**Author’s response to reviews**

**Title:** Dissecting genetic factors affecting phenylephrine infusion rates during anesthesia: a genome-wide association study employing EHR data

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Reviewer #3:

We appreciate the reviewer’s acknowledgement on the revised methodology of GWAS and k-means clustering. We understand and agree with reviewer’s concern regarding interpretation of the sub-phenotypes. We did clarify in the original result line 250-253:

“There were no clear boundaries between clusters when average infusion rate was plotted against mean SBP (Figure 2A), indicating the response is not a discrete trait, however the degree of overlap is modest, supporting the clinical observations.”

To further clarify this, we added additional comment in the discussion, line 378-381:

“Also, the response displayed a continuous spectrum and no clear separation due to the complex nature of phenylephrine response. However, it may serve as a starting point for such studies of phenylephrine and may shed light on clinical insight.”

As commonly seen clinically, there are many continuous features used to define a discrete trait, usually for diseases. For example, HbA1c is used to define pre-diabetes and T2DM; eGFR is used to define different stages for chronic kidney disease; HDL, LDL and triglycerides or total cholesterol are used to define hyperlipidemia; Blood pressure is used to define hypertension;
BMI is used to define overweight and obesity. These continuous features are routinely used for diagnosis and monitoring health status, as their clinical significance and utility are well-validated in various populations. The cluster analysis illustrates some variation of possible contributing factors even across the range of continuous infusion rates. However, there is no straightforward feature to define the responsiveness of phenylephrine yet. We agree that this phenotype is not perfectly separated due to its complex nature though, we believe it can shed light on clinical insight and we agree that this need to be validated in future study. As an exploratory investigation, this study has revealed many things needing more detailed data to address many issues raised, and the challenges of using highly variable clinical data, yet it may serve as an inspiration for better future studies and by other researchers and clinicians.