Letter to the editor: Does low-frequency power of heart rate variability correlate with cardiac sympathetic tone in normal sheep?

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TO THE EDITOR: We read with great interest the recent work by Martelli et al. (6), published in *American Journal of Physiology-Heart and Circulatory Physiology*, that describes experiments in conscious sheep in which cardiac sympathetic nerve activity (CSNA), heart rate variability (HRV), and baroreflex sensitivity (BRS) were measured. CSNA did not correlate with the low-frequency (LF) component of HRV across nine control and nine chronic heart failure (CHF) sheep. Whereas this study agrees with a growing body of evidence suggesting that the HRV LF component is not a specific marker for cardiac sympathetic tone (3, 4), the direct recording of CSNA makes this study particularly novel and meaningful.

That said, the idea that no relationship exists simply because a regression model does not yield a statistically significant correlation coefficient is problematic. Several issues, including model misspecification, outliers, and insufficient power, may lead to false negatives. We believe that each of these may have influenced the conclusions of this study.

Each correlation plot shows one dependent and two independent (e.g., CSNA and group) variables; however, the regression model does not account for group effects, leading to two problems: false positives and false negatives. False positives occur when between-group differences drive correlations. This is exemplified by the correlation of CSNA frequency with heart period, both of which statistically differed between the control and CHF groups. The mean square of the linear regression model does not appear to be any better than that of the groups, and no statistically significant within-group correlations were identified.

More importantly, false negatives arise when within-group correlations are obfuscated by between-group effects. This manifests in Fig. 4, C and D. One very clearly sees a positive correlation between raw LF power and both CSNA frequency and burst incidence in the control group, with one notable outlier (presumably the same animal). This correlation, which flies in the face of the article title, was confounded by the CHF animals. Raw spectral comparisons of HRV in CHF are problematic due to markedly attenuated time domain variability (1), which, by Parseval’s theorem, dictates total power. This makes appropriate normalization very important, but the decision to normalize to a vagal oscillation, i.e., high frequency (HF), seems to be a straw man. We are not aware of any claims that the LF-to-HF ratio is specific for sympathetic tone.

Because of the profound sensitivity of the correlation coefficient to outliers, any anomalous points must be carefully scrutinized. CSNA burst frequency and incidence appear to explain the majority of the variance in LF power in eight of the nine control sheep, a surprisingly positive finding. The ninth sheep appears highly aberrant.

Finally, the conclusion that no relationship exists between LF and CSNA or BRS is based on obtaining t-statistics corresponding to nonsignificant P values for the correlation coefficients of these variables, but other statistical tests that may have served as positive controls also did not reach significance. Specifically, between-group t-tests for BRS, HRV LF, and HRV LF-to-HF ratio were not significant in this study, and by the same logic, one would conclude that BRS, HRV LF power, and HRV LF-to-HF ratio are not altered in CHF, contradicting canonical differences in human CHF (2, 5, 8) and previous studies from this group (10). We are unable to explain these discrepancies, except to suggest that more power may be needed to resolve the complex relationships between LF, CSNA, BRS, and CHF in inherently noisy physiological data.

Despite these concerns about the regression analysis, we are encouraged by the overall quality of the data and the conscious ovine CSNA preparation. As the ideal general linear model to fit these data could be rather complex and the data set at hand may be underpowered to statistically resolve such a model, we propose a simple solution to address the concerns we have delineated. By providing the r² values for within-group correlations, both with and without outliers (points with Cook’s d > 1), the readers will be able to draw their own conclusions on the relationship of the variables of interest with less influence of group effects and outliers. Additionally, performing alternative normalizations of LF could increase the clarity of the CHF data. Some authors have claimed that LF power expressed as a percentage of total power minus the 0-Hz component or LF in normalized units are specific for cardiac sympathetic tone and may be ideal candidates (7, 9). We would like to thank Martelli and colleagues (6) for using their unique animal model to further our insight into the underpinnings of cardiovascular variability, and we look forward to their response.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

P.R.P. and A.M.S. drafted, edited, revised, and approved final version of manuscript.

REFERENCES


