Increased endothelin levels in congestive heart failure: does it come from the lungs? Does it matter?

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See article by von Lueder et al. [14] (pages 41–50) in this issue.

Endothelin-1 (ET) is a potent vasoconstrictor and promitogenic peptide produced ubiquitously by the vascular endothelium. It is formed by cleavage of the 39-amino acid precursor big endothelin-1 (big ET) through the action of the endothelin converting enzymes (ECEs). Although it is generally accepted that ET is released constitutively in a preferentially paracrine fashion, a smaller, measurable fraction is released into the vascular lumen. Circulating ET levels are increased in various cardiovascular conditions, including congestive heart failure (CHF) [1–3], and are related to the subsequent event rate [4].

At first glance, it could be straightforwardly concluded that higher circulating ET levels reflect activation of this system, with increased synthesis and subsequent overflow into plasma. The biology of the ET system, however, is more intricate due to the presence of endothelial ET B receptors that are capable of clearing circulating ET from plasma [5]. Thus, the increase in circulating ET could result from increased production, reduced clearance, or a combination of both. Since the lungs display the highest ET and ECE content and are recognized as the major site for circulating ET clearance, they may occupy a central role in the modulation of plasma ET. The observation that ET levels correlate especially well with the severity of pulmonary hypertension associated with CHF lends support to this hypothesis. These observations therefore raise the possibility that increased plasma ET levels could reflect the severity of pulmonary vascular endothelial dysfunction associated with CHF.

1. Evidence for increased pulmonary ET production in CHF

In the rat infarct model of CHF, lung tissue ET levels are increased together with the expression of its precursor preproET-1 mRNA [3,6]. There is no change, however, in the expression of ECE-1 mRNA. Interestingly, ET plasma levels in these animals correlate with lung expression of ET and with ET levels found in pleural effusions. Similar findings were obtained in patients with secondary pulmonary hypertension, including some with congestive heart failure, with increased ET-1 expression in the pulmonary vascular endothelium that correlated with the severity of pulmonary hypertension [7]. This increase in ET production may also come from the pulmonary artery smooth muscle cells themselves, since it has been demonstrated that two factors whose levels are increased in CHF, transforming growth factor beta and angiotensin II, can stimulate ET production and release by smooth muscle cells [8,9].

2. Evidence for reduced pulmonary ET clearance in CHF

The lungs are the major site for circulating ET clearance. In man, close to 50% of circulating ET is cleared within a single transit time [10]. Clearance is mediated by the endothelial ET B receptor and can be completely blocked by selective ET B receptor antagonists [5]. In the normal human lung, there is no or minimal arteriovenous ET gradient across the pulmonary circulation, demonstrating that the amount of ET released into the circulation is quantitatively similar to the amount extracted. In the rat infarct model of CHF, pulmonary clearance of ET is reduced and correlates with the increase in circulating ET levels. This is consistent with the observed reduction in ET B receptor density and expression found in the lungs.
of these animals [11]. In the pacing overdrive model of CHF in dogs, pulmonary clearance of ET is also reduced, and although ETB receptor density is not modified, there is a threefold reduction in ET binding affinity to lung membranes [1].

Two studies have evaluated pulmonary ET clearance in patients with CHF. The first one evaluated patients with pulmonary hypertension, including five with CHF [12], while the second evaluated 24 patients having exclusively CHF [13]. Pulmonary ET-1 extraction, measured by the single bolus indicator-dilution technique, was reduced to 32 ± 14% by comparison to historic controls (47 ± 7%). Plasma ET-1 clearance by the lungs (924 ± 588 ml/min) was also much lower than in controls (1424 ± 79 ml/min). In both of these studies, however, there was no arteriovenous ET gradient across the pulmonary circulation, and in the latter, reduced clearance did not correlate with circulating ET levels. This would suggest that although pulmonary ET clearance is reduced in human CHF, it is not a major contributor to the increase in plasma levels. As such, it is possible that reduced pulmonary clearance of ET in CHF could be a reflection of pulmonary vascular endothelial dysfunction, but its pathophysiologic significance remains uncertain.

3. Can we discern clearance and production?

Although an observed “step up” in the ET gradient across the lungs compared to baseline conditions would suggest a net contribution of the lungs to increased plasma ET, it does not allow distinction between reduced clearance and/or increased production. In this issue of *Cardiovascular Research*, von Lueder et al. [14] offer a pragmatic approach that combines simultaneous evaluation of pulmonary clearance and production of ET in the pacing overdrive model of CHF in pigs. Compared to controls, they observed a significant arteriovenous ET gradient across the lungs from CHF pigs, suggesting a net contribution of the lungs to increased plasma ET levels. They found that pulmonary clearance of ET was not modified in this model. The computed secretion of ET was therefore increased. More importantly, the authors offer a possible mechanism for this increased production since they detected increased ECE-1 activity in the congested lower lobes, especially in alveolar macrophages.

4. Can we quantify the relative contribution of the lungs to plasma ET?

Von Lueder et al. [14] used the best available approach to quantify ET production and clearance in vivo by combining the indicator-dilution technique with simultaneous measurements of plasma ET levels [12]. The major caveat of this approach, however, is that it allows a single “snapshot” of pulmonary metabolism of ET and, unless done repeatedly, does not offer the possibility of evaluating dynamic changes during the course of disease. Another limitation is that the computed production of ET relies solely on the measured plasma levels across the studied organ and thus subject to the experimental error of this measurement. The possibility of such an error is raised in the present study since ET levels in the pulmonary artery were surprisingly lower than in both the superior and inferior vena cava. More importantly, the data presented by the authors demonstrate that an important increase in the amount of ET that survives passage through the lungs contributes to the higher plasma levels. This amount more than doubled in CHF; other organs besides the lungs can therefore substantially contribute to the increase in ET levels. The liver and kidneys, for example, which also produce and clear ET from plasma, may contribute to these higher levels [15].

So, does the increase in circulating ET come from the lungs in CHF? Some of it probably does. As to its relative importance, however, it appears that the jury is still out and will be deliberating for quite some time. A new, important finding from the study by von Lueder et al. is that CHF causes increased synthesis of ET in the congested pulmonary lobes. Whether or not this contributes to increased plasma ET levels may have less importance than its potential local contribution to the development of secondary pulmonary hypertension.

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References


