Heart, Lung and Circulation (2021) **30**, 128–134
1443-9506/20/$36.00
https://doi.org/10.1016/j.hlc.2020.06.019

ORIGINAL ARTICLE

Resting Heart Rate and Heart Rate Variability in the Year Following Acute Coronary Syndrome: How Do Women Fare?

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Received 30 January 2020; received in revised form 22 May 2020; accepted 15 June 2020; online published-ahead-of-print 28 July 2020

Background Women experience poorer health outcomes following acute coronary syndrome (ACS). Heart rate (HR) and heart rate variability (HRV) have emerged as sensitive and cost-effective markers of autonomic function and prognostic risk factors of poor cardiac outcomes. The aim of the current study was to investigate whether sex-specific differences existed across HR and five parameters of HRV, at 1 and 12 months following ACS diagnosis.

Methods Between January 2013 and June 2014, a sample of 416 ACS patients was enrolled in the **A**nxiety **D**epression & Heart Rate **V**ariability in cardiac patients: **E**valuating the impact of **N**egative emotions on functioning after **T**wenty four months (ADVENT) longitudinal cohort study. At 1 and 12 months following discharge, patient HR and HRV (root mean square of successive differences [RMSDD], standard deviation of RR intervals [SDRR], high frequency power [HF], low frequency power [LF], very low frequency power [VLF]) was measured via three-lead electrocardiogram.

Results At 1 month post-ACS, sex was a significant predictor of HR and VLF power in fully- adjusted models. At 12 months post-ACS, sex was a predictor of HR, SDRR and VLF power in fully-adjusted models.

Conclusion Sex-specific differences in resting HR and HRV were observed in the year following ACS, whereby women had higher HR and lower HRV, suggestive of poorer autonomic function. Further large-scale cohort studies examining autonomic function as a driver of sex-specific outcomes following ACS are required.

Keywords Sex • Women • Acute coronary syndrome • Heart rate variability • Heart rate

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Introduction

Ischaemic heart disease is the leading cause of death worldwide [1]. While prevalence rates of acute coronary syndrome (ACS) are similar in both (post-menopausal) women and men, women experience poorer outcomes following a coronary event [2]. While conjecture remains, the evidence suggests different physiology accounts for differences in sex-specific outcomes following ACS [3].

In recent decades, heart rate (HR) and heart rate variability (HRV) have emerged as sensitive and cost-effective markers of autonomic function [4–6]. High HR and low HRV indicate a chronic imbalance of the autonomic nervous system, and are risk factors of poor cardiac prognosis [7,8].

Healthy young women typically have increased HR and reduced HRV compared to men, but these sex differentials dissipate after 50 years of age [9,10]. To date, only one study has investigated sex differences in HRV following ACS. De Oliveira Pinheiro et al. found that women over 50 years of age had significantly reduced HRV compared to age-matched men, 5–10 days post-infarction [11]. No study has yet examined whether this sex-specific differential exists beyond the initial weeks following ACS.

Therefore, the aim of the current study was to investigate whether sex-specific differences existed across HR and five parameters of HRV, at 1 and 12 months following ACS diagnosis.

Material and Methods

Study Recruitment

Participants were recruited into the **A**nxiety **D**epression & Heart Rate **V**ariability in cardiac patients: **E**valuating the impact of **N**egative emotions on functioning after **T**wenty-four months (ADVENT) cohort study through methods published previously [12]. In summary, ACS patients admitted to Monash Heart, Victoria, Australia, between January 2013 and June 2014 were invited to take part in a health and psychological assessment at that time (1 month post-discharge), and again at 12 months post-discharge. Eligibility criteria included: (i) a diagnosis of ACS (ST-elevation myocardial infarction [MI], non-ST-elevation MI or unstable angina) within 4 weeks from the recruitment date, (ii) over 21 years of age and (iii) fluent in English. Patients were not eligible to participate if they were unable to give informed consent, were pregnant, cognitively impaired, reported substance abuse, had a terminal illness and/or other illness that could impair participation, or were participating in other research trials.

Ethics

This project had ethical approval from the Human Research Ethics Committee at Monash Health (HREC Ref 12249B), Monash University (Project Number CF12/3610-2012001723) and Melbourne University (Ethics ID 1441737).

This project was funded by the National Health and Medical Research Council (NHMRC; Australia). The NHMRC did not play a role in the collection, interpretation, or analysis of the data, and did not have the right to approve or disapprove the publication of this manuscript.

Procedure

Clinical measurements (e.g. anthropometry, blood pressure [BP], pulse and HRV) were collected during a face-to-face clinical assessment conducted at the Study Centre within 4 weeks from discharge, and medication information was collected from hospital discharge scripts and self-report. Heart rate variability and BP were assessed with participants lying in a supine position in a cool, dark room using a three-lead electrocardiogram (ECG) and an automated device (OMRON HEM 7221 Automatic BP Monitor, OMRON Healthcare Manufacturing, Binh Duong Province, Vietnam, calibrated as per manufacturer's instructions), respectively. A rest period of 10 minutes occurred before having a 20-minute ECG recorded by a trained research assistant (using LabChart v7.3 for Windows, by AD Instruments, Colorado Springs, CO, USA). Patients were instructed not to talk or move before or during the ECG and were gently woken if they fell asleep. All ECGs took place in the morning, between 9 am and 12 pm. Short-term measurements of HRV, while previously reported to be less reliable in some clinical populations than healthy subjects [13], demonstrate substantial-to-good relative reliability (useful for classification or diagnostic purposes) in patients with a history of myocardial infarction [14]. A detailed description of the HRV data collection process used in the ADVENT study has been published previously [12]. Computer assisted telephone interviews (CATI) were utilised to collect questionnaire self-reported data (socio-demographic, depression, anxiety, psychosocial, sleep, mental and physical health functioning data). All aspects of the data collection protocol were repeated at 12 months following discharge from hospital.

Study Measurements

Exposure

Sex (male / female) was determined using self-reported data collected at study enrolment.

Outcome

Heart rate was expressed as beats per minute (BPM). A non-invasive measure of autonomic function, HRV comprises indices of both sympathetic and parasympathetic nervous system functioning. Heart rate variability parameters were expressed in time and frequency domains; time domains included the standard deviation of RR intervals (SDRR) and the root mean square of successive differences (RMSSD). Frequency domains of HRV included very low frequency (VLF; 0.003–0.04 Hz), low frequency (LF; 0.04–0.15 Hz) and high frequency (HF; 0.15–0.40 Hz) power [15,16]. A trained clinician examined the ECG trace prior to

Table 1 Baseline demographic and clinical characteristics, by sex.

	Males (n=327) %/Mean (95% CI)	Females (n=89) %/Mean (95% CI)	t/chi2	P
Demographics				
Age	58.37 (57.22, 59.53)	58.79 (56.51, 61.09)	−0.33	0.74
Not born in Australia	47%	36%	2.90	0.09
Completed Secondary Education	**77%**	**59%**	**9.50**	**0.002**
Full-Time Employed	**56%**	**21%**	**30.60**	**<0.001**
Clinical Measures				
STEMI (versus NSTEMI/UA)	**40%**	**25%**	**7.08**	**0.008**
Percutaneous Coronary Intervention	62%	61%	0.00	0.97
Total Cholesterol	4.63 (4.47, 4.78)	4.51 (4.25, 4.78)	0.69	0.49
Triglycerides	1.91 (1.76, 2.06)	1.74 (1.51, 1.97)	1.09	0.28
High Density Lipoprotein	**1.00 (0.96, 1.03)**	**1.09 (1.01, 1.17)**	**−2.31**	**0.02**
Low Density Lipoprotein	2.83 (2.68, 2.98)	2.64 (2.38, 2.89)	1.21	0.23
C-Reactive Protein	22.72 (15.73, 29.71)	20.00 (10.09, 29.91)	0.38	0.70
Fasting Plasma Glucose	6.32 (6.04, 6.61)	6.38 (5.70, 7.06)	−0.17	0.86
Glycosylated Haemoglobin (HbA1c)	6.49 (6.31, 6.66)	6.58 (6.13, 7.03)	−0.45	0.65
Body Mass Index	29.26 (28.67, 29.86)	30.49 (29.06, 31.92)	−1.74	0.08
Waist Circumference (cm)	**103.43 (101.96, 104.90)**	**99.46 (96.27, 102.64)**	**2.35**	**0.02**
Systolic Blood Pressure	122.43 (120.34, 124.52)	118.88 (114.81, 122.96)	1.51	0.13
Diastolic Blood Pressure	74.35 (73.16, 75.54)	73.89 (71.59, 76.19)	0.34	0.73
Current/former smoker	63%	55%	2.06	0.15
Mental Health Measures				
Cardiac Depression Score	67.38 (64.48, 70.28)	73.64 (67.56, 79.73)	−1.92	0.06
State Anxiety Inventory Score	34.74 (33.20, 36.27)	35.97 (32.93, 39.00)	−0.73	0.47
Medications Prescribed				
Beta Adrenoceptor Blocking Drugs	88%	82%	1.73	0.19
Statins / Lipid Regulating Drugs	99%	96%	3.25	0.07
ACE Inhibitors & A11RB	77%	70%	1.34	0.25
Aspirin & Other Antiplatelet Drugs	99%	99%	0.05	0.82
Psychiatric Medication	**9%**	**25%**	**13.86**	**<0.001**

T-tests used to assess group differences for continuous variables; Chi-squares tests used to assess group differences for categorical variables.
Bold: $p<0.05$.
Abbreviations: A11RB, angiotensin two receptor blocker; N/STEMI, non/ST-Elevation myocardial infarction; UA, unstable angina.

analysis, excluding patients if they were not in sinus rhythm (i.e. in atrial fibrillation or paced). The trace was then analysed in LabChart Pro 8 for Mac (using HRV Analysis Module 2.0.1), with beats detected using the "Human" preset of the HRV module. No beats were manually added. SDRR was calculated from all beats on the trace. Ectopics were identified as beats that exceeded three standard deviations from the average RR on the horizontal axis. A waveform complexity equation that assesses the extent to which beat morphology conforms to the normal QRS complex was used to identify vertical outliers, where a beat higher in complexity is more likely ectopic in origin. Ectopic beats were then excluded.

Covariates

Covariates included age, clinical variables (percutaneous coronary intervention prior to discharge, high-density lipoprotein levels, waist measurements) and psychological variables (Cardiac Depression Scale score, state anxiety score on the State Trait Anxiety Inventory, psychiatric medications). Details on the collection of this data can be found in methods published previously [12].

Statistical Analysis

Hierarchical linear regression analyses were used to determine whether sex predicted HRV at 1 month and 12 months post-ACS, after adjustment for age and covariates. Covariates (other than age) were selected based on evidence of a significant association with at least three of the HRV measures. At each timepoint, we first ran a univariate model (Model 1), and subsequently adjusted for age (Model 2), clinical variables (Model 3), and psychological variables (Model 4).

We repeated the above analytic approach for the 12-month analyses. Normalised units were used in the analysis of LF

Table 2 Raw HR and HRV values at 1 and 12 months for Men and Women.

	Males (n=327) M (SD)		Females (n=89) M (SD)	
	1 mo	12 mo	1 mo	12 mo
HR (bpm)	59.74 (10.34)	59.85 (9.30)	63.36 (8.44)	66.62 (8.21)
SDRR (ms)	43.25 (29.36)	44.42 (23.14)	34.18 (18.26)	34.26 (14.63)
RMSSD (ms)	34.19 (43.18)	31.53 (27.00)	28.40 (26.46)	25.03 (17.59)
VLF Power (ms^2)	1,114.92 (1,389.90)	1,354.19 (1794.41)	562.38 (519.65)	615.67 (622.90)
LF Power (ms^2)	533.53 (1,226.85)	566.77 (906.35)	274.85 (607.26)	304.28 (342.60)
LF Power (nu)	50.57 (19.01)	53.04 (18.76)	43.19 (18.21)	50.89 (19.29)
HF Power (ms^2)	1,178.39 (5,291.97)	631.85 (1,421.73)	593.50 (1,615.07)	350.67 (500.65)
HF Power (nu)	50.86 (18.63)	48.57 (17.91)	58.18 (17.89)	50.31 (18.89)

Abbreviations: HR, heart rate; SDRR, standard deviation of RR intervals; RMSSD, root mean square of successive differences; VLF, very low frequency; LF, low frequency; HF, high frequency; nu, normalised units.

and HF, however raw descriptive values at 1 and 12 months are also reported [16].

The magnitudes of association were presented as coefficients (Coef.) with corresponding 95% confidence intervals. All analyses were conducted using Stata Version 15 (StataCorp. 2017, StataCorp LLC, College Station, TX, USA).

Results

In total, 416 participants were enrolled into the ADVENT study, with n=368 and n=308 providing data at 1 month and 12 months, respectively (Figure 1). For the purpose of this study, cross-sectional analysis at 1 month included n=359 for whom full HRV data were obtained and 12-month analyses included n=288 participants for whom full HRV data were obtained at both 1 and 12 months. Of these, 11 HRV files at 1 month and 21 HRV files at 12 months were excluded due to poor quality trace or rhythm, leaving n=348 and n=267 at 1 month and 12 months, respectively.

Key Characteristics of Sample

Key characteristics of the sample are presented by sex in Table 1. Eighty-nine (89) of the 416 participants were female. The mean age of the sample was 58.47 (SD: 10.66). At 1 month, the profile of women differed from men with respect to a range of demographic, clinical and psychosocial measures. For example, women had much lower rates of full-time employment (21% vs. 56%), and education levels (59% had completed secondary education compared to 77% of males). Women also had higher usage of psychiatric medication (22% vs. 8%) compared with men. Table 2 presents the raw (mean and standard deviation) HR and HRV separately for men and women at 1 and 12 months post-ACS.

Table 3 displays the coefficients and 95% confidence intervals for each variable at each level of adjustment, at 1 month and 12 months post-ACS, respectively. At 1 month post-ACS, sex was a significant predictor of HR (Coef: 3.62, 95% CI: 0.98, 6.27), such that women had a higher average resting HR compared to men (M=60 bpm, F=63 bpm). This association remained after adjustment for age (Model 2; Coef: 3.65, 95% CI: 1.00, 6.30), clinical factors (Model 3; Coef: 4.70, 95% CI: 1.41, 7.99) and psychological factors (Model 4; Coef: 4.03, 95% CI: 0.57, 7.49).

At 12 months post-ACS, sex remained a significant predictor of resting HR (Coef: 6.77, 95% CI: 3.89, 9.66), following adjustment for age (Model 2; Coef: 6.81, 95% CI: 3.95, 9.67), clinical (Model 3; Coef: 7.25, 95% CI: 3.53, 10.98), and psychological factors (Model 4; Coef: 7.44, 95% CI: 3.58, 11.30), with women continuing to have higher resting HR (M=60 bpm, F=66 bpm).

At 1 month post-ACS, sex was a significant predictor of SDRR (Coef: −9.07, 95% CI: −16.35, −1.79), VLF power (Coef: −552.54, 95% CI: −887.58, −217.50), LF power (Coef: −7.38, 95% CI: −12.37, −2.39), and HF power (Coef: 7.32, 95% CI: 2.43, 12.21) with women having lower HRV than men. These associations remained after adjustment for age (Model 2; SDRR Coef: −8.68, 95% CI −15.94, −1.43; VLF Coef: −531.07, 95% CI −863.62, −198.53; LF Coef: −7.23, 95% CI: −12.22, −2.24; HF Coef: 7.16, 95% CI: 2.27, 12.05), but only the associations with SDRR (Coef: −9.53, 95% CI: −17.89, −1.17) and VLF power (Coef: −611.07, 95% CI: −1,059.16, −162.98) remained after adjustment for clinical factors (Model 3). Only the association with VLF power (Coef: −553.82, 95% CI: −1,027.25, −80.40) remained after adjustment for psychological factors.

At 12 months post-ACS, sex was a predictor of SDRR and VLF power (Model 1; SDRR Coef: −10.16, 95% CI: −17.09, −3.23; VLF Coef: −738.52, 95% CI: −1,261.14, −215.91). This held true after adjustment for age (Model 2; SDRR Coef: −10.00, 95% CI: −16.75, −3.26; VLF Coef: −731.64, −1,249.94, −213.35), clinical (Model 3; SDRR Coef: −11.15, 95% CI: −20.24, −2.07; VLF Coef: −925.16, 95% CI: −1,679.08, 171.24), and psychological (Model 4; SDRR Coef: −9.86, 95% CI: −18.95, −0.76; VLF Coef: −817.50, 95% CI: −1,559.71, −75.30) factors. Sex was not a significant predictor of RMSSD at 1 or 12 months post-ACS.

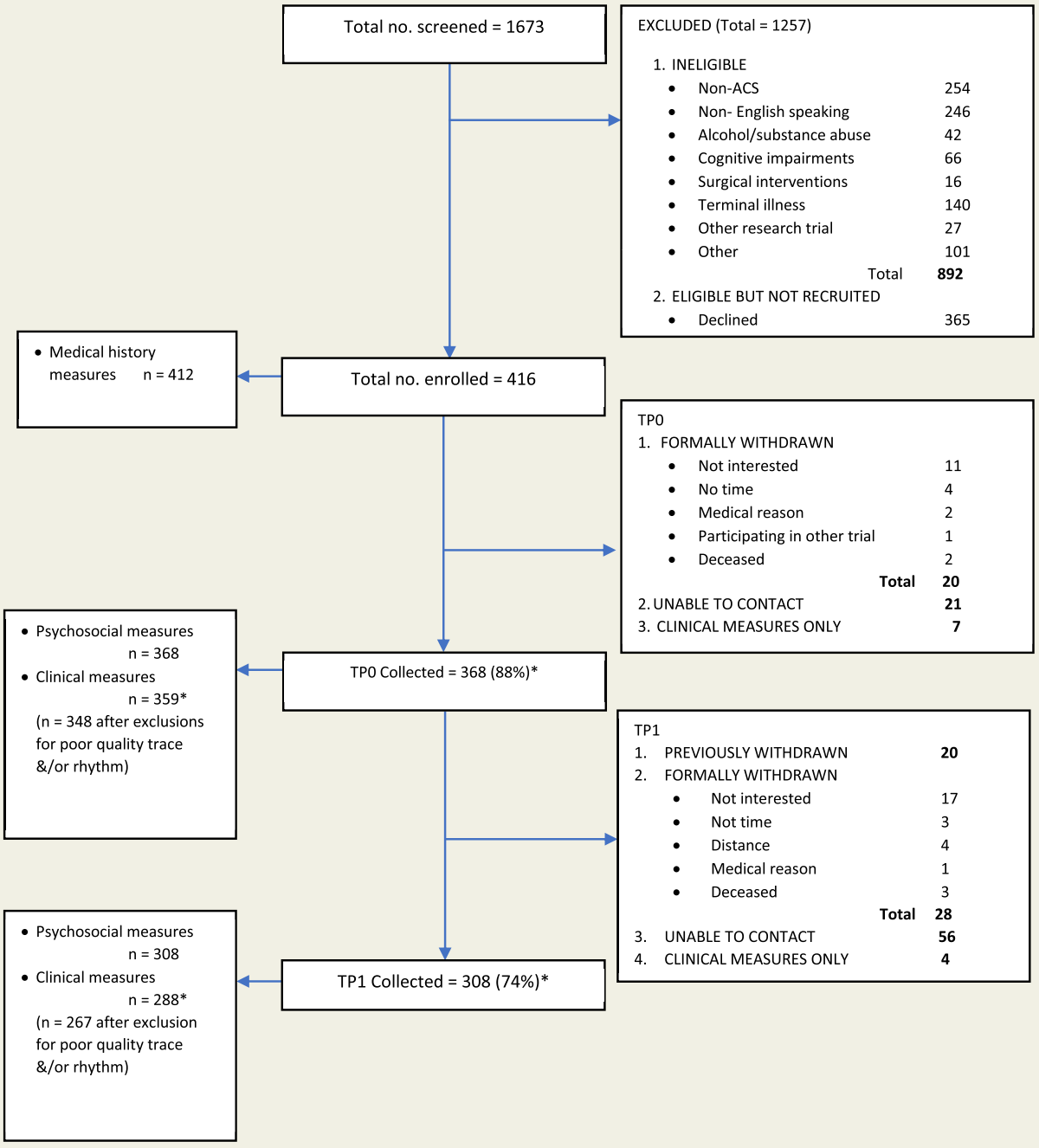

Figure 1 STROBE diagram for the ADVENT study.
Abbreviations: ACS, acute coronary syndrome; TP0, time point 0 (1 month post-ACS); TP1, time point 1 (12 months post-ACS).

Discussion

To our knowledge, this is the first study to examine sex-specific differences in HR and HRV during a 12-month period following ACS. We demonstrated that sex-specific trajectories exist for both HR and HRV, with women having a higher resting HR and lower HRV (SDRR, VLF, LF and HF powers) at 1 month post ACS, after adjusting for age. Sex remained a predictor of HR, SDRR and VLF power at 1 month after additional adjustment for clinical factors, and a predictor of HR and VLF power after additional adjustment for psychological factors. Furthermore, our results show that sex is a predictor of HR, SDRR and VLF power at 12 months post-ACS (adjusted for age, clinical and psychological factors), whereby females have higher HR and lower SDRR and VLF power. This pattern of results is consistent with a lower

Table 3 Sex as a predictor of HR and HRV at 1 and 12 months *(Coef, 95% CIs).*

	Model 1	Model 2	Model 3	Model 4
HR (bpm)				
1 mo	**3.62 (0.98, 6.27)**	**3.65 (1.00, 6.30)**	**4.70 (1.41, 7.99)**	**4.03 (0.57, 7.49)**
12 mo	**6.77 (3.89, 9.66)**	**6.81 (3.95, 9.67)**	**7.25 (3.53, 10.98)**	**7.44 (3.58, 11.30)**
SDRR (ms)				
1 mo	**−9.07 (−16.35, −1.79)**	**−8.68 (−15.94, −1.43)**	**−9.53 (−17.89, −1.17)**	−6.59 (−15.31, 2.13)
12 mo	**−10.16 (−17.09, −3.23)**	**−10.00 (−16.75, −3.26)**	**−11.15 (−20.24, −2.07)**	**−9.86 (−18.95, −0.76)**
RMSSD (ms)				
1 mo	−5.79 (−16.48, 4.91)	−5.63 (−16.35, 5.09)	−6.42 (−17.65, 4.80)	−3.40 (−15.12, 8.33)
12 mo	−6.50 (−14.61, 1.60)	−6.38 (−14.39, 1.63)	−5.80 (−16.66, 5.05)	−5.11 (−16.38, 6.16)
VLF Power (ms^2)				
1 mo	**−552.54 (−887.58, −217.50)**	**−531.07 (−863.62, −198.53)**	**−611.07 (−1,059.16, −162.98)**	**−553.82 (−1,027.25, −80.40)**
12 mo	**−738.52 (−1,261.14, −215.91)**	**−731.64 (−1,249.94, −213.35)**	**−925.16 (−1,679.08, 171.24)**	**−817.50 (−1,559.71, −75.30)**
LF Power (nu)				
1 mo	**−7.38 (−12.37, −2.39)**	**−7.23 (−12.22, −2.24)**	−5.63 (−11.44, 0.18)	−5.23 (−11.18, 0.71)
12 mo	−2.14 (−8.11, 3.82)	−2.10 (−8.05, 3.86)	−6.24 (−13.83, 1.36)	−6.74 (−14.54, 1.07)
HF Power (nu)				
1 mo	**7.32 (2.43, 12.21)**	**7.16 (2.27, 12.05)**	5.65 (−0.04, 11.35)	5.34 (−0.48, 11.16)
12 mo	1.74 (−3.98, 7.46)	1.69 (−4.02, 7.40)	5.57 (−1.71, 12.85)	6.12 (−1.36, 13.60)

Abbreviations: HF, high frequency; LF, low frequency; VLF, very low frequency; RMSSD, root mean square of successive differences; SDRR, standard deviation of RR intervals; HR, heart rate; nu, normalised units.

Bold: $p<0.05$; Model 1: Univariate, Model 2: adjusted for age; Model 3: adjusted for age and clinical variables (percutaneous coronary intervention [PCI] status, high density lipoprotein levels, waist circumference); Model 4: adjusted for age, clinical variables and psychological variables (depression, state anxiety, psychiatric medications prescribed).

parasympathetic activity (i.e. low VLF in the frequency domain) and lower HRV overall (i.e. SDRR in the time domain) in post-ACS women [16,17].

Pertaining to HR, findings from the current study indicate that sex-specific differences persist over the 12 months following ACS. Between the 1- and 12-month assessment period, men's HR remained stable (at 60 bpm), while women's increased by an absolute mean of 3 bpm (from 63 bpm to 66 bpm). When 1-month HR was included as a covariate in the 12-month analyses, sex remained a significant predictor of HR, indicating sex-specific changes in HR between the 1- and 12-month periods (data not shown). However, while there is some evidence that a resting HR of ≤62 beats per minute is protective against incident CVD in women [6], the clinical significance of this finding in a cohort with established disease may be negligible. Indeed, compared to population norms aged 50–69 years (M: 78 SD: 11; F: 74 SD: 10) [10], study participants had quite low HR.

Our HRV findings indicate that women have poorer autonomic functioning at 1 and 12 months following ACS, compared to men. These findings are consistent with those of De Oliveira Pinheiro and colleagues who reported that compared to men, women had lower HRV (triangular index, SDNN, HF, HF/LF, RMSSD and SD1) in the immediate 5–10 days following MI [11]. Indeed, our findings indicate that such differences persist after the acute period. However, it is important to note that we found this association for some but not all HRV parameters. Despite this, previous research has suggested that both SDRR and VLF predict worse outcomes following ACS. SDRR <50 ms has been associated with an increased risk of all-cause mortality. In the current study, the average SDRR for both men and women was below 50 ms, however the average for women was lower than for men (Men 1 month: 43 ms, 12 months: 44 ms; Women 1 month: 34 ms, 12 months: 34 ms, respectively). It is important to note that the utility of HRV measures up to 1 year post-ACS have been questioned. However, Bigger and colleagues identified that VLF power maintained its prognostic strength over this time [18]. In the current sample, VLF power increased for both men and women over the 12-month post-ACS period, however men improved moreso than women.

The strength of this study is that it is prospective, providing longitudinal, gold standard data for a range of autonomic, mental health and other clinical data at multiple timepoints. However, it is important to note that, due to the small sample size, our confidence intervals were large, and as such the results should be taken with caution. Additionally, the study is limited by the absence of ethnic specific data and the relatively small number of women. Women are traditionally under-represented in cardiac specific cohort studies such as ADVENT, as well as those evaluating efficacy of interventional or surgical procedures and behavioural and rehabilitation-based interventions. This is a broader issue in need of attention in cardiovascular research [19]. Moreover,

it is important to note that HRV research remains in its infancy and there is no consensus on the specific contribution of each HRV parameter on autonomic function, thus limiting detailed interpretation of the data.

Conclusion

We have provided preliminary evidence of sex-specific differences in HR, SDRR and VLF in the year following ACS, whereby women have higher HR and lower HRV, suggestive of poorer autonomic function. Large-scale cohort studies examining autonomic function as a driver of sex-specific outcomes following ACS are required.

Funding Sources

The ADVENT study was funded by a National Health and Medical Research Council Project Grant (APP1021294). AJS is supported by a Postgraduate Scholarship from the National Health and Medical Research Council (#1191061) and the Australian Government RTP Scheme. AO is supported by a Future Leader Fellowship (#101160) from the Heart Foundation, Australia.

Disclosures

The authors declare no conflicts of interest.

Acknowledgements

We thank all ADVENT participants and project staff.

References

[1] GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385:117–71.
[2] Berger JS, Elliott L, Gallup D, Roe M, Granger CB, Armstrong PW, et al. Sex differences in mortality dollowing acute coronary syndromes. JAMA 2009;302(8):874–82.
[3] Zhang Y, Liu B, Zhao R, Zhang S, Yu XY, Li Y. The Influence of Sex on Cardiac Physiology and Cardiovascular Diseases. J Cardiovasc Transl Res 2019;13:3–13.
[4] Kleiger RE, Stein PK, Bigger JT. Heart Rate Variability: Measurement and Clinical Utility. Ann Noninvasive Electrocardiol 2005;10:88–101.
[5] Huikuri HV, Stein PK. Clinical application of heart rate variability after acute myocardial infarction. Front Physiol 2012;3:41.
[6] Hsia J, Larson JC, Ockene JK, Sarto GE, Allison MA, Hendrix SL, et al. Resting heart rate as a low tech predictor of coronary events in women: prospective cohort study. BMJ 2009;338:b219.
[7] Curtis BM, O'Keefe JHJ. Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight. Mayo Clin Proc 2002;77:45–54.
[8] Goldenberg I, Goldkorn R, Shlomo N, Einhorn M, Levitan J, Kuperstein R, et al. Heart rate variability for risk assessment of myocardial ischemia in patients with known coronary artery disease: The HRV-DETECT (Heart Rate Variability for the Detection of Myocardial Ischemia) study. J Am Heart Assoc 2019;8:e014540.
[9] Voss A, Schroeder R, Heitmann A, Peters A, Perz S. Short-term heart rate variability–influence of gender and age in healthy subjects. PLoS One 2015;10:e0118308.
[10] Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. J Am Coll Cardiol 1998;31:593–601.
[11] Pinheiro Ade O, Pereira Jr VL, Baltatu OC, Campos LA. Cardiac autonomic dysfunction in elderly women with myocardial infarction. Curr Med Res Opin 2015;31:1849–54.
[12] Oldroyd JC, Cyril S, Wijayatilaka BS, O'Neil A, McKenzie DP, Zavarsek S, et al. Evaluating the impact of depression, anxiety & autonomic function on health related quality of life, vocational functioning and health care utilisation in acute coronary syndrome patients: the ADVENT study protocol. BMC Cardiovasc Disord 2013;13:103.
[13] Sandercock GR, Bromley PD, Brodie DA. The reliability of short-term measurements of heart rate variability. Int J Cardiol 2005;103:238–47.
[14] Maestri R, Raczak G, Danilowicz- Szymanowicz L, Torunski A, Sukiennik A, Kubica J, et al. Reliability of heart rate variability measurements in patients with a history of myocardial infarction. Clin Sci (Lond) 2009;118:195–201.
[15] Routledge FS, Campbell TS, McFetridge-Durdle JA, Bacon SL. Improvements in heart rate variability with exercise therapy. Can J Cardiol 2010;26:303–12.
[16] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Eur Heart J 1996;17:354–81.
[17] Shaffer F, Ginsberg JP. An overview of heart rate variabiity metrics and norms. Front Public Health 2017;5:258.
[18] Bigger JT, Fleiss JL, Rolnitzky LM, Stein PK. Frequency domain measures of heart period variability to assess risk late after myocardial infarction. J Am Coll Cardiol 1993;1993:729–36.
[19] Scovelle AJ, Milner A, Beauchamp A, Byrnes J, Norton R, Woodward M, et al. The Importance of Considering Sex and Gender in Cardiovascular Research. Heart Lung Circ 2020;29:e7–8.