Research proposal on the pulmonary consequences of participating in the UTMB and Hong Kong 100 ultramarathons

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Background and rationale: At rest the pulmonary circulation is characterized by high flow rates and low pressures, such that pulmonary vascular resistance and right ventricular (RV) work remain low, and fluid is prevented from moving outside of the pulmonary vessels and into the interstitial space [1]. However, *high-intensity exercise increases pulmonary artery (>40-50mmHg) and capillary (>20-25mmHg) pressures* to levels that may 1) exceed the upper limits of tolerable RV afterload and 2) induce fluid shifts into the interstitial space [2]. In addition to high-intensity exercise and numerous pathologies, the natural ageing process and environmental conditions also alter pulmonary vascular-alveolar interactions, leading to blood flow and gas exchange limitations [3]. Pertinently, exposure to *high-altitude increases pulmonary vascular pressures* (via hypoxic pulmonary vasoconstriction), which if coupled with exercise (requiring increased ventilation and cardiac output), further augments high pressures and blood flows through a compliant and sensitive vascular bed. This may predispose the alveolar-capillary membrane to periods of excessive stress. Moreover, *airborne pollutants can negatively impact pulmonary vascular and alveolar function*, secondary to pollutant-induced break down the alveolar capillary membrane and inflammation [4]. Indeed, cases of asthma and bronchial infections in Hong Kong have soared in recent years due to reduced air quality [5, 6].

Accordingly, when exercise is combined with extreme environmental conditions, such as at altitude or with excessive air-borne pollutants, *competitive endurance events may provoke respiratory constraints and induce acute pulmonary maladaptation* such as altered fluid regulation, congestion, edema and bronchiolar hypersensitivity. Moreover, a high pulmonary vascular reserve and lung diffusing capacity has been associated with greater exercise capacity both and sea level and altitude, and thus may predict acute pulmonary and capillary responses to the augmented pressures and flow rates associated with ultra-endurance exercise at altitude and in congested cities [7, 8].

Current evaluations of pulmonary physiology before and after ultra-endurance exercise are limited. Therefore, we aim to comprehensively evaluate pulmonary vascular, capillary and alveolar function before and after completing an ultramarathon at high-altitude (UTMB) and in poor air quality (Hong Kong 100) using novel yet relatively simple non-invasive methods. Additionally, we aim to *establish if pre- and post-event pulsed electromagnetic field therapy (PEMF, which has been proposed to attenuate inflammatory stress responses [9, 10]) can reduce the incidence of respiratory inflammation and constraint* before and after an ultramarathon event in a congested city. We hope to pursue these studies over a 2 year period as a part of the ITRA and USS foundation medical research programs at the UTMB and Hong Kong 100 ultramarathons.

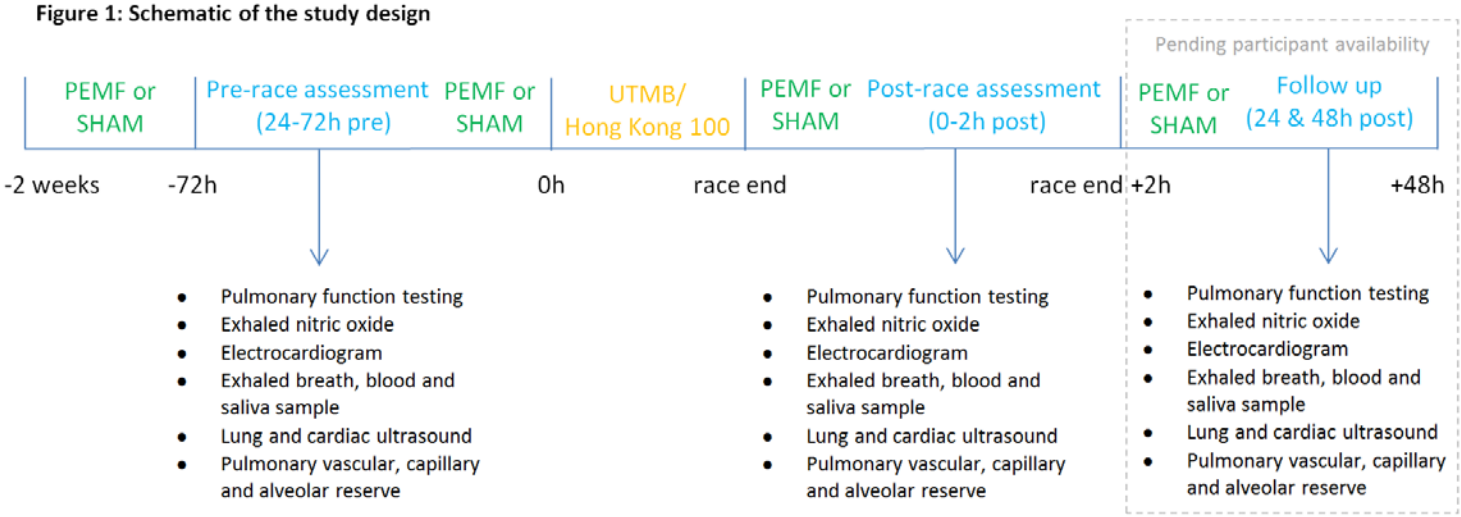
Aims: The study aims include:

1) Identify the pulmonary consequences of completing ultramarathons at altitude and in a city with poor air quality
2) Examine the relationship between pulmonary reserve and high-altitude endurance race success
3) Determine the influence of age and fitness on pulmonary responses to an ultramarathon
4) Determine the feasibility of PEMF therapy to attenuate exercise and environmental-induced inflammation

Methods: The study aims to recruit *80 athletes* participating in the UTMB and Hong Kong 100 ultramarathons *over 2 years*. Study participants will be recruited across a range of ages and fitness levels (20 younger elite; 20 younger amateurs; 20 veteran elite; 20 veteran amateurs). Participants will be recruited via advertisements on event websites and emails to registered participants, with the expectation of securing a subset of subjects who participate in both events (Hong Kong 100 is a qualifying event for UTMB). The proposed study will have been reviewed and approved by relevant intuitional review boards in accordance with the declaration of Helsinki.

Participants will undergo baseline evaluations within 24-72 hours of the race start, and post-race measurements within 2 hours of race completion, at a suitable venue (e.g., hotel and conference room) located near to the start/finish of the event. A subset of subjects (pending availability) will also be asked to partake in serial follow up measurements at 24 & 48 hours following the race. The testing protocol for before and after the race is provided in Figure 1 and measurements detailed below. Pre and post-race testing will take between 60-90 min. Subjects will be asked to undergo two weeks of PEMF therapy (50% of enrolled participants on sham & 50% on treatment) using a commercially available device (Bioboosti, Biomobie Regenerative Medicine, USA; FDA #3010626738) leading up to the UTMB and Hong Kong 100. All required equipment and expertise is available within the research team.

Figure 1: Schematic of the study design



- *Pulmonary function testing:* Spirometry tests will be performed to determine classical lung volumes and flow rates along with Forced Oscillation of airways to quantify airway resistance across large and smaller airways.
- *Exhaled nitric oxide:* Assess the viability of exhaled NO as a non-invasive index of pulmonary pressures and inflammation and observe changes induced by acute exercise and ultra-endurance exercise at high-altitude and in a congested city.
- *Electrocardiogram:* Determine heart rate and cardiac rhythm pre and post-race.
- *Biomarkers in exhaled breath, saliva and blood samples:* Determine fluid shifts, changes in inflammatory markers and breakdown of lung tissue (traces of blood, enzymes and proteins in saliva).
- *Lung ultrasound:* Assess lung edema (comet tails) pre and post-race.
- *Assessment of pulmonary vascular, capillary and alveolar reserve*: Examined during semi-recumbent cycling via echocardiographic assessment of pulmonary pressures (Philips CX50) and gas exchange assessment of alveolar gas diffusion and capillary blood flow (MGC Diagnostics; Medisoft).
- *Pulsed Electromagnetic Field Therapy:* A commercially available Bioboosti™ hand held PEMF and SHAM device (50% of subjects in each group) will be used for two weeks leading up to the event, and immediately prior to and following the event.

Funding: The study will be predominately supported by Mayo Clinic, with additional support being sought from industry partners. Additionally, partnership with the Ultra Sports Science Foundation is being sought.

Outcomes: Anticipated outcomes of the study include:

- *Publications:* The research outcomes will be presented at international conferences and published in high-ranking peer-reviewed journals.
- *Recommendations for runners:* The study outcomes will help aid pre-participation preparation for athletes participating in events held at altitude and in congested cities, and help inform coaches and athletes on suitable training and acclimation techniques. In particular, the health effects of exercising in congested air are currently inconclusive and of a major concern for governing bodies who oversee ultra-endurance events in major cities.

- *Identify an 'athletes lungs':* The study aims to identify if phenotyping of the pulmonary vasculature and lungs is evident in subpopulations of endurance athletes (elite and amateurs; young and old).
- *Lay the foundation for future studies:* The influence of the pulmonary vasculature and alveolar function on exercise capacity in hypoxic conditions (such as altitude and with numerous chronic diseases) is currently a topic of contention. This study continues on from previous studies undertaken by Mayo Clinic researchers both in laboratory and field environments (Everest, Kilimanjaro etc), and will lay the foundation for future studies combining high-altitude and extreme exercise in various environments (such as in congested cities).
- *Exposure and support for the* Ultra Sports Science Foundation: The study will provide exposure for the supporting companies and the Ultra Sports Science Foundation and help enhance the health and safely of participating in ultra-endurance sports.

Timeline:

	Jun 2017 – Jan 2018	Jan 2018 (Hong Kong)	Aug 2018 (UTMB)	Jan 2019 (Hong Kong)	Aug 2019 (UTMB)	Jan 2020
Optimize protocols, submit ethics, finalize sponsorship						
Subject recruitment						
Data collection 1						
Data collection 2						
Data collection 3						
Data collection 4						
Present preliminary findings at conferences, magazines, press releases						
Publish final results in Journal articles, press releases and magazines						

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