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Sex Differences in Beat-to-Beat Heart Rate Response to Systolic Pressure Increases

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***Abstract*—While some studies suggest that heart rate variability (HRV), systolic blood pressure (SBP), and baroreflex sensitivity (BRS) differ between males and females, others offer contradictory findings. The HYPOL database, provided for the ESGCO 2024 conference challenge, includes a balanced cohort of 272 subjects (146 males and 126 females) of the same ethnicity and similar age range. This study investigates sex differences in the average response of beat-to-beat heart rate to spontaneous increases in SBP, using bivariate phase-rectified signal averaging (BPRSA). A linear regression model revealed that the effect of sex on the BPRSA feature was significant (Estimate = -0.0062, p = 0.0015), explaining 4.06% of the variance in the BPRSA feature (p = 0.0038). These results highlight the importance of considering sex as a significant factor in cardiovascular studies, especially in autonomic regulation and its clinical and therapeutic implications. However, much of the variation in BRS remains unexplained by the included predictors like sex, and age.**

***Index Terms*—Baroreflex Sensitivity, Systolic Pressure Variability, Heart Rate Variability, Sex Differences.**

I. Introduction

Cardiovascular disease remains a leading cause of mortality worldwide, with emerging evidence suggesting that cardiovascular dynamics, including the autonomic heart rate regulation, exhibit significant sex differences that could impact clinical outcomes. Research into these differences is critical as it may inform more personalised approaches to diagnosis and treatment. However, the literature presents a fragmented view, with some studies indicating significant sex differences in autonomic markers such as heart rate variability (HRV), and baroreflex sensitivity (BRS), while others report contradictory findings [1], [2]. For example, differences in age distribution, health status of participants, and imbalances in sex ratios can all influence the outcomes of studies examining HRV and systolic blood pressure (SBP) [3].

The goal of this study, in line with the ESGCO 2024 conference challenge, is to elucidate the sex-specific characteristics of cardiovascular time series interactions, enhancing our understanding of their potential implications for personalised medical strategies in cardiovascular health. This paper aims to explore sex differences in the average response of beat-to-beat HRV to spontaneous increases in SBP, utilising bivariate phase-rectified signal averaging (BPRSA), a marker that has been previously identified as a strong predictor of mortality in heart failure patients [4]. This method is particularly suited to capturing dynamic interactions within the cardiovascular system, providing insights into the autonomic regulation of heart rate in response to blood pressure fluctuations.

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II. Materials and Methods

A. HYPOL database

The Healthy Young POLes (HYPOL) database offers a unique opportunity to explore these variables under controlled conditions [5]. This study includes a balanced cohort of 272 healthy individuals (146 females and 126 males) of the same ethnicity and within a similar age range (from 19 to 30 years old), all assessed under resting conditions.

The HRV signal is estimated from the R-waves locations provided [5], using the Integral Pulse Frequency Modulation model after ectopic beat removal [6], and sampled at $F_s =$ 4Hz. The SBP signal is obtained by interpolating at 4Hz the non-outlier samples of the instantaneous systolic pressure values provided. These systolic values are measured by Portapres 2 or Finapres Nova devices placed on the finger [5].

B. Bivariate phase-rectified signal averaging

To estimate a causal BRS, this study utilises BPRSA [4]. Essentially, an averaged HRV profile is obtained of the overall HRV response to SBP increases. For this, anchor points (AP) are initially identified. APs are defined at the maximum of the first derivative of SBP series, characterising every spontaneous increase in SBP. Once APs are identified, windows of length $2L$ are segmented around each AP over the HRV series ($L = 5 \times F_s$). Finally, the BPRSA curve is obtained by averaging all segmented windows in the HRV.

The BRS, estimated from the BPRSA curve, is quantified with a redefinition of the original capacity term, C [4]. In previous works, the capacity is characterised based on the respiratory frequency [7], [8]. Since it is not available in the HYPOL database, C is estimated as the difference between

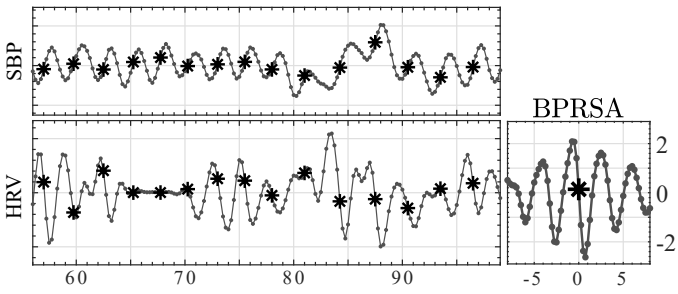

Fig. 1. Illustrative estimation of the BPRSA curve. Top-left: temporal evolution of SP with APs (asterisks) defined at up-slopes. Bottom-left: HRV signal with segments of $2L$ length around each AP. Bottom-right: BPRSA curve obtained by averaging all HRV segments at the APs.

the first maximum and the first minimum closer to the centre point, divided by the time between these two. Note that C can be either positive or negative.

III. Results and Discussion

Initial analysis using the Wilcoxon test (see Fig. 2) indicated a significant difference in C from the BPRSA analysis between males and females ($p = 0.0017$), with a small to medium effect size (Cohen's $d = 0.4037$, 95% CI [0.1686, 0.6376]). Additionally, there was a significant difference in BMI between sexes ($p \ll 0.001$), with a large effect size (Cohen's $d = -1.069$, 95% CI [-1.3286, -0.8152]). Then, two linear regression models were employed to adjust for various demographic and cardiovascular variables. The first model specifically assessed the influence of sex on C and revealed a significant effect, with sex explaining $R^2 = 4.06\%$ of the variance in C ($p = 0.0038$).

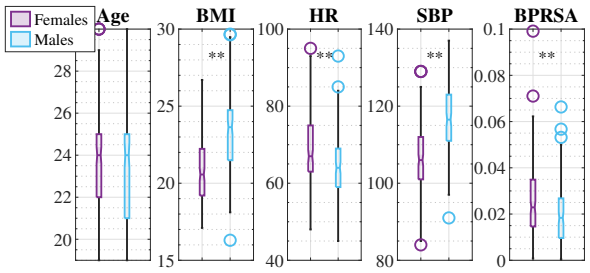

Fig. 2. Biomarkers' distribution by sex (**: p < 0.001).

The second model included C as the dependent variable and accounted for sex, age, BMI, height, weight, mean heart rate (HR), brachial SBP, and fractional pulse pressure (FPP) to control for potential confounders. Results showed that approximately 11.3% of the variance in C is explained by the predictors (Adjusted R^2 = 8.56%). This model was statistically significant with an F-statistic of 4.17 (p = 0.0001), revealing that age, sex, and mean HR significantly influence the capacity of HRV to respond to increases in SBP. Specifically, older age and higher mean HR are associated with lower C, and males have a significantly lower C compared to females. The partial R^2 was calculated only for sex with the first model. Then, adding sex to the second model model explains 5.26% of the variance in C, beyond what is explained by all others. This indicates that sex is a significant predictor of C, explaining a substantial portion of the variation.

These findings suggest that autonomic and cardiovascular function declines with age, males have different autonomic responses compared to females, and higher mean HR is linked to reduced HRV adaptability to blood pressure changes. Other factors such as BMI, height, weight, brachial SBP, and FPP did not significantly impact C. However, while the model identifies some key influences, much of the variation in C is unexplained by the included predictors.

The observed differences in the capacity of HRV to respond to increases in SBP between males and females can be attributed to several physiological factors. Males and females exhibit different balances between the sympathetic and parasympathetic branches of the autonomic nervous system, likely due to physiological differences in autonomic control and hormonal influences such as the effects of oestrogen, progesterone, and testosterone [3]. Males generally have higher sympathetic activity, while females tend to have higher parasympathetic activity [3]. Females also typically have greater BRS, leading to more pronounced HRV responses to SBP changes, which has been proven in this study. Lifestyle and behavioural factors, including physical activity levels and stress responses, further contribute to these differences. Genetic and epigenetic factors may also influence cardiovascular and autonomic responses in a sex-specific manner. These combined factors likely explain the observed sex differences in C, and underscore the importance of considering sex differences in cardiovascular studies.

IV. Conclusion

Sex significantly explains 5.26% of the variance in the capacity of HRV to respond to spontaneous increases in systolic pressure, beyond what is explained by all other variables. Age and HR are also important variables to consider when analysing baroreflex sensitivity results. This study highlights the importance of considering sex differences in cardiovascular health assessments and underscores the potential influence of autonomic control and hormonal differences on cardiovascular function.

References

[1] Q. Fu and S. Ogoh, "Sex differences in baroreflex function in health and disease," *J. Physiol. Sci.*, vol. 69, 2019.
[2] M. W. O'Brien and D. S. Kimmerly, "Is "not different" enough to conclude similar cardiovascular responses across sexes?" 2022.
[3] J. Koenig and J. F. Thayer, "Sex differences in healthy human heart rate variability: A meta-analysis," *Neurosci. Biobehav. Rev.*, vol. 64, 2016.
[4] A. Bauer *et al.*, "Bivariate phase-rectified signal averaging for assessment of spontaneous baroreflex sensitivity," *J. Electrocardiol.*, vol. 43, 2010.
[5] P. Guzik *et al.*, "Healthy young poles–hypol database with synchronised beat-to-beat heart rate and blood pressure signals: Hypol–cardiovascular time series database," *Journal of Medical Science*, vol. 92, 2023.
[6] L. Sörnmo *et al.*, "Spectral analysis of heart rate variability in time-varying conditions and in the presence of confounding factors," *IEEE Rev. Biomed. Eng.*, vol. 17, 2022.
[7] P. Armañac-Julian *et al.*, "Baroreflex sensitivity evolution before weaning from mechanical ventilation," in *CinC*, 2020.
[8] R. Sassi *et al.*, "A methodological assessment of phase-rectified signal averaging through simulated beat-to-beat interval series," in *CinC*, 2014.