Background: Endothelin (ET) is an endothelium-derived multifunctional peptide involved in the local regulation of the vascular tone.

Study objectives: To assess changes of endogenous ET production/excretion in the acute phase (36 h from the event) of pulmonary embolism (PE).

Participants: Ten patients with acute PE, nine patients with acute lung injury (ALI), and 12 healthy volunteers (HVs).

Measurements and results: ET was detected by radioimmunoassay in venous and arterial blood as well as in 24-h urine specimens. For each subject, arterial/venous immunoreactive ET (ir-ET) ratio was evaluated as an index of its pulmonary extraction/synthesis. Creatinine clearance was employed in each case to obtain a corrected renal ir-ET clearance. Renal ir-ET clearance was comparable in all three groups. Arterial/venous ir-ET ratio was comparable in PE and in ALI patients (1.3±0.2 vs 1.2±0.2; p=0.7), while it was significantly higher in PE patients than in HV subjects (0.85±0.07; p=0.0001). Accordingly, 24-h urine ir-ET excretion was higher in PE (120.5±27.3 ng/24 h) and ALI patients (135.8±21.6 ng/24 h) than in HV subjects (68.3±9.3 ng/24 h; p=0.0001).

Conclusions: Abnormalities of ET metabolism—mainly related to increased synthesis and/or defective pulmonary handling—occur in the acute phase of PE. The relevance of this finding with respect to the pathogenesis and/or management of pulmonary thromboembolism remains to be elucidated.

(CHEST 1997; 111:544-49)

Key words: Endothelin; endothelium; pulmonary embolism

Abbreviations: ALI=acute lung injury; ET=endothelin; ET-1=endothelin 1; ET-2=endothelin 2; ET-3=endothelin 3; HV=healthy volunteers; ir-ET=immunoreactive endothelin; ir-ETart=immunoreactive arterial endothelin; ir-ETur=immunoreactive urinary endothelin; ir-ETven=immunoreactive venous endothelin; PE=pulmonary embolism

Pulmonary embolism (PE) is an important cause of morbidity and mortality. Little information is available on the role of endothelial damage with respect to the pulmonary abnormalities taking place during an acute embolic event. The endothelium actively synthesizes endothelin-1 (ET-1)—a member of the endothelin (ET) family. ET-1 exerts important effects on vascular beds, including constriction and mitogenesis of smooth muscle vascular cells. Immunoreactive ET (ir-ET) is substantially cleared during pulmonary circulation.

Abnormalities in circulating levels of ET-1 have been reported in pulmonary hypertension, pre-eclampsia, and myocardial infarction. The impairment of the pulmonary clearance of ET-1 has been proposed recently as a specific marker of pulmonary endothelial dysfunction in patients with acute lung injury (ALI). Pulmonary endothelial dysfunction is poorly understood in PE patients.

In the present study, we aimed at evaluating abnormalities of ET metabolism in patients with acute PE.

Materials and Methods

Subjects

All the studies were carried out within 36 h from the onset of signs or symptoms suggestive of PE. Ten consecutive patients were referred to our department for PE (Table 1). In each case and for each patient, in addition to the criteria for the clinical suspicion of PE, the diagnosis was supported by at least one of the following criteria:...
After patients), with established symptoms septic score, HIV infection, (HVs).

Subjects and/or PE at compressibility of venous positivity following:

the following: (1) an abnormal finding from pulmonary angiography;11 (2) a segmental or greater perfusion defect with normal ventilation at the lung scan;12 and (3) in patients with deep venous thrombosis, an abnormal perfusion lung scan compatible with PE (ie, single or multiple wedge-shaped perfusion defects of any size with diversion of blood flow from unperfused regions and subsequent overperfusion of unaffected areas).13 Diagnosis of deep venous thrombosis was based on clinical aspects and positivity for at least two of the following B-mode and Doppler ultrasonography signs: (1) presence of a thrombus; (2) lack of compressibility of a venous segment; and (3) absence of venous flow and/or lack of phasicity with respiration.13,14

As control subjects, the following were used: (1) nine patients with established criteria of ALI (chest radiograph score, hypoxemia score, positive end-expiratory pressure score15) and no signs or symptoms of PE; and (2) 12 age-matched healthy volunteers (HVs). Subjects with abnormalities of major coagulation indexes, HIV infection, prolonged corticosteroid therapy, or signs of septic shock were excluded from the study. Informed consent was obtained from each subject (from relatives in the case of ALI patients). After approval of the ethical committee of our University Hospital, the study was carried out according to the principles of the Declaration of Helsinki.

Diagnostic Tests

Resting $\mathrm{PaO}_2$ and $\mathrm{PaCO}_2$ were measured with a gas analyzer (BGM 1312 Instrumentation Laboratory; Milan, Italy) and expressed in mm Hg according to the manufacturer’s recommendations.

Ventilatory and perfusional scans were carried out with a stationary large-field-of-view camera (General Electrics. Copenhagen, Denmark) equipped with a general purpose collimator. Radioaerosols of colloidal $\mathrm{99mTc}$ DTPA (15 mCi) and IV $\mathrm{99mTc}$ human serum albumin microspheres (4 mCi) were employed as tracers.

B-mode and Doppler ultrasonography were performed by a Sonos 1000 apparatus (Hewlett Packard; Andover, Mass) equipped with a probe linear array of 7.5 MHz.

Angiographic studies were performed using the cineangiographic technique (Angiomax Impact 3000; General Electric; Paris, France) during right heart catheterization with a 7F Swan-Ganz NIH catheter introduced percutaneously through a

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**Table 1—Characteristics of the Subjects Included in the Study**

<table>
<thead>
<tr>
<th>Clinical Entities</th>
<th>Sex/Age, yr</th>
<th>$\mathrm{PaO}_2$</th>
<th>$\mathrm{PaCO}_2$</th>
<th>$\mathrm{PaO}_2/\mathrm{FiO}_2$</th>
<th>N Def</th>
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<td>HV</td>
<td>M/35</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M/41</td>
<td>94.3</td>
<td>37.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F/36</td>
<td>96.9</td>
<td>38.8</td>
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</tr>
<tr>
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<td>40.2</td>
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<td>F/55</td>
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<td>42.6</td>
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<tr>
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<td>37.0</td>
<td></td>
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<td>38.1</td>
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<td></td>
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<tr>
<td></td>
<td>F/42</td>
<td>95.9</td>
<td>36.8</td>
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<tr>
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<td>40.7</td>
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<tr>
<td></td>
<td>M/60</td>
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<td>Mean±1 SD</td>
<td>44.7±8.5</td>
<td>94.9±2.0</td>
<td>38.5±2.4</td>
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<tr>
<td>PE</td>
<td>M/59</td>
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<td>44.6</td>
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<td>53.6±10.3</td>
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<tr>
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<td>M/20</td>
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<td>M/64</td>
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<td>32.9</td>
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<td>Mean±1 SD</td>
<td>54.4±20.1</td>
<td>95.3±12.8</td>
<td>37.0±6.1</td>
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</tr>
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</table>

*ALI was secondary to trauma (n=2), acute pancreatitis (n=2), pneumonia (n=3), major surgery (n=2). N Def=number of segmentary defects at perfusion lung scan; $\mathrm{FiO}_2=$ fraction of inspired oxygen.

1Positive pulmonary angiography. Because of the immediate admission to hemodynamic section of the hospital, no preliminary lung scans of the two patients are available.
brachial vein. Contrast material (Iopamiro [Bzacco; Milan, Italy] 25 mL/s) was injected into the main pulmonary arteries. Filming rates were at 25 frames per second for 3 s for each lung.

Samples Collection and Storage

During collection (24 h) and until processed, urine specimens were kept at 4°C. A 10-mL aliquot was centrifuged (300 g for 20 min at 4°C) and the supernatant was transferred to siliconized tubes and stored at −40°C until assayed. A different aliquot was employed for urinalysis. From all subjects, arterial and peripheral venous blood samples were obtained at 8AM. Six-milliliter aliquots were transferred into tubes containing EDTA and aprotinin (500 U/mL) and centrifuged (300 g for 20 min, at 4°C); the supernatant was transferred into siliconized tubes and stored at −40°C. Creatinine (picric acid) and BUN (colorimetric assay) were carried out on a different aliquot of peripheral venous blood.

ir-ET Assay

ir-ET assay was performed as previously described.26 Briefly, equal amounts (2.5 mL) of urine or arterial and venous plasma were filtered through reverse-phase cartridges (Sep-Pak C18; Waters Millipore) preconditioned with 2 mL of 100% methanol, followed by 2 mL of 10% methanol, 2 mL of 20% methanol, 2 mL of 80% methanol, and 4 mL of 10% methanol. The eluate was obtained by washing the cartridges with 2 mL of 10% methanol and 2 mL of 80% methanol, dried (Speedvac Concentrator; Savant, NY), and reconstituted with the assay buffer. The percentage of ET extracted by this method ranged from 77 to 81%, as assessed in five experiments in which the recovery of [125I]-ET-1 added to plasma or urine supernatants was evaluated. ir-ET levels in the arterial (ir-ETar), venous (ir-ETven), and urine (ir-ETur) samples were measured by a radioimmunoassay according to the manufacturer’s recommendations. The commercially available kit employed (Endothelin 1/2; Biomedica; Wien, Austria; batch No. 536) was supplied (by Cis-Diagnostici; Vercelli, Italy). All samples were determined in duplicate. The lowest detection limit of the assay was 0.8 pg/mL; the within-assay variability for duplicate determinations was 5.6%; the interassay variability was <6%. The cross-reactivity of the assay was <1% for sarafotoxin, atrial natriuretic peptide, big ET, and big ET 22-38, while it did not discriminate among ET-1 (100%), ET-2 (142%), and ET-3 (98%).

Statistical Analysis

Comparisons among multiple groups were performed by the Kruskal Wallis H test, and then analyzed by the Mann-Whitney U test; correlations between PaO2 or number of segmental perfusional defects and arterial, venous, and urine ir-ET levels were performed by the Spearman’s rank test (SPSS version 6.2 for Windows). Significance was established at a p value <0.05.

RESULTS

Plasma creatinine, BUN, and urinalysis results were normal in all subjects.

Patients with PE showed significantly higher ir-ETart levels as compared to HV individuals (7.52 ± 1.24 pg/mL vs 4.53 ± 0.50; p=0.0001). Values comparable to those found in PE patients were observed in ALI patients (8.54 ± 2.11; p=0.3). ir-ETven levels were higher in ALI patients than in all the other groups (p=0.02; Kruskal Wallis H test). In particular, they were 6.92 ± 1.70 pg/mL in ALI patients, 5.87 ± 0.96 pg/mL in PE patients, and 5.28 ± 0.46 pg/mL in HVs (p=0.2 and p=0.01, respectively, Mann Whitney U test) (Table 2).

The ir-ETart/ir-ETven ratio, an index of pulmonary synthesis/extraction of the peptide, was significantly higher in PE patients (1.31 ± 0.25) than in HV subjects (0.85 ± 0.07; p=0.0001). By contrast, no difference was found between PE and ALI patients (1.24 ± 0.20; p=0.7) (Fig 1, top). Likewise, no difference was found with respect to 24-h ir-ET urinary excretion between PE patients (120.50 ± 27.36 ng/d) and ALI patients (135.80 ± 21.60 ng/d; p=0.1). However, a difference was found between PE and HV subjects (68.33 ± 9.31; p=0.0001) (Fig 1, bottom). Renal clearance of the peptide was similar in all groups (11.65 ± 2.79 mL/min in PE patients; 10.87 ± 2.13 mL/min in HVs; 11.40 ± 2.35 mL/min in ALI patients; p=0.68). The ratio between renal clearance of ir-ET and creatinine clearance was comparable in all groups as well (0.130 ± 0.033 in PE patients; 0.117 ± 0.024 in HVs; 0.123 ± 0.033 in ALI patients; p=0.7).

No significant correlation was found between the degree of hypoxia or number of perfusion segment defects and arterial, venous, or urine ir-ET levels.

DISCUSSION

The role of ET in the local regulation of the vascular tone is well established3,4,8,17 and its pathophysio-logic relevance in a variety of clinical settings delineated.6-8 It has also been documented that the 24-h urinary excretion detects changes in endog-eneous ET production more sensitively than single blood measurements.18,19 With respect to the pathophysio-logic condition of the respiratory system, the ratio of arterial systemic/mixed venous ET-1 levels has been shown to be increased in patients with ALI.5,9 This has been taken to indicate a defective pulmonary clearance of the peptide and/or an in-crease in its pulmonary production. In both in-stances, the data were consistent with the concept of endothelial dysfunction in ALI.5,9 Our data on PE subjects show abnormalities of ir-ET metabolism consistent with increased arteriovenous gradient and enhanced urine excretion. We interpret this to be related to PE per se: (1) the transformation of urinary excretion data into renal clearance data indicates that the increase in arterial levels is almost entirely accounted for by ir-ET urine increase; therefore it is unlikely that a renal source of the peptide is comparable to that reported during—is
The assay we employed to measure blood and urine ir-ET levels does not discriminate the three major isoforms of ET. According to Ando et al.,
urine examination by reverse-phase high-pressure liquid chromatography shows a major ET-1-like immunoreactive component coeluting with synthetic ET-1. However, the arterial to venous ratio of ir-ET mostly indicates the turnover of ET-1, the only member of the ET family that is released from the endothelium. In humans, the infusion of synthetic ET-1 is followed by a 43% clearance during the pulmonary passage. Moreover, our data on PE are similar to those reported in ALI, a clinical setting in which ET-1 has been documented to be abnormally high. Nevertheless, our data cannot rule out the possibility that other ET isoforms are abnormal in PE patients as well.

The pathophysiologic relevance of such increase of ir-ET in patients with PE warrants some considerations. Thrombin, a major factor in the pathogenesis of thrombosis, is a potent inducer of ET-1 expres-

### Table 2—Results of ET Assay

<table>
<thead>
<tr>
<th>Clinical Entities</th>
<th>ir-ETart, pg/mL</th>
<th>ir-ETven, pg/mL</th>
<th>ir-ETart/ir-ETven</th>
<th>ir-ETur, ng/24 h</th>
<th>Cl ir-ET, mL/min</th>
<th>Cl ir-ET/Cl Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HV</td>
<td>4.2</td>
<td>4.7</td>
<td>0.80</td>
<td>54</td>
<td>8.92</td>
<td>0.092</td>
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<td>5.3</td>
<td>6.1</td>
<td>0.86</td>
<td>65</td>
<td>8.51</td>
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<td>4.2</td>
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<td>0.77</td>
<td>56</td>
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<td>4.9</td>
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<td>76</td>
<td>11.22</td>
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<td>10.41</td>
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<td>87</td>
<td>13.13</td>
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<td>4.1</td>
<td>4.8</td>
<td>0.85</td>
<td>72</td>
<td>12.19</td>
<td>0.129</td>
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<tr>
<td></td>
<td>5.0</td>
<td>5.2</td>
<td>0.96</td>
<td>75</td>
<td>10.41</td>
<td>0.122</td>
</tr>
</tbody>
</table>

Mean±1 SD

| HV                | 4.5±0.5        | 5.3±0.5        | 0.8±0.1          | 68.3±9.3        | 10.9±2.1        | 0.1±0.0                |
| PE                | 5.9            | 5.4            | 1.00             | 113             | 13.30           | 0.169                  |
|                   | 6.1            | 5.2            | 1.17             | 108             | 12.29           | 0.138                  |
|                   | 7.3            | 5.9            | 1.38             | 95              | 9.04            | 0.100                  |
|                   | 8.9            | 6.5            | 1.36             | 117             | 9.13            | 0.088                  |
|                   | 9.2            | 5.1            | 1.81             | 185             | 13.90           | 0.136                  |
|                   | 9.1            | 6.3            | 1.43             | 124             | 9.46            | 0.095                  |
|                   | 7.2            | 6.8            | 1.06             | 94              | 9.06            | 0.114                  |
|                   | 6.2            | 3.9            | 1.60             | 101             | 11.31           | 0.132                  |
|                   | 7.9            | 6.7            | 1.16             | 145             | 17.75           | 0.193                  |
|                   | 7.4            | 6.9            | 1.07             | 123             | 11.54           | 0.140                  |

Mean±1 SD

| ALI               | 7.5±1.2        | 5.9±1.0        | 1.3±0.3          | 120.5±27.4      | 11.7±2.8        | 0.1±0.0                |
|                   | 10.2           | 6.2            | 1.64             | 143             | 9.73            | 0.124                  |
|                   | 10.1           | 8.5            | 1.19             | 152             | 10.45           | 0.087                  |
|                   | 11.7           | 9.4            | 1.24             | 176             | 10.40           | 0.115                  |
|                   | 5.9            | 5.4            | 1.09             | 107             | 12.59           | 0.144                  |
|                   | 7.5            | 6.9            | 1.08             | 120             | 11.10           | 0.130                  |
|                   | 8.2            | 5.7            | 1.44             | 114             | 9.65            | 0.082                  |
|                   | 6.8            | 6.7            | 1.01             | 125             | 12.76           | 0.185                  |
|                   | 6.1            | 4.5            | 1.36             | 147             | 16.73           | 0.150                  |
|                   | 10.4           | 9.0            | 1.15             | 138             | 9.21            | 0.093                  |

Mean±1 SD

<table>
<thead>
<tr>
<th>Cl ir-ET/Cl Creatinine</th>
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</table>

*a Cl ir-ET=immunoreactive endothelin clearance. Each value of ir-ETart, ir-ETven, and ir-ETur is the mean of duplicate determinations; mean within-assay variability for duplicate determinations was 5.6%.

chemic renal damage; both ir-ET arteriovenous ratios and ir-ET renal clearances of patients with PE were similar to data of patients suffering from ALI, a condition in which a primary dysfunction of pulmonary endothelium has been demonstrated.

At variance with ALI patients, we did not find increased ir-ET venous levels in PE patients as compared with HVs. This supports the possibility that the net increase in pulmonary production of ET is independent of a defective clearance of the peptide occurring in this condition.

The ET values found in our normal subjects are higher than those reported by others. The methods employed in different laboratories for the extraction and measurement of the peptide could account for these discrepancies. In this respect, our data are comparable to those of some previous reports.

However, these uncertainties do not hamper the relevance of the significant difference between the data of control subjects and of PE patients in this setting.
thrombin could contribute to increased ET synthesis: in vitro hypoxia, shear stress, and several proinflammatory cytokines release ET-1 from endothelial cells.18,23

In conclusion, abnormalities of ET metabolism mainly related to its defective pulmonary clearance and/or increased pulmonary production are detectable in patients with acute PE. The relevance of these findings with respect to pulmonary abnormalities (eg, extension of the unperfused areas, vascular remodeling, evolution into chronic thromboembolic disease) taking place during and following an episode of PE is now under intensive investigation in our group.

ACKNOWLEDGMENTS: We thank Vittorio Palmieri, MD, for his assistance with statistical analysis.

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