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Sex Differences in the Association Between Cardiac Vagal Control and the Effects of Baroreflex Afferents on Behavior

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Abstract: Background: Cardiovascular disease (CVD) is the leading cause of mortality and disability worldwide. While sex differences in CVD have been well documented, the physiological mechanisms of those sex differences remain unclear. As important components of the cardiovascular system, cardiac vagal control and baroreflex serve as mechanisms of sex differences in CVD and are modifiable factors for gender-specific CVD preventions. Methods: Ninety-four healthy adults (18–44 years of age; M_{age} = 21.09 years; 46 female) were recruited to complete the assessments of heart rate variability (HRV) at a resting baseline and the cardiac timing effect on an R-wave-locked reaction time (RT) task, which were used as the indicator of cardiac vagal control and a novel behavioral measure of baroreflex activity, respectively. HRV metrics (including the root mean square of successive R-R interval differences, high frequency and low frequency heart rate variability, and low frequency-to-high frequency ratio), the cardiac timing effect (the inhibition of RT response at the phase of cardiac systole compared to diastole), and their associations were compared between female and male participants. Results: Female participants showed higher levels of vagally mediated HRV after adjusting for basal resting heart rate. Importantly, the cardiac timing effect on RT responses was positively correlated with vagally mediated HRV among males but not among females. Conclusions: Females and males exhibited different physiological processes to regulate cardiovascular functions and behavioral outcomes. The present findings will help to reduce gender disparities in the preventive care of CVD and improve cardiovascular health for both women and men.

Keywords: sex differences; cardiac vagal control; heart rate variability; baroreflex; cardiac timing effect

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and disability worldwide [1]. In 2021, CVD accounted for one-third of all deaths, and the direct medical cost of CVD in the world was estimated as $863 billion [2,3]. The population that is affected by CVD and its economic costs have been increasing over the past decades [4,5]. As CVD is a major public health challenge, it is important to understand the biological and behavioral mechanisms underlying the disease.

Although CVD affects both women and men, it has documented considerable sex differences in prevalence, age of onset, health outcomes, and mortality rate. Specifically, men tend to develop CVD at a younger age than women [6]. Also, the most prevalent type of CVD is different in women and men [7–9]. With the presence of CVD, women are more vulnerable to morbidity compared to men [10]. Moreover, women suffer from worse health outcomes and have higher death rates than men after the diagnosis of CVD [11–13].

Biological mechanisms, such as hormonal influences, genetic differences, and inflammatory activity, may contribute to the differences in CVD between women and men [14–17]. Those biological factors further interact with lifestyle and health behaviors to differentially influence cardiovascular health among females and males. For example, while men are

more likely to engage in risky behavior, show greater stress reactivity, and be smokers, women have higher rates of choosing a poor diet, lacking vigorous exercise routines, and inefficiently coping with life stressors [18–20]. Sex differences in CVD encompass various aspects that are highly intertwined. Therefore, modifiable mechanisms reflecting the net effect of a wide spectrum of factors influencing gender-specific cardiovascular health have received much research attention.

Cardiac vagal control is one mechanism that has been studied in relation to sex differences in cardiovascular health [21–23]. The autonomic nervous system (ANS) plays an important role in the regulation of cardiovascular activities and provides a window for physiological processes underlying the development of CVD [24]. The ANS has two major divisions, the sympathetic nervous system and the parasympathetic nervous system, which are associated with energy mobilization and the restorative functions of the body systems, respectively. Among healthy individuals, the activity of the two ANS divisions are dynamically balanced [25–27]. However, an imbalance of the two ANS divisions, particularly when the sympathetic nervous system dominates over the parasympathetic nervous system, may lead to abnormal physiological processes that are implicated in CVD [26–28]. As a result, reduced parasympathetic control of cardiac activity, i.e., cardiac vagal control, has been considered as a risk factor of CVD [27–31].

Heart rate variability (HRV) provides a set of indices of cardiac vagal control and ANS balance [29–31]. HRV reflects beat-to-beat changes in the time of successive R-R intervals [30,31]. It can be quantified by various metrics, which fall into the two major categories of time-domain and frequency-domain measurements. Time-domain HRV measurements (e.g., the standard deviation of R-R intervals and root mean square of successive R-R interval differences) compute variability in the series of timing lengths of R-R intervals and are often expressed in original time units (i.e., millisecond) [29,32]. Frequency-domain HRV measures are derived by using the power spectral analysis and calculate the distribution of the power at different frequency bands, including ultra-low frequency (ULF), very-low frequency (VLF), low frequency (LF), and high frequency (HF) [29,32]. Among those HRV indices, the root mean square of successive R-R intervals (RMSSD) and HF HRV have often been used as the indicators of cardiac vagal control in short-term (3–5 min) electrocardiography (ECG) assessments [29–32]. Further, although there was a debate regarding the sources of other HRV metrics, current researchers generally agree that vagal input is the main source of most HRV metrics, including LF HRV and the ratio of the power of LF to HF HRV (LF/HF ratio) that were historically thought to reflect sympathetic control over cardiac activity [31,33].

Cardiac vagal control and HRV metrics have shown substantial differences between women and men [21–23]. Females tend to have higher levels of HF HRV and standard deviation of R-R intervals, suggesting greater cardiac vagal control, while men showed more LF power and higher LF/HF ratio [21,22]. However, these sex differences are often masked by females' higher resting heart rate (HR) and are only exhibited in analyses controlling for HR [21]. Hormones, such as estrogen and oxytocin, and different stress coping and patterns of brain activation, may account for differences in HRV metrics between women and men [21,22]. In turn, sex differences in cardiac vagal control may contribute to the sex differences in the prevalence, age of onset, and prognosis of CVD [21,22].

Another mechanism contributing to sex differences in CVD is baroreflex. Baroreflex is initiated by the activation of baroreceptors and helps maintain blood pressure (BP) [34]. Specifically, arterial distension is detected by baroreceptors, a type of mechanoreceptor sensory neuron located in the carotid sinus and the vessel walls of the aorta [34]. Baroreceptors are stimulated by the distortion of the arterial wall that stimulates baroreceptors that function to reduce sudden fluctuations in BP and adjust vascular tone and HR in response to changes in environmental demands [34,35]. Baroreflex dysfunction may result from aging and pathological conditions and lead to hypertension and an increased risk for CVD [36–38]. Sex differences in baroreflex sensitivity have been reported. Compared to

men, women are shown to have higher baroreflex sensitivity, which protect them against abrupt BP changes [39,40].

Interestingly, baroreflex has neuromodulatory effects on central processing in the brain and influence behavior. Among healthy individuals, the level of baroreceptor activation increases at cardiac systole (i.e., the early phase of the cardiac cycle) and reduces at diastole (i.e., the late phase of the cardiac cycle) [41,42]. This information of cardiovascular afferents is encoded in the nucleus tractus solitarius (NTS) and relayed to the reticular formation, thalamus, periaqueductal grey matter, amygdala, and cortical areas [43,44]. According to Laceys' hypothesis, cortical inhibition is generated by afferent signals of baroreceptor activation and results in the slower processing of sensory information at cardiac systole [45,46]. In support of this hypothesis, studies reported that reaction times (RTs) were faster when the RT stimulus was present at cardiac diastole than systole [47,48]. This phenomenon that RTs vary as a function of the phase of the cardiac cycle is known as the cardiac timing effect, which has been reported in more recent studies using cognitive tasks with different sensory modalities and task complexities [49–54]. Specifically, during the cardiac systole phase, baroceptors located in the aortic arch, carotid sinus, and coronary arteries are activated by the temporarily increased blood pressure and send the neural afferent signals of the timing and strength of the heartbeat to the NTS via the vagus nerve [42,55]. In turn, the baroreflex serves to buffer blood pressure elevation by regulating heart rate, stroke volume, and vascular tone, as well as the modulation of the motor system and eye movements [42,55–57]. This series of physiological responses in a cardiac cycle interfere with sensory information processing and attention [41,42,55]. Further, RTs have been shown to vary as a function of the specific temporal location of the RT stimulus in a cardiac cycle [53]. Therefore, the cardiac timing effect on behavioral performance may serve as an indicator of the functional integrity of baroreflex.

Cardiac vagal control is closely related to baroreflex, as they are involved in the regulation of cardiovascular activity. Baroreceptors signal the NTS to increase vagal input to the heart, and higher levels of baroreflex sensitivity provide stronger sources for cardiac vagal control [58]. Likewise, cardiac vagal control ensures more precise moment-to-moment information to baroreceptors [26,59]. Moreover, impairment in both mechanisms is associated with a heightened risk of CVD and a poorer prognosis after cardiac events [60]. Although females and males exhibit differences in cardiac vagal control and baroreflex, no study has examined sex differences in the association between the two mechanisms.

Current Study

The current study aimed to investigate sex differences in cardiac vagal control and its association with baroreflex. The cardiac timing effect on behavioral performance in a choice reaction time (CRT) task was assessed as an indicator of baroreflex. In the current study, we measured short-term HRV in the lab. HRV metrics included both time-domain and frequency-domain measures. Specifically, the root mean square of successive R-R interval differences (RMSSD) and high frequency HRV (HF HRV; 0.15–0.40 Hz) were calculated as the indicators of vagally mediated HRV, while low frequency HRV (LF HRV; 0.04–0.15 Hz) and LF/HF ratio were also measured to indicate both baroreflex activity and cardiac vagal control [29–32].

Based on the literature, we hypothesized that (1) after controlling for basal resting HR, females would show higher RMSSD and HF HRV but lower LF HRV and LF/HF ratio than males; (2) CRT performance would be better when the task stimulus was displayed at cardiac diastole compared to systole (i.e., the cardiac timing effect), which would be more significant among males; and (3) the cardiac timing effect would be positively correlated with HRV metrics, and that this relationship would be stronger among males.

2. Materials and Methods

2.1. Participants

The sample of the present study consisted of 94 healthy young and middle-aged adults (18–44 years of age; M_{age} = 21.09 years; *SD* = 5.06 years; 46 female). The participants were recruited from psychology courses at Old Dominion University (ODU), and all were non-smokers and did not report histories of auditory, visual, or mental health issues. Moreover, the participants were free of cardiovascular diseases, and none was currently taking cardiovascular active medications. The participants were required to abstain from alcohol twelve hours and from caffeine six hours prior to the participation. Approval for the study was obtained from the ODU Institutional Review Board. All participants provided informed consent before participating in the study.

2.2. Electrocardiography Assessment

Electrocardiography (ECG) was recorded using a modified Lead II configuration. Specifically, the right arm (RA) electrode was placed on the upper chest and below the clavicle, the left arm (LA) electrode was placed on the left chest, and the left leg (LL) electrode was placed on the lower left side of the torso at the abdominal level. The Lead II recorded the electrical signals between the RA and LL electrodes. Although this configuration does not reflect the full details of the standard 12-lead ECG recording system, the lead system and the Lead II configuration in the present study provide sufficient information for detecting arrhythmias and identifying the P-wave, the QRS complex and the T-wave [61,62]. Moreover, the ECG electrode system in the current study allowed the participants to perform the sensorimotor task without motor constrictions and has been demonstrated to be effective in cardiac timing manipulation [50,52,54]. In addition, the participants wore a respiratory transducer belt that was placed around the upper abdomen to detect artifacts of ECG signals due to irregular respiratory activity.

To assess cardiac indices at a resting state, the participants were instructed to watch an emotionally neutral video that depicts aquatic scenes for three minutes, during which ECG was recorded. This method was consistent with the recommendation of the "vanilla baseline" that cardiac baselines should be recorded under physically and mentally stable conditions to maintain alertness while being minimally arousing [63]. The three-minute length of ECG recording was selected based on the recommendations of the minimal required duration for the frequency analysis, i.e., 10 times the wavelength of the lower frequency bound of the investigated components, HF and LF HRV [29,32].

2.3. Sensorimotor Task and Cardiac Timing Manipulation

A choice reaction time (CRT) task with two choices was used to measure participants' sensorimotor processing. In the CRT task, the symbols "←" and "→" were presented in the middle of a computer screen which served as the RT stimuli. The participants would press the left or right arrow key on a computer keyboard in response to "←" and "→", respectively. The RT stimulus was presented for 2000 ms if no key pressing was detected, or the presentation was ended by a detected response. Of note, the RT stimuli were presented at delayed times of either 300 ms (cardiac systole) or 550 ms (cardiac diastole) from a detected ECG R-wave. The timing of stimulus presentation was validated and selected based on prior reports [52,54]. Because the delivery of RT stimuli was triggered by ECG R-waves and stimuli were programmed to present during the cardiac cycle that occurred 3000 ms after the end of the last trial, inter-trial intervals (ITIs) were determined by the length of the R-R interval prior to a choice RT trial (see Figure 1). During the ITI, a "+" sign was displayed at the center of the screen as a visual fixation marker. There was a total of 200 RT trials, which included 100 trials in each cardiac condition: cardiac systole and diastole. All CRT trials were delivered in two experimental blocks, and in each block, the trials at cardiac systole and diastole were randomly counterbalanced.

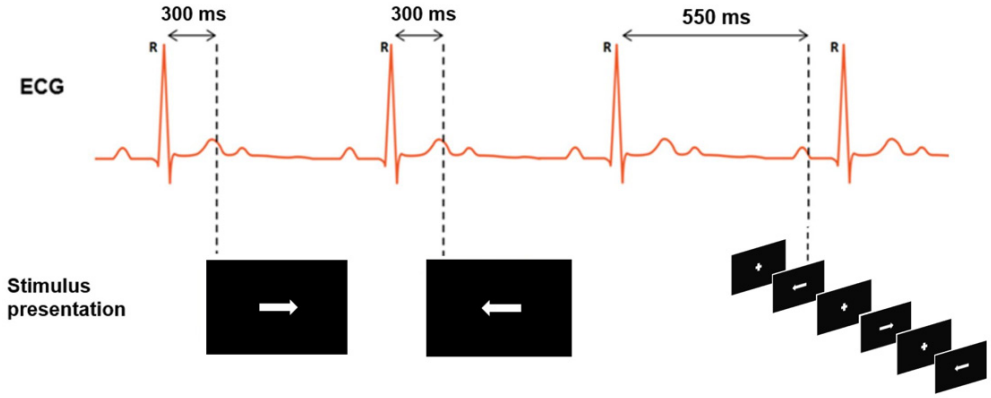

Figure 1. Stimulus presentation in relation to cardiac cycle phase. In each trial, participants were asked to press the corresponding key to indicate the direction of an arrow: Left or Right. The three exemplary trials (from the left to the right) indicated two trials of the choice reaction time (CRT) task at cardiac systole (R + 300 ms), and a CRT trial at cardiac diastole (R + 550 ms). The last exemplary trial also shows the sequence of the stimulus presentation.

2.4. Physiological Recording Device

The visual stimuli were presented on a 61 cm diagonal wide computer screen that was located 50 cm in front of the subject, using the E-Prime 3.0 software (Psychology Software Tools, Pittsburgh, PA, USA). Physiological data were collected using a BIOPAC MP160 system (BIOPAC Systems Inc., Goleta, CA, USA). Raw signals were digitized at 1000 Hz (16-bit) and analyzed with BIOPAC AcqKnowledge software 5.0 (BIOPAC Systems Inc., Goleta, CA, USA). ECG was measured with disposable, pre-gelled stress-testing spot electrodes using a modified Lead II configuration (ConMed Andover Medical, Haverhill, MA, USA). ECG R-waves were detected online by an AccuSync 71 ECG trigger monitor (AccuSync Medical Research Corp., Milford, CT, USA), which sent 5-V TTL/CMOS compatible square waves to the E-Prime software on the experimental computer to trigger the presentation of visual stimuli.

2.5. Procedure

All participants were asked to provide informed consent before the study. Following the consent procedure, participants completed a questionnaire about their health histories. Then, trained research personnel took measurements of the height and weight of the participants and helped the participants wear ECG and respiratory monitoring devices. After the physiological sensor attachment, the participants were asked to sit quietly for three minutes to adapt to the environment of the laboratory, which was followed by the three-minute ECG recording. At the end of the resting ECG recording, the participants were instructed to perform the choice RT task. They were required to press the response keys as quickly and accurately as possible. There were 10 practice RT trials, and the participants were allowed to ask any questions at the end of the practice. When the participants were ready for the actual experimental trials, the choice RT task began. The total 200 RT trials were divided into two blocks, between which the participants took a 2 min break. The second experimental block was followed by a 2 min recovery period, after which the participants were thanked and debriefed. The whole experimental protocol took approximately 45 min to complete.

2.6. Data Reduction

Raw ECG data were inspected, and artifacts were corrected manually by trained raters. If 5% or more signals during the period of resting ECG recording were influenced by artifacts, the participant's resting ECG data were excluded from analyses, which followed the guideline and the criterion in our previous studies [29,32,64,65]. All participants' resting ECG data met the criterion, and thus, no participant was excluded from analyses. Inter-beat

intervals (IBIs) were derived from the ECG signals, and mean heart rate (HR) in beats per minute (BPM) were calculated as 60,000 ms/mean IBI. HRV metrics included both time- and frequency-domain measures. Specifically, the root mean square of successive RR interval differences (RMSSD) was calculated from the IBI series as the time-domain measure of vagally mediated HRV [27,30]. As for frequency-domain HRV, high-frequency (HF; 0.15–0.40 Hz) and low-frequency (LF; 0.04–0.15 Hz) HRV and LF/HF ratio were computed from the IBI series using a fast Fourier transformation. HF and LF HRV were log-transformed to the base of the natural exponent (ln), in order to reduce the impact of skewed distributions on data analysis. Respiratory activity was assessed as the mean respiration rate during the resting baseline, and body mass index (BMI) was calculated from height and weight.

Behavioral data were recorded using E-prime software. Response accuracies were computed as the percentages of correct responses in the RT trials in cardiac systole and diastole conditions. RT outliers were defined as RTs that were out of the range of ± 3 SD from the mean of a given participant, constituting 2.53% of all trials, which was consistent with the guideline and recommendations to analyze RT data [50,66]. The RT outliers were excluded from further analyses. RT scores were calculated as the mean RT of the trials in cardiac systole and diastole conditions of the participant. Difference scores of accuracies and RTs were computed as Systole–Diastole, which indicated the effects of baroreceptor afferents on sensorimotor processing (i.e., the cardiac timing effect).

2.7. Data Analysis

Demographic, physiological, and behavioral data were compared between female and male participants by *t*-tests. To test the hypothesis regarding sex differences in cardiac vagal control, the effects of sex on HRV measures were examined by one-way analyses of covariance (ANCOVAs), which were adjusted for covariates, including age, BMI, and resting HR. Further, 2 (sex) $\times$ 2 (cardiac timing) mixed analyses of variance (ANOVAs) were used to test the hypothesis of sex differences in cardiac timing effects. In the ANOVAs, sex was the between-subjects factor, while cardiac timing condition was the within-subject factor.

To investigate the effects of sex on the relationship between HRV and cardiac timing effects, multiple regressions were constructed, in which sex, HRV measures, and their interactions were independent variables, difference scores of behavioral data were dependent variables, and age and BMI were covariates. Below is the regression equation (terms for covariates are not shown for simplicity):

$$\text{Cardiac Timing Difference Score} = \beta_0 + \beta_1\ \text{Sex} + \beta_2\ \text{HRV} + \beta_3\ \text{Sex} * \text{HRV} \quad (1)$$

In Equation (1), Cardiac Timing Difference Score represents the change scores of RT and response accuracy between cardiac systole and diastole conditions; dummy coding was used to code Sex, and female was set as the reference group; HRV metrics, RMSSD, HF HRV, LF HRV, LF/HF ratio were entered into separate regression models; and β_0, β_1, β_2, and β_3 represent the intercept term and regression coefficients for the dependent variables. The normality of all HRV variables were examined. All variables showed acceptable skewness (-1 to 1) and kurtosis (-2 to 2), except RMSSD (skewness = 1.56; kurtosis = 2.61). Therefore, the variable was transformed using natural logarithm (ln). All continuous variables were mean centered before being entered into the regression models. Significant interaction terms were probed be sex-stratified analyses. Statistical significance was tested with an alpha of 0.05, and effect sizes were estimated with partial eta-squared and R^2 in ANOVAs and regressions, respectively.

3. Results

3.1. Descriptive Statistics

Descriptive statistics are presented in Table 1. The results of the *t*-tests indicated that females had higher levels of resting HR and respiratory rate, while males had greater LF HRV and faster RTs. However, there were no sex differences in other variables (see Table 1).

Further, the mean of respiratory rates across all participants was 15.13 (*SD* = 3.44) bpm, and the range was 8.93–20.01 bpm, which resulted in 98.94% of the respiration data falling into the bandwidth of HF HRV (0.15–0.40 Hz).

Table 1. Descriptive statistics of the sample.

Variable	Female (n = 46)	Male (n = 48)	t-Test Statistics	p-Values
Age (M years, *SD*)	20.15 (4.63)	21.02 (5.48)	0.13	0.90
Body mass index (M, *SD*)	25.51 (4.45)	24.09 (3.73)	1.68	0.10
Resting heart rate (M bpm, *SD*)	86.20 (9.98)	75.58 (11.62)	4.74	**<0.001**
RMSSD (M ms, *SD*)	33.69 (24.49)	42.69 (25.43)	−1.75	0.08
HF HRV (M ln ms^2, *SD*)	5.93 (1.19)	6.17 (1.16)	−1.00	0.32
LF HRV (M ln ms^2, *SD*)	6.26 (1.17)	6.92 (1.22)	−2.70	**<0.01**
LF/HF ratio (M, *SD*)	1.07 (0.19)	1.14 (0.32)	−1.22	0.22
Respiratory rate (M bpm, *SD*)	15.97 (3.59)	14.34 (3.13)	2.34	**0.02**
Reaction time (M ms, *SD*)				
Cardiac systole	580.61 (142.70)	481.50 (152.12)	3.26	**<0.01**
Cardiac diastole	576.17 (138.09)	471.92 (150.73)	3.49	**<0.01**
Response accuracy (M %, *SD*)				
Cardiac systole	94.26 (16.68)	95.96 (7.86)	−0.64	0.53
Cardiac diastole	94.61 (16.06)	96.70 (8.18)	−0.80	0.43

Note: RMSSD = root mean square of successive RR interval difference; HF HRV = high frequency heart rate variability; LF HRV = low frequency heart rate variability. The comparisons between females and males were unadjusted. Bold numbers indicate significant results of *t*-tests.

3.2. Sex Differences in HRV Measures

Unlike the unadjusted *t*-tests, ANCOVAs indicated that, after controlling for age, BMI, and resting HR, female participants had higher levels of HF HRV compared to male participants, $F(1, 89) = 3.92$, $p = 0.049$, $\eta^2_p = 0.04$ (see Figure 2). There was also a marginal trend towards the sex difference in RMSSD, $F(1, 89) = 2.89$, $p = 0.093$. On the other hand, males showed a larger LF/HF ratio, $F(1, 89) = 4.82$, $p = 0.031$, $\eta^2_p = 0.05$, but did not differ from females in LF HRV, $F(1, 89) = 1.66$, $p = 0.20$ (see Figure 2).

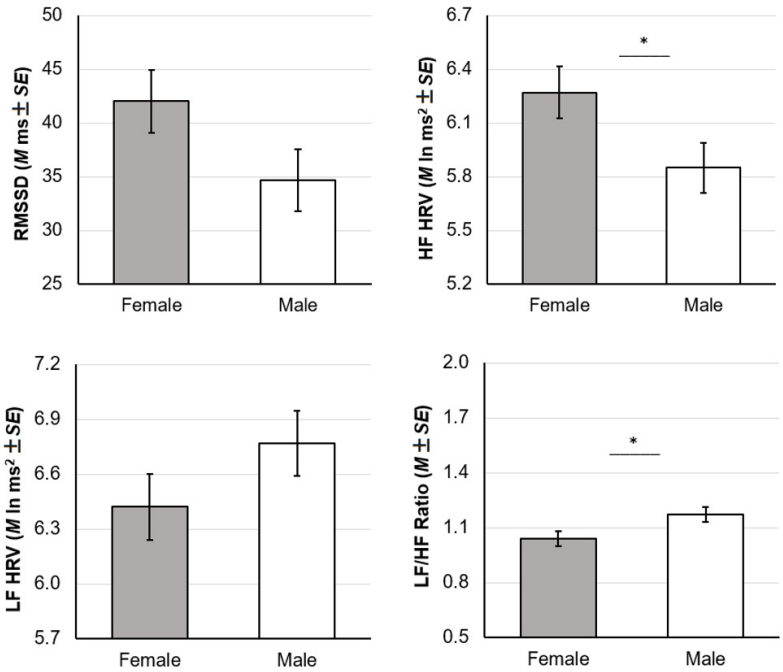

Figure 2. Adjusted comparisons of HRV metrics between sexes. RMSSD = root mean square of successive RR interval difference; HF HRV = high frequency heart rate variability; LF HRV = low frequency heart rate variability. The comparisons were adjusted for age, BMI, and resting heart rate. * $p < 0.05$.

3.3. Effects of Sex and Cardiac Timing on Behavioral Performamance

The mixed ANOVA of RTs indicates the main effects of sex, $F(1, 92) = 11.44$, $p = 0.001$, $\eta^2_p = 0.11$, and cardiac timing, $F(1, 92) = 9.23$, $p = 0.003$, $\eta^2_p = 0.09$, suggesting that RTs were faster in the cardiac diastole condition and among males. However, there was no interaction between the factors, $F(1, 92) = 1.24$, $p = 0.27$.

According to the results of the ANOVA, response accuracy was not influenced by sex, cardiac timing, or their interaction, Fs < 2.56, ps > 0.11.

3.4. Modulation of the Association Between Cardiac Timing Effect and HRV by Sex

The regression models are shown in the Table 2. None of the predictors were significantly related to the cardiac timing effect on response accuracy (see Table 2). However, the RT difference score was related to RMSSD (normalized score), β = −11.61, $SE = 5.44$, $p = 0.036$, partial $R^2 = 0.027$, and its interaction with sex, β = 16.86, $SE = 7.57$, $p = 0.028$, partial $R^2 = 0.034$. Similarly, HF HRV, β = −13.74, $SE = 6.43$, $p = 0.035$, partial $R^2 = 0.025$, and its interaction with sex, β = 20.70, $SE = 8.96$, $p = 0.023$, partial $R^2 = 0.033$, also predicted the RT difference score (see Table 2).

Table 2. Regression models of sex and heart rate variability measures.

Dependent Variable	Independent Variable	Coefficient (β)	Standard Error	*p*-Values
ΔResponse Accuracy (systole–diastole)				
	Sex	−0.02	0.04	0.333
	RMSSD	0.01	0.01	0.908
	Interaction Term	0.01	0.01	0.613
ΔResponse Accuracy (systole–diastole)				
	Sex	−0.04	0.01	0.165
	HF HRV	0.03	0.01	0.776
	Interaction Term	0.07	0.01	0.597
ΔResponse Accuracy (systole–diastole)				
	Sex	0.01	0.07	0.947
	LF HRV	−0.01	0.01	0.184
	Interaction Term	0.01	0.01	0.922
ΔResponse Accuracy (systole–diastole)				
	Sex	−0.01	0.01	0.890
	LF/HF Ratio	−0.04	0.03	0.152
	Interaction Term	0.02	0.03	0.451
ΔReaction time (systole–diastole)				
	Sex	−52.22	26.61	0.053
	RMSSD	−11.61	5.44	**0.036**
	Interaction Term	16.86	7.57	**0.028**
ΔReaction time (systole–diastole)				
	Sex	5.70	4.58	0.216
	HF HRV	−5.97	2.79	**0.035**
	Interaction Term	8.99	3.89	**0.023**

Table 2. *Cont.*

Dependent Variable	Independent Variable	Coefficient (β)	Standard Error	*p*-Values
ΔReaction time (systole–diastole)				
	Sex	5.74	4.87	0.242
	LF HRV	−1.86	2.88	0.519
	Interaction Term	2.80	3.93	0.477
ΔReaction time (systole–diastole)				
	Sex	4.61	4.69	0.329
	LF/HF Ratio	27.21	17.50	0.124
	Interaction Term	−36.53	20.24	0.922

Note: RMSSD = root mean square of successive RR interval difference; HF HRV = high frequency heart rate variability; LF HRV = low frequency heart rate variability. Difference (Δ) scores of HRV metrics between the cardiac systole and diastole conditions. The interaction term indicates the interaction between sex and the HRV metric. Bold numbers indicate significant regression coefficients.

To probe the interaction between sex and HF HRV, sex-stratified analyses were conducted. The results indicate that while HF HRV was not related to the RT difference score among females, $r = -0.22$, $p = 0.150$, a positive correlation between HF HRV and RT difference score, $r = 0.35$, $p = 0.014$ was shown in males (see Figure 3). Therefore, the sex-stratified analyses revealed that sex modulated the association between HR HRV and the effects of cardiac timing on RTs.

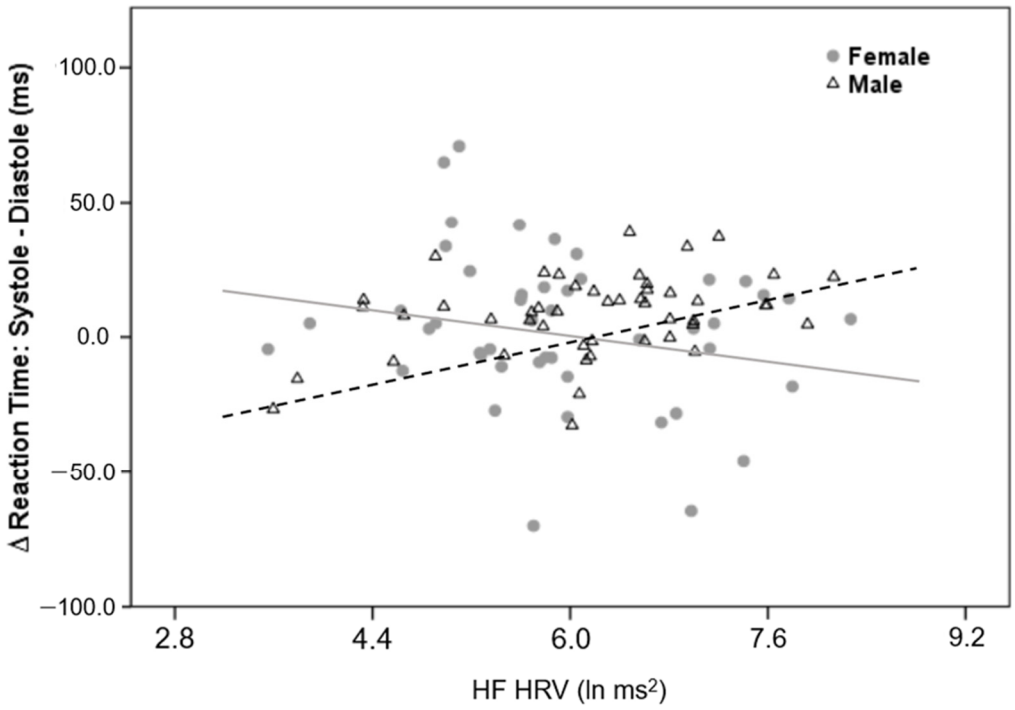

Figure 3. Modulation of association between high frequency heart rate variability (HF HRV) and difference score of reaction time (cardiac systole–cardiac diastole) by sex. Solid and dashed lines represent the lines of best fit for female and male participants, respectively.

4. Discussion

The current study focused on pre-clinical populations and investigated sex differences in cardiac vagal control and whether sex served as the moderator of the relationship between baroreflex activity and cardiac vagal control. Baroreflex activity was assessed by a novel behavioral measurement—the cardiac timing effect that reflects the inhibition of sensorimotor processing at the cardiac systole phase. Our hypotheses were partially supported. Sex differences in resting HR and HRV metrics were found in a short-term laboratory assessment. Importantly, the cardiac timing effect on RT responses was positively correlated with vagally mediated HRV (both RMSSD and HF HRV) among males but not among females.

The first hypothesis regarding sex differences in HR and HRV was supported. The present results indicated that females had higher resting HR and HF HRV relative to males, which was consistent with previous studies [21–23]. According to the calculation of HRV metrics, for a given individual, HR is negatively associated with vagally mediated HRV (RMSSD and HF HRV). However, HR reflects a net effect of multiple sources of cardiac control, while HRV measures quantify the "pure" input of the vagus nerve, or the parasympathetic nervous system [30–32]. Our findings are in line with a meta-analysis that summarized reported sex differences in HRV metrics in various assessments and confirmed better cardiac vagal control in females [21]. Higher vagally mediated HRV in females can be explained by greater cardioprotective responses, such as lower BP and bradycardia in response to environmental stimuli [21]. These responses may be beneficial outcomes of estrogen and oxytocin, as well as attenuated stress responses in brain structures, including the amygdala, parahippocampal gyrus, hippocampus, and insula [21].

The second hypothesis was partially supported. While our results replicated the cardiac timing effect on RTs, there was no sex difference in the effect of cardiac timing on behavioral performance. Previous studies suggested that while the cardiac timing effect has been observed in various sensorimotor tasks, the possible association between RT performance and cardiac phase would be evident only under specific circumstances [67]. That is, a spectrum of factors may determine the presence of the cardiac timing effect, for example, stimulus characteristics, task requirements, and experimental designs. One such factor influencing the cardiac timing effect is response complexity. Recent studies reported that cardiac systole (baroreceptor activation) selectively inhibits automatic responses that involve little cognitive control but facilitates complex sensorimotor responses that require top-down resources and attentional control [68,69]. Moreover, irrelevant sensory stimulation and cognitive load induced by a simultaneous secondary task masked the cardiac timing effect [50,54]. The dependence of the cardiac timing effect on task complexity indicates the specificity of the neural modulation effects of cardiac afferent signals on distinct cognitive processes. Therefore, we used the CRT task with only two response choices that required low levels of cognitive control and have successively elicited the cardiac timing effect. It is worth noting that although RT data showed the cardiac timing effect and sex-modulation of its association with HRV, response accuracy did not indicate the same pattern of results. This may also be because the two-choice RT task only required minimum levels of cognitive control without taxing participants' attentional recourses. As a result, most participants could maintain high accuracies in all conditions, which was also reflected by skewed distributions of response accuracy and its change scores. That is, there might be the ceiling effect for response accuracy. In that regard, RT served as a better indicator of sensorimotor processing in the present study.

Another factor that needs to be considered in studies of the cardiac timing effect is the temporal location of the stimulus. In the cardiovascular system, the activation of arterial baroreceptors increases during the time window from 90 to 390 ms after the ECG R-wave [41]. Following baroreceptor activation, the cardiovascular afferent output peaks at around 250 ms after the R-wave [41]. The selection of the timing of stimulus presentation in our study was based on the time course of the systolic BP pulse following the R-wave and of baroreceptor firing in response to this pulse. At around R + 300 ms,

reflex responsiveness, for example, the nociceptive flexion reflex and the startle reflex, is maximally attenuated by baroreceptor feedback and the transmission of cardio-afferent signals is most effective [70–73]. In contrast, at around R + 550 ms, baroreceptor afferent transmission is inhibited [70]. Thus, this timing is consistent with other studies using cardiac cycle timing manipulations [49–54,70,71].

An important finding in our study is sex differences in the association between vagally mediated HRV and the cardiac timing effect on RT, which supported the third hypothesis. As predicted, HF HRV was positively correlated with the cardiac timing difference score of RT in male participants, suggesting a pattern of co-activation of the vagus nerve and baroreceptors in the regulation of cardiovascular activities. On the other hand, females exhibited the dissociation of cardiac vagal control and baroreflex activity. Our findings echoed a review indicating that healthy women have blunted cardiovagal baroreflex sensitivity during rapid hypertensive stimuli [39]. Like sex differences in HRV, the baroreflex–HRV relationship differences between sexes may also be explained by the interaction between the endocrine and nervous systems. Specifically, hormones, such as estrogen and oxytocin, can act on neurons from the paraventricular nucleus, the NTS, the dorsal motor nucleus of the vagus, and the nucleus ambiguus, which are involved in the central regulation of cardiac activity [21,74]. From an evolutionary perspective, disassociation between cardiac vagal control and baroreflex can reduce "male-like" responses, e.g., higher activation levels of bodily systems, aggressiveness, and heightened stress reactivity, among females. However, females' blunted BP responses and less coherent activities of cardiac vagal control and baroreflex may contribute to their worse prognoses and higher mortality rates after a cardiovascular event compared to males [11–13]. Further, aging-related changes and pathological conditions have more detrimental effects on baroreflex sensitivity among women [39].

In fact, cardiovascular regulation may be fundamentally different between women and men. In addition to baroreflex, there are other sex-specific physiological processes in the cardiovascular system. Anatomically, the average size of females' hearts is smaller than that of males' hearts, and females also tend to have a smaller left and right ventricle and atrial [75,76]. Due to these sex differences in the structure of the heart, women have smaller cardiac output and stroke volume, and shorter cardiac pre-ejection period [75,77]. In contrast, women have smaller blood vasculature but more coronary blood flow compared to men [78]. Our findings add to the literature of sex differences in cardiovascular functioning and suggest that these structural and functional differences may in turn influence the central regulation of sex-specific cardiovascular processes via afferent pathways.

4.1. Implications

The present findings highlight the importance of considering sex in prevention and intervention programs of CVD. Given that HRV is modifiable, men's cardiovascular health will benefit from increasing vagally mediated HRV. Approaches to improving HRV include slow-paced breathing, exercise, the diving reflex, non-invasive brain stimulation, meditation, and biofeedback [79–84]. For women, in addition to those preventions for men, prevention programs should be designed to target other risk factors for CVD, including menopause, adverse pregnancy outcomes, polycystic ovary syndrome, and autoimmune conditions [85–87].

At behavioral and psychosocial levels, females and males may also show different sets of risk factors of CVD. A recent study reported that faster sensorimotor responses were related to impulsivity, a personality trait linked to hypertension and other CVD risk factors [88]. Our findings suggested that, in general, males have shorter RTs, and thus, may suffer from the adverse outcome of certain personality traits. In contrast, females have a higher rate of affective disorders, e.g., major depressive disorder and bipolar disorder, which have also been linked to impaired cardiovascular health [89–91]. Together, gender-specific preventions are expected to have the highest effectiveness for both women and men.

4.2. Limitations and Future Directions

The current study was not without limitations, and our findings should be considered with several limitations. First, the female participants' menstrual cycle status was not assessed. As discussed above, hormonal level is a major reason for sex differences in cardiovascular functioning. Although we obtained sex differences in HRV and its association with baroreflex afferents, the lack of hormone assessments prevented a strong conclusion about the rhythmic fluctuation of the sex differences. Second, HRV assessments should include both short-term and long-term (e.g., 24 h) recording in future studies. Compared to long-term and real-life HRV assessments, short-term HRV is more likely to be influenced by confounding factors. While our selection of the three-minute ECG recoding was consistent with the minimal required duration for the frequency analysis, the present findings should be replicated using longer baseline measurements (e.g., a more commonly used five-minute baseline) as well as long-term ambulatory HRV assessments [32]. Third, there is a debate on whether assessments of vagally mediated HRV should be controlled for respiratory activity [83,92,93]. In the current study, we did not consider the terms respiratory sinus arrhythmia (RSA) and HF HRV as interchangeable. While RSA directly reflects respiration-related variation in HR, HF HRV is largely independent of respiration [93]. However, future studies should investigate the role of respiration in sex differences in cardiac vagal control. Fourth, other cardiovascular indictors should be included in the future, including pulse wave velocity, beat-to-beat blood pressure, inflammatory biomarkers, etc. Lastly, our findings should be replicated using clinical populations.

5. Conclusions

Despite the limitations, our study has several strong features, including a sex-balanced sample, the controlled laboratory environment for ECG and behavioral assessment, and a novel indicator of baroreflex activity. In sum, the current study is among the first to report sex differences in the association between HRV and the behavioral effect of baroreflex afferents, and our findings will help to reduce gender disparities in the preventive care of CVD and improve cardiovascular outcomes for both women and men.

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