Autonomic impairment in Rheumatoid Arthritis

Main author

Dr DC Janse van Rensburg
University of Pretoria
P O Box 12651
Hatfield
0028
Pretoria
South Africa
E-mail: vrensburg@sport.up.ac.za
Fax: +27 12 362 3369
Tel: +27 12 420 6053

Co-authors

Prof JA Ker
University of Pretoria
Pretoria
South Africa

CC Grant
University of Pretoria
Pretoria
South Africa

Dr L Fletcher
University of Pretoria
Pretoria
South Africa

Abstract

Aim To determine if there is a difference between autonomic cardiac control as measured by heart rate variability (HRV) in females with rheumatoid arthritis (RA) compared to a healthy control group.

Methods The RA group (45) and control group (39) were matched for age and BMI. Three techniques were used: time domain, frequency domain and Poincarè plot analysis. All possible confounding factors were excluded and the test environment strictly regulated.

Results Basal heart rate was significantly higher in the RA patients. In the supine position significant differences existed between RA patients and controls ($p \leq 0.01$). Indicators of parasympathetic activity showed significantly lower variation in the RA group (RMSSD=14.70, pNN50=0.50, SD1=10.50, HF(ms^2)=31) compared to controls (RMSSD=29.40, pNN50=7.8, SD1=20.9, HF(ms^2)=141.00). Indicators of sympathetic variation were also significantly lower in RA patients (SD2=36.70, LF(ms^2)=65) compared to controls (SD2=49.50, LF(ms^2)=175). In the standing position 8 variables indicated autonomic impairment by significant differences ($p \leq 0.01$) between the groups. The response of the RA group to an orthostatic stressor showed less vagal withdrawal, [p-values for RMSSD=0.038, pNN50=0.022, SD1=0.043 and HF(ms^2)=0.008 respectively]; and lower sympathetic response [p-values for SD2=0.001 and LF(ms^2)<0.001] when compared to controls.

Conclusions An inability of the autonomic nervous system to efficiently compensate to internal and external environmental changes may predispose RA patients to arrhythmias thereby increasing cardiovascular mortality. All 3 methods used showed the same outcome, implying decreased HRV and thus an increased risk for arrhythmias in RA patients. Evaluating the autonomic nervous system might be critical in planning management of RA patients.

Keywords: autonomic nervous system dysfunction / impairment

rheumatoid arthritis

heart rate variability

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic, inflammatory disease of unknown cause affecting 0.5%-1% of the world population[1,2]. Although primarily considered a disease of the joints, a variety of extra-articular manifestations including cardiovascular involvement are well recognized[3].

There is a growing body of literature supporting the evidence for excess cardiovascular risk in patients suffering from RA[4-6]. Possible etiopathogenesis include conventional risk factors (hypertension, abnormal body mass index, smoking, etc.)[7,8], accelerated atherosclerosis i.e. due to inflammation (measured by high-sensitivity CRP)[6,9-11] and autonomic dysfunction (either by increased disrhythmogenic potential[12] or by neuronal pathways modulating inflammation[13-15]). The autonomic nervous system is one of a variety of neuronal pathways that have been implicated in modifying inflammation[13]. The "cholinergic anti-inflammatory pathway" is a well-studied mechanism. Signals transmitted via the vagus nerve control the release of cytokines that subsequently reduce the production of pro-inflammatory cytokines by an α-7 nicotinic acetylcholine receptor. This is followed by amelioration of inflammatory disease[14,15].

The possible role of autonomic dysfunction in RA led to a literature search conducted through Medline and Pubmed using the key words: autonomic nervous system / autonomic dysfunction or impairment / rheumatoid arthritis / heart rate variability (1963-2011), yielded only 27 original publications in English. In these publications 8 different testing protocols were used to determine the extent of autonomic nerve involvement in RA patients. Autonomic

tests used in the studies were: sweat response[16,17], cardiovascular reflex tests[18-29], divergent autonomic reactions to specific tasks[30], pre-ejection period and respiratory sinus arrhythmia[31], sympathetic skin response and RR-interval variation[32,33], pupillography[34,35], heart rate variability (HRV)[28,29,36-41] and heart rate turbulence[42]. Autonomic dysfunction was reported by some but not all authors. Review results were inconclusive as study results could not be compared due to numerous disparate tests used and heterogeneous study methodology[43]. Problems identified were incomplete information on exclusion criteria, non-stabilisation of the environment, males and females in the same small study groups and use of inappropriate statistical methods[44].

HRV quantification is an accepted, non-invasive tool, used in clinical and sport related research as an instrument to measure the activity and integrity of the autonomic nervous system. HRV is the oscillation around a mean value, between consecutive heartbeats [measured as R wave to R wave (N-N) intervals], and can be quantified by different standardised analysis techniques. Low HRV is a known predictor of mortality in many clinical populations and it is associated with several cardiovascular risk factors[45,46]. The purpose of the current study was to determine - as claimed by other authors - if there was a significant difference between autonomic cardiac control as measured by standardised HRV, in South African females suffering from RA compared to a healthy control group.

METHODOLOGY

Ethical approval was granted by the Ethical Committee of the Faculty of Health Sciences at the University of Pretoria. All participants signed informed consent.

Patients with RA according to the 1987 Revised American College of Rheumatology Criteria[47] were compared to a healthy control group according to the definition of Health by the World Health Organisation. In order to prevent possible confounders participants were matched for age, sex, height and weight. RA activity was measured with the Disease Activity Score (DAS_{28})[48,49]. Inclusion criteria for both the control group and the RA group included being of the female sex, 30-60 years of age, and that participation is strictly voluntary. Being healthy was an additional inclusion criterion for the control group, whereas controlled RA was an inclusion criterion for the RA group. The exclusion criteria for both groups included smoking, cardiovascular disease, pulmonary disease, diabetic disease, neurological disease, use of drugs that can interfere with the autonomic nervous system or the cardiovascular system, and liver or kidney disease.

HRV data sampling

The data, RR-intervals, was sampled in the morning in a quiet environment at a room temperature of about 22 ˚C. Recordings were made over a period of 30 minutes. The participants were instructed not to drink any alcohol or caffeine during the preceding 24 hours. Participants were in a fasting state

from 22:00 the previous night but were allowed to eat a low protein breakfast (cereal with milk only) on the morning of testing.

Each participant put on a Polar 810i strap and transmitter, and was then placed in a supine (resting) position for 10 minutes, breathing spontaneously without talking. This was followed by a 10 minute orthostatic stressor with participants standing (stress) in an upright position, with their backs leaning against the wall and their feet apart. RR-intervals from 5 minutes of the resting period and 5 minutes of the standing period that were least affected by artefacts, incidence of syncope and non-stationarity were used for analyses.

HRV Quantification

Standard Polar software programmes with a minimum beat protection zone of six beats per minute and a low filter power were used to remove artefacts in RR-interval data. The data (RR-interval sets) was analyzed using HRV Analysis Software obtained from the University of Kuopio, Finland. Smoothness priors for trend and Model Eye programme settings were used for detrending with an Alpha value of 500[46]. The autoregressive model order value was 16 and the interpolation rate 4 Hz. The techniques used for the evaluation of HRV from RR-interval data sets, were grouped into three categories: time domain, frequency domain and non-linear analysis (Poincarè plot analysis). There is no gold standard for HRV measurements and no one method has been identified as being better than another. Therefore it was decided to use three techniques as they are complementary to each other[50]. Table 1 explains the different HRV indicators.

Table 1

HRV techniques, HRV indicators and origins of variability[46,51]

Time domain analysis	**NN(s)**	The mean of the intervals between successive QRS complexes; result of vagal (short term) and sympathetic (long term) influence on HRV.
	SDNN(s)	Standard deviation of intervals between successive QRS complexes; indicator of vagal (short term) and sympathetic (long term) influence on HRV (Total power or variance).
	RMSSD(ms)	Root mean square of the standard deviation between NN-intervals; indicator of vagal influence (short term).
	pNN50(%)	The percentage of successive NN-interval differences larger than 50ms computed over the entire recording; indicator of vagal influence (short term) on HRV.
Poincarè plot analysis	**SD1(ms)**	Indicator of the standard deviation of the immediate, or short-term, NN variability due to parasympathetic efferent (vagal) influence on the sino-atrial node.
	SD2(ms)	Indicator of the standard deviation of the long-term or slow variability of the heart rate. It is accepted that this value is representative of the global variation in HRV.

Frequency domain analysis	**LF(ms^2)**	Indicator of sympathetic influence, but also including a parasympathetic component.
	HF(ms^2)	Indicator of only parasympathetic influence.
	LF/HF	Indicator of autonomic balance.
	LF(nu)	LF (normalised units) represent the relative power of the LF component in proportion to the total power minus the VLF component, i.e. LF/(total power-VLF).
	HF(nu)	The HF (normalised units) represent the relative power of the HF component in proportion to the total power minus the VLF component, i.e. HF/(total power-VLF)

s	seconds	ms^2	milliseconds, square
ms	milliseconds	nu	normalised units

Data analysis

Multivariate analysis-of-variance tests (MANOVAs) were conducted to determine if, overall, differences existed between the two groups. Where necessary, the variables were transformed using natural logarithms to meet the assumption of normality. To facilitate interpretation, the post hoc tests were appended with non-parametric Mann Whitney U-tests (MWU) using the original variables. IBM SPSS Statistics 19 was used to analyse the data.

RESULTS

Each group consisted of 46 participants. Records were excluded if the total record was less than 60 seconds, or if more than 20% of the intervals were affected by artefacts [52]. The sample was thus reduced to 39 subjects in the control group and 45 in the RA group with mean ages of 44.53 (±7.51) and 46.47 (±7.94) years respectively (p=0.258). The RA group had a mean disease duration of 4.26 (±1.2) years. Their mean DAS_{28} score was 3.27 (±0.90) and the mean CRP level 8.59mg/l (±3.15).

On average, the RA patients had a higher BMI (28.74 kg/m^2 ±5.46) than the controls (24.52 kg/m^2 ±3.89). This was probably caused by the non-recording of HRV data in seven of the heavier subjects in the control group. This difference was significant (p<0.001), hence BMI was assessed as a possible covariate.

Due to their positive skewness, SDNN, HR, HRSTD, RMSSD, pNN50, SD1, SD2, LF(ms^2), HF(ms^2), HF(nu) and LF/HF were all transformed using natural logarithms. The MANOVA ruled BMI out as a covariate and further confirmed that overall differences existed between the two groups (Wilks' Lambda = 0.395; Hotellings's Trace = 1.534; df = 26; p<0.001) with a large effect size (partial eta squared = 0.605).

Instead of reporting group differences on the transformed variables used in the MANOVA, which may complicate interpretation, the results of the non-parametric Mann Whitney U-tests (MWU) are reported since the two sets of tests corresponded. The descriptive statistics and the MWU-test p-values for the HRV parameters in the supine and stress positions are displayed in Table 2.

Table 2

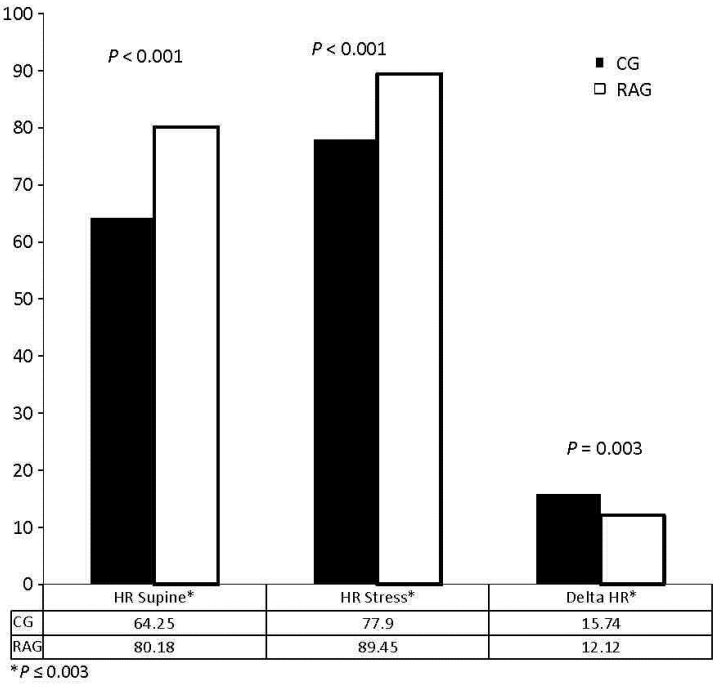
Descriptives and MWU test results of HRV indicators

HRV indicator	Supine Position					Standing position				
	CG (n=39)		RAG (n=45)		MWU	CG (n=39)		RAG (n=45)		MWU
	Mean	Median	Mean	Median	p	Mean	Median	Mean	Median	p
NN(s)	0.97 (±0.17)	0.93	0.79 (±0.10)	0.77	<0.001*	0.76 (±0.12)	0.75	0.67 (±0.08)	0.67	<0.001*
SDNN(s)	0.04 (±0.03)	0.03	0.02 (±0.01)	0.02	0.002*	0.03 (±0.02)	0.03	0.02 (±0.01)	0.02	<0.001*
HR(bpm)	63.50 (±10.25)	64.25	77.56 (±9.37)	77.90	<0.001*	81.18 (±11.91)	80.18	90.40 (±10.78)	89.45	<0.001*
HRSTD(bpm)	2.53 (±1.05)	2.62	2.40 (±0.82)	2.33	0.788	4.84 (±1.84)	4.64	3.43 (±1.40)	3.38	<0.001*
RMSSD(ms)	42.59 (±38.70)	29.40	20.30 (±14.68)	14.70	<0.001*	21.31 (±19.09)	17.10	14.12 (±9.10)	12.00	0.011*
pNN50(%)	18.88 (±24.13)	7.80	6.73 (±12.97)	0.50	0.002*	3.40 (±5.36)	1.30	1.80 (±5.17)	0.20	0.001*

SD1(ms)	30.33 (±27.48)	20.90	14.49 (±10.40)	10.50	<0.001*	15.62 (±13.56)	12.50	10.16 (±6.50)	8.80	0.006*
SD2(ms)	59.01 ±31.42)	49.50	39.33 (±16.53)	36.70	0.002*	80.19 (±29.08)	79.50	48.19 (±25.90)	41.10	<0.001*
LF(ms²)	372.92 (±478.67)	175.00	125.27 (±149.01)	65.00	<0.001*	544.59 (±552.91)	333.00	145.02 (±177.47)	88.00	<0.001*
HF(ms²)	442.44 (±759.88)	141.00	141.51 (±303.44)	31.00	<0.001*	166.69 (±568.10)	51.00	47.94 (±99.29)	16.00	0.001*
LF(nu)	51.63 (±19.29)	54.10	64.44 (±20.42)	64.60	0.010*	84.07 (±11.91)	85.10	79.80 (±13.48)	83.00	0.169
HF(nu)	49.39 (±28.15)	47.10	32.50 (±21.11)	29.80	0.003*	15.29 (±11.82)	13.00	22.01 (±24.22)	16.10	0.311
LF/HF	1.66 (±1.64)	1.15	4.97 (±6.48)	2.50	0.002*	11.50 (±13.03)	6.60	10.17 (±13.00)	6.50	0.551

CG	Control group	s	seconds	%	percentage
RAG	Rheumatoid Arthritis group	bpm	beats per minute	ms^2	milliseconds, squared
*	p≤0.01	ms	milliseconds	nu	normalised units

The RA group had a significant higher resting heart rate compared to the control group in both the supine and standing position, but observing the HR difference (rising from supine to standing) the RA group showed a significant lower delta compared to the control group (p=0.003) (figure 1).



	HR Supine*	HR Stress*	Delta HR*
CG	64.25	77.9	15.74
RAG	80.18	89.45	12.12

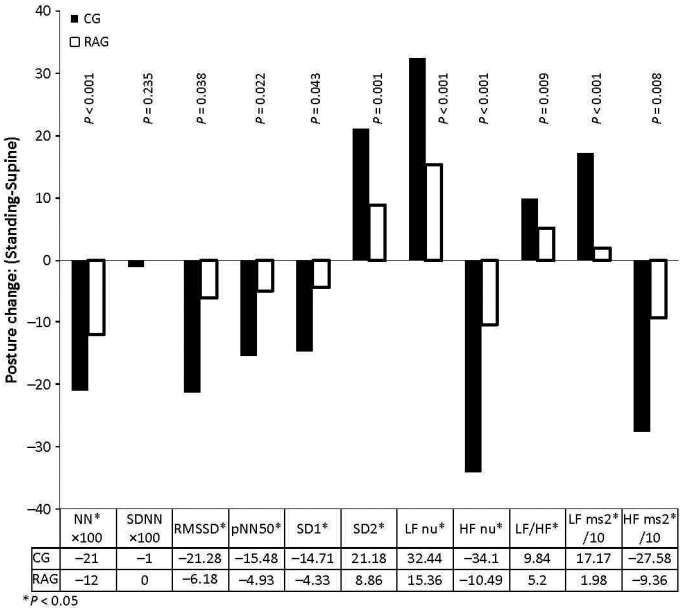
*$P \leq 0.003$

Figure 1: Median values of HR supine and HR stress in the control group (CG) and rheumatoid arthritis group (RAG).

Variables in the supine position

In the supine position all variables assessing parasympathetic induced variability [RMSSD, pNN50, SD1, HF(ms^2)] were significantly lower for the RA group. Variables assessing HRV indicators influenced by both the sympathetic and parasympathetic branches of the autonomic nervous system [NN, SDNN, SD2, LF(ms^2)] also showed significantly lower values for the RA group. Indicators for autonomic balance (LF(nu), HF(nu), LF/HF) showed significant differences with the

LF(nu) and LF/HF being higher for the RA group, but the HF(nu) being higher for the control group.



	NN* ×100	SDNN ×100	RMSSD*	pNN50*	SD1*	SD2*	LF nu*	HF nu*	LF/HF*	LF ms2* /10	HF ms2* /10
CG	−21	−1	−21.28	−15.48	−14.71	21.18	32.44	−34.1	9.84	17.17	−27.58
RAG	−12	0	−6.18	−4.93	−4.33	8.86	15.36	−10.49	5.2	1.98	−9.36

*P _ 0.003.

Figure 2: Comparison of posture change for the groups. Formula: Change = standing value minus supine value . *P < 0.05. CG, control group; RAG, rheumatoid arthritis group.

Variables in the standing position

In the standing position the variables influenced only by the parasympathetic branch were all significantly lower for the RA group. The same is also true for those variables influenced by both the sympathetic and parasympathetic branches of the ANS. Interestingly the indicators for autonomic balance did not show significant differences between the two groups in the standing (stress) position, but looking at the delta from supine to standing, the control group had a larger response. Calculating the postural change (i.e. mean standing values minus the mean supine values) for both groups, one can appreciate that the RA group had a significantly lower response for all measured indicators, except SDNN, as shown in Figure 2. In

order to get values on a similar scale to be displayed on one graph, NN and SDNN were multiplied by 100; and LF(ms^2) and HF(ms^2) were divided by 10.

DISCUSSION

In this study, using standardized methods to ascertain HRV parameters, the RA group showed less variability (i.e. less healthy heart) compared to the healthy control group. All three methods used (time domain, frequency domain and Poincare analysis) yielded the same outcome. Our results are in contrast to Evrengul's study (one of the first authors applying HRV to assess autonomic function in RA patients), who measured time domain and frequency domain, but had conflicting results[36]. For time domain parameters, Evrengul showed a slightly higher RMSSD and pNN50 (i.e. parasympathetic influence) and a significant lower SDNN (i.e. combined sympathetic and parasympathetic influence) for the patient group. The frequency domain parameters however, showed a significant lower HF(ms^2) (parasympathetic), but higher LF(ms^2) and LF/HF (sympathetic and parasympathetic). Possible explanations for the discrepancies in results might be that Evrengul included both males and females in the groups and recordings were done over an hour.

Work done by authors like Fei (1996) and Howorka (1998) stated that frequency domain analyses are better for mortality prediction when using short-term recordings[53,54]. The current study showed the same results for time domain and frequency domain analysis, using short-term recordings. Fei evaluated patients after acute myocardial infarction and Howorka evaluated diabetic patients. Our findings perhaps warrant further investigation of accuracy of time domain analysis to predict mortality when using short-term recordings (average 5 min tachograms).

Similar to our study, other authors also reported an elevated resting heart rate in the RA group compared to the control group, again indicating a lower vagal and/or an increased sympathetic drive in RA patients[19,29]. According to Jouven et al (2005), patients with a resting heart rate of ≥75 beats per minute and no clinical evidence of cardiac disease have a 4-fold risk for sudden cardiac death[55]. On average two-thirds (66%) of our patient group had a resting heart rate of 77. Only two studies measured HR response (i.e. posture change) by means of HRV in RA patients[29,40]. Aydemir and Vlcek could not show a difference for heart rate response between controls and patients; neither did they offer an explanation. Our patient group had a significant lower HR response compared to the controls[29,40]. This finding supports the other measurements in the current study, as with less heart rate variability shown in the RA group, one would expect a decreased heart rate response in comparison to the controls.

Our RA study group had relative early disease (4.26 years disease duration), with moderate disease activity (DAS_{28} 3.27, CRP 8.55mg/l) and no clinical determined signs or symptoms of autonomic impairment. Despite this, most HRV indicators showed significantly less variability in the RA patients compared to the controls, designating the RA group as having less healthy hearts. In the supine (resting) position variables assessing parasympathetic variability were all lower for the RA group. This is in agreement with other authors' work, where Anichkov using 24-hour Holter recordings showed statistical differences for RMSSD and SD1[37] and Milovanovic using 10 minute recording periods showed differences for pNN50, RMSSD and HF(ms^2) indicating less variability for the RA subjects[28]. Indicators for autonomic balance showed higher values for those indicators (LF(nu) and LF/HF) predominantly controlled by sympathetic influence and lower values for HF(nu)

(predominantly parasympathetic) for the RA group. In the resting position, normally parasympathetic dominance is to be expected, which was not the case in our patient group.

As previously pointed out, only two other studies used HRV to evaluate posture change in RA patients compared to a control group. They evaluated only frequency domain parameters, but the outcomes were the same as for our study[29,40]. Both LF(ms^2) and HF(ms^2) had significantly lower values comparing the RA group to the control group. One would expect a bigger sympathetic drive changing from supine to standing[52,56]. The RA patients had a poorer response to posture change. Vagal withdrawal, indicated by RMSSD, pNN50, SD1 and HF(ms^2), was significantly increased in the control group. Also, the indicators SD2, LF(ms^2), representing the combined influence of vagal and sympathetic cardiac control, was significantly higher in the control group, thereby indicating higher autonomic responsiveness to the posture change. Not only does an absent or decreased HRV response to posture change point to early sympathetic damage and autonomic dysfunction[52], but it has been suggested that the parasympathetic nervous system has anti-arrhythmic properties[55,57].

In conclusion this study showed that a South African female group with RA had probable autonomic impairment as compared to healthy controls. Not only did they have a higher resting heart rate and lower variability in their autonomic system, but also a poorer response to posture change. These findings implicate a higher burden of morbidity in these patients who are already subjected to chronic pain and disability. In this group of relative early disease there is already some evidence of cardiac autonomic impairment without any clinical signs or symptoms, thus subjecting these patients to higher risk for possible cardiac incidents. This study

suggests a possible increased disrhythmogenic potential in RA patients that should be considered by clinicians in planning long term management. We recommend that future research should focus on RA patients and the effect of suitable exercise modalities on HRV parameters as studies in healthy subjects have described an advantageous outcome. A possible limitation of the current study is that only heart rate variability was used to indicate the health of the autonomic system. Including tests such as analysis of blood pressure variability may add information and support results obtained by HRV analysis.

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