Pulmonary Release and Coronary and Peripheral Consumption of Big Endothelin and Endothelin-1 in Severe Heart Failure

Acute Effects of Vasodilator Therapy

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Background—We investigated plasma endothelin (ET) levels in patients with congestive heart failure (CHF) during treatment for acute decompensation; we also measured imbalances in ET peptides across the pulmonary, coronary, and peripheral circulation.

Methods and Results—In patients with severe CHF (n=21; cardiac index [CI], 1.9±0.2 L · min⁻¹ · m⁻²; pulmonary capillary wedge pressure [PCWP], 31±1 mm Hg), vasodilation was achieved with the nitric oxide donor sodium nitroprusside (n=11) or with the α₁-antagonist urapidil (nitric oxide–independent, n=10). ET concentrations were determined from arterial blood and blood from the pulmonary artery, coronary sinus, and antecubital vein. Depending on sites of measurement, baseline big ET and ET-1 levels were, respectively, 12 to 16 times and 5 to 11 times higher than in controls (n=11), and 4 to 6 times and 2 to 3 times higher than in patients with moderate CHF (n=10; CI, 2.7±0.3 L · min⁻¹ · m⁻²; PCWP, 14±2 mm Hg). Patients with severe CHF demonstrated pulmonary net release and coronary and peripheral net consumption of both peptides (ie, arterial levels [big ET, 7.3±1.3 pmol/L; ET-1, 1.8±0.1 pmol/L] were higher than levels in the pulmonary artery [6.7±1.2 pmol/L; 1.3±0.1 pmol/L], coronary sinus [6.4±1.0 pmol/L; 1.4±0.1 pmol/L], and antecubital vein [6.6±1.1 pmol/L; 1.3±0.1 pmol/L]). In these patients, sodium nitroprusside (SNP) and urapidil resulted in comparable hemodynamic improvement after 6 hours (CI: SNP, 63±2%; urapidil, 72±3%; PCWP: SNP, −50±2%; urapidil, −47±2%) and a maximum decrease in ET peptides by >50%. After 3 hours, pulmonary net release and coronary and peripheral net consumption were no longer detectable.

Conclusions—In patients with severe CHF, the lungs act as a producer and the heart and the periphery act as consumers of elevated circulating ETs. Short-term vasodilator therapy decreases ETs and restores their pulmonary, coronary, and peripheral balance. (Circulation. 2000;102:1132-1138.)

Key Words: heart failure ■ endothelin ■ lung ■ hemodynamics

Accumulating evidence indicates that the endothelin (ET) system makes an important contribution to the pathophysiology of congestive heart failure (CHF). In patients with the disease, plasma levels of ET-1 and, in particular, its precursor big ET closely correlate with severity of disease.¹

The lung is a major site for both ET-1 secretion and extraction; under physiological conditions, ET-1 is balanced across the pulmonary circulation.² We demonstrated in a rabbit model that the lung releases a substantial amount of endogenous big ET, which, after coronary conversion to ET-1, may act as a remote modulator of coronary tone.³

In humans, however, an investigation of pulmonary and coronary gradients of big ET (ie, of concentration differences across these vascular beds indicating net production or consumption) has not yet been performed. Moreover, no conclusive data exist on the concentration gradients of big ET and ET-1 among patients who have different stages of CHF. For peripheral circulation in CHF, a negative ET-1 gradient, which reflects net consumption of the peptide (mainly by skeletal muscle), has been demonstrated.⁴ Finally, the impact of acute cardiac decompensation and recompensation on circulating ETs is unknown.

In this article, we document in CHF patients the plasma levels of big ET and ET-1; the corresponding pulmonary, coronary, and peripheral concentration gradients; and various hemodynamic variables in the course of intensive care treatment for acute left heart decompensation.
Methods

Patients and Protocol

Patients were enrolled in the study using the following design.

Group 1: Severe CHF and Sodium Nitroprusside Treatment

Eleven patients with CHF who had a functional New York Heart Association class of IV were enrolled (3 women and 8 men; mean age, 58±7 years; mean left ventricular ejection fraction [LVEF], 17±3%). Six patients suffered from CHF secondary to ischemic heart disease (IHD), and 5 demonstrated dilated cardiomyopathy. Inclusion criteria were as follows:

1. Need for intensive care treatment for acute left heart decompensation (orthopnea, signs of severe pulmonary congestion). Acute ischemia was excluded on the basis of ECG, enzyme kinetics (troponins, creatine kinase), and myoglobin.
2. A pulmonary capillary wedge pressure (PCWP) >25 mm Hg and a cardiac index (CI) <2.3 L · min⁻¹ · m⁻².

We treated patients over 24 hours with a sodium nitroprusside (SNP) dosage that decreased systemic vascular resistance (SVR) to a range of 800 to 1000 dynes · s⁻¹ · cm⁻² without lowering mean arterial blood pressure (MAP) below 60 mm Hg. The mean dose of SNP was 3.0±0.4 µg · kg⁻¹ · min⁻¹. Intravenous furosemide was given according to clinical requirements; intravenous nitrates, catecholamines, and phosphodiesterase inhibitors were not administered.

Group 2 (discussed below) served to exclude the possibility that changes in ETs were due to the SNP-induced liberation of nitric oxide, which is known to suppress ET-1 expression.

Group 2: Severe CHF and Urapidil Treatment

The 10 CHF patients enrolled in this group (3 women and 7 men; age, 54±6 years; 6 with IHD and 4 with dilated cardiomyopathy; LVEF, 16±3%) fulfilled the same criteria as patients in group 1. However, acute vasodilatation in this group was achieved with the α₁-adrenoceptor antagonist urapidil. In addition to its peripheral effects, urapidil displays central activity via the stimulation of serotoninergic 5-hydroxytryptamine 1A receptors in the medulla oblongata, which explains the lack of reflex tachycardia; for this profile, urapidil has been used for the short-term treatment of CHF and is known to evolve advantageous hemodynamic effects. A test dose of 50 mg IV was followed by a bolus dose of 25 mg and continuous infusion rates between 25 and 75 mg/h to attain the same hemodynamic effects as in group 1. The furosemide regimen was the same as in group 1. Because of the occurrence of transit syndrome (state of confusion and agitation) in 2 patients at a cumulative dose of 350 mg, this high-dose regimen was terminated for safety reasons in all patients after 6 hours; Thereafter, conventional intensive care treatment was continued. After urapidil cessation, the transit syndrome was fully reversible.

Group 3: Moderate CHF and SNP Treatment

To clearly differentiate between pulmonary congestion and moderately altered pulmonary hemodynamics, we chose different cutoff points for PCWP in patients with severe CHF (>25 mm Hg) and in those with moderate CHF (<20 mm Hg). Thus, CHF patients were assigned to the moderate CHF group (n=10; 3 women and 7 men; age, 54±6 years; LVEF, 29±4%) if they were (1) in New York Heart Association class II and (2) if they displayed a PCWP<20 mm Hg and a CI>2.3 L · min⁻¹ · m⁻². Individuals were recruited among patients undergoing hemodynamic evaluation before a partial ventriculotomy. Six patients suffered from CHF secondary to IHD, and 4 demonstrated dilated cardiomyopathy. Target hemodynamic criteria were the same as in group 1; the mean dosage of SNP was 2.0±0.7 µg · kg⁻¹ · min⁻¹.

Group 4: Controls

Eleven controls (4 women and 7 men; age, 56±5 years; LVEF, 63±5%) were recruited from among individuals who underwent catheterization for suspected IHD and in whom no structural cardiovascular disease was detected. Blood samples were drawn once after catheterization from the left ventricle (LV), pulmonary artery (PA), coronary sinus (CS), and antecubital vein.

Oral Medication

Oral medication was maintained throughout the protocol. In Groups 1 through 3, all patients were on angiotensin-converting enzyme inhibitors and diuretics. In Group 1, 8 patients were on nitrates, 6 on β-blockers, and 5 on digitalis; in Group 2, 8 were on nitrates, 6 on β-blockers, and 5 on digitalis; and in Group 3, 8 were on nitrates, 6 on β-blockers, and 4 on digitalis.

Instrumentation and Blood Sampling

In Groups 1 through 3, catheters were positioned in the PA (Swan-Ganz), CS, and LV under fluoroscopic control. For safety reasons, the LV and CS catheters were removed after baseline measurements and after 4 hours, respectively. MAP was measured invasively in the radial artery. Heart rate, MAP, and pulmonary arterial pressure (PAP) were continuously monitored, and cardiac output (CO) was determined by thermodilution.

Blood sampling and hemodynamic measurements were conducted at baseline and 2, 3, 4, 6, 12, 18, and 24 hours after the initiation of therapy. At baseline, arterial blood was simultaneously drawn from the LV and from the radial artery to prove the comparability of these sites; during treatment, arterial blood was from the radial artery. In addition, blood was taken from the PA, CS (CS only throughout 4 hours), and antecubital vein.

This study was designed to reveal relationships between hemodynamics and plasma ETs. Therefore, no follow-up data on ETs were sampled after the discharge of patients from the intensive care unit because of the lack of corresponding hemodynamic data.

Exclusion criteria were as follows: renal failure (creatinine >250 µmol/L); need of intravenous treatment other than SNP, urapidil, and furosemide; severe noncardiovascular systemic diseases; and primary pulmonary hypertension. This study was approved by the local ethics committee. All patients gave informed, written consent.

Determination of ET Peptides

Big ET and ET-1 were determined using commercial ELISA kits (Immundiagnostik). The big ET kit (detection limit, 0.05 pmol/L) is selective for all 3 isoforms of big ET1-3, with cross-reactivity for big ET-2-3 and all ET isoforms measuring <1%. The ET-1 kit (detection limit, 0.1 pmol/L) displays selectivity for ET-1; with this kit, cross-reactivity for ET-2 and ET-3 (<5% for both) and big ET (<1%) is low.

Methodology

The single-bolus indicator-dilution technique with 125I-labeled ET-1 allows for a detailed investigation of ET extraction and production across different vascular beds2 and is, therefore, superior to a determination of concentration gradients. However, we did not consider this method feasible in our critically ill patients because it would have required the administration of significant amounts of exogenous ETs and repeated selective catheterization of the coronary system and LV.

Pulmonary Net Release of ETs

This parameter was derived using individual pulmonary concentration gradients (PCG), as follows.

PCG=arterial – pulmonary arterial concentration (in pmol/L)

Individual pulmonary plasma flow (PPF) was equal to the CO determined by thermodilution (CO in L/min) and corrected for individual hematocrit (HC), which was determined at each point in time using the following equation: PPF=CO×(1-HC). Using these values, we calculated pulmonary net release (in pmol/min) as follows.

Net release=PCG×PPF=PCG×CO×(1-1HC)
Data Analysis

Data are presented as mean±SEM unless otherwise indicated. An error probability of P<0.05 was regarded as significant.

Baseline hemodynamic parameters for all groups are shown in Table 1.

**Results**

**Hemodynamics**

Hemodynamic parameters for all groups are shown in Table 1.

**Baseline**

No significant differences existed between the severe CHF groups (groups 1 and 2). However, both groups demonstrated a significantly lower MAP, a higher mean PAP (MPAP) and PCWP, a lower CI, and a higher SVR and pulmonary vascular resistance (PVR) than controls (group 4). When comparing patients with severe CHF (groups 1 and 2) with those with moderate CHF (group 3), we determined that MPAP, PCWP, and PVR were significantly higher in those with severe CHF. SVR and PVR were significantly higher in patients with moderate CHF (group 3) than in controls (group 4).

**Vasodilator Therapy**

In patients with severe CHF, SNP (group 1) and urapidil (group 2) induced similar hemodynamic changes in MAP (after 2 hours: SNP, −25±2%; urapidil, −25±1%), MPAP (SNP, −38±2%; urapidil, −36±1%), PCWP (SNP, −47±2%; urapidil, −40±2%), SVR (SNP, −62±3%; urapidil, −62±2%), PVR (SNP, −53±3%; urapidil, −59±3%), and CI (SNP, 68±2%; urapidil, 78±3%). Maximum effects were achieved within 2 hours of treatment.

In patients with moderate CHF (group 3), only the decreases in MAP (2 hours: −31±1%) and SVR (3 hours: −53±3%) were significant. In 4 of the 10 patients, CI did not increase in response to SNP; therefore, the increase in mean CI over 24 hours did not attain significance.

**Determination of ET Peptides**

For Groups 1 and 2, the values and time course of peptide levels are shown in Figures 1 and 2. All concentrations are in pmol/L.
Baseline

In patients with severe CHF (group 1), mean plasma levels of ET in blood from the artery, PA, CS, and antecubital vein ranged from 6.3±0.9 (CS) to 7.0±1.2 pmol/L (arterial blood) for big ET and from 1.3±0.2 (PA) to 1.8±0.3 pmol/L (arterial blood) for ET-1 (Figures 1A and 2A). Results for big ET were 4 to 5 times higher than corresponding values in patients with moderate CHF (group 3; arterial blood, 1.4±0.2; PA, 1.3±0.2; CS, 1.4±0.2; and antecubital vein, 1.2±0.2) and 12 to 15 times higher than those in controls (group 4; arterial blood, 0.47±0.07; PA, 0.53±0.05; CS, 0.46±0.05; and antecubital vein, 0.52±0.05). ET-1 levels in group 1 were 2 to 3 times higher than those in group 3 (arterial blood, 0.66±0.09; PA, 0.59±0.09; CS, 0.59±0.08; antecubital vein, 0.51±0.08) and 5 to 11 times higher than those in controls (arterial blood, 0.17±0.05; PA, 0.26±0.05; CS, 0.21±0.04; and antecubital vein, 0.19±0.05). Furthermore, all values obtained in patients with moderate CHF

Figure 1. Circulating levels of big ET (in pmol/L) in patients with severe CHF, detected in arterial blood and blood from the PA, CS, and antecubital vein at baseline and during vasodilator therapy with SNP (A) or urapidil (B). P<0.05 #vs arterial blood and *vs baseline (* applies to all sites of determination if not indicated NS).

Figure 2. Circulating levels of ET-1 (in pmol/L) in patients with severe CHF, detected in blood from the artery, PA, CS, and antecubital vein at baseline and during vasodilator therapy with SNP (A) or urapidil (B). P<0.05 #vs arterial blood or *vs baseline (* applies to all sites of determination if not indicated NS).
(group 3) were significantly higher than those determined in controls (group 4).

Group 2 (severe CHF and urapidil) values were similar to those determined in group 1. Levels of big ET ranged between 6.5±1.4 (CS) and 7.5±1.8 pmol/L (arterial blood), and levels of ET-1 ranged between 1.3±0.1 (antecubital vein) and 1.8±0.1 pmol/L (arterial blood; Figures 1B and 2B).

In both severe CHF groups (1 and 2), big ET and ET-1 values obtained in arterial blood were significantly higher than values from PA blood (group 1, 7.0±1.2 versus 6.5±1.1 pmol/L for big ET and 1.8±0.3 versus 1.3±0.2 pmol/L for ET-1; group 2, 7.5±1.8 versus 7.0±1.6 pmol/L for big ET and 1.8±0.1 versus 1.4±0.1 pmol/L for ET-1). These concentration gradients indicate pulmonary net release of big ET and ET-1. Moreover, big ET and ET-1 values in blood from the CS (group 1, 6.3±0.9 and 1.4±0.2; group 2, 6.5±1.4 and 1.4±0.2) and antecubital vein (group 1, 6.4±1.1 and 1.4±0.2; group 2, 6.9±1.8 and 1.3±0.1) were significantly lower than those in arterial blood, indicating coronary and peripheral net consumption of big ET and ET-1 in both groups.

No significant differences between the sites of measurement were observed in patients with moderate CHF (group 3) and in controls (group 4).

Baseline levels of big ET and ET-1 did not differ between the LV and the radial artery in group 1 (LV, 7.0±1.2 and 1.8±0.3 pmol/L; radial artery, 7.0±0.9 and 1.8±0.2 pmol/L), group 2 (LV, 7.5±1.8 and 1.8±0.1; radial artery, 7.6±1.3 and 1.9±0.3), and group 3 (LV, 1.4±0.2 and 0.66±0.09; radial artery, 1.4±0.3 and 0.68±0.08), which proves the reliability of concentrations detected in the radial artery for monitoring the subsequent treatment throughout 24 hours.

**Vasodilator Therapy**

In patients with severe CHF (group 1), SNP significantly decreased concentrations of big ET and ET-1 in blood from the artery, PA, CS, and antecubital vein (Figures 1A and 2A). Big ET levels fell by 54±4% (arterial blood), 51±3% (PA), and 52±3% (antecubital vein) after 24 hours; ET-1 concentrations decreased by 61±3% (arterial blood), 46±2% (PA), and 53±3% (antecubital vein). Most of the decrease occurred within 6 hours. Values in CS dropped by 32±2% for big ET and 26±1% for ET-1 after 4 hours. Parallel to the drop in absolute values, pulmonary, coronary, and peripheral gradients for big ET and ET-1 vanished and were no longer detectable after 2 hours of treatment.

Figure 3 shows the time course of the pulmonary net release of big ET and ET-1, demonstrating positive values at baseline (big ET, 0.96±0.13 pmol/min; ET-1, 0.83±0.10 pmol/min), a continuous decline during the first 2 hours of treatment, and a restored balance during the rest of treatment. Except for the slightly longer persistence of the ET-1 gradients, results in patients with severe CHF treated with urapidil (group 2) were fully comparable to those in severe CHF treated with SNP (group 1; Figures 1B, 2B, and 3B).

In patients with moderate CHF (group 3), SNP treatment changed neither big ET nor ET-1 values (data not shown).

**Correlations Between ETs and Hemodynamics**

Results are summarized in Table 2.
To assess the contribution of certain vascular beds to elevated circulating ETs, we determined the concentration gradients for big ET and ET-1 across the pulmonary, coronary, and peripheral circulation. For ET-1, pulmonary net release has not been described in patients suffering from secondary pulmonary hypertension due to CHF or in controls. A key finding of our study was the significant pulmonary net production of big ET and ET-1 in patients with severe CHF but not in those with moderate CHF or in controls.

There are differences between our observations and those of others, which can be explained by considering the severely compromised hemodynamic status of our patients. In the study performed by Dupuis and coworkers, patients had MPAP values of 20 to 35 mm Hg whereas MPAP in our patients was ~45 mm Hg. Dupuis et al showed that the compromised pulmonary clearance of ET-1, which is likely due to pulmonary ETβ receptor downregulation, can be detected even in patients with moderate CHF but is not necessarily followed by a pulmonary imbalance of ET-1. Our results from severe CHF patients, therefore, suggest not only a deteriorated pulmonary clearance of ET-1, but also an increase in pulmonary ET-1 spillover due to heightened synthesis of this peptide. Concerning big ET, the situation is similar; however, clearance of big ET occurs mainly through the activity of the ET-converting enzyme(s) and, until now, there were no conclusive data on the regulation of pulmonary ET-converting enzyme(s) in CHF.

We provide the first evidence that in patients with severe CHF, the heart is a consumer of elevated circulating ETs, as indicated by a negative coronary gradient for big ET and ET-1. The pathophysiological relevance of this coronary consumption may lie in the induction of coronary vasoconstriction, the initiation of ventricular arrhythmias, the maintenance of the contractile status of the compromised myocardium, and the contribution to ventricular remodeling.

In patients with severe CHF, Tsutamoto and coworkers found a net consumption of ET-1 across the circulation of the lower limb. For forearm circulation, we established a similar net consumption of ET-1; moreover, we also verified this for big ET. The peripheral consumption of ETs may significantly contribute to increased SVR, which correlates with baseline levels of ET peptides in patients with severe CHF.

Altogether, our findings may reinforce a therapeutic concept that includes the early administration of ET receptor antagonists in the intensive care treatment of patients with severe heart failure.

### Vasodilator Therapy

In patients with severe CHF (group 1), the SNP-induced reduction of afterload and preload resulted in a pronounced improvement of hemodynamics. Simultaneously, plasma big ET and ET-1 decreased markedly, and the physiological balance across pulmonary, coronary, and peripheral vascular beds was restored. The question is whether this decrease in circulating big ET and ET-1 can be primarily attributed to nitric oxide liberation by SNP or whether it results from improved hemodynamics. To work around this question, we chose 2 different approaches.

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**Table 2: Correlations Between Levels of ETs and Hemodynamic Parameters**

<table>
<thead>
<tr>
<th></th>
<th>Big ET</th>
<th>ET-1</th>
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<tr>
<td><strong>Baseline</strong></td>
<td></td>
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<tr>
<td>All patients</td>
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<tr>
<td>CI vs A</td>
<td>−0.73</td>
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<td>MPAP vs A</td>
<td>0.81</td>
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<td>PCWP vs A</td>
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<td>SVR vs A</td>
<td>0.62</td>
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<td>PVR vs A</td>
<td>0.84</td>
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<td><strong>Severe CHF (groups 1 and 2)</strong></td>
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<tr>
<td>CI vs A</td>
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<td>MPAP vs A</td>
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<td>SVR vs A</td>
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<td>0.041</td>
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<tr>
<td>PVR vs A</td>
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<td>0.044</td>
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<td><strong>Percent Changes During Therapy</strong></td>
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<td>Severe CHF (group 1)</td>
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<tr>
<td>CI vs A</td>
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<td>MPAP vs A</td>
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<td>PCWP vs A</td>
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<td>SVR vs A</td>
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<td>PVR vs A</td>
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<td>0.022</td>
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<tr>
<td>Severe CHF (group 2)</td>
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<td>CI vs A</td>
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<tr>
<td>MPAP vs A</td>
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<td>0.109</td>
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<tr>
<td>PVR vs A</td>
<td>0.65</td>
<td>0.029</td>
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* A indicates arterial concentration of endothelin peptides. Comparable results of regression analyses were obtained for pulmonary arterial and antecubital venous levels (data not shown).
1. Using urapidil, a peripheral α1-adrenoceptor antagonist and central 5-HT1A agonist, in a group of patients with severe CHF (group 2), we induced hemodynamic improvements comparable to those evoked by SNP. These improvements were accompanied by similar alterations of ET peptides. Peripheral α1-adrenoceptor antagonists do not affect circulating ETs in healthy humans. Furthermore, there is no suggestion in the literature of any relationship between central serotoninergic stimulation and peripheral ET peptides. We may, therefore, reasonably argue that in our patients with severe CHF, the hemodynamic improvement initiated by urapidil, which is nitric oxide–independent, represents the crucial step to a decrease in circulating big ET and ET-1.

2. For both therapeutic regimens for patients with severe CHF (SNP and urapidil), we found significant correlations between the decrease in big ET and ET-1 and the decrease in pulmonary pressures and PVR. This again represents an argument in favor of a causal relationship between improved hemodynamics and the decrease in ETs.

Hypothetically, the elimination of pulmonary net release may be attributed to the substantial lowering of pulmonary pressures, which may induce a decrease in the synthesis of ET-1 by pulmonary vascular endothelial and/or smooth muscle cells and, consequently, decrease PVR. However, for pulmonary vascular endothelial and smooth muscle cells, the relationship between ET-1 synthesis and flow-related parameters (perfusion pressure and shear stress) is not well defined and remains to be investigated.

Concerning coronary and peripheral circulation, both the increased contribution of ETB receptors to peripheral vasoconstriction and the increased density of cardiac ETα receptors have been demonstrated in CHF. Provided that the density of coronary ETα receptors (as part of the entire cardiac receptor population) is also elevated, an increase in vascular ET receptor density would lead to a substantially increased binding of free luminal ET peptides. Hence, these conditions might contribute to the peripheral and coronary net consumption of ET-1 observed at baseline, and they may be affected by hemodynamic improvements.

**Study Limitations**

No attempt was made to measure coronary or forearm blood flow. Currently, the combination of flow wires with quantitative coronary angiography or intravascular ultrasound represents the most exact method for measuring coronary flow in humans. In our study, this would have required repetitive catheterization of the left main stem and the right coronary artery, which is not ethically justified in view of the clinical situation in patients with severe CHF. Because the measurement of coronary circulation was not feasible, we prospectively decided to measure only ET concentration gradients for the heart and for peripheral circulation. Nevertheless, because a significantly negative concentration gradient implies net consumption, irrespective of the absolute values, this limitation does not detract from the principal finding.

For similar safety reasons, the CS catheter was removed after 4 hours, with the result that peptide concentrations in the CS could only be monitored for this restricted period of time.

**Conclusions**

In severe heart failure, the lungs play a major role in increasing the circulating levels of big ET and ET-1. This phenomenon is attributed not only to diminished pulmonary clearance of ET peptides, but also to pulmonary net release. Elevated ETs may exert effects on the coronary vascular bed and the myocardium, as indicated by the coronary net consumption of big ET and ET-1, and on the peripheral circulation, which also consumes ET peptides in severe CHF. Short-term vasodilator therapy, independent of nitric oxide involvement, decreases high circulating levels of ETs within hours and restores physiological balance across pulmonary, coronary, and peripheral vascular beds.

**References**


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