Current perspectives

Impedance to gas transfer across the alveolar-capillary membrane in chronic cardiac failure

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One of the consequences of an elevation of the pulmonary capillary pressure in chronic heart failure is the occurrence of structural and functional changes at the level of the alveolar-capillary interface. These changes are called stress failure of the membrane, and consist of thickening of the interstitium, increase in capillary permeability to water and ions, and disruption of local regulatory mechanisms for gas exchange.

Functional correlates are an augmented impedance to gas transfer (DL), a reduction in the alveolar-capillary membrane conduction (D_M) and an increase in the volume of the pulmonary capillary blood (V_C). D_M and V_C are the two subcomponents of DL. D_M has been identified as the strongest respiratory predictor of oxygen uptake at peak exercise in patients with chronic heart failure, suggesting that impeded lung diffusion may significantly contribute to exercise limitation and ventilatory abnormalities.

The evidence relating to the pathophysiological and clinical significance of the impairment in lung diffusion capacity in patients with chronic heart failure, as well as the response to treatment are the main subjects of this review.

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One of the prominent features of chronic heart failure (CHF) is the inability of the alveolar-capillary membrane to provide an effective exchange of respiratory gases between air in the alveoli and blood in the pulmonary capillaries. Since pulmonary gas transfer is influenced by the integrity of the membrane, and is one of the determinants of exercise maximal oxygen uptake, it seems appropriate that some aspects be focused on concerning CHF, namely the structural and functional changes that occur in the syndrome, their clinical significance and contribution to functional impairment, and whether they may be reversed with treatment.

As the literature pertaining to these issues has received little attention to date and at times opinions seem contradictory, there is a need to review the evidence relating to pulmonary gas transfer abnormalities in subjects with CHF.

Alveolar-capillary membrane function

The components of the alveolar-capillary membrane are the surface layer of surfactant, the alveolar epithelial layer (with type I and type II cells, which provide a mechanical and metabolic support, respectively), the interstitial space and the capillary endothelium. The endothelium is permeable to small molecules and ions, but much less to proteins; the epithelium opposes passive diffusion of small ions and solutes and actively pumps water and solutes from the alveolar space to the interstitium[1].

One side of the blood-gas barrier is thinner than the other, due to a different interstitial composition. In the thinner side, the interstitium is limited to the two fused basement membranes of the alveolar epithelium and the vascular endothelium; the thicker portion shows a wider interstitial space with an increased fibroblast and collagen concentration. This configuration facilitates gas diffusion, through the thinner portion, and impedes flooding of the interstitium. Hydrostatic and colloid osmotic pressures in the capillary and in the interstitium are traditional mechanisms governing the fluid partitioning between intra- and extravascular spaces. Nonetheless, removal of excessive fluid in

the distal air spaces is regulated by cellular local pathways that work independent of hydrostatic or protein oncotic pressures. In fact, water reabsorption from the alveolar lumen is mediated by an active sodium extrusion process generating a transepithelial osmotic gradient[2-4], and the rate of Na^+ and water removal is importantly enhanced by adrenergic mechanisms[5-8].

Although comprehension of the fluid balance across the alveolar membrane in physiological conditions has expanded, more has to be learned about pathological conditions[9].

According to the Fick s law, $V_G = k \cdot A/d \cdot \alpha/\rightarrow MW \cdot (P_1-P_2)$, the membrane area (A) and thickness (d), the gas molecular weight (MW) and solubility (α) and the partial pressure difference of the gas through the membrane (P_1-P_2) regulate the rate of gas transfer across a surface (V_G). For a given partial pressure in the alveoli the pressure gradient depends upon the gas partial pressure in the capillary blood, which is determined by the dynamics between the gas bound to hemoglobin and the amount dissolved in plasma.

Factors involved in oxygen diffusion are the distributional relation of alveolar ventilation to pulmonary capillary perfusion, the transfer properties of the alveolar-capillary interface, the pulmonary capillary volume of blood available for gas exchange, the hemoglobin concentration and the rate of reaction between oxygen and hemoglobin. Therefore, according to Roughton and Forster[10], gas transfer (DL) depends on the membrane conductance component (D_M) and the erythrocyte component (θV_C), which, in turn, is based on the reaction rate of the gas with hemoglobin (θ) and the pulmonary capillary blood volume (V_C).

Carbon monoxide (CO) transfer (DL_{CO}) is currently utilized as an index of the lung diffusing capacity[11]. Because CO crosses the alveoli and has an affinity for hemoglobin 240-fold greater than that of oxygen, the pressure gradient remains maximal and the amount of CO taken up in the circulation reflects primarily the diffusion properties of the membrane.

Alveolar-capillary membrane stress failure

According to the Laplace s law, an increase in hydrostatic capillary pressure results in a rise of wall stress, which involves the alveolar-capillary membrane, particularly the extracellular matrix of its thinner portion[12]. The vulnerability seems to vary according to animal species and preexisting hemodynamic conditions[13]. West and co-workers[14] have studied the consequences of capillary pressure rise, and have described them as stress failure of the alveolar-capillary membrane. The occurrence of a progressive derangement of capillary endothelial and alveolar epithelial layers has been reported by Tsukimoto et al.[15], in a rabbit model; starting from a pressure of 24 mmHg there is a transition from a hydrostatic and low permeability (leakage of proteins into the interstitium) to a high permeability form of pulmonary edema (leakage of proteins and red blood cells in the alveolar lumen). As observed in a canine model of pace-induced heart failure, or in patients with mitral stenosis and pulmonary venous hypertension[16,17], sustained elevation in capillary pressure augments total thickness of the alveoli[18] and the main structural changes involve the extracellular matrix. Alveolar-capillary interstitium has been reported to thicken, mainly because of an increased type IV collagen deposition, and to raise the resistance to the molecular diffusion of gas across the membrane. It has also been interpreted as causing a reduction in membrane permeability to salt and water and an increase in resistance to alveolar edema[18,19].

As a matter of fact, in patients with CHF, development of pulmonary edema may be dissociated from an increase in hydrostatic forces, thus questioning the interpretation of a reduced endothelial capillary permeability to salt, as well as of altered hydrostatic forces as exclusive mechanisms for pulmonary edema in CHF. Epidermal growth factor can upregulate alveolar epithelial sodium transport[9]; proinflammatory cytokines and, particularly, tumor necrosis factor-α upregulate sodium and fluid transfer of the endothelial barrier in a rat model[20] and have been suspected to alter the selectivity of the barrier[21,22]. Information regarding the Na^+ and water transport system across the microvascular endothelium in CHF is lacking. In a recent report[23], the effects of volume loading on lung gas diffusion were tested in 10 patients with mild left ventricular dysfunction in NYHA functional class I. Compared to 8 normal healthy controls, an infusion of 0.9% saline at 10 ml/kg body weight significantly lowered total DL_{CO} and its D_M subcomponent. This reflects an accumulation of fluid in the interstitial space that was probably not exclusively related to hydrostatic phenomena. In fact, in another recent study[24], carried out in a larger population with overt CHF, both a 150 ml amount (corresponding to the pulmonary capillary blood volume in the supine position) and a 5-fold greater amount (750 ml) of 0.9% saline produced a significant reversible (within 1 hour or less) reduction in alveolar-capillary membrane gas conductance despite no changes in hydrostatic forces. This led to the interpretation that an excessive fluid filtration, possibly due to an enhanced Na^+ transport, increased the alveolar-capillary thickness and impeded the transfer of gas.

Clinical significance of abnormal pulmonary gas diffusion in chronic heart failure

Only recently, attention has been addressed to the pathophysiological correlates of a reduced diffusing capacity in CHF[19,25-29].

As CHF is generally associated with a reduction in lung volume, an abnormal DL_{CO} might be interpreted as due to a reduced availability of lung surface area for gas exchange. In a few studies DL_{CO} has been corrected

with lung volumes, and results are not conclusive[25,30]. A number of observations, however, bespeak reduction in lung volume as an unlikely major putative factor. As mentioned previously, specific alterations of the membrane have been identified and, when DL_{CO} has been analyzed and partitioned in its membrane (D_M) and capillary blood volume (V_C) subcomponents, membrane abnormalities accounted for overall changes in gas transfer[25,30]. In CHF an increase in V_C may compensate for the observed reduction in D_M; consistently, in a recent report[31], a normal DL_{CO} was found when normalized for alveolar volume (VA) in the setting of an abnormal D_M/VA.

Long-term follow-up of heart transplant recipients has documented that hemodynamic improvement reverses lung volume abnormalities, but does not affect lung diffusion[32,33].

In a study of Puri et al.[25] it has been proven that an augmented resistance to gas transfer strongly predicts oxygen uptake at peak exercise, and there is a relationship of the reduced DL_{CO} with the severity of pulmonary hemodynamic alterations and functional deterioration. These observations agree with the suggestion of Kraemer et al.[34], that an impairment in DL_{CO} exhibits a correlation with peak oxygen consumption better than all the other pulmonary abnormalities in CHF. These contributions have substantially expanded understanding of mechanisms involved in exercise intolerance in these patients. Exercise exacerbates factors, such as capillary wedge pressure rise and fluid-flux transition, underlying membrane stress failure. The physiological rise in gas exchange on exercise, therefore, is restrained both at the level of the alveolar-capillary membrane (decrease in membrane conductance) and at the blood level (inadequate capillary recruitment causing a limited increase in V_C and reduced red blood cell transit time). Reliability and reproducibility of measurements of DL_{CO} during an incremental exercise are poor, because of the lack of a steady-state. There is, however, extensive documentation of a ventilation/perfusion (V/Q) mismatch during exercise in CHF, as reflected by an excessive ventilatory requirement for a given amount of CO_2 production, a blunted tidal volume increase secondary to an augmented physiological dead space and waste ventilation[35-37]. According to preliminary observations, the increase in DL_{CO} during a constant submaximal workload is significantly lower than predicted in CHF[38].

Arterial oxygen desaturation during exercise is not a prominent feature in CHF. This is the main reason why the importance of pulmonary diffusion inadequacy, as a factor limiting exercise performance, has been questioned[39,40]. Excessive ventilation during exercise in CHF patients, might on one hand maintain oxygen alveolar tension, on the other hand could cause exhaustion of the ventilatory reserve[25] and an early exercise termination. The level at which a decrease in oxygen saturation could be relevant is somewhat controversial. In healthy individuals[41] and athletes[42], even a 2-3% reduction in oxygen saturation during a maximal exercise testing, may critically limit physical performance. It is, indeed, remarkable that in patients with heart failure oxygen supplementation during exercise, by reducing the alveolar-arterial oxygen difference, elevated oxygen saturation by 2-3% and significantly increased peak oxygen uptake and exercise time[43]. In a heart transplanted population, Braith et al.[44] found that patients with a relevant impairment in DL_{CO} (< 70% of normal predicted value) exhibited severe hypoxemia (PaO_2 70 mmHg) since the initial stages of exercise, and heart transplantation did not ameliorate DL_{CO}, PaO_2 and exercise capacity in these patients.

If it is true that the present review is devoted to the analysis of the structural and functional alterations of the alveolar-capillary interface in CHF, the reader should not however get the impression that the increased resistance to oxygen diffusion be the main respiratory problem in patients with CHF, both at rest and during exercise. Suffice it to mention a few points indicating that the content has not been fully demonstrated.

One is the influence that the impaired V/Q ratio may exert on gas transfer. A stressed interstitial membrane reduces the alveolar compliance and the peribronchial edema increases the upstream airway resistance; the increased variance of the lung time constant gives rise to a mismatch of V/Q, with an increase in physiological dead space ventilation[35-37]. In studies in CHF patients, that considered both D_M and the dead space to tidal volume ratio, a decrease of the former and an increase of the latter have been found[26,30] and a close correlation was shown between their respective changes with treatment. These data altogether may raise the question of what is the role of the true diffusion capacity. DL_{CO} measurement, in addition, is affected by uneven distribution of V/Q[45] and because of this, some authors use CO_2 transfer factor rather than CO_2 diffusion capacity .

On the basis of the present evidence, it seems fair and safe to say that patients with CHF have an uneven distribution of V/Q which may impede the respiratory gas transfer, and, therefore, the impaired true diffusion capacity may be just one of the respiratory problems in CHF.

Therapeutic aspects

Some meaningful questions remain unanswered: 1) may abnormalities in blood gas barrier function be reversed with treatment? 2) what are the mechanisms of hypothetical benefits? and 3) what is the impact that improvement in gas exchange may have in the context of the syndrome? As impairment of DL_{CO} has been suspected to limit physical performance, a therapeutic intervention that improves DL_{CO} is expected to affect exercise, as well. CHF is a multifactorial syndrome and alterations in lung function could have a relevant part in some patients and a marginal one in others. The hypothesis has been tested that the prostaglandin-stimulating

properties of ACE-inhibitors can improve gas exchange in CHF[26]. Prostaglandins, in fact, are important regulators of lung vessel tone and permeability and ACE is highly concentrated on the luminal surface of the lung microvessels[46]. This hypothesis was based on the following considerations: circulating bradykinin is inactivated during its passage through the lung by the same enzyme (kininase II-ACE) that converts angiotensin I to angiotensin II; blockade of kininase II may increase local kinin concentration; this may enhance the formation of nitric oxide and vasodilator prostaglandins, mainly PGI_2. In a comparative study, pulmonary function and exercise tests with respiratory gas analysis were assessed in CHF patients and controls during four therapeutic regimens: placebo, enalapril (20 mg/daily), enalapril plus aspirin (325 mg/daily) as a cyclooxygenase blocker, or aspirin alone in random order[26]. In CHF and not in controls, enalapril significantly improved DL_{CO}, peak oxygen consumption and exercise tolerance. This was the first demonstration that ACE-inhibition has a favorable modulatory activity on lung diffusing properties in CHF patients. A strong correlation was also detected of changes in DL_{CO} with variations in peak oxygen consumption. In a 1 year follow-up in a similar patient population, enalapril-mediated changes in DL_{CO} persisted over time[47]. Attenuation of the improvement in DL_{CO} by acetylsalicylic acid suggests that vasodilator prostaglandins may be the mediators of this effect[26,48]. This concept is corroborated by the following considerations: the luminal surface of the lung vessels is an important site of prostaglandin production[49], release[50] and metabolism[51]; in the presence of vasoconstriction, hypoperfusion and V/Q mismatch, nitric oxide and PGI_2 production is inversely linearly related to angiotensin II concentration; the balance between these counteracting substances critically influences permeability and tone of the lung vessels[52,53]. Therefore, potentiation of the bradykinin-prostaglandin pathway along with angiotensin system inhibition, would be an effective combination for lowering impedance to gas exchange. Accordingly, a crossover study with enalapril and losartan has shown that ACE-inhibition and not AT_1 receptor blockade is effective on DL_{CO}[54], and that their combination has no additive effect on pulmonary gas exchange[55].

Acute reduction of the wedge capillary pressure and increase of cardiac index with enalapril were not paralleled by immediate variations in DL_{CO}; hydralazine-isosorbide dinitrate combination failed to affect DL_{CO} in spite of a decrease of pulmonary pressures[26]; there is also evidence that heart transplantation, despite restoring a normal lung compliance, is not effective on lung diffusion[32,33,44]. It seems, therefore, that improvement in hemodynamics and normalization in pulmonary pressure are not the only requirements for the alveolar-capillary membrane stress failure to be reversed. In order to elucidate this topic more in depth, pulmonary function testing was performed, and D_M and V_C were measured, according to the classic Roughton and Forster method[10], in CHF patients who were given enalapril for 8 weeks[30]. The only variation that occurred within 48 hours was a decrease in V_C (as a possible consequence of a lower pulmonary capillary pressure). In tests performed at 4 and 8 weeks, D_M was raised, even when the effective alveolar volume was accounted for, resulting in a significant improvement in DL_{CO}, despite a decrease in V_C. The slow onset improvement in D_M is in favor of a gradual effect of ACE-inhibition on alveolar-capillary membrane gas conduction, which is likely dissociated from variations in pulmonary capillary pressure and V_C.

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