from bioelectrical impedance, and isometric leg strength using the Cybex II Norm dynamometer (Cybex, New York, NY) are given in the online supplement. Percent-predicted FEV₁ calculated from Reference 16.

TABLE 2. BLOOD LACTATE AND PLASMA AMMONIA CONCENTRATIONS AT REST AND RESPONSE TO INCREMENTAL EXERCISE IN ALL SUBJECTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (n = 18) AFTER DICHLOROACETATE AND SALINE INFUSION

	Lactate (mmol/L)		Ammonia (μ mol/L)	
	Saline	DCA	Saline	DCA
Rest	0.69 (0.19)	0.51 (0.15)*	56.0 (11.7)	53.9 (11.5)
1 min exercise	0.90 (0.25)	0.51 (0.14)*	66.9 (11.5)	55.5 (13.5) [†]
2 min exercise	1.04 (0.35)	0.58 (0.16)*	72.7 (11.8)	58.0 (14.4) [‡]
Peak exercise	1.85 (0.70)	1.50 (0.53) [‡]	85.1 (17.4)	71.1 (12.8)*
2 min post exercise	2.09 (0.76)	1.64 (0.63) [‡]	79.0 (13.4)	65.7 (12.9)*
Exercise-induced change	1.46 (0.71)	1.16 (0.57) [§]	31.4 (14.5)	19.3 (10.4)*

Definition of abbreviation: DCA = dichloroacetate.

Values are expressed as mean (SD).

* $P < 0.001$.

[†] $P = 0.004$.

[‡] $P = 0.003$.

[§] $P = 0.02$.

load increased significantly from a mean (SD) of 67 W (26 W) under control conditions to 75 W (27 W) after DCA (mean [SE] difference, 8 [1] W, 12.5%; $P < 0.001$). Both peak oxygen consumption and peak ventilation increased significantly after DCA infusion compared with control (mean [SE] difference, 1.2 [0.5] ml/kg/min, 8%; $P = 0.03$; and 3.7 [1.4] L/min, 11%; $P =$

TABLE 3. EXERCISE DATA FROM MAXIMAL CYCLE TEST IN SUBJECTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (n = 18) AFTER DICHLOROACETATE AND SALINE INFUSION

	Subjects with COPD	
	Saline	DCA
Exercise duration, s	410 (155)	467 (181)*
Peak workload, W	67 (26)	75 (27) [†]
$\dot{V}O_{2\text{ peak}}$, ml/kg/min	15.9 (4.2)	17.0 (4.2) [‡]
Peak $\dot{V}E$, L/min	36 (13)	39 (14) [§]
Peak $\dot{V}E$, % MVV	91 (27)	98 (28) [§]
Peak RER	0.92 (0.06)	0.96 (0.06) [†]
Peak PE, median (IQR)	17 (16–17)	17 (16–17)
Peak heart rate , % predicted	74 (9)	73 (9)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; DCA = dichloroacetate; IQR = interquartile range; MVV = maximum voluntary ventilation (calculated as $FEV_1 \times 35$); PE = perceived exertion at peak exercise; RER = respiratory exchange ratio

Values are expressed as mean (SD) unless otherwise indicated.

* $P < 0.01$.

[†] $P < 0.001$.

[‡] $P = 0.03$.

[§] $P = 0.018$.

^{||} Predicted peak heart rate in beats per minute is calculated as $220 - \text{age}$ in years.

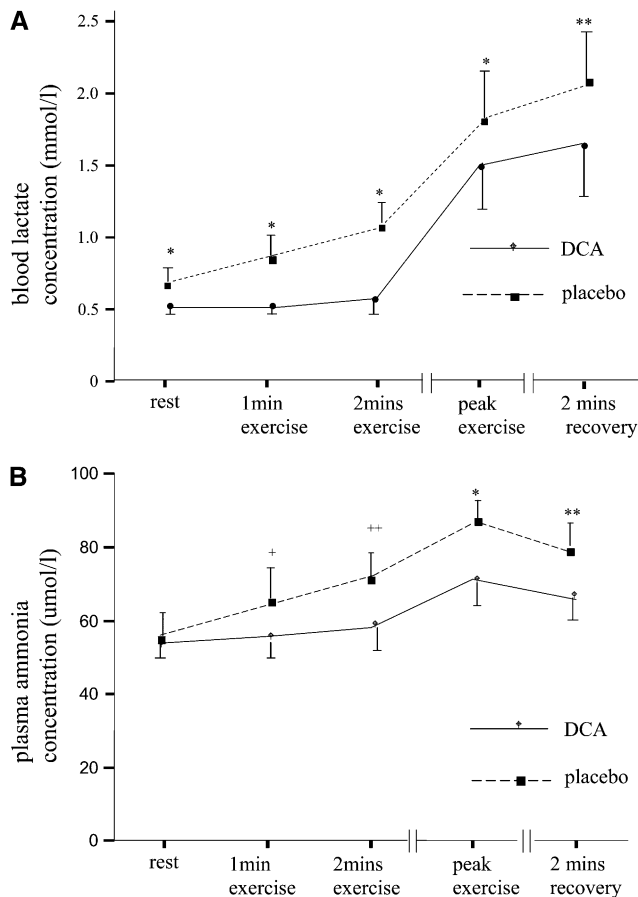


Figure 1. Graph to show mean (SD) lactate accumulation (A) and mean (SD) ammonia accumulation (B) with exercise after dichloroacetate (DCA) and saline (placebo) infusion in patients with chronic obstructive pulmonary disease. * $P < 0.001$; ** $P = 0.001$; [†] $P = 0.003$; ^{††} $P = 0.004$.

0.018, respectively). Figure 2 shows the changes in the mean oxygen consumption (Figure 2A) and ventilation (Figure 2B) during exercise after DCA and control infusion. Isotime values (measurements recorded at the equivalent time that exercise ceased in the control test) for the DCA group are shown to allow comparison with peak exercise values for the control group. Fifteen subjects showed an increase in exercise performance after DCA compared with placebo, two showed a slight decrease and one showed no change. For the individual who showed no change, isotime and peak values are identical. For the individuals showing a decrease in performance, peak values are included but isotime values are missing. For both $\dot{V}O_2$ and $\dot{V}E$, there was a small reduction in isotime data with DCA (mean [SE] difference for oxygen consumption, 1.0 [0.5] ml/kg/min; $P = 0.059$; and for ventilation, 1.8 [0.8] L/min; $P = 0.044$). The trajectory of change of $\dot{V}O_2$, $\dot{V}E$, and V_{CO_2} during exercise was not different between the DCA and placebo tests. Plots of changes in these variables standardized for peak placebo performance are shown in the online supplement (Figures E1–E3). There was no statistically significant difference between absolute values in the placebo and DCA groups at rest or during exercise for these variables, although peak values are higher in the DCA group (Table 3). Respiratory exchange ratio (RER) at peak exercise was significantly greater after DCA (Table 3). Isotime values for RER were not significantly different between placebo and DCA exercise tests.

DISCUSSION

In this study, we have demonstrated for the first time that a pharmacologic intervention known to reduce the inertia in mitochondrial (oxidative or aerobic) ATP generation and the reliance on anaerobic (nonoxidative) ATP resynthesis at the onset of exercise can improve maximal exercise performance in patients with COPD. After DCA infusion, blood lactate and ammonia accumulation decreased at all stages of exercise, and maximal cycling workload and maximum oxygen consumption increased. The results of this study indicate that PDC could be a novel therapeutic target for improving exercise capacity and therefore disability in this population.

The likely explanation for our observations is that DCA-mediated activation of PDC overcame the inertia in mitochondrial

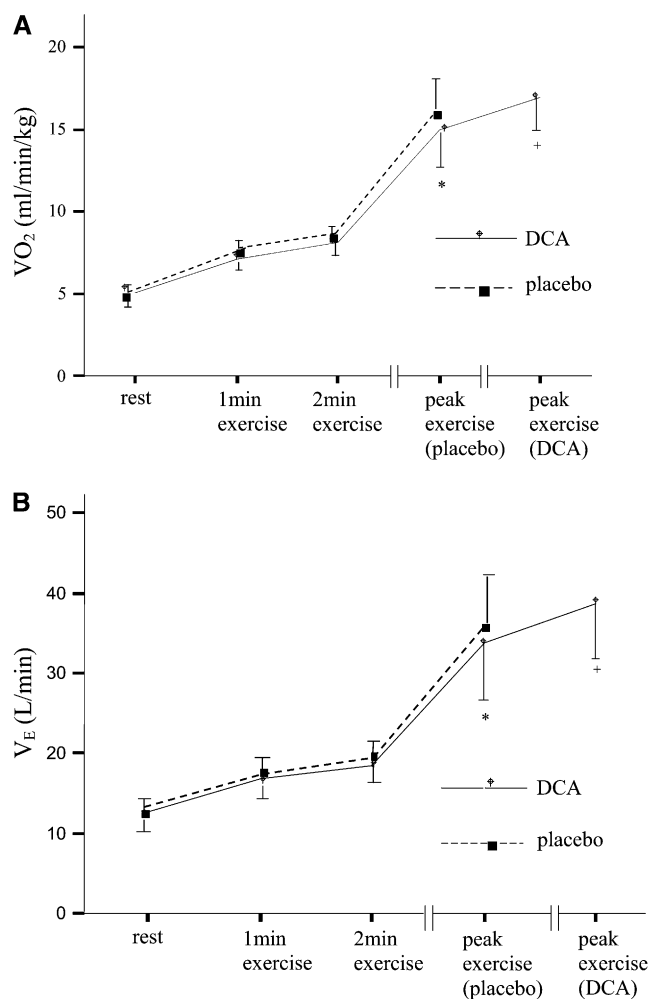


Figure 2. Graph to show mean (SD) oxygen consumption, \dot{V}_{O_2} (A), and mean (SD) ventilation, \dot{V}_E (B), at rest and during exercise after dichloroacetate (DCA) and saline (placebo) in patients with chronic obstructive pulmonary disease. (A) Between group $*P = 0.059$; within group $\dagger P = 0.03$. (B) Between group $*P = 0.044$; within group $\dagger P = 0.018$.

ATP production at the onset of exercise through an increase in the provision of acetyl CoA for mitochondrial utilization. This results in increased mitochondrial ATP resynthesis rates and reduced muscle adenosine 5'-diphosphate (ADP) and adenosine 5'-monophosphate (AMP) accumulation. Consequently, there is reduced activation of anaerobic glycolysis and thus lower blood lactate accumulation (9, 10, 18). This is supported by our observation of reduced blood ammonia accumulation after DCA. Ammonia is a product of adenine nucleotide deamination, which occurs during intense exercise when muscle ATP resynthesis rates cannot meet demand. Blood ammonia accumulation has been shown to occur during intense exercise in healthy humans (19, 20), and we have recently confirmed that this also occurs during maximal incremental exercise in patients with COPD (17).

Our results indicate that in COPD, overcoming metabolic inertia at the onset of exercise can increase maximal exercise performance. Mitochondrial ATP production does not increase instantaneously at the onset of exercise, and recent evidence suggests that this inertia resides at the level of PDC. The activation of PDC during the transition from rest to exercise results in an increase in the supply of mitochondrial acetyl CoA paralleled by an exponential rise in mitochondrial ATP pro-

duction (9, 10, 21). This initial period of metabolic inertia may be particularly relevant in conditions such as COPD in which the capacity for mitochondrial energy delivery is already reduced and where the short duration and low intensity of exercise that patients can customarily achieve may not achieve full activation of PDC. As a result of a single DCA infusion, we observed an increase in peak workload and peak oxygen consumption of 8 W and 1.2 ml/kg/minute, respectively, compared with placebo. Although these differences were modest in absolute terms, they represented a 12.5 and 8% improvement, respectively, relative to control exercise performance. Large improvements in maximal exercise performance are difficult to achieve in patients with COPD. Although the wider and longer term clinical benefits of activating PDC are unknown, we believe our data justify further investigations in this area.

The majority of patients in the current study demonstrated ventilatory limitation during maximal exercise. We had expected improvements in exercise performance after DCA infusion to be associated with a reduction in ventilation at a given workload because of reduced blood lactate levels. However, whereas we observed a small reduction in isowork ventilation after DCA infusion compared with placebo, we also found that the increase in peak workload was associated with an increase in peak ventilation in the DCA group. In other words, after DCA infusion, patients were able to exercise further into their ventilatory reserve despite most patients almost reaching predicted maximal voluntary ventilation. This may have been due to a reduction in lower limb muscle fatigue due to an increase in oxidative ATP delivery and a concomitant reduction in phosphocreatine hydrolysis, inorganic phosphate accumulation, anaerobic glycolysis, and lactate accumulation. However, we cannot rule out other mechanisms such as improvements in mitochondrial ATP delivery in the respiratory muscles that would allow greater maximum ventilation. We also found that RER increased at peak exercise after DCA. Although a reduction in peak lactate might be expected to reduce RER, this observation may be explained by the fact that the DCA-mediated activation of PDC will result in the preferential utilization of carbohydrate during exercise (10, 22). This increase in carbohydrate oxidation will reduce fat oxidation and therefore produce a decline in the oxygen cost of substrate oxidation and the observed increase in the RER.

This study is the first to report the effects of DCA on muscle energy metabolism in patients with exercise limitation due to COPD. Several studies indicate that the capacity of mitochondrial oxidative energy production is reduced in the skeletal muscles of patients with COPD, particularly in the ambulatory muscles (2–6). The action of DCA in activating PDC and thereby reducing the lag in mitochondrial ATP production at the onset of exercise means that in healthy subjects its effects are generally restricted to the first few minutes of exercise (9, 11–13). In contrast to this, we observed a reduction in blood lactate and ammonia not only after 1 and 2 minutes of exercise but also at peak workload. We speculate that in COPD, where mitochondrial oxidative capacity is reduced and maximum exercise intensity and duration are low (the mean duration of exercise after control was 403 s), exercise fails to completely activate PDC, thus providing scope for DCA to exert its effects even at peak exercise.

We acknowledge some limitations to the current study. We did not directly measure the activity of PDC in the current study, but numerous previous reports in humans have confirmed the efficacy of DCA in this respect (7, 11, 23). We were unable to correlate improvements in exercise performance with changes in blood lactate or ammonia and therefore cannot make definitive conclusions about the physiologic mechanisms underpinning our observations. The effects of DCA may be of greatest magnitude

during high-intensity exercise in which reliance on anaerobic sources of energy is important. This may not necessarily translate into clinically significant benefits during other exercise modalities, such as constant work-rate exercise. Further investigation will be needed to explore these issues and provide greater understanding of the underlying mechanisms.

There is increasing recognition of the importance of the systemic consequences of COPD and in particular the role of skeletal muscle dysfunction in exercise limitation and disability (1). For many patients with COPD, currently available therapies aimed at improving lung function do not adequately relieve their symptoms. Because lung function impairment is largely irreversible in COPD, alternative approaches are needed, and targeting the systemic features of the disease, such as impaired skeletal muscle function, may be of therapeutic benefit. The established benefits of pulmonary rehabilitation in improving skeletal muscle function and exercise performance in this population confirm that this approach can be successful. Our findings suggest that inertia in mitochondrial ATP production during exercise is of functional significance in COPD and that interventions to reduce this phenomenon, such as DCA, may have therapeutic value. DCA is safe when given as a single intravenous dose, and although it has been used in oral form to treat congenital lactic acidosis (24), concerns remain over its longer term safety because chronic dosing has been associated with the development of a peripheral neuropathy in some patients (25). However, our results indicate that clinical trials of DCA or other agents that activate PDC are warranted to evaluate the efficacy and safety of such an intervention. The integration of such interventions with established therapies such as exercise training also requires investigation. Importantly, any therapeutic advances are likely to have a wide application given the similarities seen in skeletal muscle abnormalities between COPD and other chronic diseases, such as heart failure and peripheral vascular disease, in which where exercise limitation is a key feature.

In summary, we have demonstrated that DCA infusion given before a maximal exercise challenge reduces exercise-induced blood lactate and ammonia accumulation and increases whole body exercise performance in patients with COPD. Pharmacologic modulation of the skeletal muscle metabolic response to exercise may be of therapeutic benefit in the treatment of reduced functional capacity and disability in COPD.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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