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Reduced Alveolar–Capillary Membrane Diffusing Capacity in Chronic Heart Failure

Its Pathophysiological Relevance and Relationship to Exercise Performance

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Abstract

Background The pulmonary diffusing capacity for carbon monoxide (DLCO) is reduced in chronic heart failure (CHF) and is an independent predictor of peak exercise oxygen uptake. The pathophysiological basis for this remains unknown. The aim of this study was to partition DLCO into its membrane conductance (D_M) and capillary blood volume components (Vc) and to assess if alveolar–capillary membrane function correlated with functional status, exercise capacity, and pulmonary vascular resistance.

Methods and Results The classic Roughton and Forster method of measuring single-breath DLCO at varying alveolar oxygen concentrations was used to determine D_M and Vc in 15 normal subjects and 50 patients with CHF. All performed symptom-limited maximal bicycle exercise tests with respiratory gas analysis; 15 CHF patients underwent right heart catheterization. DLCO was significantly reduced in CHF patients compared with normal subjects, predominantly because of a reduction in D_M (7.0±2.6 versus 12.9±3.8 versus 20.0±6.1 mmol · min^{-1} · kPa^{-1} in New York Heart Association class III, class II, and normal subjects, respectively, $P<.0001$), even when the reduction in lung volumes was accounted for by the division of D_M by the effective alveolar volume. The Vc component of DLCO was not impaired. D_M significantly correlated with maximal exercise oxygen uptake ($r=.72$, $P<.0001$) and inversely correlated with pulmonary vascular resistance ($r=.65$, $P<.01$) in CHF.

Conclusions Reduced alveolar–capillary membrane diffusing capacity is the major component of impaired pulmonary gas transfer in CHF, correlating with maximal exercise capacity and functional status. D_M may be a useful marker for the alveolar–capillary barrier damage induced by raised pulmonary capillary pressure.

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Although impairment of cardiac performance is the primary abnormality in chronic heart failure, symptoms and exercise capacity correlate poorly with hemodynamic indices of left ventricular function.[1] [2] Recent studies have shown that abnormalities of skeletal muscle[3] [4] and lung function[5] are prominent features of heart failure and that such secondary abnormalities may explain much of the variability of exercise tolerance observed in patients with left ventricular dysfunction.

Reduction in the pulmonary diffusing capacity for carbon monoxide (DLCO) is well documented in chronic heart failure.[6] [7] [8] The functional significance of this reduction remains controversial; DLCO is an independent predictor of peak exercise oxygen uptake in heart failure,[5] and increasing the inspired oxygen concentration has been shown to improve both arterial oxygen saturation and exercise performance in patients.[9] These reports would suggest that impairment of pulmonary gas exchange may play a role in the limitation of exercise capacity in chronic heart failure. However, as arterial oxygen desaturation is not prominent in the majority of patients with heart failure,[10] [11] the proportion of patients with heart failure exhibiting oxygen desaturation during exercise and the pathophysiological process leading to desaturation remains controversial.

DLCO may be partitioned into its two subcomponents using the classic Roughton and Forster method[12] [13] : D_M, the molecular diffusion of carbon monoxide across the alveolar–capillary membrane, and θ. Vc, the chemical reaction (θ) of carbon monoxide with pulmonary capillary blood (Vc). Recent experiments have highlighted a possible mechanism leading to a reduction of DLCO and the diffusing capacity of the alveolar–capillary membrane (D_M) in heart failure. In animal models, raising lung capillary transmural pressures leads to disruption and fractures of the endothelial and epithelial layers.[14] The response to pressure-induced trauma in the pulmonary microvasculature is proliferation of alveolar type II cells, thickening of the alveolar–capillary interstitium, and some fibrotic change.[15] Such changes would increase alveolar–capillary membrane thickness and reduce D_M. Extensive studies of pulmonary function have been performed in patients with mitral stenosis,[16] [17] including measurement of D_M and pulmonary capillary blood volume.[18] The reduction in DLCO and D_M in this patient group with elevated left atrial pressure correlates with New York Heart Association (NYHA) functional class[18] and the severity of histological lung damage,[19] supporting the hypothesis that D_M may reflect stress failure of the alveolar–capillary interface induced by pulmonary capillary hypertension.

The aim of the present study was to determine if the reduction in DLCO reported in heart failure was secondary to impairment of alveolar–capillary membrane function and whether alveolar–capillary membrane function correlated significantly with functional status, exercise capacity, and pulmonary vascular resistance.

Methods

Subjects

This study was approved by the Hammersmith Hospital Ethics Committee, and all subjects gave informed consent. Subjects who were currently smoking or gave a history of respiratory disease were excluded. None of the subjects had smoked for at least 12 months before being studied. Forty-eight

male and 2 female patients with stable symptomatic chronic heart failure of greater than 6 months' duration were studied. Table 1⇓ summarizes the clinical characteristics of this group. All were receiving treatment with loop diuretics at a dose equivalent to 46±20 mg of furosemide (mean±SD, and assuming that 1 mg bumetanide is equivalent to 40 mg furosemide) and angiotensin-converting enzyme inhibitors. Three patients were receiving amiodarone and 4 patients were taking digoxin. Drug therapy had remained unaltered in the 8 weeks before the study.

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Table 1.

Clinical Characteristics of Patients With Chronic Heart Failure

Fifteen healthy volunteers (14 men, 1 woman; mean age, 52 years; range, 34 to 66 years) without a history of cardiorespiratory disease and with a normal physical examination were also studied.

Pulmonary Function Testing

The forced expiratory volume in 1 second (FEV_1) and vital capacity (VC) were measured in a bellows spirometer (Vitalograph). The best of three measurements made was recorded. Any subject with evidence of airways obstruction, as defined by an FEV_1 to VC ratio <70% was excluded. DLCO was measured using a standard modified Krogh single-breath technique (PK Morgan).[13] This maneuver was performed in duplicate using as a test gas 0.28% carbon monoxide (CO), 14% helium (He), 21% O_2, balance nitrogen, and then repeated (again in duplicate) using a test gas with a higher oxygen (O_2) concentration (0.3% CO, 10% He, 89.7% O_2). All results were corrected for the subject's hemoglobin concentration. The alveolar partial pressure of O_2 (PAO_2) was recorded for all DLCO measurements, being estimated from the fractional expired O_2 concentration of the same expired gas sample used for the measurement of DLCO (Servomex O_2 analyzer 570A). Alveolar–capillary membrane diffusing capacity (D_M) and the pulmonary capillary volume of blood available for physiological gas exchange (Vc) were determined using the classic Roughton and Forster method, which is described in detail elsewhere.[12 13] This method partitions pulmonary diffusing capacity into its component resistances: the diffusive resistance of the alveolar–capillary membrane ($1 \cdot D_M$) and the reactive resistance due to pulmonary capillary blood ($1^{-1} \cdot \theta Vc$, where θ=the rate of reaction of CO with hemoglobin). The Roughton and Forster equation[12]

links these resistances. As CO and O_2 compete directly for the available hemoglobin binding sites, θ is inversely proportional to PAO_2. 1/θ was determined using the following equation, which assumes that the red cell membrane has a negligible resistance to gas exchange[13]:

where Hb=the subject's hemoglobin (g/dL) and PAO_2 is measured in kPa. If DLCO is measured at different PAO_2 values, a plot of 1/DLCO against 1/θ will yield a straight line with a *y*-intercept of $1/D_M$ and a gradient of 1/Vc.

Exercise Testing

All subjects performed upright symptom-limited maximal exercise tests on an electronically controlled bicycle ergometer (Siemens EM840). A progressive exercise protocol was used, 10-W/min increments being used in heart failure patients and 20-W/min increments in normal subjects. Subjects who terminated exercise for reasons other than breathlessness or fatigue were excluded. Carbon dioxide production, oxygen consumption, and minute ventilation were recorded on a breath-by-breath analyzer (Amis 2000 Respiratory Mass Spectrometer, Innovision). Heart rate and ECG were monitored continuously, while blood pressure was measured at 1-minute intervals.

Radionuclide Ventriculography

All patients with heart failure had left ventricular ejection fraction (EF) measured at rest by multigated radioisotope analysis in the supine position.

Right Heart Catheterization

Fifteen patients with heart failure underwent standard right heart catheterization with a balloon-tipped pulmonary artery flotation catheter. Cardiac output (using the thermodilution technique), pulmonary artery pressure (PAP), and pulmonary capillary wedge pressure (PCWP) were measured. The average of three consecutive measurements was used for subsequent analysis. Pulmonary vascular resistance (PVR) in Wood units was calculated by dividing the mean transpulmonary gradient (mean PAP−mean PCWP) by cardiac output. The results of resting hemodynamics in these patients are recorded in Table 2⇓.

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Table 2.

Resting Hemodynamic Variables in 15 Subjects With Chronic Heart Failure

Statistical Analysis

Comparison of results between normal subjects and patients in NYHA classes II and III was performed by ANOVA (Scheffe's F test). Correlation coefficients were calculated by univariate linear regression analysis. All values are expressed as mean±SD unless otherwise stated. $P<.05$ was considered statistically significant.

Results

Pulmonary Function

Table 3⇓ illustrates the mean results of spirometry, effective alveolar volume (VA), and anthropometric details for all subjects studied. Fig 1⇓ plots the individual results of all subjects with respect to DLCO, D_M, and Vc.

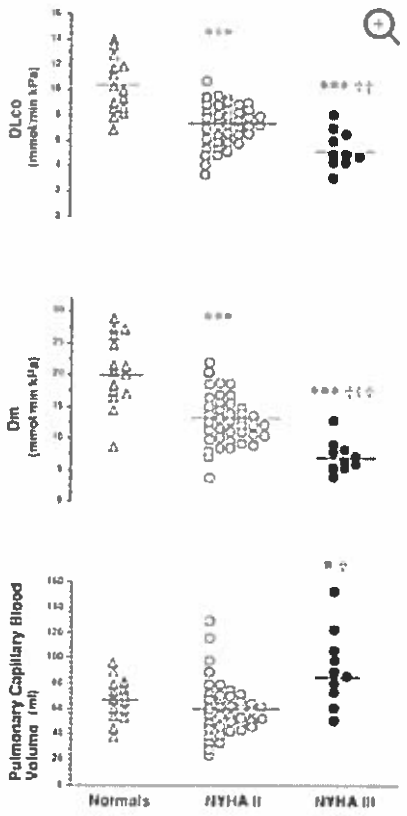

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Figure 1.

Plots of individual results and mean values of the pulmonary diffusing capacity for carbon monoxide (DLCO), alveolar–capillary membrane diffusing capacity (Dm), and pulmonary capillary blood volume for all normal subjects and heart failure patients. Statistical analysis was performed using ANOVA (Scheffe's F test). Compared with normal subjects **P*<.05, ***P*<.001, ****P*<.0001. Compared with New York Heart Association (NYHA) class II †*P*<.05, ††*P*<.01, †††*P*<.001.

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Table 3.

Results of Routine Lung Function Tests and Anthropometric Details of All Subjects Studied

DLCO and lung volumes (FEV_1, VC, and VA) were reduced in patients compared with normal subjects and were lower in patients in NYHA class III than those in NYHA class II ($P<.01$, Fig 1⇑ and Table 3⇑). The FEV_1/VC ratio remained within the normal range (Table 3⇑). The reduction in DLCO was predominantly due to a reduction in D_M (Fig 1⇑) and persisted even when the reduction in lung volumes was taken into account by plotting D_M/VA (Fig 2⇓). In patients with heart failure, the alveolar–capillary membrane diffusive resistance formed a greater proportion of the total pulmonary diffusive resistance ($DLCO/D_M$) than in normal subjects (Fig 2⇓). Vc was similar in normal subjects and patients in NYHA class II (61±23 versus 68±15 mL) but was increased in patients in NYHA class III (84±26 mL, $P<.05$).

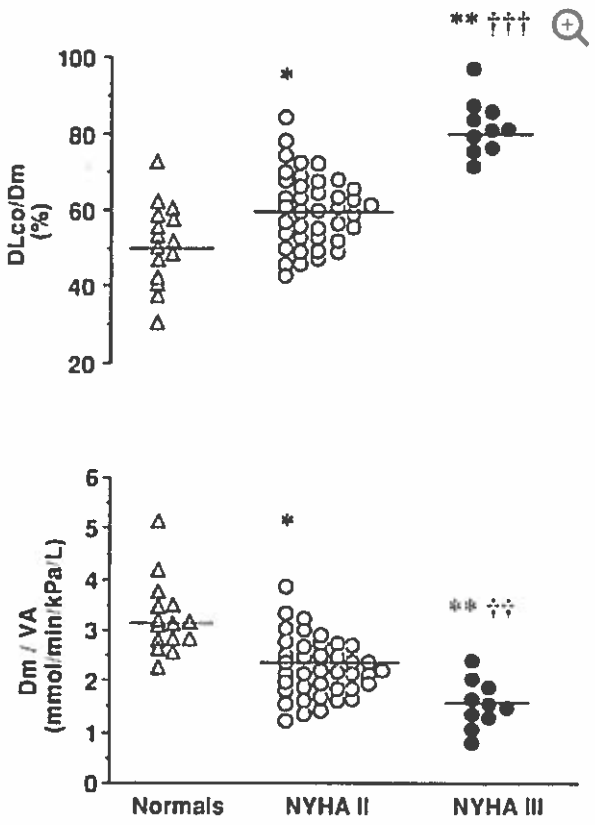

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Figure 2.

Plots of individual results and mean values of the proportion of total pulmonary diffusive resistance due to the alveolar–capillary membrane (DLCO/Dm) and the alveolar–capillary membrane diffusing capacity per unit effective alveolar volume (Dm/VA) in all normal subjects and heart failure patients. Statistical analysis was performed using ANOVA (Scheffe's F test). Compared with normal subjects *$P<.05$, **$P<.001$, ***$P<.0001$. Compared with New York Heart Association (NYHA) class II ††$P<.01$, †††$P<.001$.

Patients who were lifelong nonsmokers and those who were ex-smokers had a similar severity of heart failure (EF, 30±14% versus 29±10%; maximal oxygen consumption on exercise [MVO_2], 12.1±3.2 versus 13.0±4.2 mL · min^{-1} · kg^{-1}, respectively), and no significant differences were observed in spirometry, lung volumes (FEV_1, VC, VA), or pulmonary diffusion tests (DLCO, D_M). This would imply, therefore, that smoking history did not have a major effect on the differences in pulmonary function test results observed between the groups that were studied.

Exercise Testing

Table 4⇓ shows the pressure-rate product achieved and MVO_2 attained in all subjects. As expected, the patients with heart failure performed significantly worse than normal subjects.

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Table 4.

Exercise Test Results of All Subjects Studied

MVO_2 in heart failure patients correlated significantly with DLCO (r=.6, P=.001), but an even stronger correlation was observed with the D_M component of DLCO (Fig 3⇓, r=.72, P<.001). No such correlations were present in our normal subjects (r=.35, P=NS). In subjects who underwent right heart catheterization (Table 2⇑), significant correlation of D_M with MVO_2 was again observed (r=.7, P<.005). In addition, D_M inversely correlated with PVR (Fig 4⇓). No significant correlations were observed between any of the other resting hemodynamic indices measured (Table 2⇑) and MVO_2 or D_M.

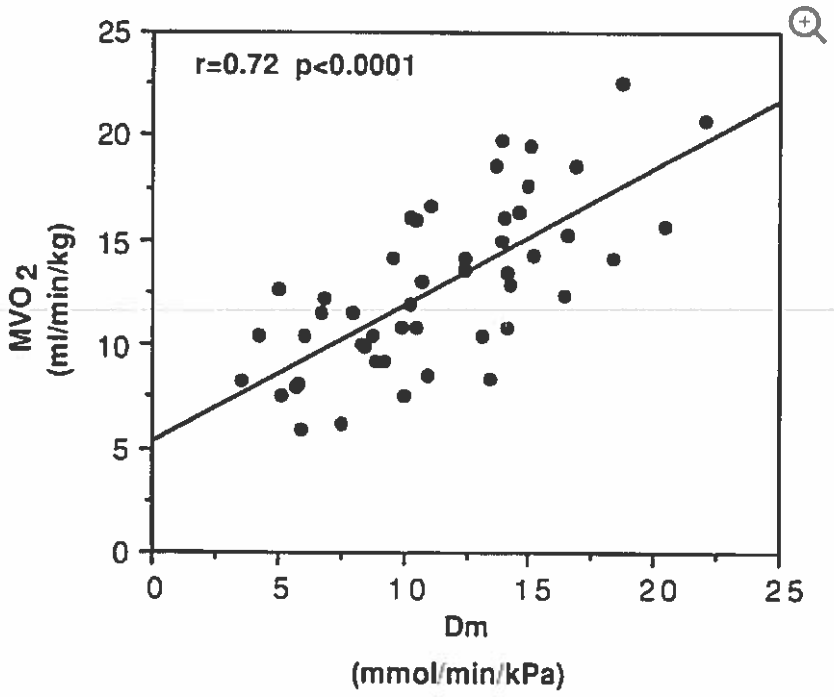

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Figure 3.

Correlation of maximal oxygen uptake on exercise (MVO_2) with alveolar–capillary membrane diffusing capacity (Dm) in patients with chronic heart failure. Linear regression analysis was performed to determine the correlation coefficient (*r*).

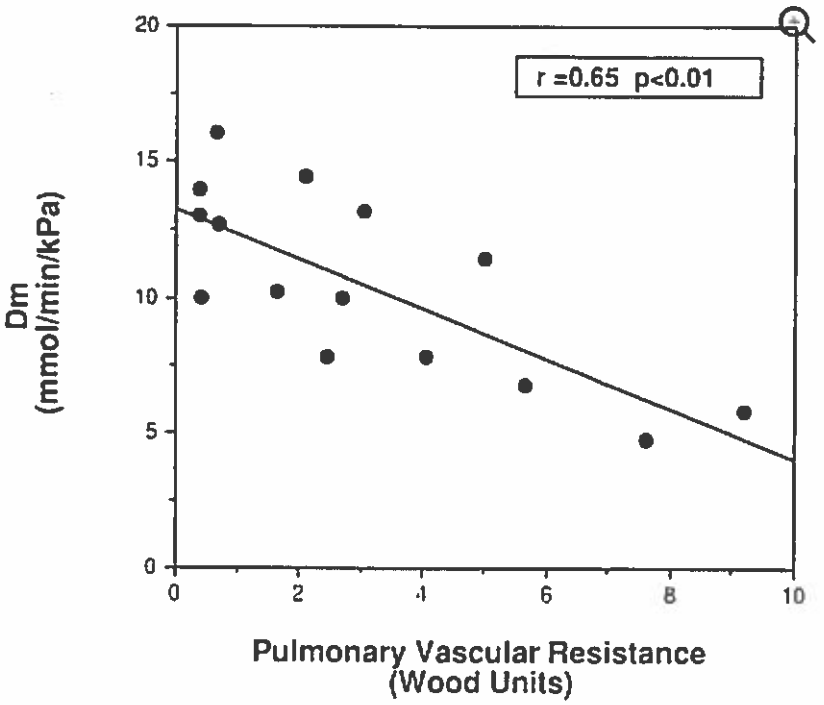

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Figure 4.

Inverse correlation of pulmonary vascular resistance and alveolar–capillary membrane diffusing capacity (Dm) in patients with chronic heart failure. The correlation coefficient (*r*) was determined using linear regression analysis.

Discussion

Our results confirm the presence of impaired pulmonary gas transfer at rest in chronic heart failure. The reduction in DLCO and lung volumes (FEV_1, VC, VA) in this study was in keeping with previous reports.[6 7 8] Pulmonary capillary blood volume was similar in control subjects and patients with heart failure, implying that reduced alveolar–capillary membrane diffusing capacity (D_M) was the major determinant of impaired pulmonary diffusing capacity. In normal subjects, 50% of the total pulmonary

diffusive resistance relates to the alveolar–capillary membrane, irrespective of age.[20] The results in our control group were similar to this value. In heart failure patients, however, a larger proportion of the total pulmonary diffusive resistance was caused by a reduction in D_M. Abnormalities in alveolar–capillary membrane diffusing capacity were greatest in those subjects with the greatest reduction in MVO_2 and the most severe symptoms, although there was clearly a degree of overlap between normal subjects and patients with milder symptoms. Theoretically, a reduction in the alveolar–capillary membrane surface area available for gas exchange, or an alteration in the physical properties of the membrane itself, may be responsible for the reduction in D_M.

D_M and Lung Volume

Reduced lung volumes are a feature of chronic heart failure[6 7] and would decrease the surface area available for gas exchange. A reduction in lung volumes was observed in this study in heart failure patients (Table 3⇑), but the reduction in D_M that was also noted persisted even when this reduction was accounted for (Fig 2⇑), implying that an intrinsic abnormality of the alveolar–capillary membrane, such as thickening, also exists. Further support for this hypothesis comes from failure of DLCO to improve after cardiac transplantation[21] despite normalization of lung volumes.[22]

D_M and Inhomogeneity of Lung Function

Maldistribution of ventilation and ventilation-perfusion mismatch are possible mechanisms that could reduce the effective surface area for gas exchange. In the absence of significant airflow obstruction, as in our patients (Table 3⇑), marked inhomogeneity of ventilation distribution is unlikely. Ventilation-perfusion mismatch would be expected to cause not only a reduction in effective DLCO and D_M, leaving the proportions of both ($DLCO/D_M$) relatively unchanged, but to reduce the volume of pulmonary capillary blood available for gas exchange (Vc). No reduction in Vc was seen in this study. By contrast, those patients with the greatest reduction in D_M (NYHA class III) exhibited an increase in Vc. Pulmonary capillary volume is determined by the radius of the capillary and the surface area of the alveolar–capillary interface available for physiological gas exchange. The increase in Vc seen in NYHA class III patients may, therefore, reflect pulmonary capillary distension secondary to elevation of left atrial pressure. Alternatively, improved ventilation-perfusion matching at rest in these patients[23 24] may be responsible for the increase in Vc.

D_M and Pulmonary Oxygen Diffusion Limitation on Exercise

Pulmonary diffusion limitation has not been thought to be an important mediator of exercise impairment in heart failure because exertional arterial oxygen desaturation is not prominent.[10 11] In addition, prolonged pulmonary capillary blood transit time may allow greater time for gas transfer, thereby limiting the importance of any impairment of diffusion that might be present at the alveolar–capillary membrane.[25] Higher than normal levels of ventilation occur on exercise in chronic heart failure. This increased level of ventilation should elevate alveolar oxygen tension and subsequently increase arterial oxygen saturation in the absence of significant oxygen diffusion limitation or ventilation-perfusion mismatch. Alveolar-arterial gradients of oxygen ($AaPO_2$) up to 32 mm Hg, however, occur on exercise in heart failure,[10] implying that either singly or in combination, some degree of oxygen diffusion limitation or ventilation-perfusion mismatch exists. A reduced D_M may contribute to the widened $AaPO_2$ gradient in patients with heart failure. $AaPO_2$ gradients of ≈30 mm Hg, however, would not in themselves cause significant arterial hypoxemia, and therefore alternative mechanisms may be responsible for the correlation of D_M with MVO_2.

D_M as a Marker for Raised Pulmonary Vascular Resistance

Transient elevation of pulmonary artery pressure has been shown to cause alveolar epithelial and pulmonary endothelial damage in experimental models.[14] Elevation of pulmonary capillary pressures may occur at rest in heart failure[26] and increase further on exercise,[2 27 28] providing a possible mechanism for stress failure of the alveolar–capillary membrane[29] and its subsequent dysfunction. In mitral stenosis, reduced DLCO correlates with the degree of pulmonary vascular damage.[19] The inverse correlation between pulmonary vascular resistance (PVR) and D_M in this study suggests that these two variables may be different measures of the same pathological process, namely, pulmonary microvascular damage.

Interventions that improve pulmonary hemodynamics also improve exercise capacity.[30 31 32] In addition, failure to decrease PVR on exercise has been implicated in impaired exercise performance.[33] Conventional pulmonary hemodynamics, as measured by right heart catheterization, can only provide an instantaneous assessment of the pulmonary circulation under laboratory conditions. Measurement of D_M may reflect long-term cumulative pulmonary microvascular damage, providing a more sensitive and noninvasive marker than hemodynamics measured in the cardiac catheterization laboratory.

Conclusions

We have identified reduced alveolar–capillary membrane diffusing capacity as the major component of impaired pulmonary gas transfer in chronic heart failure. D_M significantly correlates with functional status as measured by NYHA class and maximal exercise capacity in such patients. Whether this impairment is simply a marker for the severity of the disease process or plays a pathophysiological role remains uncertain. Prospective studies are required to assess if modulation of alveolar–capillary membrane function is possible and has any effects on exercise performance in heart failure.

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