

CHAPTER FOUR: RESULTS

4.1 PHASE 1: HEALTHY CONTROL GROUP VERSUS RHEUMATOID ARTHRITIS GROUP

4.2 PHASE 2: RHEUMATOID ARTHRITIS EXERCISE GROUP VERSUS RHEUMATOID ARTHRITIS CONTROL

The results are reported in two phases. The various statistical tests that were used are explained in greater detail in the chapter on methodology (Chapter 3). In PHASE ONE a healthy control group (HCG) is compared to a rheumatoid arthritis group (RAG). Data on *anthropometry*, *age* and *HRV* are compared. Explanations for the meaning of the different HRV indicators can be found in Chapter 3, Table 3.4 (page 85). The HRV indicators are reported for both supine (resting) and standing (stress) positions and include: RR, RRSD, HR, HRSD, RMSSD, pNN50, SD1, SD2, LF(ms²), HF(ms²), LF/HF, LF(nu) and HF(nu).

In PHASE TWO a RA control group (RAC) and an RA exercise group (RAE) are compared at baseline (i.e. pre-intervention) and at 12 weeks after completion of the supervised training programme (i.e. post-intervention). The delta between pre- and post-intervention are reported within each group. The parameters reported on include:

4.2.1 DEMOGRAPHIC BACKGROUND

For both groups, including age, anthropometric characteristics, disease duration, RA medication, the presence or absence of rheumatoid factor (RF), and the presence or absence of anti-citrillunated peptide antibodies (ACPA).

4.2.2 HEART RATE VARIABILITY INDICATORS

For supine and standing positions as in PHASE 1.

4.2.3. DISEASE ACTIVITY SCORE, HEALTH ASSESSMENT QUESTIONNAIRE AND VISUAL ANALOGUE SCALE

4.2.4 FUNCTIONAL PARAMETERS

- *Flexibility*: wrist flexion and extension, knee flexion and extension, hip flexion and

- extension, lateral flexion, scratch test, sit and reach test
- *Strength*: handgrip, leg strength, arm curls, sit to stand
 - *Aerobic fitness*: Rockport 1 mile walk, VO₂ max relative.

4.1 PHASE ONE: HEALTHY CONTROL GROUP (HCG) VERSUS RHEUMATOID ARTHRITIS GROUP (RAG)

The parameters reported on are:

4.1.1 Demographic background

4.1.2 HRV

Each group consisted of 46 participants. The healthy control group was matched to the RA group according to age, sex, height and weight. Records were excluded if the total record was less than 60 seconds or if more than 20% of the intervals were affected by artefacts⁽¹⁾. The sample was thus reduced to 39 subjects in the HCG and 45 in the RAG. The RA group had a mean disease duration of 4.26 (± 1.2) years. Their mean DAS₂₈ score was 3.27 (± 0.90) and the mean CRP level 8.59mg/l (± 3.15).

4.1.1 DEMOGRAPHIC BACKGROUND

The anthropometric data was affected as the subjects in the HCG that were excluded were the heavier ones, leading to a significantly higher body mass index (BMI) in the RAG (MWU=469.5, $p < 0.001$) as illustrated in Table 4.1.

Table 4.1: Descriptive background data of the HCG and RAG

	HCG (n=39)				RAG (n=45)				MWU
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	p
BMI	24.52	3.89	23.56	4.14	28.74	5.46	28.52	7.5	<0.001**
Age	44.53	7.51	45.17	11.41	46.47	7.94	47.08	12.59	0.258

SD Standard deviation
IQR Interquartile range

** p<0.01

BMI has been reported to be a confounding factor in analysing HRV data⁽²⁾. We therefore assessed BMI as a possible covariate. To assess the effect of BMI, the same battery of analyses as explained in Chapter 3, Table 3.5 (page 102), was performed. BMI was ruled out as covariate for both supine and stress values and excluded from further statistical analyses of the HRV parameters.

4.1.2 HRV

Instead of reporting group differences based on the In-transformed univariate ANOVA results (i.e. the tests of between-subjects effects of the MANOVA) which may complicate interpretation, non-parametric Mann Whitney U-tests (MWU) were performed on the original variables instead. The descriptive statistics and the MWU-test p-values for the HRV parameters in the supine and stress position can be observed in Tables 4.2 and 4.3. These results corresponded with those of the MANOVA using the In-transformation, i.e. statistically significant differences are observed between the HCG and the RAG for all the HRV variables except for HRSD (supine), LF(nu) (stress), HF(nu) (stress) and LF/HF (stress).

4.1.2.1 Variables in the supine (resting) position

In Table 4.2 the mean, standard deviation of the mean, and median of the HRV indicator values in the supine position, for the HCG and the RAG, are reported. The level of significance of differences found between the HCG and RAG is also displayed. All indicators, except HRSD, showed significant differences ($p \leq 0.01$) between the two groups. The RAG not only showed significant lower variability, but the autonomic balance indicators [LF(nu), HF(nu), LF/HF] also indicated significant lower vagal cardiac control.

Table 4.2: Descriptives and MWU test results of HRV indicators in the supine position for the HCG and the RAG

HRV indicator	HCG (n=39)				RAG (n=45)				MWU
	Mean	Standard Deviation	Median	IQR	Mean	Standard Deviation	Median	IQR	p
RR(s)	0.97	0.17	0.93	0.93	0.79	0.10	0.77	0.10	<0.001**
RRSD(s)	0.04	0.03	0.03	0.031	0.02	0.01	0.02	0.01	0.002**
HR(bpm)	63.50	10.25	64.25	14.97	77.56	9.37	77.90	9.91	<0.001**
HRSD(bpm)	2.53	1.05	2.62	1.57	2.40	0.82	2.33	1.17	0.788
RMSSD(ms)	42.59	38.70	29.40	42.10	20.30	14.68	14.70	15.20	<0.001**
pNN50(%)	18.88	24.13	7.80	28.50	6.73	12.97	0.50	4.20	0.002**
SD1(ms)	30.33	27.48	20.90	30.00	14.49	10.40	10.50	10.80	<0.001**
SD2(ms)	59.01	31.42	49.50	40.00	39.33	16.53	36.70	20.60	0.002**
LF(ms ²)	372.92	478.67	175.00	310.00	125.27	149.01	65.00	123.00	<0.001**
HF(ms ²)	442.44	759.88	141.00	285.00	141.51	303.44	31.00	104.00	<0.001**
LF(nu)	51.63	19.29	54.10	25.30	64.44	20.42	64.60	34.10	0.010**
HF(nu)	49.39	28.15	47.10	24.10	32.50	21.11	29.80	37.10	0.003**
LF/HF	1.66	1.64	1.15	1.01	4.97	6.48	2.50	4.92	0.002**

IQR Interquartile range bpm beats per minute ms² milliseconds, squared
 S seconds ms milliseconds nu normalised units
 % percentage ** $p \leq 0.01$

In the supine position all variables assessing parasympathetic variability were significantly lower for the RAG [RMSSD, pNN50, SD1, HF(ms²)] (Figures 4.1 and 4.2).

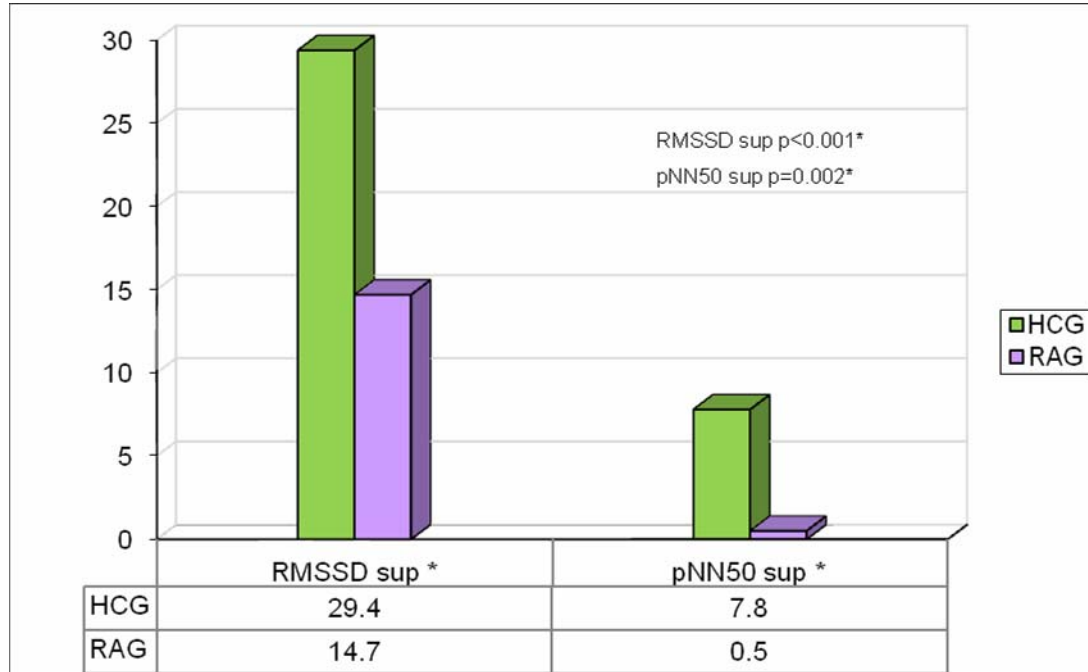


Figure 4.1: Medians of RMSSD supine and pNN50 supine in the HCG and RAG

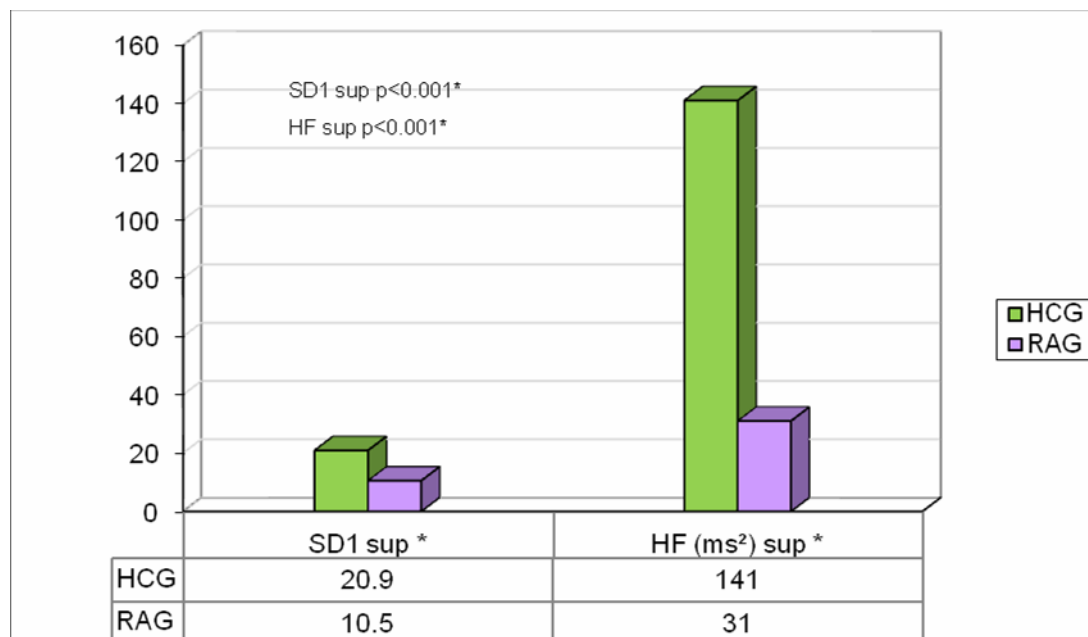


Figure 4.2: Medians of SD1 supine and HF(ms²) supine in the HCG and RAG

Variables assessing HRV indicators influenced by both the sympathetic and parasympathetic branches of the autonomic nervous system [RR, RRSD, HRSD, SD2, LFms²] also showed statistically significant lower values for the RAG, except for HRSD (Figures 4.3 and 4.4).

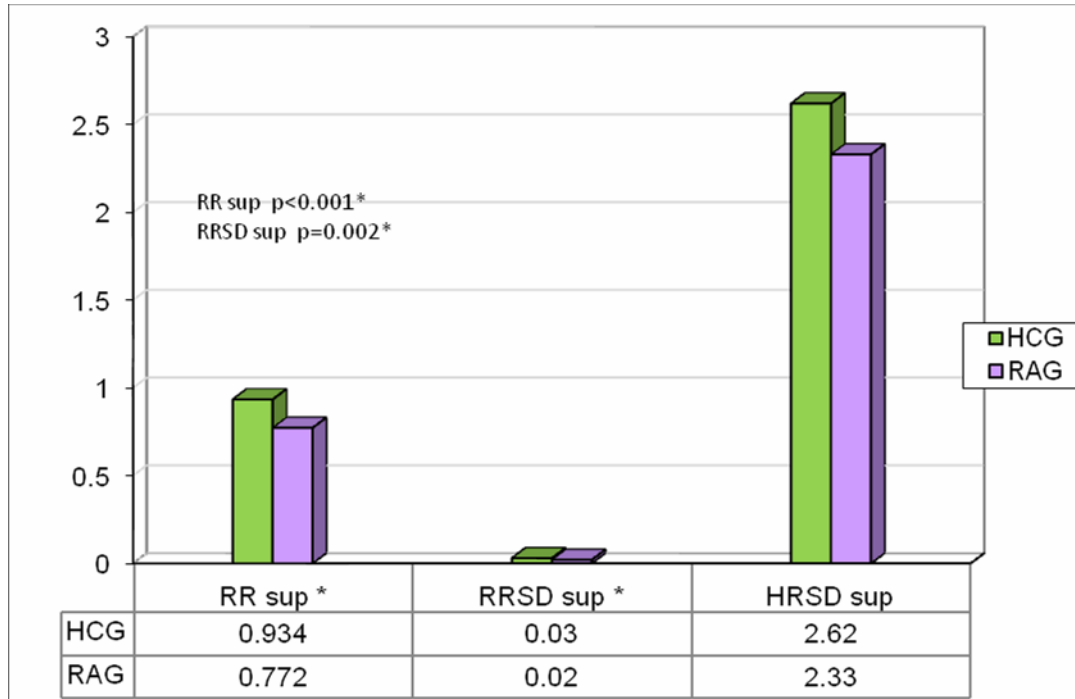


Figure 4.3: Medians of RR supine, RRSD supine and HRSD supine in the HCG and RAG

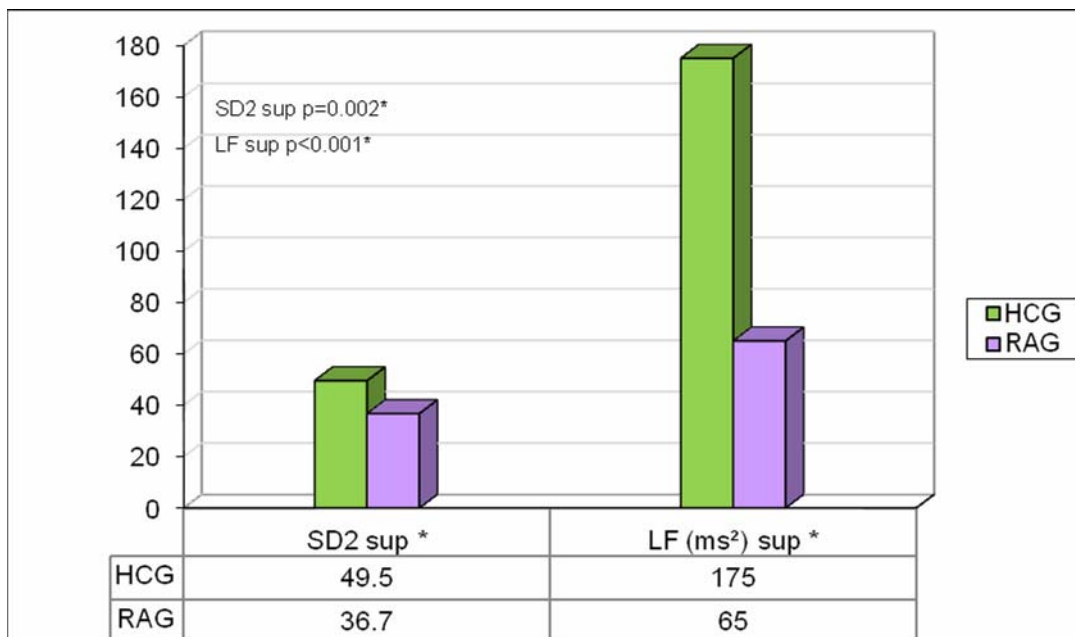


Figure 4.4: Medians of SD2 supine and LF(ms²) supine in the HCG and RAG

Indicators for autonomic balance [LF(nu), HF(nu), LF/HF] showed statistical significant differences with the LF(nu) and LF/HF being higher for the RAG, but the HF(nu) being higher for the HCG (Figure 4.5).

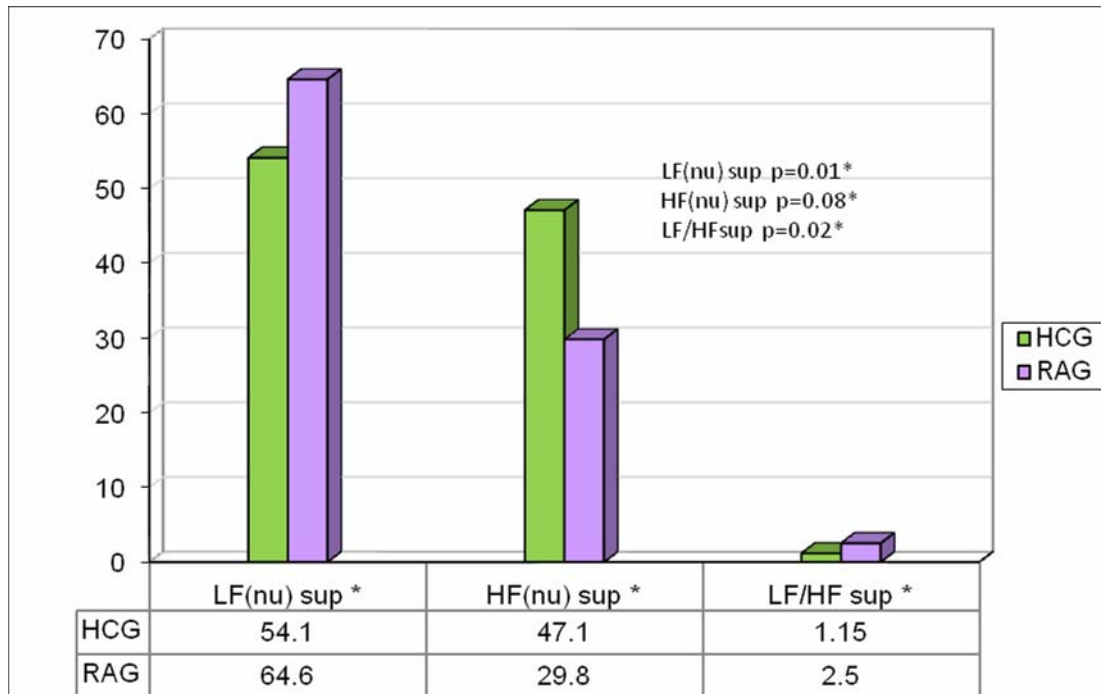


Figure 4.5: Medians of LF(nu) supine, HF(nu) supine and LF/HF supine in the HCG and RAG

4.1.2.2 Variables in the standing (stress) position

In Table 4.3 the mean, standard deviation of the mean, and median values of the standing HRV indicators, for the HCG and the RAG are displayed. The level of significance in differences found between the two groups is also reported. Most standing HRV indicators showed highly significant differences between RAG and HCG ($p \leq 0.01$). All indicators, except the ANS balance indicators [LF(nu), HF(nu), LF/HF] showed significant lower variability for RAG in the standing position.

Table 4.3: Descriptives and MWU test of HRV indicators in the standing position for the HCG and the RAG

HRV Indicator	HCG (n=39)				RAG (n=45)				MWU
	Mean	Standard deviation	Median	IQR	Mean	Standard deviation	Median	IQR	P
RR(s)	0.76	0.12	0.75	0.13	0.67	0.08	0.67	0.09	<0.001**
RRSD(s)	0.03	0.02	0.03	0.02	0.02	0.01	0.02	0.01	<0.001**
HR(bpm)	81.18	11.91	80.18	13.31	90.40	10.78	89.45	12.12	<0.001**
HRSD(bpm)	4.84	1.84	4.64	2.15	3.43	1.40	3.38	1.72	<0.001**
RMSSD(ms)	21.31	19.09	17.10	14.60	14.12	9.10	12.00	13.20	0.011*
pNN50(%)	3.40	5.36	1.30	3.10	1.80	5.17	0.20	1.50	0.001**
SD1(ms)	15.62	13.56	12.50	10.20	10.16	6.50	8.80	9.30	0.006**
SD2(ms)	80.19	29.08	79.50	42.70	48.19	25.90	41.10	36.70	<0.001**
LF(ms ²)	544.59	552.91	333.00	450.00	145.02	177.47	88.00	155.00	<0.001**
HF(ms ²)	166.69	568.10	51.00	98.00	47.94	99.29	16.00	38.00	0.001**
LF(nu)	84.07	11.91	85.10	12.20	79.80	13.48	83.00	21.80	0.169
HF(nu)	15.29	11.82	13.00	10.90	22.01	24.22	16.10	18.40	0.311
LF/HF	11.50	13.03	6.60	7.02	10.17	13.00	6.50	8.77	0.551

IQR	Interquartile range	ms ²	milliseconds, squared
s	seconds	nu	normalised units
bpm	beats per minute	**	p<0.01
ms	milliseconds	*	p<0.05
%	percentage		

In the standing position the variables influenced only by the parasympathetic branch [RMSSD, pNN50, SD1, HF(ms^2)] were all significantly lower for the RAG (Figures 4.6 and 4.7).

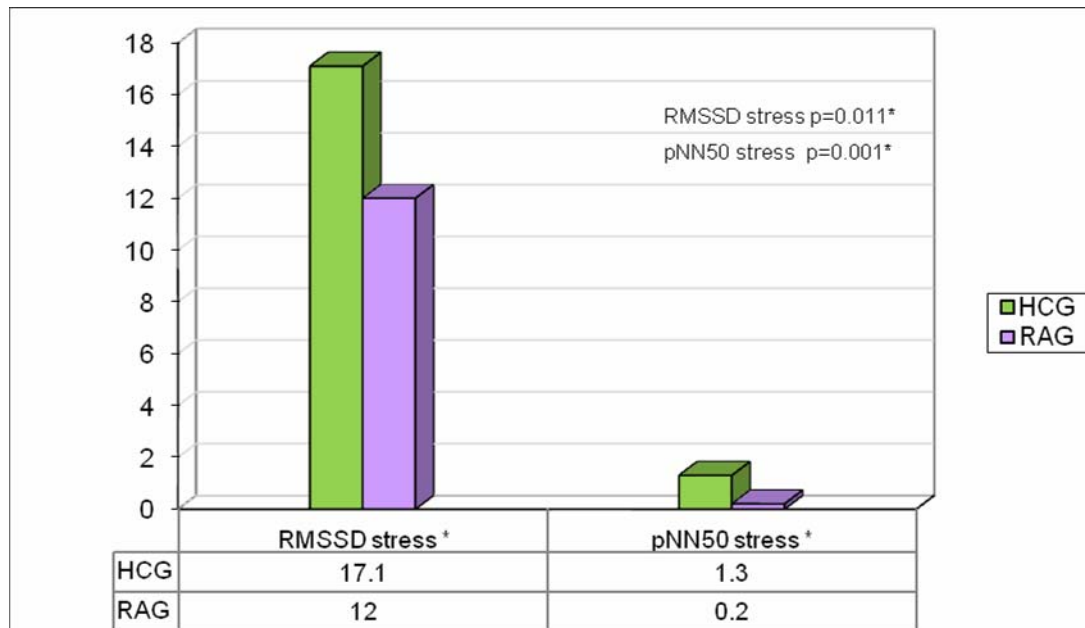


Figure 4.6: Medians of RMSSD stress and pNN50 stress in the HCG and RAG

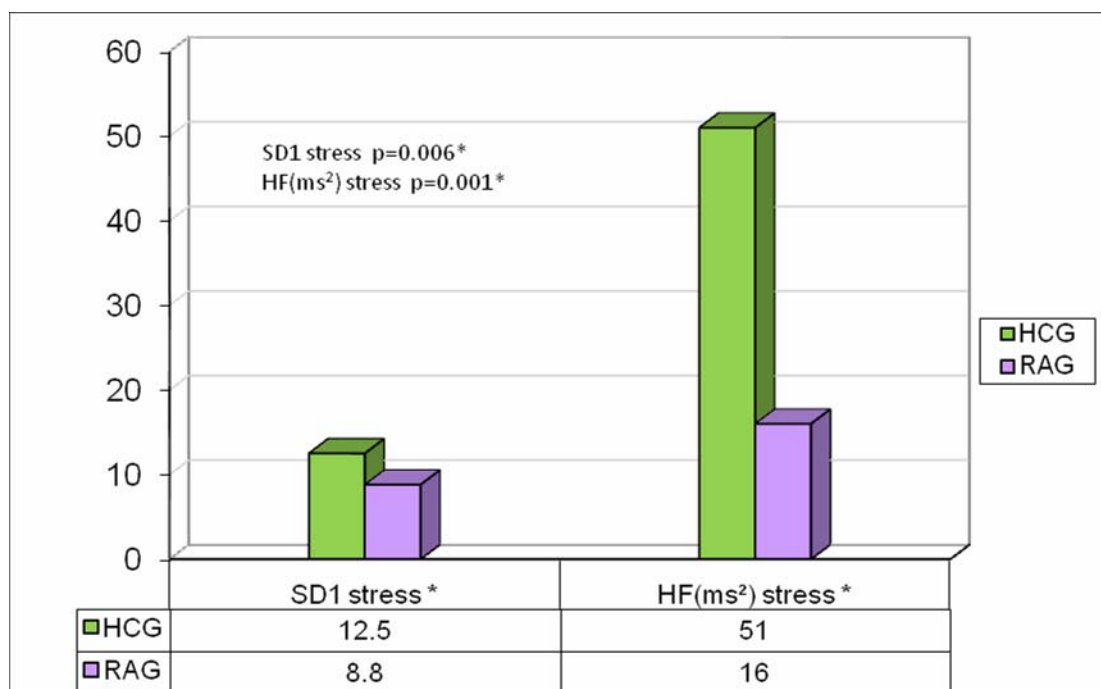


Figure 4.7: Medians of SD1 stress and HF(ms^2) stress in the HCG and RAG

The variables influenced by both the sympathetic and parasympathetic branches of the ANS were also significantly lower in the RAG [RR, RRSD, HRSD, SD2, LF(ms²)] (Figures 4.8 and 4.9).

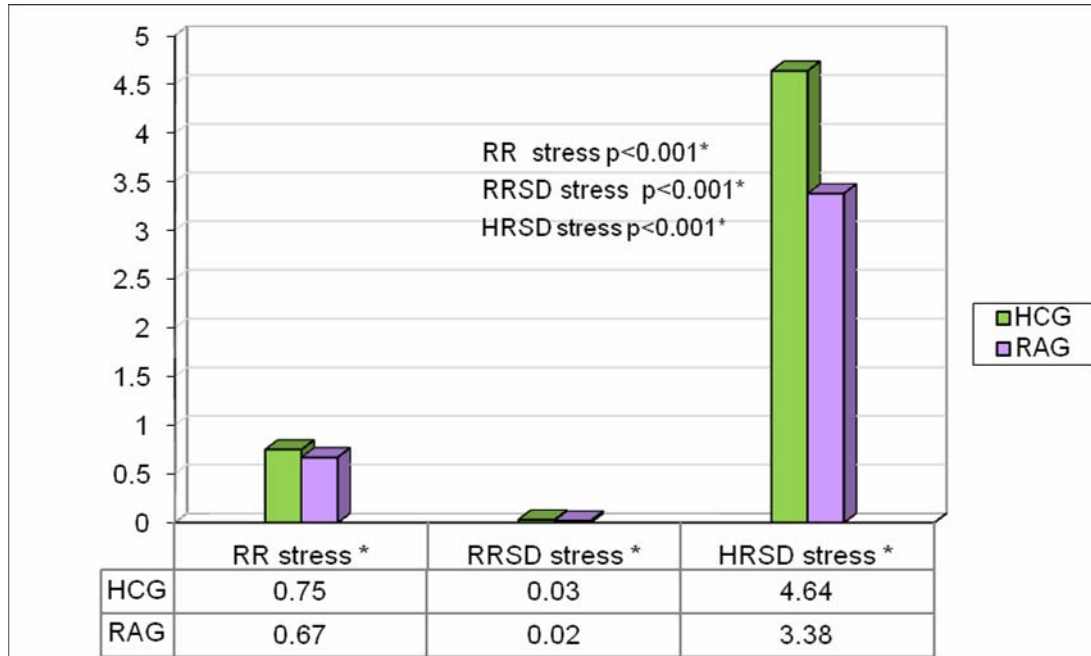


Figure 4.8: Medians of RR stress, RRSD stress and HRSD stress in the HCG and RAG

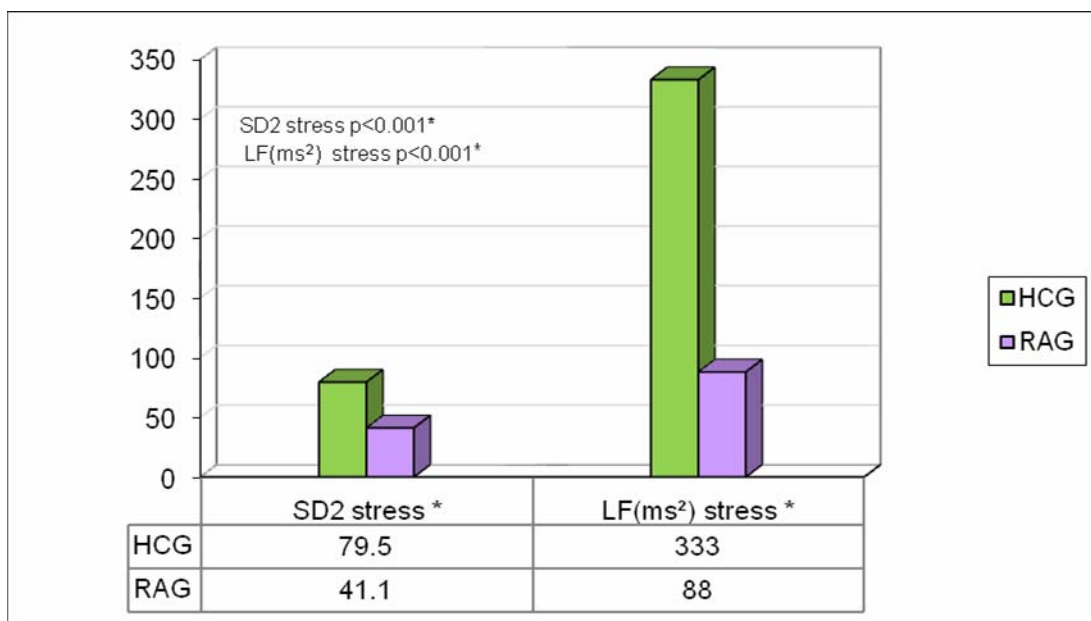


Figure 4.9: Medians of SD2 stress and LF(ms²) stress in the HCG and RAG

The indicators for autonomic balance [HF(nu), LF(nu) and LF/HF] did not show statistical significant differences between the two groups in the standing (stress) position.

4.1.2.3 Heart rate and heart rate response

The RAG had a significant higher resting heart rate compared to the HCG in both the supine and standing position, but observing the HR difference (rising from supine to standing) the RAG showed a significant lower delta compared to the HCG ($p=0.003$) (Figure 4.10).

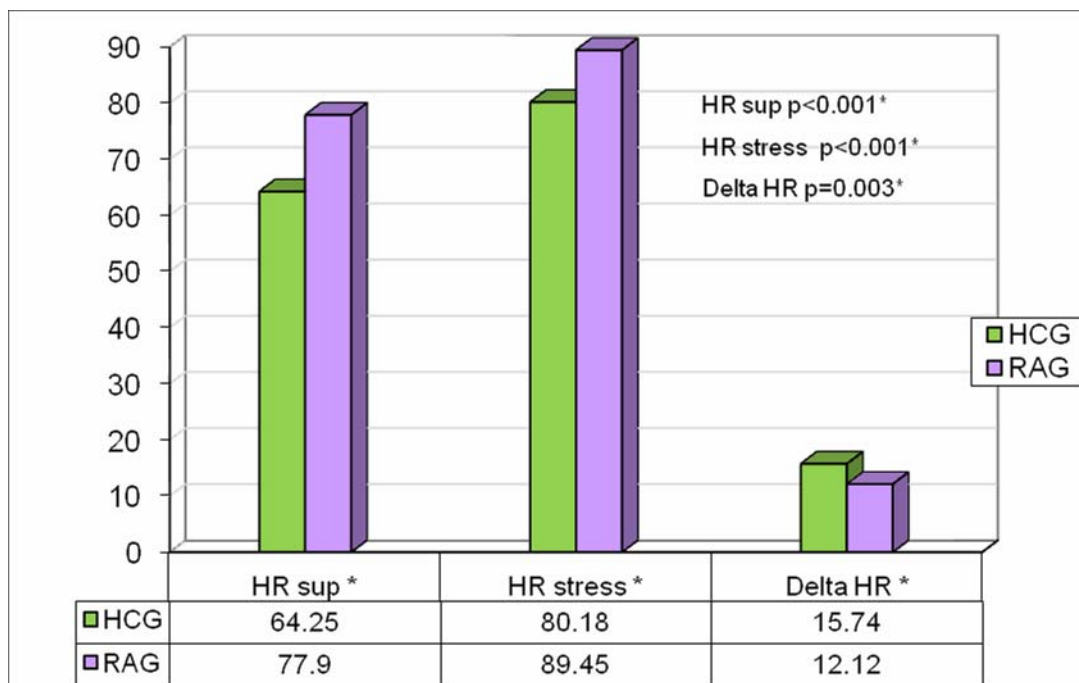
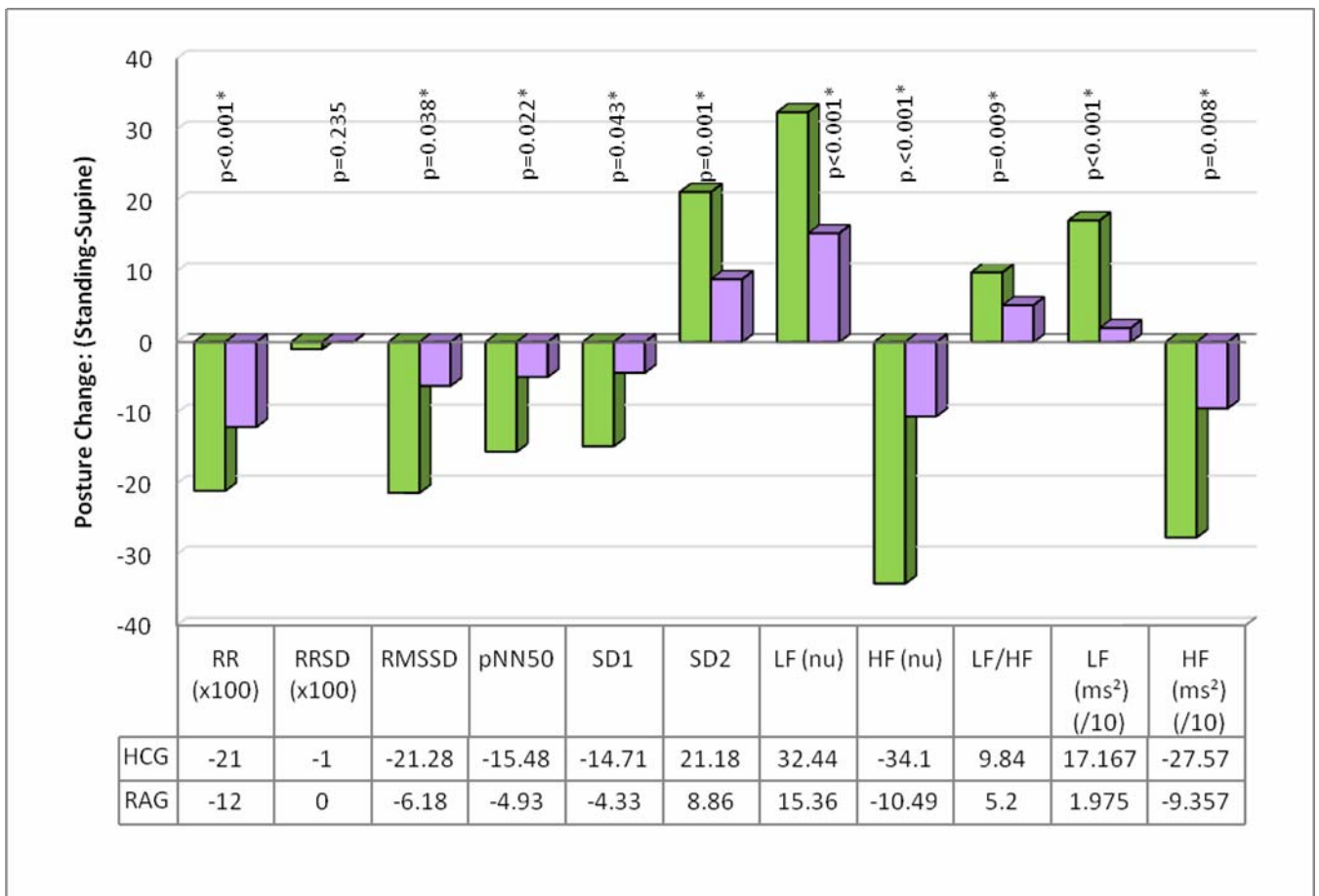


Figure 4.10: Medians of HR supine and stress in the HCG and RAG

4.1.2.4 Postural change

Calculating the influence of postural change on HRV (i.e. mean standing HRV indicator value minus the mean supine HRV indicator value) for both groups, one can appreciate that the RAG had a statistical significant lower response for all measured indicators, except RRSD, as shown in Figure 4.11. In order to represent the values on the same scale, RR and RRSD were multiplied by 100; and LF(ms²) and HF(ms²) were divided by 10.



*p<0.05

Figure 4.11: Comparison of posture change for the groups
Formula: Delta = mean standing value minus mean supine value

4.2 PHASE 2: RHEUMATOID ARTHRITIS EXERCISE GROUP (RAE) VERSUS RHEUMATOID ARTHRITIS CONTROL GROUP (RAC)

The parameters reported on, are clustered as follows:

4.2.1 Demographic background

4.2.2 Heart Rate Variability

4.2.3 Disease Activity Score (DAS₂₈)

Health Assessment Questionnaire (HAQ)

Visual Analogue Scale (VAS)

4.2.4 Functional parameters

The same colours displayed above, are used at the beginning of the report on that specific parameter to distinguish different parameters, e.g. HRV burgundy, DAS lilac, etc.

The results in PHASE 2 (4.2.2 to 4.2.4) are discussed in the following order:

A) Descriptive statistics to summarise the information

B) Analyses performed to assess whether there is any initial bias between the two groups before the intervention (exercise) is started, i.e. pre-RAE vs. pre-RAC

C) Analyses performed to determine if there were changes within each group after study completion, i.e. post-values minus pre-values for each of the two groups (delta)

D) Analyses performed to evaluate whether the changes (delta) at study completion favoured the RAE group

Tables in the different sections are displayed in the colours illustrated above, i.e. Section A (Descriptive statistics) orange, Section B (Initial bias) yellow, etc.

At study onset, RAE consisted of 24 subjects and RAC of 22. In RAE, 5 (20.83%) of the subjects did not complete the study, versus 4 (18.18%) in RAC. Reasons for not completing the study included difficulty to conform to time and frequency of training (4 from the RAE group), moved to another town (1 from the RAE group), not available for post-intervention measurements due to other commitments (2 from the

RAC group) and loss of interest (2 from the RAC group). Data analyses were only performed on those subjects who completed the study (RAE 19, RAC 18), because the study focuses on the effect of an intervention and we did not want to bias results by including subjects not completing the study. This sample size is similar to the average sample size of clinical studies evaluating HRV modification via exercise intervention⁽³⁾. Routledge reported 19 published articles with the average sample size calculated as 21.2 (± 10.6).

4.2.1 Demographic background

Information on age, anthropometric data, disease duration, medication used with regards to RA and presence of autoantibodies can be seen in Table 4.4. Subjects were required to stay on the same medication regime for the duration of the study and no intramuscular or intra-articular corticosteroid injections were allowed.

Table 4.4: Demographic information on RAE and RAC

Descriptor		RAE (n=19)	RAC (n=18)
Mean age (years)		46.81 (±9.23)	47.08 (±7.05)
Mean height (meters)		1.64 (±0.07)	1.65 (±0.08)
Mean weight (kilograms)		69.9 (±11.5)	80.30 (±16.18)
Mean BMI (mean)		25.98 (±3.53)	29.52 (±6.04)
Mean disease duration (years)		4.53 (±0.90)	3.98 (±1.10)
DAS ₂₈		3.29 (±0.72)	3.25 (±1.08)
HAQ		0.48 (±0.56)	0.52 (±0.65)
RA Medication			
Prednisone*		10	10
Disease modifying drugs	Methotrexate	18	17
	Sulphasalazine	0	1
	Chloroquine	4	2
	Leflunomide	3	2
Non-steroidal anti-inflammatory drugs [‡]		18	17
Biologics [◇]		4	6
Antibodies			
Positive Rheumatoid Factor		17	15
Positive ACPA [⊕]		9	10
BMI	Body mass index		
DAS ₂₈	Disease Activity Score		
HAQ	Health Assessment Questionnaire		
*	Maximum dose of Prednisone allowed was 10mg per day		
‡	Only therapeutic doses allowed		
◇	Biologics: Medication made from living organisms, used as a therapeutic agent e.g. Infliximab, Etanercept, Adalimumab		
⊕	Anti-citrullinated peptide antibodies		

As explained in section 4.1.1 BMI has previously been reported as a confounding factor. From the median test, the medians of the BMI were the same across the two groups (p=0.127) although evidence exists that the distribution of the BMI was not

the same across the two groups (MWU $p=0.0496$) (see Figure 4.12). BMI was therefore not further assessed as a possible covariate.

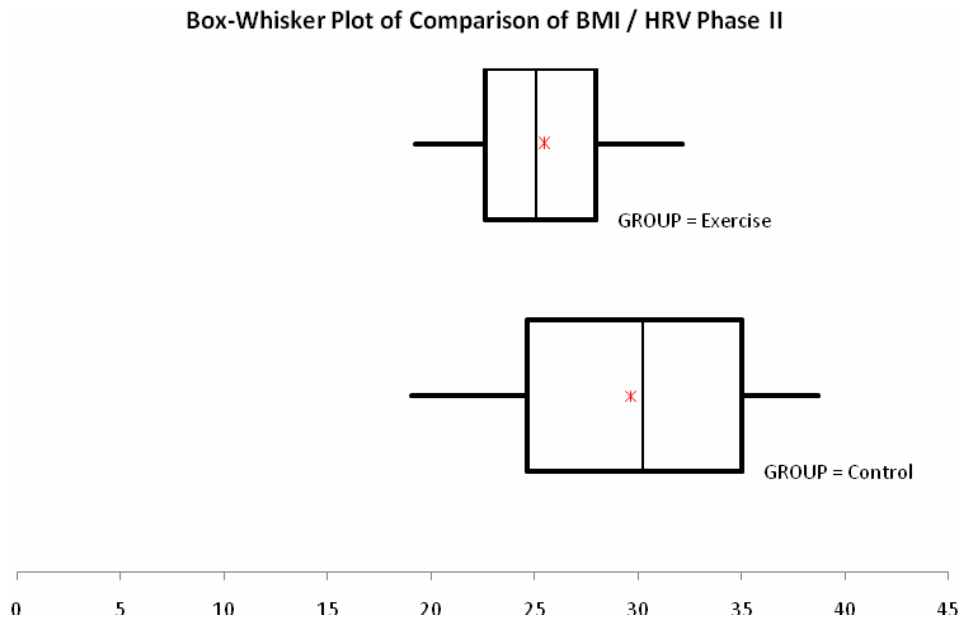


Figure 4.12: Box-Whisker plot of comparison of BMI

4.2.2 Heart Rate Variability

4.2.2(A) DESCRIPTIVE STATISTICS

The descriptive statistics for both groups are summarized in Table 4.5 (pre-intervention variables) and Table 4.6 (post-intervention variables). HRV records were excluded if the total record was less than 60 seconds or if more than 20% of the intervals were affected by artefacts⁽¹⁾.

In Table 4.5 the mean, standard deviation of the mean, and median values of the pre-intervention HRV indicators, in the supine and standing position, for RAE and RAC are reported.

Table 4.5: Descriptive statistics for RAE and RAC pre-intervention

Indicator	RAE (n=19)				RAC (n=18)			
	Mean	Standard Deviation	Median	IQR	Mean	Standard Deviation	Median	IQR
Supine (Resting)								
RR(s)	0.75	0.07	0.76	0.11	0.83	0.10	0.79	1.16
RRSD(s)	0.02	0.01	0.02	0.01	0.02	0.01	0.02	0.02
HR(bpm)	80.60	8.21	79.17	11.70	73.36	7.89	76.12	13.56
HRSD(bpm)	2.29	0.84	2.38	1.38	2.53	0.79	2.30	1.16
RMSSD(ms)	16.50	10.65	12.20	9.70	25.94	17.25	18.15	32.10
pNN50(%)	3.26	7.87	0.00	2.20	11.46	16.98	1.70	30.50
SD1(ms)	11.78	7.55	8.70	6.85	18.49	12.22	13.00	22.78
SD2(ms)	32.66	12.61	29.90	13.10	46.33	18.53	41.00	25.55
LF(ms ²)	60.41	49.58	46.00	56.00	207.33	202.01	147.50	182.00
HF(ms ²)	34.35	42.67	13.00	42.00	285.83	440.94	60.00	396.00
LF(nu)	66.87	17.76	62.50	33.10	58.03	18.92	59.75	37.30
HF(nu)	30.26	17.39	36.10	30.85	38.41	21.24	31.85	43.83
LF/HF	4.19	4.12	1.70	5.90	2.86	2.31	2.23	3.70
Stress (Standing)								
RR(s)	0.65	0.08	0.67	0.07	0.70	0.07	0.70	0.07
RRSD(s)	0.02	0.01	0.01	0.01	0.02	0.01	0.02	0.01
HR(bpm)	93.87	13.05	90.19	9.77	86.31	7.87	86.08	9.12
HRSD(bpm)	2.69	1.09	2.49	1.90	4.21	1.35	4.07	1.66
RMSSD(ms)	9.51	5.63	7.50	7.63	18.93	10.43	19.25	10.33
pNN50(%)	0.20	0.48	0.00	0.01	3.95	7.77	1.20	2.90
SD1(ms)	6.85	4.02	5.40	5.45	13.65	7.41	13.80	7.43
SD2(ms)	33.54	16.61	28.35	14.88	63.18	29.32	57.80	27.58
LF(ms ²)	59.38	51.52	38.50	69.00	250.78	232.84	174.50	263.00
HF(ms ²)	10.32	11.99	5.00	13.50	94.06	144.60	38.00	74.30
LF(nu)	84.71	8.98	86.30	14.43	75.23	13.28	73.85	24.83
HF(nu)	18.16	21.22	12.10	14.88	27.62	29.70	21.90	25.13
LF/HF	14.76	18.70	7.55	13.10	5.76	4.61	3.68	7.61
IQR	Interquartile range		%	percentage				
s	seconds		ms ²	milliseconds, squared				
bpm	beats per minute		nu	normalised units				
ms	milliseconds							

In Table 4.6 the mean, standard deviation of the mean, and median values of the post-intervention HRV indicators, in the supine and standing position, are displayed for both groups.

Table 4.6: Descriptive statistics for RAE and RAC post-intervention

Indicator	RAE (n=19)				RAC (n=18)			
	Mean	Standard Deviation	Median	IQR	Mean	Standard Deviation	Median	IQR
Supine (Resting)								
RR(s)	0.78	0.09	0.76	0.20	0.81	0.10	0.78	0.18
RRSD(s)	0.02	0.01	0.02	0.01	0.03	0.02	0.03	0.01
HR(bpm)	77.73	9.03	78.90	19.84	75.81	9.48	77.40	17.68
HRSD(bpm)	2.45	0.90	2.11	1.17	3.26	1.12	3.00	1.83
RMSSD(ms)	17.67	15.59	15.30	9.20	24.70	16.18	20.25	17.70
pNN50(%)	4.11	14.05	0.00	0.50	5.34	8.92	2.10	5.60
SD1(ms)	12.53	11.04	10.90	6.60	14.70	8.22	13.65	11.00
SD2(ms)	34.91	14.17	31.20	15.10	46.79	20.05	39.30	30.30
LF(ms ²)	79.20	129.72	34.00	100.00	260.64	295.44	177.09	349.73
HF(ms ²)	46.01	118.91	15.00	28.00	172.32	239.08	82.55	130.30
LF(nu)	52.72	35.91	69.20	85.80	50.05	30.85	58.85	57.70
HF(nu)	36.62	31.59	24.10	57.10	42.13	26.78	37.20	33.90
LF/HF	3.55	3.46	2.95	6.13	2.28	2.16	1.70	2.39
Stress (Standing)								
RR(s)	0.68	0.09	0.71	0.17	0.66	0.11	0.67	0.18
RRSD(s)	0.02	0.02	0.02	0.02	0.04	0.02	0.03	0.02
HR(bpm)	89.69	12.72	85.30	24.19	94.47	20.12	89.14	24.24
HRSD(bpm)	3.29	1.69	2.80	2.73	5.21	3.06	4.26	3.91
RMSSD(ms)	12.03	8.49	8.70	10.40	13.13	6.29	13.30	11.90
pNN50(%)	1.27	3.47	0.00	0.60	0.92	1.14	0.50	1.40
SD1 (ms)	8.54	6.05	6.20	7.40	9.34	4.45	9.60	8.30
SD2(ms)	39.73	21.74	35.30	21.20	51.56	21.77	48.70	23.70
LF(ms ²)	101.23	94.97	86.50	137.00	229.43	175.89	194.00	226.00
HF(ms ²)	12.67	14.58	5.50	20.50	58.2	77.64	22.00	75.20
LF(nu)	79.67	30.59	90.85	15.60	75.23	29.10	83.10	21.80
HF(nu)	16.83	24.76	6.20	13.90	16.75	13.53	14.70	17.20
LF/HF	18.59	15.98	14.87	26.43	9.88	9.43	5.82	10.99
IQR	Interquartile range			%	percentage			
S	seconds			ms ²	milliseconds, squared			
bpm	beats per minute			nu	normalised units			
ms	milliseconds							

4.2.2(B) ASSESSMENT FOR INITIAL BIAS BETWEEN THE TWO GROUPS

Tests for normality were performed and most variables needed transformation, however, a logarithmic transformation cannot be executed on zero values, hence the MANOVA could not be conducted. As the analyses on the data in section 4.2.3 (DAS, HAQ, VAS) demonstrated similar results for transformed and untransformed variables, only MWU tests were performed to assess for initial bias between groups. In Table 4.7 the pre-intervention mean, standard deviation of the mean, and median values of variables displaying initial bias, are shown. Evidence of bias existed for some variables in the supine and most variables in the stress positions between RAE and RAC. At baseline RAC had significantly higher HRV compared to RAE, for some of the supine variables, and most of the standing variables. RAE did not show significant higher variability than RAC for any variable pre-intervention, i.e. RAC was favoured in all instances.

Table 4.7: Values of variables displaying initial bias

Indicator	RAE				RAC				p	Group favoured
	Mean	SD	Median	IQR	Mean	SD	Median	IQR		
Supine (Resting)										
RR(s)	0.75	0.07	0.76	0.11	0.83	0.10	0.79	0.16	0.045*	RAC
HR(bpm)	80.60	8.21	79.17	11.70	73.36	7.89	76.12	13.56	0.049*	RAC
pNN50(%)	3.26	7.87	0.00	2.20	11.46	16.98	1.70	30.05	0.022*	RAC
LF(ms ²)	60.41	49.58	46.00	56.00	207.33	202.01	147.50	182.00	0.002**	RAC
Stress (Standing)										
RRSD(s)	0.02	0.01	0.01	0.01	0.02	0.01	0.02	0.01	0.006**	RAC
RMSSD(ms)	9.51	5.63	7.50	7.63	18.93	10.43	19.25	10.33	0.002**	RAC
pNN50(%)	0.20	0.48	0.00	0.01	3.95	7.77	1.20	2.90	0.001**	RAC
SD1(ms)	6.85	4.02	5.40	5.45	13.65	7.413	13.80	7.43	0.002**	RAC
SD2(ms)	33.54	16.61	28.35	14.88	63.18	29.32	57.80	27.58	0.001**	RAC
LF(ms ²)	59.38	51.52	38.50	69.00	250.78	232.84	174.50	263.00	<0.001**	RAC
HF(ms ²)	10.32	11.99	5.00	13.50	94.06	144.60	38.00	74.30	<0.001**	RAC
LF(nu)	84.71	8.98	86.30	14.43	75.23	13.28	73.85	24.83	0.042*	RAC
LF/HF	14.76	18.70	7.55	13.10	5.76	4.61	3.68	7.61	0.020*	RAC
SD	Standard deviation			ms ²	Milliseconds, squared					
IQR	Interquartile range			ms	Milliseconds					
s	seconds			nu	normalised units					
bpm	beats per minute			*	p<0.05					
%	percentage			**	p<0.01					

4.2.2(C) WITHIN GROUP ANALYSES

Wilcoxon signed rank tests were performed to evaluate any changes that occurred within each group from the start of the intervention to the completion. In Tables 4.8 and 4.9 the changes that occurred, as well as the level of significance, the effect size and whether it was an improvement or deterioration are reported for the RAE and RAC groups respectively. A non-parametric statistical test was used to determine the significance of the difference between pre- and post-intervention; hence confidence intervals for the difference between the means are not reported. Due to the fact that some records were excluded as explained in 4.2.2.A, different means would be obtained for each variable depending on the data availability. This will complicate the reporting of such intervals. These intervals were however calculated and are reported in [Appendix 11 -T08165 Confidence Intervals.docx](#) for the interested reader.

The RAE group showed statistical significant changes for RRSD in the supine position and for RRSD and pNN50 in the stress position. Although not statistically significant at the specified 5% level of significance, there was moderate evidence ($\alpha < 0.10$) of change in many variables as is displayed in Table 4.8. It should be borne in mind that the power of the tests is low due to relatively small sample sizes.

The RAC group showed statistical significant changes for RRSD (supine), RRSD (stress), RMSSD (stress), pNN50 (stress), SD1 (stress) and LF/HF (stress). These variables are displayed in Table 4.9. The variables that changed significantly, amounted to a medium to large effect⁽⁴⁾, and within RAE showed mostly an improvement, but within RAC mostly a deterioration.

Table 4.8: HRV variables that showed a change from pre- to post-intervention in RAE

Indicator	Mean pre-value	Mean post-value	Mean difference	↑↓	Median pre-value	Median post-value	p	Effect size	↑↓	I/D
Supine (Resting)										
RR(s)	0.75	0.78	0.03	↑	(0.758*) 0.76	(0.762*) 0.76	0.096°	0.34	↑	I
RRSD(s)	0.02	0.02	0.00	~	(0.017*)0.02	(0.022*) 0.02	0.022*	0.52	↑	I
LF(nu)	66.87	52.72	-14.15	↓	62.50	69.20	0.087°	0.35	↑	D
Stress (Standing)										
RR(s)	0.65	0.68	0.03	↑	0.67	0.71	0.082°	0.36	↑	I
RRSD(s)	0.02	0.02	0.00	~	0.01	0.02	0.002**	0.74	↑	I
HR(bpm)	93.87	89.69	-4.18	↓	90.19	85.30	0.087°	0.35	↓	I
RMSSD(ms)	9.51	12.03	2.52	↑	7.50	8.70	0.078°	0.37	↑	I
pNN50(%)	0.20	1.27	1.07	↑	0.00	0.00	0.014*	0.57	~	~
SD1(ms)	6.85	8.54	1.69	↑	5.40	6.20	0.087°	0.35	↑	I
SD2(ms)	33.54	39.73	6.19	↑	28.35	35.30	0.087°	0.35	↑	I
LF(ms ²)	59.38	101.23	41.85	↑	38.50	86.50	0.063°	0.40	↑	I
s	seconds	**	p<0.01				°	Reflects true value where rounded off value could be misleading		
bpm	beats per minute	*	p<0.05					I	Improvement on median values	
nu	normalised units	°	p<0.10					D	Deterioration on median values	
ms	milliseconds									
ms ²	milliseconds, squared									

Table 4.9: HRV variables that showed a change from pre- to post-intervention in RAC

Indicator	Mean pre-value	Mean post-value	Mean difference	↑↓	Median pre-value	Median post-value	p	Effect size	↑↓	I/D
Supine (Resting)										
RRSD(s)	0.02	0.03	0.01	↑	0.02	0.03	0.049*	0.41	↑	I
Stress (Standing)										
RRSD(s)	0.02	0.04	0.02	↑	0.02	0.03	0.013*	0.54	↑	I
RMSSD(ms)	18.93	13.13	-5.80	↓	19.25	13.30	0.038*	0.43	↓	D
pNN50(%)	3.95	0.92	-3.03	↓	1.20	0.50	0.035*	0.44	↓	D
SD1(ms)	13.65	9.34	-4.31	↓	13.80	9.60	0.036*	0.44	↓	D
HF(ms ²)	94.06	58.20	-35.86	↓	38.00	22.00	0.094°	0.32	↓	D
HF(nu)	27.62	16.75	-10.87	↓	21.90	14.70	0.071°	0.36	↓	D
LF/HF	5.76	9.88	4.12	↑	3.68	5.82	0.042*	0.42	↑	D
s	seconds									
ms	milliseconds									
%	percentage									
ms ²	milliseconds, squared									
nu	normalised units									
		*	p<0.05							
		°	p<0.10							
		I	Improvement on median values							
		D	Deterioration on median values							

4.2.2(D) DIFFERENCES BETWEEN THE TWO GROUPS AT STUDY COMPLETION

The pre-intervention HRV indicator (baseline data) for both supine and stress variables were subtracted from the post-intervention HRV indicator (study completion) to assess if the exercise intervention had caused changes that favoured any of the two groups. Due to the small samples, and as most variables did not follow a normal distribution, non-parametric MWU analyses were performed. The variables that showed significant changes are displayed in Table 4.10.

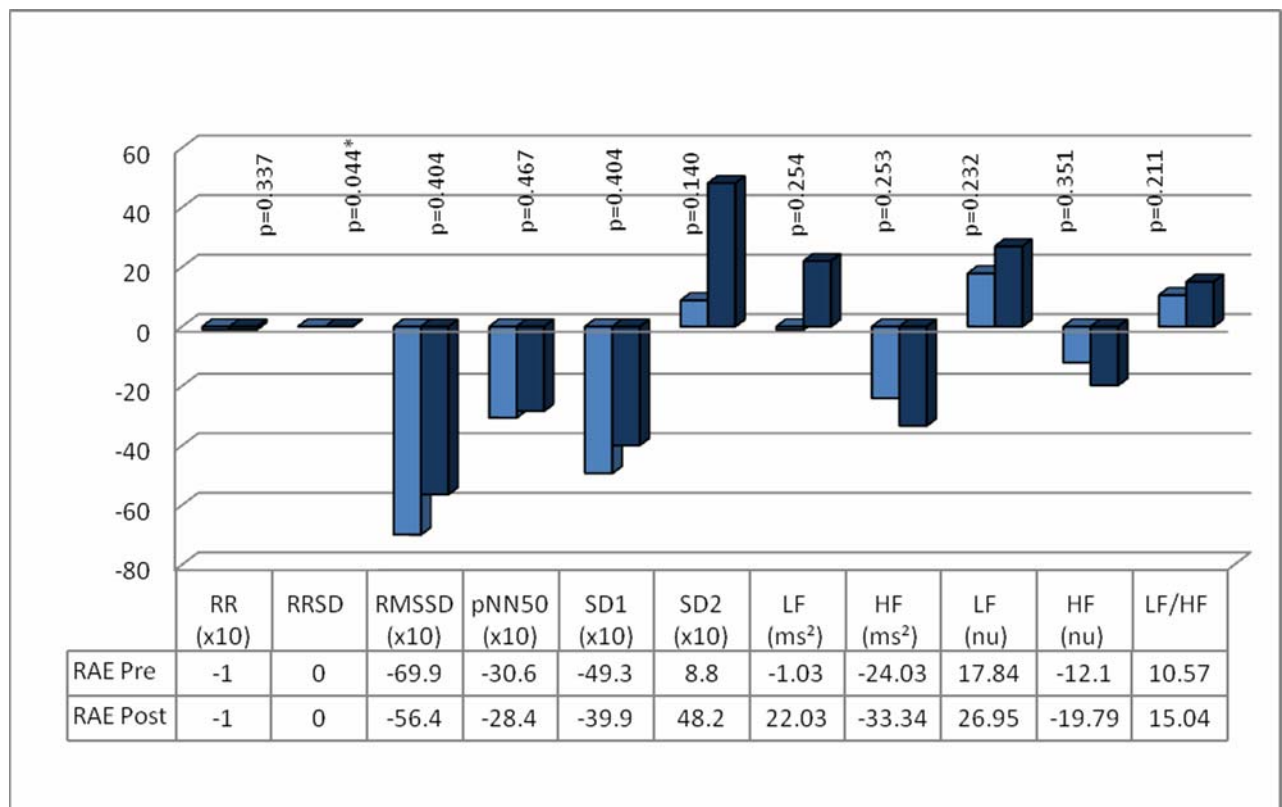
Table 4.10: Variables that showed significant changes between the RAE and RAC groups at study completion

Indicator	Differences		p	Effect size	Group favoured
	RAE	RAC			
Supine (Resting)					
RR(s)	0.07	-0.01	0.022*	0.52	RAE
HR(bpm)	-6.79	1.47	0.029*	0.49	RAE
Stress (Standing)					
RR(s)	0.03	0.00	0.033*	0.47	RAE
HR(bpm)	-6.91	-0.31	0.021*	0.52	RAE
RMSSD(ms)	1.40	-3.90	0.012*	0.59	RAE
pNN50(%)	0.00	-0.20	0.005**	0.66	RAE
SD1(ms)	0.90	-2.80	0.011*	0.59	RAE
SD2(ms)	3.40	-3.40	0.050*	0.42	RAE
s	seconds	%	percentage		
bpm	beats per minute	**	p<0.01		
ms	milliseconds	*	p≤0.05		

Despite the fact that the initial biases were in favour of the control group (Table 4.7), one can appreciate the observation that the significant differences from baseline to study completion are now in favour of the exercise group. The variables that showed significant changes amounted to a medium to large effect⁽⁴⁾.

Postural change

Comparing posture change (i.e. standing value minus supine value) from pre- to post intervention, it is evident that for RAE the frequency domain parameters [LF(ms²), HF(ms²), LF(nu), HF(nu), LF/HF], all changed as anticipated (i.e. increased vagal withdrawal and increased sympathetic influence), but time domain and Poincaré parameters displayed a mixture of outcome, with no change in RR-interval and RRSD, less change in RMSSD, pNN50 and SD1, and a notable improvement in SD2. However, only RRSD showed a significant change (Figure 4.13).

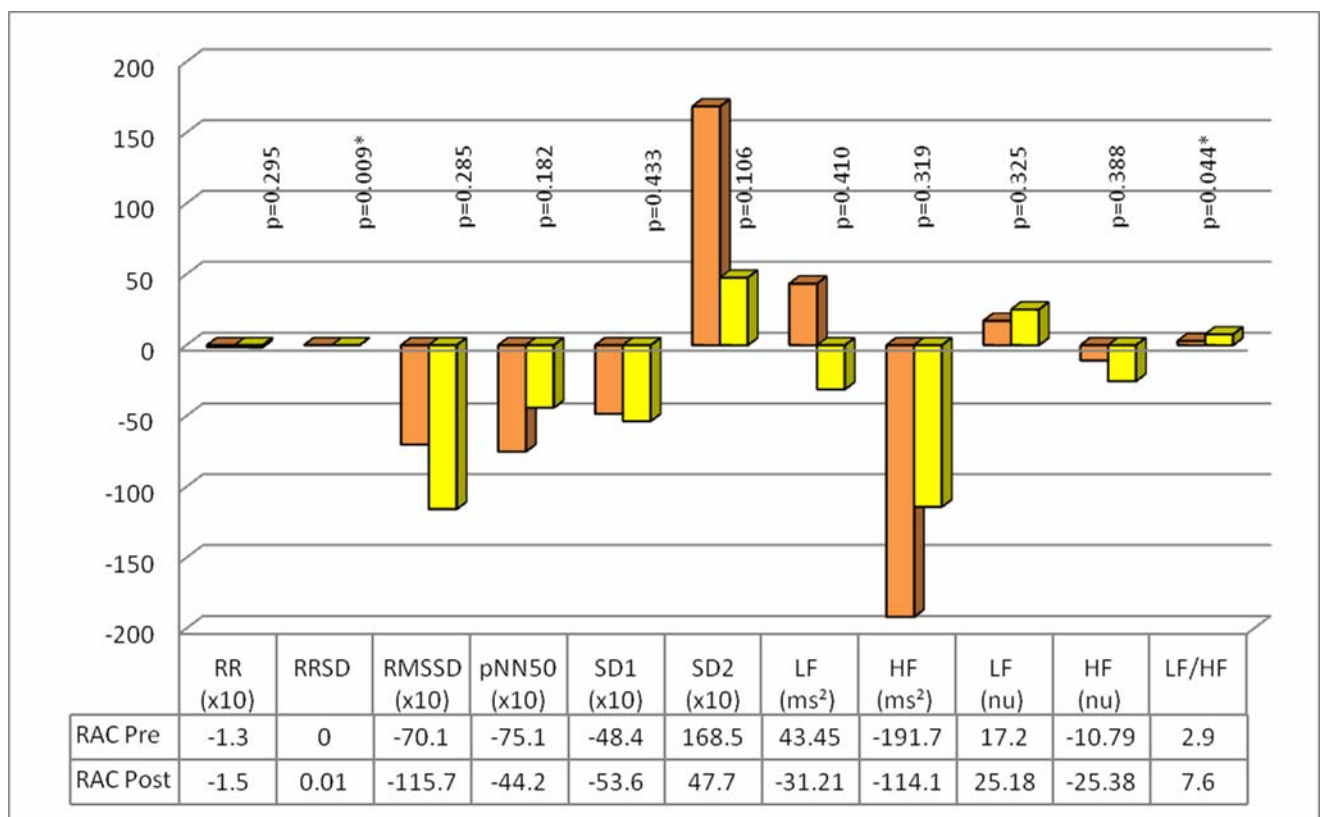


*p<0.05

Figure 4.13: Comparison of the influence of posture change on the HRV indicator values in the RAE group from pre- to post-intervention

Formula: Delta = mean standing value minus mean supine value

Observing RAC the three HRV analysis techniques display a mixture of outcome with the time domain analysis being the most consistent. The RR-interval and RMSSD decreased more, as is expected, but pNN50 decreased less. For Poincaré the vagal withdrawal showed (SD1), but SD2 changed in the wrong direction. Indicators for autonomic balance [LF(nu), HF(nu), LF/HF] changed as expected, but LF(ms²) and HF(ms²) deteriorated (Figure 4.14). RRSD and LF/HF were the only two variables that showed a significant change. In both Figures 4.13 and 4.14 some values were multiplied by 10 in order to get values on a similar scale to be displayed on one graph.



*p<0.05

Figure 4.14: Comparison of the influence of posture change on the HRV indicator values in the RAC group from pre- to post-intervention

Formula: Delta = mean standing value minus mean supine value

4.2.3 DAS₂₈, HAQ and VAS

4.2.3(A) DESCRIPTIVE STATISTICS

The summary statistics of all the parameters are displayed in Table 4.11. The mean, standard deviation of the mean, and median values of the tender joint count, swollen joint count, patient global assessment, physician global assessment, CRP-level, disease activity score, health assessment questionnaire and visual analogue scale, for RAE and RAC are reported.

Table 4.11: Descriptive statistics of the RAE and RAC groups

Indicator	RAE (n=19)				RAC (n=18)			
	Mean	Standard Deviation	Median	IQR	Mean	Standard Deviation	Median	IQR
Pre-intervention								
TJ1	3.05	3.17	2.00	3.00	3.78	2.49	4.00	4.00
SJ1	3.89	2.71	4.00	4.00	3.00	2.88	2.00	3.00
PaGA1	30.68	26.60	26.00	45.00	30.56	23.68	23.50	44.00
PhGA1	22.58	12.21	20.00	22.00	21.33	15.73	14.00	24.00
CRP1	10.07	15.53	3.60	9.10	7.02	10.27	3.05	6.95
DAS1	3.29	0.72	3.32	1.15	3.25	1.08	3.03	1.62
HAQ1	0.48	0.56	0.35	0.60	0.52	0.65	0.20	0.93
VAS1	46.05	25.25	50.00	42.00	35.28	24.70	30.50	51.00
Post-intervention								
TJ2	1.11	1.66	0.00	2.00	3.94	2.49	4.00	4.00
SJ2	1.58	1.71	1.00	3.00	3.50	2.79	2.50	3.00
PaGA2	29.74	17.21	27.00	28.00	27.44	21.72	27.50	41.00
PhGA2	9.68	5.42	8.00	6.00	19.61	14.45	17.00	26.00
CRP2	4.99	3.59	4.20	6.10	5.31	5.08	3.50	6.75
DAS2	2.51	0.61	2.43	0.93	3.27	1.01	3.39	1.80
HAQ2	0.32	0.32	0.25	0.65	0.41	0.55	0.18	0.66
VAS2	35.58	18.85	41.00	23.00	30.17	20.25	27.50	41.00
IQR	Interquartile range		PhGA	Physician's Global Assessment		VAS	Visual Analogue Scale	
TJ	Tender joint count		CRP	C-reactive protein		1	Pre-intervention values	
SJ	Swollen joint count		DAS	Disease Activity Score		2	Post-intervention values	
PaGA	Patient's Global Assessment		HAQ	Health Assessment Questionnaire				

4.2.3(B) ASSESSMENT FOR INITIAL BIAS BETWEEN THE TWO GROUPS

Once again multiple variables have to be assessed, hence to protect against an inflated Type 1 error (i.e. against capitalizing on chance to find a significant result) when performing multiple MWU tests on the pre-variables, MANOVA tests were performed. Since many of the variables are positive skew, tests of normality were performed first to determine which pre-variables, if any, need to be transformed. The following variables were transformed: TJ_1 , $PhGA_1$, CRP_1 , HAQ_1 , VAS_1 . The variables were transformed using natural logarithms (CRP_1) or by taking the square root (TJ_1 , $PhGA_1$, HAQ_1 , VAS_1). Both ln-transformation and square root transformation are commonly used when the variables have a positive skew distribution. Results of the normality tests and transformations can be found in [Appendix 12 – T08165 Phase II HAQ Analysis p1-6](#).

The multivariate test results of the MANOVA (Pillai's Trace, Wilks' Lambda, Hotelling's Trace and Roy's Largest Root) on the transformed variables all had p-values larger than 0.5. There was thus no statistical evidence of bias between the two groups at the start of the experiment. From the univariate ANOVA results (i.e. t-tests) on the transformed variables, the p-values for all variables were ranging from 0.219 to 0.993, i.e. no statistical differences exist between the two groups for any of the variables.

Performing a MANOVA on the original (untransformed) variables and consequently non-parametric MWU-tests, yielded similar results, and the same conclusion of no evidence of initial bias between the two groups was reached.

Table 4.12 shows the results of the tests performing MANOVA on the transformed variables, MANOVA on the untransformed variables and MWU tests on the untransformed variables with exercise as the factor.

Table 4.12: p-values of the MANOVA on transformed variables, MANOVA on untransformed variables and MWU on untransformed variables.

Indicator	MANOVA Transformed variables	MANOVA Untransformed variables	MWU Untransformed variables		
TJ1	(sqrt) 0.32	0.45	0.22		
SJ1	0.34	0.34	0.21		
PaGA1	0.99	0.99	0.73		
PhGA1	(sqrt) 0.68	0.79	0.64		
CRP1	(ln) 0.27	0.49	0.22		
DAS1	0.91	0.91	0.73		
HAQ1	(sqrt) 0.99	0.85	0.82		
VAS1	(sqrt) 0.22	0.20	0.27		
TJ	Tender joint count	CRP	C-reactive protein	VAS	Visual Analogue Scale
SJ	Swollen joint count	DAS	Disease Activity Score	sqr	Square root
PaGA	Patient's Global Assessment	HAQ	Health Assessment Questionnaire	ln	Natural logarithm
PhGA	Physician's Global Assessment				

4.2.3(C) WITHIN GROUP ANALYSES

Wilcoxon signed rank tests were performed to assess the changes that occurred within each group from the start (pre-values) to completion (post-values) of the study. In Tables 4.13 and 4.14 the changes that occurred, the level of significance, the effect size and whether it was an improvement or deterioration can be observed for RAE and RAC respectively. The RAE showed statistically significant improvements for the TJ, SJ, PhGA, DAS₂₈ and the VAS values. The RAC did not show any statistical differences, except for the HAQ score that improved.

Table 4.13: Differences between the pre- and post-values for RAE

Indicator	Mean pre-value	Mean post-value	Mean difference	↑↓	Median pre-value	Median post-value	p	Effect size	↑↓	I/D
TJ	3.05	1.11	-1.94	↓	2.00	0.00	0.002**	0.69	↓	I
SJ	3.89	1.58	-2.31	↓	4.00	1.00	0.001**	0.76	↓	I
PaGA	30.68	29.74	-0.94	↓	26.00	27.00	0.398	0.06	↑	D
PhGA	22.58	9.68	-12.9	↓	20.00	8.00	0.001**	0.79	↓	I
CRP	10.07	4.99	-5.08	↓	3.60	4.20	0.071	0.34	↑	D
DAS	3.29	2.51	-0.78	↓	3.32	2.43	0.001**	0.74	↓	I
HAQ	0.48	0.32	-0.16	↓	0.35	0.25	0.304	0.12	↓	I
VAS	46.05	35.58	-10.47	↓	50.00	41.00	0.032*	0.43	↓	I
TJ	Tender joint count	CRP	C-reactive protein	**			p<0.01			
SJ	Swollen joint count	DAS	Disease Activity Score	*			p<0.05			
PaGA	Patient Global Assessment	HAQ	Health Assessment Questionnaire	I			Improvement on median values			
PhGA	Physician Global Assessment	VAS	Visual Analogue Scale	D			Deterioration on median values			

Table 4.14: Differences between the pre- and post-values for RAC

Indicator	Mean pre-value	Mean post-value	Mean difference	↑↓	Median pre-Value	Median post-value	p	Effect size	↑↓	I/D
TJ	3.78	3.94	0.16	↑	4.00	4.00	0.402	0.06	≈	≈
SJ	3.00	3.50	0.50	↑	2.00	2.50	0.091	0.32	↑	D
PaGA	30.56	27.44	-3.12	↓	23.50	27.50	0.262	0.15	↑	D
PhGA	21.33	19.61	-1.72	↓	14.00	17.00	0.332	0.10	↑	D
CRP	7.02	5.31	-1.71	↓	3.05	3.50	0.295	0.13	↑	D
DAS	3.25	3.27	0.02	↑	3.03	3.39	0.472	0.02	↑	D
HAQ	0.52	0.41	-0.11	↓	0.20	0.18	0.037*	0.42	↓	I
VAS	35.28	30.17	-5.11	↓	30.50	27.50	0.172	0.22	↓	I
TJ	Tender joint count		DAS	Disease Activity Score		≈	Unchanged			
SJ	Swollen joint count		HAQ	Health Assessment Questionnaire		I	Improvement on median values			
PaGA	Patient Global Assessment		VAS	Visual Analogue Scale		D	Deterioration on median values			
PhGA	Physician Global Assessment		*	p<0.05						
CRP	C-reactive protein									

Arrows used in Tables 4:13 and 4:14 indicate improvement or deterioration. The RAE improved in most parameters (medium to large effect), excluding PaGA and CRP (which deteriorated by a narrow margin; small to medium effect). In fact, taking the mean value of both these parameters, PaGA improved from 30.68 to 29.74 and CRP from 10.07 to 4.99. The RAC, contrary to the RAE, deteriorated in most parameters (small to medium effect). However their VAS improved slightly and their HAQ statistically significantly so.

4.2.3(D) DIFFERENCES BETWEEN THE GROUPS AT STUDY COMPLETION

To determine whether the changes between the two groups are different the pre-values were subtracted from the post-values, e.g. $TJ_{diff} = TJ_2 - TJ_1$. Although not all the variables followed a normal distribution, they could not be transformed using natural logarithms or square roots because some of them are negative. Since there was such good correspondence between the transformed and untransformed MANOVAs in the previous analyses and the MANOVA is performed solely to protect against an inflated Type I error, it was decided to run the MANOVA on the untransformed variables to assess whether there are differences between the 2 groups in the multivariate space.

The MANOVA analysis had a p-value of 0.008 for the multivariate tests (partial eta squared =0.492), thus indicating significant differences between the 2 groups. To

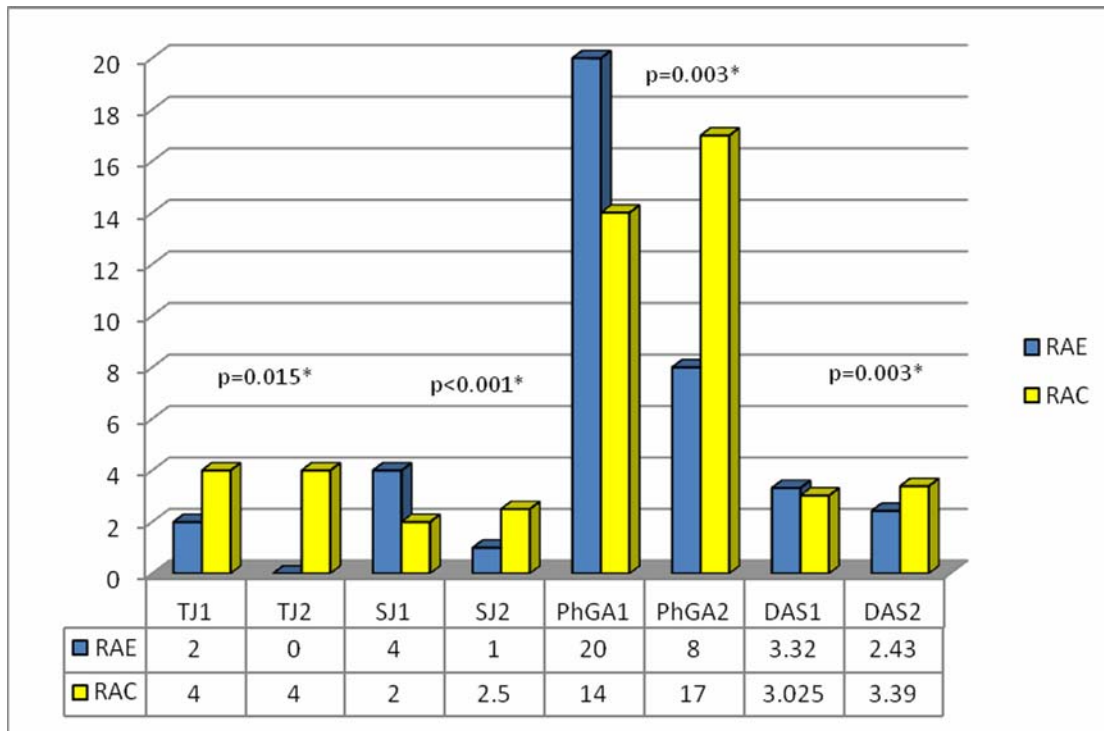
determine if the change in RAE is larger than in RAC, MWU-tests were performed. As can be seen in Table 4.15, significant improvements in favour of RAE were found for tender joint count, swollen joint count, physician’s global assessment and disease activity score.

Table 4.15: p-values for differences between the two groups at study completion

Indicator	Median differences RAE	Median differences RAC	p	Group favoured
TJdif	-2	0	0.015*	RAE
SJdif	-2	0.50	<0.001**	RAE
PaGAdif	0	-1.50	0.365	RAE
PhGAdif	-12	-3	0.003**	RAE
CRPdif	-1	-0.15	0.222	RAE
DASdif	-0.85	0.16	0.003**	RAE
HAQdif	0	-0.025	0.164	RAC
VASdif	-4	-6.5	0.377	RAC

TJ	Tender joint count	HAQ	Health Assessment Questionnaire
SJ	Swollen joint count	VAS	Visual Analogue Scale
PaGA	Patient Global Assessment	dif	post-value minus pre-value
PhGA	Physican Global Assessment	**	p<0.01
CRP	C-reactive protein	*	p<0.05
DAS	Disease Activity Score		

The graph in Figure 4.15 displays the parameters that were statistically significant in favour of the RAE at study completion (median values were used).



*p<0.05

Figure 4.15: Parameters that changed in favour of the RAE group at study completion

(1 refers to pre-intervention, and 2 refers to post-intervention)

Studying a box plot of VAS (one of the statistical non-significant parameters) at baseline and on study completion, one can observe the following in Figure 4.16:

- i) The distribution of the middle 50% of scores (i.e. the box) for both groups moved downward with the top edge (i.e. Q3) much lower at study completion.
- ii) The top whiskers (i.e. top 25% of scores) however, show a larger improvement for RAE, moving down from approximately 85 to approximately 60.

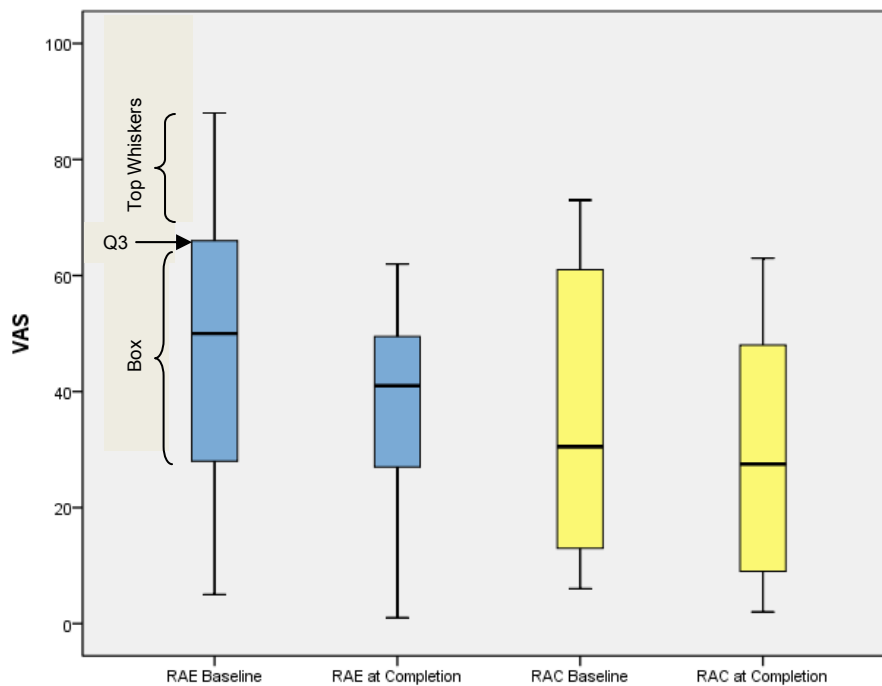


Figure 4.16: Clustered Box Plot on VAS at baseline and at completion of study for both groups

4.2.4 Functional Parameters

4.2.4(A) DESCRIPTIVE STATISTICS

The summary statistics of the two groups are divided into different categories, i.e. flexibility, strength and aerobic fitness parameters, and are displayed in Tables 4.16 to 4.18. The mean, standard deviation of the mean and median values for pre- and post-intervention measurements, for both groups are reported.

Table 4.16: Descriptive statistics of RAE and RAC group for flexibility parameters

Indicator	RAE (n=19)				RAC (n=18)			
	Mean	SD	Median	IQR	Mean	SD	Median	IQR
Pre-intervention								
Wrist flexion (deg) right	69.11	12.47	68.00	16.00	67.11	19.74	68.00	37.00
Wrist flexion (deg) left	67.11	12.81	70.00	14.00	67.89	12.35	71.00	15.00
Wrist extension (deg) right	58.16	12.83	60.00	14.00	54.67	10.56	54.00	20.00
Wrist extension (deg) left	63.42	11.56	66.00	20.00	60.44	11.57	59.50	15.00
Knee flexion (deg) right	138.26	9.53	139.00	10.00	132.50	10.88	131.00	17.00
Knee flexion (deg) left	138.74	9.43	140.00	13.00	132.56	9.70	130.50	16.00
Knee extension (deg) right	-2.74	3.75	-3.00	6.00	-0.17	4.83	0.50	7.00
Knee extension (deg) left	-3.42	3.55	-4.00	3.00	-0.50	5.79	0.00	10.00
Hip flexion (deg) right	71.47	14.46	70.00	25.00	64.72	11.34	65.00	11.00
Hip flexion (deg) left	74.32	13.11	78.00	23.00	65.00	11.61	65.00	13.00
Hip extension (deg) right	-12.95	12.84	-12.00	16.00	-16.39	14.29	-17.50	17.00
Hip extension (deg) left	-11.21	10.48	-10.00	14.00	-15.33	11.14	-15.00	15.00
Lateral flexion (cm)right	47.01	6.29	47.10	6.50	44.13	7.05	42.00	12.30
Lateral flexion (cm) left	48.60	5.69	47.90	10.90	44.84	8.27	42.50	12.70
Chair sit and reach (cm)right	-6.38	11.55	-6.10	13.00	-9.03	12.71	-8.90	17.90
Chair sit and reach (cm)left	-7.27	11.68	-6.20	17.20	-7.81	13.47	-8.05	19.20
Scratch test right (cm)	-4.76	10.71	-6.00	20.80	-2.12	11.23	0.50	19.80
Scratch test left (cm)	-8.48	10.58	-9.50	19.50	-7.71	14.47	-9.35	21.20
Post-intervention								
Wrist flexion (deg) right	64.63	12.40	64.00	17.00	68.11	12.12	71.00	18.00
Wrist flexion (deg) left	67.89	12.00	65.00	13.00	66.06	10.39	68.00	12.00
Wrist extension (deg) right	61.68	14.72	65.00	15.00	50.50	13.87	52.00	22.00
Wrist extension (deg) left	66.74	10.81	68.00	12.00	56.56	14.59	55.00	21.00
Knee flexion (deg) right	137.68	8.56	137.00	11.00	131.67	13.85	134.00	18.00
Knee flexion (deg) left	142.26	7.59	142.00	11.00	134.56	9.24	133.00	14.00
Knee extension (deg) right	-0.63	3.10	-2.00	2.00	0.17	2.41	0.00	2.00
Knee extension (deg) left	-1.37	3.47	-2.00	4.00	0.22	3.30	0.00	5.00
Hip flexion (deg) right	75.11	10.74	72.00	11.00	69.00	8.89	71.00	12.00
Hip flexion (deg) left	75.53	12.30	72.00	19.00	65.89	7.00	65.00	11.00
Hip extension (deg) right	-8.37	9.79	-5.00	17.00	-16.56	10.09	-15.50	14.00
Hip extension (deg) left	-5.84	10.96	-1.00	16.00	-17.56	12.19	-19.00	17.00
Lateral flexion (cm) right	47.63	5.16	46.10	9.40	45.42	8.85	45.20	13.40
Lateral flexion (cm) left	47.54	4.03	46.50	6.10	44.31	10.28	43.80	20.00
Chair sit and reach (cm)right	0.37	13.16	0.00	19.60	-9.86	11.10	-7.75	21.40
Chair sit and reach (cm)left	3.56	11.39	3.00	17.50	-9.51	11.29	-6.75	21.20
Scratch test right (cm)	-0.25	7.24	0.00	11.20	-4.73	9.36	-3.90	14.00
Scratch test left (cm)	-4.97	9.85	-4.50	16.50	-7.44	11.03	-7.25	21.70
SD	Standard deviation		deg	degrees				
IQR	Interquartile range		cm	centimetres				

Table 4.17: Descriptive statistics of RAE and RAC group for strength parameters

Indicator	RAE (n=19)				RAC (n=18)			
	Mean	SD	Median	IQR	Mean	SD	Median	IQR
Pre-intervention								
Hand grip strength (kg) right	17.00	6.27	19.10	5.40	21.19	8.24	24.05	13.70
Hand grip strength (kg) left	16.56	5.03	16.70	5.00	20.19	8.01	22.15	11.10
Leg strength (kg)	49.42	21.65	55.00	24.50	60.16	16.74	59.25	23.50
Arm-curl test (s)	51.54	23.73	46.87	27.43	40.30	24.80	31.96	10.31
Sit-to-stand test (s)	65.37	45.62	49.53	28.75	49.94	23.81	38.94	20.91
Post-intervention								
Hand grip strength (kg) right	24.76	6.13	25.50	6.40	24.16	7.65	25.95	10.70
Hand grip strength (kg) left	22.52	4.27	23.50	3.70	23.62	6.90	25.40	12.60
Leg strength (kg)	61.63	20.72	68.00	28.50	65.06	16.44	62.50	23.10
Arm-curl test (s)	31.06	7.31	30.69	7.15	29.93	7.35	29.92	6.42
Sit-to-stand test (s)	36.88	9.62	35.97	17.72	39.41	8.70	36.89	8.22
SD	Standard deviation			kg	kilogram			
IQR	Interquartile range			s	seconds to perform 20 repetitions			

Table 4.18: Descriptive statistics of RAE and RAC group for aerobic fitness parameters

Indicator	RAE (n=19)				RAC (n=18)			
	Mean	SD	Median	IQR	Mean	SD	Median	IQR
Pre-intervention								
1mile walk test (min)	16.91	1.84	16.49	2.15	17.12	2.24	16.24	3.77
Heart rate rest (bpm)	80.32	7.85	79.00	11.00	73.50	8.92	76.50	16.00
Heart rate post (bpm)	138.74	14.61	140.00	23.00	131.17	23.93	134.50	37.00
Systolic blood pressure (mmHG) pre-walk	120.11	19.52	122.00	23.00	121.67	18.75	124.00	25.00
Diastolic blood pressure (mmHG) pre-walk	71.11	11.64	70.00	20.00	74.50	14.67	77.00	21.00
Systolic blood pressure (mmHG) post-walk	139.16	12.39	140.00	20.00	140.00	21.15	138.00	21.00
Diastolic blood pressure (mmHG) post-walk	84.84	8.44	86.00	14.00	86.71	10.14	86.00	20.00
VO ₂ max	26.51	6.94	26.74	11.42	24.54	10.58	21.46	15.73
Post-intervention								
1mile walk test (min)	14.93	1.56	15.30	2.12	16.65	2.59	15.81	2.56
Heart rate rest (bpm)	77.95	8.80	79.00	16.00	79.22	9.99	78.00	16.00
Heart rate post (bpm)	151.68	14.80	156.00	25.00	134.78	18.51	136.50	27.00
Systolic blood pressure (mmHG) pre-walk	116.63	12.08	116.00	16.00	115.89	11.24	113.00	15.00
Diastolic blood pressure (mmHG) pre-walk	67.53	7.63	67.00	12.00	72.39	10.12	71.50	18.00
Systolic blood pressure (mmHG) post-walk	134.21	20.50	128.00	18.00	137.72	13.64	133.50	21.00
Diastolic blood pressure (mmHG) post-walk	72.53	7.94	72.00	10.00	77.00	9.26	80.00	5.00
VO ₂ max	30.83	5.62	30.74	8.96	25.34	8.99	25.51	7.12
SD	Standard deviation			bpm	beats per minute			
IQR	Interquartile range			mmHG	millimetres of mercury			
min	minutes							

4.2.4(B) ASSESSMENT FOR INITIAL BIAS BETWEEN THE TWO GROUPS

Tests of normality were performed to assess which variables need to be considered for transformation, but because some of these variables have negative or zero values, they could not be transformed successfully.

MANOVA tests were then performed and all variables had a p-value of more than 0.05. There was thus no evidence of bias between the two groups at the start of the intervention when assessing using multivariate tests (Pillai's, Trace, Wilks' Lambda, Hotelling's Trace and Roy's Largest Root). However, when using non-parametric MWU tests, three of the variables (knee flexion left, hip flexion left and the arm curl test) had p-values of less than 0.05, thus indicating evidence of bias in these variables between the two groups at baseline. The median values of these variables can be observed in Table 4.19.

Table 4.19: Median values of variables showing initial bias between RAE and RAC

Indicator	RAE Median (IQR)	RAC Median (IQR)	p	Group favoured
Knee flexion (deg) left	140 (13.00)	130.50 (16.00)	0.029*	RAE
Hip flexion (deg) left	78 (23.00)	65 (13.00)	0.039*	RAE
Arm curl test (s)	46.87 (27.43)	31.96 (10.31)	0.022*	RAC

IQR Interquartile range
deg degree
s seconds to complete 20 repetitions
* <0.05

The RAE had better knee- and hip flexion on the left hand side when the study was started, but it took them longer to complete the arm curl test compared to the RAC.

4.2.4(C) WITHIN GROUP ANALYSES

Wilcoxon signed rank tests were performed to assess changes within each group from baseline (pre-values) to study completion (post-values). Table 4.20 indicates the direction of improvement.

Table 4.20: Parameter measurement descriptions

Parameter	Descriptor	Direction of improvement
Flexibility:		
Knee flexion	Degrees	↑
Knee extension	Degrees	↓
Hip flexion	Degrees	↑
Hip extension	Degrees	↓
Lateral flexion (sideways bend)	Middle finger distance from floor (cm)	↓
Chair sit and reach	Middle finger distance from toe (cm)*	↑
Scratch test	Reaching behind back: distance from middle finger to inferior angle of scapula (cm)**	↑
Strength:		
Hand grip	Dynamometer (kg)	↑
Leg strength	Dynamometer (kg)	↑
Arm curls	Time to execute 20 (s)	↓
Sit to stand	Time to rise from chair to standing position 20 times (s)	↓
Fitness:		
1 mile walk test	Time to walk 1 mile (min)	↓
VO ₂ max	ml/kg/min	↑
* The toe is the zero point. The distance before the toe is a minus value, and the distance beyond is a plus value.		
** The angle of the scapula is the zero point. The distance before this is a minus value, and the distance beyond is a plus value.		

In Tables 4.21 and 4.22 the changes that occurred for the functional parameters from baseline to study completion, as well as the level of significance, the effect size and whether it was an improvement or deterioration are reported for RAE and RAC respectively.

The RAE group showed statistical significant differences (medium to large effect) from the start of the exercise programme to study completion for knee flexion (left), knee extension (right and left), hip extension (left), chair sit and reach (right and left), scratch test (right and left), hand grip strength (right and left), leg strength, arm curl test, sit to stand test, 1mile walk, VO₂ max, heart rate post walk and diastolic blood pressure post walk.

Table 4.21: Functional parameters that changed significantly from baseline to study completion for RAE

Indicator	Mean pre-value	Mean post-value	Mean Difference	↑↓	Median pre-value	Median post-value	p	Effect size	↑↓	I/D
Flexion										
Knee flexion(deg) left	138.74	142.26	3.52	↑	140.00	142.00	0.027*	0.44	↑	I
Knee extension (deg) right	-2.74	-0.63	2.11	↑	-3.00	-2.00	0.010*	0.53	↑	D [▲]
Knee extension (deg) left	-3.42	-1.37	2.05	↑	-4.00	-2.00	0.008**	0.56	↑	D [▲]
Hip extension (deg) left	-11.21	-5.84	5.37	↑	-10.00	-1.00	0.042*	0.40	↑	D
Chair sit and reach (cm) right	-6.38	0.37	6.75	↑	-6.10	0.00	0.011*	0.53	↑	I
Chair sit and reach (cm) left	-7.27	3.56	10.83	↑	-6.20	3.00	0.001**	0.79	↑	I
Scratch test (cm) right	-4.76	-0.25	4.51	↑	-6.00	0.00	0.007**	0.56	↑	I
Scratch test (cm) left	-8.48	-4.97	3.51	↑	-9.50	-4.50	0.011*	0.53	↑	I
Strength										
Hand grip strength (kg) right	17.00	24.76	7.76	↑	19.10	25.50	<0.001**	0.88	↑	I [~]
Hand grip strength (kg) left	16.56	22.52	5.96	↑	16.70	23.50	<0.001**	0.87	↑	I [~]
Leg strength (kg)	49.42	61.63	12.21	↑	55.00	68.00	0.003**	0.63	↑	I [~]
Arm-curl test (s)	51.54	31.06	-20.48	↓	46.87	30.69	<0.001**	0.88	↓	I [~]
Sit-to-stand test (s)	65.37	36.88	-28.49	↓	49.53	35.97	<0.001**	0.80	↓	I [~]
Aerobic										
1mile walk test (min)	16.91	14.93	-1.98	↓	16.49	15.30	<0.001**	0.88	↓	I
Heart rate (bpm) post walk	138.74	151.68	12.94	↑	140.00	156.00	0.001**	0.74	↑	◇
Diastolic blood pressure (mmHG) post walk	84.84	72.53	-12.31	↓	86.00	72.00	<0.001**	0.83	↓	I
Vo ₂ max	26.51	30.83	4.32	↑	26.74	30.74	<0.001**	0.88	↑	I
deg	degree	bpm	beats per minute				I	Improvement on median values		
cm	centimetres	mmHG	millimetres of mercury				D	Deterioration on median values		
kg	kilogram	**	p<0.01							
s	seconds	*	p<0.05							
min	minutes									
▲	Although knee extension deteriorated in numeric values, one can argue that less knee-extension (i.e. less hyper mobile joint) might be the better outcome.									
~	All strength parameters improved significantly at study completion.									
◇	The heart rate post walk (156 bpm) was higher after the 12 week exercise intervention compared to the baseline (140 bpm). This implies one of two possibilities: either the effort made was bigger, or the ability to increase heart rate was better.									

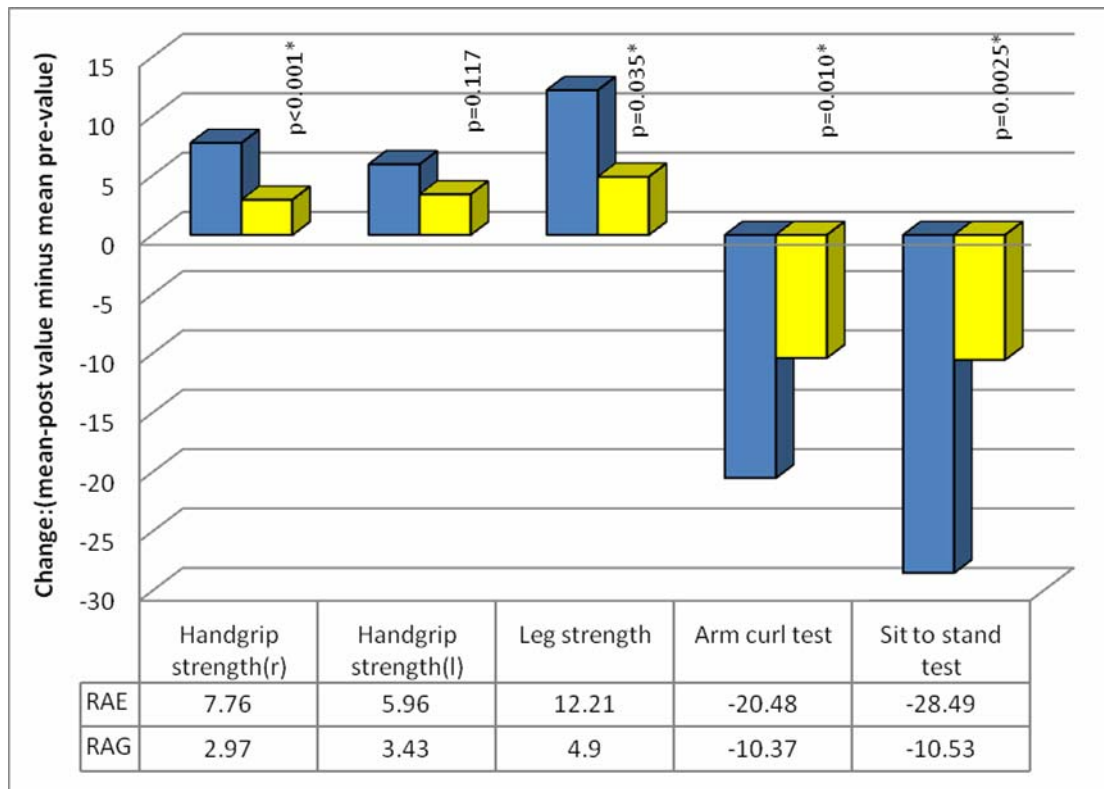
The RAC group showed statistical significant changes (medium to large effect) for wrist extension (right and left), hip flexion (right), lateral flexion (right), hand grip strength (right and left), arm curl test, sit to stand test and diastolic blood pressure post walk.

Table 4.22: Functional parameters that changed significantly from baseline to study completion for RAC

Indicator	Mean pre-value	Mean post-value	Mean Difference	↑↓	Median pre-value	Median Post-value	p	Effect size	↑↓	I/D
Flexibility										
Wrist extension (deg) right	54.67	50.50	-4.17	↓	54.00	52.00	0.033*	0.44	↓	D
Wrist extension (deg) left	60.44	56.56	-3.88	↓	59.50	55.00	0.010*	0.56	↓	D
Hip flexion (deg) right	64.72	69.00	4.28	↑	65.00	71.00	0.042*	0.41	↑	I
Lateral flexion (cm) right	44.13	45.42	1.29	↑	42.00	45.20	0.043*	0.41	↑	D
Strength										
Hand grip strength (kg) right	21.19	24.16	2.97	↑	24.05	25.95	0.001**	0.73	↑	I
Hand grip strength (kg) left	20.19	23.62	3.43	↑	22.15	25.40	0.005**	0.62	↑	I
Arm-curl test (s)	40.30	29.93	-10.37	↓	31.96	29.92	0.002**	0.71	↓	I
Sit-to-stand test (s)	49.94	39.41	-10.53	↓	38.94	36.89	0.006**	0.59	↓	I
Aerobic										
Diastolic blood pressure (mmHG) post walk	86.71	77.00	-9.71	↓	86.00	80.00	0.002**		↓	I
deg	degree									
cm	centimetre	mmHG	millimetres of mercury				I	Improvement on median values		
kg	kilogram	**	p<0.01				D	Deterioration on median values		
s	seconds	*	p<0.05							

Only hip flexion (right) improved significantly in this group, while most of the flexibility measurements did not change or even deteriorated. Most of their strength parameters, as well as their diastolic blood pressure after the 1 mile walk, improved from baseline to study completion.

Although both groups had changes in their strength parameters, the RAE group had bigger changes as can be viewed in Figure 4.17. The statistical tests were conducted using non-parametric methods; however, for the purpose of reporting the changes, the means of the respective groups were used. In all instances the direction of change in the mean and the median between the two groups was the same.



*p<0.05

Figure 4.17: Comparison of changes in the strength parameters from pre- to post-intervention for both groups

Formula: Change=mean post-value minus mean pre-value

4.2.4(D) DIFFERENCES BETWEEN THE TWO GROUPS AT STUDY COMPLETION

Pre-values (baseline) were subtracted from post-values (study completion) to determine if the exercise intervention has favoured any of the groups. The MANOVA performed to evaluate effect size had a p-value of 0.365, but still had a very large effect size (partial eta squared value of 0.923).

As most variables followed a normal distribution and ln or square root transformation cannot be done on negative values, MWU-tests were performed consequently to determine whether the changes in RAE are larger than in RAC. The following parameters showed significant changes: wrist extension (right and left), hip extension (left), chair sit and reach (right and left), scratch test (right), hand grip strength (right), leg strength, arm curl test, sit to stand, 1 mile walk test, heart rate before walk and VO₂ max (Table 4.23)

Table 4.23: Parameters that showed significant changes between the two groups at end of study

Indicator	Median difference RAE	Median difference RAC	p	Group favoured	
Flexibility					
Wrist extension (deg) right	3.00	-1.00	0.016*	RAE	
Wrist extension (deg) left	-1.00	-3.00	0.013*	RAE	
Hip extension (deg) left	6.00	-3.00	0.049*	RAC	
Chair sit and reach (cm) right	4.80	2.05	0.038*	RAE	
Chair sit and reach (cm) left	7.20	-0.75	0.001**	RAE	
Scratch test (cm) right	3.80	-1.40	0.012*	RAE	
Strength					
Hand grip strength (kg) right	7.00	3.15	<0.001**	RAE	
Leg strength (kg)	13.00	0.00	0.035*	RAE	
Arm-curl test (s)	-11.26	-3.71	0.010*	RAE	
Sit-to-stand test (s)	-15.90	-3.80	0.025*	RAE	
Aerobic					
1 mile walk test (min)	-2.00	-0.47	<0.001**	RAE	
Heart rate (bpm) before walk	-6.00	2.50	0.023*	RAE	
VO ₂ max	4.07	1.63	0.007**	RAE	
deg	degree	s	seconds	dif	post-value minus pre-value
cm	centimetres	min	minutes	**	p<0.01
kg	kilogram	bpm	beats per minute	*	p<0.05

On study completion wrist extension on both sides deteriorated for RAC, while hip extension on the left deteriorated for RAE. However, upper body flexibility (chair sit and reach; scratch test) was significantly better for RAE. Also, RAE showed significant improvement for all strength parameters (except left hand grip) compared to RAC. Their 1 mile walk test was faster and their resting heart rate lower, causing their VO₂max to improve statistically significantly in comparison to RAC.

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