Authors’ reply: role of natriuretic peptide receptor C signalling in obesity-induced heart failure with preserved ejection fraction with pulmonary hypertension

Vineet Agrawal1 and Anna R. Hemnes2
1Division of Cardiology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA; 2Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

Keywords
pulmonary hypertension, heart failure, natriuretic peptides

Date received: 10 February 2020; accepted: 11 February 2020
Pulmonary Circulation 2020; 10(1) 1–3
DOI: 10.1177/2045894020910979

We thank Eroume-A Egom and Kamgang for their interest in our article and the opportunity to further discuss our work,1 particularly in the context of existing literature on the role of the natriuretic peptide clearance receptor (NPRC) in pulmonary hypertension and heart failure with preserved ejection fraction (PH-HFpEF).

Growing evidence suggests that lower circulating levels of natriuretic peptides (NPs) in PH-HFpEF and decreased downstream cGMP/PKG signaling are important pathogenic mechanisms.2–4 Since circulating NPs can be decreased either by neprilysin-mediated degradation or NPRC-based clearance, and recently studies have shown a neutral effect of neprilysin inhibition upon outcomes in PH-HFpEF,5 it is plausible that increased expression of NPRC may play an important role in promoting PH-HFpEF as it does in promoting known comorbid conditions such as obesity and metabolic syndrome.6 In general, progress in identifying therapies for PH-HFpEF has been hampered by the lack of pre-clinical models that faithfully recapitulate human manifestations of PH-HFpEF,7 including models that utilize Ang2 stimulation.8–11 Unfortunately, human studies investigating ACE inhibition and ARB therapies have not proven effective in HFpEF,7,12 calling into question the relevance of this model to HFpEF pathobiology. Alternatively, there is a growing acceptance that obesity and metabolic syndrome may play a pathogenic role in the development of PH-HFpEF in a subset of patients.13–17 Thus, while no single model is likely to perfectly recapitulate the heterogeneous syndrome of PH-HFpEF,12 we believe that our model of obesity-induced PH-HFpEF is highly relevant to this important subpopulation of PH-HFpEF and shares similar findings of disproportionate RV remodeling.15

We read with interest the potential role that the NPRC may play in the development of PH and sinoatrial disease.8–11 While the findings are certainly intriguing and further investigation of NPRC’s role in PH-HFpEF is warranted, we respectfully disagree with the overall conclusion that NPRC must be regarded as a protective receptor in the heart. Rather, there is an alternative explanation for the previously cited findings. NPRC is well known to play an important role in modulating blood pressure,18 and the lack of development of systemic hypertension may have been a confounding explanation for why a “protective” effect of NPRC was observed in previous studies.8,9,11 In the studies directly investigating PH-HFpEF phenotypes in NPRC−/− mice or with administration of NPRC agonist, ANP-4-23,10,11 the authors...
have nicely demonstrated the potential protective effects of ANP-4-23. Notably, Fig. 7 of our study shows a similar finding. However, their measured right ventricular systolic pressure (RVSP) of 2–5 mmHg in one study11 outside the widely accepted normal RVSP range of 20–30 mmHg19–23 perhaps may be accounted for by placement differences of the catheter, i.e. atrial/diastolic pressure waveform vs. ventricular/systolic waveform as demonstrated in Fig. 4 of one of the referenced studies.10 This technical difference would also account for differences in conclusions of the role of NPRC in the heart in the previously cited studies.8–11

Finally, Eroume-A Egom and Kamgang suggest that increased lung expression of NPRC may account for our findings of RV hypertrophy. We did probe NPRC expression and, as shown in Fig. 4, we did not find any increase in lung NPRC expression. We do agree with the comments from Eroume-A Egom and Kamgang that investigation in how the pulmonary vasculature may be affected by variants in NPRC, and the role of NPRC in HFpEF-PH is worthy of future study. Confirmation of rodent findings in humans and multiple animal models will enhance understanding of these early findings as well.

We overall appreciate the growing interest in the role of NPRC in the development of PH-HFpEF and very much look forward to ongoing studies to clarify the mechanistic role of NPRC in cardiovascular disease. NPRC is known to serve as a “clearance” receptor that binds, internalizes, and sequesters endogenous natriuretic peptides.18,24 It is also known to alter non-cGMP-mediated downstream signaling.25 While our study and others1,11 have now shown a potential protective role for NPRC agonist, ANP-4-23, in modulating PH-HFpEF phenotypes, mechanistically it is not clear whether this is due to decreased “clearance” of endogenous natriuretic peptides by competitive inhibition or a direct effect of downstream signaling. Future studies, including both relevant animal models and an understanding of the mechanistic effect of identified variants in NPRC associated with disease in humans,26 are necessary to answer these questions that have important therapeutic implications.

Conflict of interest
The author(s) declare that there is no conflict of interest.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD
Vineet Agrawal https://orcid.org/0000-0002-8457-6722

References
1. Agrawal V, Fortune N, et al. Natriuretic peptide receptor C contributes to disproportionate right ventricular hypertrophy in a rodent model of obesity-induced heart failure with preserved ejection fraction with pulmonary hypertension. *Pulm Circ* 2019; 9: 2045894019878599.
2. Tromp J, Khan MAF, et al. Biomarker profiles in heart failure patients with preserved and reduced ejection fraction. *J Am Heart Assoc* 2019; 6(4): pii: e003989.
3. van Heerebeek L, Hamdani N, et al. Low myocardial protein kinase G activity in heart failure with preserved ejection fraction. *Circulation* 2012; 126: 830–839.
4. Schiattarella GG, Altamirano F, et al. Nitrosative stress drives heart failure with preserved ejection fraction. *Nature* 2019; 568: 351–356.
5. Solomon SD, McMurray JJV, et al.; PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019; 381(17): 1609–1620.
6. Wu W, Shi F, et al. Enhancing natriuretic peptide signaling in adipose tissue, but not in muscle, protects against diet-induced obesity and insulin resistance. *Sci Signal* 2017; 10: eaam6870.
7. Valero-Muñoz M, Backman W and Sam F. Murine models of heart failure with preserved ejection fraction. *JACC Basic to Transl Sci* 2017; 2: 770–789.
8. Egom EE, Vella K, et al. Impaired sinoatrial node function and increased susceptibility to atrial fibrillation in mice lacking natriuretic peptide receptor C. *J Physiol* 2015; 593: 1127–1146.
9. Mackasey M, Egom EE, et al. Natriuretic peptide receptor-C protects against angiotensin II-mediated sinoatrial node disease in mice. *JACC Basic to Transl Sci* 2018; 3: 824–843.
10. Egom EE-A, Feridooni T, et al. New insights and new hope for pulmonary arterial hypertension: natriuretic peptides clearance receptor as a novel therapeutic target for a complex disease. *Int J Physiol Pathophysiol Pharmacol* 2017; 9: 112–118.
11. Egom EE, Feridooni T, et al. A natriuretic peptides clearance receptor’s agonist reduces pulmonary artery pressures and enhances cardiac performance in preclinical models: new hope for patients with pulmonary hypertension due to left ventricular heart failure. *Biomed Pharmacother* 2017; 93: 1144–1150.
12. Parikh KS, Sharma K, et al. Heart failure with preserved ejection fraction expert panel report: current controversies and implications for clinical trials. *JACC Heart Fail* 2018; 6: 619–632.
13. Savji N, Meijers WC, et al. The association of obesity and cardiometabolic traits with incident HFpEF and HFrEF. *JACC Heart Fail* 2018; 6: 701–709.
14. Gopal DM, Santhanakrishnan R, et al. Impaired right ventricular hemodynamics indicate preclinical pulmonary hypertension in patients with metabolic syndrome. *J Am Heart Assoc* 2015; 4: e001597.
15. Obokata M, Reddy YNV, et al. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation* 2017; 136: 6–19.
16. Reddy YNV, Carter RE, et al. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 2018; 138: 861–870.
17. Packer M and Kitzman DW. Obesity-related heart failure with a preserved ejection fraction. *JACC Heart Fail* 2018; 6: 633–639.
18. Matsukawa N, Grzesik WJ, et al. The natriuretic peptide clearance receptor locally modulates the physiological effects of the natriuretic peptide system. *Proc Natl Acad Sci USA* 1999; 96: 7403–7408.
19. Meng Q, Lai Y-C, et al. Development of a mouse model of metabolic syndrome, pulmonary hypertension, and heart failure with preserved ejection fraction. *Am J Respir Cell Mol Biol* 2017; 56: 497–505.

20. Tabima DM, Hacker TA and Chesler NC. Measuring right ventricular function in the normal and hypertensive mouse hearts using admittance-derived pressure-volume loops. *Am J Physiol Heart Circ Physiol* 2010; 299: H2069–H2075.

21. Chen X, Talati M, et al. Estrogen metabolite 16α-hydroxyestrone exacerbates bone morphogenetic protein receptor type II-associated pulmonary arterial hypertension through MicroRNA-29-mediated modulation of cellular metabolism. *Circulation* 2016; 133: 82–97.

22. Fessel JP, Flynn CR, et al. Hyperoxia synergizes with mutant bone morphogenic protein receptor 2 to cause metabolic stress, oxidant injury, and pulmonary hypertension. *Am J Respir Cell Mol Biol* 2013; 49: 778–787.

23. Hemnes AR, Maynard KB, et al. Testosterone negatively regulates right ventricular load stress responses in mice. *Pulm Circ* 2012; 2: 352–358.

24. Cohen D, Koh GY, et al. Molecular determinants of the clearance function of type C receptors of natriuretic peptides. *J Biol Chem* 1996; 271: 9863–9869.

25. Anand-Srivastava MB. Natriuretic peptide receptor-C signaling and regulation. *Peptides* 2005; 26: 1044–1059.

26. Pereira NL, Redfield MM, et al. A functional genetic variant (N521D) in natriuretic peptide receptor 3 is associated with diastolic dysfunction: the prevalence of asymptomatic ventricular dysfunction study. *PLoS One* 2014; 9: e85708.