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REVIEW

Subclinical pulmonary edema in endurance athletes

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ABSTRACT: ***Subclinical pulmonary edema in endurance athletes. M. Bussotti, S. Di Marco, G. Marchese, P.G. Agostoni.***

Strenuous exercise may cause progressive and proportional haemodynamic overload damage to the alveolar membrane, even in athletes. Despite the high incidence of arterial desaturation reported in endurance athletes has been attributed, into other factors, also to the damage of the alveolar-capillary membrane this evidence is equivocal. Some studies demonstrated flood of the interstitial space and consequent increase in pulmonary water content, but most of them were able to show this through indirect signs of interstitial oedema.

The present review illustrates the literature's data in favour or against pulmonary interstitial edema due to intense exercise in athletes.

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Clinical Background

The first report of alteration of vital capacity after intense physical effort dates back to 1923, following the Boston Marathon. Since then, several reports have described the presence of alterations in pulmonary mechanics and gas exchange process in athletes.

Description of hemoptysis in a soccer player [1] and pulmonary edema after a marathon [2, 3] have demonstrated that, at least occasionally, edema may occur in the athletes.

Furthermore the incidence of pulmonary edema even in apparently healthy people during efforts such as sexual intercourse, emotional stress, or exertion in a cold environment [4] was described in later reports.

Since the 1980s, many studies have also proved the elevated incidence of arterial hypoxemia occurring in the advanced phases of an intense exercise and very often persisting in the first phases of the recovery.

Dempsey and Wagner described the manifold causes at the origin of exercise-induced hypoxemia (table 1) [5]. Among this long list of causes, some authors have mostly focused their own attention on the fatigue of respiratory muscles [6, 7], and some others on the formation of interstitial edema as the main causes of the alterations of pulmonary mechanics and the kinetics of gas exchanges [8-13].

Considerable evidence both in favour and against the formation of pulmonary edema after exercise has been proposed.

This has been at the core of an intriguing debate within the scientific community over the last decade that still continues today.

The aim of this work is to review the literature about this multifaceted topic through an updated exposition of the currently recognized physiopathological mechanisms involved in the formation of interstitial edema.

Data in favour of the hypothesis of an exercise-induced interstitial edema

Some studies focused their attention on ventilation-perfusion (VA/Q) inequality as it has been shown to increase with exercise in many people. As a matter of fact interstitial oedema occurring during exercise will affect the VA/Q ratio due to the consequent compression of small airways and blood vessels.

Using a multiple inert gas technique (MIGET) for measuring VA/Q inequality in healthy subjects during and after hypoxic exercise (p_iO_2 = 91 mmHg) Schaffartzik found persistent changes in ventilation-perfusion inequality up to 30 min into recovery [14], and considered them consistent with the formation of pulmonary edema. Moreover two patterns of VA/Q distribution were recorded during heavy exercise: group 1 with an increase in log standard deviation Q (logSDQ) as index of VA/Q mismatch deterioration (0.35 ± 0.02 at rest and 0.44 ± 0.02 at exercise; $p > 0.05$), and group 2 with no change in VA/Q mismatch. Subjects in the Group 1 were characterised not only by a significantly greater VA/Q inequality, but also by a

Table 1. - Causes of exercise-induced arterial hypoxemia

- An excessive alveolar-to-arterial PO_2 difference (> 25-30 Torr)
  - I. Ventilation-Perfusion inequality (↑ during exercise)
    - a) bronchoconstriction
    - b) transient formation of pulmonary interstitial edema
  - II. Failure of alveolar-end capillary diffusion equilibration
  - III. Right-to-left shunt
  - IV. ↓ PO_2 in mixed venous blood
- Inadequate compensatory hyperventilation (arterial PCO_2 > 35 Torr)
  - I. Mechanical constraint (airways show un upper limit to flow rate)
  - II. Increased receptor sensitivity to the inhibitory feedback influences from mechanoreceptors
  - III. Blunted chemoreceptor response

greater cardiac index both during exercise and recovery. This last observation strengthened the hypothesis that a greater blood flow and, presumably therefore, higher pulmonary vascular pressures in the subjects of group 1 can contribute to edema formation and to increase in VA/Q inequality during exercise.

An increasing edema score in subjects after maximal exercise has been highlighted in radiological studies.

Zavorsky *et al*. after an intense interval training session observed a deterioration of the typical radiographic signs of edema; the overall edema score increased from 1.3 ± 1.6 before exercise to 1.9 ± 2.0 after exercise ($p < 0.05$; $\Delta = +0.7 \pm 1.8$, 95% CI = 0.2 to +1.1) [15].

Caillaud proved accumulation of water within the lungs after exercise through computerized tomography scan (CT) [16]. The authors examined CTs of the thorax in pair with DLCO in eight male athletes before and after a triathlon race. DLCO and alveolar volume (VA) were simultaneously measured during 9 seconds of breath holding and the transfer coefficient (KCO = DLCO/VA) was then calculated. CT scanning was performed during breath holding on the athletes lying in a supine position. Scanner analysis was featured by 1) counting linear and polygonal opacities (index of interstitial fluid accumulation) and 2) calculating physical mean lung density and mean slice mass. Results evidenced a significant reduction in DLCO (44.9 ± 2.3 vs. 42.9 ± 1.7 $ml.min^{-1}.mmHg^{-1}$; $p < 0.05$) and KCO (6.0 ± 0.3 vs. 5.6 ± 0.3 $ml.min^{-1}.mmHg^{-1}.l$ of VA^{-1}; $p < 0.05$) associated with an increase in mean lung density (0.21 ± 0.009 vs. 0.25 ± 0.01 g/cm^3; $p < 0.0001$). The number of polygonal and linear opacities increased after the race ($p < 0.001$). This study confirmed that DLCO and KCO decrease in elite athletes after a long-distance race recognises a pathological substrate represented by the concomitant increase in lung density and in the number of opacities at CT scan.

Further studies confirmed a decline of the diffusive properties of membranes at the end of an intense physical exercise.

Measuring DLCO and its subcomponents, together with thorax magnetic resonance scan, McKenzie demonstrated a decrease of 12% (p = 0.004) in DLCO and 21% (p = 0.017) in pulmonary capillary blood volume (Vc) 1h after 45-min cycle test exercise, without significant changes in membrane's diffusing capacity (DM) (fig. 1A) [17]. At the same way the magnetic resonance scans confirmed a 9.4% increase (p = 0.043) in pulmonary extravascular water 90 min after exercise (fig. 1B).

In another study, Miles described a significant decrease in DLCO, and DM but an increase in closing volume after a marathon while Vc remained similar to pre-race values [18]. The significant increase in alveolar-capillary membrane resistance implied the occurrence of subclinical edema that could decrease lung elastic recoil and explain the increase in closing volume.

The time course of changes in post-exercise DLCO, DM and Vc in highly trained (HT), moderately trained (MT), and untrained (UT) male subjects (n = 8/group) was furtherly investigated in

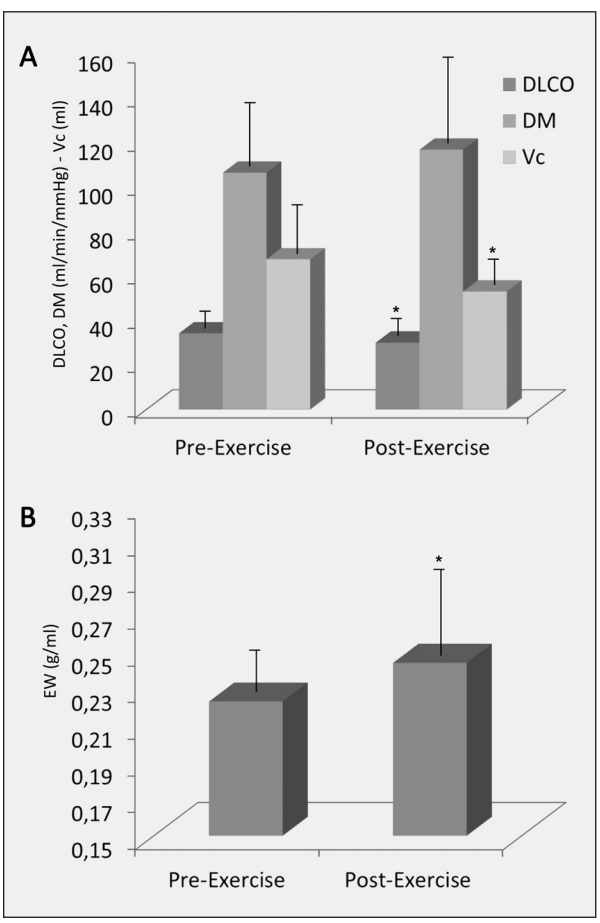

Fig. 1. - The effect of sustained heavy exercise on carbon monoxide lung diffusion and pulmonary extravascular water in trained cyclists. **A** DLCO = Lung diffusion of carbon monoxide breathing 21% oxygen; DM = membrane diffusion; Vc = capillary volume. Data are means ± SD. * = significant difference from pre (p < 0.01); B EW = extra-vascular lung water measured by magnetic resonance before and after 45 min of sustained cycling. * = Significant difference from pre (p = 0.043) (modified from McKenzie DC *et al*. [17]).

another study by McKenzie. Subjects were assigned to three groups based on their aerobic capacity from a preliminary VO_{2max} test (HT $VO_2 \geq 65$, MT $VO_2 = 50\text{-}60$, UT $VO_2 \leq 50$ ml·kg^{-1}·min^{-1}). Resting DLCO, DM and Vc^C were obtained, then subjects cycled to fatigue at the highest work rate obtained during the preliminary tests. Diffusion measurements were then achieved at 1, 2, 4, 6 and 24 h after exercise: DLCO values were reduced at 1 h, even lower at 6 h, and at the end approached baseline values at 24 h in all groups. The DLCO change was paralleled by a change in Vc. Alterations to Vc were similar among the groups, except at 24 h, when MT and HT subjects had returned to baseline values, while UT subjects had not. DM was significantly lower than baseline at 1, 2, 4, and 6 hours, and it was similar among the groups. In conclusion the changes in DLCO after exercise appear to be due to a decrease both in Dm and in Vc. Comparable diffusion reduction was observed in all subjects, suggesting that post-exercise alterations in DLCO, DM, and Vc are not related to aerobic capacity (fig. 2) [19]. Other studies focused their attention on the signs of possible damage of the alveolar-capillary barrier.

The importance of the mechanical disruption of the blood-gas barrier in lungs was suggested by Hopkins *et al*. who used bronchoalveolar lavage (BAL) techniques in elite athletes after an intense exercise protocol. They found that intense exercise resulted in higher concentration of proteins, leukotriene B4 and red blood cells in the bronchoalveolar lavage fluid. These changes occurred in the absence of higher concentrations of inflammatory markers (other than LTB4) in the BAL fluid, so these findings were considered by the authors as consistent with an effect of mechanical stress on the integrity of the blood-gas barrier [20]. The same results were not confirmed using a submaximal exercise protocol [21].

As a consequence of the alveolo-capillary barrier damage caused by an increased capillary pressure induced by exercise, surfactant protein-B (SP-B) can leak into the blood stream from the alveoli. In this way, some authors tried to demonstrate an increase of circulating surfactant protein-B levels during exercise even in normal people, as it has been previously proved in subjects affected by heart failure [22] or in healthy subjects after a high altitude sojourn (unpublished data of our group).

De Pasquale failed to demonstrate the same results in healthy subjects with a normal echocardiographic pattern during a maximal effort, but these subjects were too aged (58 ± 3 years) and not fit [23]. There are no further studies that have investigated the presence of alveolo-capillary damage due to particularly intense exercise in athletes population.

In another study, Doyle tested the hypothesis that the composition of alveolar surfactant may be influenced by the pattern of breathing and level of fitness. Three major components of surfactant were sampled by the authors: surfactant protein A (SP-A), desaturated phospholipids (DSP), and cholesterol (CHOL) in BAL fluid from 12 healthy men before and after exercise; they found that the composition of surfactant can change rapidly with exercise [24].

Strenuous exercise may also be a significantly contributing factor for the development of high-altitude pulmonary edema, particularly at low or moderate altitudes.

Eldridge investigated the effects of heavy cycle ergometer exercise (90% maximal effort) under hypoxic conditions. They studied the combined effects of a definite increase in pulmonary blood flow and a non-uniform hypoxic pulmonary vasoconstriction as main elements of the augmented mechanical stress on pulmonary microcirculation [25]. The authors postulated that intense exercise at altitude would result in an increased permeability edema. They recruited eight endurance athletes and examined their BAL fluid for red blood cells (RBCs), protein, inflammatory cells, and soluble mediators, at 2 and 26 h after intense exercise under normoxic and hypoxic conditions. After heavy exercise, under all conditions, the athletes developed a permeability edema with high BAL RBCs and protein concentrations in the absence of inflammation. Exercise at altitude (3.810 m) caused a significantly greater leakage of RBCs (9.2 ± 3.1 x 10^4 cells/ml) into the alveolar space than in normoxic exercise (5.4 ± 1.2 x 10^4 cells/ml) (fig. 3). At altitude, the 26-h post-exercise BAL fluid revealed significantly higher RBCs and protein concentrations, suggesting an ongoing capillary leak. Interestingly, the BAL fluid profiles following exercise at altitude were similar to those of early high-altitude pulmonary edema. The authors concluded suggesting that pulmonary capillary disruption occurs with intense exercise in healthy humans, and that hypoxia raises mechanical stresses on pulmonary microcirculation.

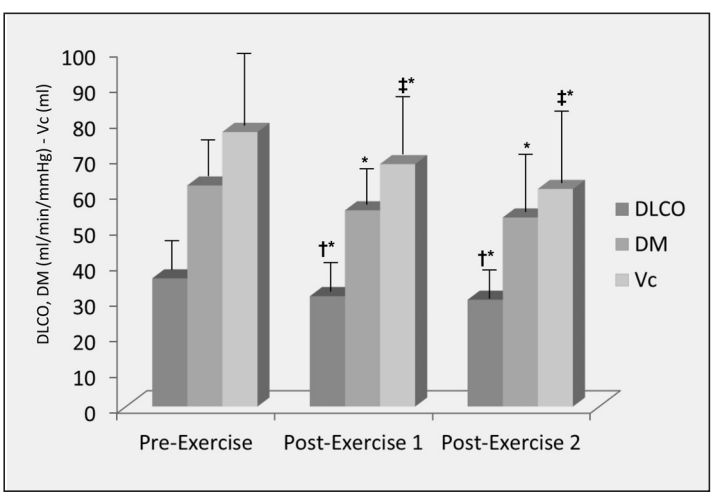

Fig. 2. - Changes in pulmonary diffusing capacity pre- and post-exercise in trained athletes. Black bars, pulmonary diffusing capacity (DLCO); dark grey bars, membrane diffusing capacity (DM); light grey bars, pulmonary capillary volume (Vc). Data are means ± SD. * = significant difference between post-exercise and pre-exercise; † = significant difference between post-exercise 2 and post-exercise 1 ($p < 0.05$) (modified from McKenzie DC *et al*. [19]).

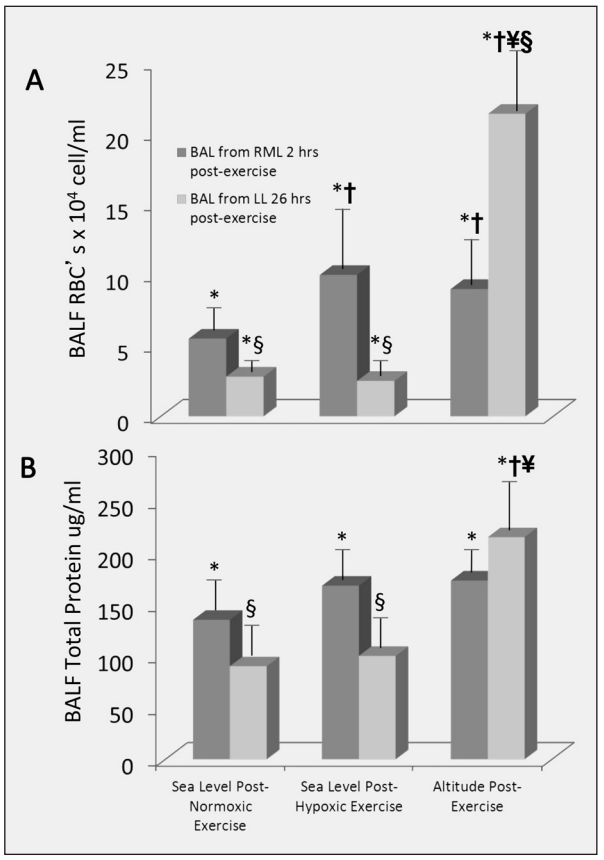

Fig. 3. - Changes in red blood cell (A) and total protein (B) concentration in the bronchoalveolar lavage fluid post-exercise in athletes at sea level and altitude.
RBC = red blood cell concentration; BALF = bronchoalveolar lavage fluid; RML = right middle lobe, where BAL was performed 2 hours post-exercise (dark grey bars); LL = left lingual, where BAL was performed 26 hours post-exercise. * = different from athletes' non exercising sea level value; § = different from 2 h post-exercise; † = different from sea-level post-normoxic exercise; ¥ = different from sea level post-hypoxic exercise (modified from Eldridge MW *et al*. [25]).

Finally, we must remember that in recent years chest sonography has been established as a new method of estimating extravascular lung water, through the recognition of lung comet-tail (ULC) artifacts. Pingitore and coll. studied 31 ironmen after a race at sea level [26]. None of the athletes was symptomatic for clinical signs of pulmonary edema. Immediately after the race, a score of more than five comet tail artifacts, the threshold for a significant detection, was present in 23 athletes (74%; 16.3 ± 11.2; $P < 0.01$ ULC after the race vs. rest) but decreased 12 hours after the end of the race (13 athletes; 42%; 6.3 ± 8.0; $P < 0.01$ vs. soon after the race). Multiple factor analysis showed significant correlations between ULCs and cardiac-related variables and NH(2)-terminal probrain natriuretic peptide.

Data against the hypothesis of an exercise-induced interstitial edema

Other investigators, however, reported evidence against the formation of pulmonary edema after exercise.

The post-exercise decrease in DLCO is suggested to exclusively depend on the observed changes in cardiac output [18, 27]. Likewise, Hanel inferred that pulmonary edema did not have any detrimental role in changes of DLCO after exercise being instead the alteration in central blood volume the relevant factor [28, 29].

Literature is rich in studies based on imaging techniques, but with such a large variability of methods which is responsible for so different results.

Radiographic evidence of pulmonary edema after a short-duration maximal exercise bout was excluded by Gallagher *et al*. [30]; similarly Brasileiro, at a high-resolution CT scan evaluation, confirmed the absence of interstitial pulmonary edema after maximal exercise in normal subjects, differently from what occurs in NYHA Class II and III patients [31].

In order to evaluate the presence of pulmonary oedema CT thorax scanning was performed by Manier on nine trained runners who ran for 2 h on a treadmill at a rate corresponding to 75% of VO_{2max}. CT measurements were made before and immediately after the exercise test, the subject lying supine, but not significant change in post-exercise lung mass was demonstrated in this study [32].

Hodges used magnetic resonance imaging (MRI) to examine the effects of exercise on extravascular lung water [33]; in this study, 10 male subjects underwent maximal exercise consisting in 60 min of cycling both in normoxic (N) and hypoxic (H, F_iO_2 = 15%) conditions. Lung density was measured by quantified MRI before, 50 and 100 min following 60 min of cycling exercise in N (intensity = 61.6 ± 9.5% of VO_{2max}) and in H (intensity = 65.4 ± 7.1% of hypoxic VO_{2max}). Nine subjects demonstrated mild or moderate exercise-induced arterial hypoxemia. Mean lung densities, measured once before and twice after exercise, were 0.177 ± 0.019, 0.181 ± 0.019, and 0.173 ± 0.019 g/ml (N) and 0.178 ± 0.021, 0.174 ± 0.022, and 0.176 ± 0.019 g/ml (H), respectively, without significant differences between before and after exercise in either condition, nor between conditions. In conclusion, the study failed to detect any evidence of pulmonary edema following exercise.

Physiopathology of exercise-induced edema

Provided that interstitial pulmonary edema can also occur after exercise in healthy subjects, we consider relevant to mention the possible hypotheses about its formation: the capillary hypothesis and the post-capillary hypothesis.

Capillary hypothesis

Exercise-induced pulmonary edema is known to occur in some animals, such as horses [34], greyhound dogs [35], and pigs [36]; in the same animals also pulmonary hemorrhage after strenuous exertion is not so uncommon.

It has been postulated that the first step taken in this series of events is an excessive increase in blood flow through the pulmonary capillary bed. When complete recruitment of capillary bed is achieved, the pressure in pre-capillary vessels rises, causing fluid transudation. An excessive and

sudden increase of blood flow in pulmonary circulation determines an overload of volume, that overcomes the maximal recruitment capabilities of the capillary bed.

Edema represents the effect of a very high cardiac output, with increased recruitment of capillaries causing an increased capillary surface area for filtration and, therefore, an increase in extravascular lung water, beyond the re-absorption capacity of lungs.

This blood volume overload is associated with a blood pressure overload, which depends on the increased flow, the exhaustion of vasodilatory reserve, and an increase of the filling pressures of the left cardiac chambers, due to excessive blood return through pulmonary veins. The latter causes an increase of the pressures of the post-capillary pulmonary circuit.

Moreover, it has been suggested that the alveolar-capillary membrane is damaged under extreme conditions, such as during an exercise that triggers an important increase in cardiac output or if performed in hypoxic conditions.

Regardless of the underlying causes, the final result is an excessive wall stress, that translates into a failure of the normal properties of the alveolar-capillary membrane.

This means that we can observe an overt alveolar flooding and collapse due to the initial extravasations of fluid into the interstitial space surrounding the conducting vessels and airways.

Contrary to sheep, where data exist supporting the idea of an increase of lung lymphatic flow after the onset of exercise [37], there are no data in humans regarding the possible involvement of a lymphatic drainage as a defense mechanism against the formation of interstitial or overt alveolar edema.

As suggested by several authors [38, 39] and demonstrated in heart failure patients by our group [40], pulmonary edema is not an homogeneous phenomenon in the lungs. Poliedric shape of alveola and presence of surfactant are the main defense mechanisms against edema. Until the alveolar unit shape is kept with its many corners, the extravasated fluid is drained into the corners, maintaining alveolar walls free and disposable for gas exchange. But when the overload of fluid is excessive, the membrane of surfactant is damaged, parietal tension becomes excessive, and the alveolar unit loses its shape: at this moment, an alveolar flooding occurs (fig. 4).

There is no reason not to support this physiopathological mechanism also in the development of edema in healthy subjects.

The effects of high pulmonary vascular blood flow together with an hypoxic vasoconstriction on lung fluid filtration were described by Younes and Bshouty. At high flow rates, such as could be seen during exercise, lung weight progressively increased, even with a normal left atrial pressure. These results suggest that high cardiac output, when accompanied by hypoxic vasoconstriction as used in this model, results in the formation of edema [41].

The clinic of High Altitude Pulmonary Edema (HAPE) can help us understand this model, in which high flow and hypoxic vasoconstriction are involved [42].

Two fundamental mechanisms determine HAPE: the quantity of liquid escaping from the pulmonary vasculature and the rate of its clearance by the alveolar respiratory epithelium. The former is directly related to the degree of hypoxia-induced pulmonary hypertension, whereas the latter is determined by the alveolar epithelial sodium transport. HAPE seems therefore to have the same mechanism as the high-pressure (''stress failure'') edema [43], as mentioned before in racehorses [34], greyhounds [35], or pigs [36] after strenuous exercise.

HAPE usually produces regional non-gravitationally distributed edema, often described as patchy radiographic opacifications.

HAPE is believed to occur in those parts of the lung which have not been affected or have been affected to a lesser extent by hypoxic vasoconstriction, that is, in HAPE, edema radiographically appears to occur where there is very high flow (redistributed from vasoconstricted areas).

Post-capillary hypothesis

Contrary to untrained subjects, who typically demonstrate a plateau in stroke volume beyond the early stages of an acute bout of progressive exercise, the stroke volume pattern in highly trained endurance athletes progressively rises to the point of maximal exercise [44]. Increased end-diastolic volume and systolic function can be strong determinants in generating cardiac output in these athletes. However an hypertrophic left ventricle with

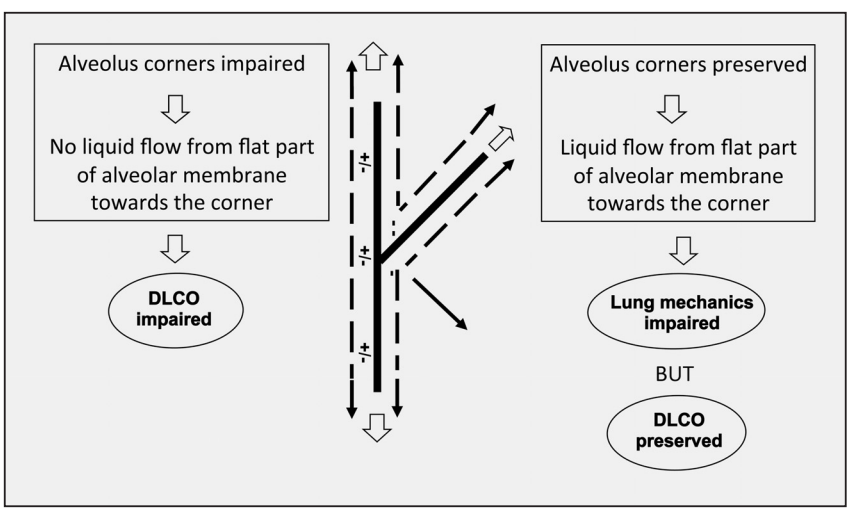

Fig. 4. - Mechanisms for preservation of lung diffusion in alveolar edema.
For the explanation see the text. - and — represent a negative pressure gradient into alveolar corners; +/- represents a null gradient.

altered lusitropic properties can also contribute in raising the filling pressure. At present, the magnitude of ventricular remodeling and diastolic function impairment in athletes' heart is not known. The mechanisms of cardiac phenotype plasticity remain uncertain, and they probably involve underlying genetic factors, as well as length, duration, type, intensity, and age of beginning of the training stimulus [45].

On the other side, during exercise, the mean left ventricular filling time is shortened by more than 70%, with the maximum transmitral flow velocity more than doubled, and with a tenfold increase in the mean transmitral pressure gradient [46].

A spectral doppler measurement of transmitral E velocity and mitral annular velocity together with a contemporary right heart catheterization monitoring during exercise were recorded by Talreja *et al*. in a group of 12 athletes. They evidenced both the E/e' ratio and pulmonary artery wedge pressure (PAWP) increased at peak exercise (from 11.7 ± 0.5 to 14.4 ± 0.6, and from 14 ± 4 to 23 ± 10 mmHg, respectively), demonstrating that an E/e' ratio higher than 15 during exercise can be considered as a good predictor of a PAWP higher than 20 mmHg [47].

This demonstrates that the increased pressure in the pulmonary capillary circulation can undoubtedly have a backwards origin from left heart chambers with an initial hypertension of pulmonary venous system.

This mechanism can be associated with the previously exposed one where the excessive increase in cardiac output maybe associated with environmental conditions of hypoxia.

Conclusions

We are used to considering the healthy human lung as overbuilt in a sedentary situation. But under excessive physiological stressors, such as during intensive, and prolonged exercise, especially if accompanied by psychological stress, exposure to cold or to moderate altitude, the lung appears to be underbuilt.

If it is well recognised that interstitial edema is one of the possible mechanisms leading to a significant hemoglobin desaturation during intense exercise, we still do not know the real impact of this phenomenon on healthy subjects exercising at the sea level.

While we must recognise that an overt pulmonary edema is a rare condition in healthy subjects, the most recent studies have begun to outline the formation of pulmonary interstitial edema in endurance athletes as a common phenomenon related to the physiological behaviour of the lung, without a significant clinical impact.

Indeed, values of arterial oxygen content appear to be preserved, except in elite athletes when engaged in strenuous exercise. This could be related to efficient defense mechanisms that are able to preserve gas exchange along the flat part of the alveolar membrane until the fluid overload is excessive.

It is very difficult to prove this in vivo. Each method used has limitations that may affect the results. This is particularly true about imaging techniques, because the results depend on long running (and edema is a transient phenomenon), and criteria for an objective interpretation are still poor.

At present exercise-induced pulmonary edema is only a "likely" hypothesis having, of its underlying mechanisms, only spot information so we are, at present, unable to draw a complete scenario having only few pieces of its puzzle on place.

On the other side, arterial desaturation phenomena are quite frequently observed, but their real meaning is not known: if, on one side, oxyhemoglobin desaturation is a direct consequence of a particularly excessive effort, on the other side it could represent a cause of limitation for endurance performance [48].

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