Influence of ACE-inhibition on salt-mediated worsening of pulmonary gas exchange in heart failure

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Aims In congestive heart failure (CHF), pulmonary gas exchange, as evaluated by carbon monoxide diffusion (DL_{CO}), is impaired. ACE-inhibition improves DL_{CO} . Infusion of saline worsens DL_{CO} , because of upregulated sodium and water transport to the alveolar interstitium, which thickens the alveolar–capillary interface and lengthens the diffusion path for gas exchange. We investigated whether enalapril can readjust the capillary permeability to sodium.

Methods In 10 NYHA class II–III CHF patients, we measured DL_{CO} , its two subcomponents (V_C , capillary blood volume available for gas exchange, and D_M , alveolar–capillary membrane diffusion), left and right ventricular filling pressures, plasma noradrenaline, aldosterone and renin activity, at baseline and following saline infusion in the main pulmonary artery stem, before and after 1 week enalapril treatment (20 mg daily).

Results Saline (150 ml) significantly reduced DL_{CO} (−9.1%) and D_M (−9.8%) and augmented V_C (+10.7%). Responses to 750 ml saline were somewhat greater and qualitatively similar. Enalapril produced a significant improvement of DL_{CO} and D_M at rest as well as after saline, that was not associated with variations in ventricular filling pressures, cardiac output and left ventricular ejection fraction, and was not accounted for by humoral changes.

Conclusions In CHF, ACE-inhibition attenuates the deterioration of pulmonary gas transfer produced by saline infusion, suggesting an ability to readjust the upregulated sodium transport across the pulmonary microvascular endothelium.

Keywords: enalapril, heart failure, pulmonary function

Introduction

For normal gas exchange between alveoli and blood, fine adjustments of local vessel tone and microvascular permeability are critical. In congestive heart failure (CHF), long-standing increase of the pulmonary venous pressure may disrupt the alveolar–capillary membrane, enhance the resistance to pulmonary gas transfer [1, 2], and contribute to exercise intolerance [1, 3–5]. In such circumstances, the ability of the microvessels to appropriately adjust the transport of sodium seems to be lost. The infusion of

normal saline in CHF patients [6], even in an amount (150 ml) which approximates to the pulmonary capillary blood volume in man in the supine position, is devoid of significant influences on right and left ventricular filling pressures [7], and worsens the molecular diffusion of carbon monoxide (D_M component of DL_{CO}) across the alveolar–capillary interface. This effect suggests that upregulated sodium transport through the microvascular barrier [7] lengthens the diffusion path for gas exchange by causing subclinical oedema of the alveolar interstitial space.

Since ACE-inhibitors improve pulmonary gas transfer in CHF [8, 9], we aimed to investigate whether these agents can readjust the lung microvascular permeability to salt in CHF patients. Attenuation with ACE-inhibition of the salt mediated impedance to gas transfer would reflect a readjustment of the sodium transport.

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Methods

Patients

The 10 patients investigated in this study were in chronic stable NYHA functional class II to III due to cardiac dysfunction. They received digoxin ($0.25 \pm 0.06 \text{ mg day}^{-1}$) and frusemide ($70 \pm 30 \text{ mg day}^{-1}$), and left ventricular ejection fraction (LVEF) was $\leq 40\%$. We excluded patients who had: pulmonary diffusing capacity for carbon monoxide $\leq 75\%$ of predicted normal value; history of smoking (> 10 cigarettes per day during one of the past 5 years); history of renal disease with serum creatinine concentration $\geq 1.5 \text{ mg dl}^{-1}$, or respiratory disease with forced expiratory volume in 1 s (FEV_1) to vital capacity (VC) ratio $< 70\%$; ACE-inhibitor [8, 9], acetylsalicylic acid or other cyclooxygenase inhibitor [8, 10] therapy within the last 2 months. Seven of the selected patients were in NYHA class II and three in class III; nine had idiopathic dilated cardiomyopathy, and one had ischaemic heart disease due to previous myocardial infarction.

We investigated the responses to infusion of 0.9% saline in the pulmonary circulation before and after combination of enalapril to the baseline antifailure treatment of these patients. None had been investigated previously in our laboratory; all gave their written informed consent and the procedures were approved by the Ethics Committee of the Institute of Cardiology, University of Milan, and were in accordance with the institutional guidelines.

Pulmonary and biochemical evaluations

DL_{CO} was determined (Sensor Medics 2200 Pulmonary Functional Test System, Yorba Linda, CA) in duplicate on each occasion, with washout intervals of at least 4 min (the average was the final result), with a single breath technique [11] and with correction for the patient's haemoglobin concentration. We obtained measurements of the two subcomponents of DL_{CO} , the diffusing capacity of the membrane (D_M) and the volume of pulmonary capillary blood available for gas exchange (V_C), using the classic method of Roughton & Forster [12]. As proposed by these authors, the overall resistance to gas transfer ($1/\text{DL}$) depends on the membrane resistance component ($1/\text{D}_\text{M}$) and the red blood cell component ($1/\theta \text{ V}_\text{C}$); the latter is based on the reaction rate of the gas with haemoglobin (θ) and the lung capillary blood volume (V_C). We obtained all measurements with a test gas containing 0.28% CO , 14% He and 21% O_2 and the balance nitrogen. The DL_{CO} measurements were then repeated with a test gas containing 0.3% CO , 10% He

and 89.7% O_2 . Consecutive measurements of D_M showed a correlation coefficient of 0.95 and coefficient of variation $< 6\%$. FEV_1 , VC, total lung capacity and DL_{CO} are presented as percent of normal values as predicted from standard nomograms incorporating age, sex, weight and height [13]. The ratio of D_M to VA (alveolar volume derived by single breath methane dilution) was utilized to account for hypothetical pulmonary volume variations with fluid infusion.

Aldosterone plasma concentration and plasma renin activity (PRA) were determined by radioimmuno-assay. Circulating noradrenaline was assessed by high performance liquid chromatography. Urine electrolytes were assessed by ion selective electrodes.

Design

All patients had no clinical signs of fluid retention and were maintained on optimal stable doses of digoxin and frusemide and on a constant isocaloric diet containing 130 mmol Na^+ , 90 mmol K^+ and 1500 ml water day^{-1} throughout the study. After 5 days of controlled diet, patients were admitted to the hospital where urinary Na^+ , K^+ and creatinine were monitored in the first 24 h and the achievement of sodium balance was confirmed. In the second and in the third 24 h periods, patients were subjected to 0.9% NaCl solution infusions in amounts of 150 and 750 ml, respectively. Then, enalapril (20 mg day^{-1}) was added to the baseline treatment that was kept constant, and patients were discharged and readmitted to hospital 1 week later for repeat of the same procedures while continuing enalapril. The investigators were blind to the patient's clinical condition and drug treatment. Studies were started at 08.00 h after an overnight fast. A triple-lumen, flow-directed, thermodilution, balloon-tipped catheter was introduced percutaneously into an antecubital vein under local anaesthesia and advanced to the pulmonary circulation while patients were supine; then, their chest wall was elevated at 45° and this comfortable position was maintained throughout the study. Water and sodium excretion was measured in urine collected in the 3 h periods preceding and following saline. Infusions were into the main pulmonary artery stem, at a rate of $0.2 \text{ ml kg}^{-1} \text{ min}^{-1}$; right atrial and wedge pulmonary pressures were monitored through each study; DL_{CO} , D_M and V_C were measured twice in the 2 h before saline, soon after completion of infusion, and 1 and 2 h later. Haematocrit (Htc), haemoglobin (Hb), plasma protein (PPC), noradrenaline, aldosterone concentrations and renin activity, cardiac index (CI) and LVEF were measured 10 min before and 10 min after each infusion.

Statistical methods

One-way ANOVA for repeated measures and *post hoc* Newman-Keuls procedure were utilized for the analysis of changes after saline. Responses to different amounts of saline or to the same amount with enalapril were compared by paired *t*-test. Data are means $\pm$ 1 s.d. For mean differences in DL_{CO}, D_M and D_M/VA between before and after enalapril, values were calculated with 95% confidence intervals (CI). Differences were considered significant for $P < 0.05$.

Results

Patients were males with a mean age of 58 ± 11 years. Their 24 h urinary output was 1560 ± 210 ml and sodium excretion was 94 ± 6 mmol. Systolic and diastolic arterial pressures were normal; FEV₁, VC, total lung capacity and DL_{CO} were 84 ± 10 , 79 ± 11 , 77 ± 9 , $77 \pm 3\%$ of normal values. Baseline mean right atrial and wedge pulmonary pressures, Hb, PPC and Htc were within normal limits; LVEF and CI were depressed; plasma aldosterone and noradrenaline concentrations and PRA were raised (Table 1). Differences in the preinfusion data between sessions both without and with the test drug were not significant. There were no symptoms or complaints during the studies.

Saline significantly reduced DL_{CO}, D_M and D_M/VA, and changes were qualitatively similar with 150 and 750 ml amounts (Figure 1). While on enalapril, DL_{CO}, D_M and D_M/VA were significantly ($P < 0.01$) raised at baseline. Mean differences between before and after ACE-inhibition in DL_{CO}, D_M and D_M/VA, in $\text{ml min}^{-1} \text{mmHg}^{-1}$, respectively, were 1.70 (95% CI 1.25–2.15), 3.30 (95% CI 2.87–3.73), 0.94 (95% CI 0.22–1.66). Percent reduction of these variables with either saline solution were comparable with those before enalapril, and, because of this, absolute values of DL_{CO}, D_M and D_M/VA following infusion of salt were significantly ($P < 0.01$) improved after the ACE-inhibitor. Mean differences between before and after enalapril, in $\text{ml min}^{-1} \text{mmHg}^{-1}$, following 750 ml of saline, were 1.63 (95% CI 1.10–2.16), 3.80 (95% CI 3.42–4.18), 1.13 (95% CI 0.62–1.64), respectively. While on enalapril, V_C was reduced at baseline, and levels attained with saline were lower than those before the drug. Both with and without ACE-inhibitor, values of DL_{CO}, D_M and D_M/VA and V_C at 1 and 2 h after infusions were not significantly different from preinfusion values, indicating that in these patients the pulmonary effects of saline disappeared within less than 60 min.

As shown in Table 1, administration of 150 ml saline was associated with a reduction of aldosterone and PRA, and with an increase of circulating noradrenaline. There

Table 1 Mean values of cardiac, pulmonary, haematological and humoral variables at baseline and immediately after 150 ml and 750 ml saline infusions, before and after combination of enalapril to the background treatment.

	Before enalapril		After enalapril		Before enalapril		After enalapril	
	Baseline	150 ml saline	Baseline	150 ml saline	Baseline	750 ml saline	Baseline	750 ml saline
Mean right atrial pressure (mm Hg)	2.1 ± 0.9	2.0 ± 1.2	1.8 ± 0.8	2.1 ± 0.7	2.1 ± 0.8	2.0 ± 1.1	1.8 ± 0.8	2.2 ± 0.7
Mean wedge pulmonary pressure (mm Hg)	10 ± 3	9.5 ± 2	8.4 ± 3	8.9 ± 1.8	9.5 ± 2	9.7 ± 1.4	9 ± 1.8	9.2 ± 2
LV ejection fraction (%)	32 ± 6	32 ± 7	34 ± 5	35.2 ± 6	33 ± 5	33 ± 4	35 ± 6	36 ± 5
Cardiac index ($\text{ml min}^{-1} \text{m}^{-2}$)	2336 ± 430	2382 ± 455	2468 ± 500	2556 ± 478	2310 ± 410	2379 ± 440	2410 ± 420	2530 ± 395
Haemoglobin concentration (g dl^{-1})	13.5 ± 2	13.5 ± 2.1	13.4 ± 1.9	13.3 ± 2	13.4 ± 2.1	12.7 ± 2.1	13.3 ± 1.9	12.6 ± 2.8
Plasma protein concentration (g dl^{-1})	6.9 ± 2	6.8 ± 1.8	6.8 ± 2.1	6.9 ± 2.3	6.8 ± 2.5	6.4 ± 2.3	6.7 ± 2.4	6.3 ± 2.2
Haematocrit (%)	40.0 ± 5	40.6 ± 4	39.8 ± 4	39.7 ± 3.7	40.2 ± 4	39.0 ± 2.2	39.6 ± 5	37.8 ± 3.8
Noradrenaline (pg ml^{-1})	458 ± 109	567 ± 101	463 ± 98	411 ± 89	442 ± 97	622 ± 84	458 ± 91	417 ± 86
Aldosterone (pg ml^{-1})	251 ± 45	226.2 ± 41	139 ± 48	128 ± 43	247 ± 49	161 ± 53	141 ± 47	90.7 ± 54
Plasma renin activity ($\text{ng ml}^{-1} \text{h}^{-1}$)	4.9 ± 2.5	4.3 ± 3.1	9.4 ± 2.9	7.3 ± 2.5	5.0 ± 2.1	2.6 ± 1.9	9.9 ± 3.1	7.2 ± 2.7

$P < 0.05$ vs baseline; † $P < 0.01$ vs baseline; * $P < 0.01$ vs before enalapril; § $P < 0.01$ vs 150 ml saline.

Figure 1 Means (± 1 s.d.) of pulmonary diffusion capacity for carbon monoxide (DL_{CO}), of its two subcomponents (V_C , pulmonary capillary volume, and D_M , alveolar-capillary membrane diffusion), and of the ratio of D_M to alveolar volume (D_M/V_A), in the baseline and soon after 150 and 750 ml of saline before (open bars) and after enalapril treatment (full bars). Saline-induced average percent variations (Delta percentage) from baseline are also reported. $\Delta P < 0.01$ compared with the corresponding value before enalapril. $\star P < 0.01$ compared with baseline.

were no significant changes in Hb, PPC and Htc, suggesting that the smaller amount of saline did not produce a blood dilution effect. 750 ml saline infusion was somewhat more effective than 150 ml in reducing aldosterone and PRA, and in raising noradrenaline; the small but significant decrease of Hb, PPC and Htc was probably due to some dilution effect. Notably, saline infusion did not affect significantly right and left ventricular filling pressures (mean right atrial and wedge pulmonary pressures), cardiac index and left ventricular ejection fraction. Enalapril increased PRA, lowered aldosterone and did not produce significant changes in

the baseline levels of the other humoral and haemodynamic variables.

Discussion

In agreement with recent reports [6, 7], the infusion of saline into the pulmonary circulation in CHF patients enhanced the impedance to carbon monoxide transfer, because of worsening of the gas conductance (D_M) across the alveolar capillary membrane. Deterioration of DL_{CO} was greater than that suggested by the reduction in D_M , considering that the other determinant of DL_{CO} , the

capillary blood volume available for gas exchange (V_C), was significantly augmented by saline. Following enalapril, DL_{CO} , D_M and D_M/VA at rest were raised as previously described [8, 9], and the percent reduction of these variables under the challenge of salt was unvaried. This suggests that the greater improvement of gas diffusion at rest, the lower deterioration of gas transfer with the infusion of sodium. Accordingly, values of DL_{CO} , D_M and D_M/VA following saline were significantly increased after enalapril. Thus, a novel finding in this study is that ACE-inhibition attenuates the salt-mediated enhancement in diffusion resistance in patients with congestive heart failure.

We infused 150 ml and 750 ml of saline even though it had been proven in a previous study [7], that both the smaller and the greater amounts do not cause any significant variations in right and left ventricular filling pressures, and produce an equivalent depression on the alveolar-capillary membrane function [7]. We reasoned, however, that this method would bring greater understanding to the mechanism of action of enalapril, because ACE-inhibition interferes with the same hormones (PRA, noradrenaline, aldosterone) involved in the response to sodium, and different amounts of saline possess a different blood dilution and humoral stimulating ability.

The acute decrease of DL_{CO} with saline, despite an augmented capillary blood volume available for gas exchange (V_C), suggests an acute deterioration of the membrane diffusing properties. The absence of any hydrostatic imbalance and of changes in cardiac output and left ventricular ejection fraction exclude a significant haemodynamic participation in this event. On the contrary, the rapid regression of the salt-mediated impedance to gas transfer (within less than a hour), is consistent with the interpretation of an excessive sodium transport across the microvascular endothelium as a cause of subclinical oedema formation in the alveolar interstitial space [7]. This can lengthen the diffusion path for gas exchange and decrease D_M . A dilution of plasma proteins with saline probably was not a main mechanism for interstitial pulmonary oedema formation, because the smaller amount of saline was able to depress the membrane conductance without producing any dilution effect.

The lung benefits of ACE-inhibition were dissociated from changes in circulating aldosterone and noradrenaline, because D_M improved at rest with enalapril while aldosterone reduced and noradrenaline was unchanged; D_M worsened with saline while there was a further reduction of aldosterone and a decrease of noradrenaline; and the relationship between humoral variations and amount of saline was not linear. The hypothesis of adrenergic inhibition mediated by enalapril, as a mechanism of the pulmonary gas exchange protection, is reasonable [14]. However, it is not consistent with D_M

improvement at rest in the absence of changes in plasma noradrenaline, and with the observation in previous studies [8, 10] that cyclooxygenase blockade with aspirin counteracts the benefits of enalapril on gas diffusion. This finding is strongly in favour of a potentiation by ACE-inhibitors of the bradykinin-mediated prostaglandin synthesis [8, 10]. Angiotensin converting enzyme is identical to kininase II, one of the kinin-degrading enzymes, and blocking this enzyme inhibits the kinin breakdown [15]. The luminal surface of the lung vessels is an important site of prostaglandin production, release and metabolism [16]. This interpretation raises the question of whether a substrate for the pulmonary prostaglandin activity is sodium transport across the pulmonary microvascular endothelium. This possibility, although not proven, is supported by the fundamental role that prostaglandins have in the maintenance of a normal pulmonary fluid conductance [17].

The 'before and after design' with no adequate placebo control and the small number of patients are obvious limitations of this study. These were the consequence of the need for invasive procedures. However, there was no overlap between the individual values of D_M following saline while on enalapril and those before the drug. This pattern is not consistent with a placebo effect of the ACE-inhibitor.

These findings are compatible with upregulation in sodium transport from blood in producing interstitial pulmonary oedema in CHF, and show, for the first time, that ACE-inhibition is able to at least partially readjust the microvascular permeability of the lung to sodium. This offers a novel interpretation of the mechanisms that make salt retention harmful in congestive heart failure patients, and indicates ACE-inhibition as an effective remedy.

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