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## Comments on Point:Counterpoint: Pulmonary edema does/does not occur in human athletes performing heavy sea-level exercise

### MILD INTERSTITIAL PULMONARY EDEMA OCCURS DURING SEA LEVEL STRENUOUS EXERCISE

TO THE EDITOR: We read with interest the Point:Counterpoint opinion piece titled “Pulmonary edema does/does not occur in human athletes performing heavy sea-level exercise” (3).

We do not think there is much debate to this opinion piece. Several studies using healthy human subjects (2, 4, 5, 7) demonstrate evidence of pulmonary edema from sea-level exercise. In a recent review (6), 51 of 78 subjects (65%) demonstrated mild, interstitial pulmonary edema from maximum effort exercise. In fact, the likelihood of developing mild, interstitial edema from maximum effort exercise was four times more compared with submaximal, prolonged exercise not of maximum effort (6). Also, independent of whether exercise was performed in normoxic or mildly hypoxic environments, the percentage of subjects developing edema were nearly the same (62–69%) (6).

The timing of the postexercise imaging does not influence the determination of pulmonary edema (6). This argues convincingly that the diagnosis of edema assessed within the first 10 min postexercise (1) or between 60 and 120 min postexercise (1, 2, 5) reflects true pulmonary edema. Furthermore, irrespective of whether chest radiographs or CT/MRI imaging was used to detect pulmonary edema, these modalities were equally sensitive for detection of edema (6).

The real question is not whether mild interstitial pulmonary edema is triggered from heavy exercise but whether this edema is meaningful. So far the limited data suggest that arterial-blood gases are not related to mild interstitial pulmonary edema (8); however, it is unclear what effect, if any, it may have on endurance exercise performance.

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### INTEREST OF CHEST ULTRASONOGRAPHY IN THE DETECTION OF EXERCISE-INDUCED PULMONARY EDEMA

TO THE EDITOR: We agree with Dr. Hopkins (4); several studies have demonstrated that pulmonary edema can be induced by exercise performed at sea level in healthy subjects (6).

Consequently, the real questions are: why do some athletes develop pulmonary edema during exercise? What influence does pulmonary edema have on health and sport performance? To document the extravasation of fluid, authors have used various imaging techniques such as radiography, computed tomography (CT), or magnetic resonance imaging.

In further studies, an alternative and interesting method might be ultrasonography. In clinical practice, ultrasonography has many advantages over other techniques such as the absence of ionizing radiation and the possibility of use at the patient's bedside. Ultrasonography can visualize alveolo-interstitial syndrome using specific images called “Ultrasound lung comets” (ULC). ULC are signs of extravascular lung water that originate from water-thickened interlobular septa. A correlation between ultrasound lung comet score and interstitial edema has been documented by CT scanning (5) and measurements of extravascular lung water (1). Chest ultrasonography was initially used in critically ill patients, and it has recently been used to detect an increase in extravascular lung water in subjects exposed to environmental stressors that could promote pulmonary edema (2, 3). In these circumstances, hand-held ultrasound units are particularly interesting.

Consequently, chest ultrasonography might provide an interesting method for identifying stressors contributing to minor pulmonary edema during exercise. It might also help identify susceptible individuals.

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#### EDEMA IN ATHLETES VS. INTERSTITIAL EDEMA IN ANYONE

TO THE EDITOR: Where does interstitial edema leave off and frank alveolar edema begin? Not with the radiographic or CT finding. Consider the histology of the structures that develop interstitial edema. The surrounding fluid is a microscopic layer, and consequently invisible radiologically. In other words, when a confident diagnosis of interstitial edema can be made radiologically, there is already a layer of edema in the neighboring alveoli, i.e., pulmonary edema. Kerley lines represent early alveolar edema.

Interstitial edema is probably very frequent, with stress that falls short of capillary damage and red cell leakage. In fact, any time the left atrial pressure is raised substantially, there is likely to be interstitial edema, simply by application of Starling's law. This probably explains the V/Q changes that occur with exercise.

What happens to interstitial edema should be considered when one talks about seasoned athletes. It is recognized that lymphatic drainage of edema in patients with chronically elevated left atrial pressure is greatly increased compared with normal. An increase in fluid that would cause pulmonary edema in a normal individual would be simply drained away in someone with chronic hypertrophied lymphatic drainage. I believe that athletes have similar hypertrophy, due to recurrent episodes of interstitial edema in training. Therefore, they are much less likely to progress to clinical alveolar edema when stressed maximally than would a novice.

What's the argument (1)? Of course athletes develop interstitial edema, and under extreme conditions, may develop alveolar edema. You and I would develop edema much sooner, speaking physiologically!

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#### PULMONARY EDEMA DURING BREATH-HOLD DIVING IMMERSION

TO THE EDITOR: It has been demonstrated several years ago that the strength of the alveolar-capillary membrane is high and that the stress failure of the wall may occur when the pulmonary capillary pressure is raised to abnormal levels as it may happen during heavy exercise (6). If this stimulus is associated with changes on thoracic geometry and modifications of lung gas volume, the final result is the increase in the transpulmonary pressure, which acts on the alveolar-capillary wall with the

consequence of pulmonary edema (2). Anyway there is no common consensus on these issues (1, 5). One model accounting entirely for this scenario is breath-hold diving. During breath-hold immersion it is common to have decrease in thoracic elasticity, increase in the airway resistance, severe reduction of inspired gas volume to the value of residual volume, increase in the pulmonary capillary pressure due to increase in pulmonary capillary blood volume. All these factors contribute to mechanically stimulate the alveolar-capillary barrier to its progressive weakness to the breaking point with the dramatic consequences of shortness of breath, cough productive of blood tinged and/or pink frothy sputum, crepitations on auscultation, and chest radiograph findings of pulmonary edema (3, 4). A recent observation study on pulmonary diffusion capacity following sea diving up to 30-m depths got results compatible with the occurrence of pulmonary injury in 16% of our breath-hold diver population. This proportion could be even higher if one considers that the increase in pulmonary capillary blood volume, consistently observed early in the post-diving period, can mask short-lived alterations at the level of the alveolar-endothelial membrane (4).

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#### PULMONARY EDEMA IN ATHLETES: METHODOLOGY OR MEANINGFUL PHYSIOLOGY?

TO THE EDITOR: There is little debate that exercise is capable of causing pulmonary edema in some athletes as highlighted by Dr. Hopkins (4). What can be debated, however, is whether pulmonary edema is common in athletes. Most of the well-conducted studies using objective imaging techniques would suggest that it isn't (2, 3, 5, 6). Is it possible that these "negative" studies are due to methodological problems as argued by Dr. Hopkins or are these studies truly reflecting meaningful physiological responses to exercise? We believe the latter is true. Some will argue that the delay in acquiring the post-exercise scans remains the single biggest methodological concern regarding these imaging studies. On the one hand, an appropriate delay is necessary so that exercise-induced increases in pulmonary blood flow are not mistakenly interpreted as edema. On the other hand, a delay may permit enough time for any edema formation to subside through various clearance

mechanisms. Despite this limitation, some studies have demonstrated that edema can persist >1.5 h postexercise in humans (1). Therefore, we would argue that if the edema in these imaging studies were of any meaningful physiological significance, then the imaging techniques (i.e., CT and MRI) would have been able to detect it. In our opinion, we can draw two equally plausible conclusions from these “negative” imaging studies: 1) pulmonary edema does not occur or 2) any edema that did occur but was not detected is probably so minor that it is of little physiological relevance to the athlete.

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## EXERCISE-INDUCED PULMONARY EDEMA IN THE ATHLETE, OR COUCH POTATO?

TO THE EDITOR: The authors (1) discuss evidence for/against exercise-induced pulmonary edema in “human athletes.” As noted by Hopkins (1), pulmonary artery wedge pressure (PAWP; said to reflect mean left-atrial pressure and pulmonary venous pressure) increases with exercise. Reeves and Taylor (3) have shown that 80% of the variance in pulmonary artery pressure (PAP) during exercise is explained by PAWP. In other words, the higher the PAWP, the higher the PAP (and the more likely to develop pulmonary edema). If we assume that, unlike the heart, there is no pulmonary vascular adaptation to chronic exercise, pulmonary vascular resistance would be similar between untrained individuals and athletes, and therefore athletes must have a higher pulmonary driving pressure (PAP – PAWP) because of their higher cardiac output at maximal exercise. Many have assumed that the increased driving pressure is accomplished in the athlete by having a higher PAP (and therefore more likely to develop edema). However, with exercise training the left ventricle becomes more compliant (2), allowing the athlete to have a lower cardiac filling pressure (i.e., PAWP) at a given stroke volume. Exercise hemodynamic data supports this (4), and it appears that athletes accomplish the increased driving pressure during maximal exercise not by an exaggerated PAP, but rather by having better diastolic function and, as a consequence, a lower PAWP at peak exercise. As researchers continue to examine “physiologically significant” exercise-induced pulmonary edema, they may con-

sider investigating groups that would have the greatest PAWP (and PAP) response to exercise, such as the couch potato, or worse, the heart failure patient.

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## PULMONARY EDEMA FOLLOWING EXERCISE: AN INDIVIDUAL RESPONSE?

TO THE EDITOR: The evidence cited by both parties appears undeniable in support of their respective positions (2, 6). That pulmonary edema has not occurred in controlled experiments is undeniable (1), but equally undeniable is that it has been observed following strenuous exercise (3–5). It appears that many of the cases of transient edema involve small numbers of individuals rather than all subjects involved in a controlled exercise intervention. The case of ultra marathon runners (4) involved only two individuals; the case of a cyclist (3) involved only one individual (albeit not at sea level); and the positive findings of McKenzie's previous work (5) were driven largely by two subjects. Therefore, neither position is supported when all the evidence is considered. Should we not be careful to examine all the evidence and let it lead us to the conclusion rather than draw our conclusions and then pick the evidence to support it? In this light, a potential conclusion supported by all the evidence is that transient edema during exercise is an individual response that occurs only in relatively few individuals. This possibility merits further investigation.

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#### THE EXERCISE-INDUCED PULMONARY EDEMA STORY DOESN'T HOLD WATER

TO THE EDITOR: There is no direct evidence that pulmonary edema occurs during exercise in healthy humans as pointed out by Drs. Sheel and McKenzie (2). Dr. Hopkins (2) did an excellent job identifying the exceptions when humans develop pulmonary edema postexercise. Hopkins (2) proposes that the cause of the edema is high pulmonary pressures. If high pulmonary pressures were the primary cause of pulmonary edema, then most humans of average fitness would get pulmonary edema as Stickland et al. (5) demonstrated that the least fit individuals have the highest pressures. Thus a more likely cause of edema would be an increase in capillary permeability that is independent of high vascular pressures. Pfeil et al. (3) demonstrated that a 10 cmH<sub>2</sub>O increase in left atrial pressure resulted in a fivefold increase in the capillary filtration coefficient in normoxia using an isolated, ventilated and perfused murine lung. However, stabilization of pulmonary microvascular permeability with the application of exogenous intermedin/adrenomedullin-2, which is expressed by pulmonary endothelial cells and binds to the calcitonin receptor-like receptor (1, 4), prevented an increase in the capillary filtration coefficient that would be expected with increased left atrial pressure (3). These data demonstrate that intrinsic microvascular permeability may be most important in edema development. Thus the few subjects who do develop pulmonary edema with exercise may have altered stability of their pulmonary microvascular permeability. Future studies that make direct measurements of edema during exercise and investigate alternative mechanisms of pulmonary edema will likely reveal why a few individuals develop pulmonary edema postexercise, but most do not.

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#### INTERSTITIAL EDEMA DOES OCCUR WITH LIMITED ADVERSE EFFECT IN THE LONG TERM

TO THE EDITOR: There is little doubt that interstitial pulmonary edema occurs in some athletes during strenuous exercise (3). Several studies reported the occurrence of radiographic or CT scan evidence of interstitial pulmonary edema following strenuous exercise both at sea level and high altitude (1, 2). It is also true that only a very small number will experience severe alveolar flooding. The questions that need to be asked are why some athletes do not show any interstitial edema, whether it is frequent in a given individual and whether it has any long-term effect.

Interstitial edema is identified by various techniques in 65% of athletes when exercise is both exhaustive and at maximal effort (5). This is more likely to occur during races when the motivation to perform is high and exercise duration longer. However there is still a significant proportion of athletes without sign of interstitial edema and it is likely that anatomical characteristics such as lung or left ventricular size play a role. In addition, if interstitial edema results from a mismatch between fluid extravasation and lymphatic drainage (3), it is expected to happen frequently in a given individual, probably without any significant adverse effect in the long term. Indeed studies conducted in master athletes who have been cycling for more than 30 yr, a significant proportion of them probably having experienced recurrent pulmonary interstitial edema, did not show any pulmonary function abnormality (4). This suggests that there is probably minor adverse effect of interstitial pulmonary edema.

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#### EXERCISE-INDUCED PULMONARY EDEMA—THE DEBATE CONTINUES

TO THE EDITOR: The issue as to whether interstitial and/or alveolar pulmonary edema develops with heavy normoxic exercise is an interesting and long-standing physiological question that remains unanswered. Despite the application of mul-

tiple novel and promising imaging modalities, none have definitively proven exercise-induced pulmonary edema. Hopkins (2) cites various case reports of postexercise pulmonary edema as evidence. However, Sheel and McKenzie (6) correctly point out that these cases represent unique isolated situations where the primary edema factor is likely some underlying pathology and not the exercise per se. Newman et al. (4) showed in sheep that lung lymphatic flow dramatically and progressively increases with exercise, which strongly suggests an increase in microvascular filtration. However, this is not direct evidence for interstitial or alveolar fluid accumulation. Indeed, multiple edema safety factors are in play, including an increase in the protein osmotic pressure gradient, a fall in postmicrovascular resistance, and augmented lymphatic drainage (5). Possibly the best evidence for exercise-induced alveolar edema are the bronchoalveolar lavage studies of Hopkins et al. (3) and Eldridge et al. (1), which clearly show red blood cell and protein accumulation in the alveolar space in elite athletes following heavy sea-level exercise. However, as noted by Sheel and McKenzie (6), these invasive studies in a select subject population have limitations and may not reflect the physiology of the general population. Indeed, if exercise-induced pulmonary edema does occur, it is likely non-homogeneously distributed, small, and ever changing. The final

answer awaits a clever, direct measurement method. Until then the debate continues.

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