Alveolar–capillary membrane dysfunction in chronic heart failure: pathophysiology and therapeutic implications

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ABSTRACT

Chronic heart failure (CHF) disturbs the alveolar–capillary interface and increases the resistance to gas transfer. Alveolar–capillary membrane conductance ($D_M$) and capillary blood volume ($V_c$) are subcomponents of the lung diffusion capacity. Elevation of the capillary pressure causes alveolar–capillary membrane stress failure (i.e. increase in capillary permeability to water and ions, and disruption of local regulatory mechanisms for gas exchange), leading to a decrease in $D_M$, an increase in $V_c$ and subsequent impairment of diffusion capacity. Renewed recent interest in abnormalities in lung diffusion in patients with CHF has brought about new pathophysiological insights. A significant contribution of the altered gas transfer to the pathogenesis of exercise limitation and ventilatory abnormalities has been reported, and $D_M$ has been identified as the best lung function predictor of oxygen uptake at peak exercise. This review examines the pathophysiological and clinical significance of assessing lung diffusion capacity in patients with CHF.

INTRODUCTION

The failing heart is associated with a series of functional and structural changes at the level of the lung that occur as an integrated reaction to a transient or, in some instances, sustained pressure-induced insult [1–3]. The impact and the relevance that these alterations may have in the context of the syndrome become clinically evident when water retention and pulmonary congestion precipitate that dramatic and life-threatening event that is alveolar oedema. Aside from this acute condition, it is still debatable whether, in patients with an optimal therapeutic regimen and asymptomatic left ventricular dysfunction, a chronic elevation in capillary wedge pressure and the consequent derangement of the pulmonary microvasculature have pathophysiological significance. It is remarkable that breathlessness and dyspnoea are composite symptoms that have been shown repeatedly to be dissociated from pulmonary haemodynamic and functional alterations in the lung [4,5].

Several lines of evidence, however, suggest that, even in patients without symptoms and/or limitations to the activities of daily life, it is important to explore whether an inability of the alveolar–capillary membrane to provide normal permeability and to maintain effective gas exchange may contribute to affect the functional impairment and the clinical status of these subjects [6–9]. Although the impact of these abnormalities in patients with primary lung disease is well established [10], their possible involvement in chronic heart failure (CHF) has received much less attention.

This review will focus on the pathophysiological relevance of changes that occur in the alveolar membrane; the adaptive or maladaptive nature of these abnormalities,
and the rationale for contrasting them, will also be discussed.

**PHYSIOLOGICAL CONSIDERATIONS AND ALVEOLAR–CAPILLARY MEMBRANE FUNCTION**

Alveolar gas exchange (i.e. O$_2$ uptake and CO$_2$ removal by the lung) depends on ventilation ($V_A$) and blood flow ($Q_d$). In normal circumstances, although the pulmonary vasculature is not completely perfused at rest, leading to some regional $V_A/Q_d$ imbalance, it has a considerable capability to increase its volume through the recruitment and distension of underperfused microvessels. This ability helps, even under extreme physiological conditions such as strenuous exercise, to maintain an adequate $V_A/Q_d$ ratio and to keep the alveolar–arterial O$_2$ difference within normal limits.

The overall efficiency of gas diffusion through the lung, however, is critically dependent on the anatomical and functional integrity of the alveolar–capillary membrane. The alveolar wall consists of a surface layer of surfactant, an epithelial layer with two differentiated types of cells (type I or epithelial cells, whose main function consists of a mechanical support, and type II cells, which provide metabolic support), the interstitial space and the capillary endothelium. The capillary endothelium is permeable to solutes, such as small molecules and ions, but has low permeability to proteins, whereas the epithelium is quite resistant to the passive diffusion of small ions and solutes, and actively pumps water and solutes from the alveolar space to the interstitium [11].

The ultrastructural appearance of the blood–gas barrier clearly shows one side of the membrane to be thinner than the other, and this difference is mainly related to the interstitial composition. On the thinner side, the interstitium is limited to the two fused basement membranes of the alveolar epithelium and the vascular endothelium; the thicker portion has a wider interstitial space with an increased concentration of fibroblasts and collagen. This double configuration allows the alveolar–capillary unit not only to promote gas diffusion, through the thinner portion, but also to protect the interstitium from fluid flux and electrolyte transition (Figure 1). Maintenance of this equilibrium and preservation of the functional properties of the membrane is dependent on a complex interplay of several mechanisms. As inferred from Starling’s equation (Figure 1), of some importance are mechanisms governing fluid partitioning between intra- and extra-vascular spaces, such as hydrostatic and colloid osmotic pressures in the capillary and in the interstitial space respectively. However, several recent observations, providing evidence that the alveolar epithelium plays a primary active role in removing oedema fluid from alveolar spaces through sodium-mediated transport, have substantiated the concept that removal of excessive fluid

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**Figure 1  Schematic presentation of the alveolar–capillary unit**

![Diagram of the alveolar–capillary unit](https://via.placeholder.com/150)

Laplace’s law (centre): $\sigma$, wall stress; $P$, pressure; $r$, radius of the cavity; $t$, wall thickness. Starling’s equation (upper left): $L_v$, volume flow across the exchanging area; $L_p$, hydraulic conductivity; $\delta P$, hydrostatic pressure gradient; $\sigma$, capillary wall reflection coefficient to protein; $\delta \pi$, protein osmotic pressure gradient.

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accumulation in the distal air spaces is regulated by cellular local pathways working independently of changes in hydrostatic or protein oncotic pressures.

Specifically, reabsorption of water from the apical membrane to the basolateral side of the alveolar epithelium is facilitated by the Na⁺/K⁺-ATPase enzyme generating a transepithelial osmotic gradient; inhibition of this enzyme impairs alveolar clearance under various experimental conditions [12–14]. The rate of Na⁺ and water removal is enhanced by endogenous adrenaline [15,16] and by administration of β₂-adrenergic agonists [17,18].

These important observations have raised the question of the relevance of potentiating these local regulatory mechanisms in order to facilitate and accelerate fluid clearance and oedema resolution in patients with pulmonary oedema. Although remarkable progress has been made in understanding the physiology of the alveolar membrane barrier in regulating lung fluid balance, more needs to be learned about the local and systemic factors involved under pathological conditions [19].

Movement of gas across the alveolar–capillary unit occurs by diffusion, as described by Fick’s law:

\[ V = k \cdot A \cdot \alpha / \sqrt{M \cdot (P_1 - P_2)} \]

According to this relationship, the rate of transfer of a gas across a surface \( V \) is directly proportional to the membrane surface area \( A \), the gas solubility \( \alpha \) and the difference in partial pressure of the gas across the membrane \( P_1 - P_2 \), and inversely proportional to the membrane thickness \( d \) and the \( M \), of the gas.

For a given partial pressure in the alveolar space, the pressure gradient is dependent on the gas partial pressure in the capillary blood, which is determined by the dynamics between the gas bound to haemoglobin and the amount dissolved in the plasma. In addition, \( O_2 \) diffusion is a phenomenon involving the distributional relationship of alveolar ventilation to alveolar–capillary perfusion, the \( O_2 \) transfer properties of the alveolar–capillary interface, the capillary volume, the haemoglobin concentration and the reaction rate between \( O_2 \) and haemoglobin.

Consequently, as proposed by Roughton and Forster [20] and as depicted in Figure 2, the overall resistance to gas transfer \( 1/DL \), where \( DL \) is the lung diffusion capacity) depends on: (1) the membrane resistance component \( 1/D_M \), where \( D_M \) is membrane conductance) and (2) the red blood cell component \( 1/V_c \). The latter is based on the reaction rate of the gas with haemoglobin \( (\theta) \) and the capillary blood volume \( V_c \).

The diffusion characteristics of the lung are commonly assessed by using tests of carbon monoxide (CO) transfer [21]. CO diffuses across the alveoli and binds to haemoglobin with a 240-fold greater affinity than \( O_2 \). As a consequence, the pressure gradient remains maximal and the amount of CO taken up in the circulation depends primarily on the diffusion characteristics of the membrane.

**The Concept of the Alveolar Membrane ‘Stress Failure’: Acute Versus Chronic Alveolar–Capillary Injury**

One common mode of injury to the alveolar–capillary membrane consists of a pressure-induced trauma: any rise in the hydrostatic capillary pressure, in fact, causes, according to Laplace’s law (Figure 1), an increase in wall stress which is directly related to the radius of the cavity and inversely related to the thickening of its wall. This challenges the alveolar–capillary membrane, particularly in its thinner and more vulnerable portion, the resistance and strength of which are provided mainly by the extracellular matrix, and specifically by collagen type IV [22]. The vulnerability of the membrane seems to vary according to pre-existing haemodynamic conditions, and has been reported to be significantly different in various animal species [23].

The consequences of an abrupt acute rise in capillary pressure have been extensively studied by West and coworkers [24], who described the so-called ‘stress failure’ phenomenon of the alveolar–capillary membrane. The unfavourable processes that occur in the alveolar ultrastructure during an experimental stepwise increase in the pulmonary microvascular pressure have been characterized by Tsukimoto et al. [25] in a rabbit model preparation. These authors noted that, starting from a pressure of 24 mmHg, a sequential morphological disruption of the alveolar–capillary membrane occurs, with
a progressive derangement of both the capillary endothelial and alveolar epithelial layers, leading to a transition from a hydrostatic and low-permeability form (leakage of protein into the interstitium) to a high-permeability form (leakage of proteins and red blood cells into the alveolar lumen) of pulmonary oedema. These findings have provided insight into the pathogenesis of different clinical presentations of pulmonary oedema, all of which involve stress failure of the alveolar–capillary membrane.

When the elevation in the capillary pressure is sustained, additional ultrastructural changes take place whose functional significance is not completely understood. In a canine model of pace-induced heart failure, morphometric analysis of the alveolar–capillary unit showed that the total thickness of the alveoli was significantly increased compared with that in controls [26]. Similar to findings in patients with mitral stenosis and pulmonary venous hypertension [27,28], increased thickness of the extracellular matrix accounted for the more important structural changes. Thickening of the alveolar–capillary interstitium, related partially to increased interstitial accumulation of fluid and mainly to increased deposition of type IV collagen, has been reported, and its pathophysiological significance has been ascribed to reduced membrane permeability and increased resistance of the lung to the development of alveolar oedema [6,26]. This, in turn, increases resistance to molecular diffusion across the membrane and impairs gas transfer. Capillary permeability in patients with CHF has been poorly investigated, and the only two studies aimed at defining this topic have produced conflicting results [29,30].

In patients with CHF, pulmonary oedema may be present despite no elevation of the hydrostatic pressure [31]. This raises the issue of whether altered haemodynamics are the exclusive cause of pulmonary oedema in heart failure, or whether abnormalities in the capillary and/or the alveolar epithelium barrier contribute to changes in salt, water and gas transfer. Epidermal growth factor can up-regulate alveolar epithelial transport [19]; pro-inflammatory cytokines, particularly tumour necrosis factor-α, mediate up-regulation of sodium and fluid transfer in a rat model [32] and have been suspected to be responsible for experimental pulmonary oedema via alterations in the selectivity of the endothelial barrier [33,34].

Information regarding the Na⁺ and water pump transport system in CHF is lacking, but the occurrence of local regulatory disruption, as a part of the cellular abnormalities that characterize membrane stress failure, could be reasonably suspected. In a recent report [35], the effects of fluid volume loading on lung gas diffusion were tested in 10 asymptomatic patients with mild left ventricular dysfunction (NYHA class I). Compared with eight normal healthy controls, a 30-min infusion of 0.9% saline at 10 ml·kg⁻¹ body weight was able to induce a significant decrease in total diffusing lung capacity and alveolar conductance. In another recent study [36], involving a larger number of patients with overt CHF, the hypothesis of an endothelial up-regulation in Na⁺ handling was probed by monitoring changes in alveolar transfer during infusion of two different amounts (150 ml and 750 ml) of 0.9% saline and 5% D-glucose solutions. Saline, unlike glucose, even when the smaller amount was administered, produced a significant decrease in alveolar membrane conductance, despite the vascular hydrostatic pressure remaining unchanged.

**ABNORMALITY OF ALVEOLAR DIFFUSION: CLINICAL RELEVANCE IN CHF**

Although an abnormal pulmonary diffusion capacity in CHF has long been recognized by physiologists and clinicians [37], only recently has attention been addressed to its pathophysiological role [6,8,9,38–40].

Table 1 summarizes studies in which lung diffusion capacity was tested in patients with CHF. It is important to emphasize that, in each single study and over a total number of 514 patients, mostly in NYHA class II or III, a significant overall decrease in diffusion capacity, as assessed with the single-breath technique for carbon monoxide (DLCO), has been described. Because a decrease in lung volume is common in patients with CHF, it might be anticipated that an abnormal DLCO is the natural consequence of a reduced total lung surface area available for gas diffusion. Correction of DLCO to take into account lung volume has been carried out in a few studies, and results in this regard do not seem to be conclusive. A number of observations, however, suggest that the concomitant reduction in lung volume is unlikely to be a major factor. As mentioned above, specific alterations in the membrane have been identified and, when DLCO has been analysed by separating it into its two subcomponents [the membrane component (DM) and the capillary blood volume (Vc)], abnormalities in the former accounted for overall changes in gas transfer [7,38,41]. In patients awaiting heart transplantation, DLCO does not correlate with forced vital capacity [39], and long-term follow-up of recipients has documented that haemodynamic improvement reverses lung volume abnormalities, but does not affect lung diffusion [42–47].

The first study to investigate the functional significance of a decrease in DLCO was performed by Puri et al. [7] in 1995. It showed that augmented resistance to gas transfer is a strong predictor of O₂ uptake at peak exercise, and that a relationship exists between the decrease in DLCO and the severity of pulmonary haemodynamic alterations and functional status. These observations confirmed and expanded information previously provided by Kraemer and co-workers [39], i.e. among all pulmonary abnor-
Table 1  Studies on diffusing lung capacity in patients with CHF

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients investigated</th>
<th>NYHA functional class</th>
<th>DLCO (% of predicted)</th>
<th>DLCO/Va (% of predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright et al. (1990) [42]</td>
<td>132</td>
<td>III–IV</td>
<td>64.5</td>
<td>ND</td>
</tr>
<tr>
<td>Singel et al. (1990) [43]</td>
<td>34</td>
<td>II–III</td>
<td>63</td>
<td>90</td>
</tr>
<tr>
<td>Davies et al. (1992) [29]</td>
<td>14</td>
<td>III</td>
<td>85</td>
<td>87</td>
</tr>
<tr>
<td>Naum et al. (1992) [44]</td>
<td>56</td>
<td>III–IV</td>
<td>71</td>
<td>ND</td>
</tr>
<tr>
<td>Ravenscraft et al. (1993) [45]</td>
<td>38</td>
<td>III–IV</td>
<td>82.3</td>
<td>106</td>
</tr>
<tr>
<td>Ohar et al. (1993) [46]</td>
<td>32</td>
<td>III</td>
<td>69</td>
<td>ND</td>
</tr>
<tr>
<td>Kraemer et al. (1993) [39]</td>
<td>50</td>
<td>II–III</td>
<td>81</td>
<td>ND</td>
</tr>
<tr>
<td>Messner-Pellenc et al. (1995) [40]</td>
<td>10</td>
<td>II–III</td>
<td>90</td>
<td>82</td>
</tr>
<tr>
<td>Guazzi et al. (1997) [8]</td>
<td>24</td>
<td>II–III</td>
<td>82.5</td>
<td>ND</td>
</tr>
<tr>
<td>Assayag et al. (1998) [38]</td>
<td>47</td>
<td>II–III</td>
<td>88</td>
<td>91</td>
</tr>
<tr>
<td>Guazzi et al. (1999) [41]</td>
<td>27</td>
<td>II–III</td>
<td>80</td>
<td>ND</td>
</tr>
<tr>
<td>Total (average)</td>
<td>514</td>
<td>(77.6)</td>
<td>(89)</td>
<td></td>
</tr>
</tbody>
</table>

malities, those in DLCO exhibit the best correlation with peak \( O_2 \) uptake. The contribution of these investigators has provided important information regarding the mechanisms involved in exercise intolerance in these patients. Exercise exacerbates factors underlying membrane stress failure (i.e. increase in capillary wedge pressure and fluid-flux transition), and the physiological increase in gas exchange on exercise is restrained at the level of the alveolar–capillary membrane (by an impeded increase in \( D_m \), due to interstitial fluid accumulation) as well as of the blood (by a limitation in the increase in \( V_c \), mainly related to inadequate capillary recruitment and a progressive decrease in the red blood cell transit time).

Measuring DLCO during incremental exercise remains a difficult task, because of the limited reliability and reproducibility of measures, in the absence of a steady-state condition. There is, however, an extensive body of literature documenting the occurrence of \( V_{a}/Q \) mismatch during exercise in CHF, as revealed by an excessive ventilatory requirement for a given amount of \( CO_2 \) production, and a blunted increase in tidal volume because of an increased physiological dead space and waste ventilation [48–51]. Preliminary observations have also shown that the extent of the increase in DLCO during a constant submaximal workload is significantly lower than predicted in CHF patients when compared with normal subjects [52].

Some authors have noted that exertional arterial oxygen desaturation is not a prominent feature in CHF, and have questioned the importance of pulmonary diffusion inadequacy as a mediator of limited exercise performance [53,54]. Excessive ventilation, as occurs during exercise in CHF patients but not in normal individuals, might have a protective role in maintaining \( O_2 \) alveolar tension within a normal range; this, however, could precipitate early exhaustion of the ventilatory reserve [7] and early exercise termination. The level at which a decrease in \( O_2 \) saturation during exercise could be considered relevant is somewhat controversial. In this context, repeated findings in healthy subjects [55] and athletes [56] have provided important clues, showing that, during maximal exercise testing, even a small decrease in \( O_2 \) saturation (2–3%) may critically limit physical performance. It is, indeed, remarkable that, in a study by Moore et al. [57], \( O_2 \) supplementation during exercise, by reducing the alveolar-arterial oxygen difference, elevated \( O_2 \) saturation by 2–3% and significantly increased peak \( O_2 \) uptake and exercise duration. Braith et al. [58] examined changes in \( O_2 \) partial pressure during exercise in a CHF population before and after heart transplantation: patients with an impairment in DLCO (< 70%) exhibited severe exercise hypoxaemia (\( O_2 \) partial pressure = 70 mmHg) from the initial phases of exercise. Heart transplantation did not affect DLCO, \( O_2 \) partial pressure or exercise capacity in these patients, providing an alternative and intriguing explanation for the well documented persistence of exercise intolerance in organ recipients.

**THERAPEUTIC IMPLICATIONS**

The opportunity of considering the lung as a specific target for therapy has been stressed in the past [59]. Important unresolved questions in this regard include the following: (1) whether abnormalities in alveolar function may be reversed, and whether specific anti-failure therapy could be more effective; (2) what the underlying mechanisms of hypothetical benefits may be; and (3) what is the impact that improvements in gas exchange may have in the context of the syndrome. Because abnormalities in DLCO have been suggested to be involved in limiting
physical performance, therapeutic intervention aimed at improving DLCO would be expected to also affect exercise. It seems important, however, to stress that exercise intolerance in CHF is multifactorial, and the relative contribution of abnormalities in lung function could be very relevant in one subset of patients but marginal in others.

Accordingly, patients with a documented impairment in DLCO were included in a double-blind, placebo-controlled study, performed by our group [8], to test the hypothesis that inhibition of angiotensin-converting enzyme (ACE) may improve gas exchange in CHF by readjusting lung vessel tone and permeability, and alveolar–capillary membrane function. The possible influence of this class of drugs on pulmonary function in CHF patients has been underestimated in the past, even though ACE is highly concentrated on the luminal surface of the lung microvessels [60], and ACE inhibitors affect not only the angiotensin system, but also the kinin system [61]. Our hypothesis was based on the fact that circulating bradykinin is inactivated mainly during its passage through the lung by the same enzyme (kininase II/ACE) that converts angiotensin I into angiotensin II; thus blockade of this enzyme may increase the local kinin concentration, leading to the enhanced and sustained formation of NO and vasodilator prostaglandins, mainly prostacyclin (prostaglandin I\(_2\)). In 16 CHF patients and 16 controls, pulmonary function and exercise tests with respiratory gas analysis were assessed using four different therapeutic regimens: placebo, enalapril (20 mg/day), enalapril plus aspirin (325 mg/day) as a cyclo-oxygenase blocker, or aspirin alone, in random order and double-blind, for 15 days each [8]. In patients with CHF, enalapril induced significant improvements in DLCO (Figure 3), peak O\(_2\) uptake and exercise tolerance. This was the first demonstration that inhibition of ACE has a favourable modulatory activity on lung diffusing properties of patients with CHF. Interestingly enough, a strong correlation was found between changes in DLCO and variations in peak O\(_2\) uptake, thus reinforcing the concept that pulmonary derangements related to the syndrome are additional targets for the benefits of ACE inhibitors. A 1-year prospective follow-up study performed in a similar patient population showed that enalapril-mediated changes in DLCO are reproducible and persist over time [62].

The finding that the improvement in DLCO is inhibited by acetylsalicylic acid supports the interpretation that vasodilator prostaglandins may be the mediators of this effect [8,63]. The luminal surface of the lung vessels is an important site of prostaglandin production [64,65], release [66] and metabolism [67]. Experimental studies have shown that, in the presence of vasoconstriction, hypoperfusion and \(V_{A}/Q\) mismatch, NO and prostacyclin production is inversely linearly related to angiotensin II concentration, and the balance between these counter-acting substances critically influences the permeability andtone of the lung vessels [68,69]. It seems, therefore, that potentiation of the bradykinin/prostaglandin pathway, along with inhibition of the angiotensin system, is an essential combination for reducing excessive resistance to respiratory gas exchange. Accordingly, a parallel crossover evaluation of DLCO while on ACE inhibition with enalapril compared with AT\(_1\) receptor blockade with losartan showed small variations with the latter and a significant improvement with the former [70]. Moreover, the combined administration of losartan and enalapril did not promote an additive effect on pulmonary gas exchange [71].

What is the role of the vasodilatory and pulmonary hydrostatic pressure lowering properties of enalapril in improving DLCO? An acute decrease in the wedge capillary pressure and an increase in the cardiac index on enalapril treatment were not associated with acute variations in DLCO, and a hydralazine/isosorbide dinitrate combination failed to affect DLCO, in spite of a decrease in pulmonary pressure [8]. Remarkably, there is a general consensus showing that heart transplantation, despite restoring normal lung compliance, is ineffective with regard to diffusion capacity [45,46,58]. Although the reasons for this are not clear, improvement in haemodynamics and normalization of pulmonary pressure are not the only requirements for reversing alveolar–capillary membrane stress failure, and it seems safer that ACE inhibitor withdrawal should be delayed in these patients.

In order to elucidate more in-depth mechanisms whereby ACE inhibitors exert a protective effect on the lung when the heart is failing, we followed up CHF
patients who were given enalapril for 8 weeks with pulmonary function testing and determination of \(D_M\) and \(V_e\) according to the classic Roughton and Forster method [20]. The only change observed in the short term (48 h) was a decrease in \(V_e\), a likely consequence of a decrease in the capillary pulmonary pressure. At 4 and 8 weeks, \(D_M\) was raised, even when the effective alveolar volume was taken into account, resulting in a significant improvement in DLCO, despite a decrease in \(V_e\). The observed slow-onset improvement in \(D_M\) suggests the emergence of a gradual specific modulatory effect of ACE inhibition directly at the membrane level, which is probably dissociated from changes in capillary pulmonary pressure and \(V_e\).

The possibility that treatment of arrhythmias with amiodarone may be a concurrent mechanism responsible for diminished pulmonary diffusion in CHF, in view of the well-known pulmonary toxicity of this drug, has been ruled out by Singh et al. [72] in a multicentre prospective trial. The effects of amiodarone on DLCO were assessed over an interval of 1 year without evidence of worsening.

Finally, because \(\beta\)-blockers have been consistently proven to ameliorate systolic and diastolic function and to reduce the size and filling pressure of the left ventricle, an intriguing question is whether lung function and gas exchange may also be improved. The influence of \(\beta\)-blockade with carvedilol on DLCO, \(D_M\), \(V_e\), and their relationship with left ventricular performance and peak \(O_2\) uptake were investigated in a prospective, randomized, placebo-controlled trial [73]. Despite an excellent effect on left ventricular function, carvedilol exerted a neutral effect on pulmonary gas transfer, thus proving that anti-failure treatment may not be similarly effective on cardiac and pulmonary function. This suggests that persistence of lung impairment may contribute to the lack of improvement in exercise performance and \(O_2\) uptake at peak exercise with carvedilol.

**CONCLUSIONS**

The experimental and clinical evidence reviewed in this article indicates that CHF is associated with impairment in gas exchange across the alveolar membrane. An acute increase in the pulmonary intravascular capillary pressure is the stimulus for so-called alveolar–capillary stress failure. However, in the long term, a pressure-induced trauma does not seem to be the only mechanism sustaining alveolar–capillary dysfunction. It is conceivable that a disorder in local and systemic mechanisms that regulate fluid removal from distal air spaces may cause further impairment of alveolar function, which increases the resistance to molecular diffusion across the membrane and disturbs gas transfer. The pathophysiological relevance of these changes has been a recent focus of attention; several studies have suggested that inadequate alveolar diffusion has a key role in limiting exercise performance in these patients. Abnormalities in gas exchange should be considered a specific target of anti-failure strategies. ACE inhibition has been shown to be successful in this respect.

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