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Effects of oleic acid-induced lung injury on oxygen transport and aerobic capacity

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ABSTRACT

We tested the hypothesis that oleic-acid (*OA*) infusion impairs gas exchange, decreases total cardiopulmonary O_2 delivery and lowers maximal aerobic capacity ($\dot{V}_{O_2max}$). We infused 0.05 ml *OA* kg^{-1} (~3 ml) and ~563 ml saline into the right atria of four goats [59.1 ± 14.0 (SD) kg] prior to running them on a treadmill at $\dot{V}_{O_2max}$ 2-h and 1-d following *OA*-induced acute lung injury, and with no lung injury. Acute lung injury decreased $\dot{V}_{O_2max}$, O_2 delivery, arterial O_2 concentration and arterial O_2 partial pressure compared to no lung injury. The $\dot{V}_{O_2max}$ positively correlated with O_2 delivery and inversely correlated with alveolar–arterial O_2 partial pressure difference, suggesting that impaired pulmonary gas exchange decreased O_2 delivery and uptake. Results indicate *OA* infusion may be a useful model for acutely impairing pulmonary gas exchange for exercise studies. Seven *OA* infusions induced smaller chronic gas exchange and arterial O_2 partial pressure changes than acute infusion.

1. Introduction

We have previously shown that breathing hypoxic and/or CO-containing gases decreases O_2 transport and maximal aerobic capacity ($\dot{V}_{O_2max}$) in goats, and the effects of these gases on $\dot{V}_{O_2max}$ are attenuated when administered in combination (Crocker and Jones, 2014; Crocker et al., 2013). These findings are applicable to soldiers in combat, rescue workers, and miners who work in poorly ventilated environments in which materials are burning. In addition to having to deal with effects of breathing these gases, explosions may also occur in the vicinity of these individuals, *e.g.*, blasts from improvised explosive devices. Injuries from these blasts may impair pulmonary gas exchange and further reduce O_2 delivery and $\dot{V}_{O_2max}$. The purpose of this study was to develop an acute lung-injury model that impairs gas exchange and quantify its effects on O_2 transport and $\dot{V}_{O_2max}$ in goats breathing air. Such a lung-injury model could be used for future studies in animals running at $\dot{V}_{O_2max}$ when O_2 transport is impaired due to breathing hypoxic and/or CO-containing gases combined with acute impairment of pulmonary gas exchange.

Ideally, such a lung-injury model would produce regions of pulmonary edema, ventilation–perfusion heterogeneity and shunting that would simulate the effects of a blast injury (Irwin et al., 1997). However, inflicting traumatic blast injury humanely requires anesthetization of an animal. Therefore, in order to simulate acute traumatic blast injury, animals would need to recover from anesthesia and then perform intense exercise shortly afterward, potentially affecting their exercise response. Repeated traumatic blast injuries could lead to variable effects of the lung injury on pulmonary gas exchange due to the location of the focal point of the traumatic injury and pulmonary remodeling in response to previous injuries. Repeated injuries could potentially lead to differences in pulmonary gas exchange or diffusing capacity over time. Therefore, we desired to develop a reproducible lung-injury model in order to repeatedly impair pulmonary gas exchange to a similar extent.

Free fatty acids, such as oleic acid (*OA*), chemically react with capillary endothelium and increase endothelial permeability, inducing pulmonary edema and impairing gas exchange (King et al., 1971; Peltier, 1956). Those effects disappear over a period of days to weeks depending on the *OA* dose (Julien et al., 1986; Schoene et al., 1984), although multiple discrete *OA* injections can result in persistent interstitial fibrosis (Derks and Jacobovitz-Derks, 1977). We hypothesized that *OA*-induced acute lung injury would impair

Abbreviations: *ALI*, two-hours post-oleic acid-induced acute lung injury; ALI_{30}, breathing FIO_2 0.30 with *ALI*; *ALI*+1, one-day post-oleic acid-induced acute lung injury; CaO_2, arterial oxygen concentration; fH, heart rate; FIO_2, inspired O_2 fraction; Hb, hemoglobin; NLI_{post}, post-study *NLI* (no lung injury); NLI_{pre}, pre-study *NLI*; *OA*, oleic acid; PaO_2, arterial O_2 partial pressure; $PA\text{-}aO_2$, alveolar-arterial PO_2 difference; PO_2, O_2 partial pressure; $\dot{V}_{O_2max}$, mass-specific maximal aerobic capacity.

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Table 1
Oxygen transport values for four goats at $\dot{V}_{O_2max}$ prior to any lung injuries (NLI_{pre}), 2-h post-acute lung injury (*ALI*), 1-d post *ALI* (*ALI* + 1) and 7-wk after the last of seven acute lung injuries (35 ± 5 week after NLI_{pre}; NLI_{post}). Values are means and SD for four goats. *P*-values are for comparisons among the four treatments. * denotes differences from NLI_{pre}, † differences from *ALI* and ‡ differences from *ALI* + 1. Gas volumes are STPD unless stated otherwise.

		NLI_{pre}		*ALI*		*ALI* + 1		NLI_{post}		*P*
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Speed	$m\,s^{-1}$	3.52	0.80	2.22	0.34*	2.78	0.21	3.20	0.24†	0.007
$\dot{V}_{O_2max}$	$ml\,O_2\,min^{-1}\,kg^{-1}$	44.1	9.4	29.7	6.2*	33.5	5.9*	41.3	3.5†	0.010
$\dot{V}_{O_2max}$	$l\,O_2\,min^{-1}$	2.28	0.47	1.70	0.54*	1.85	0.37	2.85	0.53*†‡	<0.001
Time	min	2.90	0.06	3.00	0.29	2.78	0.26	2.75	0.43	0.279
Mb	kg	53.0	11.6	57.5	14.5	56.3	13.0	69.8	15.7*†‡	<0.001
R		1.02	0.03	1.11	0.05	0.99	0.05	1.01	0.12	0.204
$\dot{M}$LA	$mM\,min^{-1}$	1.30	1.12	1.26	0.23	0.99	0.32	1.16	0.35	0.861
[LA]	Mm	5.32	2.25	5.53	0.93	4.38	0.92	3.46	0.88	0.043
$\dot{T}_{O_2max}$	$ml\,O_2\,min^{-1}\,kg^{-1}$	49.1	10.9	32.8	6.6*	37.1	6.9	45.2	4.6	0.008
$\dot{Q}$	$ml\,min^{-1}\,kg^{-1}$	6.25	1.06	5.00	0.86	5.33	0.71	5.85	0.36	0.162
fH	min^{-1}	238	10	169	54*	187	30	234	13†	0.010
VS	$ml\,kg^{-1}$	1.57	0.25	1.93	0.75	1.74	0.33	1.51	0.17	0.257
CaO_2-$C\bar{v}O_2$	$ml\,O_2\,dl^{-1}$	11.7	0.8	9.8	0.5*	10.5	0.7*	11.8	1.4†‡	0.001
CaO_2	$ml\,O_2\,dl^{-1}$	13.0	0.8	10.9	0.5*	11.6	0.9*	12.9	1.5†‡	0.001
[Hb]a	$g\,dl^{-1}$	11.5	0.9	12.1	1.3	11.5	0.8	12.1	0.9	0.106
SaO_2	%	83.4	7.0	67.0	5.8*	74.8	6.5	78.8	5.8†	0.002
$C\bar{v}O_2$	$ml\,O_2\,dl^{-1}$	1.31	0.48	1.03	0.16	1.10	0.27	1.10	0.34	0.329
$[Hb]_{\bar{v}}$	$g\,dl^{-1}$	11.5	0.9	12.2	1.4	11.6	0.9	12.1	1.0	0.090
$S\bar{v}O_2$	%	8.50	3.51	6.35	1.51	7.03	1.99	6.56	2.06	0.260
T	°C	41.1	1.1	40.8	0.2	40.8	0.3	40.9	0.2	0.928
pHa		7.30	0.12	7.30	0.04	7.33	0.05	7.33	0.02	0.723
$PaCO_2$	Torr	52.1	8.1	52.1	3.5	53.0	2.3	56.8	3.8	0.386
$[HCO_3^-]$a	mM	22.4	3.4	23.6	1.2	26.0	2.0	27.6	0.6*	0.013
PIO_2	Torr	147	1	149	1*	149	0*	148	0†	<0.001
PAO_2	Torr	96	7	101	5	95	3	91	9	0.185
PaO_2	Torr	92.4	9.8	63.9	4.6*	71.9	7.3*	79.8	7.9*†‡	<0.001
PA-aO_2	Torr	3.2	3.6	36.9	3.9*	23.3	5.8*†	10.8	5.2*†‡	<0.001
$\dot{V}CO_2$	$ml\,CO_2\,min^{-1}\,kg^{-1}$	0.753	0.165	0.543	0.095*	0.557	0.105*	0.700	0.125	0.016
$\dot{V}$A	$ml\,BTPS\,min^{-1}\,kg^{-1}$	13.1	4.6	9.1	1.4	9.2	2.0	10.9	2.5	0.080
$P\bar{v}O_2$	Torr	24.3	1.6	19.8	4.7	19.7	3.3	18.7	2.7*	0.028
D'TO_2	$ml\,O_2\,min^{-1}\,Torr^{-1}\,kg^{-1}$	1.8	0.4	1.6	0.7	1.7	0.3	2.2	0.1	0.139
EO_2	%	90.0	3.5	90.6	1.4	90.6	1.6	91.5	2.1	0.562

Speed, speed eliciting maximal aerobic capacity; $\dot{V}_{O_2max}$, maximal aerobic capacity; Time, running time at $\dot{V}_{O_2max}$; Mb, body mass; *R*, respiratory exchange ratio; $\dot{M}$LA, blood lactate accumulation rate; [LA], end-run [lactate]; $\dot{T}_{O_2max}$, total cardiopulmonary O_2 delivery; $\dot{Q}$, cardiac output; fH, heart rate; VS, cardiac stroke volume; CaO_2-$C\bar{v}O_2$ arterial-mixed-venous [O_2], CaO_2, arterial [O_2]; $C\bar{v}O_2$, mixed-venous [O_2]; [Hb]a, arterial [hemoglobin]; SaO_2, arterial O_2 saturation; $[Hb]_{\bar{v}}$, mixed-venous [hemoglobin]; $S\bar{v}O_2$, mixed-venous O_2 saturation; *T*, blood temperature; pHa, arterial pH; $PaCO_2$, arterial CO_2 partial pressure; $[HCO_3^-]$a, arterial bicarbonate ion concentration; PIO_2, inspired O_2 partial pressure; PAO_2, ideal alveolar O_2 partial pressure; PaO_2, arterial O_2 partial pressure; PA-aO_2, ideal alveolar-arterial O_2 partial-pressure difference; $\dot{V}CO_2$, rate of CO_2 production; $\dot{V}$A, alveolar ventilation; $P\bar{v}O_2$, mixed-venous O_2 partial pressure; D'TO_2, index of peripheral tissue diffusing capacity ($\dot{V}_{O_2max}/P\bar{v}O_2$); EO_2, O_2 extraction fraction.

pulmonary gas exchange, decrease cardiopulmonary O_2 delivery and reduce $\dot{V}_{O_2max}$ in goats when they breathe air. To our knowledge, this is the first study to exercise animals at $\dot{V}_{O_2max}$ following *OA*-induced acute lung injury.

2. Methods

2.1. Experimental design

Four goats trained by running on a treadmill 5 d wk^{-1} for 10–15 min d^{-1} at increasing speeds for 14–16 week until they demonstrated reproducible $\dot{V}_{O_2max}$ (coefficient of variation for $\dot{V}_{O_2max}$ varied by <5% at highest speeds). Once trained, goats ran at $\dot{V}_{O_2max}$ while breathing air [pre-study no lung injury (NLI_{pre})] as well as hypoxic or CO-containing gases as part of another study (Crocker and Jones, 2014). Then, 17 ± 5 week after NLI_{pre}, we infused the goats with *OA*, following which they ran at $\dot{V}_{O_2max}$ while breathing air 2-h and 1-d following *OA*-induced acute lung injury (*ALI* and *ALI* + 1, respectively). The *ALI* + 1 measurement was to determine if partial recovery from the initial *OA* effects would yield an intermediate response to the acute effects of *OA*. Following these studies, goats ran again at $\dot{V}_{O_2max}$ while breathing air [post-study no lung injury (NLI_{post})]. These NLI_{post} measurements occurred 35 ± 5 week after NLI_{pre} measurements (19 ± 1 week after *ALI* and *ALI* + 1 measurements) to test for effects of repeated *OA*-infusions on $\dot{V}_{O_2max}$ and other O_2-transport variables. The long intervals between measurements were necessary because the goats were infused with *OA* six additional times (once before and five times after *ALI* and *ALI* + 1 measurements) and needed time between to recover from *OA* infusions and arterial catheterizations. The *ALI* and *ALI* + 1 measurements occurred 3–5 week after an initial *OA* infusion. The NLI_{post} measurements occurred 7 week after the final *OA* infusion. The UC Davis Animal Care and Use committee approved this study.

2.2. Animals

Four Boer goat yearling wethers were studied (pre- and post-study caprinometrics at $\dot{V}_{O_2max}$ in Table 1). Clinical chemistry panel, complete blood count and blood gas values for the goats were all within normal reference ranges for goats at the UC Davis Veterinary Medical Teaching Hospital. During the initial training phase (prior to NLI_{pre} measurements), each goat had its left carotid artery surgically transposed subcutaneously to facilitate arterial catheterization. Throughout the study, goats were housed in a covered, outdoor pen at the Veterinary Medical Teaching Hospital on the UC Davis campus (elevation 16 m) and fed grass hay twice daily.

On the day prior to an experiment, the goat was catheterized with a 20-ga × 12-cm catheter (Arrow ES-04150) in its superficial carotid artery and a 7-Fr × 10-cm introducer (Arrow SI-09700) and 16-ga × 16-cm catheter (Arrow ES-04306) in its jugular vein