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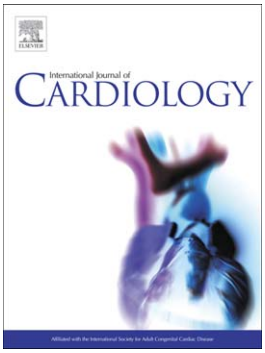

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Lung Fluid Clearance in Chronic Heart Failure Patients

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Keywords: Chronic heart failure; Pulmonary fluid clearance; Aerosol scintigraphy; Catecholamines

Abstract

Chronic elevation of pulmonary microvascular pressure (Pmv) consistently leads to alveolocapillary barrier thickening and reduction in the filtration coefficient. In animal models of chronic heart failure (CHF) the lung remains dry despite hydrostatic forces. As fluid flux is bi-directional, it has been postulated that an increase in alveolar fluid clearance may facilitate the dry lung when Pmv is chronically elevated. In this study we aimed to examine alveolar fluid clearance in ambulatory patients with CHF secondary to left ventricular (LV) systolic dysfunction compared against non-CHF controls. Lung clearance following aerosol delivery of ^{99m}technetium (Tc)-diethyl triaminepentaacetic acid (DTPA) was measured non-invasively by scintigraphy and half time of ^{99m}Tc-DTPA clearance (T (1/2)) was calculated by mono-exponential curve fit. Alveolar fluid clearance measured as half time DTPA clearance was significantly faster in CHF patients than controls (P = 0.001). This was further defined by NYHA classification. No correlation was found between DTPA clearance and plasma epinephrine, norepinephrine or aldosterone hormone ($P > 0.05$). Our results support an association between increasing alveolar fluid clearance and disease severity in CHF, and the concept of controlled bi-directional fluid flux in CHF associated with increasing Pmv, and represents another defence mechanism of the lung against pulmonary oedema.

Introduction

Chronic elevation of pulmonary microvascular pressure (Pmv) consistently leads to thickening of the endothelial and epithelial basement membranes, and reduction in the filtration coefficient [1, 2]. In animal models of chronic heart failure (CHF) there is strain dependent variation in the balance between fibrotic remodelling and alveolar type II cell (ATII) hyperplasia, likely reflecting clinical differences in response to chronic elevation of Pmv. However, all models manifest a heavier dry lung without apparent pulmonary oedema despite hydrostatic forces favouring its development [2-5]. As fluid flux is bi-directional it has been postulated that an increase in alveolar fluid clearance (outflow) may facilitate the dry lung when Pmv is chronically elevated and favouring fluid influx [6, 7].

Using a rodent model of CHF, we recently demonstrated increased tolerance of the *ex vivo* isolated perfused lung to acute left atrial pressure elevation, but reduced clearance of alveolar lung fluid in the non-perfused isolated lung [8]. These processes occurred on a background of increased dry lung weight, previously found to correlate with lung collagen and a decrease in endothelial aquaporin (AQP)1 [5, 8]. These data are consistent with reduced bi-directional fluid flux due to both structural and cellular remodelling. Preliminary clinical data from patients admitted to ICU with acute pulmonary oedema similarly suggested slower plasma refill in patients with CHF compared to patients without, which we hypothesised may be due to slower alveolar clearance of oedema fluid [8]. In a previous study, again utilising the rodent model of CHF, we found greater lung accumulation of the intravascular hydrophilic radio marker ^{99m}technetium (Tc)-diethyl triaminepentaacetic acid (DTPA), suggesting increased pulmonary permeability *in vivo* in animals with CHF [4].

In this study we aimed to further clarify these findings clinically by examining alveolar fluid clearance in ambulatory patients with CHF secondary to left ventricular (LV) systolic dysfunction compared against non-CHF controls. The study complies with the Declaration of Helsinki, the protocol was approved by the Flinders Clinical Research Ethics Committee, Flinders Medical Centre, and all participants provided written informed consent.

Methods

Adult participants attending Flinders Medical Centre, Adelaide, Australia were classified as: CHF - a clinical diagnosis of CHF of at least 6 months duration, or non-CHF - no history of heart failure in healthy

volunteers recruited through poster advertisement, age and gender matched to CHF patients. Lung clearance following aerosol delivery of ^{99m}Tc-DTPA was measured non-invasively by scintigraphy with a γ-camera in the Dept. of Medical Imaging, using standard nuclear medicine diagnostic protocols, as previously described [9]. Half time of ^{99m}Tc-DTPA clearance (T (1/2)) was calculated by mono-exponential curve fit. Plasma epinephrine, norepinephrine (Abnova Corp, Taiwan) and aldosterone (Cayman Chemical, Ann Arbor, MI) were assessed by Enzyme Linked Immunosorbent Assay.

Continuous data are presented as median (25^{th}-75^{th} percentiles) and analysed by Jonkheere-Terpstra test for ordered variables, 2 groups by Mann-Whitney U test and categorical variables as number (%) and analysed by Chi-square test. Correlations were examined by Pearsons Correlation. $P \leq 0.05$ was considered significant.

Results

Participants differed only in cardiac parameters (Table 1). Alveolar fluid clearance measured as half time DTPA clearance was significantly faster in CHF patients than controls (55.1 (47.6-71.6) versus 75.9 (70.3-84.8) min, median (25^{th}-75^{th} percentiles); P=0.001). This was further defined by NYHA classification (Table 2). No difference was found in any measured plasma hormone between groups, nor was any correlation found between DTPA clearance and plasma hormone (P > 0.05). There was however a significant correlation between norepinephrine and aldosterone (r^2 = 0.416, P = 0.007, by Pearson correlation).

Discussion

This study aimed to reconcile the conflicting findings from previous investigations into alveolar fluid regulation in CHF via the utilisation of a sensitive and specific marker of fluid movement in a well-defined patient cohort compared against matched non-CHF controls.

Lung water in CHF is increasingly recognised as a complex but critical component of the CHF syndrome which is incompletely understood pathophysiologically [10] and has been historically under recognised. Indeed, in recent clinical studies of discharge decompensated CHF, the presence of congestion on chest X-ray or via increased ultrasound B-lines is independently predictive of poor clinical outcome (hospitalisation and mortality) [10, 11].

Our results appear to support an association between increasing alveolar fluid clearance and disease

severity in CHF. This result supports previous animal investigations in isolated perfused lungs from volume overload CHF [12, 13], as well as the trend observed in a decompensated patient population [14], in which there is an increase in alveolar fluid clearance, but is inconsistent with our previous findings in the isolated non-perfused rat lung [8].

In looking at this result it is important therefore to examine the difference between models used. In non-perfused isolated CHF rat lungs *ex vivo* we showed reduced alveolar fluid clearance [8]. In the study by Kaestle *et al* [13] alveolar fluid clearance was examined in perfused isolated CHF lungs *ex vivo* and increased rate of clearance reported. However, this increase was only apparent when left atrial pressure was raised to 15cmH_2O. This suggests that there is a change in the rate of alveolar fluid clearance dependant on current Pmv. In chronic renal failure dialysis patients an increased rate of DTPA clearance from lungs is found to decrease after dialysis, ie following reduction in intravascular volume and therefore Pmv [15]. This suggests that while Pmv is high, such as in severe CHF (NYHA III) or the intravascular overloaded state of pre-dialysis, alveolar clearance increases with increased fluid influx, but when Pmv is lower (NYHA II) or at the end of dialysis following loss of intravenous volume, the rate of fluid flux is decreased, thereby manifesting as slower clearance.

Whether the clinically important presence of ongoing excess lung water in decompensated CHF represents a failure adequate lung fluid clearance or an issue of timing in the dynamic decompensated state is unknown [10, 11]. The model of increased Pmv resulting in increased fluid influx balanced by increased fluid clearance does not hold in models of acute heart failure, or acute rise in Pmv, where alveolar fluid clearance has been found to decrease and pulmonary oedema manifest [13, 16-18]. Therefore, we may assume that in the presence of chronically elevated Pmv the pulmonary system is intrinsically changed in a manner which facilitates an increase in alveolar fluid clearance in parallel with increased fluid input, but that this can be overwhelmed, possibly by a sudden Pmv increase, or which may be less effective in a cohort of patients. In order to adequately understand the relationship between bi-directional fluid flux and Pmv we must therefore examine the controlling mechanisms.

It has been suggested that increased rate of alveolar fluid clearance in CHF may be due to an increase in the absolute expression and activation of vectorial fluid channels on both endothelial and epithelial cells, controlled through a nitric oxide negative feedback mechanism [12, 13]. This mechanism, which allows for an increase in fluid flux capacity of the lung in CHF, provides a possible explanation for our previous finding of

resistance to elevation in Pmv in isolated perfused lungs from CHF. However, in order to explain our finding of decreased alveolar clearance in the non-perfused CHF lung, this mechanism would necessitate a sequential activation whereby the endothelium is activated prior to activation of these channels on the epithelium. In addition, changes in the expression of these channels have not been consistently observed, including in our animal study [8, 12].

Tandon and Kasturi first reported that in patients with CHF from mitral stenosis, pulmonary remodelling in response to chronically elevated Pmv results not only in thickening of the alveolocapillary barrier, but also in dilatation of the lymphatics [19]. This was supported more recently using ultrasound where patients with CHF were found to have an average thoracic duct diameter of 6.3mm in comparison with 2.5 mm in healthy subjects [20]. While this increase in lymphatic diameter provides for greater capacity for removal of accumulated interstitial fluid due to elevated Pmv in the isolated perfused lung or whole animal, in the absence of arterial pressure or mechanical muscle forces in our non-perfused, non-ventilated lung, this enhanced lymph drainage system would be less effective [21, 22]. In conclusion, this study supports the concept of controlled bi-directional fluid flux in CHF associated with increasing Pmv and represents another defence mechanism of the lung against pulmonary oedema. This increase in clearance rate may be due to enhanced lymphatic drainage with a contribution by specific ion and water channels, however, the mechanisms facilitating the dry lung in CHF require further elucidation.

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Table 1. Baseline Characteristics

	Control	CHF - NYHA II	CHF - NYHA III	*P* ≤
n	8	5	5	
Age (years)	65 (53-71)	56 (53-63)	63 (62-71)	0.68
Gender (male)	5 (63)	4 (80)	3 (60)	0.76
Hypertension	3 (38)	2 (40)	2 (40)	0.99
Diabetes	1 (13)	0 (0)	2 (40)	0.22
Inflammatory Disease	1 (13)	0 (0)	0 (0)	0.09
Atrial Fibrillation	0 (0)[a]	3 (60)[b]	2 (40)[ab]	**0.05**
Smoking <5yr cessation	0 (0)	0 (0)	0 (0)	1.00
Alcohol >2 glasses/day	1 (13)	0 (0)	0 (0)	0.09
Medications (Yes)				
Spironolactone	0 (0)[a]	5 (100)[b]	5 (100)[b]	**0.001**
ACE Inhibitors	0 (0)[a]	5 (100)[b]	3 (60)[b]	**0.001**
ARB	1 (11)	0 (0)	2 (40)	0.42
β-Blocker	1 (11)[a]	5 (100)[b]	5 (100)[b]	**0.001**
Loop Diuretic	0 (0)[a]	4 (80)[b]	4 (80)[b]	**0.001**
Statins	0 (0)[a]	0 (0)[a]	4 (80)[b]	**0.003**
Aspirin	1 (11)	0 (0)	3 (60)	0.12
Digoxin	0 (0)	1 (20)	0 (0)	0.56
Amiodarone	0 (0)	0 (0)	1 (20)	0.56
Echocardiogram				
LVEDD (cm)	-	6.1 (5.5-6.5)	6.2 (5.1-6.9)	0.84
Ejection Fraction (%)	-	29 (23-34)	35 (24-36)	0.55
LA size (cm^2)	-	24 (20-38)	30 (18-38)	1.00
IVC size (cm)	-	2.1 (2.0-)	2.5 (2.0-)	0.40
E:E’	-	12 (10-15)	15 (9-21)	0.69

Continuous data are presented as median (25^{th}-75^{th} percentiles) and analysed by Jonkheere-Terpstra test for ordered variables, 2 groups by Mann-Whitney U test and categorical variables as number (%) and analysed by Chi-square test. Superscripts represent differences by pairwise comparison at $P \leq 0.05$. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; IVC, inferior vena cava; LA, left atrial; LVEDD, left ventricular end-diastolic diameter.

Table 2. Outcome Measures

	Control	CHF - NYHA II	CHF - NYHA III	*P* ≤
n	8	5	5	
T^c-DTPA Clearance				
Half clearance time (min)	75.9 (70.3-84.8)[a]	71.2 (54.0-73.2)[b]	48.4 (40.2-58.1)[c]	**0.001**
Plasma catecholamines				
Epinephrine (pg/ml)	75 (31-126)	152 (62-199)	126 (108-161)	0.136
Nor-epinephrine (pg/ml)	1171 (781-1499)	1169 (936-1169)	1776 (1137-1986)	0.112
Aldosterone (pg/ml)	417 (381-417)	741 (502-957)	747 (538-791)	0.145

Data are presented as median (25^{th}-75^{th} percentiles) and analysed by Jonkheere-Terpstra test for ordered variables. Superscripts represent differences by pairwise comparison at $P \leq 0.05$. T^c-DTPA, technetium-99m-diethyltriaminepentaaceticacid.

Highlights:

- Alveolar fluid clearance measured as half time DTPA clearance was significantly faster in CHF patients than controls
- This was further defined by NYHA classification supporting an association between increasing alveolar fluid clearance and disease severity in CHF
- This finding supports the concept of controlled bi-directional fluid flux in CHF associated with increasing Pmv, and represents another defence mechanism of the lung against pulmonary oedema.