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Evolving changes in lung interstitial fluid content after acute myocardial infarction: mechanisms and pathophysiological correlates

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Guazzi M, Arena R, Guazzi MD. Evolving changes in lung interstitial fluid content after acute myocardial infarction: mechanisms and pathophysiological correlates. *Am J Physiol Heart Circ Physiol* 294: H1357–H1364, 2008. First published January 11, 2008; doi:10.1152/ajpheart.00866.2007.—In acute myocardial infarction (AMI), alveolar interstitium edema is generally attributed to a hydrostatic imbalance. However, inflammatory burden and/or neural/hormonal/hemodynamic stimulation might injure the microvascular endothelium, eliciting interstitial overflow and altering alveolar-capillary gas diffusion. In 118 patients with AMI (ejection fraction $\geq 50\%$ and wedge pulmonary pressure < 16 mmHg), admission alveolar-capillary gas diffusing membrane conductance (DM) averaged $35.1 \text{ ml} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ and was 27% lower than in 25 controls ($P < 0.01$). Infusion of saline in the pulmonary circulation (to test sodium exchange across the pulmonary capillary wall) lowered DM by 7.1% ($P < 0.01$) and was neutral in controls. At 1 wk, 83 patients that showed DM improvement $> 5\%$ were assigned to group 1, and 28 patients with DM worsening $> 5\%$ were assigned to group 2. Saline retained efficacy in group 2 and had no DM effect in group 1 (supporting a link between changes in baseline DM and those in microvascular salt exchange). Ventricular function was unchanged in group 1, whereas group 2 had developed diastolic dysfunction. At 1 yr, 3% of cases in group 1 and 37% of cases in group 2 had alveolar edema. Thus, AMI is frequently associated with abnormal pulmonary microvascular sodium transport/water conductance that, in the case of ventricular dysfunction supervenience, may persist and worsen the outcome. In 37 AMI similar patients and 11 control subjects, nitric oxide overexpression with L-arginine improved baseline DM and in AMI patients prevented DM reduction by saline, suggesting a mechanistic role of an impaired nitric oxide pathway in the microvascular barrier dysfunction.

gas diffusion; myocardial function; pulmonary edema

ACUTE ALVEOLAR FLOODING, a prognostically severe complication of acute myocardial infarction (AMI) (1, 13, 21, 22, 31, 32, 40, 41, 42, 43), is currently interpreted as the result of an imbalance in hydrostatic forces by severe myocardial damage and left ventricular (LV) dysfunction and/or mitral insufficiency (4, 14, 15, 38). A less striking form of pulmonary edema after AMI is excessive fluid leakage from capillaries to the alveolar interstitium without alveolar space flooding. The pathophysiological correlates of this occurrence have attracted less attention of investigators and have been the subject of limited research. As stressed by Møller and colleagues in a recent review (25), a basic, still-unanswered question is why pulmonary congestion is frequently seen after what appears to be only minor myocardial damage with only mildly reduced LV ejection fraction (EF). These authors alluded to diastolic rather

than systolic dysfunction as a primary mechanism. Another possibility, however, might be that factors different from, or additional to hydrostatic forces, are at work. The inflammatory burden carried by the lungs in the case of AMI or the neural/hormonal stimulation elicited by an abrupt coronary occlusion are putatively blamable to damage the microvascular pulmonary endothelial barrier, which is critical in preventing interstitial fluid overflow and deterioration of alveolar-capillary gas diffusion. An animal study (10) has shown that in experimental AMI, even if of small size and with normal cardiac index at rest, the expression of pulmonary endothelial nitric oxide (NO), a basic regulator of the lung vessel motility and permeability, is unequivocally blunted. We considered the issue worthy of investigation in humans and designed this study accordingly. Basic requirements were that in the acute phase of myocardial infarction, LV systolic and diastolic function impairment were least and that a simple and reliable method was available for monitoring the variations in alveolar interstitial fluid content. We deemed that the assessment of the diffusion capacity of the alveolar-capillary membrane could be such a method, because an increase or a decrease in the fluid amount lengthens or shortens, respectively, the diffusion path between alveoli and capillaries (16) and changes in the same direction the conductance of the blood gas barrier.

METHODS

Patients and controls. Consecutive patients admitted to the coronary unit, for first AMI (typical chest pain, evolving ST elevation > 1 mm in contiguous leads, development of abnormal Q waves, or transient elevation of creatine kinase-MB ≥ 20 U/l), within 4 h of the beginning of symptoms, were eligible under the following criteria: they did not have clinical or chest X-ray evidence of congestive heart failure, aortic valve disease, diabetes (17), pulmonary disease, cardiac hypertrophy, and a pack year index of smoking ≥ 10 ; they had not smoked over the last 8 mo; mitral regurgitation, when present, did not exceed grade 2 on a scale from 0 to 5 as evaluated by the area of the regurgitant jet by color Doppler (4) and by the amplitude of the v wave in the wedge pulmonary pressure (WPP) tracing; LV EF was $\geq 50\%$; and the mean WPP did not exceed 16 mmHg. The patients' ages were between 40 to 70 yr. One hundred eighteen patients were enrolled in the study. Twenty-five healthy subjects, who were similar in age and physical characteristics to the patients and who were nonsmokers or ex-smokers of at least 8 mo with a pack year index of smoking ≤ 10 , volunteered to serve as controls; they had been admitted to the hospital because of atypical chest pain and had no history of respiratory disease. Physical examination, electrocardiogram, echocardiogram, chest X-ray, and coronary angiography were all normal for the healthy subjects.

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Table 1. Clinical and demographic characteristics of the study cohorts

	Controls	Study Patients	
		Group 1	Group 2
No. of subjects	25	83	28
Age, yr	61±4	60±3.1	65±3.2*
Gender, men/women	22/3	74/9	24/4
Body mass index, kg/m ²	25.9±2	24.8±2	24.4±3
Blood pressure, mmHg			
Systolic	138.0±7.6	156.9±11.3	153.3±12.2
Diastolic	84.0±3.8	92.3±4.1	91.4±5.4
LV mass index, g/m ²	123±4	127±5	122±5
AMI			
Anterior		21 (25%)	11 (39%)*
Inferior		62 (75%)	17 (61%)
Mitral regurgitation			
Incidence, %		22	20
Severity		1.6	1.5
Infarct-related artery			
Left anterior descending		17 (20%)	11 (39%)*
Large diagonal		4 (5%)	
Right coronary artery		44 (53%)	11 (39%)
Posterior descending		18 (22%)	6 (21%)
Receiving β -blocker		83	28
Receiving ACE inhibitor		83	28

Values are means \pm SD. Blood pressure values were taken at admission. Group 1, diffusing membrane conductance (DM) improved group; group 2, DM worsened group; LV, left ventricular; AMI, acute myocardial infarction; ACE, angiotensin-converting enzyme. * $P < 0.01$ vs. group 1.

The institutional Ethics Committee approved the protocol, and written informed consent was obtained from each subject. The procedures followed were in accordance with institutional guidelines.

Echocardiographic and Doppler experiments. Two-dimensional and Doppler measurements were performed according to recommendations of the American Society of Echocardiography (35) with a Hewlett-Packard (Andover, MA) Sonos 5500 cardiac ultrasound unit using a 2.5-MHz transducer. Blood pressure and heart rate were monitored simultaneously. LV volume and EF were determined using Simpson's method. Mitral and venous pulmonary (4-mm sample volume placed in the right upper pulmonary vein) flows were evaluated by pulsed Doppler techniques in the apical four-chamber view, and values were calculated from an average of five consecutive cardiac cycles. Pulmonary venous flow was obtained in 87% of cases. Standard presets, optimized to eliminate background noise and en-

hance tissue signals, and a 5- to 10-mm sample volume placed at the lateral and septal mitral annular margins in the four-chamber view were used to acquire medial and lateral early diastolic mitral annular velocities by tissue Doppler imaging (E_a) and E/E_a values; medial and lateral E_a values were averaged (26). Systolic LV performance was evaluated with EF, systolic wall stress versus endocardial shortening, end-systolic pressure (ESP) versus end-systolic volume (ESV), and the slope of this relationship (E_{es}). Diastolic function (45) was assessed with E_a , relationship of the WPP versus LV end-diastolic volume (EDV), ratios of E/E_a [an index that has been demonstrated to correlate with mean left atrial pressure (28)] and EDV, ratios of mitral E to mitral A velocity (E/A), ratios of venous systolic pulmonary flow velocity to peak diastolic velocity (S/D), and the deceleration time of mitral E velocity (DT). LV midwall systolic stress (MWSS) and midwall fractional shortening (MWFS) were calculated by preset formulas (36, 44).

Pulmonary function. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and carbon monoxide diffusing capacity (DL_{CO}) were measured with the Sensormedics 2200 Pulmonary Function Test System (Sensormedics, Yorba Linda, CA) according to reference equations (17). DL_{CO} was determined with a standard single breath technique using a test gas with 0.28% carbon monoxide, 0.3% acetylene, 0.3% methane, and 21% oxygen with the balance made up of nitrogen. Measurements were then repeated using test gases with 40% and 60% oxygen concentrations. The alveolar-capillary membrane conductance (DM) and pulmonary capillary blood volume (V_c) were assessed with the classic method of Roughton and Forster (34), which partitions pulmonary diffusion into the diffusive resistance of the alveolar-capillary membrane and the reactive resistance due to pulmonary capillary blood.

Study design. Soon after patient arrival in the coronary care unit, before coronary angiography and primary percutaneous reperfusion, measurements were performed of the echocardiographic variables and WPP through a double-lumen catheter introduced percutaneously into an antecubital vein and advanced through the pulmonary artery far out into the lung field until its end became impacted in one of the smaller branches; the wedge tracing had a characteristic configuration, and blood withdrawn from the catheter had an oxygen saturation within the systemic arterial range. In patients in whom values of EF and WPP satisfied the eligibility criteria, we proceeded to the assessment of FVC, FEV_1 , DL_{CO} , and its two subcomponents DM and V_c ; in each of these patients, we then infused 150 ml of 0.9% NaCl solution into the main stem of the pulmonary artery over 10 min and estimated the effects on alveolar capillary membrane conductance by repeating DL_{CO} , DM, and V_c measurements after the infusion. Details of this procedure have been described in a previous report (18). Right atrial

Table 2. Pulmonary function, hematocrit, and C-reactive protein levels in controls, group 1, and group 2 at admission and at 1 wk and 1 mo after admission

	Controls	Group 1			Group 2		
		Admission	1 wk	1 mo	Admission	1 wk	1 mo
No. of patients	26	83	83	81	28	28	27
FVC, liters	3.57±0.4	3.64±0.5	3.52±0.7	4.14±0.5	3.38±0.6	3.01±0.7	3.40±0.5
FVC, %predicted	98.7±8	95.8±10	93.6±9	100.0±11	101.0±12	96.8±9	106.0±10
FEV_1 , liters	2.83±0.38	2.75±0.47	2.62±0.41	3.08±0.49	2.81±0.47	2.71±0.42	2.63±0.39
FEV_1 , %predicted	92.7±7	91.2±8	85.4±7	92.5±10	95.7±12	93.3±6	101.6±10
DL_{CO} , ml·min ⁻¹ ·mmHg ⁻¹	31.6±5.5	23.6±3.8†	28.1±4.3	28.9±4.0	22.0±4.6†	18.4±5.7*†‡	19.0±4.1*†‡
DL_{CO} , %predicted	97.2±4.1	78.1±5.5†	92.9±6.1	93.4±5.1	82.1±6.4†	68.3±5.5*†‡	70.6±5.9*†‡
DM, ml·min ⁻¹ ·mmHg ⁻¹	47.9±5.3	35.2±4.3†	41.5±3.8*	42.3±4.5*	34.0±3.7†	23.7±4.2*†‡	24.9±3.7*†‡
V_c , ml	114.3±32.4	120.7±26.2	83.0±24.3	93.5±29.5	72.3±25.6	101.1±28.2*‡	107.4±31.3*‡
Hematocrit, %	42.6±2.5	43.4±2.8	42.9±2.0	43.1±1.8	42.8±2.1	43.1±1.9	43.0±2.2
C-reactive protein, mg/l	2.58±1.36	15.57±2.41	5.49±1.34*	2.3±1.62*	14.24±2.02	4.88±1.56*	2.5±1.77*

Values are means \pm SD. FVC, forced vital capacity; FEV_1 , forced expiratory volume in 1 s; DL_{CO} , carbon monoxide diffusing capacity; DM, alveolar capillary membrane conductance; V_c , pulmonary capillary blood volume. * $P < 0.01$ vs. admission; † $P < 0.01$ vs. controls; ‡ $P < 0.01$ vs. corresponding values in group 1.

pressure and WPP were continuously recorded before, during, and after the saline infusion. The catheter was withdrawn after the procedure and was reintroduced percutaneously on *day 7* for measurements and infusions. Studies of reproducibility have shown a high level of agreement between consecutive measurements of $1/DM$ with a correlation coefficient of 0.94 and a coefficient of variation of $<5\%$. Under the present study protocol, we found no evidence of significant carbon monoxide backpressure effects on serial DL_{CO} , DM , and V_c determinations. All procedures were completed within 1 h or less and were repeated, by the same examiners, 7 days after. The same protocol for the evaluation of the lung diffusion capacity and of the effects on it of saline infusion was also applied, before coronary angiography, in patients with atypical chest pain, and results in 25 subjects without angiographic evidence of coronary disease were used as reference values.

Ultrasound images were stored onto a magnetic optical disk and analyzed by an echocardiologist blinded to clinical, hemodynamic, and pulmonary function data. Those performing the pulmonary tests were blinded to the ultrasound results. Patients having an increase of $DM >5\%$ or a decrease $>5\%$ from admission to 1 wk followup were categorized to have improvement or worsening of the alveolar-capillary interface conductance, respectively; seven patients with variations $\leq 5\%$ were classified as having DM unchanged. By these criteria, 83 patients were assigned to the improvement group (*group 1*) and 28 patients were assigned to the worsening group (*group 2*).

Primary percutaneous coronary reperfusion was performed in all patients but four and was successful in 77% of cases in *group 1* and 81% of cases in *group 2*. The infarct-related artery was determined from ECG, wall motion, and evidence of residual thrombus in the culprit stenosis (the most severe proximal stenosis) at angiography.

All patients continued aspirin (100 mg/day), metoprolol (50–100 mg/day) or atenolol (50 mg/day), ramipril (5 mg/day), and statin during the 1-yr followup. At the end of the first month, echocardiographic variables and alveolar-capillary membrane conductance were evaluated again in each patient. Death from cardiac pump failure and development of acute alveolar edema were the outcome variables and were assessed by clinical databases, a bimonthly return visit at the outpatient clinic, and review of readmission records during followup. In a few cases in which vital or clinical status could not be determined from these methods, the patient's physician was visited and interviewed.

L-Arginine infusion. For mechanistic insights, we investigated whether endogenously synthesized lung capillary NO, a basic regulator of lung vessel tone and permeability (6), may be implicated in the presumed nonhydrostatic interstitial fluid swelling in the acute phase of myocardial infarction. To this end, we investigated the alveolar-capillary interface conductance correlates of NO pathway overexpression with L-arginine in 37 additional patients. Eligibility criteria were those reported above. Hemodynamic, ultrasound, and lung function procedures were also the same. On *day 1*, DL_{CO} , DM , and V_c were assessed at baseline, after an infusion of saline (150 ml) or L-arginine (200 mg/kg vehicled by 150 ml of saline over 10 min), and again 10 h later after an infusion of saline with or without L-arginine, according to a double-blind crossover design. On *day 7*, DL_{CO} , DM , and V_c were reassessed at the baseline as well as after saline and L-arginine vehicled by saline infusion with the same modalities as on *day 1*. Patients having an increase of baseline $DM >5\%$ or a decrease of $>5\%$ from *days 1* to *7* were categorized to have improvement or worsening of the alveolar-capillary membrane conductance, respectively; 3 patients with variations $\leq 5\%$ were classified as having DM unchanged. According to this, the improvement group (*group A*) was composed of 24 patients, and the worsening group (*group B*) was composed of 10 patients. The effects of L-arginine and DM were also tested in 11 healthy control subjects whose age and somatic characteristics were similar to those of the patients.

Statistical analysis. Data are presented as means \pm SD. Descriptive parameters were compared by χ^2 -analysis. Data were analyzed by

Table 3. Hemodynamic variables and lung diffusion capacity in controls, group 1, and group 2 at baseline and immediately after 150-ml saline infusion in the pulmonary circulation

	Controls at Admission		Group 1 at Admission		Group 1 After 1 wk		Group 2 at Admission		Group 2 After 1 wk	
	Baseline	Saline	Baseline	Saline	Baseline	Saline	Baseline	Saline	Baseline	Saline
Heart rate, beats/min	73 \pm 3	73 \pm 4	78 \pm 4	77 \pm 5	75 \pm 3	76 \pm 4	77 \pm 6	75 \pm 5	73 \pm 3	74 \pm 4
Blood pressure, mmHg										
Systolic	128 \pm 7.2	126 \pm 6.5	132 \pm 8.1	131 \pm 7.3	128 \pm 6.2	130 \pm 7.4	137 \pm 6.6	135 \pm 4.4	133 \pm 7.1	134 \pm 5.2
Diastolic	79 \pm 3.7	80 \pm 3.5	85 \pm 4.2	86 \pm 4.4	81 \pm 5.1	82 \pm 4.3	87 \pm 5.5	85 \pm 6.2	84 \pm 6.3	85 \pm 5.5
Mean right atrial pressure, mmHg	1.5 \pm 1.2	1.3 \pm 1.0	1.8 \pm 1.1	1.8 \pm 1.2	1.6 \pm 1.0	1.5 \pm 1.2	1.7 \pm 1.2	1.8 \pm 1.1	1.6 \pm 1.3	1.5 \pm 1.4
Mean WPP, mmHg	8.2 \pm 1.1	8.0 \pm 1.4	14.7 \pm 1.2	14.6 \pm 1.3	14.9 \pm 1.0	14.5 \pm 0.9	13.8 \pm 1.3	13.4 \pm 1.4	18.4 \pm 1.8†	18.5 \pm 1.6†
DL_{CO} , ml·min ⁻¹ ·mmHg ⁻¹	31.6 \pm 5.5	32.4 \pm 5.1	23.6 \pm 3.8	22.2 \pm 2.4*	28.1 \pm 4.3†	28.4 \pm 3.7†	22.0 \pm 4.6	20.6 \pm 4.0*	18.5 \pm 5.7†	17.0 \pm 4.1*†
DM , ml·min ⁻¹ ·mmHg ⁻¹	47.9 \pm 5.3	46.8 \pm 4.8	35.2 \pm 3.3	32.8 \pm 2.2*	41.5 \pm 3.8†	40.7 \pm 3.5†	34.0 \pm 3.7	31.3 \pm 2.9*	23.7 \pm 4.2†	21.7 \pm 3.8*†
V_c , ml	114.3 \pm 32.4	118.4 \pm 29.2	120.7 \pm 26.2	131.1 \pm 22.2*	83.0 \pm 24.3†	87.5 \pm 25.2†	72.3 \pm 25.6	82.8 \pm 28.1	101.1 \pm 28.2†	110.3 \pm 24.6†

Values are means \pm SD. WPP, wedge pulmonary pressure. * $P < 0.01$ vs. baseline; † $P < 0.01$ vs. corresponding values at admission.

Table 4. LV systolic performance at admission at the 1-wk and 1-mon follow-up

	Group 1			Group 2		
	Admission	1 wk	1 mo	Admission	1 wk	1 mo
No. of patients	83	83	81	28	28	27
LV ejection fraction, %	52.4±0.7	53.6±0.8	54.6±0.6	53.2±0.6	52.5±0.5	52.9±0.7
ESP/ESV, mmHg/ml	2.68±1.1	2.62±1.0	2.57±0.9	2.70±1.0	2.86±0.9	2.84±1.1
E_{es} , mmHg/ml	2.21±0.7	2.18±0.9	2.23±0.6	2.20±0.7	2.34±0.9	2.37±0.5
MWFS, %	30.5±4	29.1±5	35.6±3	36.5±3	36.7±5	39.4±4

Values are means ± SD. ESP, end-systolic pressure; ESV, end-systolic volume; E_{es} , slope of the relationship between ESP and ESV; MWFS, midwall fractional shortening.

two-way repeated-measures ANOVA with the Neumann-Keuls multiple-comparison procedure. We conducted linear univariate regression analysis to assess the significance of associations between DM and its possible correlates. To determine which of these factors were significant independent determinants of DM, we used multivariate regression analysis.

RESULTS

Clinical characteristics. Groups 1 and 2 did not differ with respect to body mass index, gender, blood pressure, or LV mass index, which, in no cases, exceeded 134 g/m² (9). These variables were similar in control subjects. Mitral regurgitation and drug treatment in groups 1 and 2 were also similar. Patients in group 2 were slightly older and more often had anterior AMI (Table 1).

Pulmonary function. Values of FVC and FEV₁ exceeded 90% normal predicted in both groups, were comparable with those in controls, and did not show variations at 1-wk measurements (Table 2). The two cohorts of patients were also homogeneous with respect to baseline DL_{CO} and DM. In both cohorts, these variables at admission were significantly lower than in 25 healthy control subjects. At 1 wk, according to the grouping criteria, DL_{CO} and DM were raised in group 1 to values comparable with those in the control group, whereas in group 2, they were further reduced. In group 1 and group 2, V_c was reduced and augmented, respectively. Hematocrit was similar and steady in either group; C-reactive protein, as a marker of inflammation, was also similar at admission and exhibited a comparable decay (Table 2).

Saline infusion. In healthy subjects, saline did not interfere with the alveolar-capillary membrane conductance (Table 3). In contrast, in patients with AMI, after the administration of

150 ml of saline we recorded a significant reduction from baseline of DL_{CO} and DM in both group 1 (DL_{CO}: −5.9% and DM: −6.8%) and group 2 (DL_{CO}: −6.4% and DM: −7.9%; Table 3). One week later, the saline infusion was ineffective in patients with DL_{CO} and DM recovery (group 1) and still interfered with DL_{CO} (−8.1%) and DM (−8.4%) in patients with DL_{CO} and DM worsening (group 2).

Systolic performance. Parameters reflecting LV systolic performance were comparable at admission in the two groups of patients (Table 4). EF, ESP/ESV, E_{es} , and MWFS did not vary after 1 wk, and no significant group differences were evident over this period. When values of MWFS/MWSS were plotted, values for patients having DM improvement were scattered among those of patients having DM deterioration at both admission (Fig. 1, left) and 1 wk later (Fig. 1, right), suggesting that the LV afterload-fiber shortening relationship was similar on either occasion in the two groups.

Diastolic function. At admission, there were no group differences in variables related with LV diastolic function (Table 5). Notably, WPP tightly and significantly ($r = 0.89$, $P < 0.01$) correlated with LVEDP, as obtained during coronary angiography. At 1 wk, group 2 but not group 1 showed an increase in DT, E/A , WPP, E/E_a /EDV, WPP/EDV, and left atrial area and a decrease of E_a velocity and S/D ratio. In group 2, the anterior location of the AMI as well as E/A and S/D at day 7 were weakly correlated with DM (anterior AMI, $r = 0.33$ and $P = 0.01$; E/A , $r = -0.28$ and $P = 0.03$; and S/D , $r = 0.30$ and $P = 0.02$), whereas DT ($r = -0.53$ and $P < 0.001$), WPP ($r = -0.62$ and $P < 0.001$), left atrial area ($r = -0.77$ and $P < 0.01$), WPP/EDV ($r = -0.67$ and $P < 0.001$), and E_a ($r = +0.71$ and $P < 0.001$) were strongly correlated with DM. The

Fig. 1. Relationship between midwall fractional shortening (MWFS) and midwall systolic stress (MWSS) in patients in group 1 [diffusing membrane conductance (DM) improved] and group 2 (DM worsened). Values for patients in group 1 were scattered among those of patients in group 2 both at admission (left) and on day 7 (right).

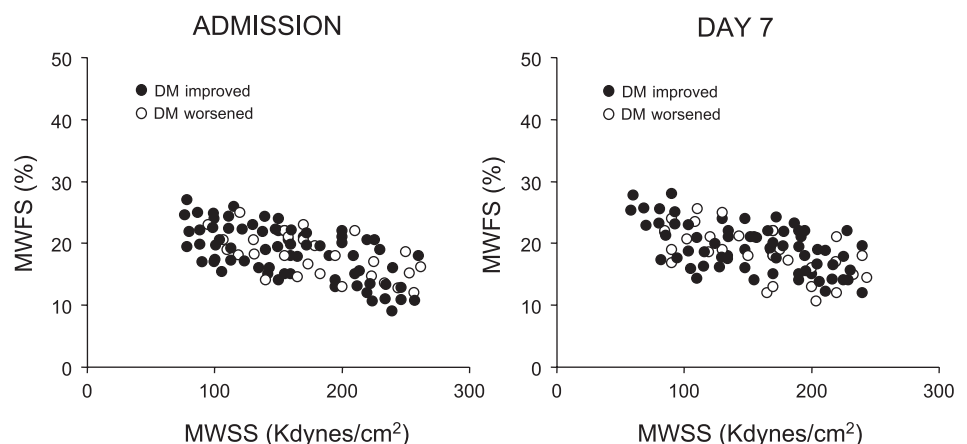


Table 5. Variables reflecting LV diastolic function at admission and at 1 wk and 1 mo after admission

	Group 1			Group 2		
	Admission	1 wk	1 mo	Admission	1 wk	1 mo
No. of patients	83	83	81	28	28	27
DT, ms	184.7±30	183.7±27	198±31	183±26	212.5±32*†	215.1±33*†
E/A ratio	1.03±0.5	0.86±0.3	0.89±0.4	0.95±0.2	1.08±0.3	0.93±0.2
S/D ratio	1.23±0.3	1.23±0.2	1.20±0.2	1.26±0.4	1.15±0.2*†	1.18±0.3*†
E _a , cm/s	8.1±0.6	8.2±0.5	9.1±0.7	8.4±0.8	5.1±0.5*†	4.9±0.4*†
WPP, mmHg	14.7±1.2	14.9±1.0		13.8±1.3	18.4±1.8*†	
LVEDP, mmHg	13.4±1.1			12.9±1.0		
Left atrium area, cm ²	17.7±2.1	16.6±2.4	18.3±1.8	17.2±2.4	19.2±1.7*†	19.8±2.3*†
E/E _a /LVEDV ratio	0.12±0.01	0.11±0.02	0.12±0.02	0.11±0.01	0.15±0.01*†	0.15±0.02*†
WPP/LVEDV ratio	0.14±0.02	0.14±0.01		0.13±0.02	0.18±0.03*†	

Values are means ± SD. LV end-diastolic pressure (LVEDP) values were obtained during coronary angiography. DT, mitral inflow velocity deceleration time; E/A ratio, ratio of early to late mitral inflow velocity; S/D ratio, ratio of peak systolic to peak diastolic velocity of the pulmonary venous flow; E_a, early diastolic mitral annular velocity; LVEDV, LV end-diastolic volume. **P* < 0.01 vs. admission; †*P* < 0.01 vs. corresponding values in group 1.

multivariate regression model showed that DT, WPP, E/a, WPP/EDV, and left atrial area were significant independent variables, and the association was more evident for left atrial area ($\beta = 0.49$ and $P < 0.0001$) and E_a ($\beta = 0.41$ and $P < 0.001$) compared with DT ($\beta = 0.29$ and $P = 0.0006$) and WPP/EDV ($\beta = 0.25$ and $P = 0.0007$). When WPP versus EDV at admission and on day 7 were plotted (Fig. 2), admission coordinates were not different between the groups; on day 7, EDV was still similar, but WPP was significantly augmented, in group 2, which is consistent with an upward shift of the diastolic pressure-volume relationship in group 2.

Followup. After a month, two patients in group 1 and one patient in group 2 were lost to followup (for family reasons or because they moved to another town). Compared with day 7, lung diffusion capacity and alveolar-capillary membrane conductance (Table 2), LV systolic performance (Table 4), and ultrasound variables reflecting diastolic function (Table 5) were unchanged.

Clinical outcomes are reported in Table 6. During the 1-yr followup, 13 patients in group 2 developed dyspnea and X-ray evidence of lung congestion, and 10 of them had 1 or more episodes of acute alveolar edema. In the same group, there were nine cardiovascular deaths. All these results were significantly greater than in group 1.

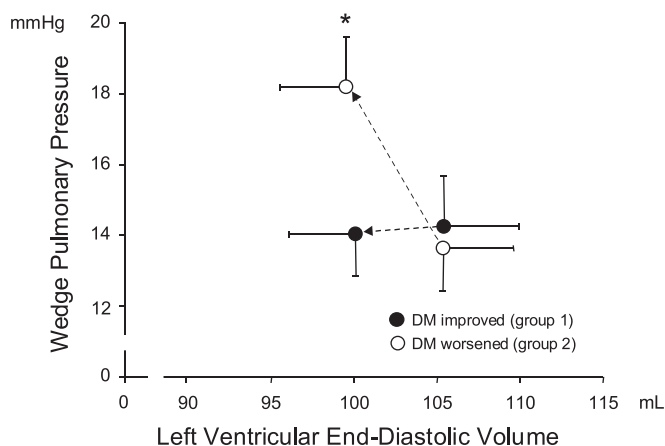


Fig. 2. Mean wedge pulmonary pressure/left ventricular end-diastolic volume coordinates at admission and the corresponding coordinates (arrows) detected after the 1-wk followup. Values are means ± SD. **P* < 0.01 vs. admission.

L-Arginine infusion. Results of L-arginine infusions are shown in Table 7. Among patients specifically recruited for endogenous NO synthesis overexpression testing with L-arginine, 24 patients (group A) had DM improvement at 1 wk without systolic and diastolic function variations and 10 patients (group B) developed DM worsening and diastolic dysfunction, duplicating the same pattern already described for group 2 in the main study population. On day 1, baseline DM values were similar in groups A and B; in both groups, saline was effective in reducing DM (by 8.0% in group A and by 7.6% in group B). In contrast, when L-arginine was added to saline, DM was raised by 36.3% of baseline in group A and by 34.4% in group B. On day 7, DM was lowered by 6.9% with saline alone and was increased by 55.6% by L-arginine combination in group B; saline was ineffective and L-arginine raised DM by 16.3% in group A. Notably, a comparable increase of DM (+18.5%, $P < 0.01$) with L-arginine was recorded in 11 normal control subjects of similar age and somatic characteristics. In neither cohort were variations in mean pulmonary arterial pressure and WPP with L-arginine significant.

DISCUSSION

The observations of the present study apply to patients with first AMI, with only a mildly depressed EF. In the acute phase, DM values are reduced in these patients compared with values reported as normal in the literature (27) and with results in healthy subjects with similar demographic characteristics. Saline infusion in the pulmonary circulation makes more critical the resistance to gas transfer. Alveolar-capillary membrane function recovers and saline becomes ineffective within a week, unless LV dysfunction supervenes.

Table 6. Clinical outcomes

	Group 1		Group 2	
	No. of Patients	Percentage of Patients	No. of Patients	Percentage of Patients
Cardiovascular deaths	3	3.7	9*	33.3*
Dyspnea and lung congestion	4	4.9	13*	48.1*
Acute alveolar edema	2	2.5	10*	37.0*

Values are means ± SD. There were 81 patients total studied in group 1 and 27 patients total studied in group 2. **P* < 0.01 vs. group 1.

Table 7. Lung diffusion capacity in groups A and B at baseline and after infusion of saline alone and saline with L-arginine

	Group A on Day 1				Group A on Day 7				Group B on Day 1				Group B on Day 7			
	Baseline	Saline	Saline + L-arginine		Baseline	Saline	Saline + L-arginine		Baseline	Saline	Saline + L-arginine		Baseline	Saline	Saline + L-arginine	
DL _{CO} , ml·min ⁻¹ ·mmHg ⁻¹	23.3±3.5	21.4±2.3*	30.4±3.7*†		29.3±3.8†	28.8±3.4†	33.6±3.18*†		23.4±4.1	21.1±3.8*	31.5±3.5*†		19.1±4.3‡	17.3±3.8*‡	27.5±2.7*†‡	
DM, ml·min ⁻¹ ·mmHg ⁻¹	33.6±3.0	30.9±2.4*	45.8±2.9*†		42.7±3.4†	41.8±3.2†	49.6±2.88*†		35.1±3.2	32.4±3.1*	47.2±2.9*†		24.6±4.5‡	22.9±4.1*‡	38.3±3.1*†‡	
V _c , ml	108.8±25.4	117.2±21.7*	100.2±27.3*		86.6±21.9†	90.7±23.8†	95.7±20.7‡		98.5±27.9	89.7±26.9	94.8±30.2		103.2±28.4‡	115.4±25.5‡	106.5±26.5‡	
MPAP, mmHg	17.6±2.0	19.3±1.9	16.6±1.6		18.1±1.7	17.2±1.8	16.7±1.5		18.6±1.1	18.3±1.3	19.0±1.0		23.3±1.8	23.5±1.4	22.8±1.5	
WPP, mmHg	12.5±1.2	12.3±1.8	12.1±1.5		12.1±1.9	11.9±1.1	12.0±1.7		13.2±0.9	13.1±1.2	13.4±1.3		17.9±2.0‡	18.1±1.6‡	17.8±1.4‡	

Values are means ± SD. There were 24 patients total studied in the DM improved group (group A) and 10 patients total studied in the DM worsened group (group B). MPAP, mean pulmonary artery pressure. **P* < 0.01 vs. baseline; †*P* < 0.01 vs. saline; ‡*P* < 0.01 vs. corresponding values at admission.

Lung interstitial fluid in AMI. Conductance of the alveolar-capillary membrane depends on its functional and structural properties and on the distance separating the alveolar epithelium from the capillary endothelium. The main determinant of the distance is the interstitial fluid, whose amount is regulated by hydrostatic and osmotic forces and by the sodium exchange/water conductance across the pulmonary capillary wall.

The interpretation that the reduced membrane conductance in AMI reflects a hydrostatic imbalance due to dysfunction of the LV, although simple and rational, is not fully satisfactory for the following reasons. In this study, LV EF was, by selection, ≥50%, and WPP averaged 14.1 mmHg in group 1 and 13.8 mmHg in group 2. At 1 wk, reversion of DM to normal in group 1 was not associated with any changes from admission regarding cardiac performance and WPP. In AMI patients and not in healthy subjects, 150 ml of saline were effective in worsening the blood gas barrier conductance. Previous studies (18, 33) have shown that the infusion of saline in the pulmonary circulation with contemporary DM measurement is a reliable method to probe sodium transport across the pulmonary capillary endothelium and that, when transport is challenged, even an amount of saline as small as the pulmonary blood capillary volume in a supine individual (150 ml) may significantly depress the membrane conductance (18). After 1 wk, saline had no measurable effect on gas diffusion in patients with DM recovery (group 1) and still impeded gas transfer in those without DM recovery (group 2), prospecting a link between improved DM and restored salt exchange/water conductance.

Taken together, these considerations support the concept that an altered translocation of fluid from the intravascular to alveolar interstitial compartment are not unusual in AMI. Because of the inflammatory burden carried by the lung, as suggested by C-reactive protein levels, and/or of the remarkable neural, hormonal, and hemodynamic alterations that occur with an abrupt interruption of coronary flow, AMI is putatively blamable for deranging physiology of the blood gas barrier. We can only speculate about the factors involved. Because in many patients DM recovered within 1 wk, discussion should be restricted to mechanisms that can hurt the blood gas barrier in a reversible manner (12), such as the following: 1) lung vascular remodeling mediated by alveolar hypoxia through an increase in gene expression of extracellular matrix proteins (2); 2) upregulation of sodium transport across capillaries (8) or downregulation across the alveolar epithelium (29) due to the release of cellular growth factors and proinflammatory cytokines or to circulating microparticles (3); and 3) failure of the capillary membrane to withstand stress (43) imposed by a sudden and transient rise of the pulmonary capillary transmural pressure that accompanies abrupt cessation of coronary flow and raises the endothelium permeability to sodium (16).

Pulmonary NO synthesis. Several animal (39) and human (23) studies have demonstrated an improvement in endothelial function and an increase in NO production (7) in response to oral or intravenous supplementation of L-arginine, the precursor of NO synthesis. Increasing NO substrate availability has also been shown to restore endothelium-dependent relaxation in the pulmonary circulation of hypoxic rats (11) and overcome the pulmonary vasoconstrictor activity of N^G-monomethyl-L-arginine, an antagonist of NO synthesis, in normal children (5). On this basis, we utilized supplementation of the NO substrate

L-arginine in the lesser circulation to probe a possible involvement of altered NO pathway synthesis in the alveolar-capillary membrane dysfunction produced by AMI. Findings are strongly in favor of a mechanistic role of NO impairment in the impeded gas transfer in AMI, given the ability of L-arginine to bring DL_{CO} and DM back toward normal, to increase DM under normal conditions as well, and, even more impressively, to modulate the endothelial transport of sodium and water. This belief is in agreement with studies showing blunted NO expression in experimental AMI (10) and improved alveolar-capillary interface conductance in heart failure patients in whom the molecular pathway originated from NO is enhanced by phosphodiesterase-5 inhibition (19, 20, 30). NO is a known pulmonary vasodilator, and a confounding effect of reduced impedance to right ventricular ejection cannot be ruled out. However, failure to detect in our patients significant changes in arterial pressure and WPP does not corroborate this possibility.

LV diastolic function. An explanation for the within-group variations and the between-group differences in alveolar-capillary interface conductance might be that changes in hematocrit modified the binding capacity for carbon monoxide or that patients with DM improvement were those in whom inflammation caused by AMI had resolved. These explanations, however, are inconsistent with the similar decay in C-reactive protein levels and the persistent similarity of hematocrit in groups 1 and 2.

The study emphasizes LV relaxation, WPP, E_a , the wedge pulmonary pressure-EDV relationship, and left atrial dimension (25) as remarkable contributors to the enhancement of the alveolar-capillary interface dysfunction in group 2 patients. Although the exact time relationship between DM worsening and diastolic impairment is unknown (data from the interval between admission and day 7 are not available), a cause-and-effect relationship seems reasonable. Whether diastolic deterioration alone augmented the alveolar interstitial fluid and worsened gas diffusion, or whether there was an interaction with the initial injury of the blood gas barrier, is basically unproven. Nonetheless, the shift of DM from a value of 29% lower than in healthy controls at admission to a value of 50% lower at 1 wk and 48% lower at 1 mo is in favor of an additive or synergistic effect. The ability of L-arginine supplementation to improve DM and counteract saline at 1 wk in similar patients and under the same experimental conditions suggests that NO synthesis impairment maintains a role in depressing the blood gas barrier conductance also after supervenience of diastolic dysfunction and hydrostatic imbalance. On this basis, the alveolar-capillary membrane injury in AMI does not seem to be just a reversible epiphenomenon but rather a disorder that in the case of supervenient LV function deterioration persists and interacts with a hydrostatic imbalance in facilitating fluid translocation to the interstitial compartment.

Diastolic dysfunction in group 2 might have resulted from the contribution of age (3, 16), stunning (24, 37), and predominance of an anterior site of AMI (with anterior AMIs, which are generally larger, a persistent demand of increased performance put on the controlateral area to maintain stroke volume and an inability to meet this demand would facilitate impaired relaxation and compliance).

Clinical perspectives. This study reinforces the concept that, despite only mildly reduced LV EF, the AMI outcome may be unfavorable (25) and liability to alveolar flooding may be

enhanced in a considerable proportion of patients developing diastolic dysfunction and LV filling pressure elevation (25). Although the final achievement of DM was not assessed and changes in LV function that apply to late alveolar edema are unknown, the study adds another piece of knowledge to the pathophysiology of congestive heart failure in AMI. In fact, it shows that an impaired alveolar-capillary membrane sodium exchange/water conductance may have a role in the fluid translocation to the interstitial compartment and prelude the development of alveolar flooding. This may lead to new opportunities of reducing risk and improving outcomes and attribute a predicting significance to serial assessments of the blood gas barrier conductance.

GRANTS

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