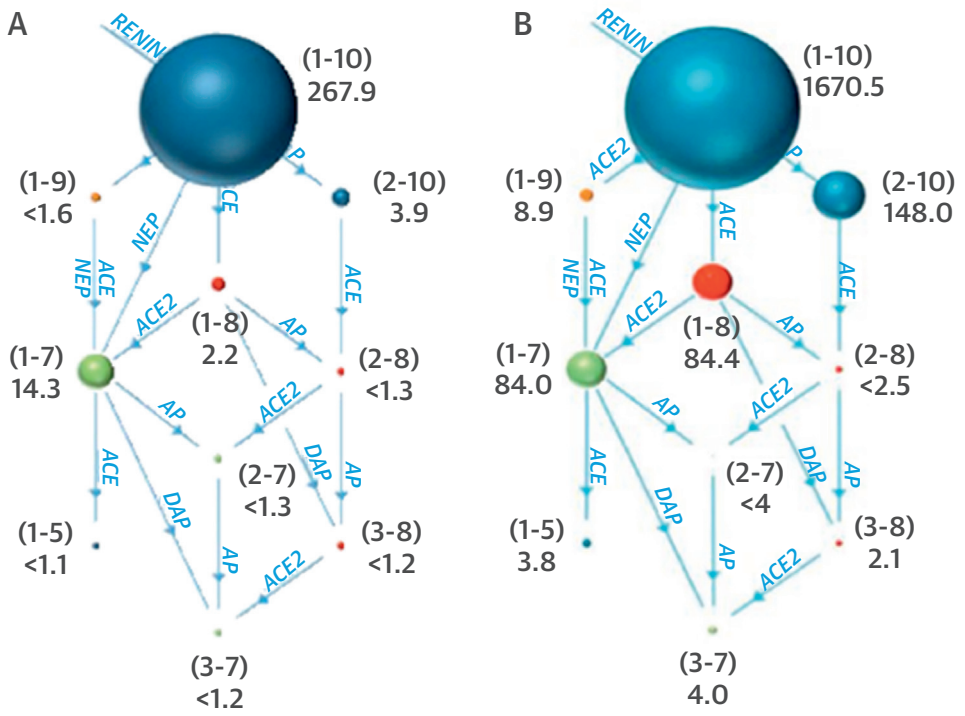
FIGURE 1 Data Comparison



Sphere sizes are proportional to angiotensin (Ang) peptide concentrations, and numbers are median Ang concentrations (pg/ml). **(A)** Pavo et al. (2) found Ang II levels (1–8) smaller than the Ang (1–7) levels. **(B)** Basu et al. (1) found Ang II levels (1–8) and Ang (1–7) levels to be equally high. ACE = angiotensin-converting enzyme; AP = aminopeptidase; DAP = aspartyl aminopeptidase; NEP = neprilysin. Reproduced with permission from Pavo et al. (2) and Basu et al. (1).

discrepancy between these 2 studies is uncertain (ACEI dosage, variable ejection fraction, HF duration, ACE inhibition duration, comorbidities, and so forth). We would appreciate the authors' interpretation of these conflicting data for a better understanding of the evermore complex RAS system.

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REPLY: RAS Fingerprint

Dr. Haugli and colleagues raised the issue that 2 recent papers published in the *Journal* on angiotensin (Ang) peptide levels in heart failure patients might have presented contradicting Ang data for heart failure patients treated with angiotensin-converting enzyme (ACE) inhibitors. The statement by Dr. Haugli and colleagues, that Ang levels in comparable cohorts are 40-fold higher than those in the report by Basu et al. (1), is simply wrong. Haugli et al. compared the

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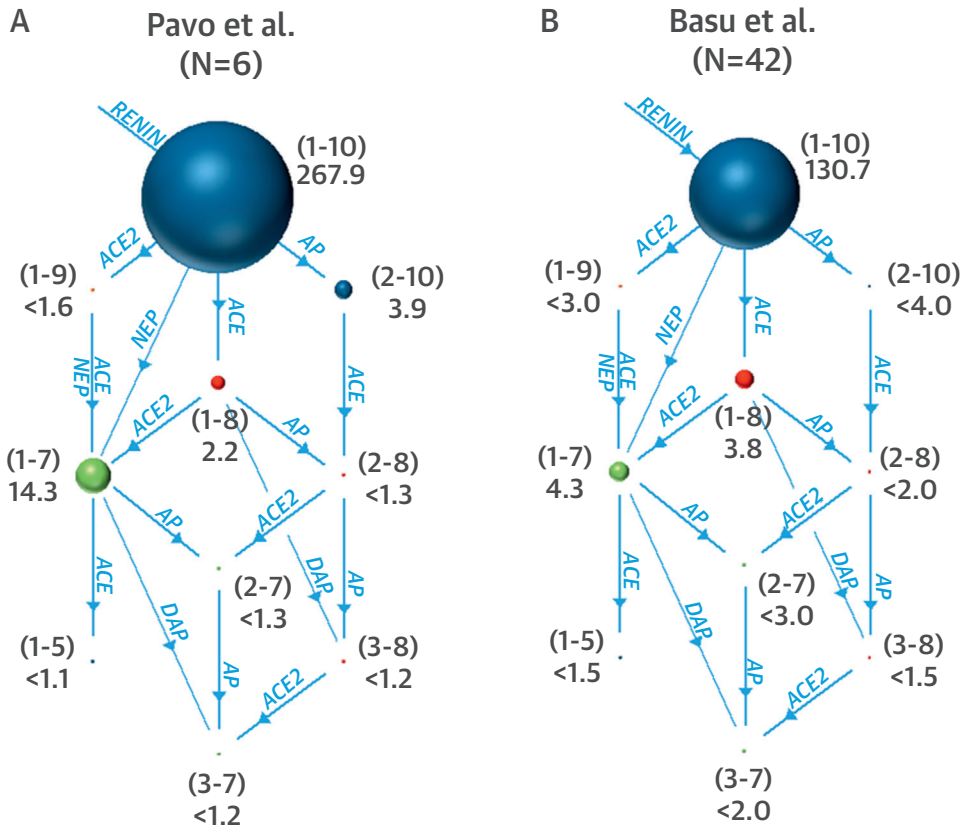
FIGURE 1 RAS Fingerprints for Circulating Angiotensin Levels in Heart Failure Patients Treated With ACE Inhibitors



Direct comparison between data reprinted with permission from Pavo et al. (1) and with permission from Basu et al. (2). The Ang metabolite sequence is shown **(brackets)**, and the corresponding metabolite concentration is given in pg/ml. For median values below the LLOQ of the method, nondiscrete values are given, as indicated by "<." Differences in LLOQs arise from methodological improvements. Ang I = 1–10; Ang II = 1–8; Ang 1–7 = 1–7. ACE = angiotensin-converting enzyme; Ang = angiotensin; AP = aminopeptidase A; DAP = aspartyl aminopeptidase; LLOQ = lower limit of quantification; NEP = neutral endopeptidase.

results from 2 different methodological approaches. Although circulating Ang levels are presented in the report by Pavo et al. (2) (**Figure 1A**), the figure they refer to in our study is based on RAS equilibrium analysis (**Figure 1B**, right panel), which is a novel diagnostic approach that is extensively described in our study (2). Indeed, median circulating Ang II levels in ACE inhibitor-treated heart failure patients (n = 42) reported by Basu et al. (1) (**Figure 1B**, left panel) were 3.8 pg/ml and not significantly different than the values reported by Pavo et al. (2) (n = 6), 2.2 pg/ml (**Figure 1**). Assay-specific features of RAS fingerprint analysis of circulating versus equilibrium analysis were clearly addressed by Basu and colleagues (2). Although a special protease inhibitor cocktail is required to determine circulating Ang levels, sampling is much easier for RAS equilibrium analysis, because it is compatible with standard serum or Li-heparin sampling, underlining its potential to be used for comprehensive biochemical evaluation of the RAS in clinical settings.

Dr. Haugli and colleagues did raise a valid point regarding the Ang 1-7-to-Ang II ratio. The difference in the ratio between the 2 reports (Pavo 6.2 vs. Basu 1.1) (**Figure 1**) may indicate a difference in the pharmacologic efficacy of ACE inhibition and its impact on plasma Ang 1-7 levels. The time from drug administration to sampling, which was different between the 2 studies is likely a key variable. In order to simulate clinical applicability, Basu et al. (1) sampled between 10 AM and 1 PM. Assuming drug intake by individual patients between 6 and 8 AM,

samples were collected between 2 and 7 h after drug administration. Pavo et al. (2) collected their samples 4 h after drug administration, which is close to the pharmacokinetic peak of plasma levels of the ACE inhibitor. Although the cohort in Pavo et al. (2) is small (n = 6), higher Ang I levels and a lower Ang II-to-Ang I ratio support the hypothesis of more efficient ACE inhibition. More efficient ACE inhibition would result in higher levels of Ang 1-7 because ACE converts Ang 1-7 to Ang 1-5, and ACE inhibitor use is associated with increased plasma Ang 1-7 levels (2).

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Please note: Dr. Poglitsch is managing director of Attoquant Diagnostics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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