3.1 HYPOTHESES

3.1.1 PHASE 1
The Null Hypothesis has been stated that there is no difference in the cardiac autonomic function as measured by short-term heart rate variability (HRV) parameters between healthy subjects and patients with RA.

The alternative hypothesis has been stated that there is a difference in the cardiac autonomic function as measured by short-term HRV parameters between healthy subjects and patients with RA.

3.1.2 PHASE 2
The Null Hypothesis is constructed in such a manner that it will show that exercise will not have a meaningful effect on cardiac autonomic function as measured by short-term HRV, or disease activity and/or functional capacity in female patients with RA.

The Alternative Hypothesis will aim to prove that exercise will have a meaningful effect on cardiac autonomic function as measured by short-term HRV, disease activity and/or functional capacity in female patients with RA.
3.2 STUDY AIMS AND OBJECTIVES

This study has a number of aims and objectives.

3.2.1 PHASE 1
The first part of the study aims to describe cardiac autonomic nervous system (ANS) function (as measured by HRV) in RA patients and to compare it to a healthy Control Group (HCG).

3.2.2 PHASE 2
The remainder of the objectives are all related to an exercise intervention and forms the second part of the study.

3.2.2.1 Objective 1
The first aim in this phase is to evaluate the effect of training on cardiac autonomic function (as measured by HRV) in RA patients.

3.2.2.2 Objective 2
The effect of training on disease activity in RA patients is measured by the Disease Activity Score (DAS-28).

3.2.2.3 Objective 3
The Health Assessment Questionnaire (HAQ) is used to measure the effect of training on the quality of life, and the Visual Analogue Scale (VAS) to measure the subjective pain levels of the patient.

3.2.2.4 Objective 4
The fourth aim is to assess the efficacy of this exercise program on endurance, strength of muscles and range of motion (ROM) of joints in RA patients. Endurance is measured by the Rockport walking test and VO$_2$ max relative. Strength is measured by leg strength, handgrip strength, arm curls and sit to
stand test, while ROM is measured by flexibility of the wrist, knee, hip joints, lateral flexion, scratch test, and the sit and reach test.
3.3 STUDY DESIGN

The first phase of the study consisted of a comparison between a Healthy Control Group (HCG) and RA patients. The accepted definition of health as used by the World Health Organisation (WHO) since 1948, is “a state of complete physical, mental, and social well-being and not merely the absence of infirmity” (Appendix 1). The HCG was recruited to fulfill these criteria.

The second phase was a Prospective Analytical Pre-Post Group Comparison. The study was a randomized experimental design. Patients with RA who conformed to the in- and exclusion criteria, were invited by the investigator to an information and orientation meeting before the study commenced. Colour coded buttons representing each group (RA Control = Yellow, RA Exercise = Blue) were put in a non-transparent bag. Each participant had to draw one of these colour coded buttons. The administrator allocated the participants into the different groups according to the colour of the buttons. An informed consent form was signed by all participants.

Group 1: Exercise group consisting of RA Patients (RAE)
Group 2: Control group consisting of RA Patients (RAC)

The RAE was required to train 2-3 times per week, while the RAC was instructed to continue with their sedentary lifestyle (i.e. current lifestyle). The programme was conducted over 3 months (12 weeks). All exercise sessions were supervised by a Biokineticist (Exercise Specialist). Exercise intervention consisted of warm-up exercises, strengthening exercises, aerobic exercises and a cool-down period which included stretching. The duration of each session was approximately 45 minutes. The exercise programme is demonstrated in Table 3.1.
### Table 3.1: Exercise programme

**Warm-up**  
5 min at 40-50% of peak heart rate (HR). This was walking, pool jogging or pool noodle cycling.

**Aerobic Exercise**  
15 min at 60-80% of peak HR doing either treadmill walking, water cycling or water jogging.

**Flexibility**  
Stretching exercise was done for each of the major joints. For each exercise the participants performed 5 repetitions held for 30 seconds each. Stretching exercises included:
- Neck stretch
- Shoulder rolls
- Lying hamstring stretch
- Standing hip flexor stretch
- Calf stretches
- Pectoral stretch

<table>
<thead>
<tr>
<th>Strength</th>
<th>Exercises</th>
<th>Intensity</th>
<th>Repetitions (Sets)</th>
</tr>
</thead>
</table>
| Week 1&2 | Chest press  
Bicep curls  
Lat pull downs  
Hip extension  
Leg presses  
Hamstring curls  
Hip abduction | 50% 1 RM | 1 set of 10 repetitions |
| Week 3&4 | Chest press  
Bicep curls  
Lat pull downs  
Hip extension  
Leg presses  
Hamstring curls  
Hip abduction | 50% 1 RM | 1 set of 15 repetitions |
| Week 5&6 | Chest press  
Bicep curls  
Lat pull downs  
Seated row  
Hip extension  
Leg presses  
Hamstring curls  
Hip abduction  
Calf raises | 60-70% 1 RM | 2 sets of 10 repetitions |
### 3.4 SETTING

The participants exercised in a well equipped gym environment at the Department of Biokinetics, Sport and Leisure Sciences at the Sports Centre of the University of Pretoria.

### 3.5 PATIENT / RESEARCH OBJECT SELECTION

Participants attended an information and orientation session. A medical questionnaire was distributed to all participants at this session *(Appendix 2)*. The questionnaire was explained to them whereupon it was completed *(5)*.

A full clinical examination was done by a rheumatologist. This included an examination of the cardiovascular system, the pulmonary system, the gastrointestinal tract, as well as the ear, nose and throat for possible systemic disease. The musculo-skeletal system was assessed for arthritic activity. The HCG was matched to the RA group according to age, sex, height and weight. The HCG was recruited from family and friends of the research team and of the RA group.
RA patients were recruited from all rheumatology practices in Pretoria. Before entering the study, participants had to comply with all inclusion– and exclusion criteria, as explained in section 3.5.1 for the HCG and 3.5.2 for the RA group.

3.5.1 HEALTHY CONTROL GROUP (PHASE 1 OF THE STUDY)

Inclusion Criteria:

- Participants must be healthy – as per the WHO definition (*Appendix 1*)
- Participants must be of the female sex
- Participants must be between 30-60 years of age
- Participation is on a strictly voluntary basis

Exclusion Criteria:

- Participants are not to have any of the following diseases:
  - RA
  - Cardiovascular disease (CVD)
  - Pulmonary disease
  - Diabetic disease
  - Neurological disease
  - Liver or kidney disease
- Participants must have no history of smoking

3.5.2 RHEUMATOID ARTHRITIS GROUP (PHASE 1 AND 2 OF THE STUDY)

Inclusion Criteria:

- Participants must have active RA according to the 1987 Revised American College of Rheumatology Criteria for RA*(6)* (*Appendix 3*):
  - Participants must fall into Class I or II of the Classification of Global Functional Status in RA*(7)*, where Class I is completely able to perform usual activities of daily living (self-care, vocational, and avocational), and Class II is able to perform usual self-care and vocational activities, but limited in avocational activities (*Appendix 4*)
• Participants’ RA disease must be controlled, i.e. on stable evidence-based medication for at least 3 months

• Participants must be of the female sex
• Participants must be between the ages of 30-60 years
• Participants must be willing to participate in the study

Exclusion Criteria:

• No history of smoking
• No history of CVD
• No history of pulmonary disease
• No history of diabetic disease
• No history of neurological disease (including symptoms and/or signs of peripheral neuropathy)
• Participants are not to use drugs that interfere with the
  - autonomic nervous system (ANS), and
  - cardiovascular system (CVS)
• No history of liver or kidney disease
• Participants are not to be on a physical training programme for the last year
• Participants are not to be allergic to pool chemicals
3.6 EQUIPMENT

The equipment used for measurements are explained in Table 3.2 and shown in Figures 3.1 to 3.11

Table 3.2: Equipment for pre-test and post-test measurements

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height(^8)</td>
<td>Steel anthropometer (fig. 3.1)</td>
</tr>
<tr>
<td>Body mass(^8)</td>
<td>Detecto standing scale (fig. 3.2)</td>
</tr>
<tr>
<td>Heart Rate(^9)</td>
<td>Polar 810i heart rate monitor system (fig. 3.3)</td>
</tr>
<tr>
<td>Blood Pressure(^10)</td>
<td>Sphygmomanometer, Stethoscope (fig. 3.4-3.5)</td>
</tr>
<tr>
<td>Flexibility</td>
<td></td>
</tr>
<tr>
<td>Wrist flexion and extension(^5)</td>
<td>Goniometer (fig. 3.6)</td>
</tr>
<tr>
<td>Knee flexion and extension(^5)</td>
<td>Goniometer (fig.3. 6)</td>
</tr>
<tr>
<td>Hip flexion and extension(^5)</td>
<td>Goniometer (fig. 3.6)</td>
</tr>
<tr>
<td>Lateral flexion(^5)</td>
<td>Measuring tape (fig. 3.7)</td>
</tr>
<tr>
<td>Back scratch test(^5)</td>
<td>Ruler (fig. 3.8)</td>
</tr>
<tr>
<td>Chair sit and reach test(^6)</td>
<td>Ruler (fig. 3.8)</td>
</tr>
<tr>
<td>Strength</td>
<td></td>
</tr>
<tr>
<td>Hand grip strength test(^5)</td>
<td>Dynamometer (fig. 3.9)</td>
</tr>
<tr>
<td>Isometric leg strength test(^5)</td>
<td>Leg dynamometer (fig. 3.10)</td>
</tr>
<tr>
<td>Arm curl test(^5)</td>
<td>5lb / 2.27kg dumbbells (fig. 3.11)</td>
</tr>
<tr>
<td>Sit to stand test(^5)</td>
<td>No apparatus required</td>
</tr>
</tbody>
</table>

Figure 3.1: Anthropometer
Figure 3.2: Scale
Figure 3.3: Polar heart rate monitor
Figure 3.4: Sphygmomanometer

Figure 3.5: Stethoscope
Figure 3.6: Goniometer

Figure 3.7: Tape measure
Figure 3.8: Ruler
The HCG was only measured at baseline. Measurements included height, weight, body mass index and HRV.

For the RA group, measurements were done at:

- Baseline, at the onset of the programme, and
- 12 weeks, on completion of the exercise programme

The RA group was measured according to all parameters explained below.
3.7.1 HEIGHT
The anthropometer was used to calculate the height to the nearest 0.1cm with height being defined as the distance between the soles of the feet and the vertex (Figure 3.12). The participant was required to stand up straight, barefoot with the heel, gluteus maximus, upper-back and back of the head against the anthropometer. The ears, acromion, greater trochanter of the femur, back of patella and front of calcaneus were in the same vertical line. The angle of the eye and the upper hole of the ear were in the same horizontal level (Frankfurt plane). The measurement was taken while the participant inhaled deeply. No asymmetry was allowed\(^{(8)}\).

![Figure 3.12: Measurement of height](image)

3.7.2 BODY MASS
Body mass was recorded on a calibrated scale and recorded to the nearest 100g. Participants were weighed in minimum clothing, three to four hours post-prandial\(^{(8)}\).
3.7.3 HEART RATE
The resting heart rate was measured in the supine position with a Polar 810i heart rate monitor system as is explained under 3.7.5.1 and demonstrated in Figures 3.3 and 3.13(9).

![Figure 3.13: Measurement of resting heart rate](image1)

3.7.4 BLOOD PRESSURE
Blood pressure was measured with a normal sized adult (32cm) blood pressure cuff, a Sphygmomanometer, and a stethoscope (Figure 3.14). The cuff was placed around the arm in such a position that its inflation compressed the brachial artery. The stethoscope was placed over the artery. The cuff was inflated to approximately 30mmHg above systolic blood pressure to collapse the artery completely and stop the flow of blood. The air was then slowly released at a rate of approximately 2mm per second. The first sound heard is at peak systolic pressure. As soon as the sound became muffled or disappeared that pressure was recorded as diastolic pressure (Korotkoff 4)(10).

![Figure 3.14: Measurement of blood pressure](image2)
3.7.5 HEART RATE VARIABILITY (HRV)

HRV is a validated, non-invasive method to study the influence of the ANS on the heart. The parasympathetic and sympathetic nerves act on the intrinsic rhythm and this causes beat to beat variations in the RR-interval on the electrocardiogram (ECG)\(^{11,12}\). The ANS functioning and balance were determined by quantification of the variability of the inter-beat interval detected with the Polar 810i heart rate monitor system. Time domain, frequency domain and non-linear analysis (Poincarè plot analysis) techniques were used for the HRV quantification.

3.7.5.1 Method of HRV Data Sampling

The data, RR-intervals, was sampled in the morning (supine) 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 and not to smoke during the preceding 24 hours. They were in a fasting state from 22:00 the previous night. They were allowed to eat a low protein breakfast (cereal with milk) on the morning of testing.

Each participant put on a Polar 810i strap and transmitter (Figure 3.15). The participants then had to be in a supine position for 20 minutes, breathing spontaneously without talking (Figure 3.16). This was followed by a 10 minute orthostatic stressor where they had to stand in an upright position, with their backs leaning against the wall and their feet apart (Figure 3.17). RR-intervals with an accuracy of 1 milliseconds (ms) from the last 10 minutes of the resting period and the following 10 minutes standing, were used for analyses.
3.7.5.2 Heart rate variability quantification

The data (RR-interval sets) was analyzed using HRV Analysis Software obtained from the University of Kuopio, Finland\(^9\). Smoothness priors for trend and Model Eye programme settings were used for detrending with an Alpha value of 500\(^{12}\). The auto regressive 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\(^{13}\).
3.7.5.2.1 Time domain

HRV time domain indicators were determined by direct statistical analysis of the time (ms) between consecutive heart beats. Calculated indicators included average heart rate (beats per minute), mean RR-interval, the standard deviation of normal-to-normal inter-beat intervals (RRSD) estimating overall HRV, the square root of the mean squared differences (RMSSD) of successive RR-intervals (estimate of short-term HRV components), pNN50 i.e. the percentage of successive RR-interval differences larger than 50ms computed over the entire recording; an indicator of vagal influence on HRV\(^{(11,14,15)}\).
3.7.5.2.2 Frequency domain

Spectral analysis of HRV produces a decomposition of total variation of the data series into its frequency components, which can be expressed in the form of a spectral density function that depicts spectral power as a function of frequency. This allows for plotting of each of the spectral components as a function of its frequency and the computation of the power in each defined frequency region. Power spectrum analysis of the RR-interval data sets distinguishes between the intrinsic sources of HRV, as these rhythms occur at different frequencies. These variations allow for the mapping of the RR-interval power spectra into indices that reflect autonomic mediation of the heart rate. In this study the spectral components analysed by frequency domain analysis included high frequency (HF), low frequency (LF), HF normalised units (nu), LF normalised units (nu), and the LF/HF ratio. The (HF) respiratory component is found in the power spectrum between 0.15 – 0.40 Hz. HF power reflects mostly the power of parasympathetic efferent (vagal) modulation of the heart. A LF component is found between 0.04 – 0.15 Hz. Both parasympathetic and sympathetic outflows are considered to determine LF. HF(nu) represent the relative power of the HF component in proportion to the total power minus the VLF component, i.e. HF/(total power-VLF), while LF (nu) represent the relative power of the LF component in proportion to the total power minus the VLF component, i.e. LF/(total power-VLF). The LF/HF ratio is used to assess the fractional distribution of power and is an indicator of the cardiac autonomic balance\(^{11,14,16}\).
3.7.5.2.3 Poincaré plots

The Poincaré plot is a scatter gram in which each RR-interval of a tachogram is plotted as a function of the previous one. During this study a quantitative analysis of each of the Poincaré plots was performed with Polar software. The two quantitative indicators that were determined were Standard Deviation 1 (SD1) and Standard Deviation 2 (SD2). SD1 is an indicator of the standard deviation of the immediate or short-term RR variability due to parasympathetic efferent (vagal) influence on the sinus node. SD2 is an indicator of the standard deviation of the long term RR variability and it is indirectly proportional to the sympathetic influence. This value represents the global variation\(^{(17,18)}\).

An example of the recordings that were used for the HRV analyses is displayed in Figure 3.18. A summary of the HRV analysis techniques, specific HRV indicators and origins of variability is explained in Table 3.3.

Fig 3.18: Example of a tachogram
### Table 3.3: HRV techniques, HRV indicators and origins of variability

<table>
<thead>
<tr>
<th>Time domain analysis</th>
<th>RR(s)</th>
<th>The mean of the intervals between successive QRS complexes, result of vagal and sympathetic influence on HRV.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RRSD(s)</td>
<td>Standard deviation of intervals between successive QRS complexes, indicator of vagal and sympathetic influence on HRV (Overall HRV).</td>
</tr>
<tr>
<td></td>
<td>RMSSD(ms)</td>
<td>Root mean square of the standard deviation between RR-intervals, indicator of vagal influence.</td>
</tr>
<tr>
<td></td>
<td>pNN50(%)</td>
<td>The percentage of successive RR-interval differences larger than 50ms computed over the entire recording, indicator of vagal influence on HRV.</td>
</tr>
<tr>
<td>Poincaré plot analysis</td>
<td>SD1(ms)</td>
<td>Indicator of the standard deviation of the immediate RR variability due to parasympathetic efferent (vagal) influence on the sino-atrial node.</td>
</tr>
<tr>
<td></td>
<td>SD2(ms)</td>
<td>Indicator of the standard deviation of the slow variability of the heart rate. It is accepted that this value is representative of the global variation in HRV.</td>
</tr>
<tr>
<td>Frequency domain analysis</td>
<td>LF(ms(^2))</td>
<td>Indicator of sympathetic influence, but also including a parasympathetic component.</td>
</tr>
<tr>
<td></td>
<td>HF(ms(^2))</td>
<td>Indicator of only parasympathetic influence.</td>
</tr>
<tr>
<td></td>
<td>LF/HF</td>
<td>Indicator of autonomic balance.</td>
</tr>
<tr>
<td></td>
<td>LF(nu)</td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td>HF(nu)</td>
<td>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).</td>
</tr>
</tbody>
</table>

| LF | Low frequency |
| HF | High frequency |
| VLF | Very low frequency |
3.7.6 DISEASE ACTIVITY SCORE (DAS)\(^{(19,20)}\)

The disease activity is a calculated measure including the following parameters: tender joint count (TJC), swollen joint count (SJC), Patient Global Assessment (PGA), Physician Global Assessment (PhyGA) and C-reactive protein (CRP).

3.7.6.1 Tender joint count
The 28 joints examined included the shoulders, elbows, wrists, metacarpophalangeal joints 1-5, proximal interphalangeal joints 1-5, and knees on the left and right side of the body. The total number of joints tender to touch makes up this score. Figures 3.19 and 3.20 demonstrate examining of the hand- and knee joints.

![Figure 3.19 Examining of tender joints: hands](image1)

![Figure 3.20: Examining of tender joints: knees](image2)

3.7.6.2 Swollen joint count
The same joints were examined for soft tissue swelling. The total number of swollen joints identified makes up this score. Figure 3.21 demonstrates swelling of small hand joints.

![Figure 3.21: Swollen joint count](image3)
3.7.6.3 **Patient Global Assessment**

The patient’s global assessment is measured in millimeters. The patient was requested to indicate on a 100mm line the extent to which the arthritis was affecting her on that day (Figure 3.22).

![Figure 3.22: Scale for measuring Patient Global Assessment](image)

3.7.6.4 **Physician Global Assessment**

This measurement is also done in millimeters. The physician indicated on a 100mm line the extent to which the arthritis was affecting the patient on that day (Figure 3.23).

![Figure 3.23: Scale for measuring Physician Global Assessment](image)
3.7.6.5 C-reactive protein
Blood samples were taken and standard laboratory tests were used to establish the milligram per liter reading of the C-reactive protein.

The calculation of the DAS$_{28}$ (TJC, SJC, PGA, CRP) has clinical implications$^{(21)}$:

| ≤2.6 | Remission |
| >3.2 | Moderate RA activity |
| ≥5.1 | High RA activity |
3.7.7 QUALITY OF LIFE

The Quality of Life was measured by the Health Assessment Questionnaire (HAQ) \(^{(22,23)}\). The HAQ is designed to assess the patient’s abilities using their everyday equipment over the past week. It is an instrument to measure patient reported outcomes.

The HAQ comprises of 20 items. There are eight categories. Within each category a patient reports the amount of difficulty they have in performing sub-category items. Scoring the HAQ:

- Score each item within the 8 categories
- Select and add the highest score within each category
- Divide the sum of the category scores by the number of answered categories.
- If the item score is zero, but an assistive device is used: score 1.
  Help from another person is required: score 2.
  Both a special device and help is required: score 3.

A score of 0-3 is possible, with 3 being the worst disability.
3.7.8 VISUAL ANALOGUE SCALE\textsuperscript{24,25}

This is a subjective pain measurement where the participant had to indicate on a 100mm line the degree of pain she experienced over the past week (Figure 3.24).

![Visual Analogue Scale](image)

Figure 3.24: Scale for measuring pain

3.7.9 FUNCTIONAL CAPACITY

3.7.9.1 Flexibility

Flexibility is tested to assess active and passive ROM around the different joints most likely affected by RA. All participants did a light warm-up and static stretching before flexibility was tested\textsuperscript{26}. 
### 3.7.9.1.1 Wrist flexion (Figures 3.25-3.26)

<table>
<thead>
<tr>
<th>Body position</th>
<th>Axis of rotation</th>
<th>Stationary arm</th>
<th>Moving arm</th>
<th>Starting position</th>
<th>End position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting</td>
<td>Lateral aspect of wrist over the triquetrum</td>
<td>Lateral midline of ulna</td>
<td>Lateral midline of 5th metacarpal</td>
<td>Forearm rests on the table in mid-position; wrist in neutral position. The fingers are relaxed</td>
<td>The hand has moved toward the volar forearm to the limit of motion(26)</td>
</tr>
</tbody>
</table>

Figure 3.25 Wrist flexion: starting position

Figure 3.26: Wrist flexion: end position

### 3.7.9.1.2 Wrist extension (Figures 3.27-3.28)

<table>
<thead>
<tr>
<th>Body position</th>
<th>Axis of rotation</th>
<th>Stationary arm</th>
<th>Moving arm</th>
<th>Starting position</th>
<th>End position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting</td>
<td>Lateral aspect of wrist over the triquetrum</td>
<td>Lateral midline of ulna</td>
<td>Lateral midline of 5th metacarpal</td>
<td>Forearm rests on the table in mid-position; the wrist in neutral position, the fingers should be relaxed</td>
<td>The hand has moved toward the dorsal forearm to the limit of motion(26)</td>
</tr>
</tbody>
</table>

Figure 3.27: Wrist extension: starting position

Figure 3.28: Wrist extension: end position
3.7.9.1.3 Knee flexion (Figures 3.29-3.30)

<table>
<thead>
<tr>
<th>Body position</th>
<th>Axis of rotation</th>
<th>Stationary leg</th>
<th>Moving leg</th>
<th>Starting position</th>
<th>End position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prone</td>
<td>Lateral epicondyle of the femur</td>
<td>Lateral midline of the femur</td>
<td>Lateral midline of the fibula and the lateral maleolus</td>
<td>Patient in prone position. Knee in extension</td>
<td>Knee flexed towards the back to the limit of motion&lt;sup&gt;(26)&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Figure 3.29: Knee flexion starting position: patient in prone position

Figure 3.30: Knee flexion in end position

3.7.9.1.4 Knee extension (Figures 3.31-3.32)

<table>
<thead>
<tr>
<th>Body position</th>
<th>Axis of rotation</th>
<th>Stationary leg</th>
<th>Moving leg</th>
<th>Starting position</th>
<th>End position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>Lateral epicondyle of the femur</td>
<td>Lateral midline of the femur</td>
<td>Lateral midline of the fibula and the lateral maleolus</td>
<td>Patient supine with knee straight</td>
<td>Knee extended to limit of motion&lt;sup&gt;(26)&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Figure 3.31: Knee extension starting position

Figure 3.32: Knee extension in end position
3.7.9.1.5 Hip flexion (Figures 3.33-3.34)

<table>
<thead>
<tr>
<th>Body position</th>
<th>Axis of rotation</th>
<th>Stationary leg</th>
<th>Moving leg</th>
<th>Starting position</th>
<th>End position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>Greater trochanter</td>
<td>Lateral midline of the pelvis</td>
<td>Lateral midline of the femur</td>
<td>Patient in the supine position with hip in straight line</td>
<td>Hip flexed toward abdomen to limit of motion(26)</td>
</tr>
</tbody>
</table>

Figure 3.33: Hip flexion starting position
Figure 3.34: Hip in flexed position

3.7.9.1.6 Hip extension (Figures 3.35-3.36)

<table>
<thead>
<tr>
<th>Body position</th>
<th>Axis of rotation</th>
<th>Stationary leg</th>
<th>Moving leg</th>
<th>Starting position</th>
<th>End position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prone</td>
<td>Greater trochanter</td>
<td>Lateral midline of the pelvis</td>
<td>Lateral midline of the femur</td>
<td>Patient in prone position with hip in straight line</td>
<td>Hip extended upwards to limit of motion(26)</td>
</tr>
</tbody>
</table>

Figure 3.35: Hip extension starting position: patient in prone position
Figure 3.36: Hip in extended position
3.7.9.1.7 Lateral flexion (Figures 3.37-3.38)

The flexibility of the spine was assessed by measuring the spinal lateral flexion. The participant stood in an upright position with the hands at the side. The distance of the finger tips to the floor was measured with a measuring tape. The participant then bent over sideways at the waist, with the hand moving down the thigh. The distance from the fingertips to the floor was measured again. The same procedure was followed for the opposite side of the body. The distance of the hand from the floor was used to express the participant’s lateral flexibility\(^{(26)}\).

![Figure 3.37: Lateral flexion](image1) ![Figure 3.38: The distance of the hand from the floor is measured](image2)

3.7.9.1.8 Back scratch test (Figure 3.39)

The back scratch test was used to measure the upper body flexibility. The participant had to reach over her shoulder and down her back with the one hand. The palm had to be down and the fingers extended. At the same time the other hand reached around and up the middle of the back, also with palm down and fingers extended. The overlap (plus score) was measured with a ruler. A gap between the middle fingers of each hand was measured for a minus score\(^{(26)}\).
3.7.9.1.9 Chair sit and reach test (Figure 3.40)

The chair sit and reach test was used to measure the lower body (hamstring) flexibility. With a chair put against the wall for stability the participant was instructed to sit on the front edge of the seat. The leg to be tested was extended in front of the hip, the heel on the floor and the ankle dorsiflexed at approximately 90°. This leg had to be as straight as possible. The other leg was flexed with the sole of the foot flat on the floor 15-20cm to the side of the body’s midline. The participant’s hands were on top of each other with the palms facing downwards. She bent slowly forward at the hip joints. The back was kept as straight as possible and the head was in a normal alignment. She then reached down the extended leg, trying to touch the toes. This position was held for 2 seconds. The measurement was taken by placing the ruler parallel to the lower leg (Figure 3.40). If the participant reached beyond the medial aspect of the end of the shoe, a plus score was recorded. If she reached short of this it was a minus score(26).
3.7.9.2 **Strength**

3.7.9.2.1 **Hand grip strength** (Figures 3.41-3.42)

Hand grip strength for both hands was measured with a dynamometer. The size of the handgrip was adjusted to a position that was comfortable for the participant. The participant had to stand in a comfortable position with the forearm in a neutral position. The dynamometer was squeezed as hard as possible using one brief maximal contraction. Three trials were conducted for each hand, allowing 1 minute rest periods in between. The best score was used as the participant’s hand grip strength\(^{(27)}\).

![Figure 3.41: Adjusting the handgrip in a comfortable position](image1)

![Figure 3.42: The dynamometer is squeezed as hard as possible](image2)
3.7.9.2.2 Leg strength test (Figure 3.43)
The isometric leg strength was measured with a leg dynamometer. The participant stood on the platform. The upper body was straight, but the knees were bent at an angle of 130-140 degrees. The hand bar which was held with a pronated grip was positioned across the thighs by adjusting the length of the chain. While straightening the legs, the participant exerted as much force as possible without using the back. This was repeated two or three times with 1 minute rest intervals. The maximum score was divided by 2.2 to convert it to kilograms\(^{(27)}\).

Figure 3.43: The patient exerting force with the leg dynamometer
3.7.9.2.3 **Arm curl test** (Figure 3.44)
The arm-curl test was used to measure the upper-body strength. The participant sat on a chair with her feet flat on the floor and her back straight. With a 5 pound (2.27kg) dumbbell held in a neutral grip in the dominant hand, the arm was to hang down at her side. The participant then curled the dumbbell by fully flexing the elbow while supinating the forearm. The arm was then returned to the starting position. The measurement was taken by noting the amount of time it took the participant to perform 20 repetitions\(^{(27)}\).

![Arm curl test](image)

3.7.9.2.4 **Sit to stand test** (Figure 3.45)
Lower body strength was measured by this test. With a chair firmly against a wall the participant sat up straight with her feet flat on the floor. Her arms were crossed at the wrist and were held against her chest. She rose to a full stand and then sat down again. The measurement was taken by noting the amount of time it took the participant to perform 20 repetitions\(^{(27)}\).

![Sit to stand test](image)
3.7.10 **Aerobic capacity**

The Rockport 1 mile walk test was used to measure aerobic capacity. This is a scientifically acknowledged and validated test to measure the aerobic fitness of both men and women between the ages of 20 and 69 years. An uninterrupted distance of 1 mile (1609m) was measured over a flat surface on an athletic track. Participants had to stretch for 5-10 minutes before walking the 1 mile as quickly as possible (Figure 3.46). Immediately after the distance was completed, the heart rate was measured by a Polar 810i heart rate monitor system and the blood pressure was taken (Figure 3.47). The VO$_2$ max was estimated by using the Rockport relative fitness charts$^{28}$. 

![Figure 3.46: Walking the 1 mile](image1) ![Figure 3.47: Patient’s blood pressure was taken after completion of 1 mile walk](image2)
3.8 DATA ANALYSIS

All data was statistically analysed by Dr. Lizelle Fletcher (University of Pretoria - Department of Statistics).

For between group analyses [PHASE 1 – Healthy Control Group (HCG) vs. Rheumatoid Arthritis Group (RAG) and PHASE 2 – Rheumatoid Arthritis Exercise group (RAE) vs. Rheumatoid Arthritis Control group (RAC)] multivariate analysis of variance (MANOVA) tests were performed, firstly because the data was multivariate in nature (HRV has thirteen supine and thirteen standing variables), and secondly to protect against an inflated Type 1 error. Tests for normality were conducted to assess whether one of the basic assumptions of a MANOVA was met\(^{(29)}\).

If the measurements were skew, the variables were transformed using a suitable transformation (e.g. natural logarithms or square root transformation). MANOVA was then performed on the transformed variables, but because transformed variables were difficult to interpret, MANOVA was also run on the untransformed variables. Since the results corresponded, further analyses were done on the untransformed variables using non-parametric methods to accommodate the skew variables.

As only 2 groups (RAG vs. HCG in PHASE 1, and RAE vs. RAC in PHASE 2) were reported on, instead of interpreting the MANOVA tests of between-subjects effects, i.e. the univariate ANOVAs which are equivalent to t-tests, non-parametric Mann Whitney U-tests were performed to determine which dependent variables differed between the 2 groups. For purposes of clarity an example of the above-mentioned analyses are discussed in Table 3.4. The analyses of the HRV parameters in PHASE 1 are used as the example.
Table 3.4: Explanation of statistical analyses on PHASE 1 HRV parameters

Many of the variables were positive skewed, as illustrated in the clustered box plot in Figure 3.48. Due to positive skewness of the data, statistical tests for normality were performed to determine which variables to transform. RRSD (supine), RMSSD (supine), pNN50 (supine), SD1 (supine), SD2 (supine), LF(ms²) (supine), HF(ms²) (supine), HF(nu) (supine), LF/HF (supine), HR (stress), HRSD (stress), RMSSD (stress), pNN50 (stress), SD1 (stress), SD2 (stress), LF(ms²) (stress), HF(ms²) (stress), LF(nu) (stress), HF(nu) (stress) and LF/HF (stress) were identified and all were transformed using natural logarithms as they deviated significantly from a normal distribution. 

Appendix 6 – T08165 HRV Normality Tests.docx

Figure 3.48: Clustered box plot of pNN50 (stress) demonstrating positive skewness

A MANOVA was consequently performed combining the ln-transformed variables and the original variables that did not need a transformation. The results of the MANOVA showed that multivariately there were differences between the two groups (HCG and RAG) with regards to some of the dependent variables (Pillai’s Trace, Wilks’ Lambda, Hotelling’s Trace and Roy’s Largest Root all have p<0.001). The partial eta-squared value was 0.61, indicating a large effect size. According to the MANOVA tests of
between-subjects effects, only 4 of the 26 variables did not have statistically significant differences between the HCG and RAG, i.e. HRSD (supine), LF(nu) (stress), HF(nu) (stress) and LF/HF (stress). Appendix 7 – T08165 HRV MANOVA using ln(HRV).docx

MANOVA on the untransformed variables were subsequently performed and the results corresponded with that of the ln-transformed MANOVA, with the exception of pNN50 (stress) and HF(ms^2) (stress). Both had between subject p-values > 0.05. This is not surprising in view of the fact that both are very skew, thus explaining why statistical differences could be observed in the MANOVA using the transformed variables. Appendix 8 – T08165 HRV analysis 24 March.docx p69-71 and p74-76.

In PHASE 2 of the study, data analysis was also performed within the 2 groups (RAE and RAC), comparing pre- and post-intervention measurements. Wilcoxon Signed Rank tests were used to determine whether there was a statistical improvement within each group.

### 3.9 ETHICAL CONSIDERATIONS

#### 3.9.1 ETHICAL APPROVAL

The protocol was submitted and approved by the Ethics Committee of the University of Pretoria.

#### 3.9.2 CONSENT

All participants in this study completed a letter of informed consent which was thoroughly explained to everyone (Appendix 9). The letter was signed, authorizing the researcher to use the data for research purposes.

#### 3.9.3 CONFIDENTIALITY

All information obtained during the course of this study is treated in a confidential manner. Data that may be reported in scientific journals will not include any information that will identify any participant.
BIBLIOGRAPHY


12. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North


21. Fransen J, Stucki G, van Riel PLCM. Rheumatoid arthritis measures: Disease Activity Score (DAS), Disease Activity Score-28 (DAS28), Rapid Assessment of Disease Activity in Rheumatology (RADAR), and Rheumatoid Arthritis Disease Activity Index (RADAI). Arthritis Care & Research 2003;49(S5):S214-S224.


