Effect of Ultramarathon Trail Running at Sea Level and Altitude on Alveolar–Capillary Function and Lung Diffusion

GLENN M. STEWART[1,2], CAITLIN C. FERMOYLE[1,3], COURTNEY M. WHEATLEY-GUY[4], PAUL ROBACH[5], NICHOLAS B. TILLER[6], BRYAN J. TAYLOR[7], BRIANA ZIEGLER[1], JESSE SCHWARTZ[1], ALICE GAVET[5], LOÏC CHABRIDON[5], ROBERT W. MURDOCK[8], KEREN CONSTANTINI[9], and BRUCE D. JOHNSON[1]

[1]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN; [2]Charles Perkins Centre, Faculty of Medicine and Health, University of Sydney, Sydney, AUSTRALIA; [3]Department of Respiratory Medicine, Royal Prince Alfred Hospital and University of Sydney, Sydney, AUSTRALIA; [4]Department of Cardiovascular Diseases, Mayo Clinic, Scottsdale, AZ; [5]Ecole Nationale des Sports de Montagne, Chamonix, FRANCE; [6]Institute of Respiratory Medicine and Exercise Physiology, Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrence, CA; [7]Department of Cardiovascular Diseases, Mayo Clinic, Jacksonville, FL; [8]Department of Cardiac Electrophysiology, Los Angeles Medical Center, Los Angeles, CA; and [9]School of public health, Sackler Faculty of Medicine, and Sylvan Adams Sports Institute, Tel-Aviv University, Tel Aviv, ISRAEL

ABSTRACT

STEWARDT, G. M., C. C. FERMOYLE, C. M. WHEATLEY-GUY, P. ROBACH, N. B. TILLER, B. J. TAYLOR, B. ZIEGLER, J. SCHWARTZ, A. GAVET, L. CHABRIDON, R. W. MURDOCK, K. CONSTANTINI, and B. D. JOHNSON. Effect of Ultramarathon Trail Running at Sea Level and Altitude on Alveolar–Capillary Function and Lung Diffusion. *Med. Sci. Sports Exerc.*, Vol. 56, No. 9, pp. 1759–1769, 2024. **Introduction:** Endurance exercise at altitude can increase cardiac output and pulmonary vascular pressure to levels that may exceed the stress tolerability of the alveolar–capillary unit. This study examined the effect of ultramarathon trail racing at different altitudes (ranging from <1000 m to between 1500 and 2700 m) on alveolar–capillary recruitment and lung diffusion. **Methods:** Cardiac and lung function were examined before and after an ultramarathon in 67 runners (age: 41 ± 9 yr, body mass index: 23 ± 2 $kg \cdot m^{-2}$, 10 females), and following 12–24 h of recovery in a subset ($n = 27$). Cardiac biomarkers (cTnI and BNP) were assessed from whole blood, whereas lung fluid accumulation (comet tails), stroke volume (SV), and cardiac output (Q) were quantified via echocardiography. Lung diffusing capacity for carbon monoxide (DLco) and its components, alveolar membrane conductance (Dm) and capillary blood volume (Vc), were determined via a single-breath method at rest and during three stages of submaximal semirecumbent cycling (20, 30, and 40 W). **Results:** Average race time was 25 ± 12 h. From pre- to post-race, there was an increase in cardiac biomarkers (cTnI: 0.04 ± 0.02 vs 0.13 ± 0.03 $ng \cdot mL^{-1}$, BNP: 20 ± 2 vs 112 ± 21 $pg \cdot mL^{-1}$; $P < 0.01$) and lung comet tails (2 ± 1 vs 7 ± 6, $P < 0.01$), a decrease in resting and exercise SV (76 ± 2 vs 69 ± 2 mL, 40 W: 93 ± 2 vs 88 ± 2 mL; $P < 0.01$), and an elevation in Q at rest (4.1 ± 0.1 vs 4.6 ± 0.2 $L \cdot min^{-1}$, $P < 0.01$; 40 W: 7.3 ± 0.2 vs 7.4 ± 0.3 $L \cdot min^{-1}$, $P = 0.899$). Resting DLco and Vc decreased after the race ($P < 0.01$), whereas Dm was unchanged ($P = 0.465$); however, during the three stages of exercise, DLco, Vc, and Dm were all reduced from pre- to post-race (40 W: 36.3 ± 0.9 vs 33.0 ± 0.8 $mL \cdot min^{-1} \cdot mm\ Hg^{-1}$, 83 ± 3 vs 73 ± 2 mL, 186 ± 6 vs 170 ± 7 $mL \cdot min^{-1} \cdot mm\ Hg^{-1}$, respectively; $P < 0.01$). When corrected for alveolar volume and Q, DLco decreased from pre- to post-race ($P < 0.01$), and changes in DLco were similar for all ultramarathon events ($P > 0.05$). **Conclusions:** Competing in an ultramarathon leads to a transient increase in cardiac injury biomarkers, mild lung-fluid accumulation, and impairments in lung diffusion. Reductions in DLco are predominantly caused by a reduced Vc and possible pulmonary capillary de-recruitment at rest. However, impairments in alveolar–capillary recruitment and Dm both contribute to a fall in exertional DLco following an ultramarathon. Perturbations in lung diffusion were evident across a range of event distances and varying environmental exposures. **Key Words:** CARDIAC FUNCTION, PULMONARY FUNCTION, ALVEOLAR MEMBRANE, GAS CONDUCTANCE, CAPILLARY BLOOD VOLUME, LUNG FLUID

Address for correspondence: Glenn M. Stewart, Ph.D., Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN 55905; E-mail: stewart.glenn@mayo.edu or glenn.stewart@sydney.edu.au.
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Participation in ultramarathon trail running has increased rapidly in recent years, with thousands of events now held annually around the world (1). Ultramarathons generally range from ~45 to >300 km, in single-stage and multistage events, and are frequently contested in mountainous regions with course profiles that include thousands of meters of cumulative ascent and prolonged periods at high altitude. Accordingly, the physiological demands of an ultramarathon are an important consideration for prescribing appropriate training programs to prospective participants and for offering suitable medical monitoring during events (2). Although physiological

profiling of acute cardiorespiratory responses to ultramarathon has been well studied (3,4), there is a paucity of data comprehensively assessing the effect of ultramarathon competitions on the pulmonary circulation and alveolar–capillary gas transfer.

The pulmonary circulation normally functions such that additional or underperfused capillaries are recruited and/or distended when cardiac output increases, and pulmonary capillary hydrostatic pressure remains low to prevent intravascular fluid from filtering out of the pulmonary vessels (5). However, strenuous exercise can increase pulmonary artery and capillary pressures above physiologically tolerable levels of alveolar–capillary membrane stress (6) and induce fluid shifts into the interstitial space (7). Indeed, studies assessing the presence of hematological substances in bronchoalveolar lavage fluid after exercise have revealed the vulnerability of the pulmonary capillaries to mechanical failure during strenuous exercise (8,9). The release of cardiac injury biomarkers such as cardiac troponin I (10) and acute decreases in systolic and diastolic cardiac function (11,12) are also known to occur with strenuous exercise, with the magnitude of effect mediated in part by the exercise intensity and duration (13,14). Although average exercise intensity throughout an ultramarathon is predominantly within the moderate-intensity domain (2), the extreme duration coupled with intermittent periods of more intense exercise and/or altitude exposure may lead to alveolar–capillarystress and possible lung fluid accumulation.

Altitude exposure can also impact alveolar–capillary interactions and lead to blood flow and gas exchange perturbations (15). Pertinently, hypoxic pulmonary vasoconstriction at altitude can alter pulmonary capillary blood volume (Vc), distribution, and pressure, which may further augment the alveolar–capillary stress that occurs with an increased alveolar ventilation and pulmonary blood flow during exercise (15). Dynamically changing ventilation–perfusion patterns throughout an ultramarathon may therefore alter the distribution of blood in the lungs (16), stress the alveolar–capillary interface (17), and impair alveolar-to-capillary membrane gas conductance (Dm) and lung diffusion (DLco) (18). These perturbations have not been studied in relation to ultramarathon running but would help inform medical monitoring at races. Accordingly, this study examined the effects of mountainous ultramarathons on cardiac injury biomarkers, lung fluid accumulation, DLco, and alveolar–capillary recruitment patterns (increases in Dm and Vc during exercise) in a large cohort of male and female ultramarathon competitors. It was hypothesized that competing in an ultramarathon would induce mild alveolar–capillary edema and central hemodynamic perturbations that transiently impair DLco, Dm, and Vc, and that this effect would be exacerbated following an ultramarathon at altitude.

METHODS

Study population and design. Experimental procedures were approved by the relevant Institutional Human Research Ethics Committees in accordance with the Declaration of Helsinki, and all participants provided written informed consent. Seventy-three healthy individuals (see Table 1 for characteristics) who were participating in either the Hong Kong 100 (HK100, n = 20), Courmayeur–Champex–Chamonix (CCC; n = 21) or Ultra-Trail du Mont Blanc (UTMB; n = 32) volunteered for the study. The HK100 (103 km, ~5500 m ascent) commences in Pak Tam Chung, Hong Kong, and undulates through coastal nature reserves without exceeding an altitude of 1,000 m. The CCC (101 km, ~6000 m ascent)

TABLE 1. Participant characteristics and race conditions at the HK100, CCC, and UTMB ultramarathons.

	Combined	HK100	CCC	UTMB	*P*
Demographics					
N (female)	67 (10)	19 (1)	20 (5)	28 (4)	
Age, yr	41 ± 10	40 ± 9	42 ± 11	41 ± 9	0.636
Height, cm	175.4 ± 7.3	174.4 ± 5.7*	171.9 ± 7.2*	178.4 ± 7.2	0.004
Weight, kg	70.0 ± 9.2	69.6 ± 7.1	66.1 ± 10.1*	72.9 ± 8.9	0.023
Body mass index	22.7 ± 2.0	22.8 ± 1.4	22.3 ± 2.5	22.9 ± 2.0	0.483
Resting HR, bpm	55 ± 8	55 ± 5	55 ± 9	55 ± 8	0.973
Resting MAP, mm Hg	90 ± 11	90 ± 11	91 ± 11	89 ± 11	0.695
Hematology					
Hct, %	43.9 ± 3.8	46.3 ± 4.7*,**	43.8 ± 2.8	42.6 ± 3.1	0.002
Hb, $g \cdot dL^{-1}$	14.9 ± 1.3	15.7 ± 1.6*,**	14.9 ± 0.9	14.5 ± 1.1	0.002
Pulmonary function					
SVC, L	5.4 ± 1.2	5.5 ± 1.1	4.8 ± 1.0*	5.6 ± 1.2	0.041
FVC, L	5.3 ± 0.9	5.3 ± 0.9	4.8 ± 0.9*	5.5 ± 0.9	0.071
FEV_1, $L \cdot s^{-1}$	4.1 ± 0.7	4.2 ± 0.7	3.9 ± 0.7	4.2 ± 0.7	0.325
FEV_1/FVC, %	79 ± 7	79 ± 4	82 ± 7	78 ± 8	0.253
$FEF_{25–75}$, $L \cdot s^{-1}$	3.9 ± 1.3	3.9 ± 1.0	4.0 ± 1.2	3.9 ± 1.4	0.975
PEF, $L \cdot s^{-1}$	9.5 ± 2.0	9.1 ± 1.4	9.6 ± 2.1	9.7 ± 2.3	0.578
Dlco, mm $Hg \cdot^{-1} mL \cdot min^{-1}$	32.5 ± 7.2	32.9 ± 5.2	30.0 ± 6.4*	34.3 ± 8.1	0.066
Race conditions					
Time, h	24.8 ± 11.8	16.4 ± 4.4*	19.6 ± 5.0*	33.5 ± 12.4	0.000
Distance, km	116.7 ± 41.5	96.8 ± 10.9*	93.1 ± 19.1*	144.3 ± 47.5	0.000
Pace, $min \cdot km^{-1}$	12.4 ± 2.6	10.1 ± 2.3*,**	12.8 ± 2.3*	13.6 ± 2.0	0.000
ITRA ranking	538 ± 99	549 ± 114	525 ± 93	541 ± 92	0.692

Data are mean ± SD.
*Significant difference ($P < 0.05$) from UTMB participants.
**Significant difference ($P < 0.05$) from CCC participants.
Hb, hemoglobin; Hct, hematocrit; ITRA, International Trail Running Association.

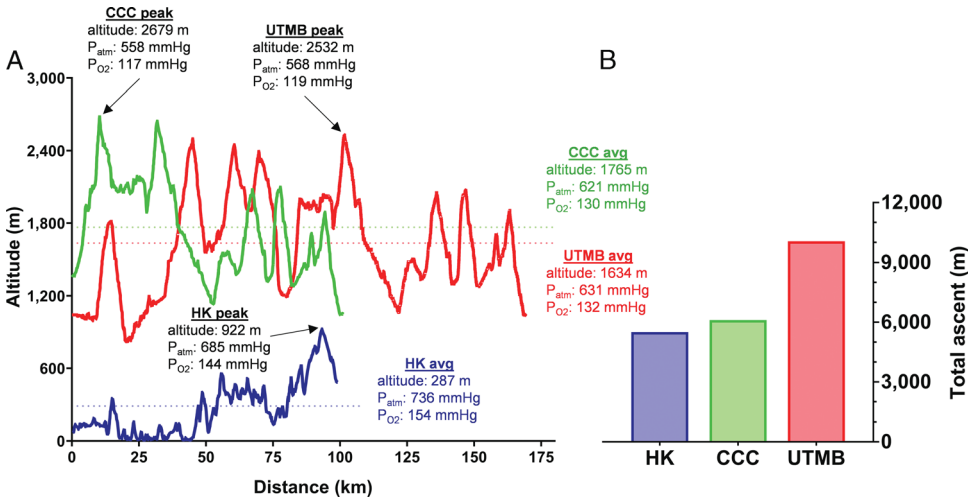

FIGURE 1—Schematic of the HK100 (blue), CCC (green), and UTMB (red) race profiles, including average and peak altitude exposure (A) and total accumulative ascent (B) for each race. P_{atm}, atmospheric pressure; PO_2, oxygen partial pressure.

commences in Courmayeur, Italy, whereas the UTMB (171 km, ~10,000 m ascent) commences in Chamonix, France, and both courses undulate through alpine regions predominantly above 1000 m with intermittent bouts over 2500 m (Fig. 1).

Participants were asked to visit a dedicated laboratory for physiological measurements 24–72 h before (Pre), 1–4 h after (Post), and 12–24 h after (Recovery) their respective races. During each visit, participants completed a series of physiological assessments including anthropometrics, blood sampling, pulmonary function testing, and simultaneous lung diffusion and echocardiographic assessments at rest and during three stages of submaximal cycling exercise (Fig. 2). The three stages of submaximal cycling were conducted at a low intensity (20, 30, and 40 W) that would increase cardiac output and ventilation, but still be manageable by all participants in the post-race setting. A small subset of participant data from CCC and UTMB has been previously published in a study comparing sex differences in ultramarathon runners, but not as it relates to the current study (19). Because of the difficulty of ultramarathon events and inability of some participants to return for post-race testing, only data for participants who completed >80% of their respective race and returned for post-race testing were included in the current study. Separate analyses were performed for pre-to-post comparisons (total $n = 67$; with $n = 19$, 20, and 28 for HK100, CCC, and UTMB, respectively) and pre-to-recovery comparisons (total $n = 27$; with $n = 11$, 5, and 11 for HK100, CCC, and UTMB, respectively).

Hematology, hemodynamics, and exhaled nitric oxide. Venous blood samples were extracted into 4 mL lithium heparin and EDTA vacutainers via venipuncture for subsequent analysis. Measures of hemoglobin (Hb), hematocrit (Hct), cardiac troponin I (cTnI), brain natriuretic peptide (BNP), and creatine kinase-MB(CK-MB) were assessed from whole fresh venous blood using a commercially available portable blood analyzer and cartridges (i-STAT Corporation, Windsor, NJ). Mean arterial blood pressure (MAP) was calculated from systolic and diastolic blood pressure (measured via a manual sphygmomanometer and auscultation), whereas heart rate (HR) was determined via three-lead electrocardiography (CX50; Philips Healthcare, Eindhoven, the Netherlands). Pulmonary function testing was performed in accordance with guidelines prescribed by the American Thoracic Society and European Respiratory Society (20,21). Spirometry measures (reported for baseline characterization only), including slow and forced vital capacities (SVC, FVC), forced expiratory volume in 1 s (FEV_1), peak expiratory flow (PEF), and forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75}$) were assessed using a portable spirometer and software (Breeze Suite 8.5 and CPFS/D USB™; Medgraphics Corporation, St Paul, MN). Fractional exhaled nitric oxide (ExNO) was measured using a handheld device (Aerocrine Niox Vero® 510(k), NIOX, Solna, Sweden, used at 2018 races; FeNObreath, Bedfont, Rochester, UK, used at 2019 races).

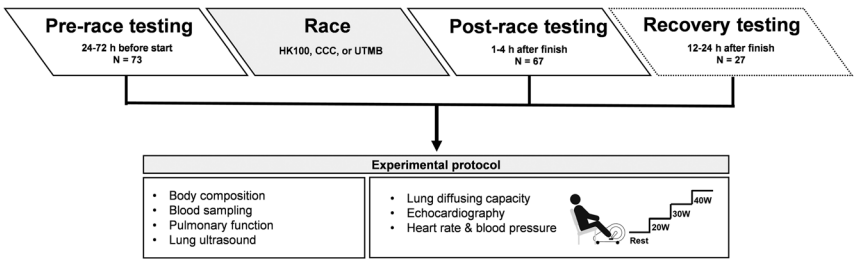

FIGURE 2—Schematic of the study design and experimental protocols.

Lung and cardiac ultrasound. Transthoracic ultrasound (CX50 and S5-1 transducer; Philips Healthcare) was performed in accordance with the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines (22). As a measure of extravascular lung fluid, the number of B-lines or "comet tails" present during lung ultrasound was determined via transthoracic sonography, as previously described (23,24). Briefly, we employed a semiquantitative classification for the presence of extravascular lung water, whereby a total lung comet tail count of <5 was considered "normal," 5–15 was mild extravascular lung water accumulation, 15–30 was moderate extravascular lung water accumulation, and >30 was severe extravascular lung water accumulation (24). For cardiac ultrasound measures, a minimum of three cardiac cycles were captured, and data were analyzed offline on a commercially available workstation (Q-Lab 13; Philips Healthcare). Stroke volume (SV) was calculated as the product of LV outflow tract cross-sectional area and pulsed-wave Doppler-derived blood velocity–time integral, measured immediately proximal to the aortic valve during systole. Cardiac output (Q) was calculated as the product of HR and SV.

Lung diffusion and alveolar–capillary recruitment. Simultaneous measurements of lung diffusing capacity for carbon monoxide (DLco) and nitric oxide (DLno) were assessed using a single-breath technique in a semirecumbent position at rest and during three stages of cycling exercise (Fig. 2). Resting DLco/DLno measures were performed in duplicate and averaged, whereas exertional DLco/DLno measures were performed once during each of the three stages of exercise (20, 30, and 40 W). Each exercise stage was 3 min in duration, with DLco/DLno and SV measurements acquired in the last 30 s of each stage. The assessment of lung diffusion *during* exertion, rather than only at rest, provides additional insight and offers a more sensitive assessment of pulmonary alveolar–capillary function (25). Details of the single-breathDLco/DLno technique and the calculation of Dm and Vc have been published previously (25–27). Briefly, subjects were coached to perform the single-breath-hold maneuver as follows: a complete expiration to residual volume, a full inspiration of the test gas (0.3% CO, 40 ppm NO, 14% He, 21% O_2, and balance N_2) from an inhalation bag, and a 4-s breath hold, followed by a full expiration into a collection bag. An automated system (Hyp'air Compact system with Exp'air software, version 1.31.05; Medisoft, Dinant, Belgium) analyzed the exhaled gases to calculate DLco and DLno from the disappearance of inhaled CO and NO during the breath hold. Each DLco/DLno test was separated by 4 min at rest and 3 min during exercise to allow for washout of the gases, and Dm and Vc were calculated using a finite θ_{NO} of 4.5 $mL \cdot min^{-1} \cdot mm\ Hg^{-1} \cdot mL^{-1}$ blood (27).

Statistical analyses. All significance testing was performed using SPSS software (v27.0; SPSS Inc, Chicago, IL). A Shapiro–Wilk test was used to confirm normality of the data, and a one-way mixed ANOVA performed to determine if baseline characteristics and race conditions differed between groups (HK100, CCC, UTMB). Two-way mixed ANOVA tests were subsequently performed to determine if 1) outcome measures differed across time (pre vs post; pre vs recovery) and between groups (HK100, CCC, UTMB), and to examine time–group interactions; 2) outcome measures differed across time (pre vs post; pre vs recovery) and between testing condition (rest and three stages of exercise), and to examine time–condition interactions; and 3) the magnitude of pre- to post-race changes in outcome measures differed between groups (HK100, CCC, UTMB) and testing condition (rest and three stages of exercise), and to examine group–condition interactions. Mauchly's test of sphericity was used to assess the assumption of equal variance, and if violated, a Greenhouse–Geisser correction was applied. Where significant main effects or interactions were observed, Bonferroni *post-hoc* adjustments were made to further examine pairwise comparisons. Data are presented as group mean and SD.

RESULTS

Race conditions and participant characteristics. All data were collected from runners competing in the HK100 event in 2018, or the CCC and UTMB events in 2018 or 2019. Participant characteristics and race conditions are presented in Table 1. Temperature and humidity during the events ranged from 6°C to 19°C and 75% to 85% during the HK100, −6°C to 28°C and 35% to 75% during CCC and UTMB in 2018, and 6°C to 29°C and 35% to 70% during CCC and UTMB in 2019. Average time from race finish to post-race testing was 118 ± 65 min, whereas average time from race finish to recovery testing was 20 ± 5 h. Lung capacity and FEV_1were within normal reference ranges across the cohort with a percent-predicted FVC of 108% (range, 86%–144%) and percent-predicted FEV_1 of 109% (range, 80%–138%). There were no significant differences in age, body mass index, resting HR, resting MAP, FEV_1, FEV_1/FVC, $FEF_{25–75}$, PEF, or International Trail Running Association ranking among participants in the HK100, CCC, and UTMB. However, UTMB participants were taller than HK100 and CCC participants, whereas CCC participants were lighter than HK100 and UTMB participants. The HK100 participants had a higher Hb and Hct than CCC and UTMB participants. The CCC participants had lower SVC, FVC, and DLco, alongside a higher proportion of female participants (n = 5 female), than HK100 (n = 1 female) and UMTB (n = 4 female). Because of differences in race distance and cumulative ascent, total race time and distance covered were similar between HK100 and CCC but longer and farther in UTMB. Moreover, average pace was faster in HK100 than both CCC and UTMB, and average pace in CCC was faster than UTMB.

Hematology, hemodynamics, and exhaled nitric oxide. A post-race increase in cardiac biomarkers (cTnI and BNP) and CK-MB was observed for all ultramarathon events (Table 2), and the magnitude of change did not differ between ultramarathon events. Although cTnI returned to pre-race values after 12–24 h of recovery, BNP and CK-MB remained elevated (Table 2). Although Hb and Hct were overall not

TABLE 2. Hematological and lung ultrasound measures before (Pre) and 1–4 h (Post) and 12–24 h (Recovery) after the HK100, CCC, and UTMB ultramarathons.

Hematological Measures		Combined	HK100	CCC	UTMB	ANOVA			
							Time	Race	Interaction
Hb, g·dL^{-1}	Pre	14.9 ± 1.3	15.7 ± 1.6	14.9 ± 0.9	14.5 ± 1.1				
	Post	14.7 ± 1.8	16.6 ± 1.4*	14.4 ± 1.0	13.7 ± 1.5	Pre vs Post	$P = 0.594$	$P < 0.001$	$P = 0.006$
	Recovery	14.7 ± 2.7	17.2 ± 1.9*	12.5 ± 1.7*	13.4 ± 1.8*	Pre vs Recovery	$P = 0.071$	$P < 0.001$	$P < 0.001$
Hct, %	Pre	43.9 ± 3.8	46.3 ± 4.7	43.8 ± 2.8	42.6 ± 3.1				
	Post	43.3 ± 5.3	48.9 ± 4.1*	42.3 ± 3.0	40.4 ± 4.4*	Pre vs Post	$P = 0.579$	$P < 0.001$	$P = 0.007$
	Recovery	42.7 ± 8.0	49.2 ± 6.9*	36.8 ± 5.1*	39.2 ± 5.3*	Pre vs Recovery	$P = 0.046$	$P < 0.001$	$P = 0.006$
BNP, ng·L^{-1}	Pre	21 ± 12	20 ± 11	20 ± 10	22 ± 13				
	Post	120 ± 85	112 ± 93*	132 ± 65*	117 ± 94*	Pre vs Post	$P < 0.001$	$P = 0.529$	$P = 0.487$
	Recovery	67 ± 64	61 ± 55*	111 ± 92*	46 ± 43*	Pre vs Recovery	$P < 0.001$	$P = 0.130$	$P = 0.132$
cTnI, µg·L^{-1}	Pre	0.02 ± 0.05	0.06 ± 0.08	0.00 ± 0.01	0.01 ± 0.03				
	Post	0.07 ± 0.09	0.13 ± 0.14*	0.06 ± 0.04*	0.04 ± 0.04*	Pre vs Post	$P < 0.001$	$P = 0.039$	$P = 0.194$
	Recovery	0.04 ± 0.06	0.06 ± 0.08	0.03 ± 0.04	0.03 ± 0.04	Pre vs Recovery	$P = 0.701$	$P = 0.029$	$P = 0.175$
CK-MB, µg·L^{-1}	Pre	7 ± 8	10 ± 14	5 ± 2	6 ± 4				
	Post	94 ± 48	78 ± 49*	96 ± 46*	103 ± 47*	Pre vs Post	$P < 0.001$	$P = 0.357$	$P = 0.138$
	Recovery	69 ± 56	68 ± 64*	80 ± 56*	64 ± 52*	Pre vs Recovery	$P < 0.001$	$P = 0.906$	$P = 0.797$
ExNO, ppb	Pre	27 ± 18	32 ± 26	25 ± 15	26 ± 14				
	Post	18 ± 12	26 ± 15*	15 ± 9*	14 ± 9*	Pre vs Post	$P = 0.001$	$P = 0.306$	$P = 0.521$
	Recovery	30 ± 23	36 ± 31	32 ± 18	22 ± 6	Pre vs Recovery	$P = 0.684$	$P = 0.419$	$P = 0.961$
Comet tails, *n*	Pre	2 ± 4	3 ± 4	2 ± 4	2 ± 4				
	Post	7 ± 6	6 ± 8*	6 ± 4*	8 ± 7*	Pre vs Post	$P = 0.001$	$P = 0.742$	$P = 0.432$
	Recovery	4 ± 4	4 ± 4	4 ± 6	4 ± 3	Pre vs Recovery	$P = 0.065$	$P = 0.992$	$P = 0.867$

Data are mean ± SD.
*Significant difference ($P < 0.05$) to Pre.

impacted by ultramarathon, a significant time–race interaction revealed that Hb and Hct increased after the HK100 and decreased after the CCC and UTMB, with the post-race changes persisting after 12–24 h of recovery (Table 2). A post-race increase in HR and a decrease in MAP were observed for all events, both at rest and during all three stages of exercise (Table 3), and the magnitude of change did not differ between ultramarathon events. Reductions in ExNO were observed from pre-to-post ultramarathon following all events, and the magnitude of change did not differ between ultramarathon events (Table 2). After 12–24 h of recovery, ExNO returned to pre-race values following all events.

Lung fluid and cardiac ultrasound. The incidence of lung comet tails increased from pre-to-post ultramarathon following all events and returned to pre-race values after 24 h of recovery (Table 2). The post-race increases in lung comet tails reached levels indicative of mild extravascular lung water accumulation in 21 participants, moderate extravascular lung water accumulation in 3 participants, and severe extravascular lung water accumulation in 1 participant. Following all events, SV decreased from pre-to-post ultramarathon at rest and during all three stages of exercise (Table 3), whereas Q increased from pre-to-post ultramarathon at rest but was not different during the three stages of low intensity exercise (Table 3).

TABLE 3. Hemodynamic and respiratory measures at rest and during three stages of low-intensity cycling before (Pre) and 1–4 h (Post) and 12–24 h (Recovery) after the HK100, CCC, and UTMB ultramarathons.

Hemodynamics and Lung Volumes at Rest and During 3 Stages of Exercise		Rest	Stage 1	Stage 2	Stage 3	ANOVA			
							Time	Exercise	Interaction
HR, bpm	Pre	55 ± 8	64 ± 8	75 ± 9	85 ± 10				
	Post	68 ± 11[a]	76 ± 12[a]	86 ± 12[a]	94 ± 11[a]	Pre vs Post	$P < 0.001$	$P < 0.001$	$P = 0.020$
	Recovery	60 ± 8	70 ± 8	81 ± 9	90 ± 9	Pre vs Recovery	$P = 0.546$	$P < 0.001$	$P = 0.322$
MAP, mm Hg	Pre	90 ± 11	92 ± 10	92 ± 11	91 ± 15				
	Post	82 ± 8*	85 ± 9*	86 ± 9*	86 ± 10*	Pre vs Post	$P < 0.001$	$P < 0.001$	$P = 0.206$
	Recovery	83 ± 8*	85 ± 9*	83 ± 9*	84 ± 9*	Pre vs Recovery	$P < 0.001$	$P = 0.472$	$P = 0.380$
SV, mL	Pre	76 ± 19	80 ± 15	87 ± 17	93 ± 18				
	Post	69 ± 14*	73 ± 13*	81 ± 14*	88 ± 14*	Pre vs Post	$P < 0.001$	$P < 0.001$	$P = 0.352$
	Recovery	76 ± 17	83 ± 14	92 ± 16	98 ± 17	Pre vs Recovery	$P = 0.453$	$P < 0.001$	$P = 0.382$
Q, L·min^{-1}	Pre	4.1 ± 1.0	5.6 ± 1.5	6.6 ± 1.7	7.4 ± 2.0				
	Post	4.6 ± 1.2*	5.6 ± 1.1	6.4 ± 1.3	7.4 ± 2.5	Pre vs Post	$P = 0.899$	$P < 0.001$	$P < 0.001$
	Recovery	4.4 ± 1.7	5.7 ± 1.4	6.8 ± 1.9	7.7 ± 2.5	Pre vs Recovery	$P = 0.950$	$P < 0.001$	$P = 0.360$
V_A, L	Pre	6.8 ± 1.2	6.8 ± 1.2	6.9 ± 1.1	7.0 ± 1.1				
	Post	6.2 ± 1.1*	6.1 ± 1.1*	6.4 ± 1.1*	6.4 ± 1.0*	Pre vs Post	$P < 0.001$	$P < 0.001$	$P = 0.664$
	Recovery	6.4 ± 1.1	6.4 ± 1.1	6.6 ± 1.2	6.7 ± 1.1	Pre vs Recovery	$P = 0.495$	$P < 0.001$	$P = 0.777$
IV, L	Pre	4.8 ± 0.9	4.7 ± 0.9	4.7 ± 0.8	4.7 ± 0.9				
	Post	4.2 ± 0.9*	4.1 ± 0.9*	4.2 ± 0.8*	4.3 ± 0.8*	Pre vs Post	$P < 0.001$	$P = 0.231$	$P = 0.004$
	Recovery	4.4 ± 0.9*	4.4 ± 0.9*	4.4 ± 0.9*	4.4 ± 0.8*	Pre vs Recovery	$P = 0.005$	$P = 0.211$	$P = 0.799$
RV, L	Pre	2.0 ± 0.5	2.1 ± 0.5	2.2 ± 0.5	2.3 ± 0.6				
	Post	2.0 ± 0.5	2.0 ± 0.6	2.1 ± 0.5	2.1 ± 0.6	Pre vs Post	$P = 0.272$	$P < 0.001$	$P = 0.015$
	Recovery	2.0 ± 0.4	2.0 ± 0.5	2.2 ± 0.5	2.3 ± 0.5	Pre vs Recovery	$P = 0.850$	$P < 0.001$	$P = 0.134$

Data are mean ± SD.
*Significant difference ($P < 0.05$) to Pre.
IV, inspiratory volume; RV, residual volume.

The magnitude of change in SV and Q did not differ between ultramarathon events. SV and Q at rest and during all three stages of exercise returned to pre-race values after 12–24 h of recovery (Table 3).

Lung diffusion and alveolar–capillary recruitment. Overall lung diffusing capacities (DLco and DLno) were reduced following the ultramarathon events, both at rest and during all three stages of exercise (Fig. 3) and remained lower than pre-race values after 12–24 h of recovery (Fig. 4). Although Vc was reduced following the ultramarathon events at rest and during exercise, Dm was not different from pre-to-post ultramarathon at rest but was reduced during all three stages of exercise (Fig. 3). Vc remained lower after 12–24 h of recovery, whereas Dm was not different from pre-race values (Fig. 4). The magnitudes of pre-to-post race changes in DLco, DLno, Dm, and Vc, at rest and during the three stages of exercise, were not different between ultramarathon events (albeit with a between-race main effect for Dm of $P = 0.051$; Fig. 5). Inspiratory (IV) and alveolar volumes (V_A) were reduced following the ultramarathon events, both at rest and during all three stages of exercise, whereas residual volume (RV) was unchanged from pre-to-post ultramarathon (Table 3). When normalized to V_A and Q, DLco was reduced from pre- to-post-race at rest and during all three stages of exercise (Fig. 3) but returned to pre-race values after 24 h or recovery (Fig. 4). The DLno/DLco ratio was unchanged from

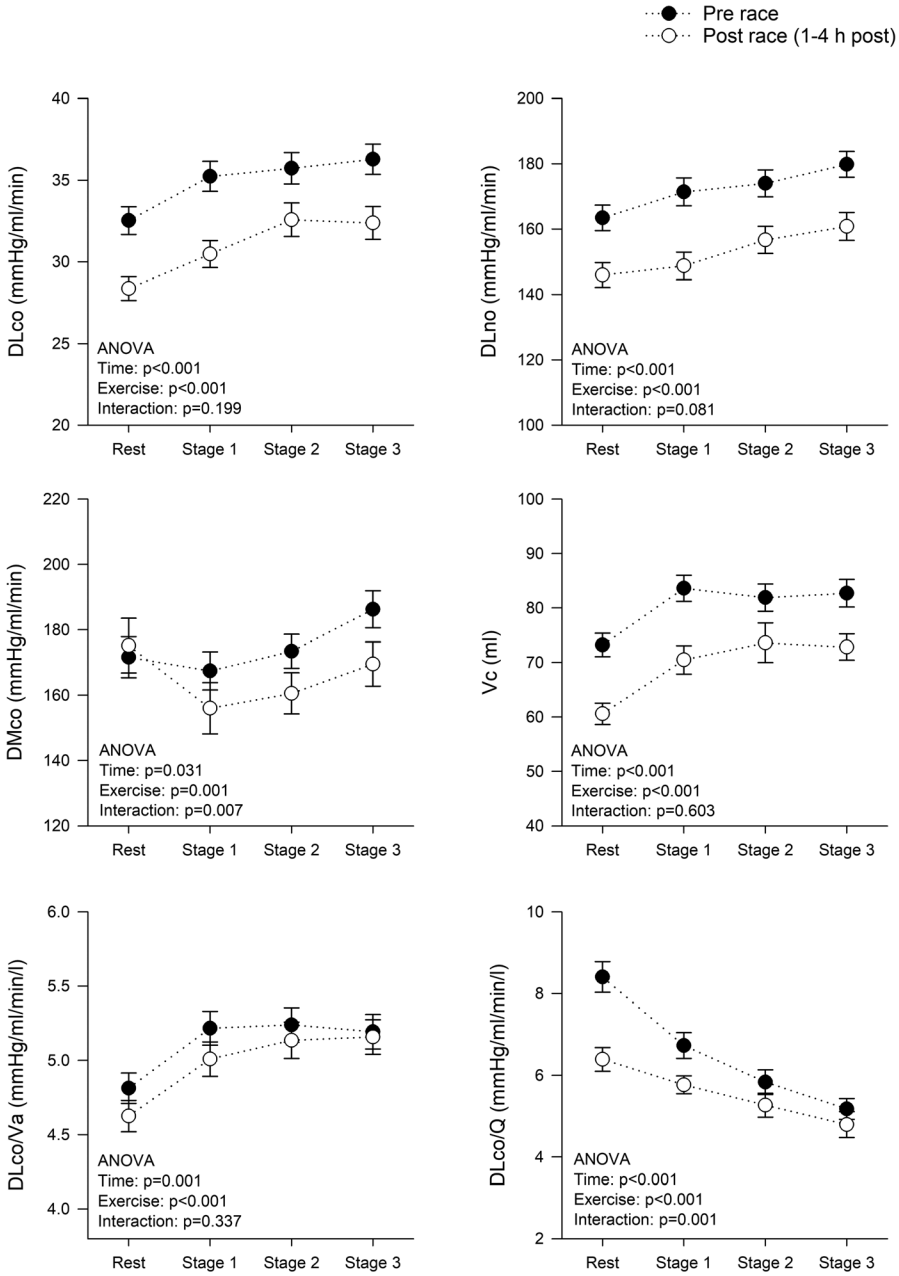

FIGURE 3—Lung diffusion parameters measured at rest and during three stages of submaximal exercise before (Pre-race) and 1–4 h after (Post-race) participating in an ultramarathon. Dlco/Q, Dlco relative to Q;DLco/V_A, DLco relative to V_A.

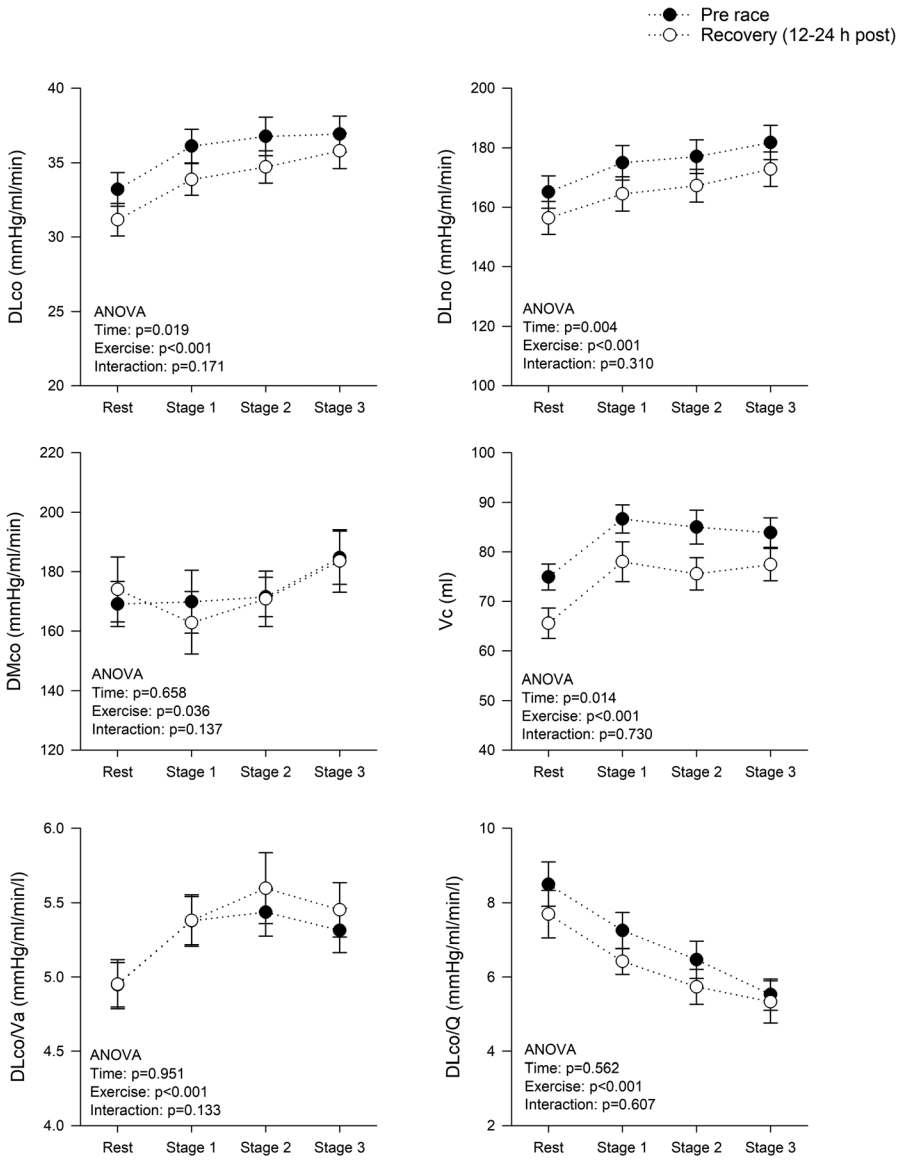

FIGURE 4—Lung diffusion parameters measured at rest and during three stages of submaximal exercise before (Pre-race) and 12–24 h after (Recovery) participating in an ultramarathon. Dlco/*Q*, Dlco relative to *Q*;DLco/V_A, DLco relative to V_A.

pre-to-post ultramarathon, both at rest (5.1 ± 0.4 vs 5.2 ± 0.5, $P = 0.096$) and during the three stages of exercise (e.g., stage 3: 5.0 ± 0.5 vs 4.9 ± 0.4, $P = 0.163$), whereas the Dm/Vc ratio increased from pre-to-post ultramarathon at rest (2.4 ± 0.9 vs 3.0 ± 1.4, $P = 0.011$) but was unchanged during the three stages of exercise (e.g., stage 3: 2.4 ± 0.9 vs 2.5 ± 0.9, $P = 0.473$).

DISCUSSION

The aim of this study was to examine the effects of mountainous ultramarathons on cardiac injury biomarkers, lung fluid accumulation, lung diffusion, and alveolar–capillary recruitment patterns (increases in Dm and Vc during exercise) in a large cohort of male and female ultramarathon competitors. The data show that ultramarathon competitions induce a transient decrease in lung diffusing capacity that is predominantly driven by a reduction in pulmonary capillary blood volume (Vc). Furthermore, when cardiac output and ventilation are augmented during the post-race setting (i.e., during the three stages of low-intensity cycling), perturbations in alveolar–capillary membrane gas conductance (Dm) also contribute to the impairments in lung diffusion that occur following an ultramarathon. Reductions in lung diffusing capacity following an ultramarathon competition were evident across a range of event distances and environmental exposures.

Although previous studies have highlighted that DLco and DLno are transiently reduced at rest following shorter duration exercise performed at a moderate-to-severe intensity at sea level (28–30), the current findings indicate that mountainous ultra-endurance exercise (12–48 h), performed at a relatively low exercise intensity, can also impair lung diffusion. The

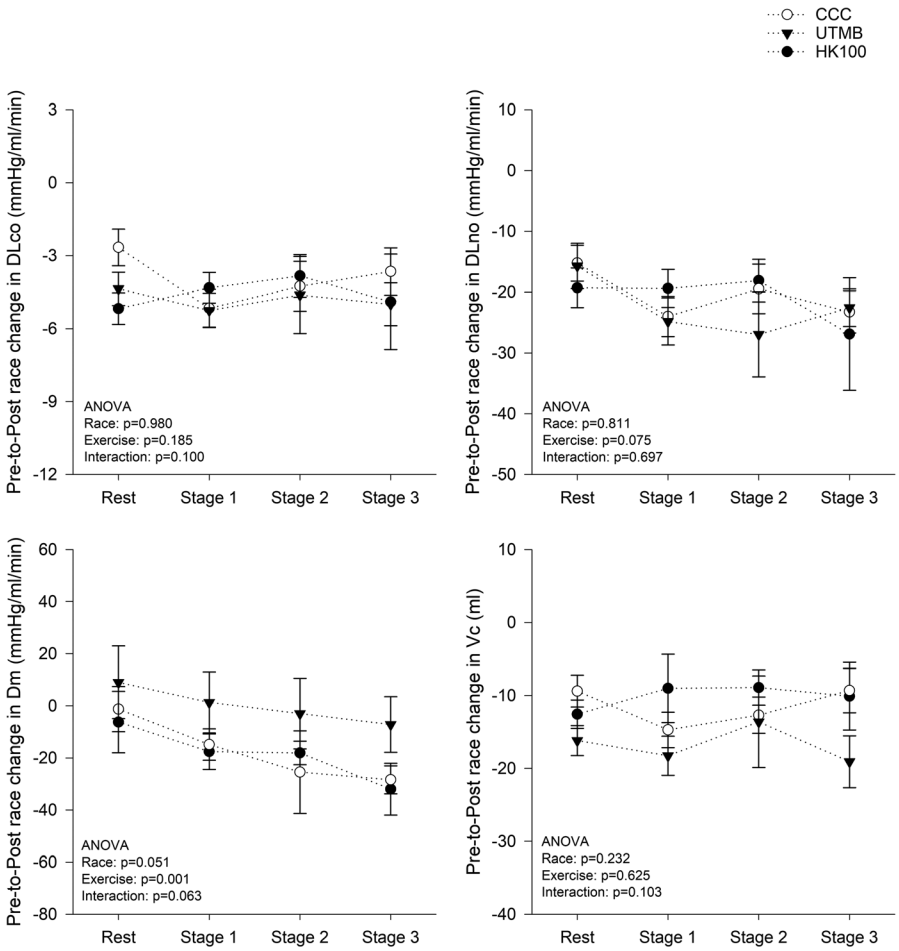

FIGURE 5—Pre-to-post race changes in lung diffusion parameters at rest and during three stages of submaximal exercise following the HK100, CCC, and UTMB ultramarathon events.

reductions in DLco and DLno were particularly evident during exertion (i.e., during the three stages of low-intensity exercise), when reductions in Vc and Dm both exerted mediating effects. In agreement with prior work, the post-race reductions in DLco and Vc at rest (without a change in Dm) suggest that pulmonary capillary de-recruitment or shunt (31–33), and/or pooling of blood in the periphery (34,35), may be primary mechanisms contributing to the fall in *resting* DLco. A reduced DLco alongside an increased Dm/Vc and no change in DLno/DLco at rest (despite a reduced V_A that would normally decrease DLno/DLco, (36)) further supports the notion that altered distribution of blood in the lung capillaries (16) may be a primary driver for the fall in DLco following an ultramarathon. This pattern is similarly observed in patient populations with known pulmonary vascular/venous abnormalities such as heart failure or pulmonary hypertension (37–39). On the contrary, the additional post-race reduction in Dm *during exercise* alongside no changes in Dm/Vc or DLno/DLco suggests that altered permeability of the alveolar–capillarymembrane (8) resulting in subclinical interstitial pulmonary edema (17) may also contribute to the fall in *exertional* DLco.

Exaggerated hypoxic pulmonary vasoconstriction and increased incidence of pulmonary edema have been associated with impaired pulmonary epithelial NO synthesis and lower ExNO levels (40,41). Given that ExNO was reduced following the ultramarathon events, an increase in pulmonary blood flow and capillary hydrostatic pressure *during* the three stages of low intensity exercise may further stress the vascular endothelium and increase permeability (9), leading to interstitial pulmonary edema and an impairment to Dm. Alternatively, an inability of the pulmonary lymph nodes to sufficiently clear any accumulated fluid (42) may have also contributed to the reduced exertional Dm. Although lung ultrasound was only performed at rest in the current study, the frequency of lung comet tails was elevated after the ultramarathon, albeit still within normal limits for some participants, suggesting that a mild increase in extravascular lung fluid may contribute to the fall in DLco and Dm after an ultramarathon (18,19,43).

There are contradictory reports of reduced lung fluid during hypoxia in healthy humans (44) alongside increases in DLco and Dm (45), and others reporting a diminished DLco and Dm in healthy participants at altitude (18). Acute high-intensity exercise has been more consistently shown to transiently increase lung fluid (46) and reduce DLco (47). However, some reports suggest that a reduced Dm is the primary factor leading to a fall in DLco (48), whereas others suggest that changes in

DLco may be predominately driven by a reduced Vc (34,49) and actually compensated in part by increases in Dm (50). Furthermore, experimentally induced pulmonary edema via rapid saline infusion increases pulmonary blood flow and Vc, and decreases Dm (44). In the current study, an increase in pulmonary blood flow during the three stages of exercise was associated with a lower Vc and impaired Dm following the ultramarathon. Collectively, these data suggest that the fall in DLco in the current study may be mediated by a combination of environmental exposures *and* ultra-endurance exercise that results in a mild post-race pulmonary capillary de-recruitment (i.e., a fall in Vc) that alters the distribution of blood in lung capillaries and a mild increase in extravascular lung fluid that collectively impairs alveolar membrane conductance (i.e., a fall in Dm).

Despite the HK100, CCC, and UTMB races being unique in terms of their distance, cumulative ascent, and peak and average altitude exposure (Fig. 1), the magnitudes of post-race reductions in DLco, DLno, and Vc were not different between events. There was, however, a trend ($P = 0.051$) for the post-race decreases in Dm to be greater in the HK100 and CCC than the UTMB, suggesting that alveolar–capillary membrane gas conductance may be more affected by exercise intensity (with UTMB being a considerably longer race with a slower pace and lower relative exercise intensity). Although further study is needed to confirm these findings, this may suggest that an exercise stimulus (i.e., prolonged elevation in ventilation and pulmonary blood flow) may have a greater impact on the alveolar–capillary unit than an environmental stimulus (exposure to dry, cold, and/or hypoxic air). Although DLco, DLno, and Vc remained below baseline at 12–24 h after any given race, Dm had returned to pre-race values and changes to lung diffusion and alveolar–capillary recruitment patterns were trending back to pre-race values, suggesting that these changes are transient and likely return to normal within 1–2 d after the event (51).

Alongside the changes in lung diffusion, hemodynamic perturbations following an ultramarathon were also observed in the current study in accordance with prior work (2). Completing an ultramarathon resulted in a post-race tachycardia, arterial hypotension, and a decrease in SV, whereas Q was elevated at rest but similar to pre-race during the three stages of exercise. Interestingly, shifts in hemodynamics (e.g., drop in SV) or V_A did not explain the fall in DLco, with DLco normalized for V_A and Q both reduced following the ultramarathon. On the contrary, vasodilation of the periphery and a possible decentralization of blood volume following the ultramarathon may have contributed to the drop in Vc (34). Although SV, MAP, and Vc were reduced at 1–4 h post-race, with these changes persisting at 12–24 h post-race, there was no association between changes in SV, MAP, and Vc (or any other lung diffusion parameters) in the current data.

In accordance with previous work, competing in an ultramarathon was associated with an increase in biomarkers of cardiac (52) and skeletal muscle (53) injury. Interestingly, post-race increases in cTnI, BNP, and CK-MB did not appear to be overtly impacted by event distance (e.g., 100 km CCC vs 171 km UTMB) or event conditions such as altitude exposure (e.g., <1000 m at HK100 vs >2500 m at CCC). Prior work has highlighted that an exercise intensity exceeding the anaerobic threshold is required to induce substantial increases in cardiac injury markers (14), and this may explain the modest increases in cTnI and BNP that were observed following an ultramarathon. Similarly, the reductions in ExNO and increases in the incidence of comet tails observed after the ultramarathon events in the current study are similar to prior works (54) and did not seem to be impacted by the event distance or environmental conditions.

On the contrary, changes in Hb and Hct were different between events, with an increase in Hb and Hct observed following HK100 and a decrease after the CCC and UTMB. The opposing shifts in Hb and Hct at HK00 versus CCC/UTMB may be caused, in part, by different environmental exposures during HK100 (warmer, humid, sea level) and CCC/UTMB (cool, dry, moderate altitude) that lead to dehydration/plasma volume reduction at HK100 and a plasma volume expansion at UTMB. Indeed, the Hb and Hct changes observed in the current CCC/UTMB participants were similar to a previous study reporting post-race plasma volume expansion in UTMB participants that is likely mediated by inflammation and an associated influence of interlukin-6 on plasma volume (55). Because of the prolonged (and varying) duration of ultramarathons, the chronology of hematological alterations throughout the event may differ to the pre-to-post race alterations observed in the current study (56).

Physiological and methodological considerations. Although the reductions in alveolar–capillary function observed in this study were mostly consistent across the different ultramarathon events, the varying environmental and physiological conditions (e.g., temperature, altitude, relative exercise intensity, total duration) likely impacted the findings to some extent. More detailed in-race monitoring, such as continuous assessment with accelerometers and cardiorespiratory ultrasound patches for monitoring lung fluid (57), or via multipoint testing throughout the race would be beneficial to provide a more accurate temporal assessment of alveolar–capillary function throughout and following ultramarathon competitions. Although the remote location of ultramarathons and the nature of "field testing" often necessitate the use of portable/point-of-care devices, the current study incorporated a dedicated laboratory setup in close proximity to the finish line to enable extensive physiological measurements. Nonetheless, athletes were required to travel a short distance for their post-race assessments. Accordingly, the execution of simulated, laboratory-based ultramarathon research, with more detailed temporal measures of physiological responses (e.g., inflammation, blood volume, and distribution, etc.), may be one way of deriving more mechanistic insights.

Interestingly, a subset of individuals tended to have more pronounced impairments in post-race DLco and Dm, including in one individual with overt signs of pulmonary edema following the UTMB, which has been presented in a case study

elsewhere (58). Further study is required to identify if individuals with more substantial changes in DLco, Dm, and comet tails represent a phenotype that is more predisposed to lung edema, similar to what has been observed with high-altitudepulmonary edema (17). Alternatively, historical training history and/or prior race experience may alter the pulmonary stress response associated with an ultramarathon. In this regard, it is currently unclear if pulmonary-specific physiological traits and/or adaptation over time predispose an individual to ultramarathon tolerance and success, and this warrants further study.

CONCLUSIONS

Participating in an ultramarathon competition induces a transient decrease in lung diffusing capacity that is predominantly driven by a reduction in pulmonary capillary blood volume and, to a lesser extent, reductions in alveolar–capillary membrane gas conductance. Although the reductions in lung diffusion and alveolar–capillary function seems transient and unlikely to pose an acute clinical concern, some individuals may be susceptible to a more severe impairment. Additional studies are required to determine if subsets of participants with a greater magnitude of impairment in lung diffusion and alveolar–capillary membrane gas conductance are at risk of developing pulmonary edema, and if adaptive remodeling of the alveolar–capillary membrane occurs with cumulative ultramarathon training and competition.

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The authors declare no conflict of interest. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

Data Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: G. M. S., B. D. J., and C. M. W. G. conceived and designed the study. All authors contributed to data collection and analysis. All authors reviewed and approved the final manuscript.

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