Pathophysiology and treatment of alveolar–capillary dysfunction in chronic heart failure

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Heart failure increases the resistance to gas transfer across the alveolar–capillary membrane. Disruption of the alveolar anatomical configuration and impairment of cellular pathways involved in the fluid–flux regulation and gas-exchange efficiency (i.e., 'stress failure' of the alveolar–capillary membrane) has been well characterized in different experimental settings of vascular–capillary injury. In heart failure, the appreciation of the pathophysiologic relevance of alveolar stress failure continues to grow. Alveolar–capillary membrane conductance and capillary blood volume are the subcomponents of lung-diffusion capacity. An alveolar–capillary membrane conductance reduction with a trend of capillary blood volume to increase and with consequent impairment of gas exchange, are typical of the heart-failure syndrome. Alveolar–capillary membrane conductance abnormalities have been shown to reflect the underlying lung-tissue damage, to bring an independent prognostic information and to play a significant role in the pathogenesis of exercise limitation and ventilatory abnormalities. This review focuses on the current knowledge on this topic.

Knowledge concerning the impact of lung diffusion abnormalities and gas exchange inefficiency in patients with cardiovascular diseases continues to grow [1]. This is, in part, related to the definite epidemiological appreciation of the burden of diastolic heart failure (HF), a common clinical entity characterized by left ventricular (LV) backward failure (impaired filling and elevated LV end-diastolic pressure for any given volume) without LV forward failure (preserved systolic function) that often results in pulmonary edema [2]. Pressure elevation in the pulmonary circulation impairs the anatomical integrity and functional properties of lung capillaries and alveolar spaces (i.e., the blood–gas barrier) whose pathophysiologic relevance and clinical implications can be explored by the identification and investigation of gas diffusion abnormalities.

Pathophysiologic bases of lung diffusion abnormalities in heart failure

Experimental insights

The alveolar–capillary unit has two major roles:

- To allow gas exchange between blood and alveolar air
- To promote passive fluid clearance (Na^+ channels) from the alveolar lumen to the interstitium and active fluid reabsorption (ATPase Na^+/K^+ pump) from the basolateral portion of epithelial cells to the interstitium and vascular bed

This continuous fluid removal is functional to the process of gas exchange. **Figure 1** reports a schematic presentation of pathways involved in the process of alveolar fluid clearance.

Alveolar–capillary stress failure

When the heart is failing, an increase in capillary pressure and/or volume challenges the integrity of lung capillaries and, as a result, the physiology of these processes. In this respect, experimental models have provided important insights. West and collegues [3] have shown that, if sufficiently elevated, pressure causes formation of breaks and discontinuities in endothelial and epithelial membranes of the blood–gas barrier, a phenomenon identified as 'stress failure' of the alveolar–capillary membrane. In a similar rat model of progressive increase of left atrial pressure (LAP), a transient alveolar fluid reabsorption decrease by 50% was observed in lungs in which LAP was raised to 15 cm H_2O or further [4].

The proneness of the lung to develop a pressure-induced trauma is critically dependent on membrane thickness and the threshold pressure for developing capillary breaks varies across different animal populations [5]. After seminal reports by West, a series of studies investigating the biology of alveolar stress failure have brought new insights into the cellular factors involved in the response to mechanical stress, suggesting that other mechanisms additional to membrane thickness may determine the capillary stress.

Keywords: alveolar–capilalry dysfunction, capillary blood volume, DLco, heart failure

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When the overload imposed on the capillaries is primarily of volume or hydraulics, such as during controlled saline infusion to the capillary (180 min of saline infusion at 0.5 ml/min/kg in the rabbit lung), the morphometric analysis obtained in the very early postinfusion phase shows that 44% of the fluid leaks to the extravascular interstitial space; a process accompanied by significant ultrastructural changes and impairment in gas conductance [6]. Changes occurring during hydraulic edema have been shown to induce matrix proteoglycan fragmentation secondary to metalloprotease activation [7], as well as a marked change in plasma-membrane composition with an increase in endothelial membrane fluidity – a feature that may decrease the tensile strength in the membrane, contributing to endothelial stress failure [8]. In patients with stress failure caused by acute cardiogenic pulmonary edema, the damage to the alveolar–capillary barrier is documented by increased levels in plasma surfactant protein A and B and tumor necrosis factor (TNF)-α [9]. Persistance of elevated TNF-α levels until 3 days after edema resolution is suggestive of pulmonary parenchimal inflammation and may explain the recurrence of fluid accumulation despite resolution of hydrostatic stress failure.

Molecular abnormalities in alveolar fluid clearance

Interestingly, in rats overexpressing by adenovirus-gene transfer, the Na^+/K^+ ATPase β_1-subunit promotes an increase in liquid-fluid clearance [10]. In the same model, Na^+ transport and alveolar fluid clearance in the presence of elevated LAP was not different from that in rats studied at normal LAP [11]. Hypoxia, another common association with chronic HF, is also capable of inhibiting alveolar Na^+/K^+ ATPase function and transalveolar fluid transport [12]. These findings support the intriguing hypothesis that impaired Na^+/K^+ ATPase gene expression occurs during acute lung injury, and provides evidence that the result of a pressure and/or volume overload on lung circulation is an increase in capillary permeability to water and ions and disruption of local mechanisms for gas exchange.

Alveolar–capillary remodeling

While there is enough evidence, from both the experimental and clinical settings, of complete reversibility during acute conditions [13], in the long term, alveolar changes are progressive and no definitive evidence of reversibility exists. In a pace-induced HF model, changes in alveolar-membrane ultrastructure consist of the development of a membrane thickness due to excessive collagen Type IV deposition, the major component of the alveolar lamina densa interposed between the epithelial and endothelial layers [14]. These changes are suggestive of a remodeling process that, similar to what has been observed in patients with secondary pulmonary hypertension may, on one hand, be protective against fluid swelling and edema development and, on the other hand, prolong the gas diffusion path [15]. Factors leading to the transition from alveolar stress failure to chronic remodeling are not clearly identified. However, re-expression of fetal genes might play a considerable role [1].

Clinical relevance of gas diffusion abnormalities in heart failure

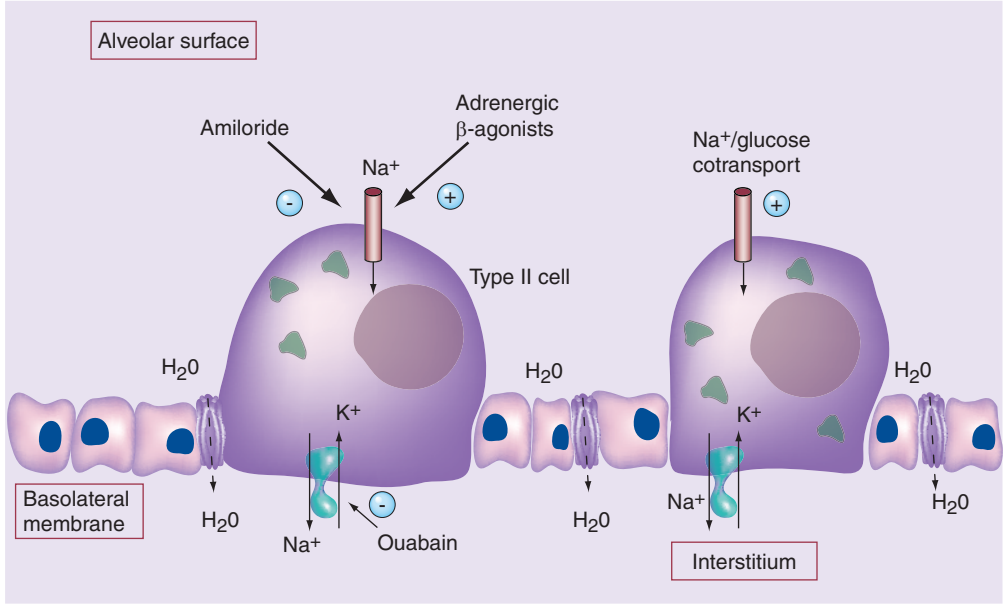
Measurement of lung-diffusing capacity for carbon monoxide (DLco) or nitric oxide (DLno) is generally used in clinical practice to evaluate the effectiveness of diffusive O_2 transport. As originally suggested by Roughton and Forster [16], for a given alveolar volume and hemoglobin concentration, gas diffusion depends on two resistances arranged in series according to the following equation:

$$1/DLco = 1/Dm + 1/\theta CO \times Vc$$

Where Dm is the alveolar–capillary membrane conductance, θCO is the rate of CO uptake by the whole blood in combination with hemoglobin measured *in vitro* and Vc is the capillary blood volume. Changes in Dm track structural alterations of the alveolar–capillary barrier, providing sensitive noninvasive indication of microvascular integrity in health and disease. Vc is related to pulmonary capillary wedge pressure. In stable HF patients, Vc tends to increase in order to compensate for a reduced Dm. It has been suggested that Vc may then reduce in advanced HF patients [17].

In a seminal paper, Puri and colleagues [18] first documented that HF patients present with a low DLco according to the disease severity, and that this correlates with increased pulmonary vascular resistances. A reduction in the Dm component rather than changes in Vc accounted for observed gas-diffusing abnormalities. Several subsequent reports [19–32] have confirmed and expanded these findings and in studies in which alveolar volume (VA) has been measured, abnormalities in DLco persisted even after VA normalization (**Table 1**). Remarkably, patients with HF and diabetes comorbidity exhibit a more severe Dm impairment than those with similar hemodynamic dysfunction without diabetes [31].

Figure 1. Molecular and cellular pathways involved in alveolar fluid clearance.



Na^+ enters the apical membrane of alveolar Type II cells, mainly through the amiloride-sensitive epithelial Na^+ channels, and is then transported across the basolateral membrane in to the interstitium through the ouabain-inhibitable Na^+/K^+ ATPase pump. On the apical surface of Type II cells, there is also a glucose cotransport system for Na^+. Passive Na^+ transport generates an osmotic gradient that induces removal of excessive intra-alveolar fluid. In several clinical conditions, such as heart failure, a defect of this mechanism predisposes patients to pulmonary edema regardless of Starling forces and lymphatic drainage.

Pathophysiologic correlates

Studies investigating the pathophysiologic role of a reduced Dm in HF patients have addressed the questions of whether Dm changes are fixed and exclusively related to chronic ultrastructural lung changes, or whether there is also a variable component related to interstitial edema and loss of fluid permeability. According to the basic experimental evidence that pulmonary interstitial fluid accumulation is secondary to a dysregulation of Na^+ handling [7,33], changes in Dm following saline infusion have been investigated in patients with chronic HF of different severity. In a study performed in postmyocardial infarction patients with normal LV systolic function an infusion of approximately 800 ml saline reduced Dm by 13% [30]. In patients with mild-to-severe HF, a 150 ml infusion of saline produced a significant Dm reduction as 750 ml saline, whereas a 750 ml infusion of isotonic glucose solution did not decrease DLco and Dm [29]. None of these infusions caused changes in right atrial and pulmonary wedge pressure (PWP) (**Table 2**). These findings support the idea that Dm abnormalities are, in part, fluid-dependent, and that Na^+ infusion may be, even in small amount, a challenge for cellular pathways involved in alveolar fluid clearance and capillary fluid reabsorption. Pulmonary abnormalities and, specifically those in gas-diffusion capacity, can explain part of the symptoms and functional limitation encountered in HF. Notably, Dm at rest and relative changes on exertion correlate with O_2 uptake at peak exercise [18,34]. However, the correlation is even greater between Dm and the excessive ventilatory requirement to CO_2 output, which is typical of these patients [35].

The putative role of lung diffusion abnormalities in the pathophysiology of exercise limitation in HF has not been definitively appreciated due to the lack of significant O_2 desaturation during exercise. In HF patients, however, despite pulmonary perfusion (Q), this may be significantly reduced as the ability to appropriately recruit Dm for that given Q preserves the Dm:Q ratio and prevents O_2 from significant drops [36]. However, there is documentation that the development of exercise-induced subclinical pulmonary edema is a common finding in HF patients as suggested by a significant and persistent Dm and Dm/Vc reduction during the recovery phase of exercise [37]. This might increase the dyspnea

Table 1. Studies on lung diffusion capacity in heart failure.

	No. of patients	NYHA functional class	DLco % predicted	DLco/VA % predicted	Ref.
Wright *et al.* (1990)	132	III–IV	64.5		[19]
Davies *et al.* (1990)	14	III	85	87	[20]
Seigel *et al.* (1990)	34	II–III	63	90	[21]
Naum *et al.* (1992)	34	II–III	63		[22]
Ravenscraft *et al.* (1993)	38	III–IV	81.3	106	[23]
Ohar *et al.* (1993)	32	III	69		[24]
Kraemer *et al.* (1993)	50	II–III	81		[25]
Messner-Pellenc *et al.* (1995)	10	II–III	90	82	[26]
Puri *et al.* (1995)	50	II–III	96	90	[18]
Guazzi *et al.* (1997)	24	II–III	82.5		[27]
Assayag *et al.* (1998)	47	II–III	88	91	[28]
Guazzi *et al.* (1999)	27	II–III	80		[29]
Puri *et al.* (1999)	10	I	89		[30]
Guazzi *et al.* (2002)	50	II–III	70	70	[31]
Abraham *et al.* (2002)	57	I–III	85		[32]

DLco: Lung diffusing capacity for carbon monoxide; NYHA: New York Heart Association; VA: Alveolar volume.

sensation by activating J receptor afferents, and there is also a suggestion that the Dm:Q ratio decreases and significant hypoxemia on exercise develops in some post-transplant patients. This is explained by the fact that pulmonary lung perfusion is reversed to normal in the presence of fixed ultrastructural membrane changes leading to exercise V/Q mismatching.

Alveolar gas-diffusion abnormalities & therapy in heart failure patients

In contrast with the increasing evidence of a pathophysiologic role, the opportunity to consider the alveolar–capillary membrane a therapeutic target is probably underestimated. The importance of considering an altered gas exchange as a target of treatment is emphasized by the demonstration that, despite major airway abnormalities observed in HF, patients may be improved by tailored therapy, DLco remains low up to several years after heart transplantation [38]. A relationship has also been established between the time course of the disease and impedance to gas exchange [39]. These findings confirm a progressive lung capillary remodeling process and suggest that a reduction in DLco reflects, at least in part, fixed structural changes. Consistently, in a prospective survival study in which the prognostic power of lung volumes, Dm and Vc, were investigated, Dm was the only independent pulmonary predictor of worse prognosis in HF patients [40].

Despite the lack of evidence of a complete DLco and Dm reversibility with treatment, a favorable modulatory activity on these variables by angiotensin-converting enzyme (ACE) inhibitors has been repeatedly reported [27,41] – an effect appearing promptly after drug administration, which persists over time and is unrelated to

Table 2. Effects of different amouts of saline glucose solutions infused in stable HF patients on DLco, Dm, Vc and pulmonary hemodynamics.

	Control subjects				HF patients			
	0.9% Saline		*Glucose 5%*		*0.9% Saline*		*Glucose 5%*	
	150 ml	*750 ml*	*150 ml*	*750 ml*	*150 ml*	*750 ml*	*150 ml*	*750 ml*
DLco (ml/min/mmHg)	=	=	=	↑	↓	↓↓	=	=
Dm (ml/min/mmHg)	=	=	=	↑	↓	↓↓	=	=
Vc (ml)	=	=	=	↑	↑	↑	=	=
Right atrial pressure (mmHg)	=	=	=	=	=	=	=	=
PWP (mmHg)	=	=	=	=	=	=	=	=

DLco: Diffusing lung capacity; Dm: alveolar–capillary membrane conductance; HF: Heart failure; PWP: Pulmonary wedge pressure; Vc: capillary blood volume.

a pulmonary pressure-lowering effect. These mechanisms also seem to be involved in the overall benefits on survival produced by this class of drugs [40]. Factors that may reasonably underlie the improvement in gas exchange with ACE inhibitors are a modulation in extracellular matrix synthesis and collagen turnover, or an improvement in endothelial permeability and increased alveolar epithelial reabsorption of Na^+ and fluid [42]. There is also experimental evidence that exposure of alveolar epithelial cells to the ACE inhibitor, lisinopril inhibits angiotensin II-mediated apoptosis and cell loss [43]. Interestingly, an association has been found between DLco and ACE genotype polymorphism [32], implying that higher ACE inhibitors doses are very likely required for treating lung abnormalities of HF patients with ACE DD-genotype. β-blockers do not provide a similar reverse remodeling of alveolar pneumocytes occurring in the biologic properties of cardiomyocites. A 6-month follow up with carvedilol did not promote any improvement in DLco, Dm [44].

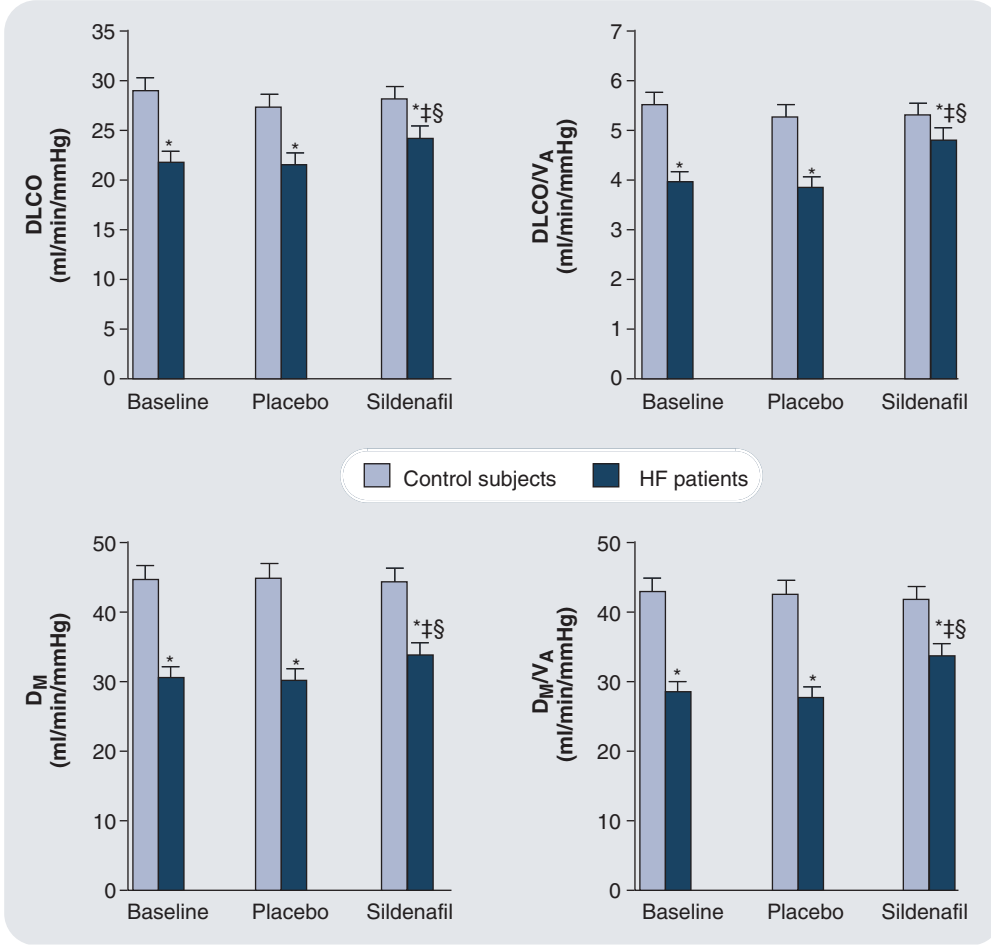
The concern that antiarrhythmic treatment with amiodarone may exert untoward effects on lung diffusion may be very likely excluded by the demonstration in a relatively large population of congestive HF patients that no DLco changes occurred after 1 year of amiodarone treatment [45]. Since DLco may not adequately reflect abnormalities intrinsic to the alveolar–epithelial and capillary layer, this question awaits further and more detailed studies.

Overexpression of NO pathway & alveolar membrane conductance

There is no question that NO from the pulmonary and venous endothelia plays an important role in lung physiology, due to its critical involvement in the maintenance of normal pulmonary vascular tone [46] and permeability, and in the tissue component, resistance to O_2 transfer from the alveolus to its uptake by hemoglobin [47]. Modulation of NO pathways has been successfully proposed for the treatment of pulmonary hypertension, and there are recent suggestions that it could be an effective therapeutic strategy for improving alveolar gas exchange and potentially reversing pulmonary capillary remodeling of HF patients. Specifically, there is the interesting perspective that interventions aimed at improving systemic endothelial function, such as aerobic exercise training, may also favorably impact gas exchange and pulmonary capillary properties.

In a group of stable HF patients, exercise training improved gas diffusion by exerting a combined effect on Dm and Vc and their normalization for alveolar volume, suggesting that repeated episodes of increased blood flow (i.e., shear stress) with exercise or metabolic effects of training may be the basis for a chronic stimulus to the release of endothelial paracrine agents, such as NO, that control vascular tone and permeability. These effects may not be confined to exercising limbs but would be imposed throughout the vasculature, including the lung [48]. Consistent with this hypothesis, we recently tested whether a greater NO availability (by blocking degradation) may be beneficial on the lung-exchange physiology of these patients. In 16 stable congestive HF patients, phosphodiesterase $(PDE)_5$ inhibition with sildenafil, improved Dlco, Dm, Dlco/Va and Dm/Va [49] (**Figure 2**), an effect that acutely promoted a significant increase in exercise peak VO_2 as well as a decrease in the VE/VCO_2 slope.

Figure 2. Acute changes in DLco, Dm and Dm/Va after acute administration of sildenafil (50 mg) in patients with stable HF and secondary pulmonary hypertension.



DLco: Lung diffusing capacity for carbon monoxide; Dm: Alveolar-capillary membrane conductance; Va: Alveolar volume (Modified from [49]).
*p < 0.01 vs. control subjects.
‡p < 0.01 vs. baseline.
§p < 0.01 vs. placebo.

Expert commentary & outlook

There is recent growing interest in the pathophysiologic correlates that link HF to abnormalities in alveolar-gas diffusion. Development of HF exposes the lung microcirculation to a pressure and/or volume overload whose functional and anatomical reflections have been outlined in different animal models and experimental conditions. Acutely, mechanical injury to the alveoli leads to alveolar-membrane stress failure, a process that causes endothelial- and alveolar-cell breaks and impairs cellular pathways involved in fluid permeability and reabsorption. When the alveolar membrane is chronically challenged, a typical remodeling process takes place characterized by fixed structural membrane changes (i.e., extracellular matrix collagen proliferation) and re-expression of fetal genes. Remodeling leads to a sustained reduction in gas diffusion and is not totally reversible, as suggested by the documentation that abnormalities in alveolar-gas diffusion persist for several years up to heart transplantation.

Some therapeutic approaches that favorably impact the natural course of cardiac remodeling, such as ACE inhibitors, are also effective on alveolar properties and gas exchange. Therapies aimed at increasing lung capillary NO availability appear promising for the cure of alveolar–capillary membrane dysfunction in patients with cardiac failure.

Highlights

- Knowledge of the pathophysiologic role of lung-diffusion abnormalities and gas-exchange inefficiency in patients with heart failure (HF) continues to grow.
- The occurrence of a pressure and/or volume overload on the lung microcirculation challenges the alveolar–capillary integrity, causes an increase in capillary permeability to water and ions and impairs local mechanisms for gas diffusion.
- Abnormalities in gas diffusion may be quantified by measuring the alveoar–capillary membrane conductance (Dm) and the capillary–blood volume (Vc). In HF patients, an abnormal Dm reflects the underlying lung-tissue damage, is an independent prognostic marker and is involved in the pathogenesis of exercise limitation.
- Although in HF patients, Dm changes partially reflect a fixed structural alteration in anatomical and functional membrane properties, ACE inhibition has been shown to improve Dm. Promising therapeutic approaches include interventions capable of increasing nitric oxide availability in lung microvessels.

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