Pulmonary Clearance of Endothelin-1 on Heart Failure: Reduced or Normal?

To the Editor:

Dupuis et al\(^1\) present a novel study in an important area, examining pulmonary clearance of endothelin-1 (ET-1). However, we suggest that the inverse relationship between ET-1 concentration and percentage extraction in the lung might be interpreted quite differently.

We argue that the null hypothesis for this study should be that the pulmonary absolute extraction rate of ET-1 is independent of ET-1 level, i.e., the extraction phenomenon obeys zero-order kinetics. Percentage extraction of ET-1 can therefore be expressed as

\[
\text{Percentage extraction} = 100 \times \frac{\text{Absolute extraction rate}}{\text{Endothelin concentration} \times \text{Blood flow}}
\]

For constant blood flow, percentage extraction is proportional to 1/endothelin concentration. When a power-law curve is applied to the data presented, the best-fit equation spontaneously returns a power of \(-1.02\), which directly supports the null hypothesis (Figure). Furthermore, the null hypothesis, of constant absolute extraction rate, shows a significant fit (\(R^2 = 0.67\)) and therefore cannot be rejected.

We suggest that the conclusion we should draw from this innovative study on an important topic is opposite to that implied in the article. Surely it shows that in heart failure, the increase in plasma ET-1 occurs despite a constant absolute pulmonary extraction rate; other candidate causes must therefore be examined.

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Application of power-law curve to relationship between plasma endothelin and percentage pulmonary endothelin extraction.

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Response

Francis et al argue that absolute removal of endothelin-1 (ET-1) by the lungs would be constant, thus invalidating our main conclusion. Their analysis is based on Figure 2 of the article,\(^1\) with assumption that the in vivo pulmonary flow rate is also constant. This second premise is, however, incorrect: although ET-1 extraction was measured in isolated lungs perfused at a constant flow rate, plasma ET-1 levels were measured in vivo, in animals with heart failure and presumably variable pulmonary flow rates. To precisely quantify absolute pulmonary ET-1 removal would necessitate the simultaneous in vivo measurements of percent ET-1 extraction, pulmonary plasma flow, and plasma ET-1 levels.

Following the reasoning of Francis et al, however, one can easily compute absolute pulmonary ET-1 removal in the isolated lung studies, since perfusion rate was kept constant with the same amount of \(^{125}\)I-ET-1 injected for each lung. In this instance, percentage extraction becomes directly proportional to absolute pulmonary ET-1 removal, thus invalidating the hypothesis of Francis et al. We have thus clearly demonstrated that isolated lungs from heart failure rats have a reduced metabolic capacity to clear ET-1 from circulation and that this correlates inversely with in vivo ET-1 levels. This, together with the presence of an increase in arteriovenous ET-1 gradient across the lungs, suggests that the process contributes to the increase in circulating levels observed in this model of heart failure.

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