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Correspondence

Nitric Oxide Synthesis and Congestive Heart Failure

To the Editor:

Recently, Katz et al1 attributed decreased urinary [15 N]nitrate excretion after the administration of L-[15N2]arginine to impaired nitric oxide production in patients with congestive heart failure (CHF). However, we think that this inference must be viewed with caution for several reasons.

First, the normalization of urinary [15 N]nitrate excretion for 24-hour urinary creatinine excretion is not an appropriate index to correct for the altered renal nitrate excretion in patients with CHF. Although plasma creatinine has a renal clearance very similar to the glomerular filtration rate, nitrate is eliminated by the kidneys with a clearance of ~20 mL/min.2 In addition, the analysis becomes more complicated when we consider that the proportion of urinary creatinine excretion due to tubular secretion increases with decreasing renal function.3

Second, because the assessment of nitric oxide production was based on the urinary excretion of [15 N]nitrate, it is important to contemplate the collection period of this isotope. On the basis of the estimates of nitrate clearance in each study group (47±11 and 28±9 mL/min), the nitrate elimination half-lives are 9.09 and 15.26 hours in the control and patient groups, respectively. The formula to determine nitrate elimination half-life (t1/2) follows:4

\[ t_{1/2} = \frac{0.693 \times \text{Volume distribution}}{\text{Clearance}} \]

Because body weights were not reported, we assumed that the nitrate volume of distribution was 37 liters; however, this figure probably underestimates the actual total body water in patients with CHF. Because the urine was collected for 24 hours, ~62.5% (1.5 half-lives) of urinary [15 N]nitrate was recovered in patients with CHF compared with 80% (2.6 half-lives) in the control group. It is likely that these dissimilar recoveries of [15 N]nitrate could have had an important contribution to the observed difference of nitric oxide production.

Third, the authors stated: “in agreement with a previous study in hypertensive patients that used similar isotope-labeling techniques,5 urinary nitrate excretion of [15 N]nitrate was completed within 24 hours after the infusion of L-[15N2]arginine.” This statement is incorrect and misleading. We did measure [15 N]nitrate enrichment in urine at ~0.4260% during the period between 24 and 36 hours.5 Katz et al emphasized that they did not detect any levels of [15 N]nitrate in urine after 24 hours. This is not surprising if we consider that the precision of their mass spectrometer was rarely better than 0.01%. The mass spectrometer used in our study has a sensitivity (±0.0004), which allows for the recovery of >90% of the [15 N]nitrate excreted in urine.

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Response

Drs Forte and Benjamin suggest that differences in renal nitrate clearance can account for our reported findings.1 We disagree for several reasons.

First, if nitrate clearance was the principal determinant of our findings, then the differences in nitrate clearance reported in our article would predict that [15 N]nitrate concentrations in plasma would be greater in patients with heart failure than in normal controls. In fact, in a small subset of 11 patients with heart failure and 4 normal subjects for whom plasma data are available, plasma [15 N]nitrate concentrations tended to be nearly 2-fold higher in normal subjects compared with patients with heart failure (250±140 versus 140±50 nmol/L; P=NS). Second, if nitrate clearance was the principal determinant of our findings, we would expect to see a correlation between nitrate clearance and [15 N]nitrate excretion. In fact, no association was found between nitrate clearance and [15 N]nitrate excretion (r=0.41; P=NS). Finally, differences in nitrate clearance cannot account for the reported disparate response to exercise in normal subjects and in patients with heart failure.

Our statement regarding the Forte et al’s2 published study in hypertensive patients was based on data published in Table 2 of that article, which indicates that only 8% to 15% of total [15 N]nitrate urinary excretion was detected in the urine collected between 24 and 36 hours after the administration of L-[15N2]arginine. Given the nearly 4-fold difference in [15 N]nitrate excretion between heart failure patients and normal subjects reported in our study, the relatively small changes in total [15 N]nitrate excretion that may have been detected by extending our urine collection to 36 hours would not alter our original conclusions.

In summary, we maintain that decreased activity of the l-arginine–nitric oxide metabolic pathway is the most likely explanation for our observations and that small differences in renal clearance of nitrates cannot account for our findings. Our original conclusions are supported by the recently published study by Agnoletti et al,3 which demonstrated that serum from patients with heart failure downregulates endothelial nitric oxide synthase expression in cultured human umbilical vein endothelial cells.
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Pablo Forte and Nigel Benjamin

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